CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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 209939/209940
Supplement #:	S-000
Drug Name:	Letermovir (MK-8228) tablets and injection
Indication(s):	Prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogenic hematopoietic stem cell transplant
Applicant:	Merck
Date(s):	Received Date: March 8, 2017 PDUFA Date: November 08, 2017
Review Priority:	Priority
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Keywords: letermovir, cytomegalovirus (CMV), allogeneic hematopoietic stem cell transplant (HSCT), pre-emptive therapy (PET).

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1 EXECUTIVE SUMMARY

Merck submitted this New Drug Application for letermovir (MK-8228) injection for the prophylaxis of clinically significant cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant. This review will focus on the applicant's prospective, randomized, double-blind, placebo-controlled, phase 3 clinical trial to evaluate the safety and efficacy of letermovir for the proposed indication. Subjects were randomized 2:1 to receive either letermovir or placebo beginning anytime from the day of transplant until 28 days post-transplant. Study medication continued through Week 14 (~100 days) post-transplant. The clinical study report submitted in this NDA describes the results of the trial when all randomized subjects had completed the Week 24 post-transplant visit or had discontinued from the study before their Week 24 visit.

In the primary efficacy analysis based on Study P001, the percentage of subjects with clinically significant CMV infection by Week 24 was 38% in the letermovir arm and 61% in the placebo arm. The corresponding risk difference was -24% in favor of letermovir with 95% CI of -33% to -15% and p-value<0.001.

The Kaplan-Meier event rate for all-cause mortality (including post-study information) was lower for the letermovir group (12%) compared to the placebo group (17%) at Week 24 post-transplant and was also lower for the letermovir group (24%) compared to the placebo group (28%) at Week 48 post-transplant. However the difference in all-cause mortality between letermovir and placebo was only statistically significant at Week 24.

2 INTRODUCTION

2.1 Overview

In this New Drug Application (NDA), Merck submitted results of their trial MK-8228P001 entitled "A Phase 3, Randomized, Placebo-controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients."

According to Merck, there were 74 sites that received IEC/IRB approval to conduct the trial. Seventy (70) sites screened at least 1 subject and 67 allocated subjects to study medication. The 67 trial centers were distributed among 20 countries. Trial centers were located in the following countries (with number of sites): Austria (2), Belgium (2); Brazil (1), Canada (1); Finland (1), France (3); Germany (4); Italy (4); Japan (5); Republic of Korea (4), Lithuania (1),New Zealand (1); Peru (1) Poland (2), Romania (1), Spain (5); Sweden (2), Turkey (4), United Kingdom (2); and the United States (21).

According to the applicant letermovir is a novel inhibitor of CMV viral terminase and the phase 3 trial (Protocol 001 (P001)) conducted in 570 adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT) forms the principle basis for characterizing the safety and efficacy of letermovir. The applicant states that the totality of the data from P001 demonstrates a favorable benefit/risk profile and supports the proposed indication (b) (4) (b) (4) The applicant considers that the robustness of the phase 3 data together with the now standard practice of initiating anti-CMV pre-emptive therapy based on the clinical endpoint of CMV viremia and the clinical condition of the patient support a traditional approval of the application.

The primary efficacy endpoint for P001 was the proportion of subjects with clinically significant CMV infection through Week 24 (~6 months) post-transplant. Clinically significant CMV infection was defined as the occurrence of either one or the following outcomes:

- onset of CMV end-organ disease

OR

- initiation of anti-CMV PET based on documented CMV viremia (as measured by the central laboratory) and the clinical condition of the subject. Initiation of PET in the trial referred to the practice of initiating therapy with the following anti-CMV agents when active CMV viral replication was documented: ganciclovir (GCV), valganciclovir (VGCV), foscarnet, and/or cidofovir.

Table 1: List of all studies included in the review

Study	Phase and Design	Treatment Duration / Interim Reporting Period	# of Subjects per Arm (efficacy analysis Tested/ control)	Study Population
P001	Phase 3, Randomized, Double-Blind Trial	48 weeks / Week 24	360 Letermovir 180 Placebo	Adult CMV-seropositive recipients [R+] of an allogenic HSCT who had no detectable CMV viral DNA (measured by the central laboratory) on Day 1 (when study medication was initiated)

The review will focus on the applicant's prospective, randomized, placebo-controlled, double-blind phase 3 study P001. The clinical study reports submitted in this NDA describe the results of the study when all randomized subjects had completed the Week 24 post-transplant visit or had discontinued from the study drugs before their Week 24 visit.

2.2 Data Sources

The application package is located at \\CDSESUB1\evsprod\NDA209939\0000. Many datasets were submitted after the original submission including Week 48 mortality data and intermediate datasets for opportunistic infections. The original submission had data for the interim Week 48 mortality analysis.

The dataset called "adeff" contains the data for the primary efficacy endpoint while "adtte" contains data for the time to event endpoints except for the 10% of patients in the interim analysis who did not reach their Week 48 visit. These datasets are in the analysis dataset folder: \\CDSESUB1\evsprod\NDA209939\0000\m5\datasets\p001v01\analysis\legacy\datasets.

On April 6, 2017 the applicant submitted corrected results for the interim Week 48 mortality analysis. The path for this submission is \\CDSESUB1\evsprod\NDA209939\0004.

On April 24, 2017 the applicant submitted datasets and the report for the final Week 48 analysis of mortality. The location for this submission is \\CDSESUB1\evsprod\NDA209939\0006. The applicant submitted updated "adtte" and "adsl" datasets at \\CDSESUB1\evsprod\NDA209939\0006\m5\datasets\p001v02\analysis\legacy\datasets and submitted an updated "adae" dataset at \\CDSESUB1\evsprod\NDA209939\0006\m5\datasets\p001v01\analysis\legacy\datasets.

On May 12, 2017 the applicant submitted two datasets as per the medical division's request for analyses of opportunistic infections. The location of the datasets for this submission is \\CDSESUB1\evsprod\NDA209939\0007\m5\datasets\p001v01\analysis\legacy\datasets.

Results that FDA reviewers obtained using the two opportunistic infection datasets did not match the results found in Table 22 of the Clinical Study Report. Merck responded to FDA's information request on June 7, 2017. The path to this submission is \\CDSESUB1\evsprod\NDA209939\0013.

After a second information request Merck admitted making an error in their calculation of subcategories of the opportunistic infections and re-submitted their revised results on June 23, 2017. The path to this submission is \\CDSESUB1\evsprod\NDA209939\0018.

On July 14, 2017, Merck sent in the updated mortality data and summaries for additional post-study information that they were able to collect on the discontinued patients whose mortality status were later confirmed. The location of the datasets for this submission is \\CDSESUB1\evsprod\NDA209939\0019.

On August 4, 2017, Merck responded to a follow-up IR pertaining to discrepancies between the number of post-study deaths in their tables and Kaplan-Meier analyses in their July 14, 2017 response. The path to this submission is \\cdsesub1\evsprod\NDA209939\0027.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted SDTM, legacy and analysis datasets along with define.pdf files and SAS programs used to analyze and create analysis datasets. Merck resubmitted the mortality analyses due to a SAS programming error discovered with proc lifetest where the treatment group and high vs. low risk stratification variables were switched. The error resulted in p-values being reported for a comparison between high vs. low risk randomization strata rather than for the comparison between letermovir vs. placebo treatment groups. Instead of a statistically significant two-sided p-value of 0.019 they should have obtained a non-significant p-value of 0.10 for the interim Week 48 analysis at the time of database lock. For the final Week 48 mortality data analysis instead of a statistically significant two-sided p-value of 0.018 they should have obtained a non-significant p-value of 0.12.

In response to an FDA Information Request sent on April 10, 2017, Merck stated that they did not proactively follow up patients who discontinued from the trial in order to determine their mortality status. Instead, Merck stated that they only counted deaths while patients were still enrolled in the trial. Merck provided additional information in the datasets about 11 additional deaths among the 87 patients who discontinued from the trial. After counting these 11 subjects as deaths, 76 subjects with unknown mortality status remained. The applicant stated on page 9 of the Week 48 Mortality Statistical Report that "post-study deaths are not included in the mortality analysis, as the reporting of information after a subject had completed the clinical trial was not required." On April 24, 2017 Merck was asked to provide additional information about the mortality status of all of the study subjects at Weeks 24 and 48 post-transplant.

This information was not submitted until July 14, 2017. According to Merck, vital status were obtained for 58 of the 76 subjects who prematurely withdrew from the trial with unknown mortality status at the time the initial (Week 24) clinical study report was written. Merck stated that the reason for not being able to collect information on the remaining subjects was largely due to country related legal issues in contacting subjects after the completion and closure of the trial as well as for those patients whose reason for early withdrawal was "withdrew consent".

The reviewers were also unable to replicate Merck's analyses of opportunistic infections using the intermediate datasets. In response to our query about the analyses of opportunistic infections and further clarifications regarding the accuracy of the numbers reported, Merck responded with their SAS code to derive the opportunistic infection tables. The path to this submission is \\CDSESUB1\evsprod\NDA209939\0013. Their response was not helpful; consequently the review team submitted more specific questions about selected discrepancies in order to elicit more information. The applicant responded on June 23, 2017 stating that they had made a programming error for individual infections like bacteremia but not total categories like all bacterial infections. The error was that they counted the number of occurrences of each infection instead of the number of patients. The path to this submission is \\CDSESUB1\evsprod\NDA209939\0018.

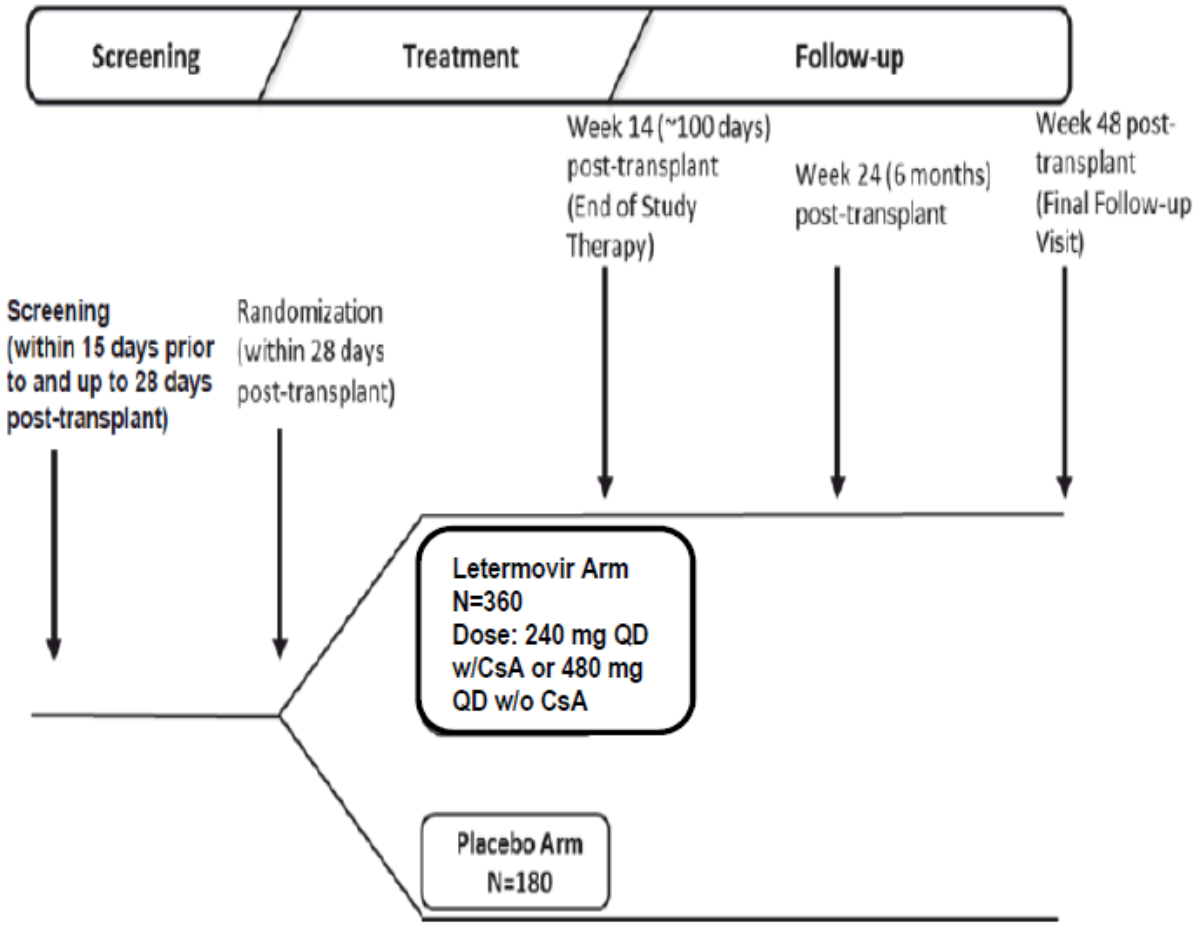
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study P001 was a randomized, placebo-controlled, multi-site, double-blind trial designed to evaluate the efficacy and safety of letermovir versus placebo, dosed for 14 weeks, for prevention of clinically significant CMV infection in adult, CMV-seropositive allogeneic HSCT recipients (R+), a population at high risk for CMV infection and /or disease. Subjects were randomized 2:1 to receive either letermovir or placebo beginning anytime from the day of transplant until 28 days post-transplant.

Study medication continued through Week 14 (~100 days) post-transplant which the applicant claims is the period of highest risk for CMV infection and/or disease in HSCT recipients. The clinical study report submitted in this NDA describe the results of the trial through a data cutoff performed when all randomized subjects had completed the Week 24 post-transplant visit or had discontinued from the study before their Week 24 visit. Subjects were followed through Week 48 post-transplant and the applicant submitted interim Week 48 mortality analyses at the time the NDA was submitted.

Figure 1 Trial Diagram



N = planned enrollment

Source: Figure 9-1 of the Clinical Study Report for P001V01

Merck provided the following description of the trial design and plan: Subjects who completed treatment through Week 14 (~ 100 days) post-transplant had follow-up assessments up to Week 24 to assess for clinically significant CMV infection, all-cause mortality and other health outcome measures after completing prophylactic therapy. During these visits subjects continued to be monitored for clinically significant CMV infections, all-cause mortality and other health outcomes measures related to the "indirect" effects of CMV infection such as the incidence of opportunistic infections and GVHD (acute and chronic).

Subjects who developed clinically significant CMV infection through Week 24 post-transplant had a CMV Infection Visit in order to discontinue study medication (if the subject was on study medication at the time of the visit) and to initiate PET or start treatment for CMV disease. It was mandatory to send a confirmatory plasma sample for CMV DNA PCR testing to the central laboratory immediately prior to initiating treatment for CMV disease or PET in all instances at this visit.

In the event that the confirmatory result obtained on the day of PET initiation was not available (e.g., sample was lost or mishandled by the investigator site prior to shipment, or was inadequate upon receipt at the central laboratory), a subsequent sample had to be obtained and sent to the central laboratory within 7 days after PET initiation (preferably within 48-72 hours) as with effective PET, the likelihood of documenting viremia would decrease the longer a subject would be on PET.

A subject was considered to have met the primary efficacy endpoint if this confirmatory laboratory result from the central laboratory was positive for CMV viral DNA. In the event test results from the central laboratory were not available within the timeframe the investigator wished to initiate anti-CMV therapy, the investigator could use a positive local laboratory test (CMV DNA PCR or pp65 antigen only) result in order to make the decision. However, as described above, plasma samples for CMV DNA PCR testing also had to be sent to the central laboratory. In such instances, the local laboratory result also had to be reported.

In this trial the applicant provided guidance on viral load thresholds for PET initiation based on the risk groups described above as well as consideration of standard practice at the Fred-Hutchinson Cancer Research Center (FHCRC), as follows:

During the study medication period [through Week 14 (~100 days) post-transplant]:
• High risk: viral DNA ≥150 copies/mL
• Low risk: viral DNA >300 copies/mL

After Week 14 (~100 days) post-transplant:
• High risk: viral DNA >300 copies/mL
• Low risk: viral DNA >300 copies/mL

Stratified Randomization
The applicant stated that randomized subjects were stratified by 1) trial center and 2) risk for CMV reactivation in order to balance any effects of these variables on letermovir safety and efficacy across treatment groups.

Merck described two categories of risk groups for CMV reactivation were identified for stratification based on available literature and input from external experts on the Scientific Advisory Committee (SAC) as follows:

1. **High risk:** Subjects meeting one or more of the following criteria at the time of randomization:
    - Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR,
    - Haploidentical donor,
    - Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1,
    - Use of umbilical cord blood as stem cell source,

- Use of *ex vivo* T-cell-depleted grafts (including *ex vivo* use of alemtuzumab [Campath™]),/
- Grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).

2. **Low risk:** All subjects not meeting the definition of high risk.

3.2.2 Statistical Methodologies

Merck stated the following (in Section 9.8.8.1.1 of the Clinical Study Report): "To test the primary hypothesis that letermovir was superior to placebo in the prevention of clinically significant CMV infection, the stratum-adjusted Mantel-Haenszel method (with continuity correction) was used to compare the two treatment groups with respect to the proportion of subjects with clinically significant CMV infection through Week 24 (~6 months) post-transplant. Risk for CMV infection and/or disease (high vs. low risk) was included as a stratification factor in the primary efficacy analysis. Cochran Mantel-Haenszel weights were used to calculate the overall between group differences across strata. Letermovir was to be considered superior to placebo if the one-sided p-value was less than or equal to 0.0249."

The company stated that they performed periodic interim safety reviews, one interim futility analysis, and one primary hypothesis test conducted at the primary time-point (Week 24 post-transplant). The applicant stated that since stopping for futility and periodic safety checks do not inflate type I error rate, no alpha spending was planned for these analyses and that there was no intention for stopping for overwhelming efficacy at the time of the interim. However Merck stated that they allocated a small amount of alpha (0.0001) for statistical rigor and consequently used a one-sided statistical significance level of 0.0249 at the end of the trial instead of 0.025 for declaring statistical significance for the primary endpoint.

A sensitivity analysis including those subjects who had detectable CMV viral DNA on Day 1 (the day of randomization) was performed. The primary missing data approach was the Non-Completer = Failure approach where failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through the Week 24 post-transplant visit window.

The primary population for efficacy evaluations in this trial was the Full Analysis Set (FAS) population, which consisted of all randomized subjects who receive at least one dose of study medication and had no detectable CMV viral DNA (measured by the central laboratory) on Day 1 (when study medication was initiated). According to the applicant, out of the 565 randomized and treated subjects, 70 (12%) of the subjects had detectable CMV DNA on Day 1, and were excluded from Full Analysis Set (FAS) population. The FAS population consisted of 495 subjects, including 325 (66%) in the letermovir group and 170 (34%) in the placebo group.

Kaplan-Meier curves were plotted by treatment group for clinically significant CMV infections and for Week 24 and 48 mortality data. The sponsor pre-specified in the protocol that the stratified log-rank test was used for comparing treatment groups for time to event analyses of

clinically significant CMV infection. Although no statistical tests were pre-specified in the protocol for the exploratory mortality analyses the applicant also used the log-rank test for time to event analyses of mortality.

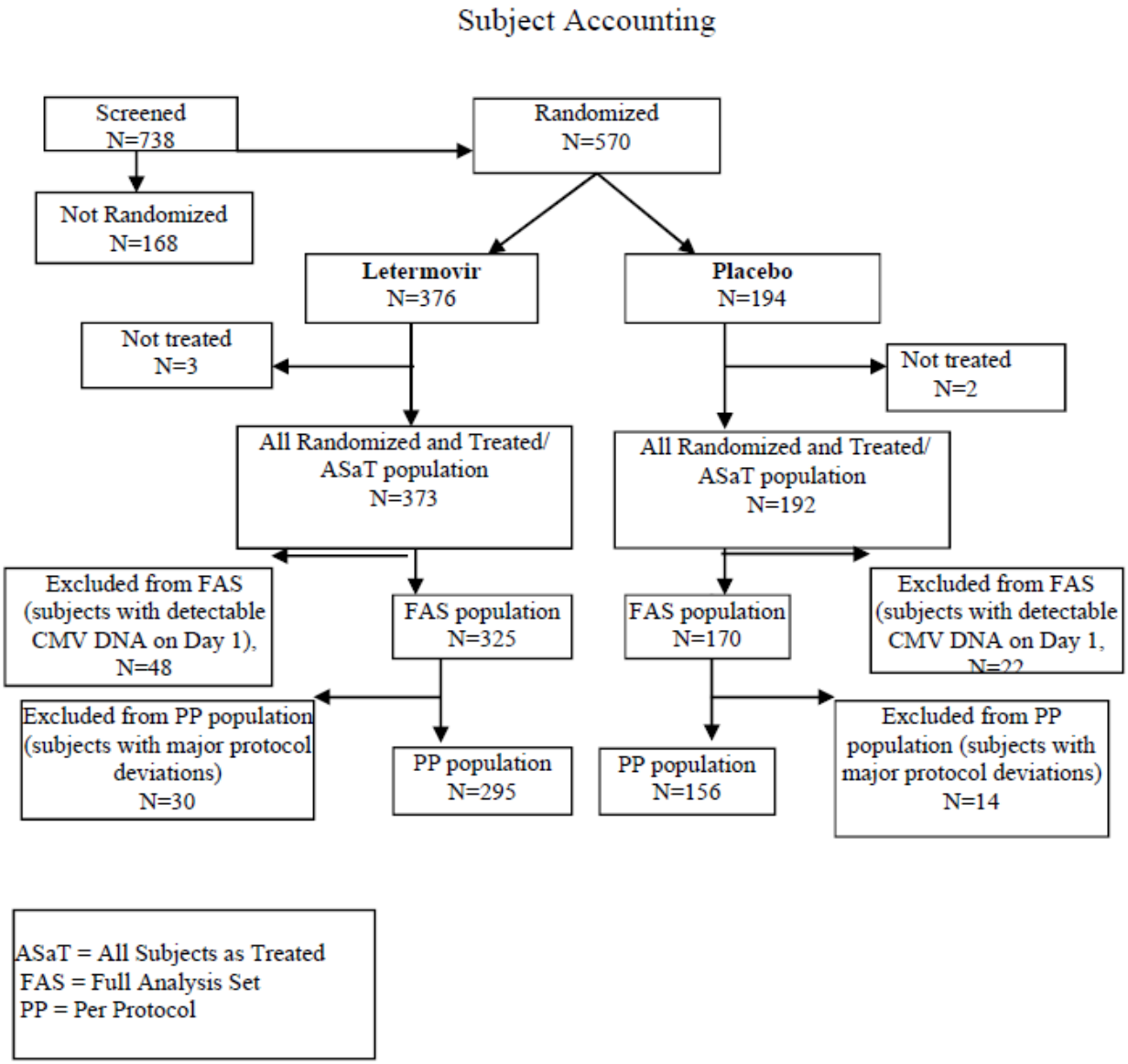
Sample Size Estimates

Based on available literature and on the results from the Phase 2b trial (P020), the incidence rate of clinically significant CMV infection through Week 24 post-transplant for subjects receiving placebo was anticipated to be approximately 35%. It was also anticipated that letermovir would reduce this incidence by half to approximately 17%. It was further anticipated that about 20% of subjects would be discontinued from the trial from both treatment arms for reasons other than virologic failure. Since the primary missing data approach is Non-Completer = Failure approach, 20% for missing outcomes was added to the expected incidence of clinically significant CMV infection for the placebo arm (55%) and the letermovir arm (37%) for sample size and power calculations. A sample size of approximately 540 subjects was planned using a 2:1 randomization ratio (~360 subjects in the letermovir arm and ~180 subjects in the placebo arm). With this sample size, the trial had at least 90% overall power to detect a treatment difference with a 1-sided p-value less than or equal to 0.0249.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Figure 2: Flow Diagram Accounting of Study Subjects



Source: Figure 10-1 of the Clinical Study Report

Table 2: Disposition of Subjects With Respect to Trial Status (All Randomized Subjects)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	376		194		570	
Status for Trial Segment Through 24 Weeks Post-transplant						
Randomized but not treated	3	(0.8)	2	(1.0)	5	(0.9)
Completed Week 24 Post-transplant	295	(78.5)	136	(70.1)	431	(75.6)
Discontinued Through Week 24 Post-transplant	78	(20.7)	56	(28.9)	134	(23.5)
Adverse Event	6	(1.6)	3	(1.5)	9	(1.6)
Death	37	(9.8)	28	(14.4)	65	(11.4)
Lost To Follow-Up	2	(0.5)	4	(2.1)	6	(1.1)
Non-Compliance With Study Drug	1	(0.3)	0	(0.0)	1	(0.2)
Physician Decision	9	(2.4)	5	(2.6)	14	(2.5)
Withdrawal By Subject	23	(6.1)	16	(8.2)	39	(6.8)
Status for Next Trial Segment Beyond 24 Weeks Post-transplant						
Entered 24 weeks post-transplant follow-up	295	(78.5)	136	(70.1)	431	(75.6)
Continuing in Study	44	(11.7)	20	(10.3)	64	(11.2)
Discontinued between Weeks 24 and 48 Post-transplant	49	(13.0)	16	(8.2)	65	(11.4)
Completed 48 weeks Post-transplant	202	(53.7)	100	(51.5)	302	(53.0)

Note: Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with cyclosporin A.
n (%) = Number (percent) of subjects in each sub-category.

Source: Table 10-2 of the Clinical Study Report

Disposition status of all randomized subjects is shown in Table 10-2 of the Clinical Study Report. Of the 570 randomized subjects (376 in the letermovir group and 194 in the placebo group), 78% of the letermovir subjects and 70% of the placebo subjects completed the trial through the Week 24 post-transplant visit.

More subjects discontinued from the trial before the Week 24 post-transplant visit in the placebo arm (29%) than in the letermovir group (21%). The most common reasons for discontinuation were death (10% and 14% in the letermovir and placebo groups respectively), subject withdrawal (6% and 8% in the letermovir group and placebo treatment groups respectively), and physician decision (2% and 3% in the letermovir group and placebo treatment groups, respectively).

All of the 431 subjects who completed the trial through Week 24 post-transplant subsequently entered the next follow-up phase from Week 24 to Week 48 post-transplant. Thirteen percent of all randomized letermovir subjects and 8% of all randomized placebo subjects discontinued between Week 24 and Week 48 post-transplant, and 53% of all randomized subjects completed the trial, which was still ongoing, through the Week 48 post-transplant visit at the time of database lock.

Table 3: Disposition of Subjects With Respect to Study Medication (All Randomized Subjects)

	Letermovir n (%)		Placebo n (%)		Total n (%)	
Subjects in population	376		194		570	
Study Medication Disposition						
Randomized but not treated	3	(0.8)	2	(1.0)	5	(0.9)
Completed	267	(71.0)	80	(41.2)	347	(60.9)
Discontinued	106	(28.2)	112	(57.7)	218	(38.2)
Adverse Event	42	(11.2)	19	(9.8)	61	(10.7)
Death	5	(1.3)	4	(2.1)	9	(1.6)
Excluded Medication*	3	(0.8)	0	(0.0)	3	(0.5)
Lack Of Efficacy	24	(6.4)	82	(42.3)	106	(18.6)
Non-Compliance With Study Drug	5	(1.3)	1	(0.5)	6	(1.1)
Physician Decision	7	(1.9)	2	(1.0)	9	(1.6)
Withdrawal By Subject	20	(5.3)	4	(2.1)	24	(4.2)

*These subjects were discontinued from study medication as they needed concomitant prohibited medications.
Note: Each subject is counted once for subject study medication disposition based on the latest corresponding disposition record.
Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with cyclosporin A.
n (%) = Number (percent) of subjects in each sub-category.

Source: Table 10-3 of the Clinical Study Report

As shown in Table 10-3 of the Clinical Study Report, out of a total of 570 randomized subjects 376 (66%) of the subjects were randomized to the letermovir treatment group and 194 34% were randomized to the placebo treatment group. There were only 3 subjects in the letermovir group and 2 subjects in the placebo group who did not receive any study medication.

The remaining 565 subjects received at least one dose of study medications. These subjects were in the All Randomized and Treated Subjects/All Subjects as Treated (ASaT) population, which was the primary population the applicant used for safety analyses. A higher percentage of subjects in the letermovir treatment group completed treatment with study medication (71% compared to 41% of the subjects in the placebo group). A much higher percentage of placebo subjects (58%) discontinued study medication early compared to only 28% of the subjects randomized to the letermovir treatment group. The higher discontinuation rate in the placebo arm was due to more subjects in the placebo group (42%) discontinuing study medication early due to lack of efficacy than in the letermovir group (6%).

The applicant noted that the categories for reason for discontinuation from study medication were mutually exclusive, and based on investigator assessment. Therefore according to the applicant, in the event that a subject discontinued due to an AE which later has a fatal outcome, the subject would be counted as a having discontinued “due to an AE”, not ”Death” in this table. However the death would still be accounted for in the all-cause mortality assessment.

Table 4: Subject Accounting for Efficacy Analyses (All Randomized Subjects)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	**376**		**194**		**570**	
Included in All Randomized and Treated	**373**	**(99.2)**	**192**	**(99.0)**	**565**	**(99.1)**
Excluded from All Randomized and Treated	**3**	**(0.8)**	**2**	**(1.0)**	**5**	**(0.9)**
Did not receive study medication	3	(0.8)	2	(1.0)	5	(0.9)
Included in FAS population	**325**	**(86.4)**	**170**	**(87.6)**	**495**	**(86.8)**
Excluded from FAS population	**51**	**(13.6)**	**24**	**(12.4)**	**75**	**(13.2)**
Not in All Randomized and Treated	3	(0.8)	2	(1.0)	5	(0.9)
Subjects with detectable CMV DNA on Day 1	48	(12.8)	22	(11.3)	70	(12.3)
Included in PP population	**295**	**(78.5)**	**156**	**(80.4)**	**451**	**(79.1)**
Excluded from PP population	**81**	**(21.5)**	**38**	**(19.6)**	**119**	**(20.9)**
Not in FAS	51	(13.6)	24	(12.4)	75	(13.2)
< 75% compliant with study therapy	8	(2.1)	4	(2.1)	12	(2.1)
> 7 consecutive days of study drug interruption	8	(2.1)	2	(1.0)	10	(1.8)
Wrong treatment administered	2	(0.5)	1	(0.5)	3	(0.5)
Did not have documented seropositivity for CMV	1	(0.3)	0	(0.0)	1	(0.2)
Had a history of CMV end-organ disease within 6 months prior to randomization	0	(0.0)	0	(0.0)	0	(0.0)
Was CMV viremic before randomization	2	(0.5)	1	(0.5)	3	(0.5)
Prohibited medication[↑]	14	(3.7)	7	(3.6)	21	(3.7)
Had previously participated in this study or any other study involving letermovir	0	(0.0)	0	(0.0)	0	(0.0)
Had previously participated or is currently participating in any study involving administration of a CMV vaccine or another CMV investigational agent during the course of this study	0	(0.0)	0	(0.0)	0	(0.0)

[↑] Use of prohibited medication with anti-CMV activity.

Note: Each criterion for the PP population was evaluated for each subject. As such, a subject may have met more than one of the exclusion criteria for the PP population and will be counted once for each exclusion that they met. Therefore , the sum of the reasons for exclusion may not equal the total number of subjects excluded from the PP population.

FAS = Full Analysis Set, PP = Per Protocol.

Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with cyclosporin A.

n (%) = Number (percent) of subjects in each sub-category.

Source: Table 10-5 of the Clinical Study Report

Table 10-5 of the Clinical Study Report displays the number and percentage of randomized subjects that were included in different efficacy analysis populations by treatment group. Only 3 randomized subjects in the letermovir arm and 2 subjects in the placebo arm did not receive study medication. The remaining 565 subjects who were randomized and treated with at least one dose of study medication were referred to as the All Randomized and Treated population. According to the applicant the FAS population consisted of all randomized subjects who received at least one dose of study medication and had no detectable CMV viral DNA (measured by the central laboratory) on Day 1 (when study medication was initiated). The FAS population was the primary population used by the applicant for efficacy analyses.

The applicant stated the following: Of the 565 subjects in the All Randomized and Treated population, 12% of the subjects had detectable CMV DNA on Day 1 and were excluded from the FAS population. Therefore, the FAS population consisted of 86% of All Randomized subjects in the letermovir group and 88% of All Randomized subjects in the placebo group.

Table 5: Summary of Treatment Compliance

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		192		565	
Treatment compliance						
<75%	9	(2.4)	4	(2.1)	13	(2.3)
≥ 75% to <90%	8	(2.1)	8	(4.2)	16	(2.8)
≥ 90% to <100%	71	(19.0)	20	(10.4)	91	(16.1)
100%	285	(76.4)	160	(83.3)	445	(78.8)
Summary statistics for treatment compliance (%)						
Mean	98.2		98.3		98.2	
SD	5.7		5.5		5.6	
Median	100.0		100.0		100.0	
Range	57.0 to 100.0		66.7 to 100.0		57.0 to 100.0	
n (%) = Number (percent) of subjects in each sub-category.						

Source: Table 10-15 of the Clinical Study Report

The majority of patients were treatment compliant (76% of letermovir subjects and 83% of placebo subjects) while 19% of the letermovir subjects and 10% of placebo subjects were ≥90% to <100% treatment compliant.

3.2.3.2 Demographic and Baseline Characteristics

Table 6: Demographic and Baseline Characteristics (ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		192		565	
Gender						
Male	211	(56.6)	116	(60.4)	327	(57.9)
Female	162	(43.4)	76	(39.6)	238	(42.1)
Race						
Asian	40	(10.7)	18	(9.4)	58	(10.3)
Black or African	8	(2.1)	4	(2.1)	12	(2.1)
Multi-Racial	22	(5.9)	9	(4.7)	31	(5.5)
Native Hawaiian	1	(0.3)	0	(0.0)	1	(0.2)
White	301	(80.7)	161	(83.9)	462	(81.8)
Missing	1	(0.3)	0	(0.0)	1	(0.2)
Age (Years)						
18 to 35	60	(16.1)	33	(17.2)	93	(16.5)
36 to 50	103	(27.6)	49	(25.5)	152	(26.9)
51 to 64	154	(41.3)	78	(40.6)	232	(41.1)
65 to 74	55	(14.7)	30	(15.6)	85	(15.0)
≥ 75	1	(0.3)	2	(1.0)	3	(0.5)
Subjects with data	373		192		565	
Mean	50.8		50.8		50.8	
SD	13.4		14.8		13.9	
Median	53.0		54.0		54.0	
Range	18.0 to 75.0		19.0 to 78.0		18.0 to 78.0	
Ethnicity						
Hispanic or Latino	30	(8.0)	10	(5.2)	40	(7.1)
Not Hispanic or Latino	328	(87.9)	176	(91.7)	504	(89.2)
Not Reported	6	(1.6)	5	(2.6)	11	(1.9)
Unknown	9	(2.4)	1	(0.5)	10	(1.8)
Weight (Kg)						
Subjects with data	373		192		565	
Mean	77.6		74.5		76.6	
SD	18.0		15.9		17.4	
Median	76.2		74.4		75.4	
Range	35.1 to 141.5		40.9 to 113.1		35.1 to 141.5	
BMI (Kg/m^2)						
Subjects with data	373		192		565	
Mean	26.5		25.5		26.2	
SD	5.2		5.1		5.2	
Median	25.6		25.1		25.5	
Range	17.0 to 49.0		16.6 to 44.7		16.6 to 49.0	

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Region						
Asia-Pacific	37	(9.9)	16	(8.3)	53	(9.4)
Latin America	7	(1.9)	2	(1.0)	9	(1.6)
Europe	185	(49.6)	97	(50.5)	282	(49.9)
North America	144	(38.6)	77	(40.1)	221	(39.1)
Region Subgroup						
US	132	(35.4)	70	(36.5)	202	(35.8)
Ex-US	241	(64.6)	122	(63.5)	363	(64.2)
Stratum[†]						
High Risk	121	(32.4)	54	(28.1)	175	(31.0)
Low Risk	252	(67.6)	138	(71.9)	390	(69.0)
Patients Engrafted at Baseline[‡]						
Yes	132	(35.4)	75	(39.1)	207	(36.6)
No	237	(63.5)	115	(59.9)	352	(62.3)
NA	4	(1.1)	2	(1.0)	6	(1.1)
Immunosuppressive Regimen Use[§]						
Cyclosporin A	193	(51.7)	100	(52.1)	293	(51.9)
Tacrolimus	160	(42.9)	79	(41.1)	239	(42.3)
Other	19	(5.1)	10	(5.2)	29	(5.1)
Missing	1	(0.3)	3	(1.6)	4	(0.7)
CMV DNA on Day 1(when study therapy is initiated)						
Detected	48	(12.9)	22	(11.5)	70	(12.4)
Not detected	325	(87.1)	170	(88.5)	495	(87.6)
Primary Reason for Transplant[‖]						
Acute lymphocytic leukaemia	35	(9.4)	17	(8.9)	52	(9.2)
Acute myeloid leukaemia	142	(38.1)	72	(37.5)	214	(37.9)
Aplastic anaemia	9	(2.4)	11	(5.7)	20	(3.5)
Chronic lymphocytic leukaemia	10	(2.7)	4	(2.1)	14	(2.5)
Chronic myeloid leukemia	17	(4.6)	6	(3.1)	23	(4.1)
Lymphoma	47	(12.6)	28	(14.6)	75	(13.3)
Myelodysplastic syndrome	63	(16.9)	22	(11.5)	85	(15.0)
Myelofibrosis	9	(2.4)	6	(3.1)	15	(2.7)
Plasma cell myeloma	14	(3.8)	10	(5.2)	24	(4.2)
Other	27	(7.2)	16	(8.3)	43	(7.6)
Donor CMV Serostatus						
Positive	229	(61.4)	114	(59.4)	343	(60.7)
Negative	139	(37.3)	78	(40.6)	217	(38.4)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Donor CMV Serostatus						
Unknown	5	(1.3)	0	(0.0)	5	(0.9)
Donor Type						
Matched related	127	(34.0)	64	(33.3)	191	(33.8)
Mismatched related	57	(15.3)	22	(11.5)	79	(14.0)
Matched unrelated	138	(37.0)	80	(41.7)	218	(38.6)
Mismatched unrelated	51	(13.7)	26	(13.5)	77	(13.6)
Stem Cell Source						
Peripheral blood	279	(74.8)	134	(69.8)	413	(73.1)
Bone marrow	82	(22.0)	47	(24.5)	129	(22.8)
Cord blood	12	(3.2)	11	(5.7)	23	(4.1)
Conditioning Regimen Use						
Myeloablative	186	(49.9)	97	(50.5)	283	(50.1)
Reduced intensity conditioning	92	(24.7)	54	(28.1)	146	(25.8)
Non-myeloablative	95	(25.5)	41	(21.4)	136	(24.1)
Baseline Acute GVHD (≥ Grade 2)						
Yes	2	(0.5)	1	(0.5)	3	(0.5)
No	370	(99.2)	191	(99.5)	561	(99.3)
Missing	1	(0.3)	0	(0.0)	1	(0.2)
Days from Transplantation to Randomization						
< 2 Weeks	237	(63.5)	121	(63.0)	358	(63.4)
≥ 2 Weeks	136	(36.5)	71	(37.0)	207	(36.6)
Subjects with data	373		192		565	
Mean	11.5		11.4		11.5	
SD	8.5		8.6		8.5	
Median	9		9		9	

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Days from Transplantation to Randomization						
Range	0 to 28		0 to 28		0 to 28	

†High risk: Subjects meeting one or more of the following criteria at the time of randomization:

1. Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR
2. Haploidentical donor
3. Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1
4. Use of umbilical cord blood as stem cell source
5. Use of ex vivo T-cell-depleted grafts
6. Grade 2 or greater graft-versus-host disease (GVHD), requiring the use of systemic corticosteroids (defined as the use of ≥ 1 mg/kg/day of prednisone or equivalent dose of another corticosteroid)

‡Low risk: All subjects not meeting definition of high risk.

‡If the engraftment status at baseline was missing for a subject but an engraftment date was recorded later, the engraftment status at baseline was imputed to be no. NA = not applicable. Subject's absolute neutrophil count did not go below 500/mm^3 at any point after transplantation due to the conditioning regimen received.

§Subjects counted in the cyclosporine A (CsA) row if they received concomitant CsA with or without any other immunosuppressants in the regimen during treatment phase. Tacrolimus containing-regimen included concomitant tacrolimus use with or without any other immunosuppressant use (except CsA). Subjects in the Other row received a regimen containing any other immunosuppressants (sirolimus, everolimus, systemic steroids, leflunomide, mycophenolate) except CsA or tacrolimus. The subjects in the missing row did not receive any immunosuppressants concomitantly.

‖Other reasons for transplant are provided in Section 14.

Note: The letermovir dose is 480 mg once daily with a dose adjustment to 240 mg once daily when administered in combination with cyclosporin A.

n (%) = Number (percent) of subjects in each sub-category.

Source: Table 10-6 of the Clinical Study Report

Demographic characteristics appeared to be fairly well balanced between the two treatment groups. The distributions of subject characteristics were similar in the FAS population, as shown in Table 14.1-5 of the Clinical Study Report. The mean age was 51 in both treatment groups, while the median age was 53 in the letermovir arm and 54 in the placebo arm. Approximately 40% of the subjects were female, while more than 80% were White, 2% of the subjects in both treatment arms were Black or African and 6% of the letermovir subjects and 5% of the placebo subjects were multi-racial. Eight percent of the letermovir subjects and 5% of the placebo subjects were Hispanic or Latino. Half of the subjects in both treatment arms were from Europe, approximately 35% of the subjects were from the US and 9% of the subjects were from the Asia-Pacific region.

The percentage of subjects who were at high risk for CMV reactivation was somewhat higher in the letermovir arm (32% vs. 28% in the placebo arm). More than 35% of the subjects were engrafted at baseline. The majority of subjects were on an immunosuppressive regimen where just over half of the subjects used cyclosporin and more than 40% used tacrolimus.

The primary reason for transplant was acute myeloid leukemia, which occurred in approximately 38% of the subjects followed by myelodysplastic syndrome which occurred in 15% of the subjects and lymphoma which occurred in 13% of the subjects.

CMV DNA was detected in approximately 12% of the subjects on Day 1. Approximately 60% of the subjects had donors who were CMV seropositive. Thirty-four percent of the donor types

were matched related while 39% were matched unrelated, 14% were mismatched related and 14% were mismatched unrelated. The stem cell source was peripheral blood for 75% of the letermovir subjects and 70% of the placebo subjects while 23% of the stem cell sources were bone marrow. Sixty-three percent of the subjects were randomized within two weeks of receiving a transplant.

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Analyses

Table 7: Reviewer's Analysis of Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant (NC=F Approach, FAS Population)

Efficacy Outcomes	**Letermovir (N=325)**	**Placebo (N=170)**
Failures by Week 24	**122 (38%)**	**103 (61%)**
1. Clinically Significant CMV Infection by Week 24	57 (18%)	71 (42%)
Week 48	58 (18%)	72 (42%)
a. Initiation of PET based on documented CMV viremia by Week 24	52 (16%)	68 (40%)
Week 48	50 (15%)	66 (39%)
b. CMV end-organ disease by Week 24	5 (2%)	3 (2%)
Week 48	6 (2%)	4 (2%)
Both a and b by Week 24	0	0
Week 48	2 (1%)	2 (1%)
2. Discontinued from study by Week 24	57 (18%)	28 (16%)
Week 48	97 (30%)	37 (22%)
3. Missing outcome in Week 24 visit window	8 (2%)	4 (2%)
Week 48	N/A[a]	N/A[a]
Stratum-adjusted treatment difference (Letermovir-Placebo) (95% CI)	-23.5 (-32.5, -14.6)	
p-value	p<0.001	
p-value for Breslow-Day Test	p=0.28	

[a] CMV DNA in the adeff dataset was only available up to Week 24. Week 48 results were based on the Week 48 adtte dataset submitted on 4/24/17 but were not complete; therefore inferential statistics were based on Week 24 data.
Source: Reviewer's Analysis

The Non-Completer=Failure (NC=F) approach was used for imputing missing data in the reviewer's analysis of the proportion of subjects who developed clinically significant CMV

infection through Week 24 post-transplant in the FAS population. In this approach, subjects who discontinued from the study prior to the Week 24 follow-up visit were considered as failures regardless of reason for discontinuation. Subjects missing CMV DNA measurements needed for efficacy assessment in the Week 24 window were also considered as failures.

At Week 24, the proportion of subjects with clinically significant CMV infection in the letermovir group (37.5%) was significantly lower than that in the placebo group (60.6%). The estimated difference (95% CI) was -23.5% (-32.5% to -14.6%), adjusted for the stratification factor (high vs. low risk of CMV reactivation) (two-sided p-value <0.001). There was no statistically significant treatment by stratification factor interaction (p-value for Breslow-Day test=0.28) which implied that the differential treatment effect between letermovir and placebo was the same in subjects with high and low risk for CMV reactivation.

The applicant's results for the primary efficacy analysis were almost the same as the reviewers. The only differences were that the applicant found one less subject in each treatment arm who discontinued from the study while the applicant found one more subject in each arm having missing outcomes in the Week 24 visit window. (The applicant's table is shown in the Appendix.)

Table 8: Analysis of Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant Including Subjects with Detectable CMV Viral DNA on Day 1 (NC=F Approach, All Randomized and Treated Subjects)

Parameter	Letermovir (N=373) n (%)	Placebo (N=192) n (%)
Failures[†]	**153 (41.0)**	**123 (64.1)**
Clinically significant CMV infection by Week 24[‡]	79 (21.2)	88 (45.8)
Initiation of PET based on documented CMV viremia	73 (19.6)	85 (44.3)
CMV end-organ disease	7 (1.9)	4 (2.1)
Discontinued from study before Week 24	64 (17.2)	30 (15.6)
Missing outcome in Week 24 visit window	10 (2.7)	5 (2.6)
Stratum-adjusted treatment difference (Letermovir-Placebo)[§]		
Difference (95% CI)	-23.6 (-31.9, -15.2)	
p-value	<0.0001	

[†] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[‡] Clinically significant CMV infection was defined as CMV end organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the subject. In one instance in both the letermovir and placebo arm, 1 subject is counted as both a case of initiation of PET and as a case of CMV end-organ disease.

[§] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

Source: Table 14.2-1 of the Clinical Study Report

Similar results were also obtained in an analysis of All Randomized and Treated Subjects (that included all randomized subjects with and without CMV viremia on Day 1). In this analysis, the proportion of subjects with clinically significant CMV infection at Week 24 post-transplant using the NC=F approach was significantly lower in the letermovir group with 41% failing in the letermovir group and 64% failing in the placebo group (one-sided p-value <0.001).

3.2.4.2 Analysis of Selected Secondary Efficacy Endpoints

This section summarizes several secondary efficacy endpoints starting with analyses of virologic endpoints. CMV virologic results are followed by exploratory mortality analyses which include the original Week 24 and 48 mortality analyses that were submitted with the NDA followed by updated mortality results that were submitted later on.

Mortality analysis results were impacted by a programming error as well as a lack of follow-up. Thus several results are presented and a detailed description of information requests and responses is provided. Finally at the end of this section the reviewer's attempts to replicate the applicant's exploratory analyses of opportunistic infections are summarized along with subsequent Information Requests and the applicant's responses.

3.2.4.2.1 *CMV DNA>1000 copies/mL*

Table 9: Proportion of Subjects with CMV DNA≥1000 copies/mL at any visit up to and including Week 24

Clinically Significant CMV Infection	Letermovir (N=325)	Placebo (N=170)
Yes	27 (8%)	45 (26%)
No	5 (2%)	1 (1%)
Total	32 (10%)	46 (27%)

Source: Reviewer's Analysis

Since many patients received PET with relatively low CMV viral loads, it was of interest to evaluate how many subjects had CMV DNA that exceeded 1000 copies/mL at any visit. Among subjects with clinically significant CMV infection a higher percentage of placebo subjects (26% compared to only 8% of the letermovir subjects) had high CMV DNA levels that were at least 1000 copies/mL at any visit up to and including Week 24. Only 2% of letermovir subjects and 1% of placebo subjects without clinically significant CMV infection were observed to have such high CMV DNA levels.

3.2.4.2.2 *Clinically Significant CMV Infection Post Transplant*

Table 10: Analysis of Proportion of Subjects with Clinically Significant CMV Infection Through Week 14 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (N=325) n (%)	Placebo (N=170) n (%)
Failures[†]	**62 (19.1)**	**85 (50.0)**
Clinically significant CMV infection by Week 14[‡]	25 (7.7)	67 (39.4)
Initiation of PET based on documented CMV viremia	24 (7.4)	65 (38.2)
CMV end-organ disease	1 (0.3)	2 (1.2)
Discontinued from study before Week 14	33 (10.2)	16 (9.4)
Missing outcome in Week 14 visit window	4 (1.2)	2 (1.2)
Stratum-adjusted treatment difference (Letermovir-Placebo)[§]		
Difference (95% CI)	-31.3 (-39.9, -22.6)	
p-value	<0.0001	

[†] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[‡] Clinically significant CMV infection was defined as CMV end organ disease or initiation of PET based on documented CMV viremia and the clinical condition of the subject.

[§] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 14 post-transplant visit window.

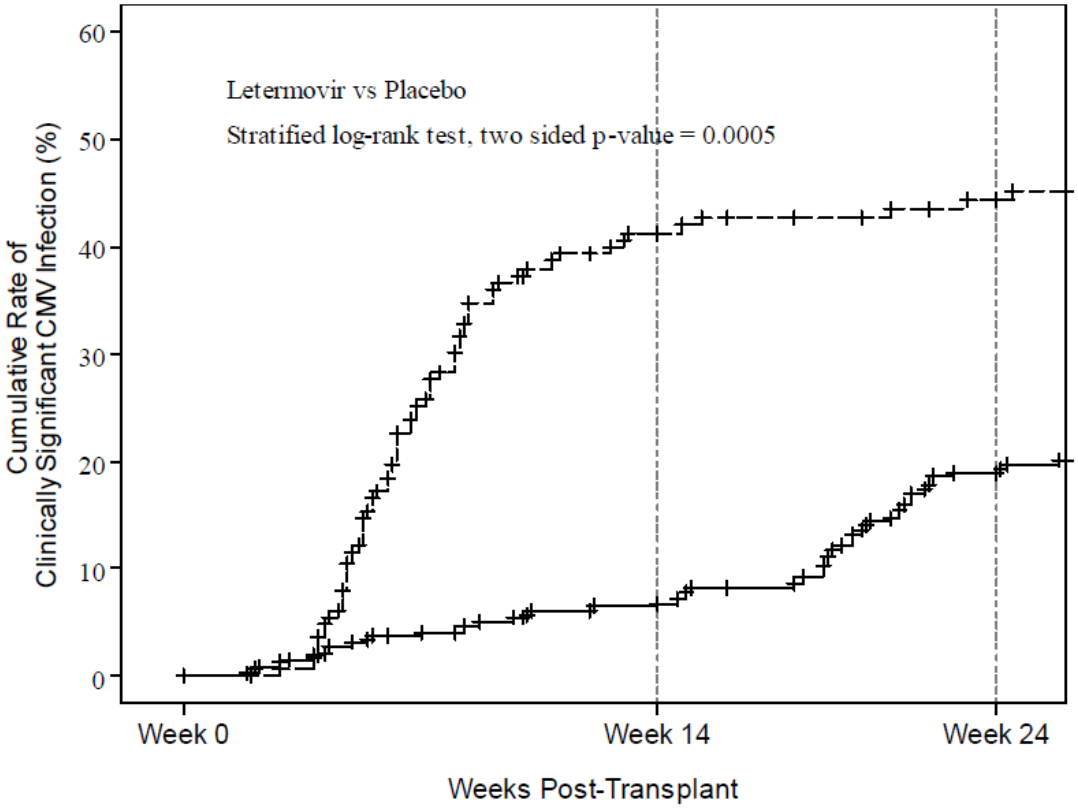
N = number of subjects in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

Source: Table 11-5 of the Clinical Study Report

According to the applicant, a key secondary efficacy endpoint was the proportion of subjects who developed clinically significant CMV infection through Week 14 post-transplant (the treatment period). At Week 14, the proportion of subjects with clinically significant CMV infection in the letermovir group (19%) was lower than that in the placebo group (50%) using the NC=F approach. The estimated difference and 95% CI, -31% (-40% to -23%), adjusted for the stratification factor (high vs. low risk of CMV reactivation), was statistically significant (one-sided p-value <0.001).

Figure 3: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 Post-Transplant (FAS Population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	270: 6.8 (4.0, 9.6)	212: 18.9 (14.4, 23.5)
Placebo	170	85: 41.3 (33.6, 49.0)	70: 44.3 (36.4, 52.1)

Source: Figure 11-1 of the Clinical Study Report

The time to onset of clinically significant CMV infection through Week 24 was also significantly longer in the letermovir group compared to placebo (p-value= 0.0005) as shown in the Kaplan-Meier (K-M) plot.

Table 11: Summary of Clinically Significant CMV Infection

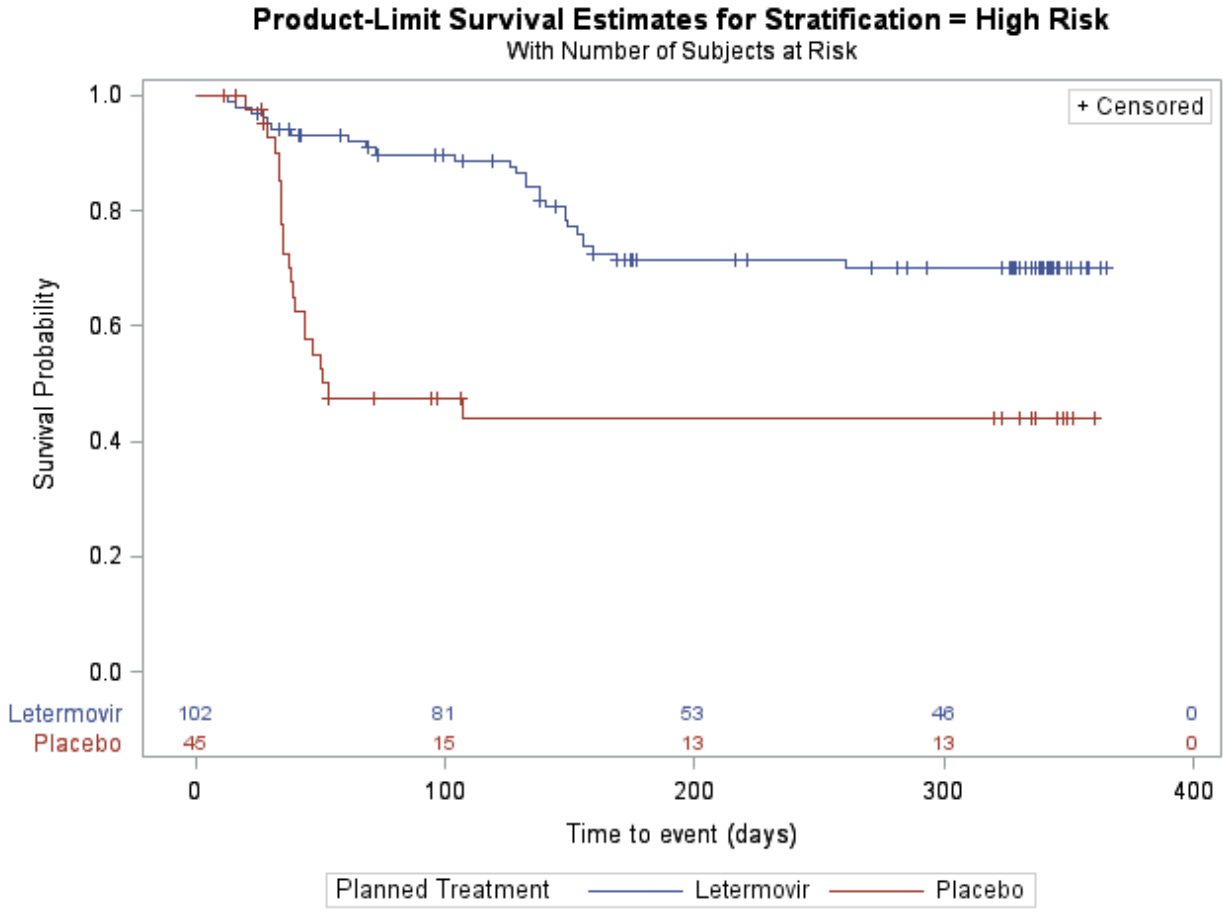
Week	Letermovir (N=325)	Placebo (N=170)	Log-Rank p-value[a]
24	57 (18%)	71 (42%)	<0.001
48	58 (18%)	72 (42%)	<0.001

a. Stratified by High and Low Risk for CMV Disease

Source: Reviewer's Analysis

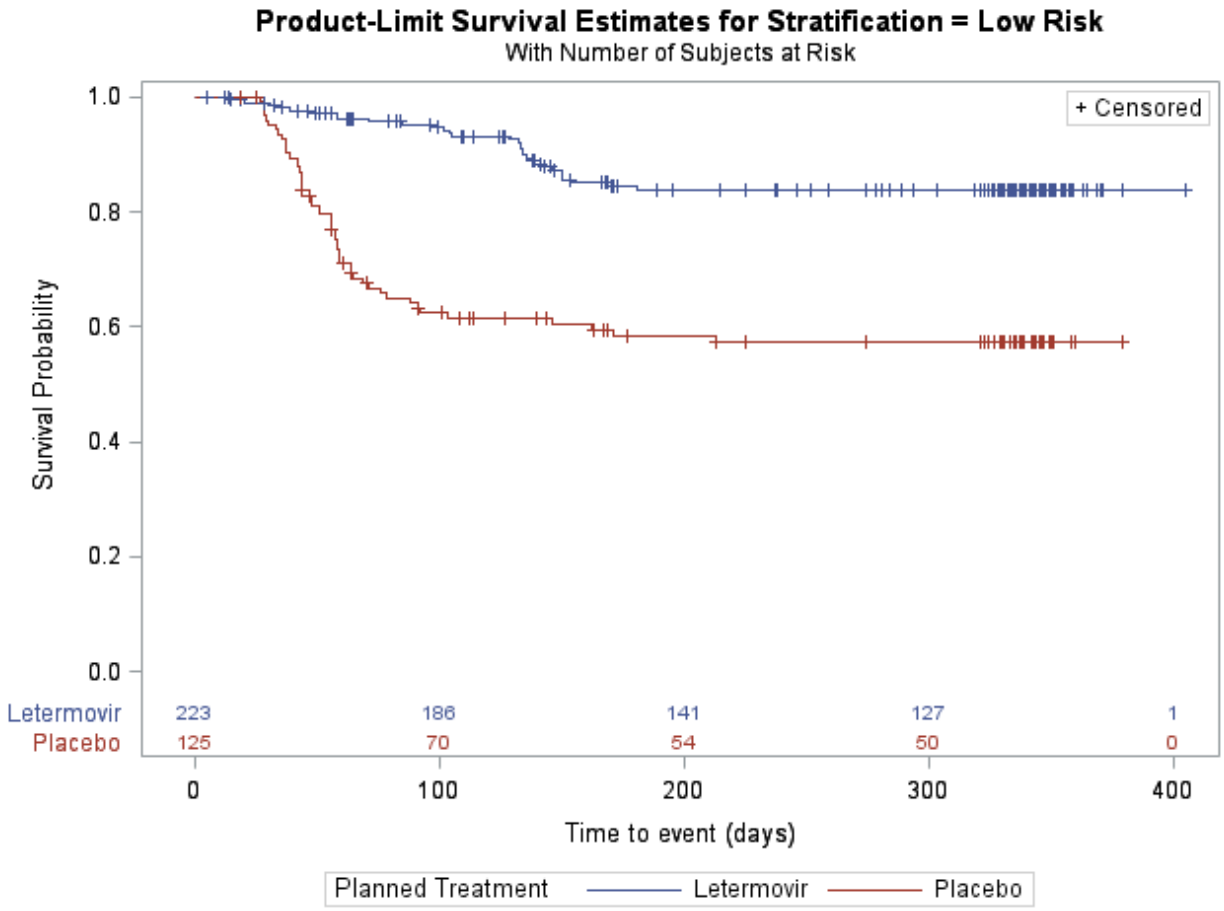
A higher percentage of placebo subjects had clinically significant CMV infection at Weeks 24 and 48 than letermovir subjects (42% vs. 18%, respectively). Note that limited CMV DNA data were collected after Week 24. These trends were also apparent within subjects who were at high and low risk of CMV reactivation, as shown in Kaplan-Meir plots below.

Figure 4: Week 48 Kaplan-Meier Analysis of Time to Clinically Significant CMV Infection



Letermovir (N=102)	Placebo (N=45)
27 (26%)	22 (49%)

Stratified analyses using Kaplan-Meier plots for subjects at high and low risk for CMV reactivation also illustrate that a higher percentage of placebo subjects had clinically significant CMV infection at Weeks 24 and 48 than letermovir subjects.



Letermovir (N=223)	Placebo (N=125)
31 (14%)	50 (40%)

Source: Reviewer's Analysis

3.2.4.2.3 *CMV End-organ Disease*

Table 12: Analysis of the Proportion of Subjects with CMV End-organ Disease Through Week 24 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (N=325) n (%)	Placebo (N=170) n (%)
Failures[†]	**76 (23.4)**	**50 (29.4)**
CMV end-organ disease	5 (1.5)	3 (1.8)
Discontinued from study before Week 24	61 (18.8)	38 (22.4)
Missing outcome in Week 24 visit window	10 (3.1)	9 (5.3)
Stratum-adjusted treatment difference (Letermovir-Placebo)[‡]		
Difference (95% CI)	-6.1 (-14.4, 2.2)	
p-value	0.0748	

[†] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

[‡] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A nominal one-sided p-value (not adjusted for multiplicity) is provided as a measure of the strength of the relationship between treatment and response.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed CMV end-organ disease or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

Source: Table 11-8 of the Clinical Study Report

Only a small number of subjects had CMV end-organ disease; five in the letermovir arm (1.5%) and three in the placebo arm (1.8%). Compared to subjects in the placebo arm, there were a lower percentage of subjects classified as failures in the analysis of CMV end-organ disease in the letermovir treatment arm. However the difference was not statistically significant at the one-sided 0.025 level of significance (one-sided p-value=0.075) and most of the difference was due to discontinuations and missing outcomes in the Week 24 window.

3.2.4.2.4 *All-Cause Mortality*

Table 13: Proportion of Subjects with All-Cause Mortality Through Week 24 Post-Transplant (FAS Population)

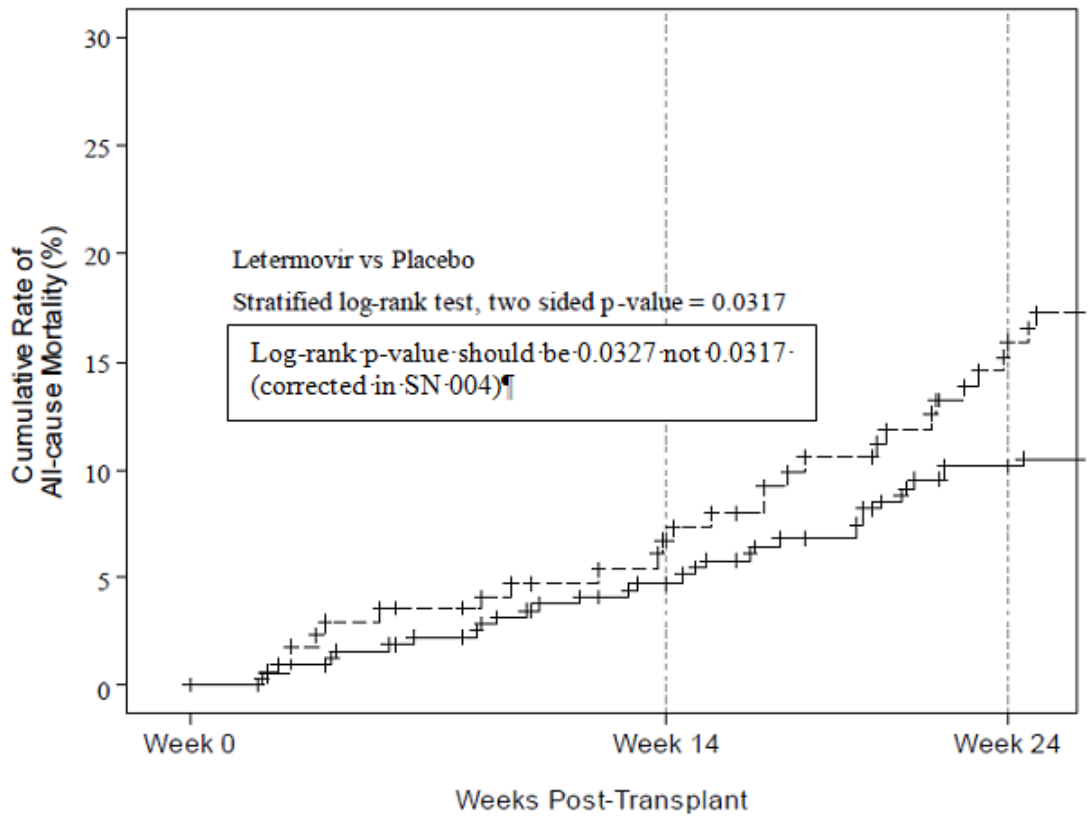
Response	Letermovir (N=325)		Placebo (N=170)	
Variable	n	% (95% CI)	n	% (95% CI)
All-cause mortality	32	9.8 (6.8, 13.6)	27	15.9 (10.7, 22.3)

N = number of subjects in each treatment group.
n = Number of subjects in each sub-category.
% = Percent of subjects in each sub-category.

Source: Table 11-16 of the Clinical Study Report

In the letermovir arm 32 subjects out of 325 (10%) died by Week 24 while enrolled in the study compared to 27 out of 170 (16%) of the placebo subjects.

Figure 5: Kaplan-Meier Plot of Time to All-Cause Mortality Through Week 24 Post-Transplant (FAS Population)

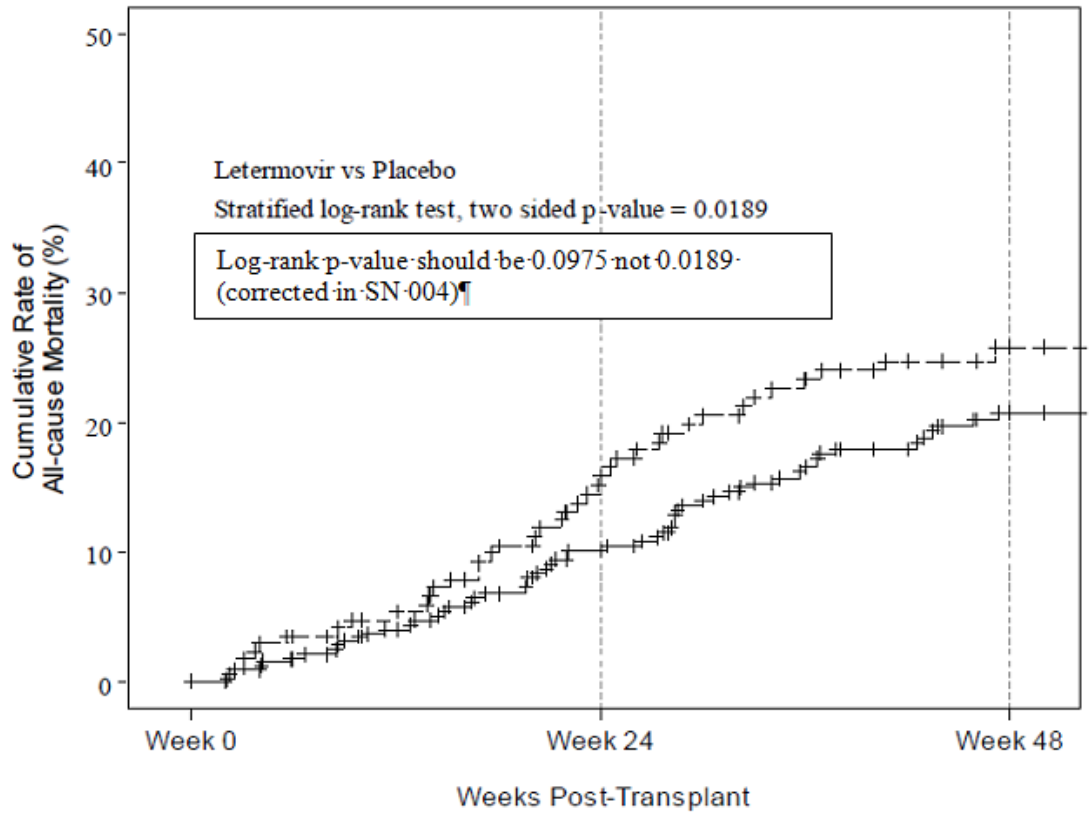


No. at risk: KM estimates % (95% CI)			
Letermovir	325	290: 4.8 (2.4, 7.2)	262: 10.2 (6.8, 13.6)
Placebo	170	147: 6.7 (2.9, 10.5)	125: 15.9 (10.2, 21.6)

Log rank test was stratified by treatment group instead of high vs. low risk for CMV infection and/or disease
Source: Figure 11-5 of the Clinical Study Report

At 24 weeks post-transplant, the incidence of all-cause mortality while enrolled in the study was significantly lower in the letermovir group compared to the placebo group (Kaplan-Meier estimates were 10% and 16% respectively) in the FAS population. Merck had to resubmit the mortality analyses due to a SAS programming error they discovered with proc lifetest where the treatment group and high vs. low risk stratification variables were switched. As shown in the figure above the corrected two-sided p-value from the log-rank test changed slightly and the conclusions remained unchanged.

Figure 6: Kaplan-Meier Plot of Time to All-Cause Mortality Through Week 48 Post-Transplant (Interim Analysis through Database Lock, FAS Population)



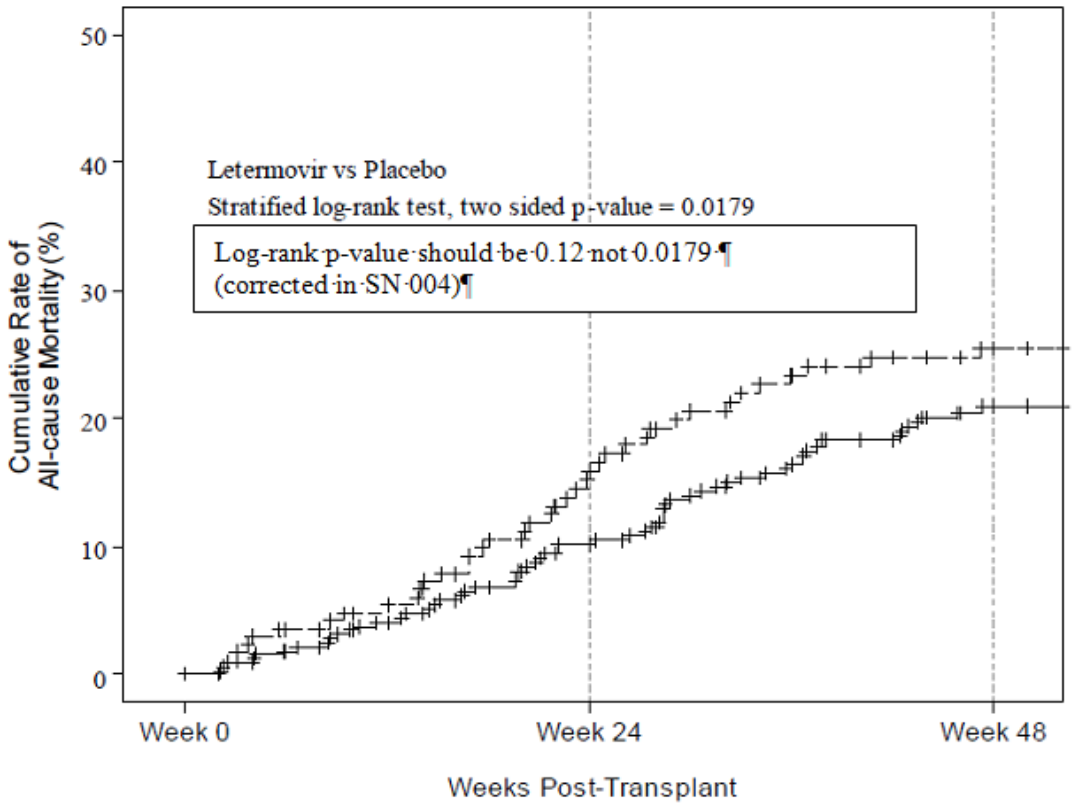
No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 10.2 (6.8, 13.6)	116: 20.8 (16.0, 25.5)
Placebo	170	125: 15.9 (10.2, 21.6)	61: 25.8 (18.7, 32.8)

Log rank test was stratified by treatment group instead of high vs. low risk for CMV infection and/or disease
Source: Figure 11-6 of the Clinical Study Report

At the time of the NDA submission, Merck submitted results for the interim analysis at 48 weeks post-transplant where the incidence of all-cause mortality while enrolled in the study was numerically lower in the letermovir group compared to the placebo group (Kaplan-Meier estimates of 21% and 26% respectively) in the FAS population. Instead of a statistically significant two-sided p-value of 0.019 attained as a result of a programming error, Merck should have obtained a non-significant two-sided p-value of 0.10 for the interim Week 48 analysis at the time of database lock. The findings suggest that there was not sufficient evidence to conclude that there was a difference in longer-term mortality between subjects randomized to letermovir treatment and subjects randomized to placebo.

After reviewing the pre-NDA Type B Meeting Background Package, the statistics reviewer sent a comment to the sponsor stating that inclusion of all mortality events in the interim analysis for subjects who did not have the potential to complete the 48 week study could artificially increase the event rates. The inclusion of mortality events for subjects who had not been enrolled for at least 48 weeks could have an impact on the estimated treatment group difference in mortality rates and the corresponding statistical significance. Results for the final analysis (shown below) were somewhat less significant than they were for the interim analysis.

Figure 7: Kaplan-Meier Plot of Time to All-Cause Mortality Through Week 48 Post-Transplant (Final Analysis, FAS Population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 10.2 (6.8, 13.6)	138: 20.9 (16.2, 25.6)
Placebo	170	125: 15.9 (10.2, 21.6)	71: 25.5 (18.6, 32.5)

Log rank test was stratified by treatment group instead of high vs. low risk for CMV infection and/or disease
Source: Figure 1 of the Mortality Report

The review team wanted to evaluate the final analyses of Week 48 mortality and did not want to delay the NDA submission so the applicant was allowed to submit final results after the NDA submission. Kaplan-Meier estimates remained the same for the final analysis at 48 weeks post-transplant, where the incidence of all-cause mortality while enrolled in the study was numerically lower in the letermovir group compared to the placebo group (Kaplan-Meier estimates of 21% and 26% respectively) in the FAS population. However instead of a statistically significant two-sided p-value of 0.018 attained via a programming error, Merck should have obtained a non-significant two-sided p-value of 0.12.

Table 14: Summary of Week 24 Mortality Outcomes (FAS Population)

Treatment	Letermovir (n=325)		Placebo (n=170)	
Outcome	n (%)	Cumulative n (%)	n (%)	Cumulative n (%)
Died while enrolled in study	32 (10%)	32 (10%)	27 (16%)	27 (16%)
Fatal AE/non-deaths	3 (1%)	35 (11%)	1 (1%)	28 (16%)
Other post-study deaths	0	35 (11%)	0	28 (16%)
Other early discontinuations	26 (8%)	61 (19%)	17 (10%)	45 (26%)
Censored	264 (81%)	325	125 (74%)	170

Source: Reviewer's Analysis

In response to an FDA Information Request sent on April 10, 2017, Merck stated that they did not proactively follow up patients who discontinued from the trial in order to determine their mortality status. Instead Merck only counted deaths while patients were still enrolled in the trial and provided additional information in the datasets about 11 additional deaths among the 87 patients who discontinued from the trial.

The applicant stated on page 9 of the Week 48 Mortality Statistical Report that "post-study deaths are not included in the mortality analysis, as the reporting of information after a subject had completed the clinical trial was not required." On April 24, 2017 Merck was asked to provide additional information about the mortality status of all of the study subjects at Weeks 24 and 48 post-transplant.

In the meantime the reviewer determined the effect of the available post-study death information and early discontinuations as shown in the table above and in Kaplan-Meier plots that follow. The first row in Table 14 summarized mortality that occurred while subjects were enrolled in the trial using the adtte dataset for the final mortality analysis submitted on April 24, 2017. The second row shown in the table added patients identified as having fatal adverse events (AEs) who were not counted as deaths (most likely because they were no longer enrolled in the trial at the time of death). At Week 24, the percentage of deaths increased by 1% in both arms (where there were three additional deaths in the letermovir arm and one additional death in the placebo arm. These comprised all of the post-study deaths in the applicant's adtte dataset for the final Week 48 mortality analysis. After counting other early discontinuations as deaths the number (percent) of deaths increased by 26 (8%) in the letermovir arm and by 17 (10%) in the placebo arm.

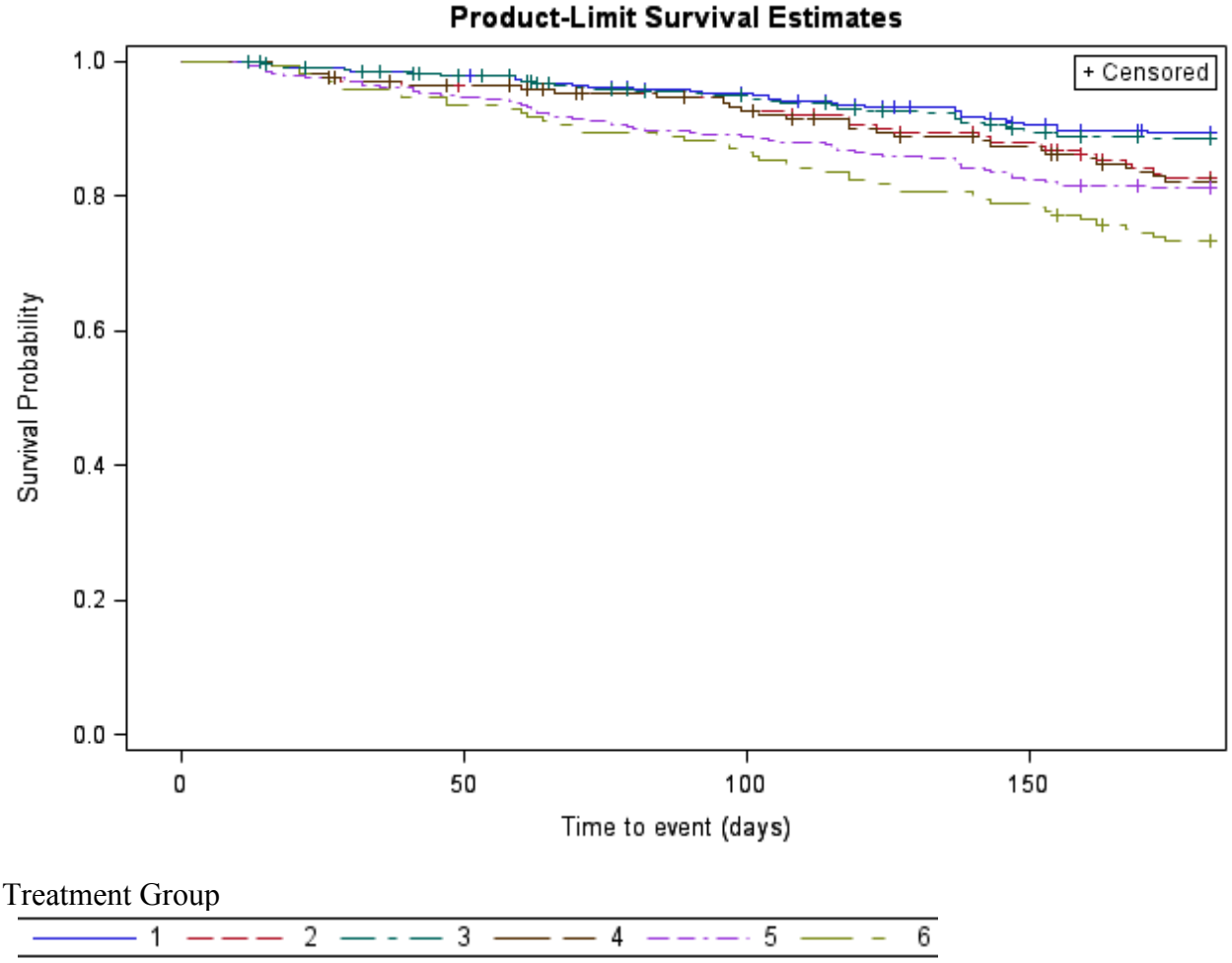
Table 15: Summary of Week 48 Mortality Outcomes (FAS Population)

Treatment	Letermovir (n=325)		Placebo (n=170)	
Outcome	n (%)	Cumulative n (%)	n (%)	Cumulative n (%)
Died while enrolled in study	61 (19%)	61 (19%)	40 (24%)	40 (24%)
Fatal AE/non-deaths	7 (2%)	68 (21%)	2 (1%)	42 (25%)
Other post-study deaths	3 (1%)	71 (22%)	0	42 (25%)
Other early discontinuations	41 (13%)	112 (34%)	21 (12%)	63 (37%)
Censored	213 (66%)	325	107 (63%)	170

Source: Reviewer's Analysis

The same analyses were performed for Week 48 mortality using the adtte dataset for the final Week 48 mortality analysis submitted on April 24, 2017. After adding patients identified as having fatal adverse events (AEs) who were not counted as deaths the percentage of deaths increased by 2% for the letermovir arm (where there were seven additional deaths) and by 1% in the placebo arm (two additional deaths). After including other post-study deaths the percentage of deaths increased by 1% (three additional deaths) in the letermovir arm and remained unchanged in the placebo arm (no additional deaths). After counting other early discontinuations as deaths the number (percent) of deaths increased by 41 (13%) in the letermovir arm and by 21 (12%) in the placebo arm.

Figure 8: Week 24 Kaplan-Meier Mortality using different imputation approaches



While enrolled in study
1=Letermovir, 2=Placebo

Also including post-study deaths
3=Letermovir, 4=Placebo

Also counting discontinuations as deaths
5=Letermovir, 6=Placebo

Source: Reviewer's Analysis

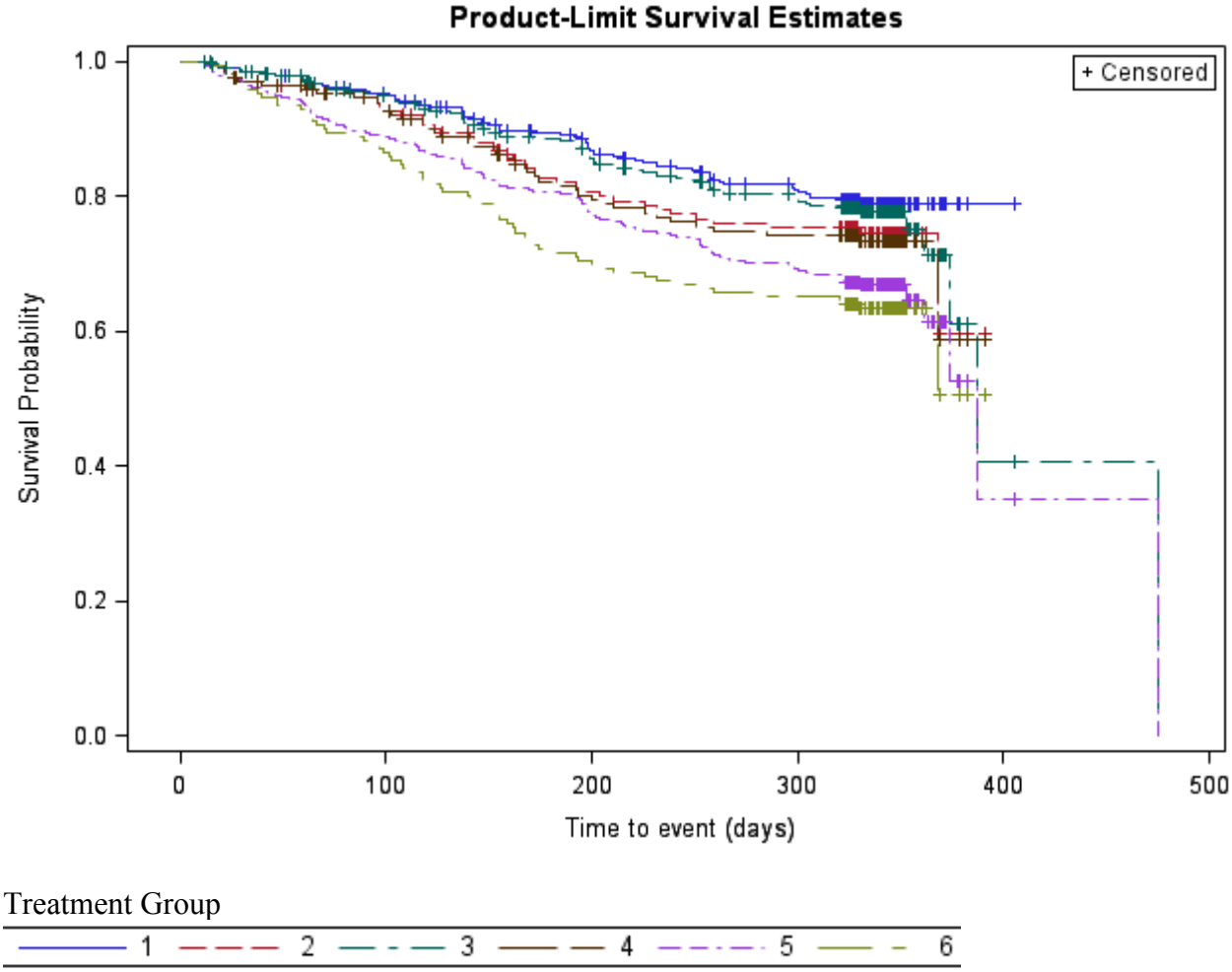
Week 24 Kaplan-Meier plots of time to mortality while subjects were enrolled in the study show earlier declines in the placebo arm (compared to letermovir). The first analysis used the same approach as the applicant (counting deaths only when subjects were still enrolled in the trial at the time of death). The reviewer's Kaplan-Meier curves have the survival probability on the y-axis instead of cumulative failure rates shown in the applicant's plots and display number of patients at risk on the x-axis.

As shown in the figures in the Appendix, this trend occurred in both high and low risk strata although the trend was more apparent in the high risk stratum. The stratified log-rank test was the analysis used by the applicant for time-to-event analyses of mortality and was statistically significant (p=0.0327) at the two-sided 0.05 level along with Peto and modified Peto tests. The Wilcoxon test was only used as a sensitivity analysis by the reviewer to assess robustness of the results and was statistically significant at the 0.10 level (p=0.096). Since the Wilcoxon test places less weight on late events, and longer term survival was of primary interest the lack of statistical significance at the 0.05 level was not of primary concern given the statistical significance of the other statistical tests.

Week 24 Kaplan-Meier curves looked similar to the previous plots after including post-study deaths that the applicant included in the adtte dataset for the final Week 48 mortality analysis submitted on April 24, 2017. Only the log-rank test was statistically significant (p=0.048) at the two-sided 0.05 level (see the Appendix for other test results).

Compared to placebo, the letermovir treatment effect in the Week 24 Kaplan-Meier curves once again appeared to be more evident in the high risk stratum after counting all discontinuations as failures. Only the log-rank test was statistically significant (p=0.046) at the two-sided 0.05 level (see the Appendix for other test results).

Figure 9: Week 48 Kaplan-Meier Mortality using different imputation approaches



While enrolled in study
1=Letermovir, 2=Placebo

Also including post-study deaths
3=Letermovir, 4=Placebo

Also counting discontinuations as deaths
5=Letermovir, 6=Placebo

Source: Reviewer's Analysis

Week 48 Kaplan-Meier plots of time to mortality while subjects were enrolled in the study show earlier declines in the placebo arm (compared to letermovir). As shown in the figures in the Appendix, this trend occurred in both high and low risk strata although the trend was more apparent in the high risk stratum. The p-value for the log-rank test was 0.12. None of the statistical tests were statistically significant at the two-sided 0.05 level (see the Appendix for other test results) indicating there was insufficient evidence that letermovir provided long-term survival benefit.

Week 48 Kaplan-Meier curves looked similar to the previous plots after including post-study deaths that the applicant included in the adtte dataset for the final Week 48 mortality analysis submitted on April 24, 2017. The p-value for the log-rank test was 0.23.None of the statistical tests were statistically significant at the two-sided 0.05 level and were less significant than in the previous analysis of mortality occurring while subjects were enrolled in the study (see the Appendix for other test results).

Survival rates were lower but similar trends were observed after counting discontinuations as failures. The p-value for the log-rank test was 0.31.None of the statistical tests were statistically significant at the two-sided 0.05 level and were less significant after counting discontinuations as failures (see the Appendix for other test results).

3.2.4.2.5 *CMV-Related Mortality*

The reviewer replicated the applicant's analyses of time to CMV-related mortality but added post-study deaths from the adtte dataset for the final Week 48 mortality analysis submitted on April 24, 2017. Kaplan-Meir plots and associated tests are shown in the Appendix. Although the results were all highly statistically significant ($p<0.001$) in favor of letermovir there were interpretability issues. What the applicant called "CMV-related mortality" was death due to any reason in subjects who met the primary endpoint. The primary endpoint of clinically significant CMV infection may or may not have caused mortality. For example a subject who died from a heart attack due to underlying cardiovascular disease could have had a clinically significant CMV infection and been counted as having CMV-related mortality. Even if there was no difference in CMV mortality between letermovir and placebo arms the "CMV-related" mortality analysis could have been statistically significant due to the very statistically significant difference in clinically significant CMV infection between the two arms.

Conversely, subjects who did not have clinically significant CMV infection were observed to have higher death rates in the letermovir arm although this difference was not quite statistically significant at the 0.05 level (two-sided stratified log-rank p-value=0.059). (Kaplan-Meier and statistical test results are shown in the Appendix.)

Table 16: Summary of Week 48 "CMV-Related Mortality" and "Non-CMV-Related Mortality" Outcomes including post-study deaths for subjects (FAS Population)

Clinically Significant CMV Infection	Letermovir (n=325)	Placebo (n=170)
Yes	11 (3%)	25 (15%)
No	60 (18%)	17 (10%)
Total	71 (22%)	42 (25%)

Source: Reviewer's Analysis

The proportion of clinically significant CMV deaths and other deaths were summarized for each treatment group. The proportion of "CMV-related deaths" appeared to be five times as high for subjects in the placebo treatment group than for the letermovir subjects. The proportion of "non-CMV-related deaths" appeared to be almost twice as high in the letermovir arm as the placebo arm. These analyses included post-study deaths that were included in the adtte dataset for the final Week 48 mortality analysis submitted on April 24, 2017

Table 17: Summary of Week 48 Mortality Outcomes including post-study deaths among subjects who had Clinically Significant CMV Infection and subjects who did not (FAS Population)

Clinically Significant CMV Infection	Letermovir (n=325)	Placebo (n=170)
Yes	11/58 (19%)	25/72 (35%)
No	60/267 (22%)	17/98 (17%)
Total	71/325 (22%)	42/170 (25%)

Source: Reviewer's Analysis

An alternative approach the applicant used was to only look at subsequent all-cause mortality by treatment group in subjects who had clinically significant CMV infection and in subjects who did not. Among subjects with clinically significant CMV infection, almost twice as many placebo subjects died (19% of letermovir subjects vs. 35% of placebo subjects). There was less of a difference among remaining subjects who did not have clinically significant CMV infection; 22% of the letermovir subjects died compared to 17% of the placebo subjects.

3.2.4.2.6 *Updated All-Cause Mortality Results*

On July 14, 2017 Merck submitted updated mortality data in response to our Information Request (IR) on April 24, 2017. Our IR and the company's response are shown below:

AGENCY COMMENT #1:

Clinical/Biometrics:

We refer to the April 24, 2017, submission that consists of your response to our April 10, 2017, request for information, specifically the statement, "there is no additional information available which impacts the efficacy or mortality results provided through Weeks 24 or 48." We note that subjects who died after study withdrawal are not included in your all-cause mortality analyses. Many of these subjects were withdrawn from the study shortly before the time of death. These deaths should be accounted for in the mortality analyses. The status of all of the clinical trial subjects is very important for the conduct of a complete and accurate mortality analysis. Please make every effort to determine if subjects who prematurely withdrew from the trial were alive or dead at Weeks 24 and 48 post-transplantation and if a subject died, determine the date of death. Please submit all of this information, as available, to the NDAs.

COMPANY RESPONSE #1:

Of the 565 subjects in P001, 87 subjects withdrew from the study for reasons other than death. While deaths following study withdrawal were not required to be reported per protocol,"post-study" deaths were reported for 11 subjects who had prematurely withdrawn from the study leaving 76 subjects who prematurely withdrew from the trial with unknown mortality status at the time the initial (Week 24) clinical study report (CSR) was written. In response to the FDA's request, Merck has made every effort to determine if these subjects who discontinued were alive or dead at Weeks 24 and 48. Vital status were obtained for 58 of these 76 subjects, ultimately resulting in vital status on 96.8% (547/565) of the safety population (All Subjects as Treated). The reason for not being able to collect information on the remaining subjects was largely due to country legal issues with contacting subjects after the completion and closure of the trial as well as for those whose reason for early withdrawl was - withdrew consent. Subject disposition including post-study information is summarized for all randomized subjects in Table 1 and for full analysis set (FAS) in Table 2.

Table 18: Merck's July 14, 2017 response to IR: Subject disposition including subjects who withdrew from the study prior to Week 48 post-transplant (All Randomized Subjects)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	376		194		570	
Status for Trial Through 24 Weeks Post-transplant						
Randomized but not treated	3	(0.8)	2	(1.0)	5	(0.9)
Completed 24 weeks Post-transplant	295	(78.5)	136	(70.1)	431	(75.6)
Discontinued Through Week 24 Post-transplant (Death)	37	(9.8)	28	(14.4)	65	(11.4)
Discontinued Through Week 24 Post-transplant (other reasons)	41	(10.9)	28	(14.4)	69	(12.1)
Post-study status: Alive	25	(6.6)	17	(8.8)	42	(7.4)
Post-study status: Death	10	(2.7)	8	(4.1)	18	(3.2)
Post-study status: Unknown	6	(1.6)	3	(1.5)	9	(1.6)
Status for Trial Through 48 Weeks Post-transplant						
Completed 48 weeks Post-transplant	244	(64.9)	119	(61.3)	363	(63.7)
Discontinued Through Week 48 Post-transplant (Death)	71	(18.9)	44	(22.7)	115	(20.2)
Discontinued Through Week 48 Post-transplant (other reasons)	58	(15.4)	29	(14.9)	87	(15.3)
Post-study status: Alive	22	(5.9)	10	(5.2)	32	(5.6)
Post-study status: Death	22	(5.9)	15	(7.7)	37	(6.5)
Post-study status: Unknown	14	(3.7)	4	(2.1)	18	(3.2)
n (%) = Number (percent) of subjects in each sub-category.						

Source: Table 1 of Merck's July 14, 2017 response to IR

Table 19: Merck's July 14, 2017 response to IR: Subject disposition including subjects who withdrew prior to Week 48 post-transplant (Full Analysis Set)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	325		170		495	
Status for Trial Through 24 Weeks Post-transplant						
Randomized but not treated	0	(0.0)	0	(0.0)	0	(0.0)
Completed 24 weeks Post-transplant	261	(80.3)	123	(72.4)	384	(77.6)
Discontinued Through Week 24 Post-transplant (Death)	31	(9.5)	26	(15.3)	57	(11.5)
Discontinued Through Week 24 Post-transplant (other reasons)	33	(10.2)	21	(12.4)	54	(10.9)
Post-study status: Alive	20	(6.2)	12	(7.1)	32	(6.5)
Post-study status: Death	9	(2.8)	6	(3.5)	15	(3.0)
Post-study status: Unknown	4	(1.2)	3	(1.8)	7	(1.4)
Status for Trial Through 48 Weeks Post-transplant						
Completed 48 weeks Post-transplant	219	(67.4)	109	(64.1)	328	(66.3)
Discontinued Through Week 48 Post-transplant (Death)	60	(18.5)	39	(22.9)	99	(20.0)
Discontinued Through Week 48 Post-transplant (other reasons)	46	(14.2)	22	(12.9)	68	(13.7)
Post-study status: Alive	17	(5.2)	9	(5.3)	26	(5.3)
Post-study status: Death	19	(5.8)	9	(5.3)	28	(5.7)
Post-study status: Unknown	10	(3.1)	4	(2.4)	14	(2.8)
n (%) = Number (percent) of subjects in each sub-category.						

Source: Table 2 of Merck's July 14, 2017 response to IR

A sensitivity analysis of the all-cause mortality analyses in the FAS population was performed by Merck at Week 24 and Week 48 including all available post-study information as of July 14, 2017. As in the Clinical Study Report (CSR) analyses, subjects reported as alive were censored at the last contact time or upper bound of the visit. The applicant stated that the following visit windows were used for the analyses: any death <=182 days post-transplant (2 weeks post Week 24 visit) was included in the Week 24 analysis; any death <= 350 days post-transplant (2 weeks post Week 48 visit) was included in the Week 48 analysis.

Table 20: Updated Summary of Week 24 Mortality Outcomes (FAS Population)

Treatment	Letermovir (n=325)		Placebo (n=170)	
Outcome	n (%)	Cumulative n (%)	n (%)	Cumulative n (%)
Died while enrolled in study	32 (10%)	32 (10%)	27 (16%)	27 (16%)
Other post-study deaths	8 (2%)	40 (12%)	5 (3%)	32 (18%)

Source: Reviewer's Analysis

Using updated data submitted on July 14, 2017 the statistics reviewer summarized the additional mortality outcomes. The number (percentage) of deaths increased by 8 (2%) in the letermovir

arm and by 5 (3%) in the placebo arm. The cumulative number of deaths including other post-study deaths agreed with Merck's totals, although Merck estimated one additional post-study death and one fewer death while still enrolled in the study in each treatment arm

Table 21: Updated Summary of Week 48 Mortality Outcomes (FAS Population)

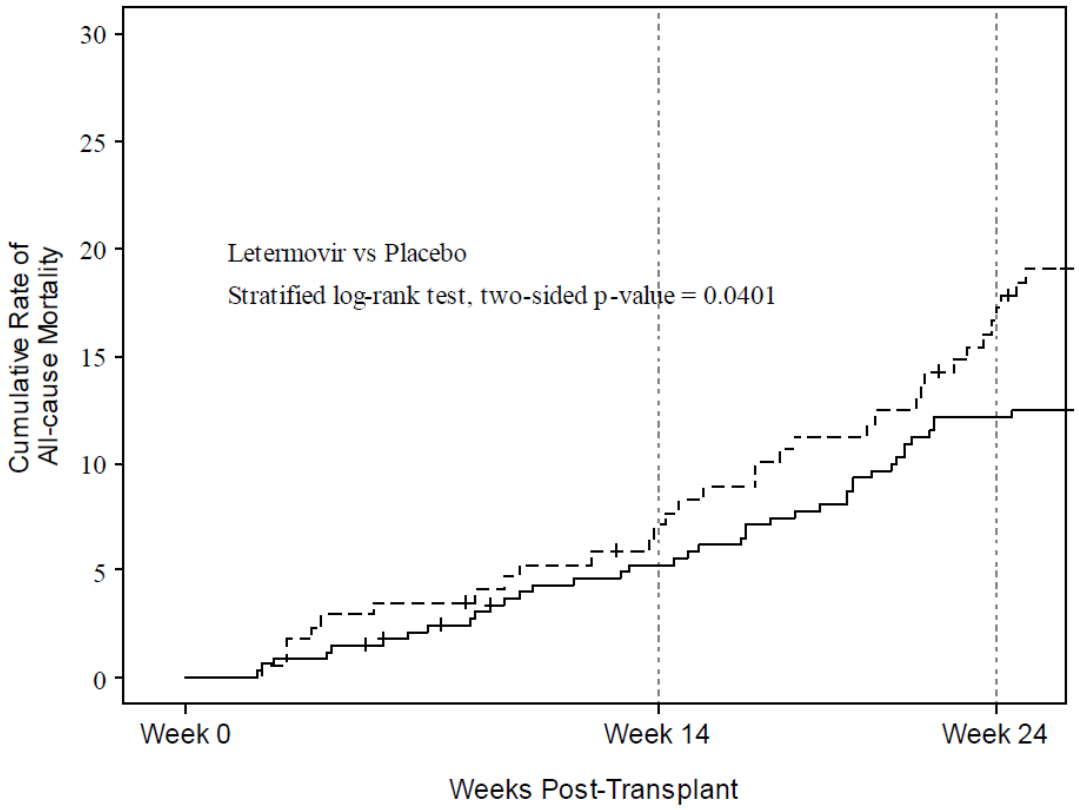
Treatment	Letermovir (n=325)		Placebo (n=170)	
Outcome	n (%)	Cumulative n (%)	n (%)	Cumulative n (%)
Died while enrolled in study	61 (19%)	61 (19%)	40 (24%)	40 (24%)
Other post-study deaths	15 (5%)	76 (23%)	6 (4%)	46 (27%)

Source: Reviewer's Analysis

Using updated data submitted on July 14, 2017 the statistics reviewer summarized the additional mortality outcomes. The number (percentage) of deaths increased by 15 (5%) in the letermovir arm and by 6 (4%) in the placebo arm. The total number of additional deaths in Merck's table appeared to higher; there were 19 additional deaths in the letermovir arm and 9 additional deaths in the placebo arm, with one less subject dying while enrolled in the study in the placebo arm in Merck's table. An information request has been sent to the applicant. The reviewer was able to replicate the sponsors Kaplan-Meier analysis and stratified log-rank test results where the number of deaths were the same as the number of deaths in the reviewer's tables.

Merck responded to our most recent IR on August 4, 2017. They stated that the extra deaths in Table 2 of the July 14, 2017 response included deaths after study day 350. However in the July 14, 2017 response to IR Merck stated that they included any death <= 350 days post-transplant in the Week 48 analysis so they appear to have used this visit window for the Week 48 KM analyses but used all post-study deaths for subject disposition in Table 2 of their July 14, 2017 response. Merck also stated that at Week 24 there should be 31 deaths in the letermovir arm and 26 deaths in the placebo arm that occurred while subjects were enrolled in the study as shown in Table 2 of their July 14, 2017 response to IR but there were 32 and 27 respectively in Table 11-16 of the CSR.

Figure 10: Merck's July 14, 2017 response to IR: Kaplan-Meier Plot of Time to All-cause Mortality through Week 24 Post-Transplant (Including Vital Status Collected Post-Study, FAS Population)

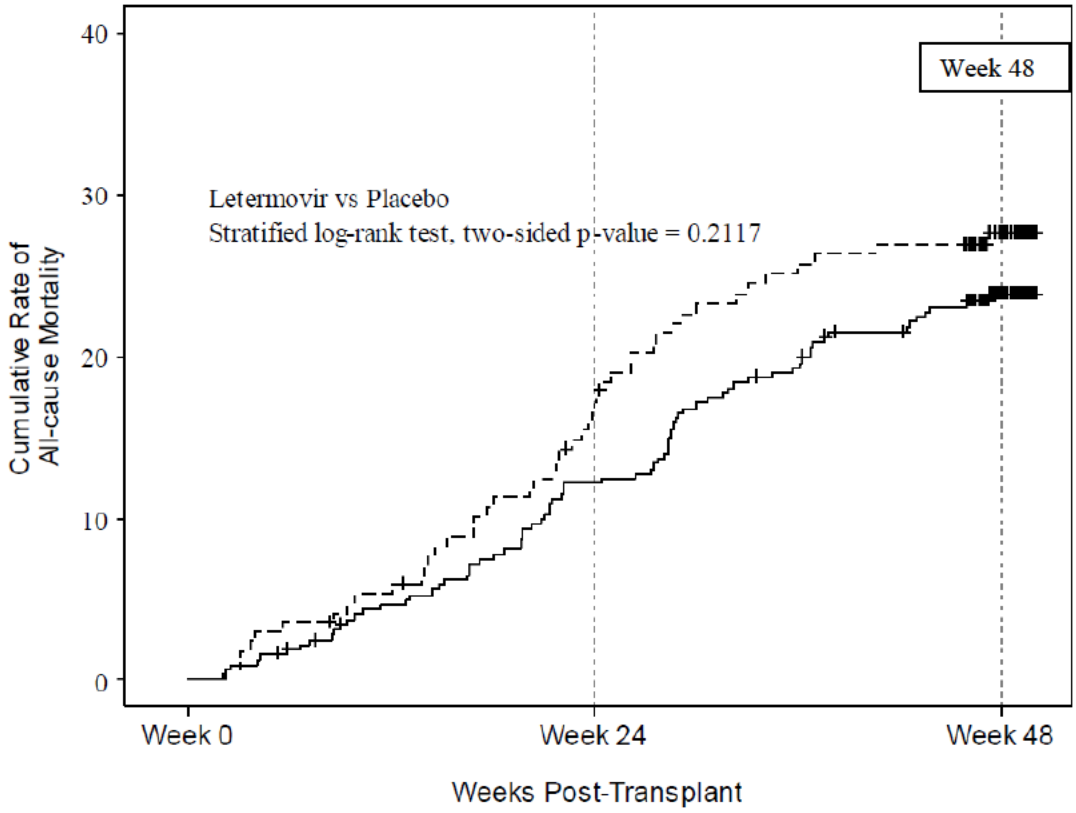


No. at risk: KM estimates % (95% CI)			
— Letermovir	325	304: 5.3 (2.8, 7.7)	282: 12.1 (8.6, 15.7)
– – Placebo	170	156: 7.1 (3.2, 11.0)	139: 17.2 (11.5, 22.9)

Source: Figure 1 of Merck's July 14, 2017 response to IR

As shown in Figure 1 of Merck's July 14, 2017 response to IR, the Kaplan-Meier (K-M) event rate for all-cause mortality at Week 24 post-transplant (including available post-study information as of July 14, 2017) was lower for the letermovir group (12.1%) compared to the placebo group (17.2%). The applicant claimed that the distribution of time to all-cause mortality through Week 24 was substantially different between the letermovir and placebo groups. However the two-sided p-value=0.040, using the stratified log-rank test was close to the 0.05 level required for statistical significance.

Figure 11: Merck's July 14, 2017 response to IR: Kaplan-Meier Plot of Time to All-cause Mortality through Week 48 Post-Transplant (Including Vital Status Collected Post-Study, FAS Population)



No. at risk: KM estimates % (95% CI)			
—— Letermovir	325	282: 12.1 (8.6, 15.7)	165: 23.8 (19.1, 28.5)
-- Placebo	170	139: 17.2 (11.5, 22.9)	81: 27.6 (20.8, 34.4)

Source: Figure 2 of Merck's July 14, 2017 response to IR

The K-M event rate for all-cause mortality at Week 48 post-transplant (including available post-study information as of July 14, 2017), was lower for the letermovir group (23.8%) compared to the placebo group (27.6%%). The applicant claimed that the absolute difference in mortality between letermovir and placebo (approximately 4-5%) was maintained from Week 24 through Week 48. However the difference in K-M event rates was 5.1% at Week 24 compared to 4.2% at Week 48 and the two-sided p-value of 0.21 for the Week 48 analysis using the stratified log-rank test was not close to reaching statistically significance at the 0.05 level. Note that the log-rank p-value obtained by the reviewer including all post-treatment deaths as of April 24, 2017 was very similar (p=0.23).

Table 22: All-Cause Mortality Analyses through Week 24 and Week 48: Comparison of Analyses Provided in the Week 24 and Week 48 CSRs with the Analyses Provided in this Response that Includes Data Collected Post-Study

Analysis Population	Letermovir n (%) subjects with complete data (N=325)	Letermovir K-M Estimate (%)	Placebo n (%) subjects with complete data (N=170)	Placebo K-M Estimate (%)	Log-rank p-value
All-cause Mortality Through Week 24					
FAS in the Week 24 CSR[†]	293 (90.1%)	10.2 (6.8, 13.6)	150 (88.2%)	15.9 (10.2, 21.6)	0.0327
FAS including post-study data	321 (98.8%)	12.1 (8.6, 15.7)	167 (98.2%)	17.2 (11.5, 22.9)	0.0401
All-cause Mortality Through Week 48					
FAS in the Week 48 CSR[†]	280 (86.2%)	20.9 (16.2, 25.4)	149 (87.6%)	25.5 (18.6, 32.5)	0.1224
FAS including post-study data	315 (96.9%)	23.8 (19.1, 28.5)	166 (97.6%)	27.6 (20.8, 34.4)	0.2117

[†] Subject 100092 in the letermovir group and 100162 in the placebo group died within 14 days from the last dose and was already included as death in the CSR.

Source: Table 3 of Merck's July 14, 2017 response to IR

Merck summarized changes in results from the final Week 24 and 48 analyses in Table 3 of their July 14, 2017 response to IR. The FAS in the Week 24 and 48 CSR only counted deaths that occurred while enrolled in the trial. The p-values for Week 24 and 48 treatment groups comparisons were less significant after all available post-study information as of July 14, 2017 were included in the mortality analyses.

3.2.4.2.7 *Opportunistic Infections*

Table 23: Proportion of Subjects with Selected Opportunistic Infections Other than CMV Infection Through Week 24 Post-Transplant (FAS Population) – Original Table

	Letermovir (N=325)		Placebo (N=170)	
	n	% (95% CI)	n	% (95% CI)
Subjects with one or more selected opportunistic infections	61	18.8 (14.7, 23.4)	36	21.2 (15.3, 28.1)
Bacterial	**41**	**12.6 (9.2, 16.7)**	**24**	**14.1 (9.3, 20.3)**
Bacteremia	41	12.6 (9.2, 16.7)	24	14.1 (9.3, 20.3)
Pneumonia	5	1.5 (0.5, 3.6)	2	1.2 (0.1, 4.2)
Sepsis	10	3.1 (1.5, 5.6)	8	4.7 (2.1, 9.1)
Fungal	**10**	**3.1 (1.5, 5.6)**	**7**	**4.1 (1.7, 8.3)**
Aspergillosis	9	2.8 (1.3, 5.2)	5	2.9 (1.0, 6.7)
Mucormycosis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
PJP Pneumonia	1	0.3 (0.0, 1.7)	1	0.6 (0.0, 3.2)
Parasitic	**0**	**0.0 (0.0, 1.1)**	**1**	**0.6 (0.0, 3.2)**
Cerebral Toxoplasmosis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
Viral	**17**	**5.2 (3.1, 8.2)**	**11**	**6.5 (3.3, 11.3)**
Adenovirus disease	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
BK virus infection	10	3.1 (1.5, 5.6)	7	4.1 (1.7, 8.3)
EBV Meningoencephalitis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
HHV-6 Meningoencephalitis	2	0.6 (0.1, 2.2)	0	0.0 (0.0, 2.1)
Influenza	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
Parainfluenzae Virus Infection	3	0.9 (0.2, 2.7)	0	0.0 (0.0, 2.1)
RSV infection	1	0.3 (0.0, 1.7)	3	1.8 (0.4, 5.1)

EBV = Epstein-Barr Virus, HHV = Human herpes virus, PJP =Pneumocystis Jirovecii, RSV = Respiratory Syncitial Virus
N = number of evaluable subjects in in each treatment group.
n = Number of subjects in each sub-category.
% = Percent of subjects in each sub-category.

Source: Table 11-22 of the Clinical Study Report

The reviewers were also unable to replicate Merck's analyses of opportunistic infections using the intermediate datasets the applicant provided in response to a Clinical IR after the NDA had been submitted. Therefore we sent an Information Request to Merck asking Merck to confirm that the numbers they reported were correct. Merck responded on June 7, 2017 by provided complex flow diagrams and SAS code but did not confirm that the numbers were correct. The path to this submission is \\CDSESUB1\evsprod\NDA209939\0013. The applicant said that the dataset OIINT1 that was submitted to FDA on 12-May-2017 could be used to produce the tables presented in Tables 11-21 and 11-22 of the CSR. Merck stated that the OIINT2 dataset (also submitted to FDA on 12-May 2017) included additional data reported through the CE (Clinical Events) domain.

Since the applicant did not explain the reasons for the discrepancies in their June 7, 2017 response we submitted another information request with more specific questions about selected discrepancies in order to elicit more information. The applicant responded on June 23, 2017

stating that they had made a programming error for opportunistic infection sub-categories like bacteremia but not total categories (e.g., bacterial and fungal infections). The error was that the number of occurrences of each infection was counted instead of the number of patients. The path to this submission is \\CDSESUB1\evsprod\NDA209939\0018. The applicant provided revised tables using the oiint1 and oiint2 datasets (shown below).

Table 24: Proportion of Subjects with Selected Opportunistic Infections Other than CMV Infection Through Week 24 Post-Transplant (FAS Population) – Revised Table using oiint1 dataset

	Letermovir (N=325)		Placebo (N=170)	
	n	% (95% CI)	n	% (95% CI)
Subjects with one or more selected opportunistic infections	61	18.8 (14.7, 23.4)	36	21.2 (15.3, 28.1)
Bacterial	**41**	**12.6 (9.2, 16.7)**	**24**	**14.1 (9.3, 20.3)**
Bacteremia	29	8.9 (6.1, 12.6)	17	10.0 (5.9, 15.5)
Pneumonia	5	1.5 (0.5, 3.6)	2	1.2 (0.1, 4.2)
Sepsis	7	2.2 (0.9, 4.4)	7	4.1 (1.7, 8.3)
Fungal	**10**	**3.1 (1.5, 5.6)**	**7**	**4.1 (1.7, 8.3)**
Aspergillosis	9	2.8 (1.3, 5.2)	5	2.9 (1.0, 6.7)
Mucormycosis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
PJP Pneumonia	1	0.3 (0.0, 1.7)	1	0.6 (0.0, 3.2)
Parasitic	**0**	**0.0 (0.0, 1.1)**	**1**	**0.6 (0.0, 3.2)**
Cerebral Toxoplasmosis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
Viral	**17**	**5.2 (3.1, 8.2)**	**11**	**6.5 (3.3, 11.3)**
Adenovirus disease	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
BK virus infection	10	3.1 (1.5, 5.6)	7	4.1 (1.7, 8.3)
EBV Meningoencephalitis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
HHV-6 Meningoencephalitis	2	0.6 (0.1, 2.2)	0	0.0 (0.0, 2.1)
Influenza	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
Parainfluenzae Virus Infection	3	0.9 (0.2, 2.7)	0	0.0 (0.0, 2.1)
RSV infection	1	0.3 (0.0, 1.7)	3	1.8 (0.4, 5.1)

EBV = Epstein-Barr Virus, HHV = Human herpes virus, PJP =Pneumocystis Jirovecii, RSV = Respiratory Syncitial Virus
N = number of evaluable subjects in in each treatment group.
n = Number of subjects in each sub-category.
% = Percent of subjects in each sub-category.

Source: June 23, 2017 Response to Information Request

Table 25: Proportion of Subjects with Selected Opportunistic Infections Other than CMV Infection Through Week 24 Post-Transplant (FAS Population) – Revised Table using oiint2 dataset

	Letermovir (N=325)		Placebo (N=170)	
	n	% (95% CI)	n	% (95% CI)
Subjects with one or more selected opportunistic infections	67	20.6 (16.3, 25.4)	40	23.5 (17.4, 30.6)
Bacterial	**44**	**13.5 (10.0, 17.7)**	**26**	**15.3 (10.2, 21.6)**
Bacteremia	32	9.8 (6.8, 13.6)	19	11.2 (6.9, 16.9)
Pneumonia	5	1.5 (0.5, 3.6)	2	1.2 (0.1, 4.2)
Sepsis	7	2.2 (0.9, 4.4)	8	4.7 (2.1, 9.1)
Fungal	**14**	**4.3 (2.4, 7.1)**	**9**	**5.3 (2.4, 9.8)**
Aspergillosis	13	4.0 (2.1, 6.7)	6	3.5 (1.3, 7.5)
Mucormycosis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
PJP Pneumonia	1	0.3 (0.0, 1.7)	2	1.2 (0.1, 4.2)
Parasitic	**0**	**0.0 (0.0, 1.1)**	**1**	**0.6 (0.0, 3.2)**
Cerebral Toxoplasmosis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
Viral	**17**	**5.2 (3.1, 8.2)**	**11**	**6.5 (3.3, 11.3)**
Adenovirus disease	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
BK virus infection	10	3.1 (1.5, 5.6)	7	4.1 (1.7, 8.3)
EBV Meningoencephalitis	0	0.0 (0.0, 1.1)	1	0.6 (0.0, 3.2)
HHV-6 Meningoencephalitis	2	0.6 (0.1, 2.2)	0	0.0 (0.0, 2.1)
Influenza	1	0.3 (0.0, 1.7)	0	0.0 (0.0, 2.1)
Parainfluenzae Virus Infection	3	0.9 (0.2, 2.7)	0	0.0 (0.0, 2.1)
RSV infection	1	0.3 (0.0, 1.7)	3	1.8 (0.4, 5.1)

EBV = Epstein-Barr Virus, HHV = Human herpes virus, PJP =Pneumocystis Jirovecii, RSV = Respiratory Syncitial Virus
N = number of evaluable subjects in in each treatment group.
n = Number of subjects in each sub-category.
% = Percent of subjects in each sub-category.

Source: June 23, 2017 Response to Information Request

As requested Merck also provided a list of all subjects identified as having bacteremia. The table in the Appendix provides a list of all subjects identified as having bacteremia in the P001 CSR Table 11-22. The applicant stated that the organism was included in the table to assist in identifying those subjects who were counted more than once in the original table. For subjects with more than one event, subsequent event entries were highlighted in grey to more clearly identify unique subjects.

As requested Merck identified the subjects who had pneumonia, sepsis and aspergillosis and for fungal infections and identified the subjects and the variable they used to identify the selected infections like aspergillosis.

The subjects who had pneumonia, sepsis and aspergillosis are identified in the Appendix. For sepsis, three subjects in the letermovir arm and one subject in the placebo arm reported more than one event. For subjects with more than one event, subsequent event entries were highlighted in grey. According to the applicant, the variable SOICOD, described in Merck's 2017-06-07 response, identified the selected infections.

3.3 Evaluation of Safety

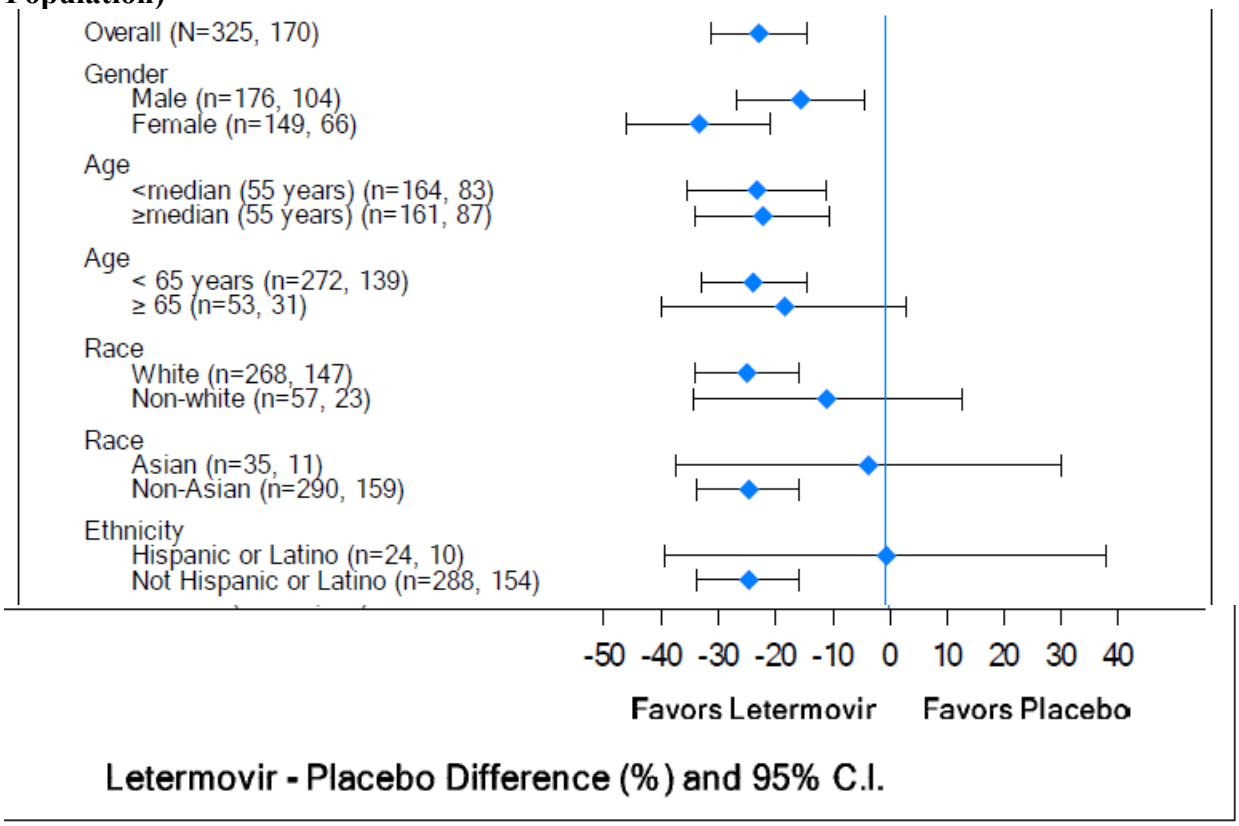
For a detailed safety evaluation, please refer to the clinical review written by Dr. Aimee Hodowanec.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Additional support of the primary endpoint was provided by subgroup efficacy analyses showing a lower incidence of clinically significant CMV infection through Week 24 post-transplant in the letermovir group compared to placebo. Both the data-as-observed [DAO] approach, and the NC=F approach were used in these analyses. The applicant stated that the DAO approach was the primary approach as the results of analyses using the NC=F approach are primarily driven by subjects who discontinued early from the study and subjects who had a missing outcome, which can be misleading in subgroup analyses with small sample sizes. Overall, the results of analyses using the DAO approach were similar to those using the NC=F analyses. Therefore only subgroup analyses for the primary analysis (NC=F) approach are shown here.

4.1 Gender, Race, Age, and other factors

Figure 12: Treatment Difference in Clinically Significant CMV Infection Through Week 24 Post-Transplant by Gender, Age, Race and Ethnicity Subgroups (NC=F Approach, FAS Population)



Source: Figure 14.2-4 in the Clinical Study Report

Without adjusting for multiplicity, the letermovir treatment group was superior to placebo in each gender, median age, Whites, Non-Asian and Non-Hispanic/Latino ethnic groups, which were the subgroups with the most patients. In addition to wider confidence intervals in smaller subgroups, treatment differences were also much smaller in Non-White, Asian and Hispanic or Latino subgroups.

Table 26: Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Gender, Age, Race, and Ethnicity Subgroups (NC=F Approach, FAS Population)

Subject Characteristic Subgroup	Letermovir		Placebo		Letermovir vs. Placebo
	n/N	% (95% CI)	n/N	% (95% CI)	Difference in % (95% CI)[†]
Total	**122/325**	**37.5 (32.3, 43.1)**	**103/170**	**60.6 (52.8, 68.0)**	**-23.5 (-32.5, -14.6)**
Gender					
Male	72/176	40.9 (33.6, 48.6)	58/104	55.8 (45.7, 65.5)	-15.7 (-27.7, -3.8)
Female	50/149	33.6 (26.0, 41.7)	45/66	68.2 (55.6, 79.1)	-34.8 (-48.5, -21.2)
Age					
< median (55 years)	56/164	34.1 (26.9, 41.9)	48/83	57.8 (46.5, 68.6)	-24.0 (-36.9, -11.0)
≥ median (55 years)	66/161	41.0 (33.3, 49.0)	55/87	63.2 (52.2, 73.3)	-22.9 (-35.3, -10.4)
Age (Years)					
< 65 years	100/272	36.8 (31.0, 42.8)	85/139	61.2 (52.5, 69.3)	-24.5 (-34.4, -14.6)
≥ 65 years	22/53	41.5 (28.1, 55.9)	18/31	58.1 (39.1, 75.5)	-18.9 (-41.7, 3.9)
Race					
Asian	18/35	51.4 (34.0, 68.6)	6/11	54.5 (23.4, 83.3)	-3.1 (-39.1, 32.9)
Black or African	1/5	20.0 (0.5, 71.6)	2/4	50.0 (6.8, 93.2)	NA
White	96/268	35.8 (30.1, 41.9)	90/147	61.2 (52.8, 69.1)	-25.9 (-35.6, -16.2)
Other[‡]	7/17	41.2 (18.4, 67.1)	5/8	62.5 (24.5, 91.5)	NA
Race Subgroup					
White	96/268	35.8 (30.1, 41.9)	90/147	61.2 (52.8, 69.1)	-25.9 (-35.6, -16.2)
Non-white	26/57	45.6 (32.4, 59.3)	13/23	56.5 (34.5, 76.8)	-10.8 (-35.8, 14.2)
Race Subgroup					
Asian	18/35	51.4 (34.0, 68.6)	6/11	54.5 (23.4, 83.3)	-3.1 (-39.1, 32.9)
Non-Asian	104/290	35.9 (30.3, 41.7)	97/159	61.0 (53.0, 68.6)	-25.5 (-34.9, -16.2)
Ethnicity					
Hispanic or Latino	12/24	50.0 (29.1, 70.9)	5/10	50.0 (18.7, 81.3)	0.0 (-41.1, 41.1)
Not Hispanic or Latino	107/288	37.2 (31.6, 43.0)	95/154	61.7 (53.5, 69.4)	-25.4 (-34.8, -16.0)
Not Reported	0/4	0.0 (0.0, 60.2)	2/5	40.0 (5.3, 85.3)	NA
Unknown	3/9	33.3 (7.5, 70.1)	1/1	100.0 (2.5, 100.0)	NA

[†] Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

[‡] Other included multi-racial, native Hawaiian or other pacific islander, and missing (declined to answer question).

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

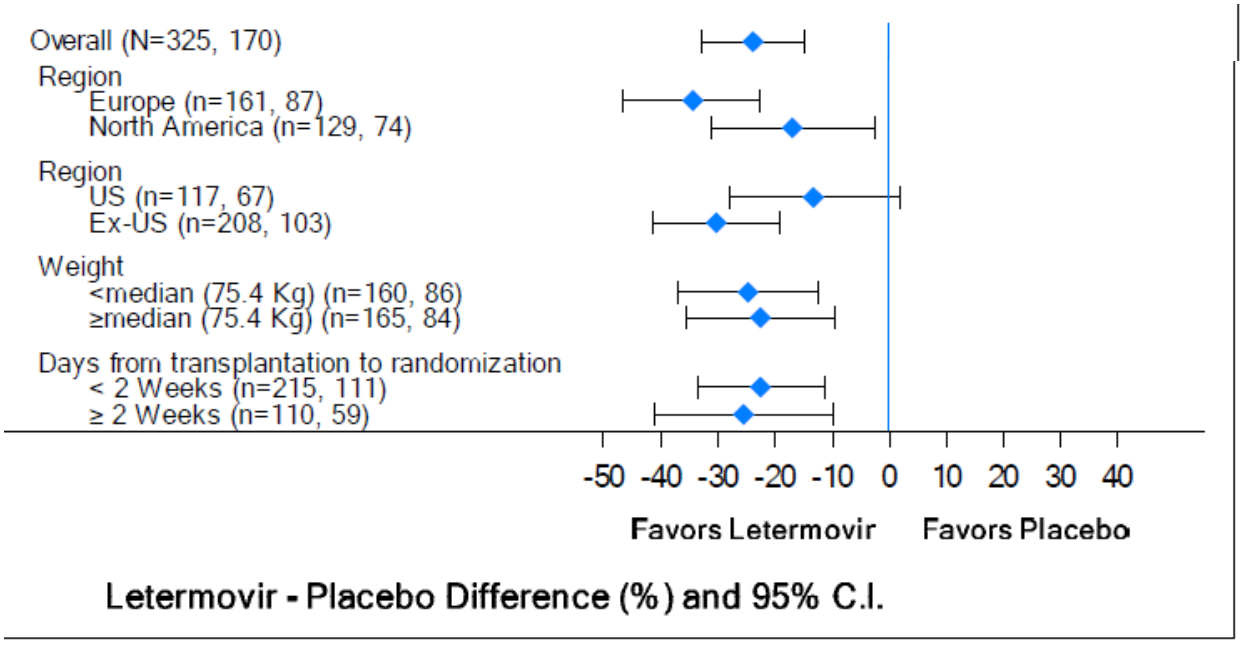
n (%) = Number (percent) of subjects in each sub-category.

NA = Not Applicable.

Source: Table 14.2-46 of the Clinical Study Report

Other Special/Subgroup Populations

Figure 13: Treatment Difference in Clinically Significant CMV Infection Through Week 24 Post-Transplant by Region, Weight and Days from Transplantation to Randomization Subgroups (NC=F Approach, FAS Population)



Source: Figure 14.2-4 in the Clinical Study Report

Without adjusting for multiplicity, the letermovir treatment group was superior to placebo in Europe and North America, the Ex-US region, both weight categories and the two days from transplantation to randomization subgroups. In addition the upper bound of the 95% CI for the treatment difference between letermovir and placebo in the US was only slightly to the right of the zero axis.

Table 27: Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Region, Median Weight and Days from Transplantation to Randomization Subgroups (NC=F Approach, FAS Population)

Subject Characteristic Subgroup	Letermovir n/N	Letermovir % (95% CI)	Placebo n/N	Placebo % (95% CI)	Letermovir vs. Placebo Difference in % (95% CI)†
Region					
Asia-Pacific	16/31	51.6 (33.1, 69.8)	3/7	42.9 (9.9, 81.6)	NA
Latin America	3/4	75.0 (19.4, 99.4)	1/2	50.0 (1.3, 98.7)	NA
Europe	55/161	34.2 (26.9, 42.0)	59/87	67.8 (56.9, 77.4)	-34.4 (-46.6, -22.3)
North America	48/129	37.2 (28.9, 46.2)	40/74	54.1 (42.1, 65.7)	-16.8 (-31.0, -2.6)
Region					
US	44/117	37.6 (28.8, 47.0)	34/67	50.7 (38.2, 63.2)	-13.1 (-28.1, 1.9)
Ex-US	78/208	37.5 (30.9, 44.5)	69/103	67.0 (57.0, 75.9)	-30.3 (-41.4, -19.2)
Weight					
< median (75.4 Kg)	60/160	37.5 (30.0, 45.5)	53/86	61.6 (50.5, 71.9)	-24.5 (-36.8, -12.3)
≥ median (75.4 Kg)	62/165	37.6 (30.2, 45.4)	50/84	59.5 (48.3, 70.1)	-22.3 (-35.3, -9.4)
Days from transplantation to randomization					
< 2 Weeks	85/215	39.5 (33.0, 46.4)	68/111	61.3 (51.5, 70.4)	-22.5 (-33.6, -11.5)
≥ 2 Weeks	37/110	33.6 (24.9, 43.3)	35/59	59.3 (45.7, 71.9)	-25.3 (-40.9, -9.7)

† Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

‡ Other included multi-racial, native Hawaiian or other pacific islander, and missing (declined to answer question).

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

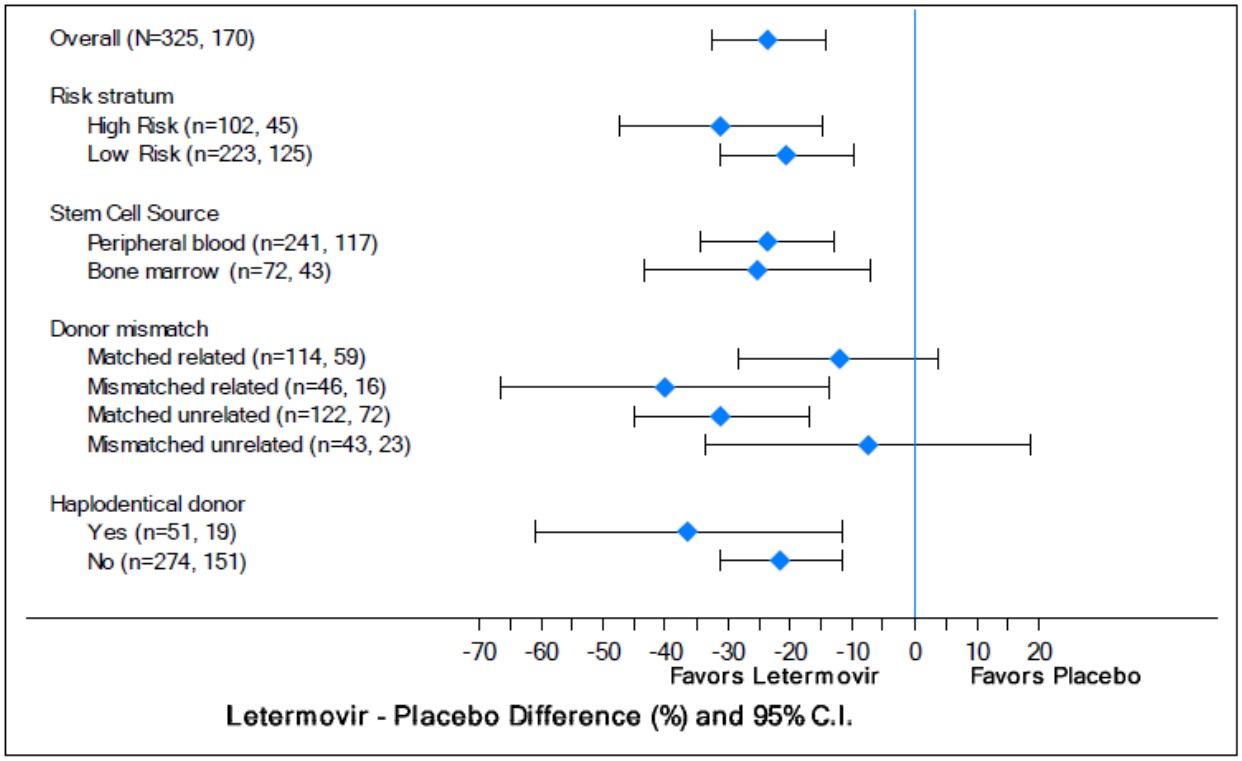
N = number of subjects in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

NA = Not Applicable.

Source: Table 14.2-46 of the Clinical Study Report

Figure 14: Treatment Difference in Clinically Significant CMV Infection Through Week 24 Post-Transplant by Risk Factor Subgroups (NC=F Approach, FAS Population)



Source: Figure 14.2-3 of the Clinical Study Report

Without adjusting for multiplicity, the letermovir treatment group was superior to placebo in the high and low risk strata, peripheral blood and bone marrow subgroups, two of the four donor mismatch subgroups, and both haplodentical donor subgroups.

Table 28: Summary of the Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Risk Categories (NC=F Approach, FAS Population)

Risk category	Letermovir n/N	Letermovir % (95% CI)	Placebo n/N	Placebo % (95% CI)	Letermovir vs. Placebo Difference in % (95% CI)†
Total	**122/325**	**37.5 (32.3, 43.1)**	**103/170**	**60.6 (52.8, 68.0)**	**-23.5 (-32.5, -14.6)**
Risk Stratum‡					
High Risk	43/102	42.2 (32.4, 52.3)	33/45	73.3 (58.1, 85.4)	-31.2 (-47.5, -14.9)
Low Risk	79/223	35.4 (29.2, 42.1)	70/125	56.0 (46.8, 64.9)	-20.6 (-31.3, -9.8)
Ex-vivo T-cell Depletion					
Yes	3/9	33.3 (7.5, 70.1)	2/4	50.0 (6.8, 93.2)	NA
No	119/316	37.7 (32.3, 43.3)	101/166	60.8 (53.0, 68.3)	-23.7 (-32.8, -14.6)
Alemtuzamab (Campath) Use					
Yes	4/11	36.4 (10.9, 69.2)	8/9	88.9 (51.8, 99.7)	NA
No	118/314	37.6 (32.2, 43.2)	95/161	59.0 (51.0, 66.7)	-21.9 (-31.2, -12.7)
Stem Cell Source					
Peripheral blood	84/241	34.9 (28.9, 41.2)	68/117	58.1 (48.6, 67.2)	-23.8 (-34.6, -13.0)
Bone marrow	31/72	43.1 (31.4, 55.3)	29/43	67.4 (51.5, 80.9)	-25.4 (-43.6, -7.3)
Cord blood	7/12	58.3 (27.7, 84.8)	6/10	60.0 (26.2, 87.8)	NA
GVHD ≥Grade 2 at Baseline					
Yes	0/1	0.0 (0.0, 97.5)	1/1	100.0 (2.5, 100.0)	NA
No	122/324	37.7 (32.4, 43.2)	102/169	60.4 (52.6, 67.8)	-23.2 (-32.2, -14.2)
Donor Mismatch					
Matched related	40/114	35.1 (26.4, 44.6)	28/59	47.5 (34.3, 60.9)	-12.1 (-28.1, 3.8)
Mismatched related	16/46	34.8 (21.4, 50.2)	12/16	75.0 (47.6, 92.7)	-40.2 (-66.5, -13.9)
Matched unrelated	43/122	35.2 (26.8, 44.4)	49/72	68.1 (56.0, 78.6)	-31.1 (-45.2, -17.1)
Mismatched unrelated	23/43	53.5 (37.7, 68.8)	14/23	60.9 (38.5, 80.3)	-7.4 (-33.7, 18.8)
Haploidentical Donor					
Yes	19/51	37.3 (24.1, 51.9)	14/19	73.7 (48.8, 90.9)	-36.4 (-61.0, -11.8)
No	103/274	37.6 (31.8, 43.6)	89/151	58.9 (50.7, 66.9)	-21.5 (-31.2, -11.8)

† Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

‡ High risk: Subjects meeting one or more of the following criteria at the time of randomization:
1. Human leukocyte antigen (HLA)-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or -DR
2. Haploidentical donor
3. Unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1
4. Use of umbilical cord blood as stem cell source
5. Use of ex vivo T-cell-depleted grafts
6. Grade 2 or greater graft-versus-host disease (GVHD), requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid)

Low risk: All subjects not meeting definition of high risk.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

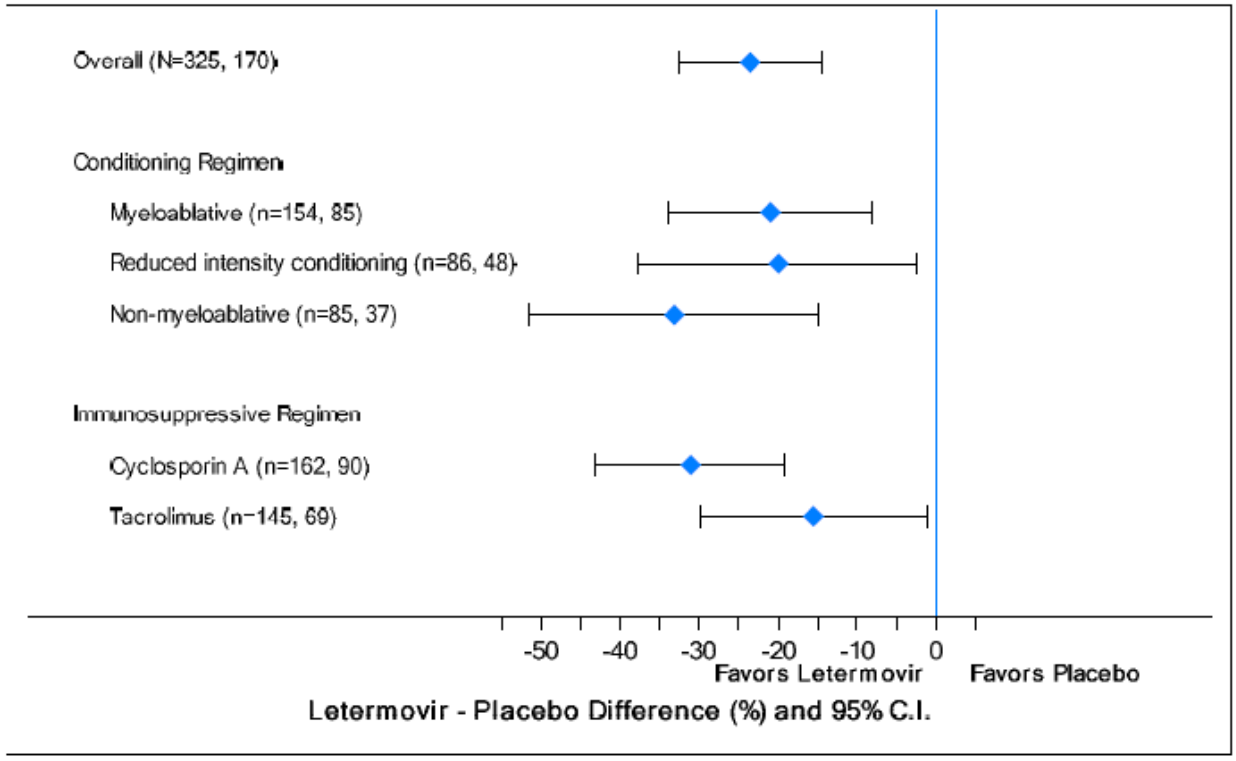
N = number of subjects in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

NA = Not Applicable.

Source: Table 14.2-45 of the Clinical Study Report

Figure 15: Treatment Difference in Clinically Significant CMV Infection Through Week 24 Post-Transplant by Conditioning Regimen and Immunosuppressive Therapy Subgroups (NC=F Approach, FAS Population)



Source: Figure 14.2-5 of the Clinical Study Report

Without adjusting for multiplicity, the letermovir treatment group was superior to placebo in each of the conditioning regimen and immunosuppressive regimen subgroups.

Table 29: Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant by Conditioning Regimen and Immunosuppressive Regimen Use (NC=F Approach, FAS Population)

Subgroup	Letermovir		Placebo		Letermovir vs. Placebo Difference in % (95% CI)[†]
	n/N	% (95% CI)	n/N	% (95% CI)	
Total	**122/325**	**37.5 (32.3, 43.1)**	**103/170**	**60.6 (52.8, 68.0)**	**-23.5 (-32.5, -14.6)**
Conditioning Regimen					
Myeloablative	60/154	39.0 (31.2, 47.1)	50/85	58.8 (47.6, 69.4)	-20.9 (-33.9, -7.9)
Reduced intensity conditioning	33/86	38.4 (28.1, 49.5)	28/48	58.3 (43.2, 72.4)	-19.9 (-37.7, -2.2)
Non-myeloablative	29/85	34.1 (24.2, 45.2)	25/37	67.6 (50.2, 82.0)	-33.2 (-51.4, -15.0)
Immunosuppressive Regimen[‡]					
Cyclosporin A	58/162	35.8 (28.4, 43.7)	60/90	66.7 (55.9, 76.3)	-31.1 (-43.2, -19.0)
Tacrolimus	56/145	38.6 (30.7, 47.1)	37/69	53.6 (41.2, 65.7)	-15.5 (-29.8, -1.1)
Other	8/18	44.4 (21.5, 69.2)	5/9	55.6 (21.2, 86.3)	NA
Missing	NA	NA	1/2	50.0 (1.3, 98.7)	NA

[†] Treatment difference and 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

[‡] Subjects were included in the Cyclosporin A (CsA) row if they received concomitant CsA-containing regimen regardless of whether they received any other immunosuppresants. Subjects in the tacrolimus row did not receive any CsA. Subjects in the "Others" row received neither CsA nor tacrolimus. Other immunosuppressive regimens include sirolimus, everolimus, systemic steroids, leflunomide, mycophenolateOther immunosuppressive regimens include sirolimus, everolimus, systemic steroids, leflunomide, mycophenolate.

Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

N = number of subjects in each treatment group.

n (%) = Number (percent) of subjects in each sub-category.

NA = Not Applicable.

Source: Table 14.2-47 of the Clinical Study Report

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The main statistical issues pertained to the mortality analyses, both in terms of errors made in the analyses, the ambiguous results and the lack of follow-up of patients who discontinued from the trial. Merck had to resubmit the mortality analyses due to a SAS programming error where the treatment group and high vs. low risk stratification variables were switched. Instead of a statistically significant two-sided p-value of 0.019 they should have obtained a non-significant p-value of 0.10 for the interim Week 48 analysis at the time of database lock. For the final Week 48 mortality data analysis instead of a statistically significant two-sided p-value of 0.018 they should have obtained a non-significant p-value of 0.12.

In response to an FDA Information Request sent on April 10, 2017, Merck stated that they did not proactively follow up patients who discontinued from the trial in order to determine their mortality status. Instead Merck only counted deaths while patients were still enrolled in the trial. Merck provided additional information in the datasets about 11 additional deaths among the 87 patients who discontinued from the trial. After counting these 11 subjects as deaths, 76 subjects with unknown mortality status remained. The applicant stated on page 9 of the Week 48 Mortality Statistical Report that "post-study deaths are not included in the mortality analysis, as the reporting of information after a subject had completed the clinical trial was not required." On April 24, 2017 Merck was asked to provide additional information about the mortality status of all of the study subjects at Weeks 24 and 48 post-transplant.

This information was not submitted until July 14, 2017. According to Merck, vital status were obtained for 58 of these 76 subjects who prematurely withdrew from the trial with unknown mortality status at the time the initial (Week 24) clinical study report was written. Merck stated that the reason for not being able to collect information on the remaining subjects was largely due to country related legal issues in contacting subjects after the completion and closure of the trial as well as for those patients whose reason for early withdrawal was "withdrew consent".

What the applicant called "CMV-related mortality" was death due to any reason in subjects who met the primary endpoint. The primary endpoint of clinically significant CMV infection may or may not have caused mortality and it can be subjective. For example a subject who died from a heart attack due to underlying cardiovascular disease could have had a clinically significant CMV infection and been counted as having CMV-related mortality. Even if there was no difference in CMV mortality between letermovir and placebo arms the "CMV-related mortality" analysis could have been statistically significant due to the very statistically significant difference in clinically significant CMV infection between the two arms.

The reviewers were also unable to replicate Merck's analyses of opportunistic infections using the intermediate datasets. In response to our query Merck about the analyses of opportunistic infections and further clarification regarding the accuracy of the numbers reported, Merck

responded with SAS code to derive opportunistic infection tables. The applicant did not confirm that the numbers they reported were correct and the review team submitted more specific questions about selected discrepancies in order to elicit more information. The applicant responded on June 23, 2017 stating that they had made a programming error for individual infections like bacteremia but not total categories like all bacterial infections. The error was that they counted the number of occurrences of each infection instead of the number of patients.

5.2 Collective Evidence

The Non-Completer=Failure (NC=F) approach was used for imputing missing data in the primary efficacy analysis of the proportion of subjects who developed clinically significant CMV infection through Week 24 post-transplant in the FAS population. In this approach, subjects who discontinued from the study prior to the Week 24 follow-up visit were considered as failures regardless of reason for discontinuation. Subjects missing the CMV DNA measurement needed for efficacy assessment in the Week 24 window were also considered as failures. At Week 24, the proportion of subjects with clinically significant CMV infection in the letermovir group (37.5%) was significantly lower than that in the placebo group (60.6%). The estimated difference (95% CI) was -23.5% (-32.5% to -14.6%), adjusted for the stratification factor (high vs. low risk of CMV reactivation) (two-sided p-value <0.001). This analysis was robust to the assumption about counting non-completers as failures.

The Kaplan-Meier (K-M) event rate for all-cause mortality at Week 24 post-transplant (including all available post-study information in the July 14, 2017 submission) was lower for the letermovir group (12%) compared to the placebo group (17%). The applicant claimed that the distribution of time to all-cause mortality through Week 24 was substantially different between the letermovir and placebo groups. However the two-sided p-value=0.0401, using the stratified log-rank test was not substantially lower than the 0.05 level required for statistical significance.

The K-M event rate for all-cause mortality at Week 48 post-transplant (including post-study information), was lower for the letermovir group (24%) compared to the placebo group (28%). The two-sided p-value of 0.21 for the Week 48 analysis using the stratified log-rank test was not statistically significant at the 0.05 level. The statistics reviewer performed many sensitivity analyses and the Week 24 and 48 mortality analyses appeared to be robust to different assumptions about discontinuations.

5.3 Conclusions and Recommendations

Despite the numerous programming errors made by the applicant, extensive sensitivity analyses indicated that the mortality analyses were fairly robust to assumptions about missing data and lack of adequate follow-up pertaining to mortality status. Given the large treatment effect that was observed for the primary efficacy endpoint (proportion of subjects with clinically significant CMV infection through Week 24 post-transplant) and supportive trends for all-cause mortality in favor of letermovir over placebo, the reviewer concludes that efficacy was demonstrated for letermovir in the phase 3 trial.

5.4 Labeling Recommendations (as applicable)

Proposed table for Section 14 of the label

Efficacy

Clinically Significant CMV Infection
The primary efficacy endpoint of P001 was the incidence of clinically significant CMV infection through Week 24 post-transplant. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viremia (using the Roche COBAS® AmpliPrep/COBAS TaqMan® assay, LLoQ is 137 IU/mL, which is approximately 150 copies/mL) and the clinical condition of the subject. The Non-Completer=Failure (NC=F) approach was used, where subjects who discontinued from the (b) (4) prior to Week 24 post-transplant or had a missing outcome at Week 24 post-transplant were counted as failures.

(b) (4)

Table 30: P001 Efficacy Results in HSCT Recipients in Section 14 of the Proposed USPI (NC=F Approach, FAS Population)

Parameter	Letermovir (N=325)	Placebo (N=170)
(b) (4)	(b) (4)	
(Proportion of subjects who failed prophylaxis)		
Reasons for Failures*		
Clinically significant CMV infection by Week 24†		
Initiation of PET based on documented CMV viremia		
CMV end-organ disease		
Discontinued from study before Week 24		
Missing outcome in Week 24 visit window		
Stratum-adjusted treatment difference (Letermovir-Placebo)‡		
Difference (95% CI)	-23.5 (-32.5, -14.6)	
(b) (4)		

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

(b) (4)

‡ 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). (b) (4)

(b) (4)

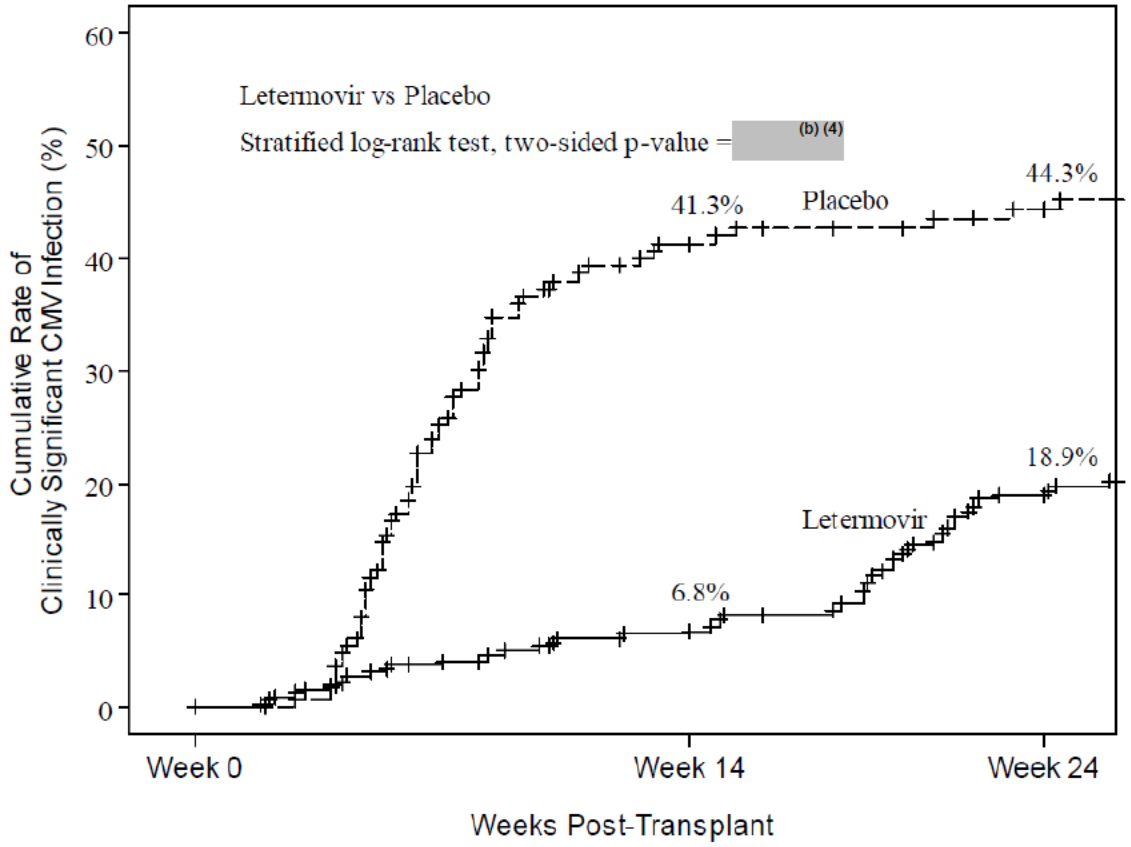
Note: FAS=Full analysis set; FAS includes randomized subjects who received at least one dose of study medication, and excludes subjects with detectable CMV DNA at baseline.[291] Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

(b) (4)

Source: Table (b) (4) of the label in the original submission

(b) (4)

Figure 16: P001: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 Post-Transplant in HSCT Recipients in Section 14 of the Proposed USPI (FAS Population)



Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

Source: Figure 1 of the label in the original submission

(b) (4)

Reviewer's note: Normally subgroup results that are not pre-specified in the statistical analysis plan are not displayed in the label. In addition, the primary efficacy analysis population (full analysis set) should be used for subgroup analyses, (b) (4) (b) (4)***.***

2 Pages Have Been Withheld In Full As Draft Labeling Immediately Following This Page

APPENDICES

Table 31: Applicant's Analysis of Proportion of Subjects with Clinically Significant CMV Infection Through Week 24 Post-Transplant (NC=F Approach, FAS Population)

Parameter	Letermovir (N=325)	Placebo (N=170)
Failures[†]		(b) (4)
Clinically significant CMV infection by Week 24[‡]		
Initiation of PET based on documented CMV viremia		
CMV end-organ disease		
Discontinued from study before Week 24		
Missing outcome in Week 24 visit window		
Stratum-adjusted treatment difference (Letermovir-Placebo)[§]		
Difference (95% CI)	-23.5 (-32.5, -14.6)	
(b) (4)		

[†] The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

(b) (4)

[§] 95% CIs and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk). A 1-sided

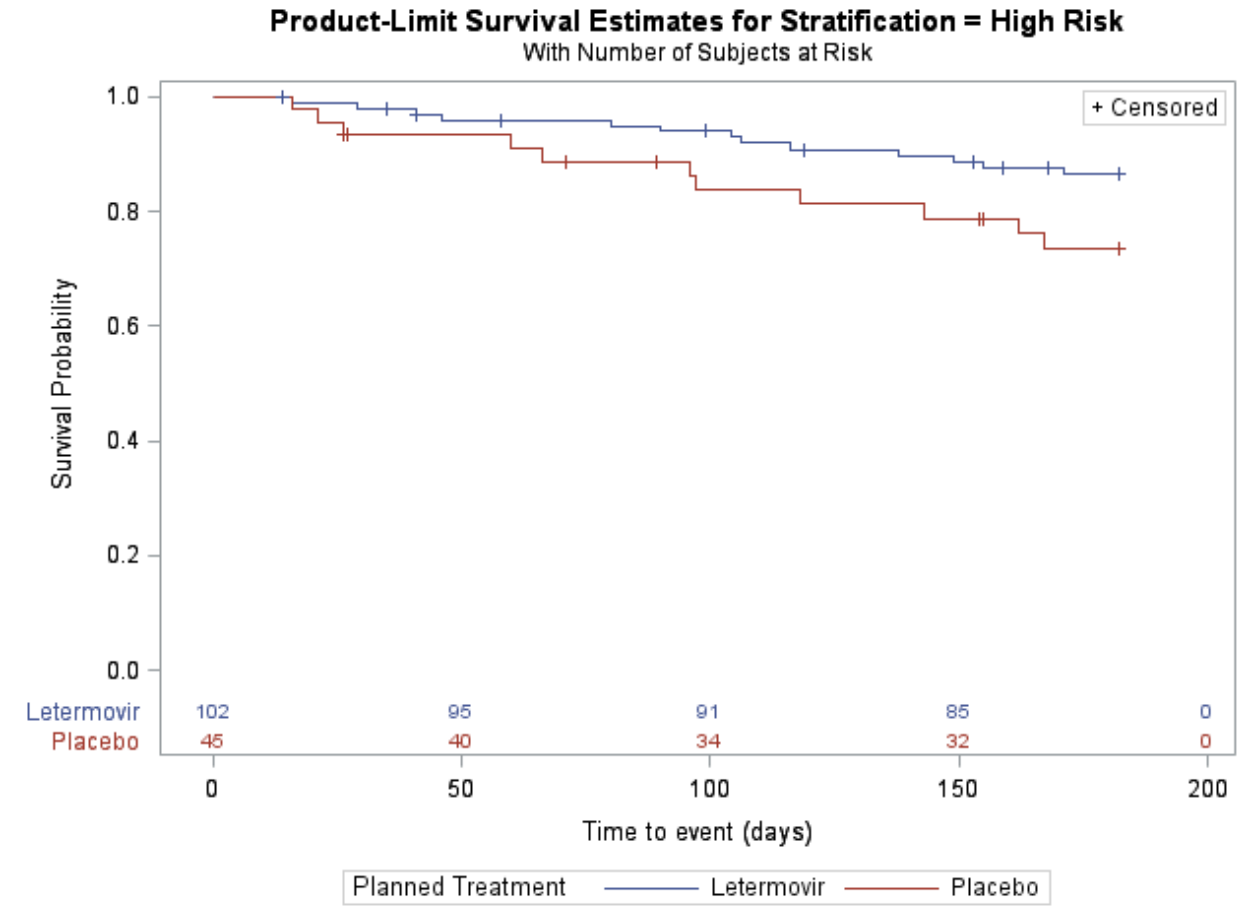
(b) (4)

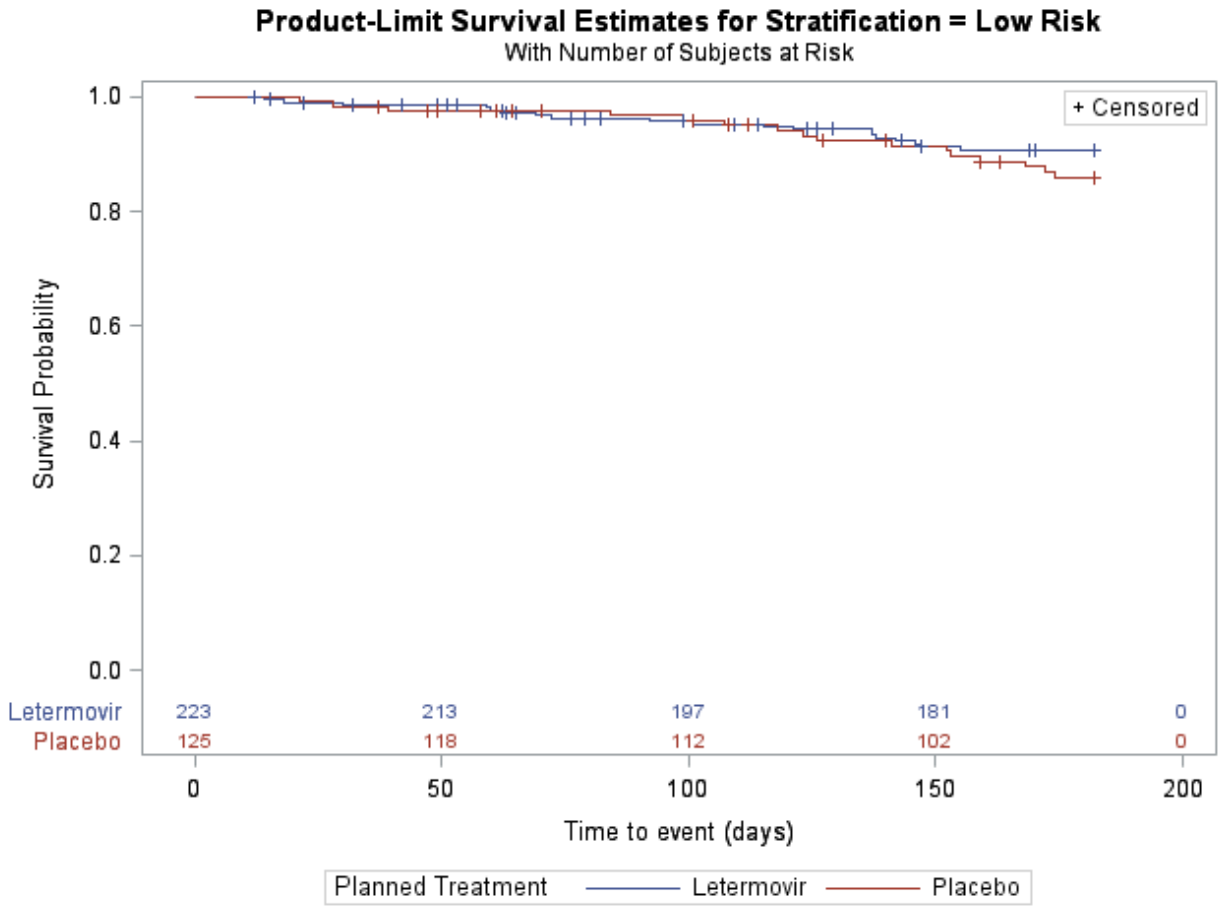
Note: Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

(b) (4)

Source: Table 11-2 of the Clinical Study Report

Figure 19: Week 24 Kaplan-Meier Analysis of Mortality occurring while enrolled in the study

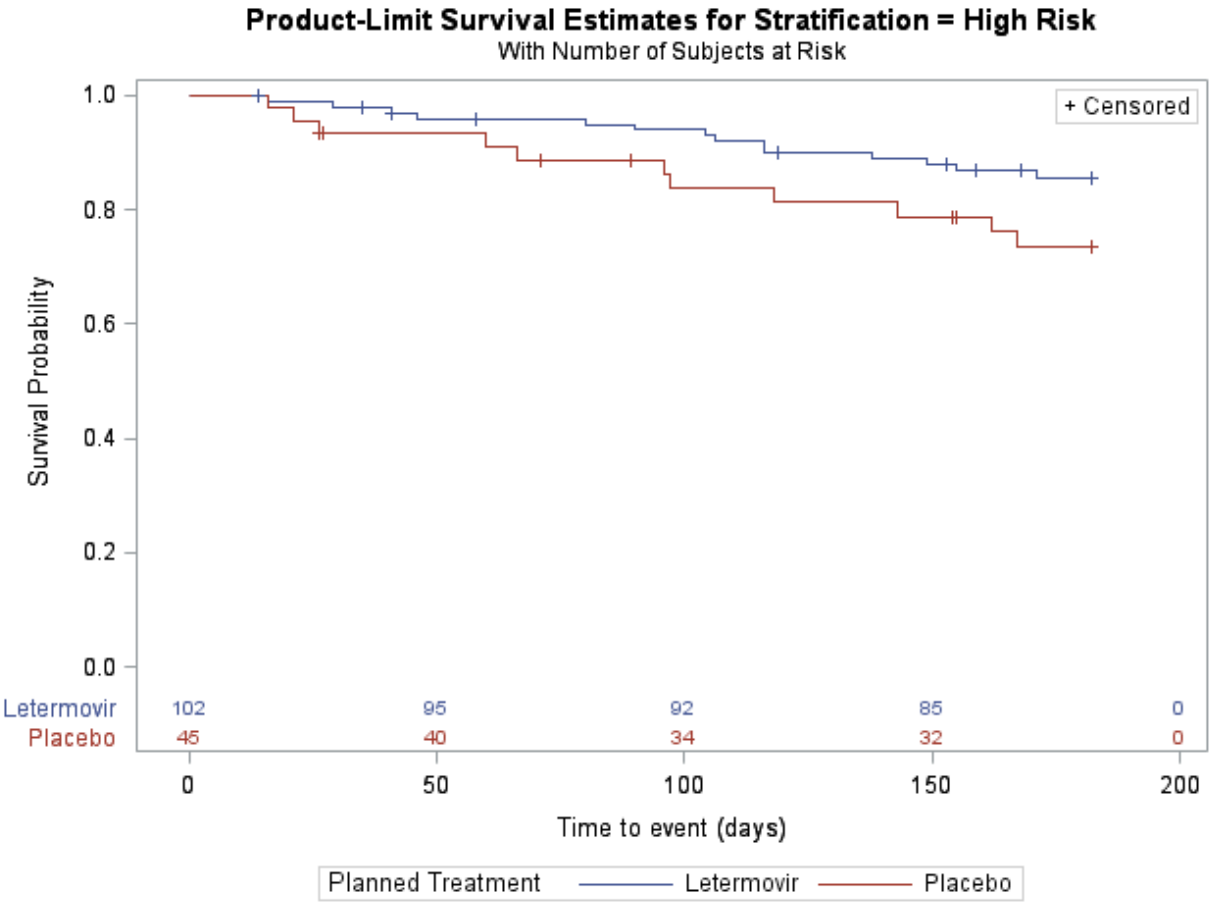


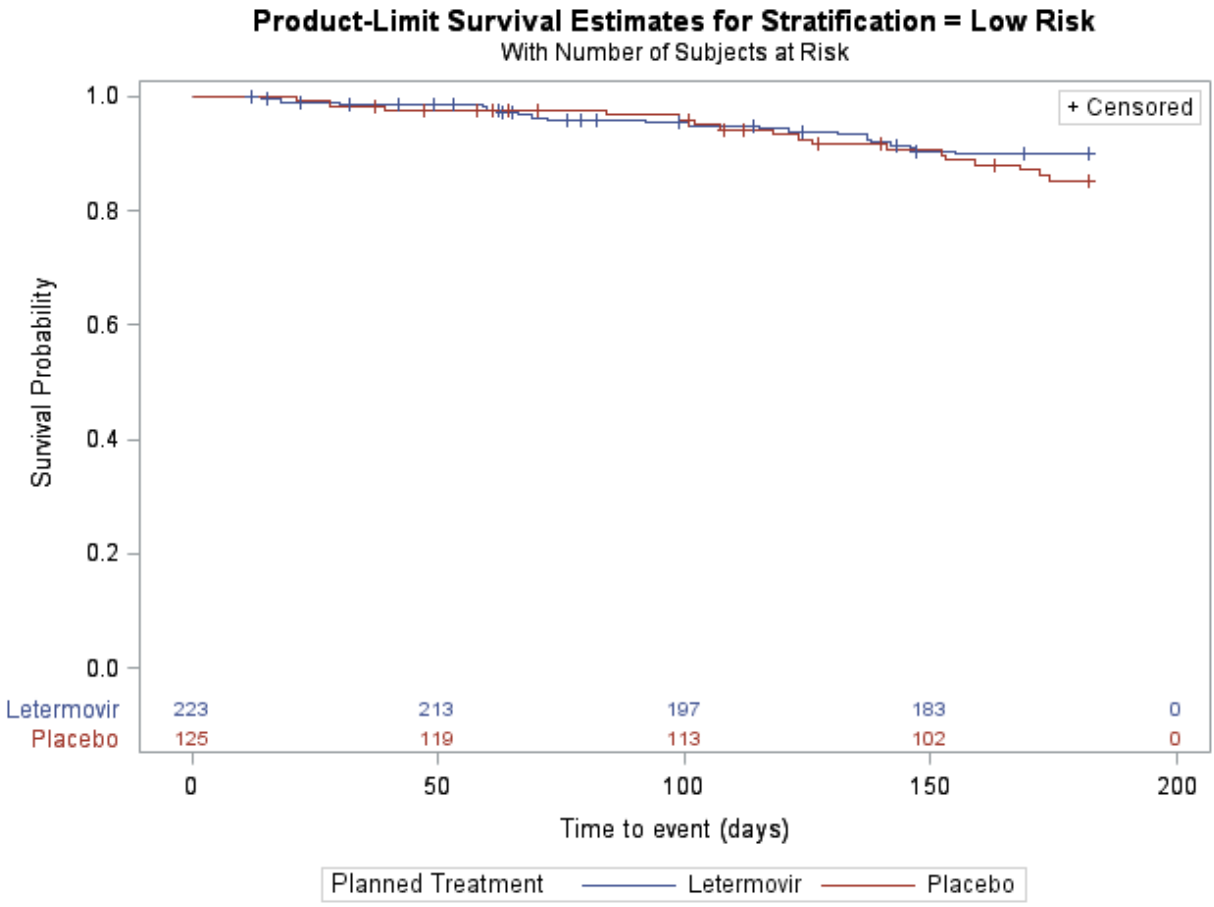


Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	4.5621	1	0.0327
Wilcoxon	2.7648	1	0.0964
Peto	4.3483	1	0.0370
Modified Peto	4.3399	1	0.0372

Source: Reviewer's Analysis

Figure 20: Week 24 Kaplan-Meier Analysis of Mortality including post-study deaths

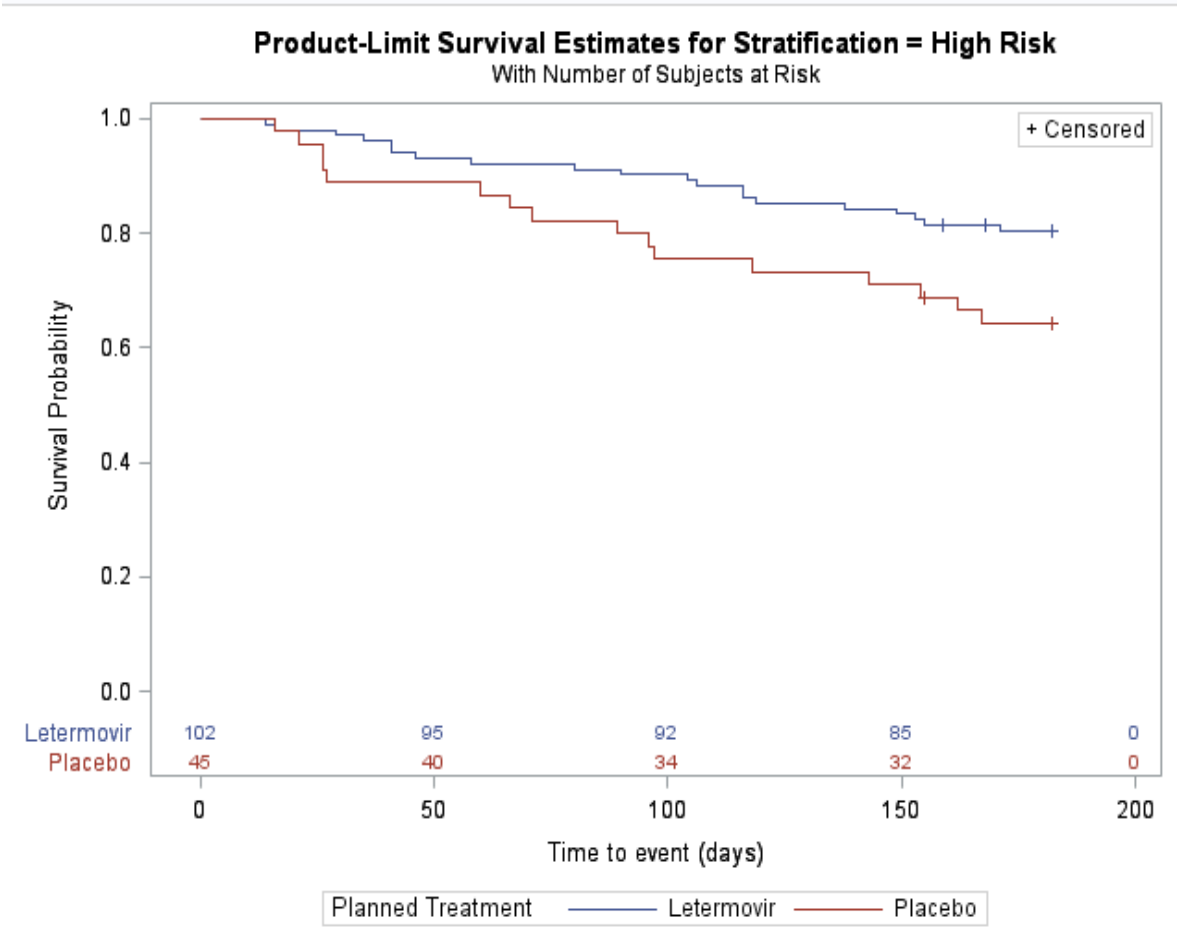


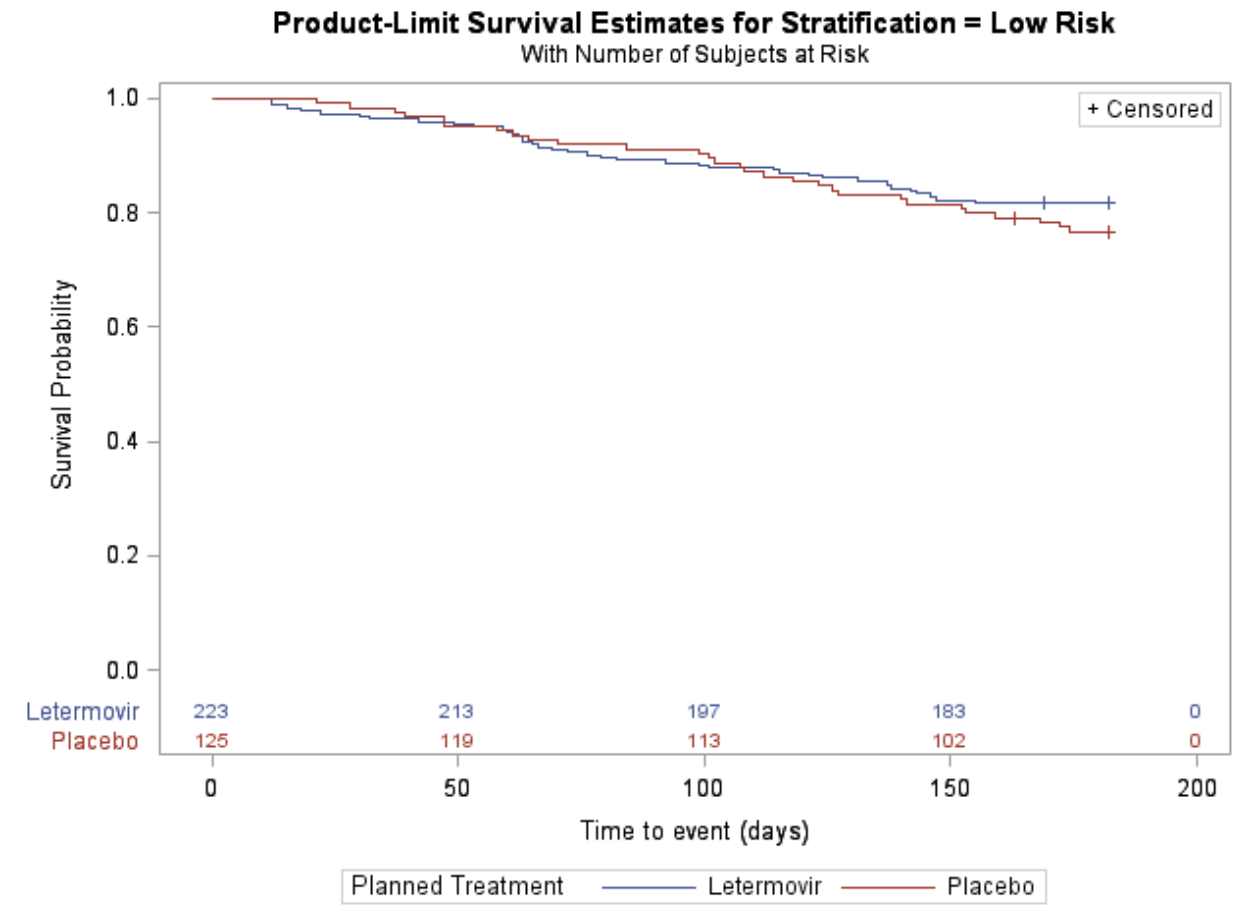


Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	3.9203	1	0.0477
Wilcoxon	2.3856	1	0.1225
Peto	3.7290	1	0.0535
Modified Peto	3.7217	1	0.0537

Source: Reviewer's Analysis

Figure 21: Week 24 Kaplan-Meier Analysis of Mortality including post-study deaths, discontinuations=failure

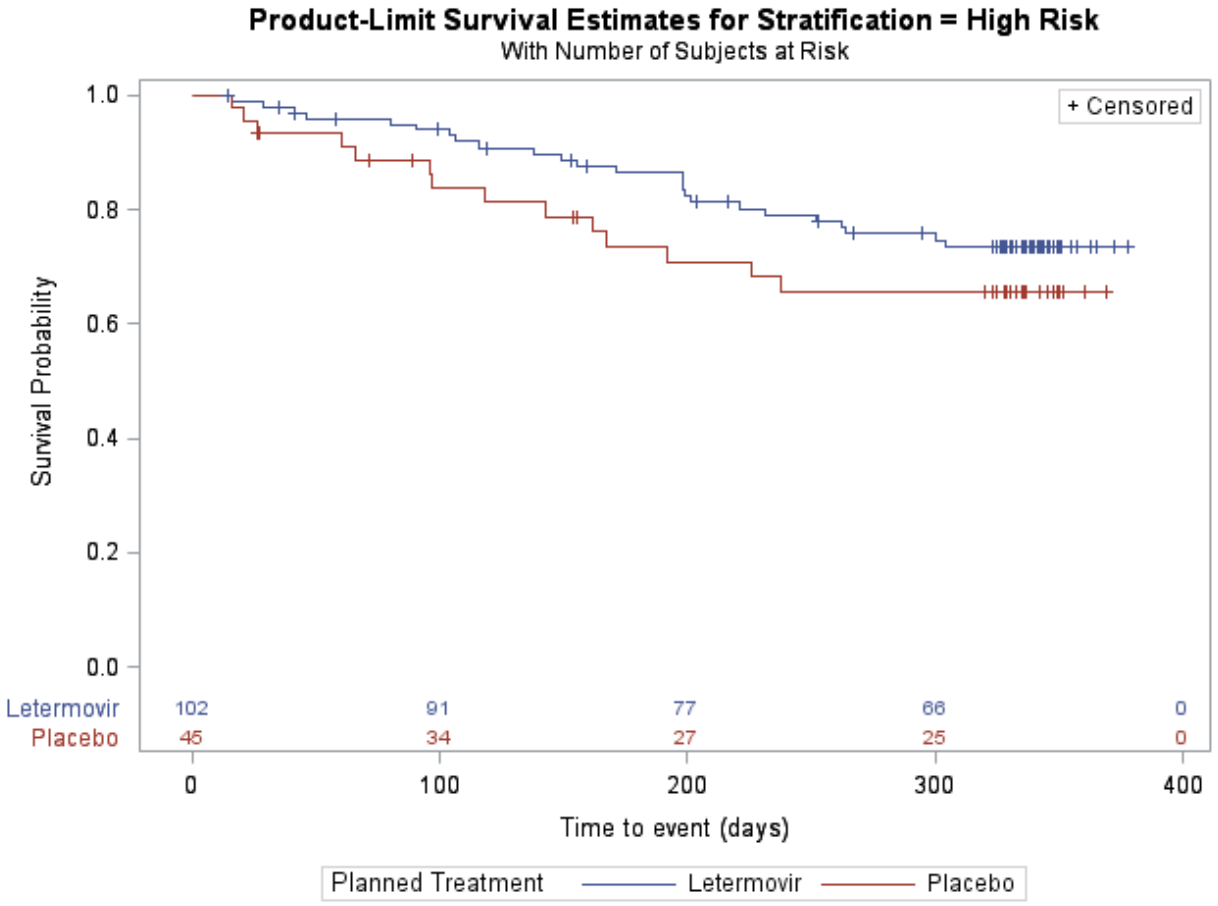


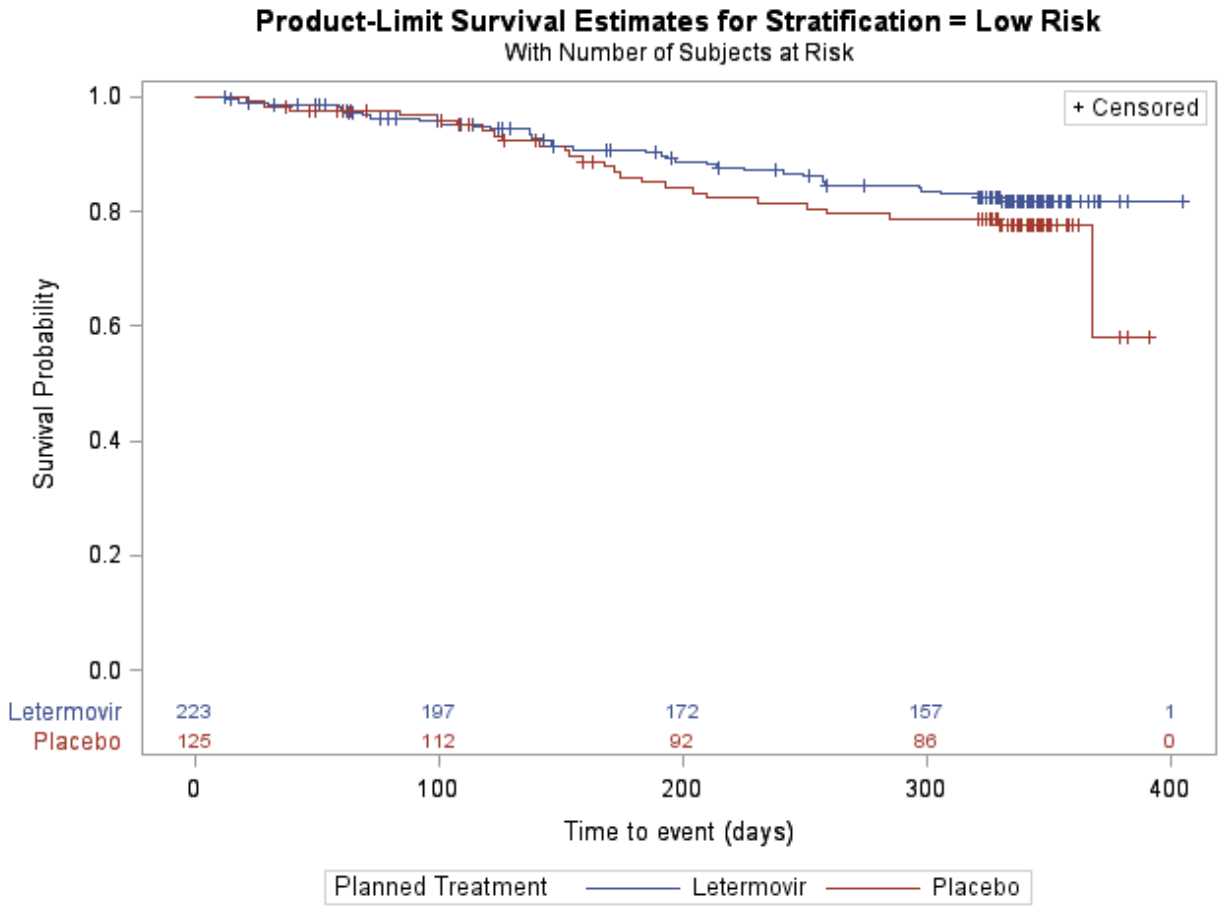


Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	3.9951	1	0.0456
Wilcoxon	1.9593	1	0.1616
Peto	3.6080	1	0.0575
Modified Peto	3.5965	1	0.0579

Source: Reviewer's Analysis

Figure 22: Week 48 Kaplan-Meier Analysis of Mortality occurring while enrolled in the study

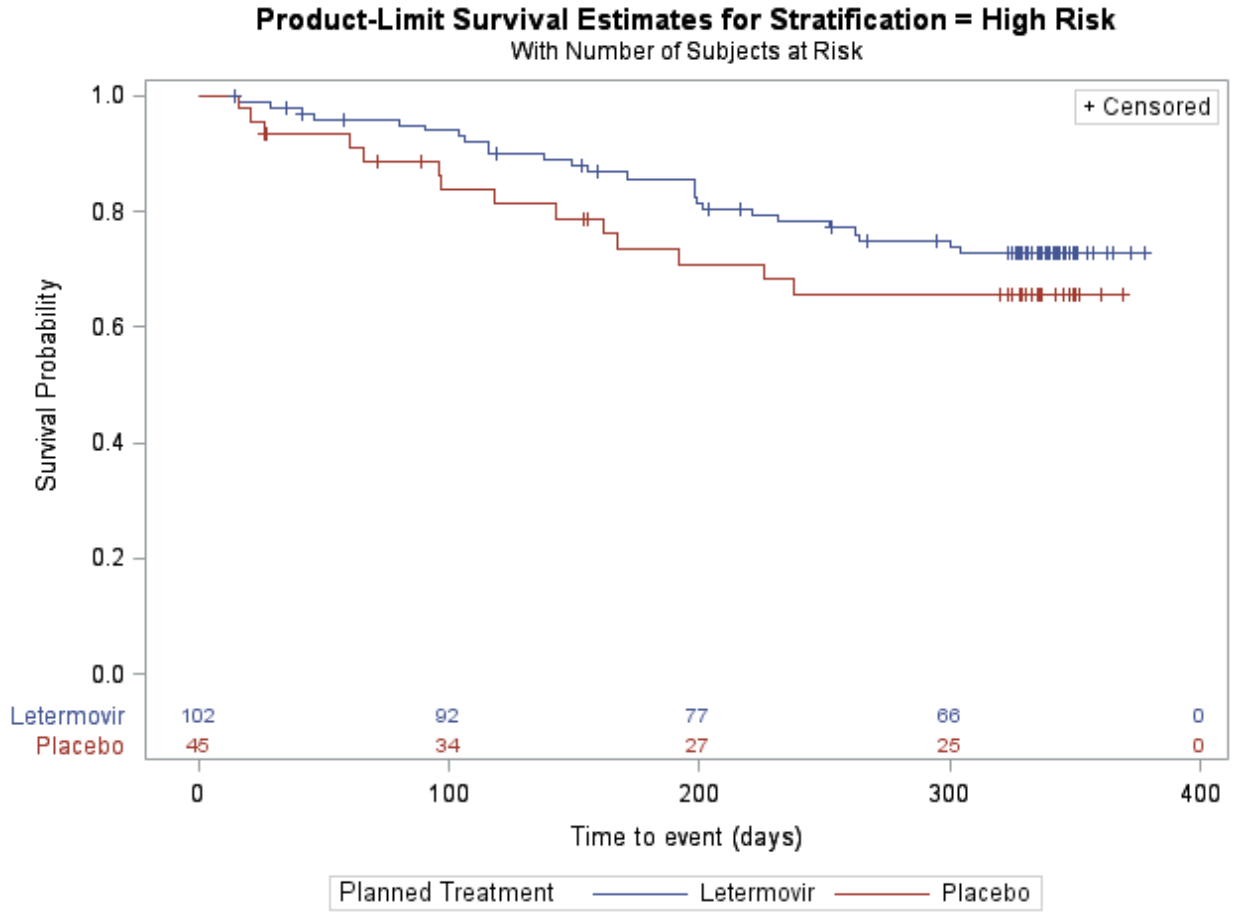


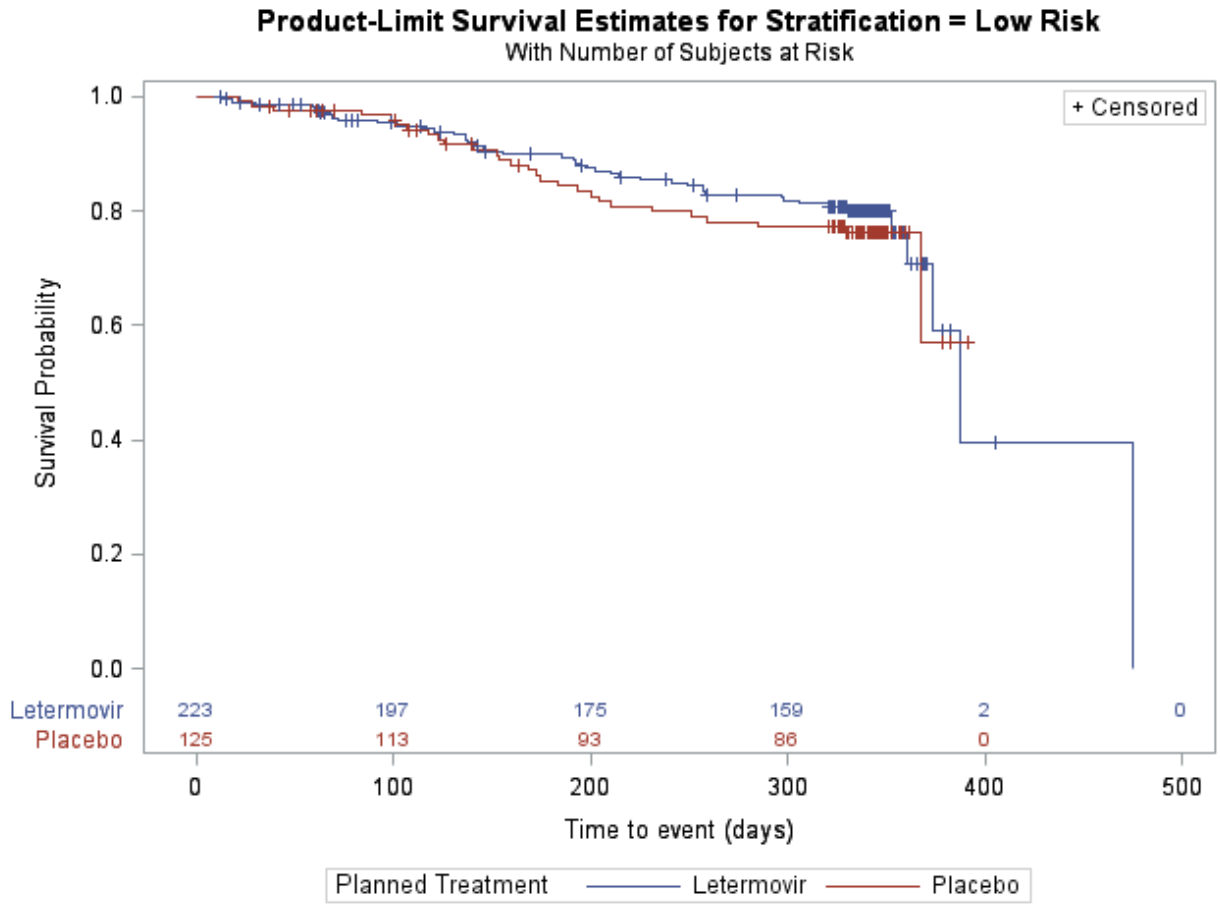


Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	2.3866	1	0.1224
Wilcoxon	1.6115	1	0.2043
Peto	2.6041	1	0.1066
Modified Peto	2.5770	1	0.1084

Source: Reviewer's Analysis

Figure 23: Week 48 Kaplan-Meier Analysis of Mortality including post-study deaths

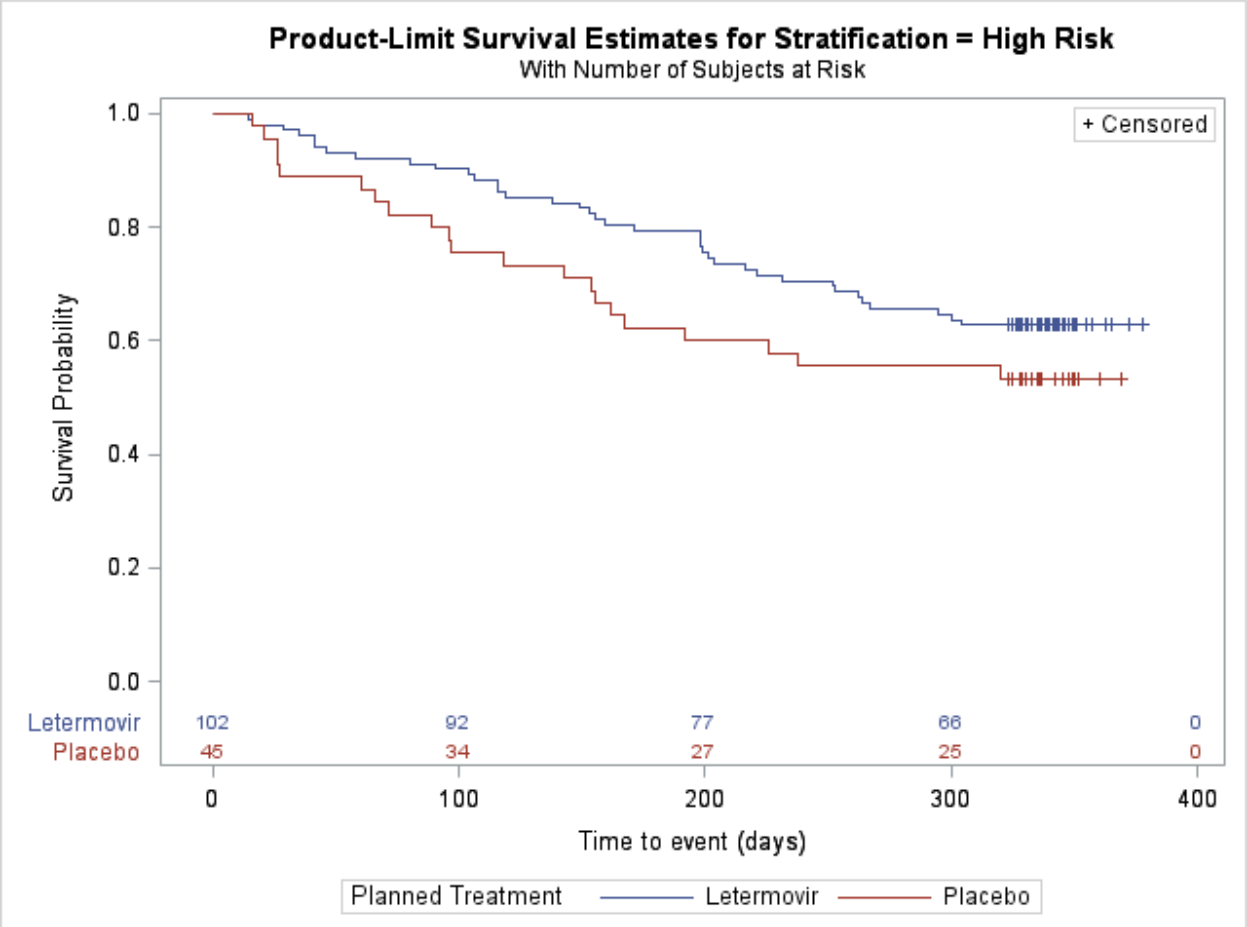


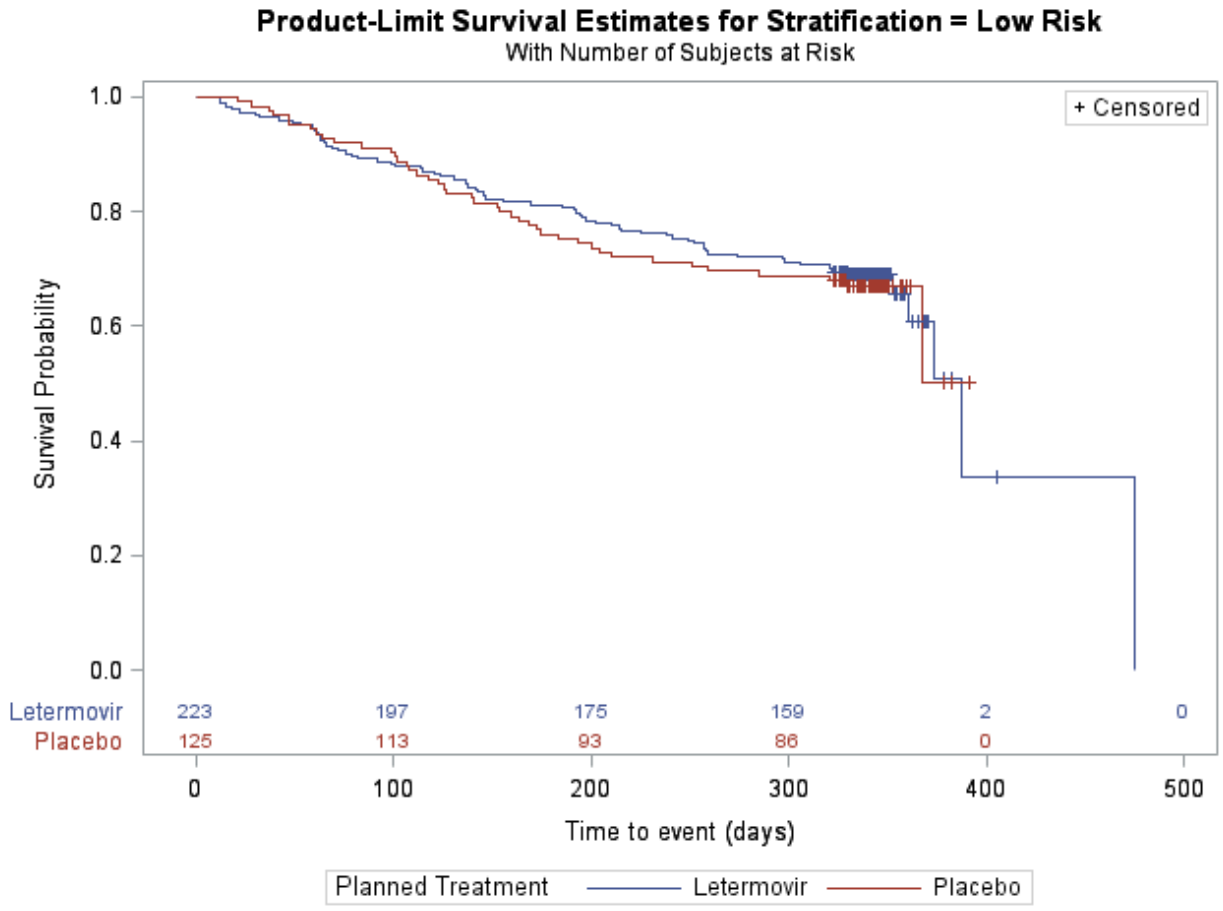


Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.4218	1	0.2331
Wilcoxon	1.3444	1	0.2463
Peto	1.7368	1	0.1875
Modified Peto	1.7580	1	0.1849

Source: Reviewer's Analysis

Figure 24: Week 48 Kaplan-Meier Analysis of Mortality including post-study deaths, discontinuations=failure

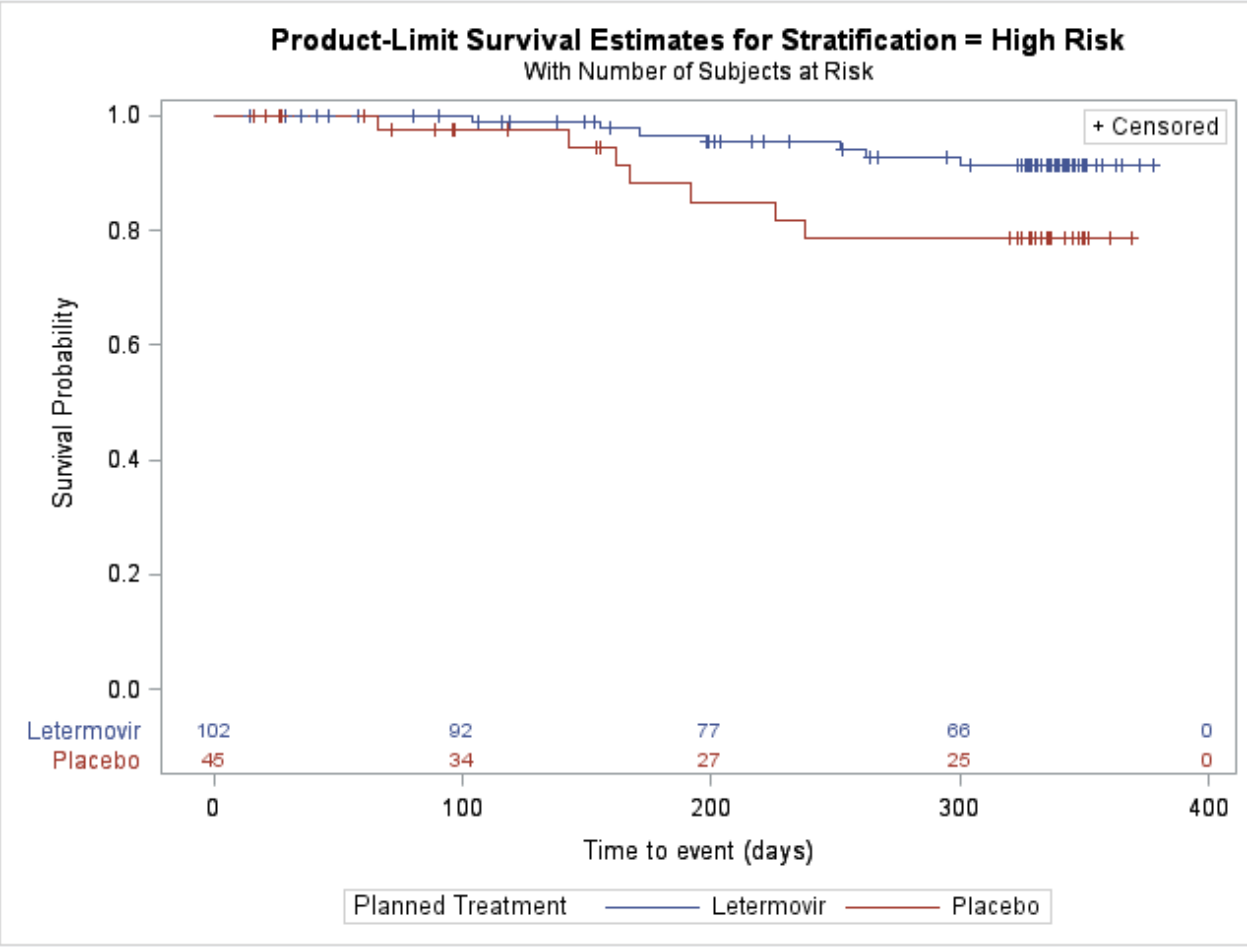


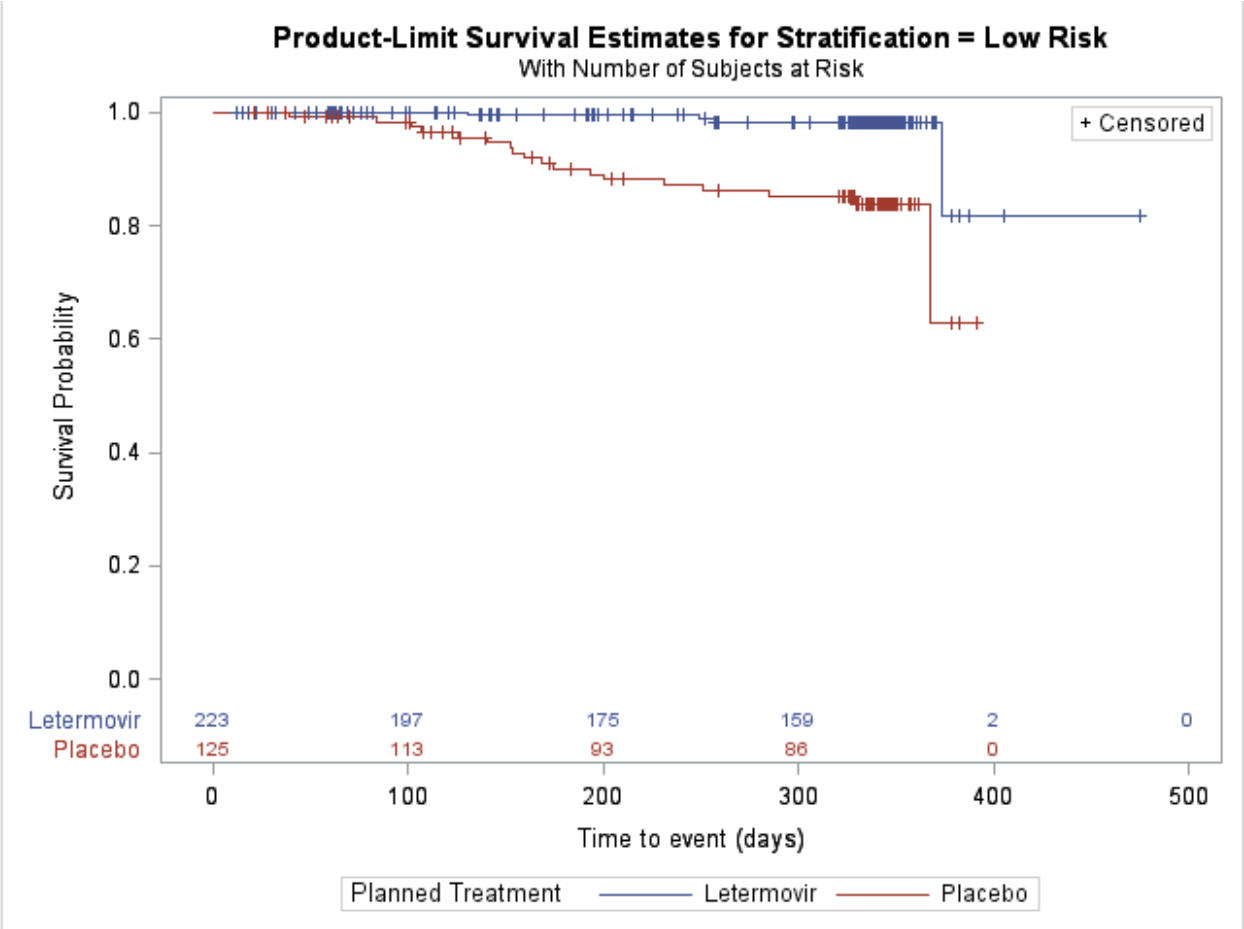


Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.0175	1	0.3131
Wilcoxon	0.6548	1	0.4184
Peto	1.3502	1	0.2453
Modified Peto	1.3596	1	0.2436

Source: Reviewer's Analysis

Figure 25: Week 48 Kaplan-Meier Analysis of "CMV-Related Mortality" including post-study deaths for patients with clinically significant CMV infection

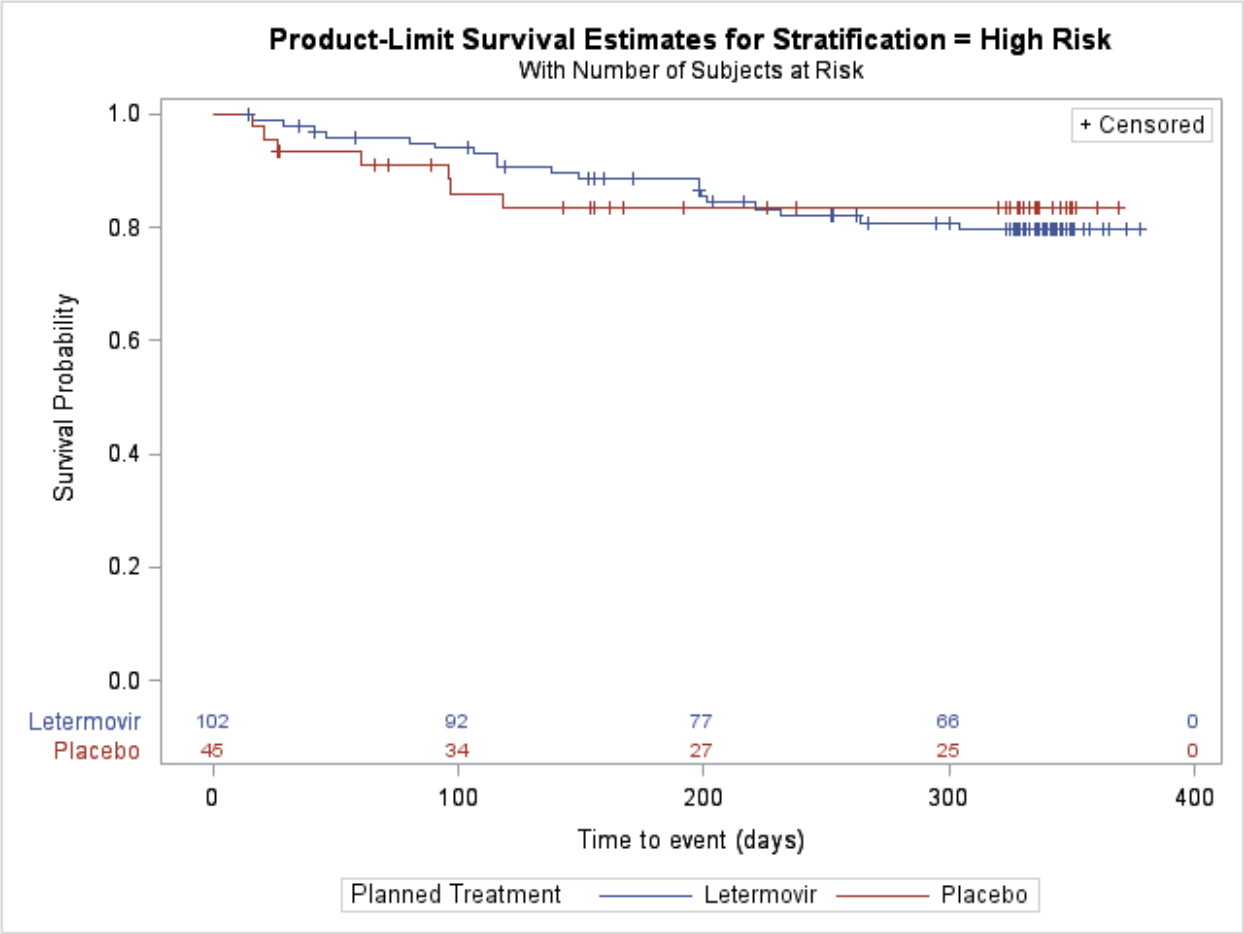


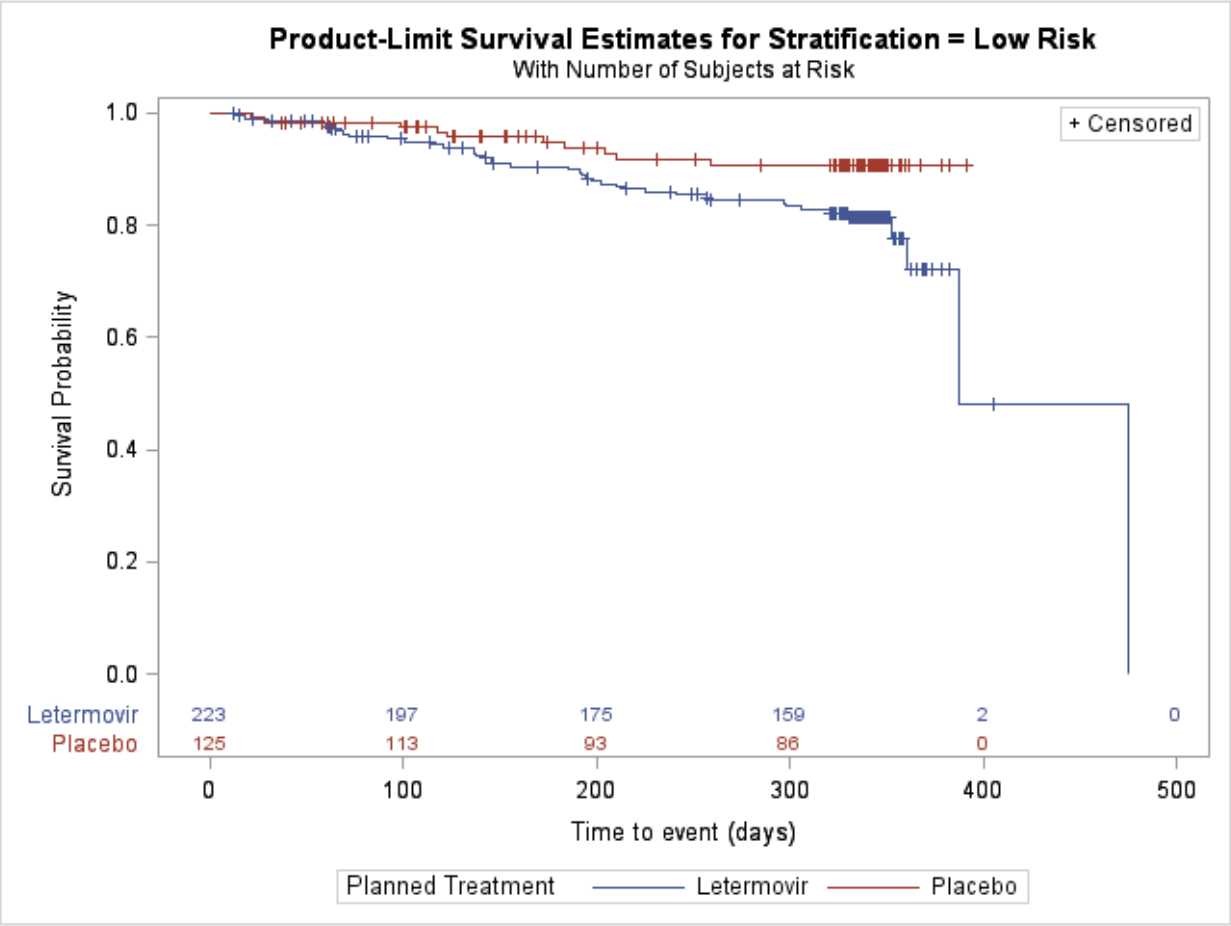


Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	23.7362	1	<.0001
Wilcoxon	25.6793	1	<.0001
Peto	24.5942	1	<.0001
Modified Peto	24.7327	1	<.0001

Source: Reviewer's Analysis

Figure 26: Week 48 Kaplan-Meier Analysis of "Non-CMV-Related Mortality" including post-study deaths for patients who did not have clinically significant CMV infection





Stratified Test of Equality over Group			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	3.5664	1	0.0590
Wilcoxon	3.3436	1	0.0675
Peto	3.1709	1	0.0750
Modified Peto	3.1392	1	0.0764

Source: Reviewer's Analysis

Table 32: Subjects Identified as Having Bacteremia in Table 11-22 of the Clinical Study Report

Subject Identifier for the Study	Actual Treatment	Category of OI orign	Organism	soicod
100091	Letermovir	BACTERIAL	ENTEROCOCCUS	Bacteremia
100091	Letermovir	BACTERIAL	STAPHYLOCOCCUS	Bacteremia
100112	Letermovir	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia
100112	Letermovir	BACTERIAL	ACTINOMYCES	Bacteremia
100129	Letermovir	BACTERIAL	CLOSTRIDIUM DIFFICILE	Bacteremia
100211	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
100223	Letermovir	BACTERIAL	ESCHERICHIA COLI	Bacteremia
100224	Letermovir	BACTERIAL	ESCHERICHIA COLI	Bacteremia
100385	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
100439	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
100454	Letermovir	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia
101647	Letermovir	BACTERIAL	KLEBSIELLA PNEUMONIAE	Bacteremia
101647	Letermovir	BACTERIAL	STAPHYLOCOCCUS AUREUS	Bacteremia
101663	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
101833	Letermovir	BACTERIAL	KLEBSIELLA PNEUMONIAE	Bacteremia
101945	Letermovir	BACTERIAL	CORYNEBACTERIUM JEIKEIUM	Bacteremia
101947	Letermovir	BACTERIAL	HAEMOPHILUS PARAINFLUENZAE	Bacteremia
101952	Letermovir	BACTERIAL	STREPTOCOCCUS	Bacteremia
101953	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
101954	Letermovir	BACTERIAL	ESCHERICHIA COLI	Bacteremia
101957	Letermovir	BACTERIAL	STAPHYLOCOCCUS AUREUS	Bacteremia
101981	Letermovir	BACTERIAL	GRAM-POSITIVE COCCUS	Bacteremia
101981	Letermovir	BACTERIAL	KLEBSIELLA PNEUMONIAE	Bacteremia
101981	Letermovir	BACTERIAL	PSEUDOMONAS AERUGINOSA	Bacteremia
101981	Letermovir	BACTERIAL	STAPHYLOCOCCUS	Bacteremia

101981	Letermovir	BACTERIAL	STAPHYLOCOCCUS AUREUS	Bacteremia
101981	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
101986	Letermovir	BACTERIAL	ESCHERICHIA COLI	Bacteremia
101986	Letermovir	BACTERIAL	ESCHERICHIA COLI, ESBL	Bacteremia
102007	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
102070	Letermovir	BACTERIAL	STREPTOCOCCUS MITIS	Bacteremia
102083	Letermovir	BACTERIAL	ENTEROCOCCUS FAECIUM	Bacteremia
102113	Letermovir	BACTERIAL	STREPTOCOCCUS VIRIDANS GROUP	Bacteremia
102126	Letermovir	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia
102172	Letermovir	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia
102172	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
102188	Letermovir	BACTERIAL	ESCHERICHIA COLI	Bacteremia
102239	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
102251	Letermovir	BACTERIAL	CORYNEBACTERIUM	Bacteremia
102251	Letermovir	BACTERIAL	ENTEROCOCCUS FAECALIS	Bacteremia
102251	Letermovir	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
100043	Placebo	BACTERIAL	ENTEROCOCCUS FAECIUM	Bacteremia
100076	Placebo	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
100109	Placebo	BACTERIAL	HAEMOPHILUS PARAINFLUENZAE	Bacteremia
100226	Placebo	BACTERIAL	KLEBSIELLA	Bacteremia
100226	Placebo	BACTERIAL	ENTEROCOCCUS FAECALIS	Bacteremia
100271	Placebo	BACTERIAL	ENTEROCOCCUS FAECALIS	Bacteremia
100271	Placebo	BACTERIAL	ENTEROCOCCUS FAECALIS	Bacteremia
101720	Placebo	BACTERIAL	STAPHYLOCOCCUS EPIDERMIDIS	Bacteremia
101729	Placebo	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia
101729	Placebo	BACTERIAL	STAPHYLOCOCCUS	Bacteremia
101846	Placebo	BACTERIAL	ESCHERICHIA COLI	Bacteremia
101846	Placebo	BACTERIAL	ESCHERICHIA COLI	Bacteremia
101893	Placebo	BACTERIAL	BACILLUS	Bacteremia
101950	Placebo	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia
101955	Placebo	BACTERIAL	ESCHERICHIA COLI	Bacteremia
101955	Placebo	BACTERIAL	KLEBSIELLA PNEUMONIAE	Bacteremia
101985	Placebo	BACTERIAL	ESCHERICHIA COLI	Bacteremia
102137	Placebo	BACTERIAL	STAPHYLOCOCCUS HAEMOLYTICUS	Bacteremia
102173	Placebo	BACTERIAL	ENTEROCOCCUS FAECIUM	Bacteremia
102220	Placebo	BACTERIAL	ESCHERICHIA COLI	Bacteremia
102221	Placebo	BACTERIAL	CLOSTRIDIUM RAMOSUM	Bacteremia
102221	Placebo	BACTERIAL	ENTEROCOCCUS FAECALIS	Bacteremia
102221	Placebo	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia
102242	Placebo	BACTERIAL	COAGULASE NEGATIVE STAPHYLOCOCCUS	Bacteremia

Source: June 23, 2017 Response to Information Request

Table 33: Subjects Identified as Having Pneumonia, Sepsis and Aspergillosis in Table 11-22 of the Clinical Study Report

Subject Identifier for the Study	Actual Treatment	Category of OI orign	Organsim	Selected OI
100021	Letermovir	FUNGAL	ASPERGILLUS FUMIGATUS	Aspergillosis
100092	Letermovir	FUNGAL	ASPERGILLUS	Aspergillosis
100111	Letermovir	FUNGAL	ASPERGILLUS	Aspergillosis
100245	Letermovir	FUNGAL	ASPERGILLUS	Aspergillosis
100392	Letermovir	FUNGAL	ASPERGILLUS TERREUS	Aspergillosis
101640	Letermovir	FUNGAL	ASPERGILLUS NIGER	Aspergillosis
101771	Letermovir	FUNGAL	ASPERGILLUS	Aspergillosis
101844	Letermovir	FUNGAL	ASPERGILLUS	Aspergillosis
102069	Letermovir	FUNGAL	ASPERGILLUS	Aspergillosis
100021	Letermovir	BACTERIAL	PROTEUS MIRABILIS	Pneumonia
101673	Letermovir	BACTERIAL	BACTERIA	Pneumonia
101765	Letermovir	BACTERIAL	ESCHERICHIA COLI	Pneumonia
101896	Letermovir	BACTERIAL	ENTEROCOCCUS FAECIUM	Pneumonia
102024	Letermovir	BACTERIAL	PSEUDOMONAS AERUGINOSA	Pneumonia
100048	Letermovir	BACTERIAL	ESCHERICHIA COLI	Sepsis
100055	Letermovir	BACTERIAL	ESCHERICHIA COLI	Sepsis
100055	Letermovir	BACTERIAL	PROTEUS MIRABILIS	Sepsis
100056	Letermovir	BACTERIAL	BACTERIA	Sepsis
101640	Letermovir	BACTERIAL	PSEUDOMONAS AERUGINOSA	Sepsis
101640	Letermovir	BACTERIAL	STAPHYLOCOCCUS HAEMOLYTICUS	Sepsis
101713	Letermovir	BACTERIAL	ENTEROCOCCUS FAECIUM	Sepsis
101713	Letermovir	BACTERIAL	ESCHERICHIA COLI	Sepsis
101966	Letermovir	BACTERIAL	STREPTOCOCCUS	Sepsis
102233	Letermovir	BACTERIAL	BACTERIA	Sepsis
100271	Placebo	FUNGAL	ASPERGILLUS FUMIGATUS	Aspergillosis
101621	Placebo	FUNGAL	ASPERGILLUS	Aspergillosis
101699	Placebo	FUNGAL	ASPERGILLUS FUMIGATUS	Aspergillosis

101714	Placebo	FUNGAL	ASPERGILLUS	Aspergillosis
101741	Placebo	FUNGAL	ASPERGILLUS	Aspergillosis
101963	Placebo	BACTERIAL	BACTERIA	Pneumonia
102003	Placebo	BACTERIAL	KLEBSIELLA PNEUMONIAE	Pneumonia
100019	Placebo	BACTERIAL	STAPHYLOCOCCUS	Sepsis
100151	Placebo	BACTERIAL	STREPTOCOCCUS VIRIDANS GROUP	Sepsis
101714	Placebo	BACTERIAL	STAPHYLOCOCCUS HAEMOLYTICUS	Sepsis
101834	Placebo	BACTERIAL	ESCHERICHIA COLI	Sepsis
101861	Placebo	BACTERIAL	CLOSTRIDIUM DIFFICILE	Sepsis
101861	Placebo	BACTERIAL	ESCHERICHIA COLI	Sepsis
101963	Placebo	BACTERIAL	STREPTOCOCCUS ALPHA-HEMOLYTIC	Sepsis
102137	Placebo	BACTERIAL	ENTEROCOCCUS FAECIUM	Sepsis

Source: June 23, 2017 Response to Information Request

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/s/

FRASER B SMITH
08/08/2017

THAMBAN I VALAPPIL
08/08/2017