CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209939Orig1s000
209940Orig1s000

OTHER REVIEW(S)

/PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA #	**209939/209940**
PMR/PMC Set (####-#)	**3295-1**
Product Name:	Letermovir
Applicant Name:	Merck Sharp & Dohme Corporation
ODE/Division:	**OAP/DAVP**

SECTION B: PMR/PMC Information

1. PMR Description

Conduct phenotypic analysis of letermovir against human cytomegalovirus (HCMV) mutants carrying the following pUL56 and pUL89 substitutions using bacterial artificial chromosome technology:

- pUL56: M3V, E237G, C325W, E485G, E485G + SNS445-447 deletion, S255L, Y575C, and R816W.
- pUL89: I531T

Include previously identified substitutions with a range of susceptibilities from low fold change (e.g. pUL56 L257I) to high fold change (e.g. pUL56 C325Y) as references.

2. PMR Schedule Milestones[2, 3]

Final Protocol Submission:	05 /2018
Study Completion:	10 /2019
Final Report Submission:	02/2020

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

There are limited clinical data with respect to the resistance pathways for letermovir. There were several amino acid substitutions that were identified in the virologic failures that are of unknown significance and need to be evaluated further. The virologic failures have serious risk of developing HCMV disease given that HCMV disease is driven by HCMV replication.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination

Other reason (describe in text box below)

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **<u>For FDAAA PMRs only</u>** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a <u>known serious risk</u> related to the use of the drug
- ☒ Assess a <u>signal of serious risk</u> related to the use of the drug
- ☐ Identify an <u>unexpected serious risk</u> when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☒ Other

FAERS data do not routinely include detailed genotypic or phenotypic resistance data.

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☒ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either "Yes" or "No" and provide the appropriate responses.]

☒ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

The phenotypic analyses need to be evaluated (b) (4) (b) (4). It will take several months to complete (b) (4) (b) (4).

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. <u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☒ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study

TYPE OF STUDY
☐ Registry-based observational study ☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*) ☐ Dose-response clinical trial ☐ Dosing trial (e.g., alternative dosing schedule) ☐ Drug interaction or bioavailability clinical trial (clinical only) ☐ Immunogenicity trial (clinical) ☐ Meta-analysis or pooled analysis of previous clinical trials ☐ Pharmacogenetic or pharmacogenomic clinical trial ☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial ☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints) ☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT* ☐ Safety outcomes trial (SOT)** ☐ Thorough Q-T clinical trial ☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8] Error! Reference source not found.

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to DARRTS electronic signature

/PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA #	**209939/209940**
PMR/PMC Set (####-#)	**3295-2**
Product Name:	Letermovir
Applicant Name:	Merck Sharp & Dohme Corporation
ODE/Division:	**OAP/DAVP**

SECTION B: PMR/PMC Information

1. PMC Description

Conduct a randomized, double-blind, placebo-controlled trial in cytomegalovirus (CMV) seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT) to evaluate the occurrence of late clinically significant CMV infection when letermovir prophylaxis is extended from 100 to 200 days.

2. PMC Schedule Milestones[2, 3]

Final Protocol Submission:	12/2018
Trial Completion:	12 /2023
Final Report Submission:	06 /2024

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

In Trial P001, there was an increased rate of clinically significant CMV infection following the discontinuation of letermovir at Day 100 post-transplant. Between Day 100 and Day 200, 32 (10%) letermovir subjects experienced late CMV reactivation compared to only 4 (2%) placebo subjects during this same period. Similarly, among solid organ transplant recipients, the rate of CMV infection is known to increase upon discontinuation of CMV prophylaxis (late CMV infection). In kidney transplant recipients, prolonging the duration of CMV prophylaxis with valganciclovir from 100 days to 200 days has been shown to reduce the rate of late CMV infection (Humar et al, Am J Transplant 2010). A longer duration of letermovir prophylaxis among HSCT recipients may also reduce the rate of late CMV infection.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☒ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☒ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe)

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☒ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8] Error! Reference source not found.

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to DARRTS electronic signature

/PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA #	**209939/209940**
PMR/PMC Set (####-#)	**3295-3**
Product Name:	Letermovir
Applicant Name:	Merck Sharp & Dohme Corporation
ODE/Division:	**OAP/DAVP**

SECTION B: PMR/PMC Information

1. PMC Description

Submit the final study report and datasets from the proposed clinical trial, P002, entitled, "A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients."

2. PMC Schedule Milestones[2, 3]

Final Protocol Submission:	04/2018
Trial Completion:	12/2022
Final Report Submission:	06/2023

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The safety and efficacy of letermovir for CMV prevention in hematopoietic stem cell transplant (HSCT) recipients was demonstrated in a randomized, placebo-controlled trial, P001. Solid organ transplant recipients, such as renal transplant recipients, are also at risk for CMV infection and disease post-transplantation. Ganciclovir and its prodrug, valganciclovir, are currently approved for CMV prophylaxis in solid organ transplant recipients. However, these drugs are associated with significant toxicity, most notably bone marrow toxicity. Therefore, determining if letermovir is a safe and effective option for CMV prevention among high risk renal transplant recipients is highly desirable as this would provide additional management options for patients. Further, it should be noted that there are many differences between HSCT and renal transplant recipients that prevent full extrapolation from Trial P001 to other transplant populations.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☒ Other reason (describe in text box below)

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

The trial proposed in this PMC will provide data in support of (b) (4) (b) (4) safety and efficacy (b) (4).

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

   a. **The purpose of the study/clinical trial is to:** ***[Select one, then go to Q.4.b]***

   - ☐ Assess a known serious risk related to the use of the drug
   - ☐ Assess a signal of serious risk related to the use of the drug
   - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

   b. **FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

   [Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

   - ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
   - ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
   - ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
   - ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **<u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?**
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☒ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☒ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☐ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

The Sponsor has already submitted a draft protocol for this PMC (Trial P002).

SECTION E: PMR/PMC Development Coordinator Statements[8] Error! Reference source not found.

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

---

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to DARRTS electronic signature

/PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA #	**209939/209940**
PMR/PMC Set (####-#)	**3295-4**
Product Name:	Letermovir
Applicant Name:	Merck Sharp & Dohme Corporation
ODE/Division:	**OAP/DAVP**

SECTION B: PMR/PMC Information

1. PMC Description

Conduct an in vitro study to determine if letermovir is an inducer of cytochrome P450 enzymes CYP2C8, CYP2C9, or CYP2C19.

2. PMC Schedule Milestones[2, 3]

Final Protocol Submission:	02/2018
Study Completion:	05/2018
Final Report Submission:	08/2018

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

In vitro, letermovir was found to induce CYP3A. Results from an in vitro study that evaluated whether letermovir is an inducer of CYP2C19 were inconclusive. It is recommended that induction of CYP2C8, CYP2C9, and CYP2C19 should be evaluated if induction of CYP3A is observed. In addition, it is suspected that letermovir is an inducer of CYP2C9 and/or CYP2C19 based on reduced voriconazole (CYP2C9 and CYP2C19 substrate) plasma concentrations when coadministered with letermovir in a drug interaction study. The results of this study will inform labeling recommendations for optimal use of letermovir with CYP2C8, CYP2C9, and CYP2C19 substrates.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial post approval and why the issue does not need to be addressed *prior to* approval.]

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** *[Select either "Yes" or "No" and provide the appropriate responses.]*

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☒ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

☐ *For non-PREA pediatric studies/trials only*: Pediatric population
☐ Geriatric population
☐ Lactating/nursing mothers
☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
☐ Orphan or rare disease population
☐ Pregnant women
☐ Racial/ethnic population
☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8] Error! Reference source not found.

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.
☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
☒ The applicant has adequately justified the choice of milestone dates.
☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to DARRTS electronic signature

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA L TYSON
11/08/2017

POONAM MISHRA
11/08/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 08, 2017
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 209939 & NDA 209940
Product Name and Strength:	Prevymis (letermovir), Tablets: 240 mg and 480 mg Injection: 20 mg/mL
Total Product Strength:	Injection: 240 mg/12 mL, 480 mg/24 mL
Applicant/Sponsor Name:	Merck Sharp & Dohme Corporation
Submission Date:	August 22, 2017 and November 7, 2017
OSE RCM #:	2017-480-1
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Antiviral Products requested that we review the revised Prescribing Information, Patient Information, container labels, and carton labeling for Prevymis (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations made during a previous label and labeling review[a] and a teleconference between Merck and the Agency, held on November 3, 2017, to discuss proposed revisions to the container label and carton labeling for Prevymis tablets[b].

2 CONCLUSION

The revised Prescribing Information, Patient Information, container labels, and carton labeling for Prevymis are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Wilson, V. Label and Labeling Review for Prevymis (NDA 209939 & NDA 209940). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 08. RCM No.: 2017-480.
[b] Tyson, V. Memorandum of Teleconference for Letermovir Tablets. Silver Spring (MD): FDA, CDER, OND, DAVP (US); 2017 NOV 08. NDA 209939.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S WILSON
11/09/2017

OTTO L TOWNSEND
11/09/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 6, 2016

To: Victoria Tyson, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for PREVYMIS™ (letermovir) tablets, for oral use, and PREVYMIS™ (letermovir) injection, for intravenous use

NDA/BLA: 209939 & 209940

In response to DAVP consult request dated March 14, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA/BLA submission for PREVYMIS™ (letermovir) tablets, for oral use, and PREVYMIS™ (letermovir) injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail and downloaded from link from DAVP (Victoria Tyson) on October 5, 2017. We have no comments at this time.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on October 6, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 22, 2017, and our comments are provided below within the individual labels.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721or wendy.lubarsky@fda.hhs.gov.

38 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WENDY R LUBARSKY
10/06/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 05, 2017
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name) Dosage Form and Route, Application Type/ Number	PREVYMIS (letermovir) tablets, for oral use NDA 209939 PREVYMIS (letermovir) injection, for intravenous use NDA 209940
Application:	Merck Sharp & Dohme Corporation

1 INTRODUCTION

On March 8, 2017, Merck Sharp & Dohme Corporation submitted for the Agency's review an original New Drug Application (NDA) 209939 for PREVYMIS (letermovir) tablets and NDA 209940 PREVYMIS (letermovir) injection, for intravenous use. The purpose of the submission is to seek approval for the use of PREVYMIS (letermovir) for the proposed indication of the prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on March 14, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for PREVYMIS (letermovir) tablets and PREVYMIS (letermovir) injection for intravenous use.

2 MATERIAL REVIEWED

- Draft PREVYMIS (letermovir) tablets and PREVYMIS (letermovir) injection PPI received on March 8, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 22, 2017.
- Draft PREVYMIS (letermovir) tablets and PREVYMIS (letermovir) Prescribing Information (PI) received on March 8, 2017 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 22, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAWNA L HUTCHINS
10/05/2017

WENDY R LUBARSKY
10/05/2017

BARBARA A FULLER
10/05/2017

LASHAWN M GRIFFITHS
10/05/2017

Clinical Inspection Summary

Date	August 11, 2017
From	Antoine El Hage, Ph.D. Susan Thompson, M.D. /Team Leader Kassa Ayalew, M.D., MPH / Branch Chief Division of Clinical Compliance Evaluation
To	Victoria Tyson, Regulatory Health Project Manager Aimee Hodowanec, Medical/Clinical Reviewer Mary Singer, M.D., Team Leader/ CTDL Division of Antiviral Products (DAVP)
NDA #	NDA 209939/209940
Applicant	Merck Sharp & Dohme Corp
Drug	Letermovir (MK-8228) tablets & IV
NME (Yes/No)	No
Therapeutic Classification	Priority
Proposed Indication(s)	(b) (4) clinically significant Human Cytomegalovirus (CMV) Infection in Adults, CMV-Seropositive Allogenic Hematopoietic Stem Cell Transplant Recipients.
Consultation Request Date	March 31, 2017
Summary Goal Date	July 31, 2017; extended to August 28, 2017
Action Goal Date	November 8, 2017
PDUFA Date	November 8, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Chemaly, Dadwal, Schmitt, Haider, and Maertens were inspected in support of the two NDAs. The pending classification of the first two domestic site inspections is No Action Indicated (NAI). The pending classification of the three foreign clinical site (Schmitt, Haider and Maertens) inspections is No Action Indicated (NAI). Data from these sites are acceptable for use in support of the pending application.

The final classification for the above five sites will be made at a later date after receiving and reviewing the EIRs provided by the field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

Based on the inspections of the five clinical sites, the study appears to have been conducted adequately and the inspectional findings support the validity and acceptability of the data as reported by the sponsor under the two NDAs.

II. BACKGROUND

Cytomegalovirus (CMV) is a significant complication after allogeneic hematopoietic stem cell transplant (HSCT). There is no oral anti-CMV drug approved for prophylaxis of CMV disease in HSCT subjects. Use of ganciclovir, valgancyclovir, and foscarnet are limited by their toxicity profiles, and renal and electrolyte abnormalities. Acyclovir and valgancyclovir are known to have limited efficacy against the CMV virus. In addition, there is an increasing emergence of resistance and cross-resistance to currently available antiviral agents. To date, no cross-resistance has been demonstrated between resistance to letermovir and resistance to ganciclovir, foscarnet, cidofovir, or acyclovir. Thus, there is a need for newer, efficacious agents with better tolerability and novel mechanisms of action for CMV prophylaxis in HSCT subjects.

Adults with receipt of allogeneic HSCT have a significant unmet medical need for CMV prevention since they are at higher risk of developing CMV-mediated sequelae. Therefore, there is a medical need for potent and well tolerated oral agents with greater efficacy, improved safety profile, and less viral resistance against CMV. New agents are needed for prophylactic treatment of HSCT to prevent CMV disease, since therapeutic options for HSCT subjects are currently limited. MK-8228 is the only available oral treatment offering the possibility of sustained off-treatment viral response, and to minimize the risk of long-term complications such as cirrhosis, gastrointestinal complications, and hepatocellular carcinoma (HCC). Since the efficacy of MK-8228 is superior to antiviral agents in adults with HSCT, this study was designed to demonstrate that prophylactic treatment with MK-8228 is effective in the prophylaxis of adults with HSCT conditions. The Applicant is seeking the indication of prophylactic treatment of CMV infection of adults post HSCT recipient.

Letermovir (MK-8228) belongs to a new class of anti-CMV agents with a novel mechanism of action, and has demonstrated potent, selective, and reversible inhibition of CMV activity in preclinical studies and efficacy against the virus *in vivo,* according to the sponsor. It inhibits the viral terminase complex, an enzyme that plays an important role in cleavage of viral deoxyribonucleic acid (DNA) into unit length genome and packaging of genome virus DNA into provirions.

Allogenic Hematopoietic Stem Cell Transplant (HSCT) subjects received MK-8228 orally once weekly for 24 weeks with dosing based on subjects receiving concomitant cyclosporine (CsA) or not. Letermovir was given 480 mg or 240 mg QD concomitantly with CsA through Week 14 (approximately 100 days) post-transplant; the dose was the same for both oral and IV letermovir formulations.

The Study Protocol 001 for the prevention of clinically significant cytomegalovirus (CMV) infection in adults was submitted in support of the pending application. The two NDAs (209939 and 209940) are identical in design; the difference is oral vs. intravenous administration of letermovir.

Protocol entitled: "A Phase III, 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 Adults, CMV-Seropositive Allogeneic Hematopoietic Stem Cell Transplant Recipients".

Subjects: 570 subjects enrolled
Sites: 67 centers distributed among 20 countries, 23 in the U.S.

The primary objective of this study was to evaluate the efficacy of MK-8228 in the prevention of clinically significant CMV infection through Week 24 (6 months) post-transplant following administration of MK8228 or placebo.

This protocol was a randomized, placebo-controlled, multicenter, double-blind trial of MK-8228 in the prevention of clinically significant human cytomegalovirus (CMV) infection in adult, CMV-seropositive allogeneic hematopoietic stem cell transplant (HSCT) recipients. Clinically significant CMV infection is defined as the occurrence of either one of the following outcomes:

- Onset of CMV end-organ disease or
- Initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viremia (as measured by the central laboratory) and the clinical condition of the subject.

A total of 565 eligible HSCT recipients were randomized in a 2:1 ratio to receive MK-8228 or placebo (i.e., 373 and 192 subjects on MK-8228 and placebo, respectively,) at any time from the day of transplant until 28 days post- transplant. Both oral tablet and intravenous (IV) formulations of MK-8228 (and placebo) were available for study therapy. Subjects were stratified by study center and risk. The dose of letermovir was 480 mg once daily (QD) with a dose reduction to 240 mg QD if given concomitantly with cyclosporin A (CsA). According to the sponsor, no significant drug related safety concerns were identified.

The CDER review division selected these sites principally due to high patient accrual in the study, high rates of dropouts/protocol deviations, and high efficacy result when compared to the other sites.

Site Selection for Study Protocol Study P001

U.S. Sites:
Site #0116 had the second highest enrollment of all U.S. and international sites; this site recorded subject visits during holidays.
Site #004 had a relatively large number of subjects, and had a high number of protocol deviations with an efficacy rate reported for the letermovir and placebo arm of 75% and 66% respectively.

Foreign sites:
Site #0064 in Germany had a relatively large number of subjects, a 32% reported rate of protocol deviations with an efficacy rate reported for the letermovir and placebo arms of 77% and 50%, respectively.
Site #0108 in Belgium had the highest enrolling number of subjects with a high number of protocol deviations; this site was inspected twice, first in 2004 and the second in 2014, and both inspections were classified VAIs.
Site #0020 in Canada had a moderate number of subjects and relatively high efficacy in the letermovir arm compare to the placebo arm (67% vs. 14%). In addition, a high number of efficacy assessment-related protocol violations (37%) were reported from this site. This site has never been inspected before.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	**Protocol # and # of Subjects**	**Inspection Date**	**Final Classification**
Roy Chemaly, M.D. Houston, TX 77030 Site #0116	P001 Subject Enrolled 43	5/16-19/2017	Pending (preliminary classification NAI)
Sanjeet Dadwal, M.D. Duarte, CA 91010 Site #004	P001 Subjects Enrolled 19	7/31-8/8/2017	Pending (preliminary classification NAI)
Michael Schmitt, M.D. Medizin V, Germany Site #0064	P001 Subjects Enrolled 19	6/19-23/2017	Pending (preliminary classification (NAI)
Johan Maertens, M.D. Leuven, Belgium Site# 0108	P001 Subjects Enrolled 26	6/17-23/2017	Pending (preliminary classification (NAI)
Shariq Haider, M.D. Hamilton, Ontario Site# 020	P001 Subjects Enrolled 19	5/29-6/2/2017	Pending (preliminary classification NAI)

Key to Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional

letter has been sent to the inspected entity.

NOTE: Site inspections focused on 100% review of informed consent documents, IRB and ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents, including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

1. **Roy Chemaly, M.D./Site #116 / Study P001**
   Houston, TX 77030

There were 48 subjects screened, five subjects were reported as screen failures, and 43 subjects were enrolled in the study. Subject 047 was randomized in error due exclusionary criteria of elevated bilirubin; it was later verified that the subject's bilirubin values were not exclusionary according to laboratory results. Twenty seven subjects were discontinued after enrollment, and nine subjects (001, 004, 016, 017, 018, 022, 037, 038, and 012) died during the follow-up period. Twenty 22 subjects did not complete the study treatment period. Of these, 10 subjects discontinued study medication, and seven of these subjects discontinued due to adverse events and the reasons were documented. Six subjects (002, 007, 011, 025, 033, and 034) stopped study medication due to CMV and pre-emptive therapy (PET) initiation

Twenty one subjects completed the study. Of these, 3 subjects (04, 018, and 036) withdrew study medication to start a beneficial trial to prevent leukemia relapse, but continued in the study.

The medical records for 20 subjects were reviewed for informed consent and primary efficacy endpoints. Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse event reporting. The audit revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA 483 was issued to Dr. Chemaly.

The data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the acceptability of the data submitted in support of the application.

2. **Sanjeet S. Dadwal, M.D./ Site #004/Study P001**
   Duarte, CA 91010

There were 24 subjects screened, five subjects were reported as screen failures, 19 subjects enrolled in the study, four subjects discontinued/did not complete study treatment, two subjects died, and 14 subjects completed the study. The field investigator reported that the primary endpoints were verified at the site. No data

integrity issues were found and no safety concerns were noted.

The medical records for all subjects were reviewed. Record*s* were organized and legible. Medical records/source documents were compared to data listings for primary efficacy endpoint and adverse events reporting. No major deficiencies were observed and no Form FDA 483 was issued. The audit revealed adequate adherence to the regulations and investigational plan.

Overall, the data generated at Dr. Dadwal's site in support of clinical efficacy and safety is considered reliable and may be used in support of the pending application.

3. Michael Schmitt, M.D./ Site #0064/Study P001
Abteilung Innere Madizin, Germany V69120

There were 27 subjects screened, eight subjects were reported as screen failures, and 19 subjects were enrolled. There were nine withdrawals/discontinuations or early terminations and the reasons were documented. Subjects 102005 and 102103 discontinued due to lack of efficacy (placebo) both died. Subjects 102006, 102007, and 102010 discontinued due to adverse events including ulcer in the oral cavity, confusion, and allergic reaction respectively; Subject 101721 discontinued to noncompliance with study drug; Subjects 102102 and 102104withdrew consent, and Subject 102106 discontinued due to lack of efficacy (placebo). Ten subjects completed the study. The medical records for all subjects were reviewed for primary efficacy endpoint and informed consent.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted.

The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued. However, minor discrepancies were observed between the signature dates of the subject and clinical investigator and observed discrepancies between drug accountability log and IVRS records. In addition, missing original central laboratory results were observed in the subject case records. However, the laboratory results were provided and the primary efficacy endpoints were verified. The discrepancies noted were resolved during the inspection. The minor observations noted had no significant impact on the study results.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

4. Johan Maertens, M.D./ Site #0108/Study P001
Leuven, Belgium 3000

There were 29 subjects screened, three subjects were reported as screen failures, 26 subjects were randomized, and 13 subjects were discontinued after study enrollment with the reasons were documented. Four subjects were discontinued due to death/adverse events (graft vs host

disease), and 10 subjects were discontinued due to lack of efficacy. Thirteen (13) subjects completed the study. The medical records for all subjects were reviewed.

The site was very organized and there was sufficient oversight of the staff by the clinical investigator. The medical records/source documents were compared to case report forms and data line listings and they were consistent. There was no o under-reporting of adverse events. The primary efficacy endpoints (laboratory results/CMV-DNA) were not available at the site and therefore, were not verified. The explanation provided during the inspection by the clinical investigator was that "the primary efficacy endpoints were centrally adjudicated and the study site was blinded and had no access to the primary efficacy results/data". This was discussed with the review division medical officer who understood the explanation provided by the clinical investigator. (However, the ORA investigator did not ask the site to request the central laboratory to provide the CMV-DNA/data during the inspection). The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations, issued.

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

5. **Shariq Haider, M.D./ Site #20/Study P001**
   Hamilton, Ontario

There were 20 subjects screened, one subject was reported as a screen failure, and 19 subjects were enrolled. Twelve (12) subjects discontinued study drug and the reasons were documented. Four subjects died and one additional subject (100028) died after completing the study. Three subjects were discontinued due to adverse events. Seven subjects completed the study. The medical records for 20 subjects were reviewed. No data integrity issues were found and no safety concerns were noted.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations, issued

The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Data from this site appear acceptable.

{See appended electronic signature page}

Antoine El Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Acting Branch Chief for
Kassa Ayalew, M.D, M.P.H, Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Enforcement
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA 209939/209940
DAVP /Division Director/Debra Birnkrant
DAVP /Medical Team Leader/Mary Singer
DAVP /Project Manager/Victoria Tyson
DAVP/Medical Officer/Aimee Hodowanec
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCPAB/Reviewer/Antoine El Hage
OSI/DCCE/GCP Program Analysts/Yolanda Patague/ Joseph Peacock
OSI/Database PM/Dana Walters

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTOINE N EL HAGE
08/14/2017

SUSAN D THOMPSON
08/14/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 4, 2017
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 209939 & NDA 209940
Product Name and Strength:	Prevymis (letermovir), Tablet: 240 mg, 480 mg Injection: 20 mg/mL
Total Product Strength:	Injection: 240 mg/12 mL, 480 mg/24 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck Sharp & Dohme Corporation
Submission Date:	March 8, 2017, April 6, 2017, and July 17, 2017
OSE RCM #:	2017-480
DMEPA Primary Reviewer:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

On March 8, 2017, Merck submitted new drug applications (NDA) 209939 and NDA 209940 for new molecular entity, letermovir. The Division of Antiviral Products requested we evaluate the prescribing information, patient information, container labels, and carton labeling to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Letermovir is a new molecular entity indicated for prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We evaluated the prescribing information (PI), patient information (PPI), container labels, and carton labeling to determine if they are acceptable from a medication error perspective and we discuss our findings in sections 3.1 and 3.2.

3.1 PRESCRIBING INFORMATION

Letermovir will be supplied in two strengths, 240 mg and 480 mg, in cartons of 14 and 28 tablets, as well as, single-dose vials containing 240 mg/12 mL and 480 mg/24 mL for administration through intravenous (IV) infusion over 1 hour. Prior to IV administration, the contents of the single-dose vials require further dilution in 250 mL of diluent. The recommended dose of letermovir will be 480 mg once daily, with dose adjustment down to 240 mg once daily when co-administered with cyclosporine. The prescribing information for the tablet and injection formulations will be included in one prescribing information (PI). We identified the following deficiencies to be addressed:

1. "Prevymis" has been found conditionally acceptable as the proprietary name for this product, as such; the PI should be updated to reflect Prevymis in place of the placeholder "TRADEMARK" throughout the PI.
2. The duration of infusion in the HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) states to administer letermovir injection "over 1 hour" while it is stated in section 2.1 of the Full Prescribing Information (FPI) (b) (4) which could lead to confusion or misinterpretation (b) (4). We recommend the language be revised for consistency in both sections and avoidance of the use of "approximately."
3. We note section 2.1 includes the statement (b) (4) (b) (4) (b) (4) We defer to DAVP to determine the acceptability of the (b) (4) (b) (4) (b) (4) statement.
4. Sections 2.4 and 2.5 of the FPI may cause confusion when determining if a dose adjustment is needed in renal impairment. (b) (4) (b) (4) (b) (4) We defer to DAVP (b) (4) (b) (4) If not, we recommend adding the statement "Prevymis is not recommended in patients with moderate or severe renal impairment combined with moderate hepatic impairment" to section 2.4 so this important information is not missed.
5. Consideration should be given to include the definition of moderate or severe renal impairment (e.g. CrCl less than XX mL/min) under section 2.5.
6. Under the subheading (b) (4) in section 2.7, the statement (b) (4) (b) (4) should be revised to be affirmative by stating "Do not use any IV bags or infusion set materials not listed below."
7. The HOW SUPPLIED/STORAGE AND HANDLING section states that a (b) (4) blister card" will be marketed, however, the use of "unit-dose" in place of (b) (4) provides a better description of the package type.

3.2 PATIENT INFORMATION (PPI)

1. We note inconsistency within the PPI regarding the storage recommendations for letermovir injection (b) (4) that does not align with section 16 of the PI, which states to "store [letermovir injection] in original carton to protect from exposure to light" (b) (4).
2. We note room temperature is not defined (e.g. XX°F to XX°F) under the "How should I (b) (4) TRADEMARK?" section.

3.3 CONTAINER LABELS AND CARTON LABELING

Among the tablet and injection formulations, there will be total of 6 carton presentations (Appendix G). Differences in color schemes or design graphics used for each carton presentation make them easily differentiable from one another, reducing the likelihood of selection errors between the 6 cartons.

The NDC between the 240 mg tablet, 480 mg tablet, 240 mg injection, and 480 mg injection are all different. Additionally, the product code within each NDC is enlarged, providing an additional visual aid for differentiating the different strengths and dosage forms.

The tablet formulation will be supplied in 14-count and 28-count cartons with the 14-count carton intended for use in healthcare settings and the 28-count carton is intended for dispensing for home use. The 14-count cartons bear the statements "this is a bulk package and not intended for dispensing" and "this package is not child resistant," which may help mitigate dispensing errors between the 14-count and 28-count cartons and we find this acceptable.

The quantity count and packaging for the tablets and injections supports the once-daily dosing regimen for letermovir.

We identified the following concern pertaining to the storage recommendations for the 28-count tablet cartons:

1. We note the inclusion of the statement (b) (4) listed on the 28-count tablet cartons. Perception (b) (4) varies from person to person and we are concerned this statement could lead to incorrect storage techniques. We recognize the 28-count carton labeling language is directed towards patients and that storage recommendations should align between labeling. We defer to the Patient Labeling Team (PLT) and Office of Pharmaceutical Quality (OPQ) to determine the appropriate language to use on the carton to inform patients of the storage recommendations.

We identified the following deficiencies to be addressed and provide recommendations to the Applicant in letter-ready format in section 4.2:

1. "Prevymis" has been conditionally approved as the proprietary name for this product, as such; the container labels and carton labeling should be updated to reflect Prevymis in place of the placeholder "TRADEMARK."
2. The perforated blister cards contained in the 14-count tablet cartons (b) (4) we recommend consideration be given to include the lot number and expiration date on each blister cell

so this information remains available to the end user up to the point at which the last dose is removed.[a]

4 CONCLUSION & RECOMMENDATIONS

Our evaluation identified areas within the full prescribing information, container labels, and carton labeling that can be improved. We provide recommendations to the Division and considerations for the Patient Labeling Team and Office of Pharmaceutical Products in section 4.1. Additionally, we provide recommendations to Merck in letter-ready format in section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

1. Prevymis has been found conditionally acceptable in a separate proprietary name review, as such; all labeling should be revised to reflect the name Prevymis in place of the placeholder "Trademark."
2. We recommend the duration of infusion in the DOSAGE AND ADMINISTRATION section be revised to state "over 1 hour" and avoidance of the use of (b) (4)
3. We defer to DAVP to determine the acceptability of the (b) (4) tablet and injection formulations. (b) (4) (b) (4)
4. We defer to DAVP to determine if moderate or severe renal impairment alone constitutes a dose adjustment. If not, then we recommend adding "Prevymis is not recommended for patients with moderate or severe renal impairment combined with moderate hepatic impairment" to section (b) (4) (Renal Impairment).
5. We recommend moderate or severe renal impairment be defined (e.g. CrCl less than 50 mL/min) in the DOSAGE AND ADMINISTRATION section of the FPI, where appropriate.
6. Under section 2.7, we recommend revising the statement (b) (4) (b) (4) to read as "Do not use any IV bags or infusion set materials not listed below."
7. We recommend revising (b) (4) 7-count blister card" under the HOW SUPPLIED/STORAGE AND HANDLING section of the FPI to read as "7-count unit-dose blister card" for clarity.

Patient Information

Inconsistent storage recommendations between labeling (i.e. (b) (4) exposure to light, lack of defined room temperature) could lead to incorrect storage of letermovir. We defer to the Patient Labeling Team to determine acceptability of the language used in the patient information (PPI) describing storage recommendations for letermovir.

[a] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Carton Labeling

1. The inclusion of the statement [redacted] could lead to incorrect storage techniques. However, we defer to the Patient Labeling Team and Office of Pharmaceutical Quality to determine the appropriate language to use on the carton to inform patients of storage recommendations.

4.2 RECOMMENDATIONS FOR MERCK

We recommend the following be implemented prior to approval of this NDA:

1. Replace "Tradename" on all container labels and carton labeling with the conditionally acceptable name "Prevymis."
2. The [redacted] blister cards contained in the 14-count tablet cartons [redacted] we recommend including the lot number and expiration date on each blister cell so this information remains available to the end user up to the point at which the last dose is removed.[b]

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Prevymis that Merck submitted on March 8, 2017.

Table 2. Relevant Product Information for Prevymis	
Initial Approval Date	N/A
Active Ingredient	letermovir
Indication	Prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).
Route of Administration	Oral Intravenous
Dosage Form	Tablet Injection
Strength	Tablet: 240 mg, 480 mg Injection: 240 mg/12 mL, 480 mg/24mL
Dose and Frequency	480 mg once daily
How Supplied	<u>Tablet</u> Supplied in cartons containing four (4) child- resistant Dosepaks®, each containing a 7-count blister card for a total of 28 tablets or into a carton containing two (2) (b) (4) 7-count blister cards for a total of 14 tablets <u>Injection</u> Supplied as a sterile, clear solution injection for intravenous use, in single-dose 30 mL vials of 240 mg (12 mL per vial) or 480 mg (24 mL per vial)
Storage	<u>Tablet</u> Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] <u>Injection</u> Store at 20°C to 25°C (68°F to 77°F); (b) (4) excursions permitted between 15°C to 30°C (59°F to 86°F). Store in the original carton to protect from exposure to light.
Container Closure	The tablets are packed in aluminum foil blister and lidding. For trade packages, the primary blister card is packaged inside a carton to provide additional child resistance.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 3, 2017, we searched the L:drive and AIMS using the terms, letermovir to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[c], and we confirmed that our previous recommendations were implemented or considered.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[c] Calderon, M. Proprietary Name Review for Prevymis (letermovir) IND 118361 and IND 104706. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 10. Panorama No.: 2016-9486176 and 2016-9317137.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VALERIE S WILSON
08/04/2017

OTTO L TOWNSEND
08/05/2017

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

DCRP Consult NDA 209939-209940

DATE: Date of Document: 3/8/2017
Date of Consult: 5/8/2017
Desired Completion Date: 6/9/2017
Date of Completion: 6/9/2017

FROM: Preston M. Dunnmon, M.D., M.B.A., Medical Officer
Division of Cardiovascular and Renal Products, HFD-110

THROUGH: Shari L. Targum, M.D., M.P.H., Medical Team Leader
Division of Cardiovascular and Renal Products, HFD-110

Norman Stockbridge, M.D., Ph.D., Division Director
Division of Cardiovascular and Renal Products, HFD-110

TO: Victoria Tyson, Consumer Safety Officer
OMPT/CDER/OND/OAP/DAVP
Aimee Hodowanec, Medical Officer
OMPT/CDER/OND/OAP/DAVP

DRUG NAME: Letermovir (MK-8228)

FORMULATION: Oral (NDA 209939) and IV (NDA 209940)

DOSAGE: 480 mg administered once daily orally (tablet) or as an intravenous (IV) infusion over 1 hour through 100 days post-transplant (240 mg once daily if administered with cyclosporine)

SPONSOR: Merck Sharp & Dohme Corporation

MECHANISM OF ACTION: Letermovir inhibits the CMV DNA terminase complex, which is required for viral DNA replication. Biochemical characterization and electron microscopy demonstrated that letermovir affects the formation of proper unit length genomes and interferes with virion maturation.

INVESTIGATIONAL INDICATION: For Prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)

DOCUMENTS REVIEWED:

- DAVP consult request (3/8/2017)
- Sponsor-proposed label (3/9/2017)
- Trial P001V01 Clinical Study Report
- Trial P001V01 Statistical Analysis Plan
- Trial P001V01 Clinical Adjudication Committee Charter
- NDA 209939 Clinical Summary
- MK-8228 (Letermovir) Week 48 Mortality Statistical Report

BACKGROUND AND CONSULT QUESTIONS:

Letermovir is a CMV viral terminase inhibitor. NDAs 209939 and 209940 (oral and intravenous letermovir, respectively) are currently under priority review for the proposed indication of CMV (b) (4) in hematopoietic stem cell transplant (HSCT) recipients. In the single Phase 3 trial for this application (Trial P001), there was an imbalance in the number of subjects experiencing treatment-emergent cardiac events between the letermovir and placebo arms (12.6% and 6.3%, respectively). The Applicant has submitted a cardiac safety assessment (see Appendix 16.1.11.1 in the P001v01 study report body under folder 5.3.5.1). The Applicant concluded that there is no evidence for a causal association between the administration of letermovir and cardiac events.

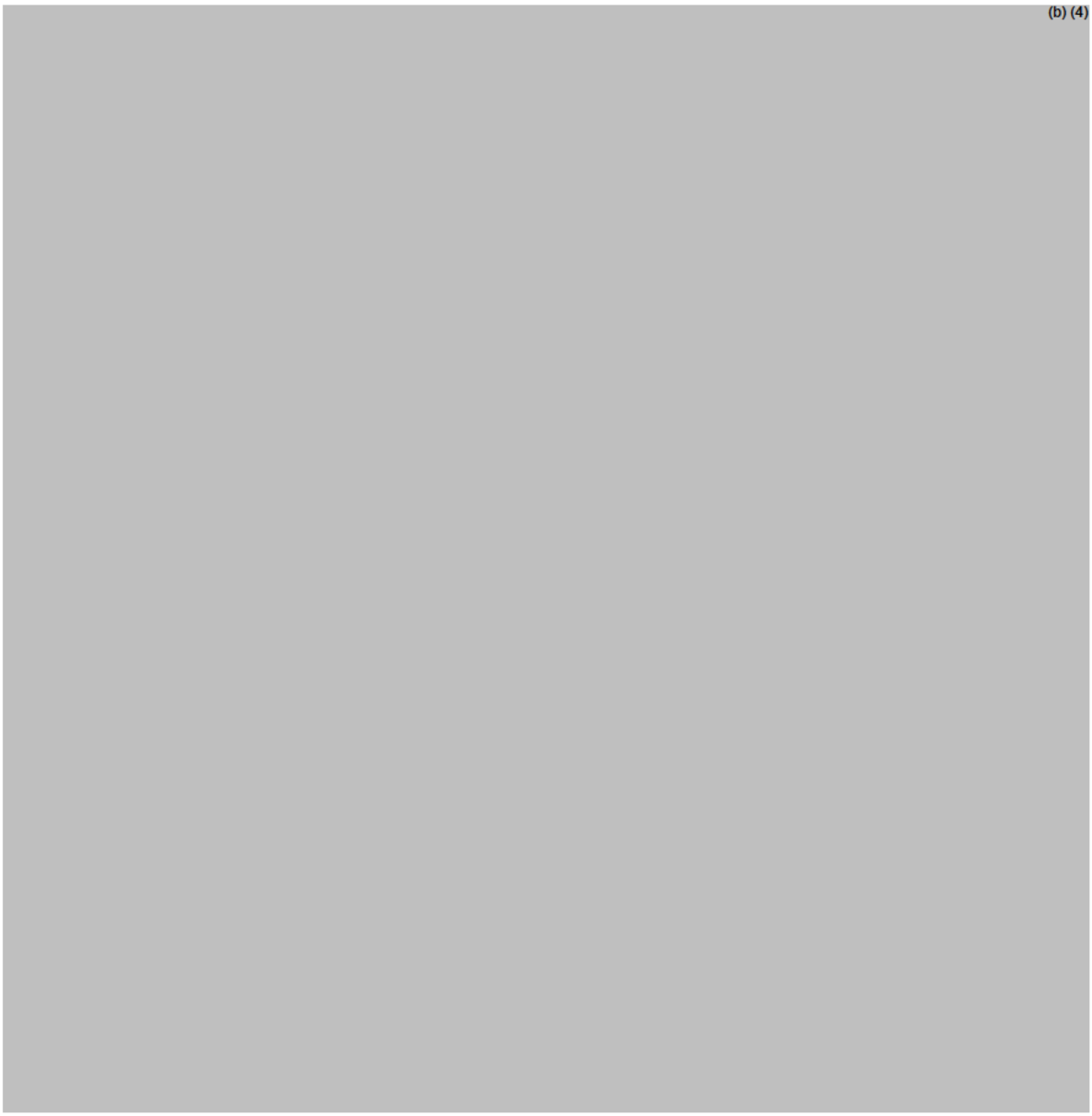
There was no apparent cardiac signal in the Phase 1 or 2 clinical programs. In the nonclinical program, no adverse cardiac findings were noted in the cardiovascular safety pharmacology studies in Beagles or in general toxicology studies of up to 26 weeks duration in rats. However, the following cardiac effects were noted in general toxicology studies in cynomolgus monkeys: minimal to mild myofiber degeneration and vacuolization in the heart in a high-dose animal, mild subepicardial myofiber necrosis and neutrophilia at the junction of the left and right ventricles in several high-dose animals with renal toxicity, and PVCs in one monkey (see attached nonclinical summary for additional details). None of these events were considered truly adverse by the nonclinical reviewer.

DAVP's preliminary review of the data from Trial P001 confirms the imbalance between the arms and identifies tachyarrhythmias and heart failure events as the most common cardiac AEs. The frequent use of cardiotoxic antineoplastic agents by study subjects and an imbalance in baseline cardiac history (higher rate in the letermovir arm) have been identified as factors that may be contributing to the cardiac adverse events. DVAP requests DCRP's assistance in further investigating this potential cardiac signal, with DCRP's input on the following questions:

1. Is the rate and type of cardiac AEs observed in the letermovir arm potentially consistent with the background rate of cardiac events among HSCT recipients (despite the imbalance in letermovir and placebo arms) or do you think this could be a chance finding?

2. Besides tachyarrhythmias and heart failure, are any other notable cardiac events or groupings of cardiac events identified in this study?
3. Although there is a clear imbalance of cardiac events between arms, most were not assessed by the investigator to be drug-related. Based on your review, do you believe that labeling of some of these cardiac events is warranted? If so, should labeling include a general statement pertaining to an increased risk of all cardiac events? Or should a specific type of cardiac event be highlighted?
4. Are there any nonclinical studies or clinical trials that you would recommend to help further explore the potential cardiotoxicity of letermovir?

CLINICAL PHARMACOLOGY (sponsor label):



    - Concomitant administration of TRADEMARK may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, leading to QT prolongation and Torsade de Pointes
    - Concomitant administration of TRADEMARK may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism
- Potentially significant drug interactions:

Concomitant Drug Class and/or Clearance Pathway: Drug Name	Effect on Concentration†	Clinical Comment
Antifungals		
voriconazole‡	↓ voriconazole	(b) (4) (b) (4) If concomitant administration is necessary, close monitoring for reduced effectiveness of voriconazole is recommended§.
HMG-CoA Reductase Inhibitors		
atorvastatin‡	↑ atorvastatin	(b) (4)
(b) (4) fluvastatin, rosuvastatin, (b) (4)	↑ (b) (4) (b) (4) HMG-CoA reductase inhibitors	
Immunosuppressants		
cyclosporine‡	↑ cyclosporine ↑ letermovir	(b) (4) Frequent monitoring of cyclosporine whole blood concentrations should be performed during and at

		discontinuation of TRADEMARK and the dose of cyclosporine adjusted accordingly[§].
sirolimus[‡]	↑ sirolimus	(b) (4) (b) (4) Frequent monitoring of sirolimus whole blood concentrations should be performed during and at discontinuation of TRADEMARK and the dose of sirolimus adjusted accordingly[§].
tacrolimus[‡]	↑ tacrolimus	(b) (4) Frequent monitoring of tacrolimus whole blood concentrations should be performed during and at discontinuation of TRADEMARK and the dose of tacrolimus adjusted accordingly[§].
(b) (4)		
CYP3A Substrates (b)		
Examples: alfentanil, fentanyl, quinidine	↑ (b) (4) (b) (4) CYP3A substrate	(b) (4)

* This table is not all inclusive.
† ↓ =decrease, ↑=increase
‡ These interactions have been studied *[see Clinical Pharmacology (12.3)]*.
§ Refer to the respective prescribing information

(b) (4)

TQT Study Results (Protocol 004-02): The effect of letermovir on doses up to 960 mg given IV on the QTc interval was evaluated in a randomized, single-dose, placebo- and active-controlled (moxifloxacin 400 mg oral) 4-period crossover thorough QT trial in 33 healthy subjects.156 Letermovir did not prolong QTc to any clinically relevant extent following the 960 mg IV dose with plasma concentrations approximately 2-fold higher than the 480 mg IV dose. There were no clinically relevant effects on RP and QRS intervals in healthy subjects.

ANIMAL TOXICOLOGY:

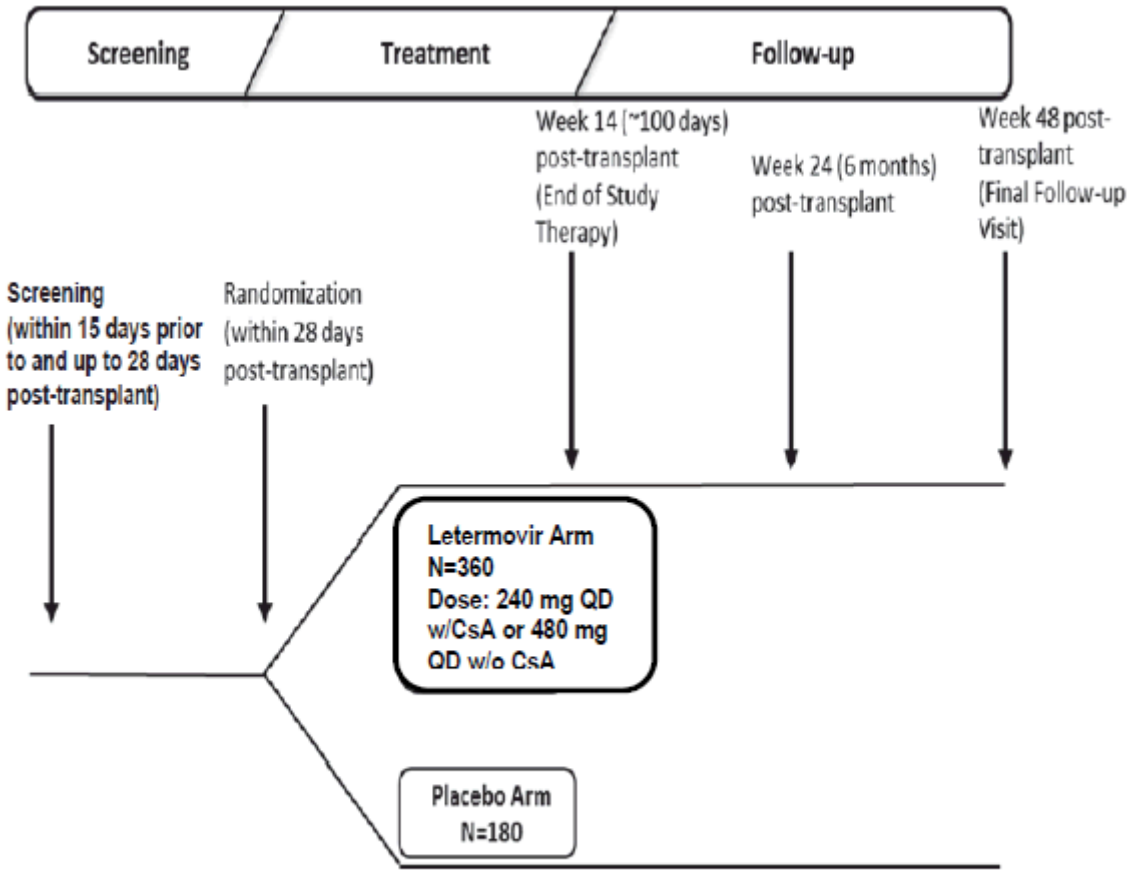
See pharm-tox review for this NDA.

PHASE 3 CLINICAL TRIAL P001: A Phase III 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 (HSCT) Recipients

The efficacy of letermovir was assessed in a multicenter, double-blind, placebo-controlled Phase 3 trial (P001) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. 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).

Subjects were randomized (2:1) to receive either letermovir at a dose of 480 mg once daily adjusted to 240 mg when coadministered with cyclosporine, or placebo. Study drug was initiated after HSCT (Day 0-28 post-transplant) and continued through Week 14 post-transplant. Study drug was administered either orally or IV; the dose was the same regardless of the route of administration. Among the 565 treated subjects, 373 subjects received letermovir (including 99 subjects who received at least one IV dose) and 192 received placebo (including 48 subjects who received at least one IV dose). The median age was 54 years (range: 18 to 78 years). At baseline, 50% of subjects received a myeloablative regimen, 52% were receiving cyclosporine, and 42% were receiving tacrolimus.280 The most common primary reasons for transplant were acute myeloid leukemia (38%), myeloblastic syndrome (15%), and lymphoma (13%). 31% of subjects were at high risk for reactivation as defined by one or more of the following criteria: 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; Grade 2 or greater Graft-Versus-Host Disease (GVHD), requiring systemic corticosteroids.

P001 Study Schematic



N = planned enrollment

P001 Efficacy

Once randomized, subjects were monitored for CMV viremia at weekly intervals during the first 14 weeks post-transplant. CMV viremia was monitored less frequently thereafter at biweekly intervals through Week 24. Plasma samples were collected for monitoring CMV viremia using CMV DNA polymerase chain reaction testing by the central laboratory. 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 pre-emptive therapy (PET) in all instances at this visit. The 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.

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.

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 of 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 one of the following anti-CMV agents when active CMV viral replication was documented: ganciclovir, valganciclovir, foscarnet, and/or cidofovir.

Efficacy was demonstrated in this trial according to the following table:

Table 6: P001 Efficacy Results in HSCT Recipients (NC=F Approach, FAS Population)[280]

Parameter	Letermovir (N=325) n (%)	Placebo (N=170) n (%)
Primary Endpoint	**122 (37.5)**	**103 (60.6)**
(Proportion of subjects who failed prophylaxis)		
Reasons for Failures*		
Clinically significant CMV infection by Week 24†	57 (17.5)	71 (41.8)
Initiation of PET based on documented CMV viremia	52 (16.0)	68 (40.0)
CMV end-organ disease	5 (1.5)	3 (1.8)
Discontinued from study before Week 24	56 (17.2)	27 (15.9)
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)
Stratum-adjusted treatment difference (Letermovir-Placebo)‡		
Difference (95% CI)	-23.5 (-32.5, -14.6)	
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 1-sided p-value ≤0.0249 was used for declaring statistical significance.
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.
N = number of subjects in each treatment group.
n (%) = Number (percent) of subjects in each sub-category.

P001 Demographics:

Imbalance in the distribution of medical history terms (by SOC) with a higher proportion of subjects in the letermovir group included the following (% letermovir vs. % placebo):

- Cardiac disorders (30.0% vs, 25.5%),
- Endocrine disorders (11.8% vs. 7.3%) and
- Infections and infestations (50.4% vs. 45.8%)

P001 Disposition of Subjects (all randomized, from the MK-8228 (Letermovir) Week 48 Mortality Statistical Report)

See Assessments section below.

P001 Safety

The All Subjects as Treated (ASaT) population was the primary population used for safety analyses in P001 and consisted of all randomized subjects who received at least one dose of study medication.

Per the sponsor, "the majority (n=554) of the subjects in both treatment groups received the oral formulation, with 367 receiving oral letermovir and 187 receiving oral placebo. The median duration of treatment with was longer with oral letermovir (78 days, range 1 to 109 days) compared to oral placebo (54 days, range 1 to 112 days). A total of 99 subjects (27%) received IV letermovir while 367 (98%) received oral letermovir. The extent of exposure to IV letermovir was similar to IV placebo."

> *Reviewer comment: The sum of the percentages of those receiving oral letermovir (98%) and those receiving IV letermovir (27%) = 125% because some subjects received both formulations during the course of therapy. The number of subjects exposed to one dose of letermovir during this study is therefore (367+99)/1.25=373, which equals the number of subjects in the "All Subjects as Treated" (ASaT) dataset. There were 192 subjects in the Placebo ASaT analysis set).*

Safety was assessed by the accumulated clinical and laboratory adverse events (AEs) (including infusion-site AEs, electrocardiogram (ECG) and vital sign measurements, physical exam, subjects' symptoms/findings, and safety laboratory values). After randomization and initiation of study therapy, AE monitoring included the collection of all AEs through Week 16 post-transplant in all subjects, including those subjects who had discontinued study therapy but continued to be followed-up in the study. Thereafter, only drug-related serious adverse events (SAEs) and SAEs leading to death were collected through Week 48 post-transplant.

Safety during the conduct of P001 was overseen by an external Data Monitoring Committee (DMC).

The Clinical Adjudication Committee (CAC) was a blinded committee composed of Infectious Disease specialists who are experts in the diagnosis and treatment of CMV infection and disease as well as the medical aspects of clinical trials. Only the occurrence of CMV end organ disease was adjudicated. Neither cause-specific death nor non-fatal CV outcomes were adjudicated.

P001 Exposures and disposition of subjects to week 24

Within the ASaT population the mean duration of exposure to letermovir was 69.4 days, while the mean duration of exposure to placebo was 55.2 days. This difference in the duration of exposure between treatment groups may have been due to the larger number of treatment discontinuations in the placebo group due to higher incidence of clinically significant CMV infection than in the letermovir group.

- 17.5% of subjects experienced AEs with fatal outcome with 16.4% in the letermovir group and 19.8% in the placebo group through Week 24 post-transplant. The most frequently reported AEs with fatal outcomes were GVHD, recurrent acute myeloid leukemia, sepsis, and septic shock.
- An imbalance in the percentage of subjects with Cardiac Disorders SOC AEs was observed between the letermovir (n=51 [13.7%]) and placebo (n=19 [9.9%]) groups through Week 24 post-transplant.
- In subjects with a cardiac history, the frequency of Cardiac Disorders SOC AEs was higher in the letermovir group (21.4%) than in the placebo group (10.2%)
- use of one or more cardiotoxic antineoplastic agents for pre-HSCT conditioning is a confounding factor for the analysis of Cardiac Disorders SOC AEs
- Sponsor rationale for concluding there is no evidence for a causal association between the administration of letermovir and Cardiac Disorders SOC AEs:
    - Letermovir has no human target. There were no preclinical cardiac findings and no findings in Phase 1 thorough QT trial to indicate that letermovir prolongs the QT/QTc interval or has a proarrhythmic potential.
    - There were no clinically relevant changes in vital signs (including diastolic and systolic blood pressure measurements and heart rate) through Study Week 16 and at the last study assessment.
    - Mean value and changes from baseline in ECG parameters (including the PR, QRS, QT/ QTc intervals, and ventricular rate) from baseline to Study Week 2 and to End of Therapy (EOT) assessments were comparable between treatment groups.
    - There was no exposure dependency for Cardiac Disorders SOC AEs over the exposure range

P001 Adverse Events through week 24

Adverse events were assessed in three tiers as follows:

- Tier 1: Specific safety hypotheses. There were no hypotheses for specific safety parameters (i.e., no Tier-1 events)
- Tier 2: AEs that occurred in 4 or more subjects in any one treatment group and also included (1) at least one adverse event; (2) a drug-related adverse event; (3) a serious adverse event; (4) a serious and drug-related adverse event and (5) an adverse event leading to discontinuation. Tier 2 events were assessed via point estimates with 95% confidence intervals provided for between-group comparisons.
- Tier 3: Descriptive safety endpoints (Tier 3) included all other safety parameters not analyzed as a Tier 2 safety endpoint (AEs, laboratory assessments, vital signs, and ECGs). Only point estimates by treatment group are provided for Tier 3 safety parameters.

Overall adverse event summary through the 14 week treatment period (sponsor FSR):

Table 12-3

Adverse Event Summary
Treatment Phase
(ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		192		565	
with one or more adverse events	365	(97.9)	192	(100.0)	557	(98.6)
with no adverse event	8	(2.1)	0	(0.0)	8	(1.4)
with drug-related† adverse events	63	(16.9)	23	(12.0)	86	(15.2)
with non-serious adverse events	361	(96.8)	189	(98.4)	550	(97.3)
with serious adverse events	165	(44.2)	90	(46.9)	255	(45.1)
with serious drug-related adverse events	3	(0.8)	3	(1.6)	6	(1.1)
who died	38	(10.2)	17	(8.9)	55	(9.7)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an adverse event	72	(19.3)	98	(51.0)	170	(30.1)
discontinued due to a drug-related adverse event	18	(4.8)	7	(3.6)	25	(4.4)
discontinued due to a serious adverse event	35	(9.4)	27	(14.1)	62	(11.0)
discontinued due to a serious drug-related adverse event	3	(0.8)	3	(1.6)	6	(1.1)

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
n = Number of patients randomized and treated in each treatment group.
Note: Treatment phase is defined as the time of first dose through 14 days following the last dose of study treatment.
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.

Source: [P001V01: analysis-adsl] [P001V01: tabulations-aeplus]

Overall adverse event summary through 24 weeks post-transplant:

Table 12-5

Adverse Event Summary
Through 24 Weeks Post-transplant
(ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		192		565	
with one or more adverse events	366	(98.1)	192	(100.0)	558	(98.8)
with no adverse event	7	(1.9)	0	(0.0)	7	(1.2)
with drug-related[†] adverse events	63	(16.9)	23	(12.0)	86	(15.2)
with non-serious adverse events	364	(97.6)	190	(99.0)	554	(98.1)
with serious adverse events	193	(51.7)	109	(56.8)	302	(53.5)
with serious drug-related adverse events	3	(0.8)	3	(1.6)	6	(1.1)
who died	61	(16.4)	38	(19.8)	99	(17.5)
who died due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	72	(19.3)	98	(51.0)	170	(30.1)
discontinued due to a drug-related adverse event	18	(4.8)	7	(3.6)	25	(4.4)
discontinued due to a serious adverse event	35	(9.4)	27	(14.1)	62	(11.0)
discontinued due to a serious drug-related adverse event	3	(0.8)	3	(1.6)	6	(1.1)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.
n = Number of patients randomized and treated in each treatment group.
Note: All AEs are reported from the time of initiation of study treatment though Week 24 post-transplant, 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.

Source: [P001V01: analysis-adsl] [P001V01: tabulations-aeplus]

Reviewer Comment: by week 24, relatively fewer subjects in the active treatment arm had died due to an adverse event (i.e. a lower death rate among a larger absolute number of deaths in a 2.1 randomization scheme).

Tier 2 AEs during the treatment phase were as follows, with potentially cardio-relevant adverse events occurring in a higher frequency in the active treatment arm highlighted (sponsor FSR):

Table 12-8

Analysis of Subjects With Adverse Events
(Incidence ≥4 Subjects in One or More Treatment Groups)
Treatment Phase
(ASaT Population)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	373		192		
with one or more adverse events	365	(97.9)	192	(100.0)	-2.1 (-4.2, -0.2)
with no adverse events	8	(2.1)	0	(0.0)	2.1 (0.2, 4.2)
Blood and lymphatic system disorders	**98**	**(26.3)**	**51**	**(26.6)**	**-0.3 (-8.2, 7.2)**
Anaemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Eosinophilia	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Febrile neutropenia	31	(8.3)	18	(9.4)	-1.1 (-6.6, 3.6)
Leukopenia	11	(2.9)	7	(3.6)	-0.7 (-4.6, 2.2)
Neutropenia	14	(3.8)	7	(3.6)	0.1 (-3.9, 3.2)
Pancytopenia	7	(1.9)	6	(3.1)	-1.2 (-4.9, 1.3)
Thrombocytopenia	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Cardiac disorders	**47**	**(12.6)**	**12**	**(6.3)**	**6.4 (1.1, 11.0)**
Atrial fibrillation	13	(3.5)	2	(1.0)	2.4 (-0.5, 5.0)
Atrial flutter	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Cardiac failure	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Sinus tachycardia	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Tachycardia	15	(4.0)	4	(2.1)	1.9 (-1.5, 4.8)
Ear and labyrinth disorders	**17**	**(4.6)**	**2**	**(1.0)**	**3.5 (0.5, 6.3)**
Ear pain	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Vertigo	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Endocrine disorders	**6**	**(1.6)**	**0**	**(0.0)**	**1.6 (-0.4, 3.5)**
Eye disorders	**62**	**(16.6)**	**32**	**(16.7)**	**-0.0 (-6.9, 6.2)**
Blepharitis	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Conjunctival haemorrhage	7	(1.9)	0	(0.0)	1.9 (-0.1, 3.8)
Dry eye	22	(5.9)	10	(5.2)	0.7 (-3.9, 4.5)
Lacrimation increased	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Vision blurred	11	(2.9)	1	(0.5)	2.4 (-0.1, 4.8)
Gastrointestinal disorders	**261**	**(70.0)**	**129**	**(67.2)**	**2.8 (-5.1, 11.0)**
Abdominal discomfort	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Abdominal distension	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Abdominal pain	44	(11.8)	18	(9.4)	2.4 (-3.3, 7.5)
Abdominal pain upper	15	(4.0)	16	(8.3)	-4.3 (-9.4, -0.3)
Angina bullosa haemorrhagica	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Aphthous ulcer	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Constipation	27	(7.2)	20	(10.4)	-3.2 (-8.8, 1.5)
Diarrhoea	97	(26.0)	47	(24.5)	1.5 (-6.3, 8.8)
Dry mouth	20	(5.4)	6	(3.1)	2.2 (-1.7, 5.6)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[†]
Gastrointestinal disorders	**261**	**(70.0)**	**129**	**(67.2)**	**2.8 (-5.1, 11.0)**
Dyspepsia	20	(5.4)	7	(3.6)	1.7 (-2.4, 5.1)
Dysphagia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Flatulence	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Gastritis	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Gastrooesophageal reflux disease	4	(1.1)	9	(4.7)	-3.6 (-7.7, -1.0)
Haematochezia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Haemorrhoids	18	(4.8)	4	(2.1)	2.7 (-0.8, 5.8)
Nausea	99	(26.5)	45	(23.4)	3.1 (-4.6, 10.3)
Proctalgia	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Stomatitis	23	(6.2)	9	(4.7)	1.5 (-3.0, 5.2)
Tongue coated	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Toothache	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Vomiting	69	(18.5)	26	(13.5)	5.0 (-1.7, 11.0)
General disorders and administration site conditions	**211**	**(56.6)**	**100**	**(52.1)**	**4.5 (-4.2, 13.1)**
Asthenia	23	(6.2)	7	(3.6)	2.5 (-1.6, 6.1)
Chest pain	16	(4.3)	5	(2.6)	1.7 (-2.0, 4.7)
Chills	14	(3.8)	4	(2.1)	1.7 (-1.8, 4.5)
Face oedema	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Fatigue	50	(13.4)	21	(10.9)	2.5 (-3.6, 7.8)
Malaise	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Mucosal inflammation	46	(12.3)	24	(12.5)	-0.2 (-6.4, 5.3)
Oedema	12	(3.2)	2	(1.0)	2.2 (-0.7, 4.7)
Oedema peripheral	54	(14.5)	18	(9.4)	5.1 (-0.8, 10.4)
Pain	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Peripheral swelling	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Pyrexia	77	(20.6)	43	(22.4)	-1.8 (-9.2, 5.2)
Hepatobiliary disorders	**22**	**(5.9)**	**15**	**(7.8)**	**-1.9 (-7.0, 2.3)**
Hepatic function abnormal	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Hyperbilirubinaemia	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Immune system disorders	**153**	**(41.0)**	**80**	**(41.7)**	**-0.6 (-9.3, 7.8)**
Drug hypersensitivity	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Graft versus host disease	146	(39.1)	74	(38.5)	0.6 (-8.0, 8.9)
Hypogammaglobulinaemia	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Infections and infestations	**241**	**(64.6)**	**139**	**(72.4)**	**-7.8 (-15.5, 0.4)**
Bacteraemia	20	(5.4)	4	(2.1)	3.3 (-0.3, 6.4)
Bronchopulmonary aspergillosis	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Candida infection	11	(2.9)	4	(2.1)	0.9 (-2.5, 3.5)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)*
Infections and infestations	**241**	**(64.6)**	**139**	**(72.4)**	**-7.8 (-15.5, 0.4)**
Clostridium difficile colitis	9	(2.4)	4	(2.1)	0.3 (-3.0, 2.8)
Conjunctivitis	6	(1.6)	1	(0.5)	1.1 (-1.4, 3.0)
Cystitis	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Cytomegalovirus infection	31	(8.3)	88	(45.8)	-37.5 (-45.1, -30.0)
Device related infection	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Epstein-Barr virus infection	14	(3.8)	6	(3.1)	0.6 (-3.2, 3.6)
Folliculitis	13	(3.5)	4	(2.1)	1.4 (-2.0, 4.2)
Herpes zoster	6	(1.6)	0	(0.0)	1.6 (-0.4, 3.5)
Human herpesvirus 6 infection	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Nasopharyngitis	15	(4.0)	4	(2.1)	1.9 (-1.5, 4.8)
Oral candidiasis	12	(3.2)	2	(1.0)	2.2 (-0.7, 4.7)
Oral herpes	7	(1.9)	4	(2.1)	-0.2 (-3.5, 2.1)
Pharyngitis	8	(2.1)	6	(3.1)	-1.0 (-4.7, 1.7)
Pneumonia	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Respiratory tract infection	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Rhinitis	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Rhinovirus infection	10	(2.7)	2	(1.0)	1.6 (-1.2, 4.0)
Sepsis	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Septic shock	4	(1.1)	5	(2.6)	-1.5 (-5.0, 0.6)
Sinusitis	7	(1.9)	2	(1.0)	0.8 (-2.0, 3.0)
Staphylococcal bacteraemia	10	(2.7)	6	(3.1)	-0.4 (-4.2, 2.3)
Upper respiratory tract infection	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Urinary tract infection	16	(4.3)	6	(3.1)	1.2 (-2.7, 4.3)
Urinary tract infection bacterial	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Viraemia	11	(2.9)	11	(5.7)	-2.8 (-7.2, 0.6)
Injury, poisoning and procedural complications	**42**	**(11.3)**	**27**	**(14.1)**	**-2.8 (-9.1, 2.8)**
Contusion	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Fall	3	(0.8)	4	(2.1)	-1.3 (-4.5, 0.7)
Skin abrasion	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Investigations	**133**	**(35.7)**	**60**	**(31.3)**	**4.4 (-3.9, 12.4)**
Alanine aminotransferase increased	24	(6.4)	16	(8.3)	-1.9 (-7.1, 2.4)
Aspartate aminotransferase increased	19	(5.1)	13	(6.8)	-1.7 (-6.5, 2.2)
Blood albumin decreased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Blood alkaline phosphatase increased	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Blood bilirubin increased	9	(2.4)	5	(2.6)	-0.2 (-3.7, 2.4)
Blood creatinine increased	36	(9.7)	13	(6.8)	2.9 (-2.3, 7.4)
Blood glucose increased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Blood potassium increased	7	(1.9)	1	(0.5)	1.4 (-1.1, 3.4)
Blood testosterone decreased	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Investigations	**133**	**(35.7)**	**60**	**(31.3)**	**4.4 (-3.9, 12.4)**
Blood urea increased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
C-reactive protein increased	11	(2.9)	1	(0.5)	2.4 (-0.1, 4.8)
Carbon dioxide decreased	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Electrocardiogram QT prolonged	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Gamma-glutamyltransferase increased	3	(0.8)	4	(2.1)	-1.3 (-4.5, 0.7)
Haematocrit decreased	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Haemoglobin decreased	6	(1.6)	0	(0.0)	1.6 (-0.4, 3.5)
International normalised ratio increased	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Lymphocyte count decreased	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Neutrophil count decreased	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Platelet count decreased	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Weight decreased	15	(4.0)	7	(3.6)	0.4 (-3.6, 3.5)
Weight increased	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
White blood cell count decreased	8	(2.1)	2	(1.0)	1.1 (-1.7, 3.3)
Metabolism and nutrition disorders	**134**	**(35.9)**	**63**	**(32.8)**	**3.1 (-5.3, 11.2)**
Decreased appetite	38	(10.2)	22	(11.5)	-1.3 (-7.2, 3.9)
Dehydration	2	(0.5)	5	(2.6)	-2.1 (-5.5, -0.1)
Diabetes mellitus	6	(1.6)	5	(2.6)	-1.0 (-4.5, 1.4)
Fluid overload	9	(2.4)	2	(1.0)	1.4 (-1.5, 3.7)
Gout	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Hyperglycaemia	25	(6.7)	10	(5.2)	1.5 (-3.1, 5.4)
Hyperkalaemia	27	(7.2)	4	(2.1)	5.2 (1.4, 8.6)
Hypernatraemia	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Hypertriglyceridaemia	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Hyperuricaemia	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Hypoalbuminaemia	10	(2.7)	7	(3.6)	-1.0 (-4.9, 1.9)
Hypocalcaemia	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Hypokalaemia	22	(5.9)	11	(5.7)	0.2 (-4.5, 4.0)
Hypomagnesaemia	23	(6.2)	15	(7.8)	-1.6 (-6.8, 2.6)
Hyponatraemia	21	(5.6)	10	(5.2)	0.4 (-4.1, 4.1)
Hypophosphataemia	5	(1.3)	5	(2.6)	-1.3 (-4.7, 1.0)
Vitamin D deficiency	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Musculoskeletal and connective tissue disorders	**121**	**(32.4)**	**57**	**(29.7)**	**2.8 (-5.5, 10.6)**
Arthralgia	26	(7.0)	10	(5.2)	1.8 (-2.9, 5.7)
Back pain	23	(6.2)	14	(7.3)	-1.1 (-6.1, 3.0)
Bone pain	14	(3.8)	5	(2.6)	1.1 (-2.5, 4.1)
Muscle spasms	12	(3.2)	7	(3.6)	-0.4 (-4.4, 2.6)
Muscular weakness	6	(1.6)	3	(1.6)	0.0 (-3.0, 2.2)
Musculoskeletal chest pain	7	(1.9)	1	(0.5)	1.4 (-1.1, 3.4)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Musculoskeletal and connective tissue disorders	**121**	**(32.4)**	**57**	**(29.7)**	**2.8 (-5.5, 10.6)**
Musculoskeletal pain	15	(4.0)	3	(1.6)	2.5 (-0.8, 5.2)
Myalgia	19	(5.1)	3	(1.6)	3.5 (0.2, 6.5)
Myopathy	2	(0.5)	5	(2.6)	-2.1 (-5.5, -0.1)
Neck pain	6	(1.6)	3	(1.6)	0.0 (-3.0, 2.2)
Pain in extremity	19	(5.1)	11	(5.7)	-0.6 (-5.2, 3.1)
Tendonitis	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**39**	**(10.5)**	**17**	**(8.9)**	**1.6 (-4.0, 6.5)**
Acute myeloid leukaemia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Acute myeloid leukaemia recurrent	11	(2.9)	8	(4.2)	-1.2 (-5.3, 1.8)
Nervous system disorders	**137**	**(36.7)**	**64**	**(33.3)**	**3.4 (-5.0, 11.5)**
Dizziness	25	(6.7)	11	(5.7)	1.0 (-3.8, 4.9)
Dysgeusia	17	(4.6)	7	(3.6)	0.9 (-3.1, 4.2)
Headache	52	(13.9)	18	(9.4)	4.6 (-1.3, 9.8)
Hypoaesthesia	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Neuropathy peripheral	8	(2.1)	6	(3.1)	-1.0 (-4.7, 1.7)
Paraesthesia	7	(1.9)	3	(1.6)	0.3 (-2.8, 2.6)
Presyncope	1	(0.3)	4	(2.1)	-1.8 (-5.0, -0.2)
Tremor	27	(7.2)	8	(4.2)	3.1 (-1.3, 6.9)
Psychiatric disorders	**78**	**(20.9)**	**30**	**(15.6)**	**5.3 (-1.6, 11.6)**
Anxiety	20	(5.4)	5	(2.6)	2.8 (-1.0, 6.0)
Confusional state	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Delirium	4	(1.1)	4	(2.1)	-1.0 (-4.2, 1.0)
Depression	11	(2.9)	3	(1.6)	1.4 (-1.8, 3.9)
Insomnia	34	(9.1)	10	(5.2)	3.9 (-0.9, 8.1)
Mental status changes	5	(1.3)	4	(2.1)	-0.7 (-4.0, 1.4)
Renal and urinary disorders	**81**	**(21.7)**	**46**	**(24.0)**	**-2.2 (-9.8, 4.9)**
Acute kidney injury	36	(9.7)	25	(13.0)	-3.4 (-9.5, 1.9)
Cystitis haemorrhagic	4	(1.1)	6	(3.1)	-2.1 (-5.7, 0.2)
Dysuria	11	(2.9)	6	(3.1)	-0.2 (-3.9, 2.7)
Haematuria	11	(2.9)	5	(2.6)	0.3 (-3.2, 3.1)
Nocturia	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Pollakiuria	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Renal failure	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Renal impairment	4	(1.1)	3	(1.6)	-0.5 (-3.5, 1.5)
Urinary retention	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Reproductive system and breast disorders	**30**	**(8.0)**	**11**	**(5.7)**	**2.3 (-2.5, 6.4)**
Respiratory, thoracic and mediastinal disorders	**147**	**(39.4)**	**71**	**(37.0)**	**2.4 (-6.1, 10.7)**
Cough	53	(14.2)	20	(10.4)	3.8 (-2.2, 9.2)
Dyspnoea	30	(8.0)	6	(3.1)	4.9 (0.8, 8.6)
Dyspnoea exertional	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Epistaxis	23	(6.2)	11	(5.7)	0.4 (-4.3, 4.3)
Haemoptysis	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Hypoxia	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Nasal congestion	8	(2.1)	1	(0.5)	1.6 (-0.9, 3.7)
Oropharyngeal pain	28	(7.5)	15	(7.8)	-0.3 (-5.5, 4.1)
Pleural effusion	10	(2.7)	3	(1.6)	1.1 (-2.0, 3.6)
Productive cough	5	(1.3)	2	(1.0)	0.3 (-2.5, 2.2)
Pulmonary oedema	6	(1.6)	4	(2.1)	-0.5 (-3.8, 1.8)
Respiratory failure	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Rhinorrhoea	12	(3.2)	9	(4.7)	-1.5 (-5.7, 1.7)
Upper-airway cough syndrome	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Skin and subcutaneous tissue disorders	**179**	**(48.0)**	**80**	**(41.7)**	**6.3 (-2.4, 14.8)**
Dermatitis contact	4	(1.1)	0	(0.0)	1.1 (-0.9, 2.7)
Dry skin	26	(7.0)	8	(4.2)	2.8 (-1.6, 6.6)
Erythema	33	(8.8)	11	(5.7)	3.1 (-1.8, 7.4)
Night sweats	7	(1.9)	2	(1.0)	0.8 (-2.0, 3.0)
Petechiae	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)
Pruritus	26	(7.0)	11	(5.7)	1.2 (-3.5, 5.2)
Rash	76	(20.4)	41	(21.4)	-1.0 (-8.4, 5.9)
Rash erythematous	4	(1.1)	2	(1.0)	0.0 (-2.7, 1.9)
Rash maculo-papular	7	(1.9)	4	(2.1)	-0.2 (-3.5, 2.1)
Rash pruritic	8	(2.1)	2	(1.0)	1.1 (-1.7, 3.3)
Skin exfoliation	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)
Skin hyperpigmentation	6	(1.6)	2	(1.0)	0.6 (-2.2, 2.6)
Skin lesion	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Swelling face	4	(1.1)	1	(0.5)	0.6 (-1.9, 2.3)
Vascular disorders	**69**	**(18.5)**	**40**	**(20.8)**	**-2.3 (-9.6, 4.4)**
Haematoma	5	(1.3)	1	(0.5)	0.8 (-1.6, 2.7)
Hypertension	31	(8.3)	21	(10.9)	-2.6 (-8.4, 2.3)
Hypotension	14	(3.8)	9	(4.7)	-0.9 (-5.2, 2.4)
Orthostatic hypotension	5	(1.3)	3	(1.6)	-0.2 (-3.3, 1.8)

	Letermovir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)†
Vascular disorders	**69**	**(18.5)**	**40**	**(20.8)**	**-2.3 (-9.6, 4.4)**
Venoocclusive disease	5	(1.3)	0	(0.0)	1.3 (-0.6, 3.1)

† Based on Miettinen & Nurminen method.

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Note: Treatment phase is defined as the time of first dose through 14 days following the last dose of study treatment

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.

Reviewer comment: It appears likely that tier 2 cardiac AEs are occurring more frequently in the letermovir arm (12.6% versus 6.3% respectively, with a lower 95% CI >1.0 for the difference). It is unclear why the conditions under the

Cardiac Disorders SoC header do not add up to the SoC total (it may be that the PT numbers are for conditions occurring in ≥ 4 subjects, but the header includes Tier 3 cases). The higher incidence of anemia adverse events in the letermovir arm could drive tachycardia. A higher thrombocytopenia rate is noted in the letermovir arm – all five venoocclusive events occurred on letermovir. Higher rates of CPR elevation are noted in the letermovir arm. Hyperkalemia appeared to be more frequent in the letermovir arm, as did cough/dyspnea. General trends in these adverse events were similar at 24 weeks.

AEs during IV dosing only

Table 14.3- 21

Subjects With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
During IV Dosing Only
(ASaT Population, Only Subjects Who Received IV Formulation)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	99		48		147	
with one or more adverse events	84	(84.8)	35	(72.9)	119	(81.0)
with no adverse events	15	(15.2)	13	(27.1)	28	(19.0)
Blood and lymphatic system disorders	**18**	**(18.2)**	**10**	**(20.8)**	**28**	**(19.0)**
Anaemia	3	(3.0)	2	(4.2)	5	(3.4)
Autoimmune haemolytic anaemia	1	(1.0)	0	(0.0)	1	(0.7)
Bone marrow failure	0	(0.0)	1	(2.1)	1	(0.7)
Disseminated intravascular coagulation	0	(0.0)	1	(2.1)	1	(0.7)
Febrile neutropenia	11	(11.1)	4	(8.3)	15	(10.2)
Haemolysis	0	(0.0)	1	(2.1)	1	(0.7)
Hyperfibrinogenaemia	0	(0.0)	1	(2.1)	1	(0.7)
Hypocoagulable state	1	(1.0)	0	(0.0)	1	(0.7)
Increased tendency to bruise	0	(0.0)	1	(2.1)	1	(0.7)
Leukopenia	1	(1.0)	1	(2.1)	2	(1.4)
Neutropenia	3	(3.0)	0	(0.0)	3	(2.0)
Pancytopenia	0	(0.0)	3	(6.3)	3	(2.0)
Thrombocytopenia	2	(2.0)	2	(4.2)	4	(2.7)
Cardiac disorders	**12**	**(12.1)**	**0**	**(0.0)**	**12**	**(8.2)**
Atrial fibrillation	2	(2.0)	0	(0.0)	2	(1.4)
Cardiac failure	1	(1.0)	0	(0.0)	1	(0.7)
Cardiac failure congestive	1	(1.0)	0	(0.0)	1	(0.7)
Myocarditis	1	(1.0)	0	(0.0)	1	(0.7)
Palpitations	2	(2.0)	0	(0.0)	2	(1.4)
Pericardial effusion	1	(1.0)	0	(0.0)	1	(0.7)
Sinus tachycardia	1	(1.0)	0	(0.0)	1	(0.7)
Tachycardia	3	(3.0)	0	(0.0)	3	(2.0)
Torsade de pointes	1	(1.0)	0	(0.0)	1	(0.7)
Ventricular tachycardia	1	(1.0)	0	(0.0)	1	(0.7)
Congenital, familial and genetic disorders	**1**	**(1.0)**	**0**	**(0.0)**	**1**	**(0.7)**
Factor XIII deficiency	1	(1.0)	0	(0.0)	1	(0.7)
Eye disorders	**6**	**(6.1)**	**3**	**(6.3)**	**9**	**(6.1)**
Blepharitis	1	(1.0)	1	(2.1)	2	(1.4)
Dry eye	0	(0.0)	1	(2.1)	1	(0.7)
Eye irritation	2	(2.0)	0	(0.0)	2	(1.4)

Subjects With Adverse Events
(Incidence > 0% in One or More Treatment Groups)
During IV Dosing Only
(ASaT Population, Only Subjects Who Received IV Formulation)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**19**	**(19.2)**	**9**	**(18.8)**	**28**	**(19.0)**
Pneumothorax	1	(1.0)	0	(0.0)	1	(0.7)
Productive cough	1	(1.0)	0	(0.0)	1	(0.7)
Pulmonary haemorrhage	1	(1.0)	0	(0.0)	1	(0.7)
Pulmonary oedema	1	(1.0)	1	(2.1)	2	(1.4)
Respiratory failure	3	(3.0)	1	(2.1)	4	(2.7)
Rhinorrhoea	0	(0.0)	1	(2.1)	1	(0.7)
Wheezing	1	(1.0)	1	(2.1)	2	(1.4)
Skin and subcutaneous tissue disorders	**16**	**(16.2)**	**6**	**(12.5)**	**22**	**(15.0)**
Alopecia	0	(0.0)	1	(2.1)	1	(0.7)
Blister	1	(1.0)	0	(0.0)	1	(0.7)
Decubitus ulcer	0	(0.0)	1	(2.1)	1	(0.7)
Dermatitis acneiform	1	(1.0)	0	(0.0)	1	(0.7)
Dermatitis bullous	0	(0.0)	1	(2.1)	1	(0.7)
Dermatitis contact	1	(1.0)	0	(0.0)	1	(0.7)
Dry skin	2	(2.0)	0	(0.0)	2	(1.4)
Erythema	3	(3.0)	0	(0.0)	3	(2.0)
Pruritus	1	(1.0)	0	(0.0)	1	(0.7)
Pruritus generalised	1	(1.0)	0	(0.0)	1	(0.7)
Rash	8	(8.1)	3	(6.3)	11	(7.5)
Rash macular	1	(1.0)	0	(0.0)	1	(0.7)
Rash maculo-papular	1	(1.0)	1	(2.1)	2	(1.4)
Rash pruritic	0	(0.0)	1	(2.1)	1	(0.7)
Skin exfoliation	0	(0.0)	1	(2.1)	1	(0.7)
Vascular disorders	**10**	**(10.1)**	**4**	**(8.3)**	**14**	**(9.5)**
Deep vein thrombosis	0	(0.0)	1	(2.1)	1	(0.7)
Hypertension	8	(8.1)	3	(6.3)	11	(7.5)
Hypotension	1	(1.0)	0	(0.0)	1	(0.7)
Venoocclusive disease	1	(1.0)	0	(0.0)	1	(0.7)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Source: [P001V01: analysis-adsl; adae] [P001V01: tabulations-aeplus]

Reviewer comment: most of the AEs associated with IV therapy occurred in subjects who received the IV formulation for at least 7 consecutive days.

P001 SAEs through week 24

SAEs during the treatment phase were as follows, with potentially cardio-relevant adverse events occurring in a higher frequency in the active treatment arm highlighted (sponsor FSR):

Subjects With Serious Adverse Events
(Incidence > 0% in One or More Treatment Groups)
Treatment Phase
(ASaT Population)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	373		192		565	
with one or more serious adverse events	165	(44.2)	90	(46.9)	255	(45.1)
with no serious adverse events	208	(55.8)	102	(53.1)	310	(54.9)
Blood and lymphatic system disorders	**16**	**(4.3)**	**4**	**(2.1)**	**20**	**(3.5)**
Anaemia	2	(0.5)	0	(0.0)	2	(0.4)
Autoimmune haemolytic anaemia	1	(0.3)	0	(0.0)	1	(0.2)
Disseminated intravascular coagulation	1	(0.3)	0	(0.0)	1	(0.2)
Febrile neutropenia	5	(1.3)	2	(1.0)	7	(1.2)
Immune thrombocytopenic purpura	0	(0.0)	1	(0.5)	1	(0.2)
Leukopenia	1	(0.3)	0	(0.0)	1	(0.2)
Neutropenia	1	(0.3)	0	(0.0)	1	(0.2)
Pancytopenia	3	(0.8)	0	(0.0)	3	(0.5)
Thrombocytopenia	4	(1.1)	1	(0.5)	5	(0.9)
Cardiac disorders	**6**	**(1.6)**	**1**	**(0.5)**	**7**	**(1.2)**
Arrhythmia	1	(0.3)	0	(0.0)	1	(0.2)
Atrial fibrillation	1	(0.3)	0	(0.0)	1	(0.2)
Atrial flutter	1	(0.3)	0	(0.0)	1	(0.2)
Cardiac failure	1	(0.3)	0	(0.0)	1	(0.2)
Cardiogenic shock	0	(0.0)	1	(0.5)	1	(0.2)
Pericarditis	1	(0.3)	0	(0.0)	1	(0.2)
Sinus node dysfunction	1	(0.3)	0	(0.0)	1	(0.2)
Endocrine disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**
Inappropriate antidiuretic hormone secretion	1	(0.3)	0	(0.0)	1	(0.2)
Gastrointestinal disorders	**12**	**(3.2)**	**7**	**(3.6)**	**19**	**(3.4)**
Constipation	1	(0.3)	0	(0.0)	1	(0.2)
Diarrhoea	2	(0.5)	5	(2.6)	7	(1.2)
Dyspepsia	0	(0.0)	1	(0.5)	1	(0.2)
Gastrointestinal haemorrhage	2	(0.5)	0	(0.0)	2	(0.4)
Intestinal ischaemia	0	(0.0)	1	(0.5)	1	(0.2)
Lower gastrointestinal haemorrhage	1	(0.3)	0	(0.0)	1	(0.2)
Nausea	2	(0.5)	1	(0.5)	3	(0.5)
Stomatitis haemorrhagic	1	(0.3)	0	(0.0)	1	(0.2)

	Letermovir		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Renal and urinary disorders	**10**	**(2.7)**	**11**	**(5.7)**	**21**	**(3.7)**
Acute kidney injury	5	(1.3)	9	(4.7)	14	(2.5)
Cystitis haemorrhagic	2	(0.5)	1	(0.5)	3	(0.5)
Haematuria	0	(0.0)	1	(0.5)	1	(0.2)
Nephrolithiasis	1	(0.3)	0	(0.0)	1	(0.2)
Renal failure	1	(0.3)	0	(0.0)	1	(0.2)
Renal impairment	1	(0.3)	0	(0.0)	1	(0.2)
Reproductive system and breast disorders	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(0.2)**
Uterine haemorrhage	0	(0.0)	1	(0.5)	1	(0.2)
Respiratory, thoracic and mediastinal disorders	**9**	**(2.4)**	**7**	**(3.6)**	**16**	**(2.8)**
Acute respiratory distress syndrome	2	(0.5)	0	(0.0)	2	(0.4)
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.5)	1	(0.2)
Hypoxia	0	(0.0)	2	(1.0)	2	(0.4)
Pleural effusion	2	(0.5)	1	(0.5)	3	(0.5)
Pleurisy	1	(0.3)	0	(0.0)	1	(0.2)
Pneumonia aspiration	1	(0.3)	0	(0.0)	1	(0.2)
Pneumonitis	0	(0.0)	1	(0.5)	1	(0.2)
Pneumothorax	1	(0.3)	0	(0.0)	1	(0.2)
Pulmonary oedema	0	(0.0)	2	(1.0)	2	(0.4)
Respiratory failure	4	(1.1)	0	(0.0)	4	(0.7)
Skin and subcutaneous tissue disorders	**1**	**(0.3)**	**0**	**(0.0)**	**1**	**(0.2)**
Stevens-Johnson syndrome	1	(0.3)	0	(0.0)	1	(0.2)
Vascular disorders	**6**	**(1.6)**	**1**	**(0.5)**	**7**	**(1.2)**
Hypertension	0	(0.0)	1	(0.5)	1	(0.2)
Hypertensive crisis	1	(0.3)	0	(0.0)	1	(0.2)
Hypotension	1	(0.3)	0	(0.0)	1	(0.2)
Hypovolaemic shock	1	(0.3)	0	(0.0)	1	(0.2)
Venoocclusive disease	3	(0.8)	0	(0.0)	3	(0.5)

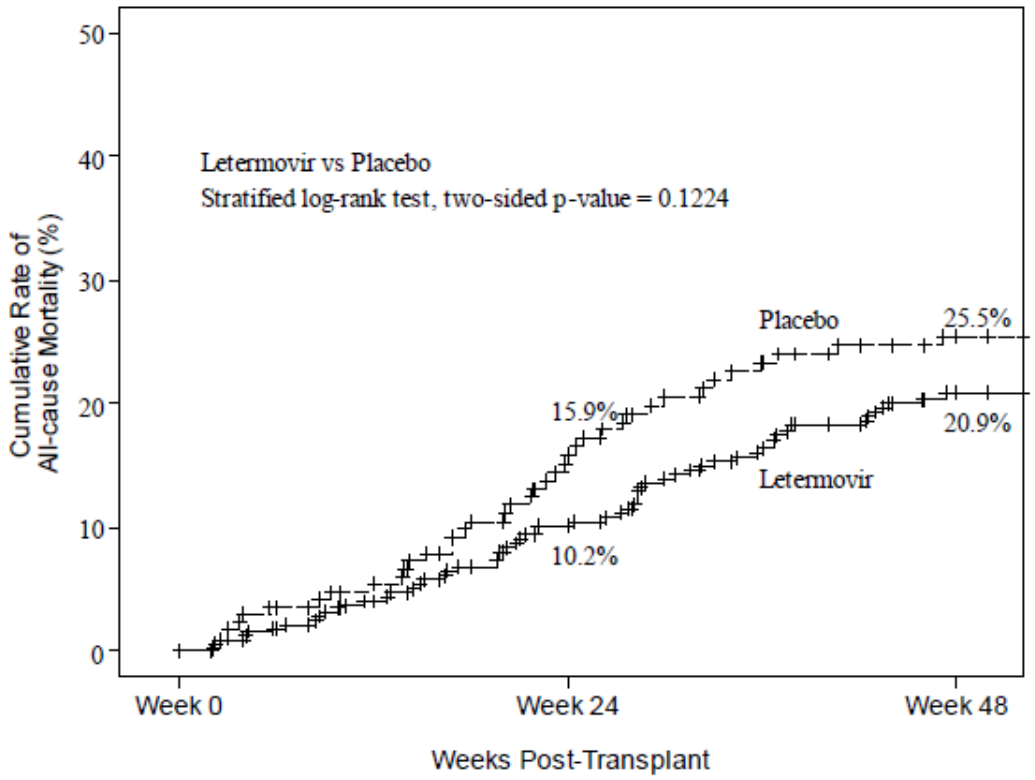
Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Source: [P001V01: analysis-adsl] [P001V01: tabulations-aeplus]

Reviewer comment: Treatment phase CV SAEs also predominantly atrial arrhythmias. Similar trends were seen at week 24. One SAE of cardiac failure in the letermovir treatment arm one SAE of cardiogenic shock in the placebo arm resulted on death. One SAE of venoocclusive disease in the letermovir treatment arm resulted in death. At week 24, CV or Venoocclusive SAEs resulting in death were equal between the active versus placebo arms (2 each). This number had not changed by database lock.

P001 Deaths

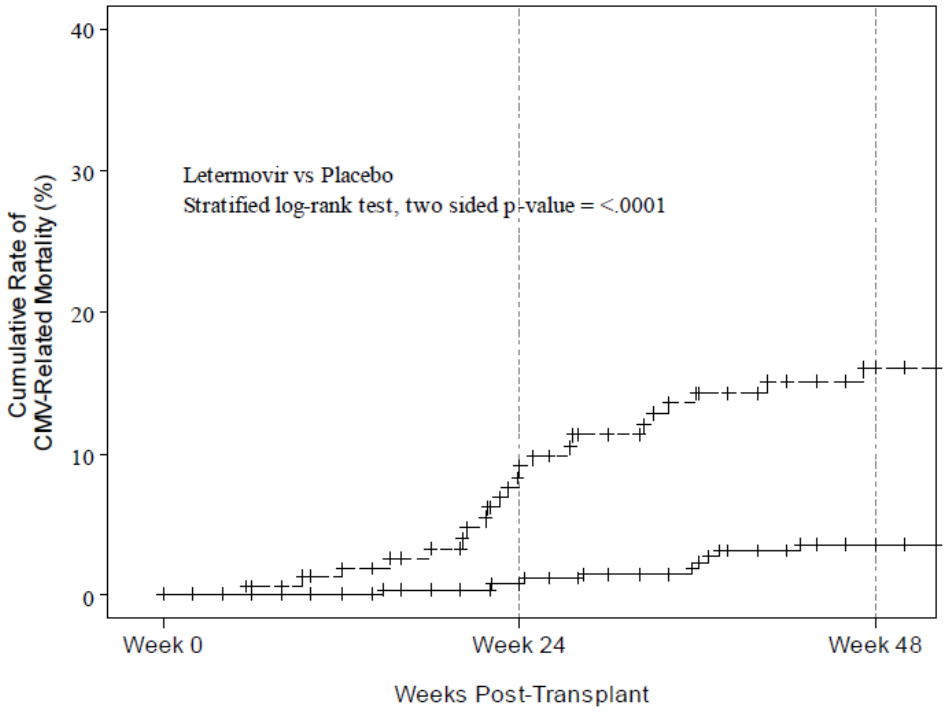
The sponsor-reported K-M event rate for all-cause mortality in the letermovir vs. placebo groups was 10.2% vs. 15.9% at Week 24 post-transplant (nominal two-sided stratified log-rank pvalue=0.0327), and 20.9% vs. 25.5% at Week 48 post-transplant (nominal two-sided stratified log-rank pvalue=0.1224, per the figure below (sponsor label):



Number of Subjects at Risk			
Letermovir	325	262	138
Placebo	170	125	71

The sponsor reported a K-M event rate for CMV-related mortality (defined as death due to any reason in patients with clinically significant CMV infection [primary endpoint]) in the letermovir vs. placebo group was 0.7% vs. 9.1% at Week 24 post-transplant (nominal two-sided stratified log-rank p-value < 0.0001), and 3.6% vs. 16.0% at Week 48 post-transplant (nominal two-sided stratified log-rank p-value < 0.0001), per the figure below (sponsor's 48 week mortality statistical report):

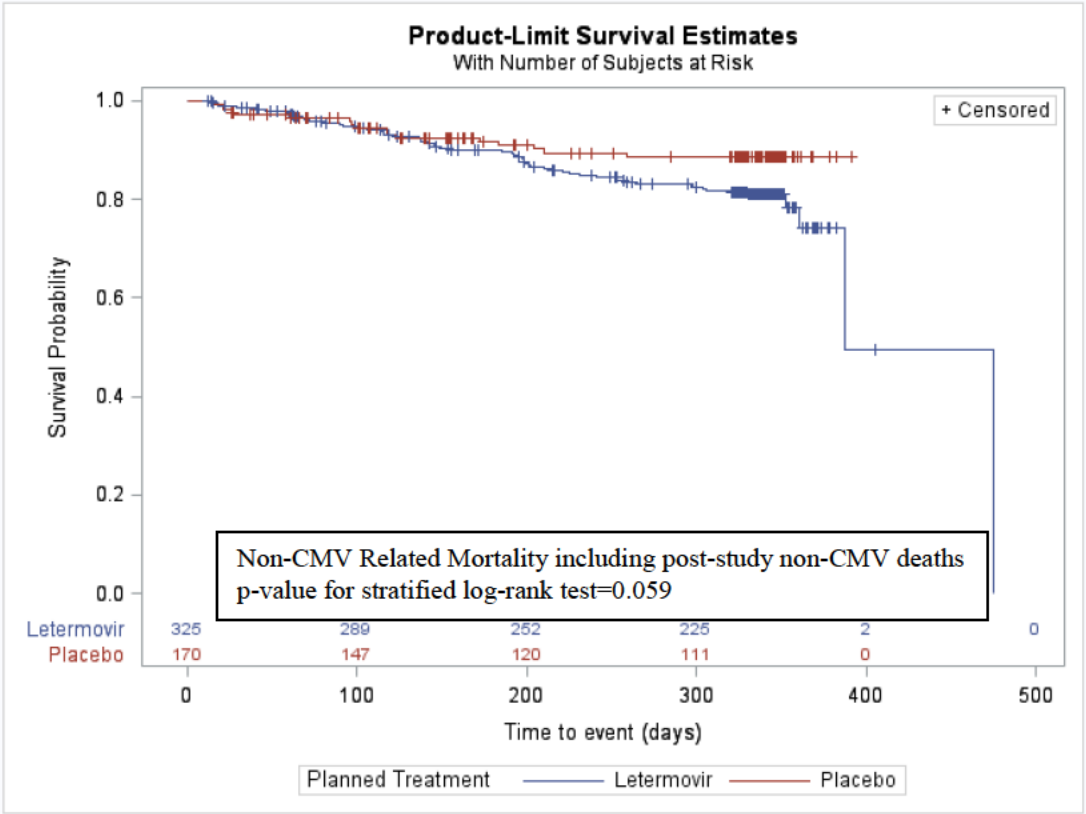
Figure 3: Kaplan-Meier Plot of Time to CMV-Related Mortality Through Week 48 Post-Transplant (FAS Population)



No. at risk: KM estimates % (95% CI)			
Letermovir	325	262: 0.7 (0.0, 1.7)	138: 3.6 (1.3, 5.9)
Placebo	170	125: 9.1 (4.3, 13.8)	71: 16.0 (9.9, 22.2)

Source: [P001V02: analysis-adtte]

However, the K-M curve for non-CMV-related mortality (the other component of the ACM result, using the sponsor's definition of CMV-related mortality) demonstrates a trend toward harm in the letermovir treatment group between weeks 24 and 48 (FDA analysis including post-withdrawal deaths that the sponsor is aware of), as shown in the K-M analysis below (Biometrics, FDA):



Reviewer comment: The causes of death between 24 and 48 weeks bear further examination, as do SAEs from this time period. The SAEs for this time period have not been submitted as of yet by the sponsor. Potential con-med commonalities could be of interest in the deaths that occurred in this time period.

DCRP ASSESSMENTS:

CV adverse events and cause specific mortality were not adjudicated in trial P001, nor were the CRFs designed to supply this information.

Subject dispositions were reported per the following table by the sponsor (MK-8228 (Letermovir) Week 48 Mortality Statistical Report):

Table 1: 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)
Discontinued between Weeks 24 and 48 Post-transplant	51	(13.6)	17	(8.8)	68	(11.9)
Completed 48 weeks Post-transplant	244	(64.9)	119	(61.3)	363	(63.7)

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: [P001V02: analysis-adsl][P001V02: tabulations-dsplus]

In trail P001, CV AEs and SAEs were imbalanced during through the 24 week safety database analysis, but CV deaths resulting from these SAEs were balanced between the treatment arms. Tier 2 CV AEs occurred in 12.6% of letermovir-treated subjects during the treatment period versus 6.3% of the placebo-treated group with a difference 6.4 (1.1, 11.0). This result was replicated more impressively in the IV only CV AEs analysis, with 12.1% versus 0% of letermovir- versus placebo- treated subjects having CV AEs, respectively. CV SAEs occurred in 1.6% versus 0.5% of letermovir versus placebo treated subjects, respectively. 2/373 (0.5%) subjects experienced death from a CV SAE in the letermovir treatment arm, versus 2/192 (1.0%) of the placebo treatment arm. CV AEs in all these groups were dominated by arrhythmias (mostly AFib, AFL, Tachycardia, and sinus tachycardia, with single cases of TdP and VT were noted in subjects receiving the IV formulation), though PT's of CHF and venoocclusive disease were also reported. By week 24, a larger percentage of placebo subjects had experienced death as the result of a CV adverse event (2 in each treatment arm).

Thus, it does appear due to the reproducibility of the finding that letermovir is causing at least some atrial arrhythmias in some subjects, but this is confounded by the facts that a higher percentage of letermovir-treated subjects had a history of CV disease at baseline (type not specified), and the exposure period on-letermovir was longer than exposure to placebo. However, even assuming that letermovir may cause transient arrhythmias in

some subjects, the all-cause mortality result at week 24 and week 48 favor letermovir therapy.

Yet the following difficulties arise in attempting to assess CV adverse event imbalances:

A. The censoring rules for safety outcomes were unclear. Of the 21-29% of subjects who withdrew prematurely from the trial through week 24, some of the subjects were apparently censored at the time of withdrawal and may have died after withdrawing from the study (it is unclear if all these deaths were counted). The censoring rules should be clarified for the early follow-up period for AEs and deaths, and all of these events counted regardless of whether subjects withdrew prematurely from study drug. Where subjects did withdraw informed consent for follow-up, vital status should be confirmed from public records in jurisdictions allowing this. Safety data and death analyses should be updated based if additional cases are identified.

B. While the ACM K-M looks favorable for letermovir to week 48, this appears to be driven by a reduction in CMV-related death in the letermovir treatment arm as this was defined by the sponsor (see figure page 26). This is a biologically plausible conclusion for a drug with efficacy against CMV. However, the complementary analysis must also be taken into consideration: that non-CMV death demonstrates a strong lean toward harm in the late follow-up period (see FDA figure page 27).

C. The K-M analyses for CMV-related death and non-CMV-related death both demonstrate fatalities occurring during the late follow-up period, but the sponsor-provided disposition table does not show deaths occurring during weeks 24-48. The censoring rules for counting deaths for the safety analysis in the late follow-up period should be clarified and the disposition table corrected based on ascertainment of all CV adverse events and vital status on all subjects for the late follow-up period regardless of whether subjects withdrew prematurely from study drug. Where subjects did withdraw informed consent for follow-up, vital status should be confirmed from public records in jurisdictions allowing this.

D. Given that adverse event data is not available for the late follow-up period, it is not possible to exclude that CV adverse events resulting in death may be occurring in this time block. The AE data for the late follow-up period should be submitted for review.

E. To further assess the types of deaths occurring in the late follow-up period, we recommend that non-CV deaths that are flagged in the dataset be subtracted from the non-CMV-death data subset (e.g. deaths due to relapse of disease, death due to GVHD, death due to sepsis). If the non-CMV/non-other-cardiac death dataset continues to lean in the direction of harm, medical review of the individual cases contributing to the late mortality result would be helpful to specifically rule out late CV deaths in that time period.

DCRP RESPONSES TOCONSULT QUESTIONS:

1. Is the rate and type of cardiac AEs observed in the letermovir arm potentially consistent with the background rate of cardiac events among HSCT recipients (despite the imbalance in letermovir and placebo arms) or do you think this could be a chance finding?

   DCRP Response: Given the reproducibility of the imbalances in the CV AEs in both formulation datasets, it is possible that these are in fact drug-induced findings in some subjects, though the increased baseline history of CV disease (type unspecified) in the demographics table and higher duration of exposure in the active treatment arm could be playing a role here. Even so, if a small minority of subjects experiences these events transiently without a negative impact on our best estimate of CV mortality (see comment E above), and all-cause mortality is favorably impacted by letermovir therapy, it would be reasonable to describe these events in labeling, but not impede an approvability determination because of them.

2. Besides tachyarrhythmias and heart failure, are any other notable cardiac events or groupings of cardiac events identified in this study?

   DCRP Response: Venoocclusive events should be included as CV adverse events in the setting of potentially drug-induced thrombocytopenia of undetermined mechanism. Note that venoocclusive AEs and SAEs occur almost exclusively in the letermovir treatment arm of P001.

3. Although there is a clear imbalance of cardiac events between arms, most were not assessed by the investigator to be drug-related. Based on your review, do you believe that labeling of some of these cardiac events is warranted? If so, should labeling include a general statement pertaining to an increased risk of all cardiac events? Or should a specific type of cardiac event be highlighted?

   DCRP Response: Assessments of relatedness in a non-cardiac trial with no adjudication of CV endpoints will be of questionable reliability. Very sick subjects often suffer transient arrhythmias, particularly atrial arrhythmias, all of which can result in transient symptoms suggestive of heart failure, particularly dyspnea. Given that no episodes of MI, stroke, or urgent coronary interventions of any type were reported in trial P001, we would favor a general description of these events in the trial results section of the label, assuming of course that no evidence of CV AEs causing late CV mortality is found in a more thorough safety assessment of the late follow-up period.

4. Are there any nonclinical studies or clinical trials that you would recommend to help further explore the potential cardiotoxicity of letermovir?

DCRP Response: In the absence of evidence for CV adverse events leading to MACE outcomes (including the careful analysis of AEs/SAEs/Deaths from weeks 24 – 48), we would not recommend additional clinical trials. Our understanding is that exposures with the IV formulation can be higher than was achieved with oral dosing, and it is notable that all almost all CV AEs/SAEs/venoocclusive events that occurred with IV therapy occurred in the letermovir treatment arm. An analysis of exposure-response with respect to the occurrence of CV adverse events may be informative from the datasets already obtained.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
06/08/2017

SHARI L TARGUM
06/09/2017

NORMAN L STOCKBRIDGE
06/09/2017

NDAs: 209939 and 209940

Medical Officer's Consultation: Request for Input from the Division of Bone, Reproductive and Urology Products (DBRUP) on an Ongoing NDA Review

To: Victoria Tyson, Regulatory Project Manager
Division of Antiviral Products (DAVP)
Office of Anti-Microbial Products (OAP)

From: Roger Wiederhorn, MD, Medical Officer
DBRUP, Office of Drug Evaluation 3 (ODE3)

Mark S. Hirsch, MD, Medical Team Leader
DBRUP, ODE3

Christine Nguyen, MD, Deputy Director of Safety
DBRUP, ODE3

Date of Sponsor Submission: March 8, 2017
Date of Consult Request: April 27, 2017
Date of Consult Completion: June 6, 2017

Product Name: letermovir

Sponsor: Merck

Indication: (b) (4) of cytomegalovirus (CMV) infection in hematopoietic stem cell transplant (HSCT) recipients

RE: DAVP requests DBRUP input on the ongoing review of an NDA. Preclinical studies revealed testicular injury in rats administered high doses of letermovir but not in mice or monkeys at any dose. In human males, sex hormone concentrations were measured in a single Phase 3 study but semen was not collected in this same study nor was semen collected in any other human study. DAVP requests DBRUP assistance to interpret the male sex hormone concentration results and to provide comments on the need for a future human study that incorporates the collection of semen**.**

1. Background

Cytomegalovirus (CMV) infection is common and generally acquired early in life. Reactivation of CMV is uncommon in individuals with intact immune systems and in these patients, it is generally asymptomatic. However, in immunocompromised patients, such as hematopoietic stem cell transplant (HSCT) recipients, CMV reactivation can cause significant morbidity and even death.

There are currently 2 approaches to preventing CMV disease in HSCT recipients: 1) prophylaxis with antivirals, and 2) pre-emptive therapy (PET). PET is the practice of active surveillance for viral replication and initiating treatment with anti-CMV agents when CMV viremia is detected. All currently available anti-CMV agents, whether used for prophylaxis or PET, are nucleoside analogues which have toxicities that limit their clinical utility, including myelosuppression and nephrotoxicity. Thus, there is an unmet medical need for an effective and well-tolerated antiviral agent for the prevention of CMV infection and disease in HSCT recipients.

Merck is developing letermovir as a novel anti-CMV agent. Letervomir inhibits the CMV terminase complex which plays a role in cleavage and packing of viral progeny DNA. Biochemical characterization and electron microscopy have demonstrated that letermovir affects the formation of proper unit length genomes from viral DNA concatemers (a long continuous DNA molecule that contains multiple copies of the same DNA sequences linked end to end) and interferes with virion maturation.

According to the Sponsor, letermovir was generally well tolerated in twenty-eight (28) Phase 1 studies, two Phase 2 studies, and one Phase 3 safety and efficacy study. The Phase 3 study is identified as P001. Also according to the Sponsor, 1) proof-of-concept was established in the Phase 2a study, 2) the safety and efficacy of letermovir for CMV prophylaxis in HSCT recipients was demonstrated in a dose-dependent manner in the Phase 2b study, and 3) efficacy and safety were confirmed in the single, randomized, placebo-controlled, double-blind, Phase 3 study, P001. An NDA for letermovir for the new indication is currently under Priority review in DAVP.

In the USPI submitted with the NDA, in P001, the Kaplan-Meier (K-M) event rate shown for clinically significant CMV infection was 18.9% in the treated group and 44.3% in the placebo group at Week 24. Also according to the proposed USPI, a total of 373 patients received letermovir and 192 received placebo for 14 weeks and were followed for 24 weeks in P001. Adverse reactions occurring in ≥1% of HSCT recipients (shown versus placebo) were: nausea (b) (4) diarrhea (b) (4) and vomiting (b) (4) Three subjects in the letermovir group were reported to experience drug-related serious adverse events (SAEs), including one subject each with pancytopenia, thrombocytopenia and delayed engraftment. Three placebo subjects experienced drug-related SAEs, including one subject each with Bowen's disease, mental status changes and acute kidney injury. Also according to the proposed labeling, a comparison of laboratory values between groups demonstrated similar percentages of subjects with potentially clinically significant changes (PCS) in laboratory values. For a discussion of the sex hormone concentration results from P001, see Section 2.2 of this review.

From the Clinical perspective, it is notable that concomitant cyclosporine A increases letermovir exposure by approximately 2-fold. Therefore, in the Phase 3 study, if the subject was not on cyclosporine A, they received 480 mg of letermovir each day (intravenously or orally), and if the subject was on cyclosporine A, they received 240 mg of letermovir each day.

Finally, in preclinical testing, testicular toxicity was observed in rats at the high letermovir doses, but not in mice or monkeys at any dose.

2. Brief Clinical Review

2.1 Preclinical

Consultant's Comment: Herein, the Clinical review team summarizes the relevant preclinical data. For more details, the reader is referred to the discipline-specific reviews conducted by the Pharmacology/Toxicology review teams in DAVP and DBRUP.

Testicular toxicity was noted in rats only, and only in the highest group in the 4-week and 13-week repeat-dose, rat toxicity studies, apparently at systemic exposures (AUC) at least 3 times the exposures observed in humans at the recommended human dose (RHD).

- In the 2-week, repeat-dose study in rats, testing doses of 0, 10, 30 and 100 mg/kg/day, while the study pathologist noted no adverse testicular histopathologic findings at 15 days, the clinical study report states that germinal cell vacuolization was observed in one of 4 rats at the 30 mg/kg/day dose and in 3 of 7 rats at the 100 mg/kg/day dose (Note: The total number of animals in the 30/mg/kg day dose group is likely 5 rats, not 7 rats.) Despite a germinal cell finding in 1 of 4 rats at 30 mg/kg/day, the 30 mg/kg/day dose is still considered to be the NOAEL in this study.

- In the 4-week and 13-week rat studies, testing doses of 0, 20, 60, or 180 mg/kg/day, histopathological changes were observed in the testes and epididymis of males in the highest dose group only (180 mg/kg/day). In that group, the changes noted consisted of vacuolization of the germinal epithelium (10 of 10 rats administered letermovir [9 grade 1 and one grade 2]) versus 3 of 10 rats administered placebo), germ cell exfoliation (10 of 10 rats administered letermovir [7 grade1 and three grade 2]) versus 1 of 10 administered placebo), tubular atrophy, and damage to Sertoli cells. In both the 4-week and the 13-week studies the NOAEL was determined to be 60 mg/kg/day. In the 26-week study (see next bullet item), no adverse testicular histopathology was observed at doses up to 150 mg/kg/day.

- In the 26-week rat study that tested doses of 0, 17, 50 and 150 mg/kg/day, no male reproductive organ changes were observed, however, the report stated "*…a trend towards increased testicular findings in the high dose (150 mg/kg/day) group representing an exacerbation of background findings related to aging in male rats*." In this study, the final NOAEL (150 mg/kg/day) was apparently 6 times the exposure observed in human HSCT males.

- In Study TT 11-7852, electron microscopy of the testes in rats administered letermovir for 15 weeks followed by a 15-week recovery period showed degenerating sperm cells and Sertoli cells with evidence suggesting non-reversibility. These findings were noted in the 180 mg/kg/day dose group and were present in 40 to 50% of the 21 males in this dose group. Other dose groups in the study were control and 30 and 60 mg/kg/day.

- Effects on male fertility, including sperm motility, were observed at the highest dose, 180 mg/kg/day, in a male rat fertility study (TT#16-7150). No drug-related effects on mating performance, fertility, or sperm parameters were observed at the lower doses (30 or 60 mg/kg/day). There were no drug-related effects on embryonic/fetal survival observed at any dose in this study. Post-mortem histopathology revealed seminiferous tubular degeneration in the majority of males at 180 mg/kg/day, and this finding correlated with a decrease in testis size and testis weight. Histopathology also revealed degenerated spermatogenic cell debris and decreased spermatozoa in the lumen of the epididymis and decreased epididymis size at 180 mg/kg/day. No drug-related postmortem findings were observed in males at 60 mg/kg/day.

Similar toxicology studies were performed in mice and in Cynomolgus and Rhesus monkeys without any further results showing testicular toxicity. In dogs, a NOAEL of ≥ 45/mg/day in a 14-day study precluded further evaluation for testicular toxicity.

Consultant's Comment: Preclinical studies appeared to show testicular toxicity limited to rats in the highest dose group in the 4-week, 13-week and 15-week repeat-dose studies, but not observed at lower doses in rats in the 26-week study and not observed in dogs, mice or monkeys. In the 26-week rat study, the NOAEL was reportedly 6 times the exposure observed in human HSCT males. There is evidence from the 15-week study that suggests that the testicular toxicity did not reverse. Based on the lack of testicular toxicity in species other than the rat, as well as lack of testicular toxicity in the rat at longer treatment durations at doses that produced exposures approximately 6-fold greater than those in observed in humans, the toxicity appears to be limited to the rat at high doses and the testicular toxicity risk to humans appears to be low.

2.2 Clinical

Consultant's Comment: To be clear, the lack of semen analysis data in the human studies precludes a meaningful interpretation of testicular toxicity risk based on human data. The male sex hormone concentrations are of some interest, but they do not reflect the health of the seminiferous tubules or germinal epithelium. None of the measurements in the Phase 3 study constitute adequate biomarkers for germinal epithelial injury.

The single Phase 3 study, Trial P001, was entitled "*A Phase III 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 TransplantRecipient."* While the study included assessment of males sex hormones, it did not include collection of semen samples for semen analysis.

According to the study protocol, to evaluate the potential for testicular toxicity associated with letermovir in human subjects, male sex hormones, proposed as markers of testicular toxicity, were monitored in male subjects. Serum LH, FSH, testosterone and inhibin B concentrations were collected in male subjects at the baseline, end-of-treatment (EOT, Week 14), and Week 24 Visits to compare the letermovir and placebo groups for shifts from baseline in each of the four hormones that were assessed. In summary, the shift data showed no clinically relevant effect of

letermovir on the male sex hormones assessed in this study (Table 12-33, on pages 357-358 of the Trial P001 clinical study report).

It should be noted, that at Week 24, in the Safety population, 5 of 373 (1.3%) letermovir-treated patients versus 0 of 192 (0.0%) placebo-treated patients [95% CI -0.6, -5.1] reported "testosterone decreased" as a clinical AE (as shown in Table 12-8, on page 262 of the P001 clinical study report). All 5 patients in whom "testosterone decreased" was reported as a clinical AE were less than 65 years of age and all received the oral formulation of letervomir (as shown in Table 14.3-30 on page 1032; and in Table 14.3-26 on page 994, respectively). Two letervomir-treated patients and 1 placebo-treated patient had received testosterone as a prior concomitant medication (as shown on page 508 of the P001 study report). The clinical meaningfulness of these AE results is unknown.

3. Clinically Relevant Comments from Other Disciplines's Reviews

A discipline-specific consultative review by DBRUP Pharmacology/Toxicology was ongoing at the time of completion of this Clinical consultative review.

4. Clinical Consultant's Overall Comments

4-week, 13-week and 15-week toxicology studies in rats revealed seminiferous tubular degeneration in male rats at a letervomir dose of 180 mg/kg/day. The 15-week repeat-dose study confirmed the finding that letervomir at a dose of 180 mg/kg/ day adversely affected germ cells and spermatogenesis in male rats, and also suggested that this effect may be non-reversible. However, testicular toxicity was not observed in the 26-week rat toxicology study at doses as high as 150 mg/kg/day, corresponding to a NOAEL in that study that exceeded the human exposure by 6-fold.

In addition, testes of male mice treated with 40, 100 and 250 mg/kg/day for 13 weeks via oral gavage were also not affected by the chronic treatment.

Finally, oral dosing of sexually mature non-human primates (60 to 240 mg/kg for 13 weeks) did not induce any adverse effects on the testes, in particular, no alterations of the male reproductive system that would indicate impaired fertility. Therefore, in Cynomologous monkeys, the NOAEL for effects on the male reproductive system was ≥240 mg/kg (an apparent safety exposure margin of approximately 2-fold from the NOAEL). The daily treatment with doses of up to 250/200 mg/kg (oral) for 39 weeks or up to 100 mg/kg (intravenous) for 4 weeks also produced no adverse effects on the male or female reproductive organs of Cynomolgus monkeys (an apparent safety margin of 2 times the NOAEL).

In human clinical studies, semen analyses were unfortunately not performed. Instead, serum LH, FSH, testosterone and inhibin B concentrations were collected in male subjects at baseline, Week 14 (EOT), and at Week 24. Shifts from baseline for each of the four hormone levels were analyzed. The shift data show no clinically relevant effect of letermovir on male sex hormones in a population of HSCT recipients. However, male sex hormones should not be considered as adequate biomarkers for potential injury to the seminiferous tubules and germ cells.

We wish to point out that within the indicated population for letervomir it is likely that at least some candidates will have previously received drug therapies (e.g., chemotherapy) that are known to cause testicular toxicity, and thus, these patients may have baseline semen analysis parameters that are well below the World Health Organization (WHO) reference ranges. Patients may also need to initiate or continue therapies that are toxic to the testicle. In this setting, it would be challenging, though not impossible, to conduct a human male testicular safety study.

While a possible adverse effect of letermovir on spermatogenesis in humans is remotely possible, the risk appears low based on the available data.

5. Clinical Consultant's Conclusion and Recommendations

1. The preclinical testicular toxicity findings should be described in product labeling. While the available data implies a low risk of testicular toxicity to human males, the ultimate risk of human testicular toxicity is currently unknown.

2. For the reasons described in this consult, a postmarketing requirement study for testicular safety would be challenging, though not impossible, to conduct.

3. The clinically meaningfulness of the minor difference between groups for the clinical AE "testosterone decreased" is unknown. For completeness, this result could be shown in product labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

A R WIEDERHORN
06/05/2017

MARK S HIRSCH
06/05/2017
I concur.

CHRISTINE P NGUYEN
06/05/2017

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	209939/209940
Brand Name	-
Generic Name	MK-8228 (letermovir)
Sponsor	Merck Sharp & Dohme Corporation
Indication	Anti-viral (Anti-human cytomegalovirus [HCMV])
Dosage Form	Intravenous (IV)
Drug Class	Anti HCMV
Therapeutic Dosing Regimen	480 mg IV
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not known
Submission Number and Date	001; 03/08/2017
Review Division	DAVP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of MK-8228 (letermovir 960 mg IV supra-therapeutic dose and 480 mg IV projected clinical dose) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-8228 (single dose of 480 mg IV and 960 mg IV) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcP for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, double-blind, four-period, 8-sequemce crossover study, 38 subjects received MK-8228 480 mg IV, MK-8228 960 mg IV, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MK-8228 (480 mg IV and 960 mg IV) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Total N	Time (hour)	ΔΔQTcP (ms)	90% CI (ms)
MK-8228 480 mg IV	35	1	2.6	(0.3, 4.8)
MK-8228 960 mg IV	36	1	5.3	(3.0, 7.5)
Moxifloxacin 400 mg*	35	4	12.7	(10.7, 14.7)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 10.0 ms.

The intended therapeutic dose of letermovir is 480 mg QD by oral or 1-hour IV infusion administration through 100 days post-transplant. There is negligible accumulation of letermovir following multiple dose administration of 480 mg letermovir. The oral dose of 480 mg produces mean C_{max} in the range of 12900 (Study P022) to 22000 ng/mL (Study P032) in healthy subjects and IV dosing of 480 mg produces mean C_{max} in the range of 28400 (Study P026) to 32600 ng/mL (TQT Study P004). The geometric mean C_{max} with the supratherapeutic dose of 960 mg IV in this TQT study is 67300 ng/mL, which gives an exposure margin of 3.1- to 5.2-fold over the therapeutic exposures with intended oral therapeutic dose and exposure margin of 2.1- to 2.4-fold over the therapeutic exposures with intended IV therapeutic dose. Furthermore, letermovir exposures in HSCT recipients following oral administration of letermovir are lower compared to healthy subjects. The severe hepatic impairment is associated with 2.3-fold increase in C_{max} with oral dosing. Concomitant use of 50 to 200 mg of cyclosporine (CsA), which is a frequently co-administered medication, increases the exposure of letermovir by ~1.5 to 2.7-fold for oral dose, due to decreased systemic clearance of letermovir and decreased first pass effect due to intestinal P-gp and hepatic OATP1B inhibition. The effect of CsA on IV letermovir is lower than that with oral administration, as CsA could only affect letermovir exposure through systemic hepatic OATP1B inhibition in case of IV administration. Overall, the supratherapeutic exposures with 960 mg IV dose reasonably cover the highest clinically relevant concentrations (worst case scenario) with intended therapeutic dosing of letermovir.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

QT-IRT's following proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

[redacted]

3 BACKGROUND

3.1 PRODUCT INFORMATION

MK-8228 (letermovir) is an anti-human cytomegalovirus agent that targets the viral terminase complex involved in cleavage and packaging of genomic virus DNA. It is available as a solution for IV injection, a 240 mg tablet, and a 480 mg tablet. The proposed dosing regimen is 480 mg once daily as a 1-hour IV infusion or as a tablet (with or without food).

3.2 MARKET APPROVAL STATUS

Letermovir is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1 for addition details.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of drug's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 118361 (DARRTs 30/07/2012) and IND 104706 (DARRTs 08/26/2013). There were concerns that the proposed dose of 200-mg i.v. (therapeutic dose) and 480-mg i.v. (supratherapeutic dose) are too low and the sample size of 30 is not adequate (DARRTs 30/07/2012). These issues had been resolved as the applicant agreed to evaluate projected clinical dose at 480 mg i.v. and supratherapeutic dose at 960 mg i.v. and increased the sample size to 38 (DARRTs 08/26/2013). In the current submission, the applicant submitted the study report P004, electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Single Dose Trial to Assess the Effect of MK-8228 (letermovir) on QTc Interval in Healthy Adult Volunteers.

4.2.2 Protocol Number

P004

4.2.3 Study Dates

Trial Initiation Date: 09 December 2013

Trial Completion Date: 20 March 2014

4.2.4 Objectives

Primary objectives:

1. To evaluate effects of a supra-therapeutic dose of MK-8228 on QTc interval.
2. To evaluate the effects of the projected clinical dose of MK-8228 on the QTc interval.

Secondary objectives:

1. To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control.
2. To evaluate the safety and tolerability of MK-8228 after administration of single supra-therapeutic IV dose (960 mg) to healthy adult subjects.

4.2.5 Study Description

4.2.5.1 Design

A single center, randomized, placebo-controlled, double-blinded 4-period, 8-sequence, crossover trial designed to evaluate the effect of a single intravenous (IV) MK-8228 (letermovir) administration (960 mg IV supra-therapeutic dose and 480 mg IV projected clinical dose) on the duration in milliseconds from the beginning of Q-wave to the end of the T-wave (QT) interval corrected by heart rate (QTc) in healthy female subjects.

4.2.5.2 Controls

The Applicant used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

MK-8228/placebo treatments were double-blinded and moxifloxacin was administered in an open-label fashion.

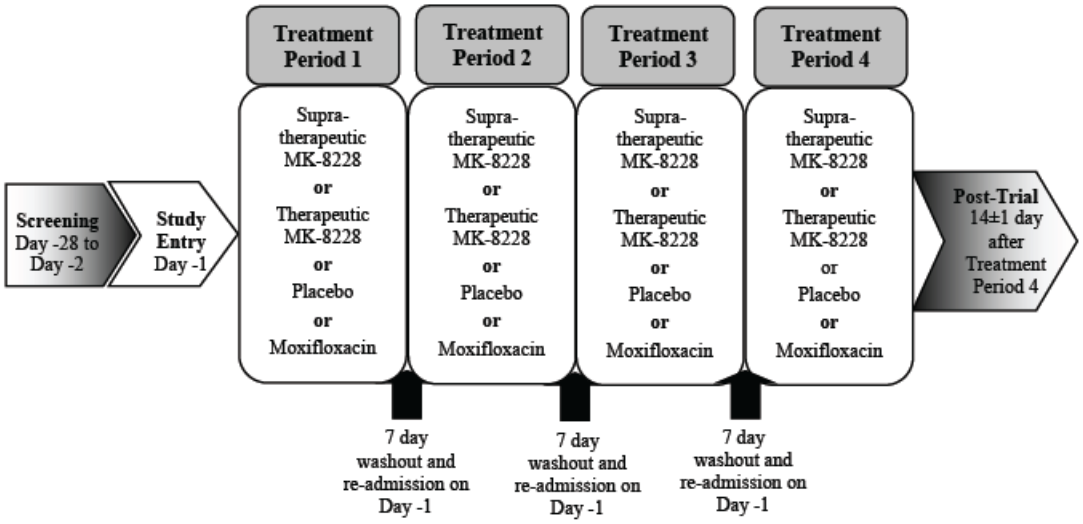
4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects received each of the following treatments in a randomized sequence:

- Treatment A: Single dose 960 mg IV MK-8228 (supra-therapeutic dose).
- Treatment B: Single dose 480 mg IV MK-8228 (projected clinical dose).
- Treatment C: Single dose IV placebo.
- Treatment D: Single dose oral moxifloxacin.

Each subject was randomized to 1 of 8 possible treatment sequences and received a single dose of each of 4 treatments in 4 treatment periods as depicted in Figure below:



4.2.6.2 Sponsor's Justification for Doses

The following information is reproduced from the protocol review (under IND 104706 dated 08/26/2013 in DARRTS):

MK-8228 is being developed for once daily administration as a tablet and an IV formulation for oral and IV administration, respectively. The dose of MK-8228 depends on whether or not there is concomitant use of cyclosporine (CsA) which is a frequently co-administered medication and increases the exposure of MK-8228 by 2 to 3-fold. In patients concomitantly dosed with CsA, the MK-8228 dose is projected to be 240 mg. In patients not on CsA, the projected clinical dose is 480 mg once daily.

In this trial, MK-8228 will be given both as a single IV dose of 480 mg and as a single IV dose of 960 mg. The dose of 480 mg is chosen to represent the projected clinical dose of MK-8228. Co-administration of 50 mg and 200 mg CsA with MK-8228 increases MK-8228 AUC by 2.3 and 3.4-fold, respectively, and mean Cmax by 2.1 and 2.7-fold, respectively. Therefore, the Cmax obtained with the dosing regimen of 240 mg co-administered with cyclosporine may slightly exceed that following the 480 mg dose used in this trial. The supra-therapeutic dose of 960 mg IV is the highest single dose concentration tested either by the oral or the IV route.

The supra-therapeutic IV dose of 960 mg is predicted to achieve a mean Cmax value (~57,000 ng/mL) that is approximately 5-fold that of the steady-state Cmax of the 480 mg clinical dose administered by the oral route, taking into account the ~2.5-fold higher Cmax upon IV dosing (60 minute infusion duration) as compared to the same dose given

orally. The exposure margin for steady-state 480 mg IV dosing to the 960 mg IV supra-therapeutic dose is estimated to be 2-fold. The observed accumulation in Cmax with multiple dosing of MK-8228 is negligible.

MK-8228 has a low likelihood to be metabolized via the CYP450 system, and is almost exclusively excreted unchanged via the biliary/fecal route, based on data from in vitro studies and in vivo animal and human ADME studies. In a hepatic impairment trial, the Cmax increased 1.4 and 2.3-fold in moderate and severe hepatically-impaired subjects, respectively. Interestingly, preliminary data of a recently completed renal impairment trial indicate some effect of renal impairment on MK-8228 concentrations, with a 1.3- and 1.1-fold increase in the Cmax of total MK-8228 (1.4- and 1.3-fold in unbound levels, respectively) in moderate and severe renally-impaired patients, respectively, which may point to more indirect mechanisms of renal functioning influencing MK-8228 concentrations. MK-8228 is a substrate and a modulator of the uptake transporter organic anion-transporting polypeptide-1B1 (OATP1B1) and OATP1B3. MK-8228 is also a substrate of UGT1A1, however, interaction via UGT1A1 is not likely to be clinically meaningful. The in vivo importance of OATP1B1/B3 has been indicated by the 2.1- and 2.7-fold increase in Cmax of sub-therapeutic doses of MK-8228 when co-administered with 50 mg and 200 mg cyclosporine, respectively; cyclosporine is an inhibitor of OATP1B1, OATP1B3 and Pgp. This was confirmed by population PK analysis of the Phase 2 trial, indicating a ~3-fold increase in MK-8228 exposure in patients on cyclosporine. As such, the dose adjustment on the basis of cyclosporine co-administration takes into account the major factor influencing MK-8228 concentrations. No major difference in the pharmacokinetics of MK-8228 between males and females has been observed. There is no evidence that racial or ethnic differences influence pharmacokinetics; however, data is limited. Based on clinical assessment of excretory pathways, drug-drug interactions, and potential for altered pharmacokinetics in disease conditions, a single supra-therapeutic IV dose of 960 mg will be used for this TQT trial to cover the maximal exposure to MK-8228 anticipated under conditions of concomitant medications, altered organ function and disease-related conditions.

Reviewer's Comment: Acceptable. The intended therapeutic dose of letermovir is 480 mg QD by oral or 1-hour IV infusion administration through 100 days post-transplant. There is negligible accumulation of letermovir following multiple dose administration of 480 mg letermovir. The oral dose of 480 mg produces mean C_{max} in the range of 12900 (Study P022) to 22000 ng/mL (Study P032) in healthy subjects and IV dosing of 480 mg produces mean C_{max} in the range of 28400 (Study P026) to 32600 ng/mL (TQT Study P004). The geometric mean C_{max} with the supratherapeutic dose of 960 mg IV in this TQT study is 67300 ng/mL, which gives an exposure margin of 3.1- to 5.2-fold over the therapeutic exposures with intended oral therapeutic dose and exposure margin of 2.1- to 2.4-fold over the therapeutic exposures with intended IV therapeutic dose. Furthermore, letermovir exposures in HSCT recipients following oral administration of letermovir are lower compared to healthy subjects. The severe hepatic impairment is associated with 2.3-fold increase in C_{max} with oral dosing. Concomitant use of 50 to 200 mg of cyclosporine (CsA), which is a frequently co-administered medication, increases the exposure of letermovir by ~1.5 to 2.7-fold for oral dose, due to decreased systemic clearance of letermovir and decreased first pass effect due to intestinal P-gp and hepatic OATP1B inhibition. The effect of CsA on IV letermovir is lower than that with oral

administration, as CsA could only affect letermovir exposure through systemic hepatic OATP1B inhibition in case of IV administration. Overall, the supratherapeutic exposures with 960 mg IV dose reasonably cover the highest clinically relevant concentrations (worst case scenario) with intended therapeutic dosing of letermovir.

4.2.6.3 Instructions with Regard to Meals

Sponsor administered the drug in a fasted state.

Reviewer's Comment: Acceptable. Because the study was conducted with IV administration, food is not expected to impact the PK.

4.2.6.4 ECG and PK Assessments

Five replicates (with approximately 1 minute intervals between ECG readings) of 10-second, 12-lead ECG recordings were acquired during each of the 4 periods at the following times: -20 minutes, -10 minutes, immediately prior to dosing, 30 minutes, and at 1, 2, 3, 4, 6, 12, and 24 hours post-dose. PK samples were scheduled for collection at the same timepoints (immediately prior to dosing, 0.5, 1, 2, 3, 4, 6, 12, and 24-hours post-dose).

Reviewer's Comment: Acceptable. For the 1-hour IV infusion, the C_{max} occurs at approximately the end of infusion (according to IV PK data from study P026). Thus, the ECG/PK sampling reasonably captures the effects near T_{max} as well as any potential delayed effects up to 24 h.

4.2.6.5 Baseline

Applicant used pre-dose QTc values on Day 1 as baseline. Baseline for the calculation of change from baseline is the mean of the Holter ECG measurements performed at 20 min and 10 min pre-dose, and at pre-dose (time 0).

4.2.1 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.2 Sponsor's Results

4.2.2.1 Study Subjects

Thirty-eight (38) subjects enrolled and 33 subjects completed the study. Table below summarizes the disposition of all enrolled subjects.

	Overall N = 38
Enrolled	38 (100.0%)
Completed the Trial	33 (86.8%)
Discontinued from the Trial	5 (13.2%)
Adverse Event	1 (2.6%)[†]
Protocol Deviation	0 (0.0%)
Consent Withdrawn	1 (2.6%)[‡]
Death	0 (0.0%)
Other	3 (7.9%)[§]

N = number of enrolled subjects; IV = intravenous

[†] One subject was withdrawn from the trial due to positive pregnancy test after receiving 400 mg moxifloxacin.

[‡] One subject withdrew consent after receiving 960 mg IV MK-8228.

[§] One subject was withdrawn from the trial due to positive urine drug screen (amphetamine) at admission to Period 4, after receiving 480 mg IV MK-8228, IV placebo, and 960 mg IV MK-8228.
One subject was withdrawn from the trial due to positive urine drug screen at admission to Period 4, after receiving placebo, 960 mg IV MK-8228, and 400 mg moxifloxacin.
One subject was withdrawn from the trial due to positive cotinine screen at admission to Period 4 after receiving IV placebo, 400 mg oral moxifloxacin, and 480 mg IV MK-8228.

Data Source: [16.2.1.1], [16.4]

4.2.2.1 Statistical Analyses

4.2.2.1.1 Primary Analysis

The primary endpoint was baseline-adjusted mean differences between MK-8228 (doses of 480 mg IV and 960 mg IV) and placebo in ΔQTcP (population rate specific QTc correction method). QTcP was employed as the following equation:

$$QTcP = QTc \times RR^{-\beta}$$

where β was the estimated slope parameter obtained from a linear mixed model with the natural log of the QT interval as the response variable and the natural log of the RR interval as a covariate, and subject as a random effect (see equation 2). The linear mixed model was fit using placebo data collected during pre and post-dose time points and active treatment (non-placebo) data collected during pre-dose time points only:

$$\ln(QTcP) = \beta 0 + \beta \ln(RR) \quad (2)$$

The applicant used an analysis of covariance (ANCOVA) and the results are presented in Table 2. The model included sequence, time, treatment as fixed effects and baseline as covariate. The applicant concluded the 2-sided 90% confident bounds of 480 mg IV and 960 mg IV dose of MK-8228 fell below 10 ms at all time points, which shown that MK-8228 did not prolong the QTc interval to a clinically significant degree.

Table 2: Sponsor's ΔQTcP and ΔΔQTcP with Supra-therapeutic and Projected Clinical Dose of MK-8228 (Per-Protocol Population)

Treatment	Time (h)	QTcP value (msec)			Change from Baseline (msec)		Difference from Placebo (msec)	
		N†	Mean	95% CI	Mean	95% CI	LS Mean Difference	90% CI
960 mg IV MK-8228	Pre-dose‡	36	405	(401, 409)	-	-	-	-
	0.5	36	407	(403, 411)	2.10	(0.657, 3.53)	0.621	(-0.916, 2.16)
	1	36	411	(406, 415)	5.58	(3.98, 7.18)	4.93	(2.81, 7.05)
	2	36	410	(405, 414)	4.47	(3.06, 5.89)	3.55	(1.92, 5.17)
	3	36	409	(405, 413)	3.76	(2.57, 4.96)	1.88	(0.621, 3.13)
	4	36	408	(404, 412)	2.84	(0.884, 4.80)	2.57	(1.09, 4.05)
	6	35	401	(398, 404)	-3.24	(-5.17, -1.31)	0.843	(-0.940, 2.63)
	12	36	404	(400, 407)	-1.70	(-4.36, 0.953)	2.44	(0.252, 4.63)
	24	36	402	(398, 406)	-2.95	(-5.12, -0.778)	0.669	(-1.46, 2.80)
480 mg IV MK-8228	Pre-dose‡	35	404	(400, 408)	-	-	-	-
	0.5	35	406	(402, 410)	2.02	(0.790, 3.25)	0.768	(-0.756, 2.29)
	1	35	407	(403, 411)	2.96	(1.59, 4.33)	2.72	(1.05, 4.38)
	2	35	406	(402, 410)	2.38	(0.695, 4.07)	1.77	(-0.489, 4.03)
	3	35	407	(403, 411)	3.03	(1.02, 5.05)	1.22	(-0.814, 3.26)
	4	35	406	(402, 411)	2.41	(0.745, 4.08)	2.62	(1.23, 4.00)
	6	35	401	(397, 405)	-2.93	(-5.08, -0.779)	0.922	(-1.01, 2.85)
	12	35	402	(398, 406)	-1.67	(-4.21, 0.880)	1.34	(-0.917, 3.60)
	24	35	400	(396, 404)	-3.48	(-5.89, -1.07)	0.073	(-2.70, 2.84)
400 mg oral Moxifloxacin	Pre-dose‡	36	405	(400, 409)	-	-	-	-
	0.5	36	412	(407, 416)	6.76	(4.34, 9.17)	5.32	(3.29, 7.35)
	1	35	414	(410, 419)	9.18	(6.39, 12.0)	8.83	(5.41, 12.3)
	2	35	413	(411, 419)	10.3	(8.81, 11.9)	9.89	(7.73, 12.0)
	3	35	417	(412, 421)	12.2	(10.5, 13.8)	10.5	(8.80, 12.2)
	4	35	417	(412, 422)	12.4	(10.6, 14.3)	12.2	(10.7, 13.8)
	6	36	406	(403, 410)	1.67	(-0.613, 3.96)	5.84	(3.69, 7.98)
	12	34	407	(403, 411)	2.32	(-0.101, 4.73)	5.91	(4.20, 7.62)
	24	36	405	(401, 410)	0.541	(-1.32, 2.40)	4.24	(2.56, 5.92)

Treatment	Time (h)	QTcP value (msec)			Change from Baseline (msec)		Difference from Placebo (msec)	
		N†	Mean	95% CI	Mean	95% CI	LS Mean Difference	90% CI
Placebo	Pre-dose‡	36	405	(401, 410)	-	-	-	-
	0.5	36	406	(402, 411)	1.21	(0.002, 2.43)	-	-
	1	36	406	(401, 410)	0.327	(-1.42, 2.07)	-	-
	2	35	406	(401, 411)	0.705	(-1.33, 2.74)	-	-
	3	36	407	(403, 411)	1.56	(-0.089, 3.21)	-	-
	4	36	405	(401, 409)	-0.298	(-1.79, 1.19)	-	-
	6	35	400	(397, 404)	-4.06	(-6.33, -1.79)	-	-
	12	36	401	(398, 405)	-3.88	(-6.64, -1.12)	-	-
	24	35	401	(397, 405)	-4.12	(-6.69, -1.54)	-	-

CI = confidence interval; LS = Least Squares; IV = intravenous; QTcP = population rate specific QT interval correction
† N denotes the number of subjects for each level of treatment used to estimate the LS means.
‡ In the descriptive summary of observed values, pre-dose represents baseline, derived as the mean of 12-lead ECG measurements performed at 20 min pre-dose, 10 min pre-dose, and at pre-dose time 0.
Data Source: [16.4]

Source: MK-8228 (LETERMOVIR) Clinical Study Report P004, Table 3, Pages 8/315

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our ΔΔQTcP results are similar as those reported by the sponsor.

4.2.2.1.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcP effect for moxifloxacin. The results are presented in Table 3. The lower bound of the 2-sided 90% CI for the mean difference between moxifloxacin and placebo was greater than 5 ms; therefore, the assay sensitivity was established.

Table 3: Sponsor's ΔQTcP and ΔΔQTcP with Moxifloxacin (Per-Protocol Population)

	400 mg Moxifloxacin Change From Baseline QTcP (msec)			Placebo Change From Baseline QTcP (msec)			Difference from Placebo Change from Baseline QTcP (msec)		
Time (h)	N	Mean	95% CI	N	Mean	95% CI	LSMean Difference	90% CI [1]	p-value [2]
1	35	9.18	(6.39, 12.0)	36	0.327	(-1.42, 2.07)	8.83	(5.41, 12.3)	0.0334
2	35	10.3	(8.81, 11.9)	35	0.705	(-1.33, 2.74)	9.89	(7.73, 12.0)	0.0003
3	35	12.2	(10.5, 13.8)	36	1.56	(-0.089, 3.21)	10.5	(8.80, 12.2)	<0.0001
4	35	12.4	(10.6, 14.3)	36	-0.298	(-1.79, 1.19)	12.2	(10.7, 13.8)	<0.0001

N = number of subjects for each level of treatment and time point used to estimate the mean value; CI = confidence interval; LS mean = least squares mean; QTcP = population rate specific QT interval correction

[1] The two-sided 90% CIs are equivalent to one-sided lower 95% CIs.

[2] The one-sided p-values, that the mean treatment difference is greater than 5 msec, are evaluated at 1, 2, 3, and 4 hours post-dose and are ranked in ascending order $p(4) \leq p(3) \leq p(2) \leq p(1)$. The p-values are compared to alpha 0.05 sequentially using Hochberg's step-up method: p(1) vs. 0.05, p(2) vs. 0.05/2, p(3) vs. 0.05/3, p(4) vs. 0.05/4.

Data Source: [16.4]

Source: MK-8228 (LETERMOVIR) Clinical Study Report P004, Table 4, Pages 10/315
Reviewer's Comments: We provided our independent analysis in Section 5.2.
Our ΔΔQTcP results are similar as those reported by the sponsor.

4.2.2.1.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTcP >450 ms or > 30 ms in MK-8228 treatments.

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our categorical results are similar as those reported by the sponsor.

4.2.2.1.4 Additional Analyses

Two subjects under placebo treatment and one subject under 480 mg IV MK-8228 treatment had HR values ≥100 bpm (range: 100 to 106 bpm); all remaining subjects had HR values of >40 and <100 bpm at all time points and under all treatments.

One subject had PR interval values >220 msec (range: 221 to 234 msec) during supra-therapeutic and projected clinical dose MK-8228 administration, all remaining subjects had PR interval values of >200 and ≤220 msec at all time points and under all treatments.

No subject had QRS interval data within the defined categories. All subject's QRS interval values ranged from 73 to 104 msec.

4.2.2.2 Safety Analysis

There were no deaths, laboratory AEs, or events of clinical interest; with two pregnancies and two SAEs (both elective abortions) reported. Five (5) subjects withdrew or were discontinued from the trial prematurely, including one discontinuation due to a pregnancy and subsequent SAE of elective abortion. The other pregnancy was reported only after all trial-related procedures had been completed, and subsequent elective abortion occurred after conclusion of the trial.

In total, 31 subjects reported 98 TEAEs, with 38 events considered related to trial drug. In general, the number and percentage of subjects reporting TEAEs, as well as the number of events were comparable between treatments. Overall, approximately 39% (38 of 98 events) of the reported TEAEs were considered related to trial drug. The majority of reported TEAEs were considered mild in intensity (89 of 98 events), with 7 events considered of moderate intensity (upper respiratory infection, headache [5 events], and nausea), and 2 events considered of severe intensity (elective abortions [2 events]).

The most commonly reported TEAEs overall were in the system organ class (SOC) "General disorders and administration site conditions", with the most commonly reported TEAE being IV catheter site pain, with 7 of 35 subjects (20.0%) under 480 mg IV MK-8228, 6 of 36 subjects (16.7%) under 960 mg IV MK-8228, 5 of 36 subjects (13.9%) under placebo, and 2 of 36 subjects (5.6%) under oral moxifloxacin treatment. The highest incidence of TEAEs under oral moxifloxacin treatment in this SOC comprised vessel puncture site pain (3 [8.3%] subjects) and vessel puncture site hematoma (2 [5.6%] subjects) during PK sampling. Headache was reported under all four treatments with comparable number of occurrences between treatments.

There were no clinically significant changes in clinical chemistry or urinalysis parameters during the trial. One subject experienced a single clinically significant change in a hematology parameter (low hemoglobin at Period 4 [pre-dose]), however, a normal hemoglobin value was returned following repeat testing of hemoglobin and the subject successfully completed the trial. No t reatment, or dose- related trend was observed for any clinical chemistry, hematology, or urinalysis parameters.
No clinically meaningful relationships were observed for differences between vital signs, physical examinations and ECGs as a function of treatment. The majority of abnormal physical examination findings were not considered clinically significant. Subscales of SPCT, including erythema, induration or swelling, pain, palpable cord, purulent drainage at the insertion site, tenderness, or warmth were not reported for the majority subjects during the trial (>90% of subjects). No subject was diagnosed with orreceivedtreatment forthrombophlebitisduringthetrial. A summary of TEAEs is presented as Table below:

Table 4: Treatment-Emergent Adverse Events (All-Subjects-As-Treated Population

	Treatment			
	IV Placebo N = 36 n (%) E	**480 mg IV MK-8228 N = 35 n (%) E**	**960 mg IV MK-8228 N = 36 n (%) E**	**400 mg oral Moxifloxacin N = 36 n (%) E**
All TEAEs	14 (38.9%) 23	11 (31.4%) 22	17 (47.2%) 24	17 (47.2%) 29
AEs 'Related to Trial Drug'	7 (19.4%) 11	6 (17.1%) 8	2 (5.6%) 4	11 (30.6%) 15
Mild TEAEs	13 (36.1%) 21	11 (31.4%) 21	17 (47.2%) 22	16 (44.4%) 25
Moderate TEAEs	1 (2.8%) 1	1 (2.9%) 1	2 (5.6%) 2	3 (8.3%) 3
Severe TEAEs	1 (2.8%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1
Deaths	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Serious TEAEs	1 (2.8%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1
TEAEs Leading to MK-8228 Discontinuation	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (2.8%) 1

N = Number of subjects exposed; n = number of subjects with at least one AE; % = percentage of subjects with at least one AE; E = number of events; AE = adverse event; TEAE = treatment-emergent adverse event
Data Source: [16.4]

4.2.2.3 Clinical Pharmacology

4.2.2.3.1 Pharmacokinetic Analysis

Mean plasma letermovir (MK-8228) concentrations are presented graphically in Figure 1 and the PK results are presented in Table 5.

Figure 1: Mean (± SD) MK-8228 Plasma Concentration–Time Profiles

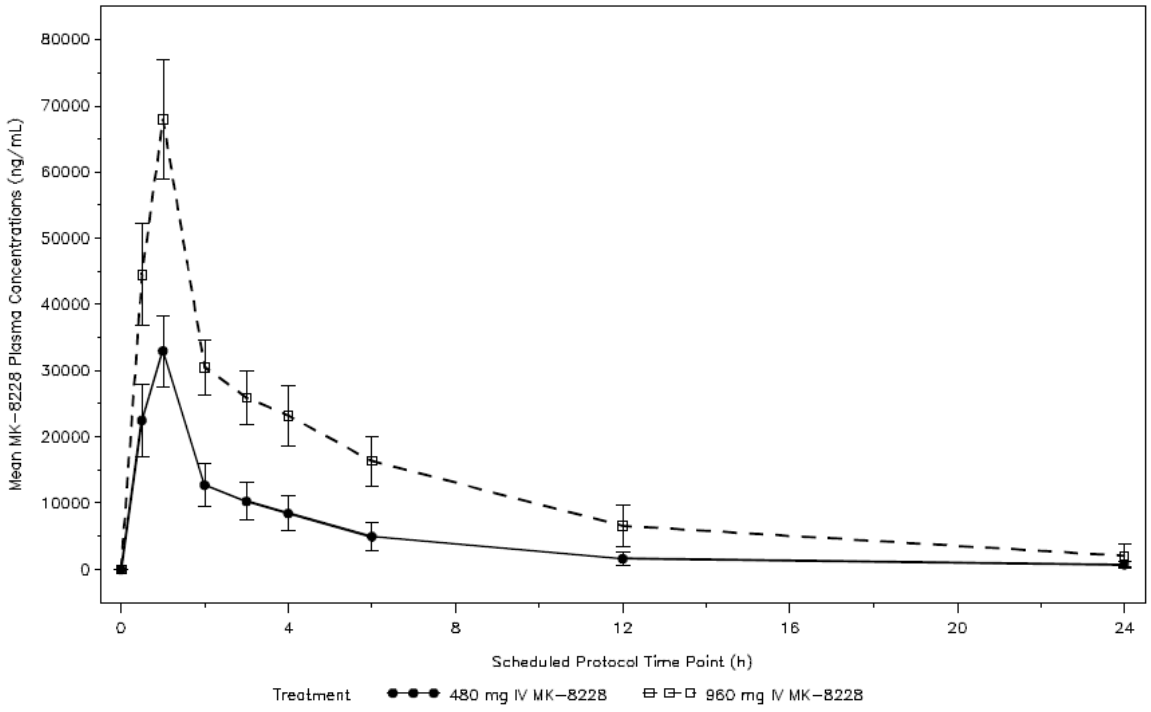


Table 5: Summary of Letermovir Plasma Pharmacokinetic Parameters Following Administration of 480 mg and 960 mg as 1-hour IV Infusions (Study P004)

	AUC0-24hr (h·ng/mL)		Cmax (ng/mL)		Tmax (h)	
Subject (AN)	960 mg IV MK-8228	480 mg IV MK-8228	960 mg IV MK-8228	480 mg IV MK-8228	960 mg IV MK-8228	480 mg IV MK-8228
n	36	35	36	35	36	35
Mean	289000	106000	67900	33000	1.01	1.01
SD	69100	30300	8960	5300	0.010	0.077
CV%	23.9	28.6	13.2	16.1	1.0	7.7
Mininum	172000	59100	46700	19400	1.00	0.60
Median	285000	102000	68700	34200	1.00	1.02
Maximum	462000	174000	82000	43600	1.03	1.17
Geometric Mean	282000	102000	67300	32600	1.01	1.00
GCV%	23.3	29.7	14.3	17.3	1.0	9.4

4.2.2.3.2 Exposure-Response Analysis

It was planned to perform an analysis of drug-placebo difference in change from baseline QTcP if the primary hypothesis is rejected (i.e. supra-therapeutic and projected clinical doses of MK-8228 does not prolong QTc interval to a clinically significant degree), using a linear mixed effects model with a fixed effect term for plasma MK-8228 concentration, and a random effect for subject. However, since the primary hypotheses were accepted this analysis was not performed, per protocol.

Since no signal was observed, PK/PD relationship analysis was not performed, per protocol.

Reviewer's Analysis: The reviewer conducted independent analyses which are presented in Section 5.3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

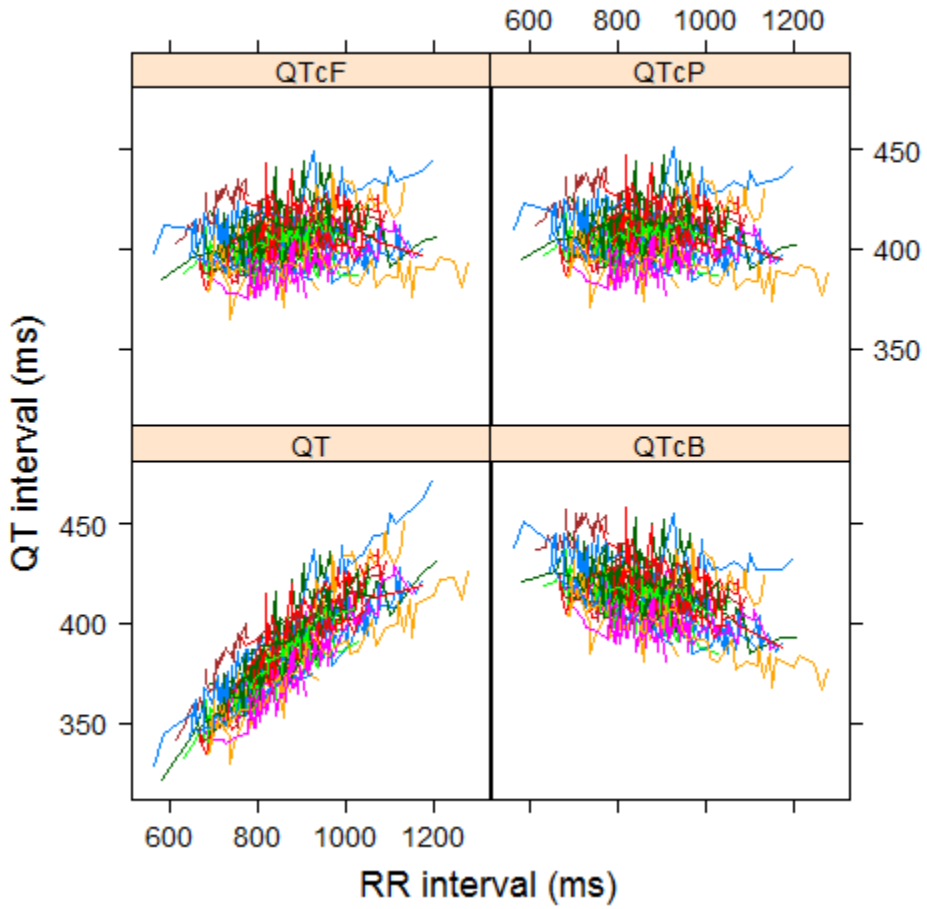
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcP is the best correction method. QTcP was estimated by a linear mixed-effects model with QTc as the dependent variable, RR as a fixed effect, and subject as a random effect. The sponsor indicated that QTcB and QTcF corrections are inadequate as the 95% CIs for the slope did not contain 0, while QTcP correction is adequate as the 95% CIs [-0.011, 0.006] for the slope estimate (-0.00245) contained 0; therefore, the primary analysis was performed on QTcP. Therefore, this statistical reviewer used QTcP for the primary statistical analysis.

Table 6: Reviewer's Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcP	
	N	MSSS	N	MSSS	N	MSSS
MK-8228 480 mg IV	35	0.0039	35	0.0031	35	0.0020
MK-8228 960 mg IV	36	0.0032	36	0.0040	36	0.0024
Moxifloxacin 400 mg	36	0.0046	36	0.0050	36	0.0035
Placebo	36	0.0041	36	0.0035	36	0.0024
All	38	0.0040	38	0.0026	38	0.0017

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcP vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for MK-8228 (letermovir)

The statistical reviewer used mixed model to analyze the ΔQTcP and ΔΔQTcP effects. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences in ΔΔQTcP between MK-8228 480 mg IV and placebo, and MK-8228 960 mg IV and placebo are 4.8 ms and 7.5 ms, respectively.

Table 7: Analysis Results of ΔQTcP and ΔΔQTcP for MK-8228 480 mg IV and MK-8228 960 mg IV

			Treatment Group							
	Placebo		MK-8228 480 mg IV				MK-8228 960 mg IV			
	ΔQTcP		ΔQTcP		ΔΔQTcP		ΔQTcP		ΔΔQTcP	
Time (h)	N	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	36	1.2	35	1.9	0.8	(-1.1, 2.6)	36	2.2	1.0	(-0.9, 2.8)
1	36	0.4	35	2.9	2.6	(0.3, 4.8)	36	5.6	5.3	(3.0, 7.5)
2	35	0.7	35	2.4	1.7	(-0.3, 3.6)	36	4.5	3.8	(1.8, 5.7)
3	36	1.6	35	2.9	1.3	(-0.5, 3.2)	36	3.8	2.2	(0.4, 4.0)
4	36	-0.3	35	2.4	2.7	(0.7, 4.7)	36	3.0	3.3	(1.3, 5.3)
6	35	-4.2	35	-3.1	1.1	(-1.2, 3.4)	35	-3.3	0.9	(-1.4, 3.2)
12	36	-3.9	35	-1.9	2.0	(-0.7, 4.6)	36	-1.6	2.3	(-0.4, 4.9)
24	35	-4.0	35	-3.6	0.4	(-2.1, 2.9)	36	-2.9	1.1	(-1.4, 3.6)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data as was used to analyze QTc data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 10.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 10.0 ms, which indicates that an at least 5 ms QTcP effect due to moxifloxacin could be detected from the study.

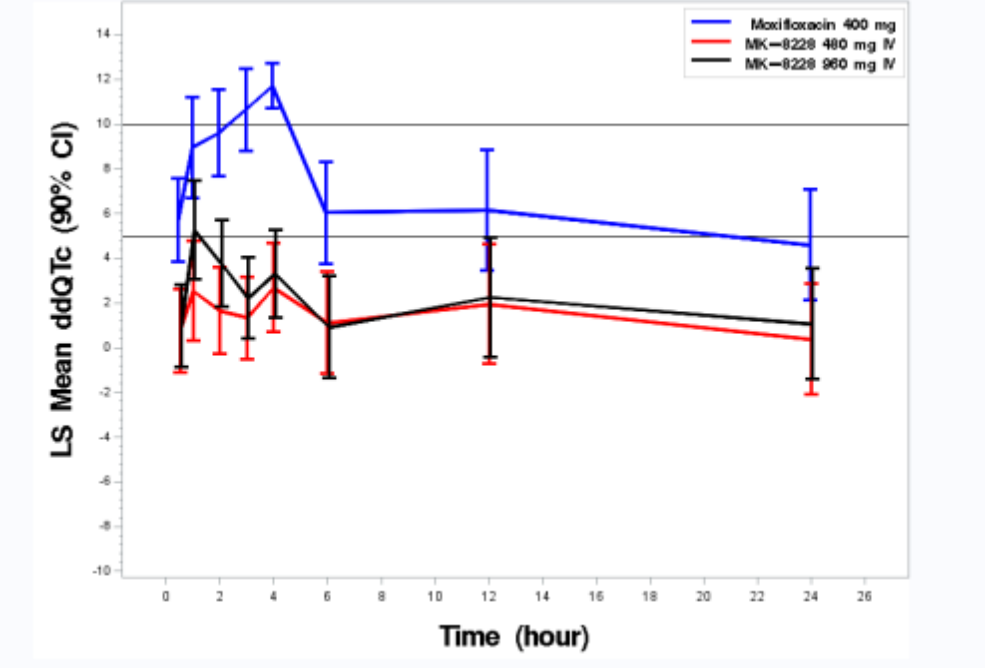
Table 8: **Analysis Results of ΔQTcP and ΔΔQTcP for Moxifloxacin 400 mg**

Treatment Group							
	Placebo		Moxifloxacin 400 mg				
	ΔQTcP		ΔQTcP		ΔΔQTcP		
Time (h)	N	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	36	1.2	36	6.9	5.7	(3.9, 7.6)	(3.2, 8.3)
1	36	0.4	35	9.3	9.0	(6.7, 11.2)	(5.9, 12.0)
2	35	0.7	35	10.3	9.6	(7.7, 11.5)	(7.0, 12.3)
3	36	1.6	35	12.2	10.6	(8.8, 12.5)	(8.1, 13.2)
4	36	-0.3	35	12.4	12.7	(10.7, 14.7)	(10.0, 15.4)
6	35	-4.2	36	1.8	6.0	(3.8, 8.3)	(2.9, 9.1)
12	36	-3.9	34	2.3	6.1	(3.4, 8.8)	(2.4, 9.8)
24	35	-4.0	36	0.6	4.6	(2.1, 7.1)	(1.2, 8.0)

5.2.1.1 Graph of ΔΔQTcP Over Time

The following figure displays the time profile of ΔΔQTcP for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcP Time Profile



5.2.1.2 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcP values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. No subject's QTcP was above 450 ms in the treatment group.

Table 9: Categorical Analysis for QTcP

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
MK-8228 480 mg IV	35	35 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MK-8228 960 mg IV	36	36 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	36	35 (97.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
Placebo	36	36 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table below lists the categorical analysis results for ΔQTcP. No subject's change from baseline was above 30 ms in the treatment group

Table 10: Categorical Analysis of ΔQTcP

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
MK-8228 480 mg IV	35	35 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MK-8228 960 mg IV	36	36 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	36	35 (97.2%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
Placebo	36	36 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-8228 480 mg IV and placebo, and MK-8228 960 mg IV and placebo are 4.2 bpm and 52 bpm, respectively. Table 12 presents the categorical analysis of HR. Two subjects in the MK-3682 doses at 480 mg IV and 960 mg IV experienced HR greater than 100 bpm. Also 1 subject in placebo group experienced HR greater than 100 bpm.

Table 11: Analysis Results of ΔHR and ΔΔHR for MK-8228 480 mg IV and MK-8228 960 mg IV

			Treatment Group							
	Placebo		MK-8228 480 mg IV				MK-8228 960 mg IV			
	ΔHR		ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	N	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	36	-1.8	35	-1.7	0.2	(-1.0, 1.3)	36	-2.4	-0.5	(-1.7, 0.7)
1	36	-2.2	35	-2.8	-0.6	(-2.0, 0.9)	36	-1.5	0.7	(-0.7, 2.2)
2	36	-0.4	35	0.5	0.9	(-0.7, 2.6)	36	-0.1	0.3	(-1.3, 2.0)
3	36	0.6	35	-0.2	-0.8	(-2.5, 0.9)	36	0.3	-0.4	(-2.0, 1.3)
4	36	0.4	35	-0.4	-0.8	(-2.7, 1.0)	36	1.8	1.4	(-0.5, 3.2)
6	36	7.6	35	9.7	2.0	(-0.1, 4.2)	36	9.9	2.3	(0.2, 4.4)
12	36	6.6	35	7.7	1.1	(-1.2, 3.3)	36	9.6	3.0	(0.8, 5.2)
24	36	3.2	35	2.1	-1.1	(-3.1, 1.0)	36	3.5	0.4	(-1.7, 2.4)

Table 12: Categorical Analysis for HR

Treatment Group	Total N	HR <= 100 bpm	HR >100 bpm
MK-8228 480 mg IV	35	34 (97.1%)	1 (2.9%)
MK-8228 960 mg IV	36	35 (97.2%)	1 (2.8%)
Moxifloxacin 400 mg	36	36 (100%)	0 (0.0%)
Placebo	36	35 (97.2%)	1 (2.8%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-8228 480 mg IV and placebo, and MK-8228 960 mg IV and placebo are 4.9 ms and 6.3 ms, respectively. Table 14 presents the categorical analysis of HR. Two subjects in the MK-8228 group experienced PR greater than 200 ms.

Table 13: Analysis Results of ΔPR and ΔΔPR for MK-8228 480 mg IV and MK-8228 960 mg IV

	Treatment Group									
	Placebo		MK-8228 480 mg IV				MK-8228 960 mg IV			
	ΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	N	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	36	1.7	35	1.9	0.2	(-1.2, 1.6)	36	3.8	2.1	(0.7, 3.5)
1	36	1.7	35	3.0	1.3	(-0.3, 2.8)	36	6.5	4.7	(3.2, 6.3)
2	35	0.6	35	3.1	2.5	(0.7, 4.4)	36	4.7	4.0	(2.2, 5.9)
3	36	-0.6	35	2.1	2.6	(1.2, 4.0)	36	3.5	4.0	(2.6, 5.5)
4	36	-0.6	35	0.6	1.1	(-0.8, 3.0)	36	1.2	1.8	(-0.1, 3.6)
6	36	-2.5	35	-2.7	-0.2	(-2.8, 2.5)	36	-1.1	1.4	(-1.2, 4.1)
12	36	-1.2	35	0.6	1.7	(-1.4, 4.9)	36	0.3	1.5	(-1.6, 4.7)
24	35	-0.7	35	-0.4	0.3	(-2.4, 3.0)	36	-1.5	-0.9	(-3.5, 1.8)

Table 14: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
MK-8228 480 mg IV	35	34 (97.1%)	1 (2.9%)
MK-8228 960 mg IV	36	35 (97.2%)	1 (2.8%)
Moxifloxacin 400 mg	36	35 (97.2%)	1 (2.8%)
Placebo	36	34 (94.4%)	2 (5.6%)

5.2.3 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between MK-8228 480 mg IV and placebo, and MK-8228 960 mg IV and placebo are 0.8 ms and 1.3 ms, respectively. Table 16 presents the categorical analysis of QRS. No subject in the MK-8228 group experienced QRS greater than 110 ms.

Table 15: Analysis Results of ΔQRS and ΔΔQRS for MK-8228 480 mg IV and MK-8228 960 mg IV

			Treatment Group							
	Placebo		MK-8228 480 mg IV				MK-8228 960 mg IV			
	ΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	N	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	36	0.1	35	0.2	0.1	(-0.2, 0.4)	36	0.5	0.4	(0.1, 0.7)
1	36	0.1	35	0.4	0.3	(-0.0, 0.6)	36	0.7	0.6	(0.3, 0.9)
2	35	-0.1	35	0.4	0.5	(0.1, 0.8)	36	0.9	1.0	(0.7, 1.3)
3	36	0.0	35	0.2	0.2	(-0.1, 0.5)	36	0.9	0.9	(0.5, 1.2)
4	36	0.1	35	0.3	0.2	(-0.2, 0.6)	36	0.7	0.6	(0.2, 1.0)
6	36	0.5	35	0.8	0.3	(-0.1, 0.8)	36	1.2	0.7	(0.3, 1.2)
12	36	0.6	35	0.7	0.1	(-0.5, 0.7)	36	0.8	0.2	(-0.4, 0.8)
24	36	-0.3	35	0.0	0.3	(-0.2, 0.7)	36	0.0	0.3	(-0.2, 0.7)

Table 16: Categorical Analysis for QRS

Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
MK-8228 480 mg IV	35	35 (100%)	0 (0.0%)
MK-8228 960 mg IV	36	36 (100%)	0 (0.0%)
Moxifloxacin 400 mg	36	36 (100%)	0 (0.0%)
Placebo	36	36 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The analysis of the submitted data and a review of the reported values in the sponsor's Clinical Study Report (CSR) for this study suggested that the letermovir concentration data submitted in the sponsor's dataset (pc.xpt) may have units of nM and not ug/mL as is reported in the dataset. With this assumption, the data was transformed into appropriate ng/mL units using the following equation:

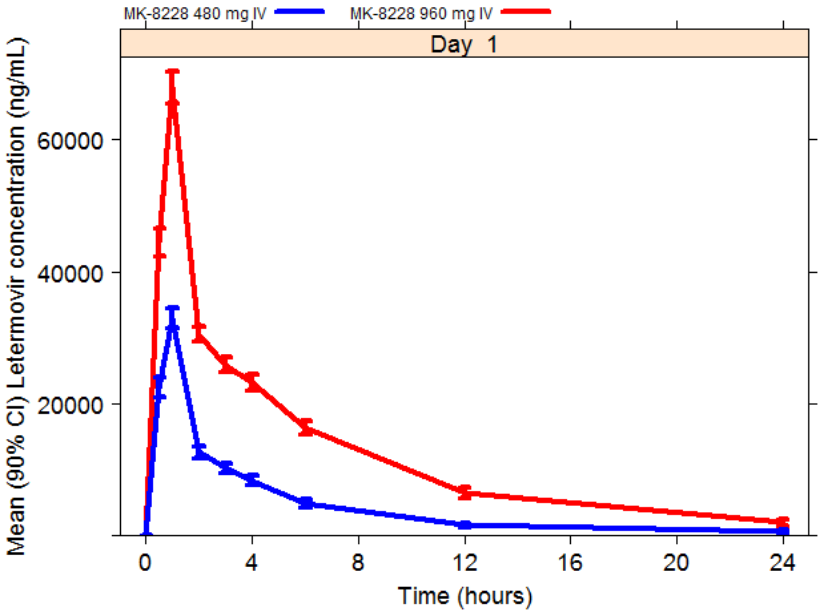
Conc. in ng/mL= Conc. in nM * Molecular weight (ng/nmol) / 1000 (mL/L)

Molecular weight of letermovir = 572.55

The individual level concentration values and the geometric mean C_{max} for subjects in each dose group matched with sponsor's reported values in CSR reasonably well after such transformation of the data.

The mean drug concentration-time profiles are illustrated in Figure 4. C_{max} value following administration of 960 mg IV letermovir (supratherapeutic dose) was 2-fold that with 480 mg IV letermovir (intended clinical dose).

Figure 4: Mean Letermovir Concentration-Time profiles for 480 mg (blue line) and 960 mg (red line) Letermovir Administered as a 1-Hour IV Infusion



The relationship between ΔΔQTcP and letermovir concentrations was investigated by linear mixed-effects modeling. Amongst three different models, a linear model with intercept was used for further analysis since this model was found to fit the data best. Table 17 summarizes the results of the letermovir concentration-ΔΔQTcP analysis. The exposure-response relationship between ΔΔQTcP and letermovir concentration is visualized in Figure 5. The relationship did not show a statistically significant positive slope.

The goodness-of-fit plot in Figure 6 shows the observed median-quantile letermovir concentrations and associated mean (90% CI) ΔΔQTcP together with the mean (90% CI) predicted ΔΔQTcP. The mean (90% CI) predicted ΔΔQTcP at the mean peak letermovir concentrations for therapeutic (480 mg IV; 32600 ng/mL) and supratherapeutic (960 mg IV; 67300 ng/mL) doses are 2.53 and 4.03 ms (shown in Figure 7) with upper bound of 90% CI of 3.48 and 5.8 ms, respectively. These upper bounds are below the 10 ms regulatory threshold.

Table 17: Exposure-Response Analysis of Letermovir-Associated ΔΔQTcP prolongation

Parameter	Estimate	p-value
Intercept (ms)	1.12 (-0.33; 2.56)	0.2008
Slope (ms per ng/mL)	4.33e-05 (4.76e-06; 8.19e-05)	0.0661
Residual Variability (ms)	5.97	

Figure 5: ΔΔQTcP vs. Letermovir Concentration

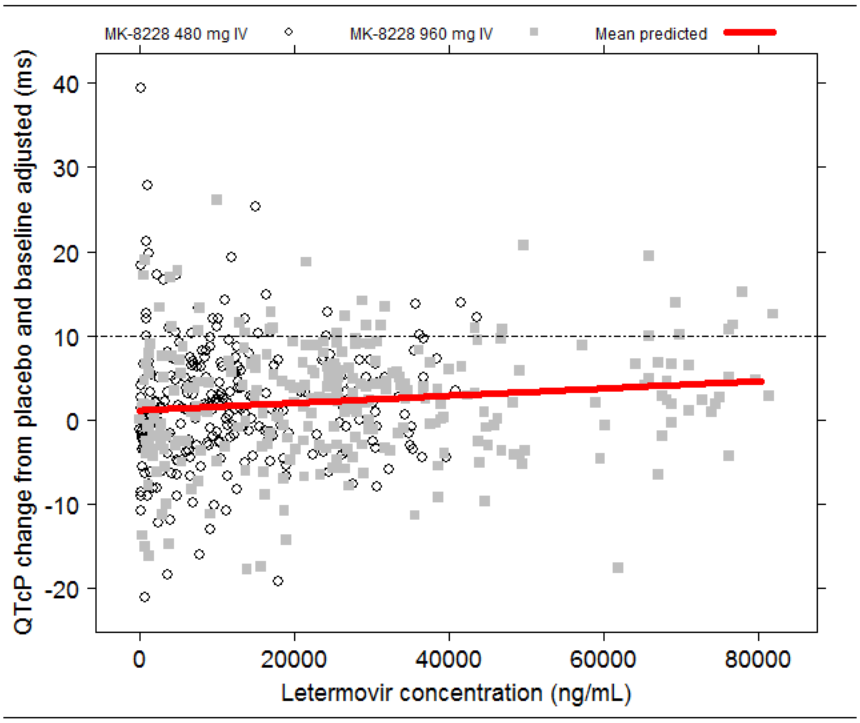


Figure 6: Model predicted ΔΔQTcP (mean and 90% CI ; black line with shaded grey area) and observed ΔΔQTcP (mean and 90% CI; colored dots) across deciles of Letermovir plasma concentrations

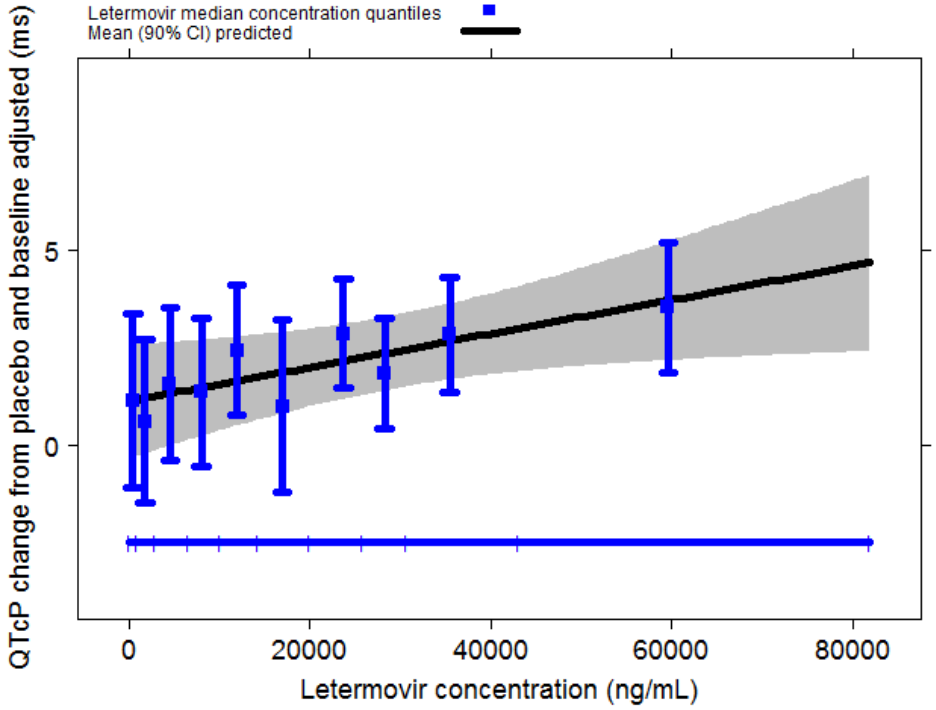
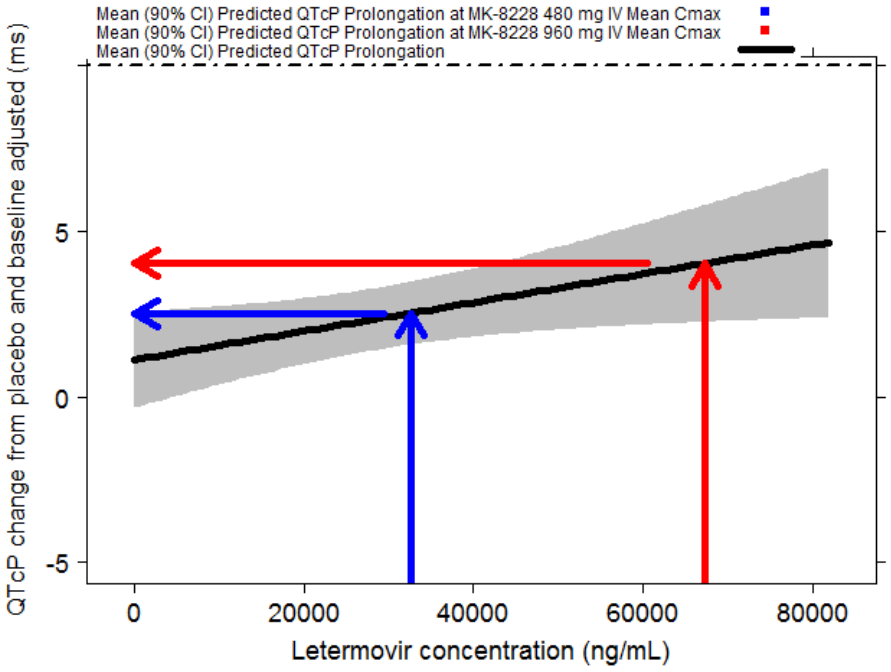


Figure 7: Mean (90% CI) Predicted ΔΔQTcP at Geo. Mean C_{max} for 480 mg and 960 mg IV Letermovir Dosing



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effects on PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Include maximum proposed clinical dosing regimen Oral once daily dose of 240 mg letermovir.	
Maximum tolerated dose	Include if studied or NOAEL dose The maximum tolerated dose was not reached so far with oral doses up to 360 mg bid letermovir and single intravenous (iv) doses up to 480 mg letermovir.	
Principal adverse events	Include most common adverse events; dose limiting adverse events No dose limiting adverse events were detected in clinical trials so far. Adverse events considered by the investigators to be at least possibly related to letermovir and reported in >1% of the subjects or patients are headache, fatigue, nausea, diarrhea, vomiting, rash, oedema peripheral, myalgia, ALAT and ASAT increased, blood alkaline phosphatase increased, dizziness, somnolence, abdominal pain or distension, blurred vision and dyspepsia. All these adverse events also occurred under placebo treatment or are usually seen in clinical trials.	
Maximum dose tested	Single Dose	Specify dose Oral: 360 mg letermovir iv: 480 mg (60 minutes infusion)
	Multiple Dose	Specify dosing interval and duration Oral: 360 mg bid letermovir for 7 days iv: trial clinically ongoing
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC <u>Oral:</u> C_{max} = 10,750 ng/mL (20%) and AUC = 71,191 ng*h/mL (39%) <u>iv:</u> C_{max} = 27,328 ng/mL (13%) and AUC = 88,585 ng*h/mL (27%)
	Multiple Dose	Mean (%CV) Cmax and AUC <u>Oral:</u> $C_{max,SS}$ = 15,441 ng/mL (29%) and $AUC_{tau,SS(12h)}$ = 103,268 ng*h/mL (44%) The latter AUC refers to a 12 h dosing interval. The AUC for a 24 h interval has to be doubled and, thus, a mean $AUC_{tau,SS(24h)}$ of 206,536 ng*h/mL has been reached.

Range of linear PK	Specify dosing regimen Single oral doses (80-360mg) and intravenous doses (30-480mg) exhibited supra-proportionality in terms of overall exposure parameters. This was particularly of note after the intravenous administrations. Multiple oral doses (30mg QD-240mg BID) gave rise to dose proportionate exposures in terms of C_{max} and AUC.	
Accumulation at steady state	Mean (%CV); specify dosing regimen Letermovir exhibits an appararent biexponential distribution and elimination phase. The initial distribution phase, after Tmax, has a half-life of 4 to 6 hours with an elimination half-life of around 10 to 17 hours. Therefore based upon the elimination half-life and a dosing frequency of once per day the accumulation factor is low. At the highest dose tested so far with once daily oral administration of 360mg, the accumulation factor was: Cmax: 0.86, AUC: 1.14.	
Metabolites	Include listing of all metabolites and activity Letermovir is metabolized in animals and in vitro to Phase 1 oxidative metabolites. However in a human [14C] radiolabelled study only one metabolite of letermovir was found in plasma and faeces. Excretion of dose related material into urine was minor accounting for less than 2% of dose material. The metabolite which was detected and accounted for less than 10% of dose related material was the 1β-O-ayclglucuronide of letermovir. Attempts to measure the activity of the acylglucuronide were not successful as the acylglucuronide exhibited instability under the bioactivity assay which had to be carried out under conditions which tended towards basicity. Under such conditions acylglucuronides exhibit chemical instability.	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) In a cross-over trial comparing a single dose of 30 mg oral letermovir with 30 mg intravenous letermovir, the absolute BA was 76 (68-84)%.
	Tmax	• Median (range) for parent 1.5h (1-4h) • Median (range) for metabolites Not applicable

Distribution	Vd/F or Vd	Mean (%CV) Vd: Mean: 195 L/h (49.24%) Range: 251.5 - 115.7 Volume of distribution decreased with increasing dose. Variability increased with the dose.
	% bound	Mean (%CV) 98.7% (7.35) to plasma protein
Elimination	Route	• Primary route; percent dose eliminated Following oral dosing of letermovir to steady-state (80mg bid, 4 days) followed by a [14C] radiotracer a mass balance study was undertaken to determine the principal routes of elimination of dose related material. Urine and faeces combined contained 94.7% of the administered dose, of this 93.3% was in the faeces. Hence the principal route of excretion of dose related material is the faeces. • Other routesUrine accounted for less than 2% of the dose
	Terminal t½	• Mean (%CV) for parent p.o.: Mean: 13.0 (22,6): Range: 9.6-21.5 hours i.v.: Mean: 14.5h (56,2%) Range 11.2-18.3 hours Terminal half life increased with the dose. Variability also increased with the dose. • Mean (%CV) for metabolites Not applicable

	CL/F or CL	Mean (%CV) CL: Mean: 9.767 L/h (19.91%) Range: 13.66 – 5.721 L/h Clearance decreased with increasing dose. Variability increased with the dose.
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC Not tested so far in a Phase 1 setting. Age was tested as a covariate in the PopPK evaluation of the Phase 2b trial AIC246-01-II-02 but was not found to be statistically significant.
	Sex	Specify mean changes in Cmax and AUC No clinically significant gender differences in body weight normalized pharmacokinetic parameters C_{max} and AUC_{τ} were observed following multiple 120, 180, and 240 mg oral bid doses to healthy male and female subjects (trial AIC246-01-I-08, Part 2) Gender was tested as a covariate in the PopPK evaluation of the Phase 2b trial AIC246-01-II-02 but was not found to be statistically significant.
	Race	Specify mean changes in Cmax and AUC Not tested so far in a Phase 1 setting. In the Phase 2 b trial AIC246-01-II-02 the effect of race was not tested because of too few subjects in the race category other than Caucasian.

	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC A hepatic impairment trial AIC246-01-I-10 was conducted to investigate the influence of severe and moderate hepatic impairment on the PK of letermovir. 60 mg letermovir was administered once daily for 8 days to moderate hepatically impaired subjects (+ healthy controls) and 30 mg letermovir was administered once daily for 8 days to severe hepatically impaired subjects (+ healthy controls). For subjects with moderate hepatic impairment, $C_{ss,max}$ and $AUC_{\tau,ss}$ values of letermovir were 1.37 and 1.59-fold higher, respectively, for total exposure and 1.57 and 1.81-fold higher, respectively, for the unbound fraction compared to healthy subjects. For subjects with severe hepatic impairment, $C_{ss,max}$ and $AUC_{\tau,ss}$ values of letermovir were 2.34 and 3.82-fold higher, respectively, for total exposure and 3.29 and 5.36-fold higher, respectively, for unbound fraction compared to healthy subjects.
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC Summary of completed DDI trials: **AIC001-1-004** A multiple dose trial in healthy male subjects to investigate safety and tolerability of letermovir and the interaction of letermovir with CsA. In Part 1 of the trial, 8 subjects received a single dose of 50 mg CsA on Days -2 and 7 as well as 80 mg letermovir bid dosing from Days 1 to 7. In Part 2 of the trial, 11 subjects received a single dose of 50 or 200 mg CsA in randomized order on Days 7 and 14 as well as a 40 mg letermovir bid dosing from Days 1 to 14.

		Results Co-administration of letermovir 80 mg bid dosed to steady-state increased the AUC of a single 50 mg dose CsA by a factor of 1.8 fold and Cmax by a factor of 1.4 fold. Conversely, a dose-dependent effect of a simultaneous administration of CsA, a CYP3A4/ ABCB1/ OATP1B3 inhibitor, on the PK of letermovir was also found. At steady-state, on 40 mg bid letermovir, coadministration of 50 mg CsA increased AUC of letermovir by 2.3 fold and Cmax by 2.1 fold; coadministration of 200 mg CsA increased AUC of letermovir by 3.4 fold and Cmax by 2.7 fold.
		AIC001-1-007 A multiple dose trial in healthy male subjects to investigate safety and tolerability of 80 mg letermovir bid and the interaction of 80 mg letermovir bid with a single oral dose of 5 mg tacrolimus.
		Results Coadministration of letermovir dosed 80 mg bid to steady-state increased the AUC for a single 5 mg dose of tacrolimus by a factor of about 1.7 and Cmax by a factor of 1.8. Conversely, there was no effect of a single 5 mg tacrolimus dose on steady state letermovir exposure.
		AIC001-2-001 proof-of-concept trial A Phase 2a, randomized, active controlled, multi-center, open-label dose ranging proof of concept trial was performed in patients with HCMV viremia following bone marrow, kidney or kidney/pancreas transplantation. Patients were randomized 1:1:1, 9 patients in each group, to the 40 mg bid letermovir or 80 mg qd letermovir treatment groups, or to an observational group (local standard of care). Pre-emptive treatment was given for 14 days.

		Results Trough levels of letermovir were increased approximately 6-fold as compared to trough levels of letermovir observed in healthy subjects. This is believed due to a DDI with co-administered CsA in the treated subjects. **AIC246-01-II-2 dose-ranging trial** In this dose ranging trial a Population Pharmacokinetic analysis of letermovir exposure showed that there was a statistically significant decrease in letermovir clearance by 43% when CsA was co-administered.
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat) The influence of a high fat, high calorie breakfast was evaluated in trial #11697 (AIC001-1-002) after an administration of 20 mg tablet of letermovir in the fed state and under fasted conditions. The high fat, high calorie breakfast led to a decreased absorption rate as reflected by prolonged t_{max} values and reduced C_{max} (median t_{max}: 1.5 versus 4 hours and lower C_{max} (least square-mean ratio [fed/fasting]: 76.40%, 90% CI: 64.61% to 90.33%). However, letermovir exposure (AUC) was not altered by the concomitant intake of food (least square-mean ratio [fed/fasting]: 97.82%, 90% CI: 91.56% to 104.52%).
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose. Based on the radiolabelled mass balance/metabolite identification	

	in healthy subjects (trial AIC246-01-I-08, Part 3), it is known that excretion of letermovir equivalents into feces (93.3% of total dose) constitutes the major elimination route of letermovir. *In vitro* data indicate that letermovir is a substrate of OATP1B1, OATP1B3, ABCB1 (P-glycoprotein) and breast cancer resistance protein (BCRP). Thus, liver transporters play a major role in the clearance of letermovir. Therefore, the inhibition of the above mentioned transporters or severe hepatic impairment is the worst case scenario in terms of increase of exposure: At 40 mg bid to 80 mg bid letermovir, coadministration of 50 to 200 mg cyclosporine (a potent OATP1B1, OATP1B3, BCRP and ABCB1 inhibitor) increased AUC of letermovir by 1.9 to 3.4-fold and C_{max} by 1.7 to 2.7-fold compared with letermovir alone (trial AIC001-I-007). In subjects with severe hepatic impairment, $C_{ss,max}$ and $AUC_{\tau,ss}$ values of letermovir were 2.3 and 3.8-fold higher, respectively, for total exposure and 3.3 and 5.4-fold higher, respectively, for unbound fraction compared to healthy subjects (trial AIC246-01-I-10).

6.2 SCHEDULE OF ASSESSMENTS

	Periods 1 through 4																		
	Day -28 to -2	Day -1	Pre-dose (Day 1)			Post-dose (Day 1)											Post-dose (Day 2)	
	Pre-Trial [a]	Admission [b]	~30 min	20 min	10 min	0 min	30 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr	6 hr	8 hr	10 hr	12 hr	24 hr Discharge	Post-trial [a]
Administrative Procedures																			
Informed Consent	X [c]																		
Informed Consent for FBR	X [c]																		
Inclusion/Exclusion Criteria	X [c]	X (review)																	
Randomization		X																	
Medical History	X [c]	X (update)																	
Concomitant Medication	X	X (update)	X----------															X	
Clinic Procedures/Assessments																			
Full Physical Examination	X	X [c]																X	X
SPCT Assessment [d]			Post-catheter placement				X		X		X				X		X	X[p]	
Height and weight [e]	X																		
12-Lead ECG [f]	X					X		X				X						X	X
24-hour Holter ECG period [g]			X----------															X	
24-hour Holter ECG extraction times [g]				X	X	X	X	X		X		X	X	X			X	X	
Vital Signs (pulse rate, BP, RR) [h]	X					X		X				X		X			X	X	X
Oral/Tympanic Temperature	X		X																
Standard Meals [i]													X			X			
Trial drug administration [j] (IV and oral)						X													
AE Monitoring	X----------																		X
Laboratory Procedures/Assessments																			
Laboratory Safety Tests [k]	X	X																X	X
β-hCG (serum)	X																		X
Urine Pregnancy Test		X																	
FSH (serum)	X																		
Urine Drug Screen (including cotinine) [l]	X	X																	
Alcohol Breathalyzer Screen	X	X																	
HIV/Hepatitis Screen	X																		
Blood for FBR [m]		X																	
PK Evaluations																			
Blood for MK-8228						X	X	X		X		X	X	X			X	X	
Blood for moxifloxacin						X	X	X		X		X	X	X			X	X	

		Periods 1 through 4																
	Day -28 to -2	Day -1	Pre-dose (Day 1)			Post-dose (Day 1)											Post-dose (Day 2)	
	Pre-Trial [a]	Admission [b]	~ 30 min	20 min	10 min	0 min	30 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	4 hr	6 hr	8 hr	10 hr	12 hr	24 hr Discharge	Post-trial [n]
Other Procedures																			
Domiciling [g]		X----------																----------X	

AE=adverse event; BP=blood pressure; CRU = clinical research unit; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; β-hCG=serum β-human chorionic gonadotropin; HIV=human immunodeficiency virus; IV=intravenous; PK=pharmacokinetics; RR=respiratory rate; SPCT=Short peripheral catheter thrombophlebitis

NOTE: All time points are relative to the start of 60-minute IV infusion (or time of moxifloxacin administration).

[a] Pre-trial evaluations were conducted within approximately 4 weeks prior to administration of the initial dose of trial drug in Treatment Period 1.
[b] Subjects reported to the CRU the day prior to each treatment period, to ensure a fasting period of at least 10 hours prior to dose administration of MK-8228 or moxifloxacin.
[c] May have been performed up to 24 hours pre-dose.
[d] Assessments were performed for both the infusion and PK arm after indwelling IV-catheter is in place. NOTE: Ultrasound examination was performed if SPCT score was ≥3.
[e] Obtained height without shoes and weight without shoes and coat/jacket.
[f] All 12-lead safety ECGs were single measurements performed after the subjects had been resting semi-recumbent for at least 10 minutes.
[g] Continuous (24-hour) Holter ECG measurements were performed from approximately 30 minutes prior to dose administration and until 24 hours post-dose. Five (5) replicate, 10-second, 12-lead ECG recordings will be extracted pre-dose at 20 minutes, 10 minutes and immediately prior to dosing (for baseline measurements) and at each post-dose time point: i.e., 30 minutes, 1, 2, 3, 4, 6, 12, and 24 hours post start of infusion. Please see Trial Operations Manual for Holter-specific procedures provided by the (b) (4)
(b) (4)
[h] Obtained vital signs after resting semi-recumbent for 10 minutes.
[i] Subjects fasted overnight for at least 10 hours prior to dose administration. Standardized meals were provided at 4 and 10 hours post-dose (including a snack at approximately 12 hours post-dose). NOTE: The caloric content and composition of meals were identical in each period.
[j] MK-8228 was administered over a 60-minute interval using an infusion pump. Moxifloxacin was administered with approximately 240 mL water.
[k] See the trial protocol [16.1.1] Section 7.1.3.1 and Appendix 12.4 for laboratory tests and algorithm for assessing out-of-range laboratory values. Pre-dose laboratory procedures could have been conducted up to 24 hours prior to dosing.
[l] Performed at pre-trial and on admission to each treatment period (including amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, cannabinoids and methadone. Cotinine (measure of smoking status) was also tested.
[m] Informed consent for future biomedical research samples was obtained before the DNA sample. DNA sample for analysis were obtained on Day -1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent was obtained.
[n] Subjects were admitted to the CRU the day prior to scheduled dose (for fasting purposes) and remained in-house until all 24 hour post-dose assessments have been completed. Subjects were discharged and instructed to return to the CRU at least 7 days later for commencement of the following treatment period.
[o] Post-trial procedures were performed 14 ± 1 day after conduct of the last trial procedure in the final treatment period.
[p] If the SPCT score was ≥1 for any of the subscales at 24 hours after dosing, additional evaluations followed at 48 hours and, if the score was still ≥1 at 48 hours, at 72 hours. Further additional evaluations may have been performed at additional times at the discretion of the investigator.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MOH JEE NG
05/31/2017

MOHAMMAD A RAHMAN
06/01/2017

MICHAEL A BEWERNITZ
06/01/2017

DHANANJAY D MARATHE
06/01/2017

MICHAEL Y LI
06/01/2017

CHRISTINE E GARNETT
06/01/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209939 NDA # 209940	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)

Proprietary Name: N/A (under review)
Established/Proper Name: Letermovir (MK-8228)
Dosage Form: tablets and injection
Strengths: Tablets: 240 mg, 480 mg, Injection: 240 mg/12 mL, 480 mg/24 mL
Routes of Administration: oral/Intravenous infusion

Applicant: Merck Sharp & Dohme Corporation, a subsidiary of Merck & Company, Incorporated
Agent for Applicant (if applicable):

Date of Application: 3/8/2017
Date of Receipt: 3/8/2017
Date clock started after Unacceptable for Filing (UN):

PDUFA/BsUFA Goal Date: 11/8/17	Action Goal Date (if different):
Filing Date: 5/7/17	Date of Filing Meeting: 4/10/17

Chemical Classification (original NDAs only) :

☒ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch
☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval)
☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)

Proposed indication: prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)

Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☒ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Numbers: 104706, 118361	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

- Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**

- Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?**

If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

- If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	☒		Orphan Drug Designation-exempt
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829 htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837 htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Conditionally approved under INDs 104706/118631
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT-IRT DBRUP-Testicular toxicity DCRP-cardiac toxicities
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 9/25/2013	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 12/14/2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** 4/28/2011	☒			Mouse and rat carcinogenicity

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 6, 2017

BACKGROUND: Letermovir (MK-8228) is a novel inhibitor of cytomegalovirus (CMV) DNA terminase complex, which is required for viral DNA replication. Letermovir was evaluated under IND 104706 (tablets) and IND 118361 (intravenous infusion) for the prevention of CMV infection in adult CMV seropositive [R+] allogeneic hematopoietic stem cell transplant (HSCT) recipients. The FDA granted Fast Track Designation on May 25, 2011 and Orphan Drug Designation on December 12, 2011, to AiCuris. IND 104706 was transferred from AiCuris to Merck on April 29, 2013. Breakthrough Therapy Designation was granted on February 27, 2017, for the tablet formulation, for the proposed indication.

NDAs 209939 (tablets) and 209940 (IV solution) were submitted and received on March 8, 2017, for the (b) (4) of CMV infection in adult CMV seropositive [R+] allogeneic hematopoietic stem cell transplant (HSCT) recipients. These New Molecular Entity (NMEs) will be managed in The Program and were granted Priority Review. The Pre-NDA Meeting was held December 14, 2016 and there were no agreements made for submission of late components. The PDUFA Due Date is November 8, 2017.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Victoria Tyson	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Andreas Pikis/Mary Singer		Y
Division Director/Deputy	Jeff Murray/Debra Birnkrant		Y
Office Director/Deputy	Ed Cox/John Farley		Y
Clinical	Reviewer:	Aimee Hodowanec	Y
	TL:	Mary Singer	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Takashi Komatsu Eric Donaldson	Y
	TL:	Julian O'Rear	Y

Clinical Pharmacology	Reviewer:	Mario Sampson	Y
	TL:	Islam Younis	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Fraser Smith	Y
	TL:	Thamban Valappil Dionne Price	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Mc Millan	Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Steve Miller	Y
	RBPM:	Luz Rivera	Y
• Drug Substance	Reviewer:	Gene Holbert	Y
• Drug Product	Reviewer:	Yong Wang	Y
• Process	Reviewer:	Ying Wang	Y
• Microbiology	Reviewer:	Jonathan Bogus	Y
• Facility	Reviewer:	Rebecca Dombrowski	N
• Biopharmaceutics	Reviewer:	Qi Zhang	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	James Laurenson		Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Susan Redwood	Y
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Wendy Lubarsky	Y
	TL:	Sam Skariah	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Valerie Wilson	Y
	TL:	Otto Townsend	Y
OSE/DRISK (REMS)	Reviewer:	Susan Bersoff-Matcha	Y
	TL:	Mihaela Jason	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Antonio El Hage	Y
	TL:	Susan Thompson	N

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: BTDR
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☒ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Edward Cox/Jeff Murray **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): June 5, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA L TYSON
05/05/2017

ELIZABETH G THOMPSON
05/05/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDAs 209939/0
209940/0

Application Type: NEW NDAs

Drug Name(s)/Dosage Form(s): letermovir, 240 mg, 480 mg tablets
letermovir, 240 mg/12mL, 480 mg/24 mL, solution for intravenous injection

Applicant: Merck Sharp & Dohme Corporation, a subsidiary of Merck & Company

Receipt Date: **3/8/2017**

Goal Date: **11/8/2017**

1. Regulatory History and Applicant's Main Proposals

Letermovir, a novel inhibitor of cytomegalovirus (CMV) DNA terminase complex, that is indicated for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of allogeneic hematopoietic stem cell transplant (HSCT). Letermovir was evaluated for the proposed indications under INDs 104706 (tablets) and 118361 (solution of IV infusion) and was granted Fast Track Designation, May 25, 2011 and Breakthrough Therapy Designation, February 27, 2017. In addition, Letermovir received Orphan Drug Designation on December 12, 2011. Letermovir will be provided in 240 mg and 480 mg tablets and 240 mg/12 mL and 480 mg/24 mL solution for intravenous infusion.

Letermovir is a New Molecular Entity that will be reviewed under the PDUFA V Program and will be granted Priority Review. The PDUFA due date is November 8, 2017. The Pre-NDA Meeting was held on December 14, 2016, and there were no agreements made for the submission of late components.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

---

4. Selected Requirements of Prescribing Information

Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

(insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch."

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *Update prior to approval*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]."*

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *New NDAs*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA L TYSON
04/13/2017

ELIZABETH G THOMPSON
04/14/2017