CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209939Orig1s000
209940Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209939 NDA # 209940	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: PREVYMIS Established/Proper Name: letermovir Dosage Form: 240 mg and 480 mg tablets 240 mg/12 mL and 480 mg/24 mL Injection		Applicant: Merck Sharp & Dohme Corporation, a subsidiary of Merck & Company Agent for Applicant (if applicable):
RPM: Victoria Tyson		Division: Division of Antiviral Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 11/8/17	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☒ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Twitter, Facebook and OHCAs newsletter
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 11/8/17
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	5/25/17 5/24/17
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 4/14/17 (PLR format) DMEPA: 8/5/17; 11-9-17 DMPP/PLT (DRISK): 10/5/17 OPDP: 10/6/17 SEALD: ☒ None CSS: ☒ None Product Quality 8/7/17
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	5/5/17 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Drug Designation	N/A
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	2/27/17 (granted; under INDs 104706 and 118361)
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	2/22/17
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	11/1/17, 11/3/17 teleconference minutes
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	12/14/2016
• EOP2 meeting *(indicate date of mtg)*	9/25/2013
• Mid-cycle Communication *(indicate date of mtg)*	6/15/2017
• Late-cycle Meeting *(indicate date of mtg)*	9/8/2017
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	11/8/17
Division Director Summary Review *(indicate date for each review)*	10/27/17
Cross-Discipline Team Leader Review *(indicate date for each review)*	10/11/17
PMR/PMC Development Templates *(indicate total number)*	4

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	8/7/17
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	8/7/17; page 155
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	6-1-17 (QT-IRT) 6-5-17 (DBRUP clinical) 6-6-17 (DBRUP nonclinical) 6-9-17 (DCRP)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	8/3/17
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	8/14/17 (review summary) 9-11-17 (letter) 10-31-17 (letter)
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	7/20/17, 8/8/17, 11/7/17
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	8/8/17
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	8/8/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	7/31/17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	209939 and 209940: Review 1-08/18/17 209939 and 209940: Review 2-11/6/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	6/1/17
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done N/A
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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/s/

VICTORIA L TYSON
11/09/2017

ELIZABETH G THOMPSON
11/09/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 3, 2017

Application Number: 209939
Product Name: Letermovir 240 mg and 480 mg tablets
Applicant Name: Merck Sharp & Dohme Corporation

Subject: Carton and Container Labeling

FDA Participants : Stephen Miller, Ph.D., Product Quality Team Leader
Aimee Hodowanec, MD, Medical Officer
Andreas Pikis, MD, Cross Discipline Team Leader
Mary Singer, MD, Ph.D., Medical Team Leader
Valerie Wilson, Pharm D., DMEPA Reviewer
Otto Townsend, Pharm D., DMEPA Team Leader
Barbara Fuller, RN, MSN, CWOCN, Patient Labeling Team Leader

Applicant Participants : Randi Leavitt, M.D., Ph.D. Executive Director, Clinical Research
Anita Shaw, Ph.D. Director, Regulatory Affairs
Laurie MacDonald, M.D., Executive Director, Regulatory Affairs
Karen Ciprero, M.S., Associate Director, Labeling
Jill Williams, B.S., Specialist, Labeling
Holly Spriggs, BFA, Associate Director, Labeling

1.0 BACKGROUND:

This teleconference was held to discuss and come to an agreement on the carton and container labels for the letermovir tablets.

2.0 DISCUSSION:

The carton and container labeling for the letermovir tablets was discussed and Merck agreed to revise the labeling to include the following recommendations:

1. "Store PREVYMIS at room temperature between 68°F to 77°F (20°C to 25°C)" [on both parts of 7-day dose pack, and 28-day carton]

2. "Take 1 PREVYMIS tablet once a day" on container labels and revise the Patient Package Insert to include this statement as well.

3. "Store PREVYMIS in the original package until you are ready to take it." (On monthly carton)

4. “Store PREVYMIS in this package until you are ready to take it.” (on both parts of 7-day dose pack)

3.0 ACTION ITEMS:

- Merck will submit clean versions of the carton and container labels that includes the revisions discussed and agreed upon.

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/s/

VICTORIA L TYSON
11/08/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: November 2, 2017

To: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs
and Clinical Safety

From: Victoria Tyson,
Senior Regulatory Project Manager

Sponsor: Merck Sharp & Dohme Corporation

NDA: 209939/0
209940/0

Drug: MK-8228 (letermovir) 240 mg, 480 mg, tablets
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL
solution for intravenous injection

Subject: Information Request-PMCs and PMR

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and as discussed during the November 2, 2017, teleconference we are establishing the following postmarketing commitments (PMCs) and postmarketing requirement (PMR) listed below. Please review the PMCs and the PMR and provide concurrence or the timeline for the milestones:

Postmarketing Requirement

Clinical Virology

1. Conduct phenotypic analysis of letermovir against 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.

PMR Schedule Milestones:

Draft Protocol Submission:	02/2018
Final Protocol Submission:	05/2018
Study/Trial Completion:	10/2019
Final Report Submission:	MM/YYYY

Postmarketing Commitments

Clinical

2. (b) (4)

3. 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."

PMC Schedule Milestones:

Draft Protocol Submission:	05/2017
Final Protocol Submission:	01/2018
Study/Trial Completion:	06/2022
Final Report Submission:	MM/YYYY

Clinical Pharmacology

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

PMC Schedule Milestones:

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

Please provide a response by response by 3:00 PM, November 3, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

_____

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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
11/02/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date:	November 1, 2017
Application Numbers:	209939/209940
Product Name:	**Letermovir, tablets and injection**
Applicant Name:	**Merck Sharp & Dohme Corporation**
Subject:	Postmarketing Commitments and Requirements
FDA Participants :	Aimee Hodowanec, M.D. Medical Officer Andreas Pikis, M.D., Cross Discipline Team Leader Mary Singer, M.D.,Ph.D., Medical Team Leader Fraser Smith, Ph.D., Biometrics Thamban Valappil, Ph.D., Biometrics Team Leader Mario Sampson, Pharm D., Clinical Pharmacology David McMillan, Ph. D., Nonclinical Takashi Komatsu, Ph.D., Clinical Virology Anamaris Colberg Poley, Ph.D., Clinical Virology Julian O'Rear, Ph.D., Clinical Virology Team Leader Poonam Mishra, M.D., MPH, Deputy Director for Safety Jeffrey Murray, M.D., MPH, Deputy Director Debra Birnkrant, M.D., Director
Applicant Participants :	Cyrus Badshah, M.D., Ph.D. Senior Principal Scientist, Clinical Research Yoshihiko Murata, M.D., Ph.D., Senior Principal Scientist, Clinical Research Randi Leavitt, M.D., Ph.D., Executive Director, Clinical Research Joan Butterton, M.D., Executive Director Clinical Research Hong Wan, Ph.D., Principal Scientist, Biostatistics Valerie Teal, Ph.D., Senior Principal Scientist, Clinical Biostatistics Lisa Lupinacci, Ph.D. Associate Vice President, Clinical Biostatistics Cameron Douglas, Ph.D., Senior Principal Scientist, Discovery Biology Suman K. Mukherjee, Ph.D. Director, Toxicology Sandrine Ferry-Martin, Director, Toxicology Sreeraj Macha, Ph.D. Senior Principal Scientist, Quantitative Pharmacology Prajakti Kothare, Ph.D., Executive Director, Pharmacokinetics Vikram Sinha, Ph.D. Associate Vice President, Quantitative Pharmacology

Karsten Menzel, Ph.D., Principal Scientist, PPDM – Preclinical ADME
Jacqueline McCrea, PharmD Senior Principal Scientist, Translational Pharmacology
Marian Iwamoto, M.D., Ph.D. Associate Vice President, Translational Pharmacology
Catherine Hardalo, M.D., Senior Principal Scientist, CSRM
Nicole Mahoney, Ph.D., Director, Global Regulatory Policy
Karen Ciprero, M.S., Associate Director, Labeling
Jill Bradley, M.S., MBA, Director, Labeling
Anita Shaw, Ph.D., Director, Regulatory Affairs
Laurie MacDonald, M.D., Executive Director, Regulatory Affairs

1.0 BACKGROUND:

This teleconference was held to discuss and come to an agreement on the Prescribing Information (PI) and the postmarketing commitments (PMCs) and postmarketing requirements (PMRs) that will be established at the time of approval of the letermovir NDAs, 209939 for tablets and 209940 for injection.

2.0 DISCUSSION:

PMCs and PMRs

On October 24, 2017, the Division of Antiviral Products (DAVP) issued proposed PMCs/PMRs that will be established with the approval of the letermovir NDAs. Merck provided their response to the proposed PMC/PMRs on October 31, 2017. Merck agreed to conduct all the proposed PMCs and PMRs (with revised timelines) except the proposed PMR to evaluate the occurrence of late CMV reactivation in HSCT recipients when letermovir prophylaxis is extended to 200 days. Merck stated that (b) (4) Division's proposal and Merck's response are as follows:

DAVP's proposed PMR:

> Conduct a trial in cytomegalovirus (CMV) seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT) to evaluate the occurrence of late CMV (b) (4) when letermovir prophylaxis is extended (200 days compared to 100 days).

Merck's proposal PMC:

(b) (4)

The DAVP stated that per their calculations, a sample size of 190 subjects per arm would be sufficient for the proposed trial. DAVP further noted that there are around 20,000 HSCTs performed worldwide per year and that clinical trial P001 enrolled quickly. In addition, DAVP informed Merck that if prolonged prophylaxis is shown to reduce the rate of late CMV reactivation, labeling changes may be warranted. The importance of identifying the optimal duration of prophylaxis to inform physicians on how to best manage these complex patients was reiterated.

Merck stated that although they had not discussed this internally, they would agree to a total sample size of 200 subjects. Merck noted that the reason their calculations suggested the need for a larger sample size than DAVP's calculations seemed to be due to the fact that DAVP planned to randomize at the time of transplant whereas they had planned to randomize at Day 100. Merck voiced a strong preference for randomizing subjects at Day 100. DAVP informed Merck their proposal is acceptable. Additional feedback will be provided following submission and review of the protocol.

Following this teleconference, on November 3, 2017, Merck agreed to conduct the 100 vs 200 CMV clinical trial as described below as a PMC:

> 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.

Letermovir IV Dose

Based on PK data from Trial P001, DAVP believes that the exposure with the 480 mg IV letermovir dose is higher than necessary. DAVP reviewed the modeling and simulation analysis submitted by Merck on October 27, and concluded that exposure with the 240 mg IV dose (without cyclosporine) may be sufficient. However, given the lack of data for the 240 mg IV letermovir dose (without cyclosporine) as well as the absence of an identified safety signal with the IV letermovir formulation, DAVP agreed that the recommended IV dose for letermovir in the absence of cyclosporine co-administration would remain 480 mg daily. However, DAVP and

Merck agreed that the optimal IV letermovir dose could be further explored in the planned renal transplant trial (described below).

> Submit the final study report and datasets from the proposed clinical trial, P002, entitled, "A Phase 3, 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."

Merck stated that they will need to give further thought to how to best study the different IV doses, particularly given the anticipated infrequent need for IV administration in the renal transplant population.

Labeling

Merck's response to our labeling dated and received October 27, 2017, was discussed. Merck rejected the following language proposed in the Dosing and Administration Section 2.2, regarding monitoring CMV patients:

> Following the completion of PREVYMIS prophylaxis, close monitoring for CMV reactivation is recommended. Monitoring should begin within 1-2 weeks of PREVYMIS discontinuation and should continue through 24 weeks post-transplantation.

DAVP informed Merck that this language is very important and based on the Guidance is appropriate for inclusion in the Dosing and Administration section of the label. Merck was informed that the other potential section of the label where such a recommendation could be made is the Warnings and Precautions Section (Section 5). Both parties agreed that a warning was not necessary. The Division proposed that the recommendation be placed in a new subsection in Section 2. Further, DAVP agreed to make the recommendation more general (i.e., remove the proposed time frame for monitoring). Merck agreed to this proposal.

The following language proposed in Section 14 was discussed:

DAVP informed Merck that this analysis was not prespecified and was therefore subject to bias. Merck remarked that this statement contains important information for clinicians. DAVP ultimately agreed that although the statistical robustness of this analysis is lacking, as the statement is conveying safety information more than efficacy information, it is appropriate to include this information in the label. However, DAVP proposed revision of the statement to convey the post-hoc nature of the analysis and the lack of certainty regarding the findings. Merck agreed to this proposal.

Clinical Pharmacology

Merck did not include rifampin in Table 3 as requested. DAVP informed Merck that given similar overlapping pathways of letermovir, glecaprevir and pibrentasvir, and that rifampin reduced glecaprevir and pibrentasvir exposures by ~90%, DAVP does not recommend using rifampin with letermovir. Merck will review the drug-drug interaction data for the examples provided and update the labeling accordingly.

The contraindication of pitavastatin and simvastatin in patients prescribed letermovir plus cyclosporine was discussed. The DAVP explained that the contraindication should be stated in labeling Section 4-Contrainidication as well as Section 7-Drug Interactions. The Division will propose language in the next labeling proposal for review and comment.

The DAVP informed Merck this was a productive discussion and plans to complete labeling negotiations by November 3, 2017, to prepare to take a positive action on or before November 8, 2017.

3.0 ACTION ITEMS:

- The DAVP will send Merck a revised description of the 100 versus 200 day PMC for review and concurrence.
- The DAVP will propose revisions to the Package Insert discussed for review and comment.
- Merck agreed to further explore the optimal IV letermovir dose in the planned renal transplant trial.

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/s/

VICTORIA L TYSON
11/08/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **October 24, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-PMC PMR**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and are establishing the postmarketing commitments (PMC) and postmarketing requirements (PMRs) listed below. Please review the PMCs and PMRs and provide concurrence and/or timelines for the milestones:

Postmarketing Requirements

Clinical

1. Conduct a trial in cytomegalovirus (CMV) seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT) to evaluate the occurrence of late CMV

[redacted] (b) (4) when letermovir prophylaxis is extended (200 days compared to 100 days).

PMR Schedule Milestones:

Draft Protocol Submission: MM/YYYY
Final Protocol Submission: MM/YYYY
Study/Trial Completion: MM/YYYY

Clinical Virology

2. Conduct phenotypic analysis of letermovir against HCMV mutants carrying the following pUL56 and pUL89 substitutions using bacterial artificial chromosome technology:

[redacted] (b) (4)

Please 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.

PMR Schedule Milestones:

Draft Protocol Submission: MM /YYYY
Final Protocol Submission: MM /YYYY
Study/Trial Completion: MM /YYYY

Postmarketing Commitments

Clinical

3. 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."

PMC Schedule Milestones:

Draft Protocol Submission: 05/2017
Final Protocol Submission: 01/2018
Study/Trial Completion: 06/2022

Clinical Pharmacology

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

PMC Schedule Milestones:

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

Please provide a response by response by noon on Tuesday, October 31, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

_____

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
10/24/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: October 24, 2017

To: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs
and Clinical Safety

From: Victoria Tyson,
Senior Regulatory Project Manager

Sponsor: Merck Sharp & Dohme Corporation

NDA: 209939/0
209940/0

Drug: MK-8228 (letermovir) 240 mg, 480 mg, tablets
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL
solution for intravenous injection

Subject: Information Request-PMC PMR

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and are establishing the postmarketing commitments (PMC) and postmarketing requirements (PMRs) listed below. Please review the PMCs and PMRs and provide concurrence and/or timelines for the milestones:

Postmarketing Requirements

Clinical

1. Conduct a trial in cytomegalovirus (CMV) seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT) to evaluate the occurrence of late CMV

[redacted] (b) (4) when letermovir prophylaxis is extended (200 days compared to 100 days).

PMR Schedule Milestones:

Draft Protocol Submission:	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study/Trial Completion:	MM/YYYY

Clinical Virology

2. Conduct phenotypic analysis of letermovir against HCMV mutants carrying the following pUL56 and pUL89 substitutions using bacterial artificial chromosome technology:

[redacted] (b) (4)

Please 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.

PMR Schedule Milestones:

Draft Protocol Submission:	MM /YYYY
Final Protocol Submission:	MM /YYYY
Study/Trial Completion:	MM /YYYY

Postmarketing Commitments

Clinical

3. 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……", to assess the safety and efficacy of letermovir versus valganciclovir [redacted] (b) (4)

PMC Schedule Milestones:

Draft Protocol Submission:	05/2017
Final Protocol Submission:	01/2018
Study/Trial Completion:	06/2022

Clinical Pharmacology

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

PMC Schedule Milestones:

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

Please provide a response by response by noon on Tuesday, October 31, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

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Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
10/24/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **October 20, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following comments and requests for additional information:

Clinical

Although the letermovir 480 mg intravenous dose was studied in phase 3, we believe that the exposures associated with this dose may be unnecessarily high. Lower exposures with oral dosing were shown to be effective. Unnecessarily high exposures put patients at potential risk of letermovir and/or beta-cyclodextrin toxicity. Please model and simulate exposures for 240 mg intravenous letermovir (without cyclosporine). Please

provide this data within one week of the receipt of this Information Request. Our strong preference is to address this issue prior to approval in this review cycle.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

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Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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VICTORIA L TYSON
10/20/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **September 11, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following comments and requests for additional information:

Clinical

Please perform exposure-adjusted safety analyses for adverse events under the cardiovascular disorders system organ class (SOC). Please perform this analysis at the SOC level (i.e. the number of subjects in each arm who experienced any cardiac adverse event) and also at the preferred term (PT) level for PTs reported in > 1 subject who received letermovir. In addition, please describe the timing and distribution of these cardiac events.

Please submit the dataset by COB on September 18, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
09/11/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **August 28, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following comments and requests for additional information:

Clinical

1. In your August 22, 2017 labeling response you claimed that some of the differences in laboratory abnormalities between the letermovir arm and the placebo arm may be due to the longer treatment phase of the letermovir arm compared to that of the placebo arm. This hypothesis may be acceptable if the timing of the occurrence of the laboratory abnormalities was well distributed across the letermovir treatment phase. Please submit an assessment of the timing and distribution of the creatinine, hemoglobin, and platelet abnormalities.

2. Please perform additional exposure adjusted safety analyses (similar to what was done for laboratory abnormalities in your labeling response of August 22, 2017) and describe the timing and distribution for each of the following:

   a. Adverse events in the Infection and infestation System Organ Class
   b. All common adverse events included in the revised Table 1 in the label (nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, and abdominal pain).
   c. All less common adverse events that we have proposed be included in Section 6 of the label (dry mouth, hemorrhoids, asthenia, pneumonia, bacteremia, myalgia, insomnia, tremor, anxiety, and dyspnea).

3. Due to the observed increased rate of cardiac events in Trial P001, we requested that The Division of Applied Regulatory Science in the Office of Clinical Pharmacology complete a computational assessment and literature review for letermovir to identify potential mechanisms of action for the observed cardiac events. This assessment is being submitted for your review (see attached). Please inform us of any searches you may have performed for potential targets for letermovir and submit all findings. Additionally, please let us know how you propose to further investigate the identified potential targets.

Please submit the dataset by COB on September 12, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

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Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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VICTORIA L TYSON
08/29/2017

From:	Thompson, Elizabeth
To:	"Shaw, Anita (anita_shaw@merck.com)"
Cc:	Tyson, Victoria; Onaga, Linda; Thompson, Elizabeth
Subject:	Letermovir: Expanded Access Information Request
Date:	Thursday, August 17, 2017 11:49:58 AM
Attachments:	image002.png
Importance:	High

Please refer to your INDs for letermovir tablet and injection (INDs 104706 and 118361) and to your pending Original NDA applications currently under review (NDAs 209939 and 209940). We have the following request for information and would like a response by next week:

The Division of Antiviral Products (DAVP) occasionally receives requests for single patient emergency INDs (EINDs) for investigational anti-CMV drugs for the treatment of resistant/refractory CMV infection. Would Merck consider making letermovir available through this expanded access program (compassionate use)? If so, what letermovir dose would you recommend and what data do you have to support any proposed dose? We are interested in discussing this matter further with you by teleconference if you are agreeable.

Please confirm receipt of this correspondence. In addition, please copy Linda Onaga (EIND coordinator) on your response.

Regards,

Elizabeth Thompson, M.S.
CDR, U.S. Public Health Service

Chief, Project Management Staff

Center for Drug Evaluation and Research
Office of New Drugs
U.S. Food and Drug Administration
Tel: 301-796-0824
elizabeth.thompson@fda.hhs.gov

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/s/

ELIZABETH G THOMPSON
08/17/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: August 8, 2017

To: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs
and Clinical Safety

From: Victoria Tyson,
Senior Regulatory Project Manager

Sponsor: Merck Sharp & Dohme Corporation

NDA: 209939/0
209940/0

Drug: MK-8228 (letermovir) 240 mg, 480 mg, tablets
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL
solution for intravenous injection

Subject: Information Request-Carton and Container Labeling

Please refer to your NDAs dated and received March 8, 2017, for letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We reviewed the carton and container labeling and have the following comments and requests for revisions:

Carton and Container Labeling

1. Replace "Tradename" on all container labels and carton labeling with the conditionally acceptable proprietary name "Prevymis."

2. The perforated blister cards contained in the 14-count tablet cartons (b) (4) (b) (4) (b) (4) 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.

3. We note that different statements are used for the storage conditions in the dosepak and containers of 14 and 28 tablets. We recommend that the following storage conditions be used for all three:

    - Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).
    - Store in original blister package until use.

4. Please add the storage condition to the Dosepak (innercard) label:

    - Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F).
    - Store in original blister package until use.

Please provide a response by COB on August 22, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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VICTORIA L TYSON
08/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Letermovir Tablet, 240 mg, 480 mg
- Letermovir Injection, 20 mg/mL in 240 mg/vial and 480 mg/ml

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by **August 18, 2017,** in order to continue our evaluation of your NDAs.

- The analytical methods provided in the NDA are not identified with the corresponding reference number. Since the test methods are frequently improved during the product life cycle, identify the non-compendial test methods listed under the specifications with the corresponding identification numbers. Please submit the revised letermovir drug substance specification table, the revised drug product specification tables for both NDAs, and other documents as appropriate.

If you have any questions, please contact me at (301) 796 4013, or luz.c.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Luz
Rivera

Digitally signed by Luz Rivera
Date: 8/03/2017 02:13:13PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Date: **July 28, 2017**

To: **Anita J. Shaw, PhD, Director, Global Regulatory Affairs and Clinical Safety**

Applicant: **Merck Sharp & Dohme Corporation**

From: **Christine Kim, PharmD, Regulatory Project Manager, DAVP**

Subject: **Information Request**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We have the following comments for clarification:

Clinical Pharmacology

1. Plot letermovir AUC versus eGFR for all subjects in study P001. Include plots of eGFR vs. study week for individual subjects. Identify which subjects have eGFR <90 mL/min for unexplained reasons, i.e where eGFR <90 mL/min is not explained by age, renal medical history, or concomitant use of nephrotoxic medications. Please submit the datasets.

2. We are evaluating whether the hepatic impairment PK study done with a dose of 60 mg would be expected to represent the worst case scenario in terms of exposure changes.
    a. Please provide a sensitivity analysis for OATP abundance versus letermovir AUC in healthy volunteers.
    b. Please use the PBPK model to predict the effect of hepatic impairment on letermovir PK at a dose of 480 mg. The model can be qualified by comparison of observed and simulated exposure changes from the hepatic impairment PK study using a dose of 60

mg. Please incorporate changes in OATP expression or activity in patients with cirrhosis into the model, for example see PMID: 27543206.

3. It was hypothesized that mucositis leads to lower oral absorption of letermovir. For drug concentrations measured after an oral letermovir dose, please plot trough concentrations as a function of time post-transplant in study P001. We are interested to know whether letermovir trough concentrations increase with time post-transplant as a result of (presumed) less mucositis.
4. Please provide the digoxin bioanalytical sample analysis report for study P018 Part C. The bioanalytical report submitted in the NDA only contains the digoxin bioanalytical protocol.

Please provide the response and all datasets by COB August 2, 2017.

We are providing the above information via electronic mail correspondence for your convenience. Please reply by email to acknowledge receipt. If you have any questions regarding the contents of this transmission, please contact Vicky Tyson, Regulatory Project Manager at 301-796-0827 or 301-796-1500.

_____

Christine Kim, PharmD
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CHRISTINE KIM
07/28/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **July 28, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Advice/Information Request-**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We also refer to the July 14, 2017, submission that consist of your response to our May 18, 2017, Filing Issue Identified letter. We reviewed this submission and have the following comments and requests for clarification:

Biometrics

Using the adttepsu dataset you have provided, our analyses produced the same KM estimates and log-rank test results as Figures 1 and 2 in your response, but have fewer additional deaths compared to Table 2 in your response and slightly different number of deaths while on study.

1. At Week 24 we counted a total of 40 (32 on-study) deaths in the letermovir arm and 32 (27 on study) deaths in the placebo arm which means there should be 8 additional deaths in the letermovir arm and 5 additional deaths in the placebo arm compared to the number who died while enrolled in the study. Please clarify the number of off-study and on-study deaths at week 24.

2. At Week 48 we observed a total of 76 (61 on study) deaths in the letermovir arm and 46 (40) deaths in the placebo arm or 15 additional deaths in the letermovir arm and 6 additional deaths in the placebo arm compared to the number who died while enrolled in the study. Please clarify the number of off-study and on-study deaths at week 48.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

CHRISTINE KIM
07/28/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **July 26, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical Pharmacology**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following comments and requests for additional information:

Clinical Pharmacology

1. Renal impairment in the phase 3 study

   a. Please provide the dataset corresponding to the analysis of letermovir PK in phase 3 subjects with and without renal impairment.

Please submit the dataset by COB on 7/26/17.

b. In the P001 lb dataset, creatinine clearance estimates were present only for the screening visit. If creatinine clearance was also estimated throughout the trial, please provide an updated lb dataset with all estimated creatinine clearance values.

2. Hepatic impairment in the phase 3 study

a. The P001 protocol says Child-Pugh score was to be assessed. Please clarify whether this was done. If so, please provide a comparison of letermovir PK in study P001 as a function of Child-Pugh category.

Please submit the information requested by Tuesday, August 2, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

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Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
07/26/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209940

INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated and received March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Letermovir Injection, 20 mg/mL in 240 mg/vial and 480 mg/ml

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by close of business **Wednesday, July 26, 2017**, in order to continue our evaluation of your NDA.

1. In the IR response submitted in 17 July 2017, the media used during the viability tests was provided. However, the media used to evaluate the (b) (4) bacterial retention test was not provided. Please specify the media employed and incubation conditions to evaluate the bacterial retention test (b) (4) (b) (4).

2. In the IR response submitted 17 July 2017, it was indicated (b) (4) (b) (4) However, we were not able to locate the data in your submissions. Please provide data (b) (4) (b) (4)

3. (b) (4)

(b) (4)

4. (b) (4)

5. Data from three media fill simulations performed in October 2016 (Batch Numbers: 0000629486, 0000631050, and 0000633858) and in March 2017 (Batch Number: 0000681344) are acknowledged. However, further information regarding these simulations is needed. Please provide the fill volume and the fill duration from these studies.

If you have any questions, please contact LCDR Luz Rivera at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Oumou Barry, MHA, MT, ASCP
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
For LCDR Luz Rivera, Psy.D.

Oumou Barry

Digitally signed by Oumou Barry
Date: 7/19/2017 01:20:58PM
GUID: 587e5a600171c0f766aa3b48afe5249b

From: Tyson, Victoria
To: Shaw, Anita (anita_shaw@merck.com)
Subject: NDAs 209939/209940-Letermovir-CMV-Information Request [Confidential]
Date: Monday, June 26, 2017 1:47:04 PM
Attachments: 060217.information_request-clinical-final.pdf
Importance: High

Good afternoon Anita,

Please let me know if you received the IR attached on 6/2/17, and when you will be able to respond. We requested a response by June 12, 2017. Thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

From: Tyson, Victoria
Sent: Friday, June 02, 2017 1:51 PM
To: Shaw, Anita
Subject: RE: NDAs 209939/209940-Letermovir-CMV-Information Request [Confidential]

Hi Anita,

I just sent you another IR and will forward this information on to the Review Team. thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

From: Shaw, Anita [mailto:anita_shaw@merck.com]

Sent: Friday, June 02, 2017 1:43 PM
To: Tyson, Victoria
Subject: RE: NDAs 209939/209940-Letermovir-CMV-Information Request [Confidential]

Confidential

Hi Vicky

We are generating a response for the information request received May 31 with respect to the OI tables in the CSR. We recognize this analysis was complicated. Our proposal is that we would provide the code used and explanation of how the tables in the CSR were generated. If desired, we could also arrange for a teleconference for the Merck programmer to explain the code and address any questions with the FDA.

I'd also like to provide an update with respect to the mortality question in the Filing Review Issues Identified letter. The Merck team is making every effort to determine if patients who discontinued prematurely are alive or dead at the Week 24 and 48 post-transplantation time points. However, we have found that the ability to gather this data may be limited in some markets by local legal and regulatory requirements. In other cases, EC, IRB and patient consent may be required. We intend to provide a response on our plan next week, but timing for additional data and analysis could be mid-July to allow gathering of as much data as possible. As a side note, I'd like to clarify that the "end of study" date is the date of last contact, not necessarily the discontinuation date. If there is additional information received after the discontinuation date, the "end of study" date may be updated after the patient has discontinued. This will be clarified in the response.

Please let me know if you have any questions or comments.

Best regards,
Anita

Anita J Shaw, PhD | Director Global Regulatory Affairs, Vaccines & Infectious Diseases | 351 N. Sumneytown Pike, PO Box 1000, UG2D68 | North Wales, PA 19454 | (tel) 267.305.1688 | (fax) 267.305.6407 | anita_shaw@merck.com | a

---

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Wednesday, May 31, 2017 3:36 PM
To: Shaw, Anita
Subject: NDAs 209939/209940-Letermovir-CMV-Information Request
Importance: High

Hi Anita,

Please confirm receipt of the Information Request attached and let me know

when you will be able to provide a response. thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

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
07/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939

INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Letermovir Tablet, 240 mg, 480 mg

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by **July 25, 2017**, in order to continue our evaluation of your NDAs.

1. The drug substance letermovir has pH dependent solubility and low solubility of approximately (b) (4) Based on the dissolution profiles presented in Fig. 11 of 3.2.P.2.2-Drug Product, (b) (4) (b) (4) We are concerned (b) (4) (b) (4) there could be an impact on dissolution and bioavailability/bioequivalence. Therefore, we request that you provide information to demonstrate (b) (4) (b) (4) beyond that of the pivotal clinical batches. Alternatively, we recommend that you add monitoring for PSD to the drug substance specifications.

2. Please clarify whether the process parameters for the (b) (4) (b) (4)

3. Submit vendor Certificates of Analysis for items used in the drug substance manufacturing process (section 3.2.S.2.3 Control of Materials). For (b) (4) (b) (4) also provide complete a brief description of its preparation and characterization information (IR, NMR, MS, etc.) as appropriate since this item does not appear to be a commodity chemical.

4. For the drug substance container/closure system: Identify the manufacturer(s) of the (b) (4) and provide certificate(s) of analysis and indicate what tests are performed upon receipt of the materials.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Luz Rivera

Digitally signed by Luz Rivera
Date: 7/17/2017 01:14:36PM
GUID: 502abbaa000025b89fdb52a977a3d336

From: Shaw, Anita <anita_shaw@merck.com>
Sent: Monday, July 17, 2017 12:52 PM
To: Rivera, Luz E (CDER)
Subject: RE: NDA 209940, Information Request, CMC [Confidential]

Dear LCDR Rivera,

Thank you for your message. I acknowledge receipt of this Information Request and confirm that my email is now available for receipt of submissions.

Have a great day!

Best regards,
Anita

APPEARS THIS WAY ON ORIGINAL

Anita J Shaw, PhD | anita_shaw@merck.com

From: Rivera, Luz E (CDER) [mailto:Luz.E.Rivera@fda.hhs.gov]
Sent: Monday, July 17, 2017 12:07 PM
To: Shaw, Anita
Subject: NDA 209940, Information Request, CMC

Good morning Dr. Shaw,

Please refer to your New Drug Application (NDA) dated March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letermovir Injection.

The Product Quality team has the following information request. We request a written response by **Tuesday, July 25, 2017**, in order to continue our evaluation of your submission. Please provide your response via email followed by an official amendment.

- The application states that letermovir solubility in the presence of HPCD at (b) (4) is similar to that at room temperature and above (b) (4) Figure 3, Section 3.2.P.2.2 in the submission show that solubility of letermovir is (b) (4) without inclusion of the temperature. What is the actual solubility of letermovir at (b) (4) proposed under specification?

We request that you acknowledge this communication upon receipt.

Best regards,

Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting) Div I/Branch I
Office of Program and Regulatory Operations
FDA/CDER/OPQ
luz.e.rivera@fda.hhs.gov
301 796 4013

U.S. FOOD & DRUG ADMINISTRATION

From: Shaw, Anita [mailto:anita_shaw@merck.com]
Sent: Thursday, July 13, 2017 2:32 PM
To: Rivera, Luz E (CDER)
Cc: Shaw, Anita
Subject: NDA 209940, Response to Information Request, CMC [Confidential]

Good Afternoon LCDR Rivera,

As mentioned yesterday, I am attaching a PDF version of the responses to the CMC Information Request we received by fax on July 3, 2017. Thank you for your flexibility in sending the document. An official copy of the response will be submitted to the NDA shortly. Please acknowledge receipt of this email and also let me know if you have any questions or comments.

Best regards,
Anita

APPEARS THIS WAY ON ORIGINAL

Anita J Shaw, PhD | Director Global Regulatory Affairs, Vaccines & Infectious Diseases 1351 N. Sumneytown Pike, PO Box 1000, UG2D60
| North Wales, PA 19454 | (tel) 267 305 1688 | (fax) 267 305 6457 | anita_shaw@merck.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

MID-CYCLE COMMUNICATION

Merck Sharp & Dohme Corporation
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph. D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for letermovir 240 mg and 480 mg tablets and 240/12 mL or 480 mg/24 mL solution for intravenous infusion.

We also refer to the teleconference between representatives of your firm and the FDA on June 15, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Victoria Tyson
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time:	June 15, 2017, 9:00 am
Application Number:	209939 209940
Product Name:	Letermovir, tablets Letermovir, solution for intravenous infusion
Indication:	Prophylaxis of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)
Applicant Name:	Merck Sharp & Dohme Corporation a subsidiary of Merck & Company, Incorporated
Meeting Chair:	Andreas Pikis, M.D., Cross Discipline Team Leader
Meeting Recorder:	Victoria Tyson, Regulatory Project Manager

FDA ATTENDEES

Division of Antiviral Products (DAVP)
Aimee Hodowanec, M.D., Medical Officer
Mary Singer, M.D., Ph.D., Medical Team Leader
Andreas Pikis, M.D., Medical Officer, Cross-Discipline Team Leader
Fraser Smith, Ph.D., Biometrics Reviewer
Takashi Komatsu, Ph.D., Clinical Virology Reviewer
Eric Donaldson, Ph.D., Clinical Virology Reviewer
Anamaris ColbergPoley, Ph.D., Clinical Virology Reviewer
Julian O'Rear, Ph.D., Clinical Virology Team Leader
Mario Sampson, Pharm.D., Clinical Pharmacology Reviewer
Islam Younis, Ph.D., Clinical Pharmacology Team Leader
Jeff Florian, Ph.D., Clinical Pharmacometrics Team Leader
David Mc Millan, Ph.D., Nonclinical Reviewer
Poonam Mishra, M.D., MPH, Deputy Director for Safety
Jeff Murray, M.D., MPH, Deputy Director
Debra Birnkrant, M.D., Director

Office of Antimicrobial Products (OAP)
Edward Cox, M.D., Director

Office of Product Quality (OPQ)
Yong Wang, Ph.D., Product Quality Reviewer
Qi Zhang, Ph.D., Biopharmaceutics Reviewer
Elsbeth Chikhale, Ph.D., Biopharmaceutics Team Leader
Derek Smith, Ph.D., Acting Branch Chief, Division of Inspectional Assessment

Office of Compliance
Francis Godwin, Division Director, Division of Drug Quality II (DDQ2)

Office of Surveillance and Epidemiology
Joyce Weaver, Pharm D., Senior Risk Management Analyst, Division of Risk Management (DRISK)
Valerie S. Wilson, Pharm D., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)

MERCK ATTENDEES
Cyrus Badshah, MD, PhD, Senior Principal Scientist, Clinical Research
Yoshihiko Murata, MD, PhD, Senior Principal Scientist, Clinical Research
Randi Leavitt, MD, PhD, Executive Director, Clinical Research
Joan Butterton, MD, Executive Director, Clinical Research
Hong Wan, PhD, Principal Scientist, Clinical Biostatistics
Valerie Teal, MS, Senior Principal Scientist, Clinical Biostatistics
Kenneth Koury, PhD, Executive Director, Clinical Biostatistics
Cameron Douglas, PhD, Senior Principal Scientist, Discovery Biology
Suman K. Mukherjee, PhD, Director, Toxicology
Sreeraj Macha, PhD, Senior Principal Scientist, Quantitative Pharmacology
Karsten Menzel, PhD, Principle Scientist, Pharmacokinetics
Jacqueline McCrea, PharmD, Senior Principal Scientist, Translational Pharmacology
Marian Iwamoto, MD, PhD, Associate Vice President, Translational Pharmacology
Catherine Hardalo, MD, Senior Principal Scientist, Clinical Safety and Risk Management
Heather Tiscia, MS, Associate Director, Regulatory Affairs
Anita Shaw, PhD, Director, Regulatory Affairs
Laurie MacDonald, MD, Executive Director, Regulatory Affairs
Ercem Atillasoy, MD, Vice President, Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your applications. In addition, we may identify other information that must be provided before we can approve these applications. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your applications during this review cycle.

2.0 SIGNIFICANT ISSUES

Chemistry Manufacturing and Control-Facility

There are substantive review issues related to manufacturing facility deficiencies. Per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the facilities proposed must comply with the current good manufacturing practice regulations. The facility assessment is ongoing. We recommend that you work with the facilities listed in your applications to ensure timely resolution of any inspectional deficiencies. Failure to resolve the inspectional deficiencies prior to the PDUFA date could affect approvability of the applications.

Clinical Pharmacology

The following clinical pharmacology issues bulleted below may impact labeling. An information request for additional analyses to address these issues was sent to you on June 14, 2017.

Additional analyses were requested to evaluate certain adverse events and laboratory values not included in the initial exposure-safety analysis.

- Because Cmax was not well described in the population PK modeling, Cmax was not evaluated in exposure-safety analyses of the phase 3 study. However, Cmax is important because it is up to 10-fold higher for IV versus oral administration while AUC is up to ~3-fold higher. We have requested exposure-safety analyses limited to subjects in the phase 3 study who participated in the intensive PK substudy.

Drug Interactions

Several factors affect interpretability of the drug interaction studies, which were conducted in healthy subjects administered various formulations of oral letermovir.

- Different formulations were used and it appears that the FMI formulation results in higher exposures compared to the PMF2 formulation. We are concerned whether letermovir exposures were sufficient to provide similar inhibition or induction across all of the interaction studies where letermovir was the perpetrator drug. PBPK modeling could be potentially used to evaluate the effect of letermovir dose on the magnitude of interaction.

- IV letermovir administration results in higher exposures compared to oral administration, and all of the interaction studies were conducted using the oral formulation. Modeling conducted by the applicant suggests that the effect of letermovir on other drugs may be greater for IV versus oral administration.

Pagination error. All pages accounted for.

- The effect of letermovir on midazolam was evaluated using a lower than recommended dose of letermovir (240 mg).

- The letermovir PBPK model could potentially be used to address the above drug interaction issues. However, its poor predictive performance would need to be addressed. We realize that the initial model attempted to describe nonlinear PK over a wide dose range. We recommend focusing on the 480 mg dose and improving the predictive performance for 480 mg letermovir given IV or PO after multiple doses.

Specific populations

- The renal and hepatic impairment studies evaluated lower than recommended doses of letermovir and may not provide sufficient information for labeling. Letermovir exposure increases may be greater if the recommended dose were used. As the phase 3 study allowed for enrollment of subjects with renal or hepatic impairment, we recommend comparing PK in this study between subjects with and without renal or hepatic impairment.

- Higher exposures have been observed in Japanese subjects in phase 1 studies and to a lesser extent in Asian subjects in phase 3 studies. The pharmacogenetic study concluded that genetic variants in major pathways involved in letermovir disposition did not affect letermovir PK. We have requested additional PK and demographic information on the phase 3 Asian subjects.

- Letermovir absorption is significantly lower in HSCT recipients compared to healthy subjects. This was attributed to intestinal mucositis from chemotherapy in HSCT recipients. We have requested additional analyses to better understand the distribution of PK parameters between these populations as well as a literature search to determine if the fraction absorbed or intestinal bioavailability has been observed to be reduced in the HSCT population.

Clinical

- The overall safety database for the IV formulation of letermovir is small. Further, most subjects who received IV letermovir received less than 2 weeks duration. Because of the limited safety database as well as the known increase in drug exposure among subjects receiving the IV formulation, we are closely analyzing all available safety data and carefully assessing the adequacy of the IV letermovir safety database.

3.0 INFORMATION REQUESTS

Outstanding/ Clinical/Biometrics:

- 74-Day Filing Letter
    - The Applicant has been asked to provide a report of the vital status of all subjects who prematurely withdrew from the trial. This report is currently pending. We acknowledge receipt of responses to the 74-Day Filing Issues Identified letter, and the response to the May 31, 2017, request for information on opportunistic infections.

Discussion:
DAVP asked Merck to provide an update on the status of the response to the request for the vital status of all subjects who prematurely withdrew from the trial. Merck provided a preliminary response on the mortality analysis and will submit a full response in mid-July. Merck anticipates being able to determine the vital status of approximately 95% of subjects. DAVP informed Merck this is acceptable.

- June 2, 2017
    - The Applicant has been asked to provide population flags (efficacy and safety populations) for the Data Tabulation Dataset Legacy for Trial P020 to allow for analysis of baseline disease characteristics across arms.
    - The Applicant has been asked to provide information on how to determine the dose (240 mg vs. 480 mg) of IV letermovir administered to individual subjects in Trial P001 to allow for a complete characterization of the IV letermovir safety database.

- June 14, 2017
    - The Applicant has been asked to provide the clinical pharmacology information outlined under Significant Review Issues.

Discussion:
DAVP requested a response to the June 14, 2017, Clinical Pharmacology Information Request on June 28, 2017. Merck requested an extension of 1-week, in providing the response, by July 7, 2017. DAVP informed Merck it is acceptable to provide the response by this date. Merck plans to submit a request for a teleconference to discuss pharmacokinetic modeling and simulation work detailed in the Information Request.

Chemistry, Manufacturing and Controls/Biopharmaceutics

We will issue product quality/biopharmaceutics information requests regarding stability and dissolution data.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

To date, we have identified the following clinical safety concerns:

1. Potential testicular toxicity based on preclinical findings.

2. An increase in letermovir exposure associated with IV administration compared to oral.

3. An increased rate of cardiac adverse events observed in the letermovir arm compared to the placebo arm.

4. An increased rate of ear and labyrinth adverse events in the letermovir arm compared to the placebo arm (most notably vertigo and ear pain/discomfort).

5. An increased rate of Grade 4 thrombocytopenia in the letermovir arm compared to the placebo arm.

6. An increased rate of infection adverse events in the letermovir arm compared to the placebo arm (after excluding cases of CMV infection).

Risk Management Update

At this time, it is not anticipated that a REMS will be needed.

5.0 ADVISORY COMMITTEE MEETING

At this time an Advisory Committee Meeting is not planned.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

a. Labeling/PMC/R Goal August 8, 2017
b. The timelines for the Late Cycle Meeting (LCM):
   - Internal LCM August 9, 2017
   - Backgrounder August 25, 2017
   - LCM September 8, 2017

The Late-Cycle Meeting between you and the review team is currently scheduled for September 8, 2017. We intend to send the briefing package to you approximately 12 days in advance of the meeting, i.e. by August 25, 2017. If these timelines change, we will communicate updates to you during the course of review.

c. PDUFA Goal Date November 8, 2017

Further discussion was not required for the issues discussed during this teleconference.

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/s/

VICTORIA L TYSON
07/14/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **July 12, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following comments and requests for additional information:

Clinical

Please submit the following additional analyses for the laboratory data from Trail P001:

1. Traditional shift tables showing the number of subjects shifting from Grade 0, 1, 2, 3, and 4 toxicity at baseline to maximum post-baseline toxicity Grade of 1, 2, 3 or 4 for the laboratory parameters hemoglobin, platelets, and creatinine (AsAT population).

2. For all subjects in the AsAT population with a treatment-emergent Grade 3 or 4 laboratory toxicity, please provide the proportion of subjects who returned to baseline by the Week 16 laboratory measurement (for hemoglobin, platelet, and creatinine laboratory parameters only).

Please submit the requested analyses by Thursday, July 20, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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
07/12/2017

From: Tyson, Victoria
To: "Shaw, Anita"
Subject: NDAs 209939/209940-Letermovir-CMV-Carton Samples-Response Date-COB 7/19/17 [Confidential]
Date: Wednesday, July 12, 2017 12:18:11 PM
Importance: High

Hi Anita,

Im sorry but paper mock-ups are not acceptable. We need the actual carton samples. Please let me know if you are able to submit the carton samples no later than Wednesday 7/19/17. Thanks, Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

From: Shaw, Anita [mailto:anita_shaw@merck.com]
Sent: Wednesday, July 12, 2017 9:08 AM
To: Tyson, Victoria
Subject: RE: NDAs 209939/209940-Letermovir-CMV-Carton Samples-Response Date-COB 7/14/17 [Confidential]

Confidential

Good morning Vicky,

I was discussing the carton samples with our team. We currently do not have printed carton samples available for Friday 7/14. We are working with our vendor to provide samples next week. Would that be acceptable? We could provide paper mockups this week, if that is helpful.

Thanks,
Anita

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Friday, July 07, 2017 11:43 AM
To: Shaw, Anita
Subject: NDAs 209939/209940-Letermovir-CMV-Carton Samples-Response Date-COB 7/14/17
Importance: High

Hi Anita,

As discussed earlier today, please submit the intend-to-market carton samples for each strength of the tablet and injection formulation for the letermovir NDAs? Please submit no later than COB 7/14/17 to aid us in our evaluation of the container labels and carton containers. Please send them to my office at the address listed below. thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☎ *301-796-0827*
☎ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

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/s/

VICTORIA L TYSON
07/12/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **July 12, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical Pharmacology**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following requests for additional information regarding bioanalytical methods for letermovir and concomitant medications:

Clinical Pharmacology

Long-term stability

1. Long term stability data were not shown in the method validation reports for letermovir method M1210 or the tacrolimus method used for study P013. Please provide these long term stability data.
2. Please provide the report (b) (4)) cited for long-term stability for the midazolam and 1-hydroxymidazolam method used in study P016.

Chromatograms

3. Please provide letermovir serial chromatograms from at least 5% of subjects in studies P005, P006, P009, P013, P016, P015, P018, P020, P021, and tacrolimus chromatograms for at least 5% of subjects in study P013.

Analysis of samples within the duration of stability

4. The maximum time between sample collection and bioanalysis was unclear for studies P014, P017, and P021. Please provide this information.

Recovery

5. In the method used for determination of tacrolimus concentrations in study P013, recovery differed significantly between QC concentrations. Please describe why this method met the acceptance criteria for recovery.

Carryover

6. Several controls blanks had letermovir peak areas >20% of LLOQ peak area in study P036. Please provide information on how carryover was evaluated when running study samples.

Please provide a response by Wednesday, July 26, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
07/12/2017

From:	Tyson, Victoria
To:	Shaw, Anita (anita_shaw@merck.com)
Subject:	NDAs 209939/209940-Letermovir-CMV-Carton Samples-Response Date-COB 7/14/17
Date:	Friday, July 07, 2017 11:43:19 AM
Importance:	High

Hi Anita,

As discussed earlier today, please submit the intend-to-market carton samples for each strength of the tablet and injection formulation for the letermovir NDAs? Please submit no later than COB 7/14/17 to aid us in our evaluation of the container labels and carton containers. Please send them to my office at the address listed below. thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

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/s/

VICTORIA L TYSON
07/07/2017

From:	Thompson, Elizabeth
To:	"Shaw, Anita (anita_shaw@merck.com)"
Cc:	Thompson, Elizabeth; Tyson, Victoria
Subject:	NDA 209940: CMC information request
Date:	Wednesday, July 05, 2017 9:43:09 AM
Importance:	High

Dr. Shaw-

Please refer to your pending Original NDA application, NDA 209940. In reference to Section 3.2.P.2.4 (container; included below), the review team cannot find Attachments 1 and 2 in the submission. Please advise where these attachments are located or submit them if they are not included.

Please confirm receipt of this correspondence.

Regards,

Beth

Chief, Project Management Staff

FDA/CDER/OAP/DAVP

301-796-0824

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/s/

ELIZABETH G THOMPSON
07/05/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939

INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Letermovir Tablet, 240 mg, 480 mg

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by **July 10, 2017**, in order to continue our evaluation of your NDA.

1. It is noted that you only (b) (4) (b) (4)

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Luz
Rivera

Digitally signed by Luz Rivera
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209940

INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Letermovir Injection, 20 mg/mL in 240 mg/vial and 480 mg/ml

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by Wednesday, July 5, 2017, in order to continue our evaluation of your NDA.

(b) (4)

2 Pages have been withheld in full as b4(CCI/TS) immediately following this page

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Luz Rivera

Digitally signed by Luz Rivera
Date: 7/01/2017 09:03:10AM
GUID: 502abbaa000025b89fdb52a977a3d336

From:	Thompson, Elizabeth
To:	"MacDonald, Laurie"
Cc:	Tyson, Victoria; "Shaw, Anita"
Subject:	RE: NDA"s 209939/209940 - letermovir (CMV): Information Request - Clinical pharmacology: Request for Clarification [Confidential]
Date:	Thursday, June 22, 2017 10:48:00 AM

Dr. MacDonald-

The DAVP agrees with your plan regarding PBPK modeling and exposure-response analysis. Regarding the PBPK model, please assess the predictive performance of the modified model in relation to both Cmax and AUC. We are interested in the entire concentration-time profile.

Regards,

Beth
Chief, Project Management Staff
FDA/CDER/OAP/DAVP
301-796-0824

From: MacDonald, Laurie [mailto:laurie_macdonald@merck.com]
Sent: Thursday, June 22, 2017 8:21 AM
To: Thompson, Elizabeth
Cc: Tyson, Victoria; Shaw, Anita
Subject: NDA's 209939/209940 - letermovir (CMV): Information Request - Clinical pharmacology: Request for Clarification [Confidential]

Confidential

Dear Elizabeth,

Vicky Tyson had informed us that you would be covering for her this week for correspondences related to the letermovir NDA's (209939/209940). As mentioned at the mid-cycle meeting (held June 15, 2017), Merck would like to ask for clarification on several items included in the FDA Information Request – Clinical Pharmacology (dated June 14, 2017).

The Agency's Information request included the following comment and requests pertaining to the PBPK model:

The PBPK model had poor predictive performance. In particular, the 5th percentile of the predicted letermovir concentration-time profile had poor overlap with observed data in multiple simulations. The model was developed to mechanistically explain the greater than proportional exposures. If the model can be altered such that it adequately predicts multiple

dose IV and oral letermovir PK for the 480 mg dose in healthy subjects and HSCT recipients, it could be potentially used to address some of the issues described below.

1. *Route of administration: Letermovir exposures are higher following IV versus oral administration and all interaction studies were conducted using oral letermovir. PBPK modeling suggested IV letermovir would increase CYP2C8 substrate exposure more than oral letermovir. PBPK modeling could be potentially used to compare the effect of IV versus oral letermovir on substrate drugs present in Simcyp and evaluated in interaction studies, such as cyclosporine, midazolam, and digoxin.*

2. *Formulations: In interaction studies with letermovir dosing of 480 mg QD, exposures were higher in studies using the FMI formulation (P036 and P013) versus a study using the PMF2 formulation (P022). It is unclear whether drug interaction magnitude is significantly affected by letermovir exposure. To address this question, please plot letermovir Cmax and AUC versus victim drug AUC ratio for interaction studies where letermovir was measured. The PBPK model could be potentially used to address the effect of different letermovir doses on victim drug exposure for substrate drugs present in Simcyp and evaluated in interaction studies, including cyclosporine, midazolam, and digoxin.* [Note from Merck: It appears that the last sentence in this bullet was inadvertently copied from the preceding bullet, and is not applicable here.]

3. *The effect of letermovir on midazolam was assessed using a lower than recommended dose of letermovir (240 mg). PBPK modeling could be potentially used to evaluate the effect of letermovir 480 mg on midazolam.*

In order to potentially use the PBPK model to compare the effect of IV versus oral letermovir on substrate drugs (as well as to evaluate the effect of letermovir 480 mg on midazolam), Merck plans to modify the relevant model parameters to provide better predictive performance for Cmax. Cmax has been selected as the target for model optimization and qualification as it is a key parameter for the assessment of perpetrator drug interactions. The predictive performance of the adapted model will primarily be assessed in healthy subjects at a dose of 480 mg PO and IV. The model will be considered qualified for the DDI related simulations if the Cmax ratio [simulated/observed] falls within a 2-fold range. The population of healthy subjects was selected for the primary assessment of the model's performance given that letermovir exposures are higher in healthy subjects than in HSCT recipients, and therefore the use of the PBPK model to evaluate the effect of letermovir on drugs in this population will provide the worst case estimate of the effect. In addition, to address the Agency's comment about the predictive performance of the current model, the performance of the adapted model in HSCT patients will be qualified by a) visual predictive check of the simulated letermovir concentration-time profiles with observed data in HSCT patients enrolled in the intensive PK sub-study of the Phase 3 clinical trial (P001) and b) comparison of predicted PK parameters (Cmax and AUC) to population PK estimates in HSCT patients. **Merck requests Agency agreement on its proposed plan for adaption of the PBPK model, and would be open to having a teleconference to further discuss.**

The Agency's Information request also included the following requests pertaining to the exposure-safety analyses:

Exposure-safety

5. *Conduct additional exposure-safety analyses using predicted letermovir exposure at the time of the event:*
   a. *Adverse events (vertigo, hypokalemia, fluid overload, hyperglycemia, cough)*
   b. *Relationship between letermovir exposure and changes from baseline in laboratory values, including creatinine, BUN, potassium, and platelets*
6. *Conduct exposure-safety analyses including Cmax and AUC as exposure metrics, limited to subjects in the Phase 3 study who participated in the intensive PK substudy.*

Merck notes that for several of the adverse events (e.g., vertigo) there is only a limited number of subjects for whom the event was reported, thus precluding a meaningful exposure-response analysis. For those events reported in fewer than 7% of subjects (the adverse event incidence cut-off for exposure-safety analysis specified in the M&S Analysis Plan), Merck proposes to provide quartile plots without conducting additional exposure-response analyses. **Merck requests Agency confirmation that this proposal is acceptable.**

I would ask that you kindly confirm receipt of this email. Thanks!

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Antivirals
Merck & Co., Inc.
Phone: 267-305-5540

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/s/

ELIZABETH G THOMPSON
06/22/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: June 15, 2017

To: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs
and Clinical Safety

From: Victoria Tyson,
Senior Regulatory Project Manager

Sponsor: Merck Sharp & Dohme Corporation

NDA: 209939/0
209940/0

Drug: MK-8228 (letermovir) 240 mg, 480 mg, tablets
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL
solution for intravenous injection

Subject: Information Request-Clinical and Biometrics

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following requests for additional information regarding the Opportunistic Infections (OI) analyses:

Clinical/Biometrics

1. Regarding Trial P001, we continue to have difficulties with the OI analyses. We are most interested in the Selected OIs presented in Table 11-22 of the original Clinical Study Report (page 226). In this table, you have identified 41 subjects with bacteremia in the letermovir arm in the first 24 weeks post-transplant. In our analysis using the variable SOICOD (following the steps outlined in the submission dated and received June 7, 2017), we have identified only 29 subjects with bacteremia in the letermovir arm using

the oiint1 dataset and 32 subjects with bacteremia in the letermovir arm using the oiint2 dataset. Using OICOD we found 29 subjects with bacteremia in the letermovir arm in the oiint1 dataset and 33 subjects with bacteremia in the letermovir arm using the oiint2 dataset.

2. Please provide a list of all subjects identified as having bacteremia as shown in Table 11-22. Please clarify if you used another variable to identify the additional subjects and which dataset you used to do so.

3. In addition, please identify the subjects you found who had pneumonia, sepsis and aspergillosis. For fungal infections, please identify the subjects and the variable you used to identify the selected infections like aspergillosis.

Please provide a response by Friday June 23, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
06/15/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: June 14, 2017

To: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs
and Clinical Safety

From: Victoria Tyson,
Senior Regulatory Project Manager

Sponsor: Merck Sharp & Dohme Corporation

NDA: 209939/0
209940/0

Drug: MK-8228 (letermovir) 240 mg, 480 mg, tablets
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL
solution for intravenous injection

Subject: Information Request-Clinical Pharmacology

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following requests for additional information:

Clinical Pharmacology:

Drug Interactions

The PBPK model had poor predictive performance. In particular, the 5th percentile of the predicted letermovir concentration-time profile had poor overlap with observed data in multiple simulations. The model was developed to mechanistically explain the greater than proportional exposures. If the model can be altered such that it adequately predicts multiple

dose IV and oral letermovir PK for the 480 mg dose in healthy subjects and HSCT recipients, it could be potentially used to address some of the issues described below:

1. Route of administration: Letermovir exposures are higher following IV versus oral administration and all interaction studies were conducted using oral letermovir. PBPK modeling suggested IV letermovir would increase CYP2C8 substrate exposure more than oral letermovir. PBPK modeling could be potentially used to compare the effect of IV versus oral letermovir on substrate drugs present in Simcyp and evaluated in interaction studies, such as cyclosporine, midazolam, and digoxin.

2. Formulations: In interaction studies with letermovir dosing of 480 mg QD, exposures were higher in studies using the FMI formulation (P036 and P013) versus a study using the PMF2 formulation (P022). It is unclear whether drug interaction magnitude is significantly affected by letermovir exposure. To address this question, please plot letermovir Cmax and AUC versus victim drug AUC ratio for interaction studies where letermovir was measured. The PBPK model could be potentially used to address the effect of different letermovir doses on victim drug exposure for substrate drugs present in Simcyp and evaluated in interaction studies, including cyclosporine, midazolam, and digoxin.

3. The effect of letermovir on midazolam was assessed using a lower than recommended dose of letermovir (240 mg). PBPK modeling could be potentially used to evaluate the effect of letermovir 480 mg on midazolam.

4. Since a significant fraction of subjects in study P001 received cyclosporine and it also has drug interaction potential, please revise labeling to provide separate drug interaction recommendations for subjects on letermovir plus cyclosporine versus letermovir alone.

Exposure-safety

5. Conduct additional exposure-safety analyses using predicted letermovir exposure at the time of the event:

    a. Adverse events (vertigo, hypokalemia, fluid overload, hyperglycemia, cough)
    b. Relationship between letermovir exposure and changes from baseline in laboratory values, including creatinine, BUN, potassium, and platelets

6. Conduct exposure-safety analyses including Cmax and AUC as exposure metrics, limited to subjects in the Phase 3 study who participated in the intensive PK substudy.

Specific populations

7. Please provide box plots and tables of letermovir PK parameters (C_{max} and AUC) between healthy subjects and HSCT recipients for both 480 mg IV and PO.

8. Renal impairment: compare letermovir PK in study P001 between subjects with and without renal impairment.

9. Hepatic impairment: compare letermovir PK in study P001 between subjects with and without hepatic impairment.

10. Asian ancestry: Exposures in Japanese subjects in phase 1 studies were ~2-fold higher than non-Japanese, while exposures for Asian subjects in study P001 were ~33% higher versus Caucasians. For subjects with Asian ancestry in study P001, please provide a dataset with variable 'usubjid', letermovir average weighted AUC, country of ancestry, country subject was living in at the time of the study, body weight, and gender.

11. Provide box plots of PK parameters comparing HSCT recipients and healthy subjects administered letermovir 480 mg.

12. Conduct a literature search to determine if the fraction absorbed or intestinal bioavailability has been observed to be reduced for other oral drugs administered to the HSCT population.

Bioanalytical

13. Submit the bioanalytical sample analysis report for the Phase 2 study.

Please address the comments above and provide your response by Tuesday, June 28, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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VICTORIA L TYSON
06/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939

INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Letermovir Tablet, 240 mg, 480 mg

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by **Thursday, June 22, 2017,** in order to continue our evaluation of your NDA.

1. Please indicate if the proposed drug product meets the requirement of (b) (4) content per day as per 21 CFR 73.1200.

2. Provide complete drug product forced degradation study results for assay, each unspecified degradation product, and total degradation products including chromatograms.

3. The proposed dissolution acceptance criterion of "NLT (b) (4)% (Q) dissolved in 45 minutes" for the proposed drug product is acceptable for Letermovir Tablets 480 mg, however; is not acceptable for Letermovir Tablets 240 mg. Based on the provided dissolution data, it is recommended that you implement a dissolution acceptance criterion of "NLT (b) (4)% (Q) in 30 minutes" for Letermovir Tablets 240 mg and revise the drug product specification Table with the updated dissolution acceptance criterion. Note that setting of the dissolution acceptance criterion is based on S2 testing (n=12) and therefore sometimes Stage 2 testing and occasional Stage 3 testing maybe needed.

4. Revise the drug product stability protocol and collect dissolution data at the 30-minute time point for the Letermovir Tablets 240 mg stability batches at the current stability pulling time point and thereafter.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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Rivera

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

PDUFA V Program Post-MidCycle Communication Agenda
NDAs 209939/209940

1.0 Applicant/FDA/ERG Independent Assessor Introductions
2.0 Introductory Comments
3.0 Significant Review Issues
- Clinical Pharmacology issues
- Size of IV letermovir safety database

4.0 Information Requests
- Outstanding information requests include those from the 74-day filing letter (May 18, 2017), as well as those sent on May 18, 2017, May 31, 2017, and June 2, 2017.

5.0 Major Safety Concerns/Risk Management
- Additional exposure-safety analyses
- A number of potential safety issues have been identified and are under review.
- At this time a REMS is not expected to be necessary.

6.0 Advisory Committee Meeting
- At this time, an Advisory Committee Meeting is not planned.

7.0 Late Cycle Meeting/Other Projected Milestones
- Labeling/PMC/R Goal Date: August 8, 2017
- Late Cycle Meeting (LCM) Timelines:
  - Internal LCM: August 9, 2017
  - Backgrounder: August 25, 2017
  - LCM: September 8, 2017
- PDUFA Goal Date November 8, 2017

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VICTORIA L TYSON
06/09/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **June 2, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following requests for additional information:

Clinical:

1. Please describe how the Safety Set and Full Analysis Set populations can be identified in the Data Tabulation Dataset Legacy for Trial P020 (all of the information regarding baseline disease characteristics seems to be located in these datasets).

2. For Trial P001, please provide the best way to identify the dose of IV letermovir administered to help facilitate a detailed assessment of IV letermovir exposure. The dose per administration variable appears to provide the dose in milligrams for oral

administration, but not for IV administration (the result for this variable is '1' for all IV administrations).

Please submit your response by Monday, June 12, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
06/02/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **May 31, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical and Biometrics**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We reviewed the May 12, 2017, response to our May 5, 2017, Information Request and appreciate the creation of the intermediate OI datasets; however, we have the following requests for clarification and additional information:

Clinical/Biometrics:

Unfortunately, we are still generating different results from what you have presented in the Trial P001 CSR (pages 222-226). Please confirm that the numbers you have reported are correct. If so, please provide a detailed description of which variables were used to generate each of the OI tables.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
05/31/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date:	**May 30, 2017**
To:	**Anita J. Shaw, Ph.D.** **Director, Global Regulatory Affairs and Clinical Safety**
From:	**Victoria Tyson,** **Senior Regulatory Project Manager**
Sponsor:	**Merck Sharp & Dohme Corporation**
NDA:	**209939/0** **209940/0**
Drug:	**MK-8228 (letermovir) 240 mg, 480 mg, tablets** **MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection**
Subject:	**Clinical Pharmacology P-004-QTc Study Report-Information Request**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We also refer to the QT Clinical Study Report P004, entitled, "A Single Dose Trial to Assess the Effect of MK-8228 (letermovir) on QTc Interval in Healthy Adult Volunteers." We are reviewing this report and have the following requests for additional information:

Clinical Pharmacology:

With reference to the submitted material for NDA 209939 / 209940, our review of the submitted data and the reported values in your Clinical Study Report for TQT Study P004 suggests that the letermovir concentration data submitted in your pc.xpt may have units of nM and not ug/mL as is reported in the dataset. Please clarify or confirm this and if that is the

case, please resubmit the dataset with appropriate units to be able to reproduce your reported PK results for this study.

We request this information to be submitted by June 6, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
05/30/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
351 N. Sumneytown Pike, PO Box 1000
UG2D-68
North Wales, PA 19454-2505

ATTENTION: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs & Clinical Safety

Dear Dr. Shaw:

Please refer to your New Drug Applications (NDAs) dated and received March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letermovir Tablets and Injection, 240 mg and 480 mg, 20 mg/mL.

We also refer to your correspondences dated and received March 9, 2017, requesting review of your proposed proprietary name, Prevymis.

We have completed our review of the proposed proprietary name, Prevymis, and have concluded that this name is conditionally acceptable.

If any of the proposed product characteristics as stated in your March 9, 2017, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3813. For any other information regarding this application, contact Victoria Tyson, Regulatory Project Manager in the Office of New Drugs, at 301-796-0827.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
05/25/2017

TODD D BRIDGES
05/25/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **May 18, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following requests for additional information:

Clinical:

In reviewing the death narratives for Trial P001, we note that labs for subject 0164-102037 are reported through Study Day 64, but the patient reportedly died on Day 12. Please provide the correct laboratory data summary for this subject. We also note that a narrative is provided for subject 0140-102003 that we believe actually corresponds to subject 0142-102003. Please confirm that this is correct. Lastly, please review the submitted narratives to confirm that there are not additional errors that we did not detect; and provide corrected narratives to the NDA.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
05/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209940

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Merck Sharp & Dohme Corporation,
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated and received March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for MK-8228 (letermovir) injection, 240 mg/12 mL and 480 mg/24 mL single dose vials.

This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

In addition, the planned date for our internal mid-cycle review meeting is June 5, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical/Biometrics

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

Clinical Pharmacology

2. Please submit the bioanalytical sample analysis report for study P001 or a link to the report if previously submitted. The Clinical Study Report (CSR) cited sections 16.1.10 and 16.1.12, but the report was not found in these sections.

3. For subjects in study P001 with prophylaxis failure occurring while receiving letermovir treatment (i.e. failure occurred before day 100), please calculate letermovir exposures (C_{max}, AUC, and C_{min}) for the day and week prior to prophylaxis failure. Evaluate exposure-efficacy relationships using these additional pharmacokinetic (PK) metrics. Please submit the revised exposure-response dataset containing columns for the additional PK metrics and containing USUBJID (see below).

4. Please add the variable USUBJID to the population PK and exposure-response datasets and submit these revised datasets.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. Your response is expected to be submitted in a timely manner and will be reviewed during this review cycle.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
05/18/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Merck Sharp & Dohme Corporation,
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDA) dated and received March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for MK-8228 (letermovir) tablet, 240 mg and 480 mg.

This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

In addition, the planned date for our internal mid-cycle review meeting is June 5, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical/Biometrics

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

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4. Please add the variable USUBJID to the population PK and exposure-response datasets and submit these revised datasets.

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Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
05/18/2017

Rivera, Luz E (CDER)

From: Rivera, Luz E (CDER)
Sent: Sunday, May 07, 2017 10:43 PM
To: 'Shaw, Anita'
Subject: NDA 209939 Information Request

NDA 209939
INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your March 8, 2017, submission for Letermovir Injection.

The Product Quality review team has the following comments and information requests. We acknowledge your April 19, 2017, amendment. This amendment was a response to our Information request, after reviewing your responses we have the following questions and comments:

1. Although the method used for the Container-Closure Integrity Test (CCIT) was described, insufficient data was presented. Please provide the data from the performed dye ingress analysis.
2. Information about the established Environmental Program (EM) is acknowledged. However, information about personnel monitoring was not addressed in the IR response. Please provide a personnel monitoring schedule, sampling sites, sampling techniques as well as alert and action limits.
3. A Media Fill simulations procedure was described. However, the IR response did not discuss the actions taken during media fill failures. Please indicate the actions taken during media fill failures.

In addition we have the following questions:

4. FDA needs additional environmental data for letermovir to assist our review of the claim for a categorical exclusion from an environmental assessment (EA), from CTD 1.12.14, Environmental Analysis. As part of our screening process for APIs with potential for hormonal effects, per recent EA guidance (USFDA, 2016) and in light of reproductive/developmental (testicular) toxicities noted in nonclinical studies discussed during pre-Phase 3, FDA utilized a fish plasma model (e.g., see Nallani et al., 2016) to help screen for aquatic environmental risk. In the process, we found a wide range of predicted log D values for letermovir (e.g. (b) (4) (b) (4)). Also, while we can use (b) (4) for the expected introduction concentration (EIC), a more accurate EIC would refine the model. Therefore provide:
   a. the estimated production in kg/year and the EIC for the active ingredient, as described in Section III of the FDA EA guidance (USFDA, 1998),
   b. any available data and analysis for this substance's log D and bioconcentration factor,
   c. any other readily available information for determining a more realistic expected environmental concentration (EEC) (e.g., metabolism and environmental degradation data), and

d. any readily available aquatic toxicity data, environmental risk assessments, or other relevant information for this or similar substances.

References (for question number 1):

Nallani, G., Venables, B., Constantine, L., & Huggett, D. 2016. *Comparison of Measured and Predicted Bioconcentration Estimates of Pharmaceuticals in Fish Plasma and Prediction of Chronic Risk.* Bulletin of environmental contamination and toxicology, 96(5), 580-584.

USFDA. 1998. *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application.* Center for Biologics Evaluation and Research. US Food and Drug Administration, Rockville, MD.

USFDA. 2016. *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity*. Center for Biologics Evaluation and Research. US Food and Drug Administration, Silver Spring, MD.

5. Per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the facilities proposed must comply with the current good manufacturing practice regulations. Please confirm that you are in contact with your contract manufacturing facilities, and that you are aware of any inspections or form FDA 483's that have been issued

We request a written response by **May 15, 2017**, in order to continue our evaluation of your submission. A partial response at that time, with clarification of the timeline for the remaining questions, would also be satisfactory. Please provide your response via email followed by an official amendment.

Please acknowledge this communication upon receipt.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Regards,
Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting), Div I, Branch I
Bldg 75, Room 4649
(301) 796-4013

FDA U.S. FOOD & DRUG ADMINISTRATION

From:	Tyson, Victoria
To:	Shaw, Anita (anita_shaw@merck.com)
Subject:	NDAs 209939/209940-Letermovir-CMV-Information Request-Clinical-Response Date-5/12/17
Date:	Friday, May 05, 2017 3:31:00 PM
Importance:	High

Hi Anita,

We are having difficulty reproducing the data pertaining to opportunistic infections that is presented in Tables 11-21, 11-22, and Tables 14.2-38 through 14.2-41. Please provide a detailed description of which datasets and variables were used to create these tables. Consider adding flags to assist in the analysis of OIs.

Please submit this information within 1 week, by May 12, 2017.
Thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

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/s/

VICTORIA L TYSON
05/05/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

PRIORITY REVIEW DESIGNATION

Merck Sharp & Dohme Corporation
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Applications (NDAs) dated and received March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for MK-8228 (letermovir) tablet, 240 mg and 480 mg and MK-8228 (letermovir) injection, 240 mg/12 mL or 480 mg/24 mL single dose vial.

We also refer to your submission dated April 26, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is November 8, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 8, 2017.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before May 21, 2017.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JEFFREY S MURRAY
05/05/2017

From: Tyson, Victoria
To: Shaw, Anita (anita_shaw@merck.com)
Subject: NDAs 209939/209940-Letermovir-CMV-P-004 Information Request
Date: Thursday, April 13, 2017 2:00:00 PM
Importance: High

Hi Anita,

Please submit the following information to NDA 209939 regarding the QT study report P004, as soon as possible:

Please provide the name of the ECG central lab, the method used to measure ECGs (manual, semi-automatic, automatic), and what ECG readers were blinded to.

Thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

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/s/

VICTORIA L TYSON
04/13/2017

From:	Tyson, Victoria
To:	"Shaw, Anita"
Subject:	RE: NDAs 209939/209940-Letermovir-CMV-Clinical and Biometrics Information Request-Response Date-4/24/17 [Confidential]
Date:	Wednesday, April 12, 2017 5:05:00 PM
Importance:	High

Hi Anita,

We reviewed your request for clarification, however, we are not comfortable that you have provided sufficient information regarding the steps taken to minimize potential bias among the single investigator with disclosable financial interests.

Please refer to the guidance below and submit a statement explicitly addressing this question?

https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

From: Shaw, Anita [mailto:anita_shaw@merck.com]
Sent: Tuesday, April 11, 2017 5:23 PM
To: Tyson, Victoria
Subject: RE: NDAs 209939/209940-Letermovir-CMV-Clinical and Biometrics Information Request-Response Date-4/24/17 [Confidential]

Confidential

Hi Vicky

We reviewed the information request and had a couple questions. Would you be able to provide some clarification?

1. Information on steps to minimize potential bias is listed in section 1.3.4 Table 3 (p. 18). Can you clarify if that information answers the question or if something else is being requested?
8. The programs used to create the adeff and adtte analyses datasets are included in in \m5\datasets\p001v01\analysis\legacy\programs\pgmsetup. The titles of the programs are

"adeff.txt" and "adtte.txt". Can you advise if this addresses the question or if something else is being requested?

Thanks in advance for your help.

Best regards,

Anita

Anita J Shaw, PhD | Director Global Regulatory Affairs, Vaccines & Infectious Diseases | 351 N. Sumneytown Pike, PO Box 1000, UG2D68 | North Wales, PA 19454 | (tel) 267.305.1688 | (fax) 267.305.6407 | anita_shaw@merck.com | a

---

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Monday, April 10, 2017 4:47 PM
To: Shaw, Anita
Subject: NDAs 209939/209940-Letermovir-CMV-Clinical and Biometrics Information Request-Response Date-4/24/17
Importance: High

Hi Anita,

Please confirm receipt of the Information Request attached and provide a response by Monday, April 24, 2017. Thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

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/s/

VICTORIA L TYSON
04/13/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **April 10, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical and Biometrics**

Please refer to your NDAs submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and request that you submit the following information by **Monday, April 24, 2017**:

Clinical:

1. Provide a description of the steps taken to minimize potential bias of investigators with disclosable financial interests.

2. Provide description of the reason an investigator has a certification of due diligence.

3. Ensure that CRFs for all subjects with CMV disease are provided (we noted that the CRF for subject 101645 is missing).

4. Add a treatment-emergent flag to the AE datasets for Trial P001.

5. Confirm that the variable AVLCAT1N in the ADLB dataset represents the laboratory toxicity grade. If not, please resubmit the laboratory data including a variable for toxicity grade.

6. We noted that several documents pertaining to Trial P020 were misfiled in Section 5.3.5.1 of the application. For example, the file labeled 'Individual Efficacy Response Data' actually contains 'Vital Signs Listings' and the file labeled 'Demographic Data' actually contains 'Adverse Events Listings.' Please ensure that all documents in Section 5.3.5.1 are correctly filed.

Biometrics

7. The analysis dataset adtte does not appear to provide the data for the Kaplan-Meier Plot of Time to All-Cause Mortality Through Week 48 Post-Transplant in HSCT Recipients (FAS Population). These data need to be submitted with the NDA in order for labeling claims to be made.

8. Please submit programs used to create the adeff and adtte analyses datasets.

9. We observed at Week 24 that approximately 20% of the subjects had either discontinued from the study before Week 24 or had missing outcomes in the Week 24 visit window. Please clarify whether you have any follow-up data on the missing patients to determine if subjects who discontinued were alive at Weeks 24 and 48. If so, please clarify as to how these patients were accounted for in the analysis and also provide revised outcome tables and Kaplan-Meier curves.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
04/10/2017

Rivera, Luz E (CDER)

From: Tyson, Victoria
Sent: Friday, April 07, 2017 7:10 AM
To: Rivera, Luz E (CDER)
Subject: RE: NDA 209940 Information Request

Good morning Luz,

Thanks and have a nice day! Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002

☎ 301-796-0827
☎ 301-796-9883 (fax)
✉ victoria.tyson@fda.hhs.gov

From: Rivera, Luz E (CDER)
Sent: Thursday, April 06, 2017 9:41 PM
To: anita_shaw@merck.com
Cc: Tyson, Victoria
Subject: NDA 209940 Information Request

NDA 209940
INFORMATION REQUEST

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your March 8, 2017, submission for Letermovir Injection.

The Product Quality review team has the following comments and information requests. We request a commitment via email by **April 8, 2017**, that you will supply the response to our information request by **Monday, April 19, 2017**, in order to continue our evaluation of your submission. Please provide your response via email followed by an official amendment.

1. A review of the manufacturing process and process controls is necessary. Please provide the following information:
    1) A description of container-closure integrity testing methods, including the time and pressure o submersion. Describe the method of screening vials, post submersion. If the dye ingress method is chosen, provide justification that this method can detect the ingress of 1 µl of dye solution into the drug product. Alternatively, if bacterial immersion is conducted, please ensure the challenge bacterial suspension concentration is at least 10^{5-6} CFU/mL. Describe positive and negative controls used in the study.
    2) An overview of the building and production facilities, including
        - A facility floorplan along with an outline of product and personnel flow.
        - Production equipment locations and ID numbers.
    3) A description of sterilization parameters for (b) (4)
    4) A summary of environmental and personnel monitoring schedules, sites, and methods, including alert and action levels for all monitoring programs.

2. More sterilization validation information is needed for review. Please provide the following information:
    1) Describe the initial validation and/or requalification studies for (b) (4) (b) (4) In your description, indicate:
        - Initial validation/requalification/proposed production parameters.
        - (b) (4)
        - Acceptance criteria for these studies as well as corresponding results.
        - A description of requalification methods and schedules, including (b) (4) performed during requalification analyses. One recent requalification study from this equipment should be provided.
    2) Describe the initial validation/requalification studies for the (b) (4) (b) (4) In your response include:
        - Whether the parameters used during initial validation/requalification are identical to the conditions employed during manufacturing of the drug product.
        - (b) (4) (D) (4)
        - Acceptance criteria for these studies as well as corresponding results.
        - (b) (4) (b) (4)
        - A description of requalification methods and schedules. One recent requalification study from (b) (4) should be provided.
    3) Media Fill simulations, including:
        - Type of media utilized in the study.
        - Incubation conditions used after filling.
        - Performance of growth promotion tests.
        - Frequency of simulations.
        - Acceptance criteria for these studies.
        - Total amount of units filled, units removed (including rejection criteria), units incubated, and positive units.
        - Interventions conducted during simulation.
        - Proposed filling parameters during production.
        - Environmental monitoring assessment during simulation.
        - Actions taken during media fill failures.
    4) Hold time studies to justify the (b) (4)
    5) (b) (4) validation studies, including:

- [redacted] (b) (4)
- Viability analysis.
- Bacterial retention evaluation.
- Acceptance criteria for these studies and corresponding results.

6) Microbiological compendial method suitability studies (i.e., sterility and endotoxin), including relevant controls.

3. Provide microbiological in-use studies to support [redacted] (b) (4)

Please refer to FDA's Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

Vitoria Tyson remains your main regulatory contact for this submission. Please copy Victoria Tyson in your email response to me.

Please acknowledge this communication upon receipt.

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov

Regards,
Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Quality Assessment Lead (Acting), Div I, Branch I
Bldg 75, Room 4649
,301) 796-4013

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tyson, Victoria
To: "Shaw, Anita"
Subject: NDA 209939/209940-Letermovir-CMV-Clinical Site Information Request-Response Date-4/10/17 [Confidential]
Date: Wednesday, April 05, 2017 11:38:00 AM
Importance: High

Good morning Anita,

We discussed this issue internally and we feel that it is important that you provide the CMV DNA levels from both the local laboratories and the central laboratory.

Please send the CDs with the Site information to my office. The CDs do not have to be submitted to the NDAs. thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☎ *301-796-0827*
☎ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

From: Shaw, Anita [mailto:anita_shaw@merck.com]
Sent: Tuesday, April 04, 2017 3:08 PM
To: Tyson, Victoria
Subject: RE: NDA 209939/209940-Letermovir-CMV-Clinical Site Information Request-Response Date-4/10/17 [Confidential]

Confidential

Hi Vicky

We have a question on the Information Request from today. With respect to the request below, can you clarify if it would be sufficient to provide central laboratory data for the CMV DNA levels?

> CMV DNA levels (negative or positive; if positive the exact CMV viral load in copies/mL) at each time point through week 24 post-transplantation. Please include confirmatory CMV DNA levels from central lab.

Also, can you confirm if the CDs would be adequate or should we also submit to the NDA?

Thanks in advance for your help.

Best regards,

Anita

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Tuesday, April 04, 2017 11:55 AM
To: Shaw, Anita
Subject: NDA 209939/209940-Letermovir-CMV-Clinical Site Information Request-Response Date-4/10/17
Importance: High

Good day Anita,

Please confirm receipt of the Information Request attached for the letermovir NDAs. thanks Vicky

Victoria Tyson
Senior Regulatory Health Project Manager
FDA/CDER/OAP/DAVP
10903 New Hampshire Ave
Bldg # 22, Room 6392
Silver Spring, MD 20993-0002
☏ *301-796-0827*
☏ *301-796-9883 (fax)*
✉ *victoria.tyson@fda.hhs.gov*

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/s/

VICTORIA L TYSON
04/05/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **April 4, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical Sites**

Please refer to your NDA submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and request that you submit the following information on a CD (1 CD for each site) for the following sites listed in the Table below:

- A copy of the study protocol
- Study visit dates for each subject through week 24 post-transplantation
- CMV serostatus (CMV IgG positive or CMV IgG negative) of subjects at enrollment
- CMV DNA levels (negative or positive; if positive the exact CMV viral load in copies/mL) at each time point through week 24 post-transplantation. Please include confirmatory CMV DNA levels from central lab.
- Serious Adverse Reactions including deaths

- List of subjects designated as high risk and documentation of which specific high-risk criteria were met for each of these subjects.
- Protocol violations
- Prohibited medications/therapy
- Discontinued subjects and the reason(s) for discontinuation

Site # (Name, Address, Phone number, email, fax #)
0116 Roy F. Chemaly 1515 Holcombe Blvd., Unit 1460 Houston, TX 77030 rfchemaly@mdanderson.org phone-(713)792-0007 fax-(713)792-5381
0004 Sanjeet Singh Dadwal 1500 E. Duarte Rd. Duarte, CA 91010 sdadwal@coh.org Phone-(626)256-4673 Fax-(626)301-8954
0064 Michael Schmitt Im Neuenheimer Feld 410,Abteilung Innere Medizin V, 69120 michael.schmitt@med.uni-heidelberg. Phone-496-221-5655 Fax-496-221-5657
0020 Shariq Haider 711 Concession St., Section A3 Room 20 Hamilton, Ontario haider@mcmaster.ca Phone-905-521-2100 Fax-905-381-7067
0108 Johan Maertens Herestraat 49,Hematology Department Leuven, 3000 johan.maertens@uzleuven.be Phone-321-634-6887 Fax-321-634-6881

Please submit the information requested no later than April 10, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
04/04/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **March 20, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical Virology**

Please refer to your NDA submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and there is missing NGS data in the application.

Clinical Virology

We cannot find the following information in your NDA application:

1. A file indicating which subjects, genes, time points were sequenced for each of the 190 fastq sequences that were submitted;

2. A frequency table showing the frequencies for each amino acid detected for each sample (above 1%) for each subject;

3. A detailed methods section describing the NGS sample preparation protocol and a detailed NGS analysis protocol providing specific details of the parameters used in the NGS analysis pipeline (We note that this information is contained in a variety of different documents in the NDA, but a specific NGS methods document should be provided).

If these data were included in the NDA please identify the directories and file names.

If these files were not included, please submit them as soon as possible and no later than March 24, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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VICTORIA L TYSON
03/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

PROPRIETARY NAME ACKNOWLEDGEMENT

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
351 N. Sumneytown Pike, PO Box 1000
UG2D-68
North Wales, PA 19454-2505

ATTENTION: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs & Clinical Safety

Dear Dr. Shaw:

Please refer to your New Drug Applications (NDAs) dated and received March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letermovir 240 mg and 480 mg Tablet and 20 mg/mL Injection.

We acknowledge receipt of your correspondences dated and received March 9, 2017, requesting a review of your proposed proprietary name, Prevymis.

If the application is filed, the goal date will be June 7, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact Victoria Tyson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Danyal Chaudhry, M.P.H.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
03/16/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Division of Antiviral Products
Food and Drug Administration
Silver Spring, MD 20993

ELECTRONIC MAIL CORRESPONDENCE-INFORMATION REQUEST/ADVICE

Date: **March 14, 2017**

To: **Anita J. Shaw, Ph.D.**
Director, Global Regulatory Affairs
and Clinical Safety

From: **Victoria Tyson,**
Senior Regulatory Project Manager

Sponsor: **Merck Sharp & Dohme Corporation**

NDA: **209939/0**
209940/0

Drug: **MK-8228 (letermovir) 240 mg, 480 mg, tablets**
MK-8228 (letermovir) 240 mg/12mL, 480 mg/24 mL solution for intravenous injection

Subject: **Information Request-Clinical**

Please refer to your NDA submitted and received March 8, 2017, Letermovir for prophylaxis of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). We are reviewing these applications and have the following comments and requests for additional information:

Clinical

In your submitted application for NDA 209939, we note that there are no treatment emergent flags in the adverse events (AE) datasets for studies P001 and P020. As part of our initial review of P001, we also looked at ADAE and found no treatment emergent flags. P020 has no analysis datasets.

Study P001:

1. We note the following statement in the synopsis for study P001:
"AEs reported during Treatment Phase (i.e., all AEs from the time of initiation of study medication through 14 days following last dose of study medication) and through Week 24 post-transplant (i.e., all AEs from the time of initiation of study medication through Week 16 post-transplant, and only drug related SAEs and deaths reported from Week 16 through Week 24 post-transplant) were analyzed."

   The variable EPOCH appears to correlate with treatment emergent events which include AEs occurring 14 days after last dose of study medication. Please confirm this is correct.

Study P020:

2. There is no treatment emergent flag or apparent dataset variable that correlates with treatment emergent AEs. In the statistical analysis plan (SAP), treatment emergent adverse events are defined as those AEs that start or worsen on or after initiation of trial medication and within 7 days after the last dose of trial medication. In our review of the datasets, it is not apparent which variables were used to create the adverse event tables in the clinical study report. Please clarify what dataset variables were used to signify whether or not an adverse event in the AE dataset was treatment emergent or not.

This request is time-sensitive; please respond by Monday, March 20, 2017.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

VICTORIA L TYSON
03/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corporation
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

We have received your New Drug Applications (NDAs) submitted under section 505(b)/pursuant of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Products:	MK-8228 (letermovir), 240 mg, 480 mg, tablets MK-8228 (letermovir) 240 mg/12 mL, 480 mg/24 mL, solution for intravenous injection
Date of Applications:	March 8, 2017
Date of Receipt:	March 8, 2017
Our Reference Numbers:	NDA 209939 NDA 209940

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file these applications on May 7, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA numbers provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-0827 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Victoria Tyson
Senior Regulatory Project Manger
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

VICTORIA L TYSON
03/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118361

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita Shaw, PhD
Director, Global Regulatory Affairs and Clinical Safety
351 North Sumneytown Pike, PO Box 1000
UG3C-28
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-8228 (letermovir) intravenous.

We also refer to your January 9, 2017, request for Breakthrough Therapy designation. We have reviewed your request and have determined that MK-8228 (letermovir) intravenous for prevention of cytomegalovirus (CMV) infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of MK-8228 (letermovir) intravenous for prevention of cytomegalovirus (CMV) infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

When Breakthrough Therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

discussion at this initial Breakthrough Therapy meeting[2].

We note your recent Pre-New Drug Application meeting held on December 14, 2016. At this point in your drug development program, holding this initial Breakthrough Therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the Breakthrough Therapy designation for MK-8228 (letermovir) intravenous for prevention of cytomegalovirus (CMV) infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Garrette Martin-Yeboah, PharmD, BCGP, PMP, Regulatory Project Manager, at (240) 402-2567.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

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/s/

DEBRA B BIRNKRANT
02/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104706

GRANT –
BREAKTHROUGH THERAPY DESIGNATION

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita Shaw, PhD
Director, Global Regulatory Affairs and Clinical Safety
351 North Sumneytown Pike, PO Box 1000
UG3C-28
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-8228 (letermovir) tablet.

We also refer to your January 9, 2017, request for Breakthrough Therapy designation. We have reviewed your request and have determined that MK-8228 (letermovir) tablet for prevention of cytomegalovirus (CMV) infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of MK-8228 (letermovir) tablet for prevention of cytomegalovirus (CMV) infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.*[1]

When Breakthrough Therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

discussion at this initial Breakthrough Therapy meeting[2].

We note your recent Pre-New Drug Application meeting held on December 14, 2016. At this point in your drug development program, holding this initial Breakthrough Therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the Breakthrough Therapy designation for MK-8228 (letermovir) tablet for prevention of cytomegalovirus (CMV) infection and/or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Garrette Martin-Yeboah, PharmD, BCGP, PMP, Regulatory Project Manager, at (240) 402-2567.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

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

/s/

DEBRA B BIRNKRANT
02/27/2017

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 104706
Request Receipt Date	1/9/17
Product	MK-8228 (Letermovir) Tablets
Indication	Prevention of CMV infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT)
Drug Class/Mechanism of Action	CMV antiviral/CMV viral terminase inhibitor
Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
ODE/Division	Office of Antimicrobial Products / Division of Antiviral Products (DAVP)
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	3/10/17

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   The indication for letermovir is for prevention of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients of an allogeneic hematopoetic stem cell transplant (HSCT).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Cytomegalovirus (CMV) is a human herpes virus that infects 40-100% of adults worldwide. Primary infection in immunocompetent subjects is usually asymptomatic or it may be associated with a self-limited mononucleosis-like syndrome and leads to a life-long latency. Persons with compromised immunity are at increased risk for CMV reactivation. CMV reactivation among allogeneic hematopoetic stem cell transplant (HSCT) recipients is associated with significant morbidity and mortality. Among approximately 27,000 allogeneic HSCTs performed each year, it is estimated that 65-80% of recipients are CMV seropositive and are therefore at high risk for CMV infection. The most common manifestation of CMV infection is CMV viremia which may be associated with fever and laboratory abnormalities. CMV infection can also cause end-organ disease, potentially involving the gastrointestinal tract, liver, lungs, and other organ systems. CMV pneumonia is the most serious manifestation and has a mortality of up to 50% among HSCT recipients. In addition to these direct effects of CMV, the virus has also been associated with

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

detrimental indirect effects such as increased rates of graft-versus host disease (GVHD), graft loss, opportunistic infections, and non-relapse mortality.

There are two approaches to preventing CMV disease among transplant recipients. First, there is a prophylactic approach, whereby transplant recipients receive antiviral therapy to prevent CMV infection and disease. Second, there is a preemptive approach, whereby transplant recipients are monitored regularly for CMV infection (usually by CMV PCR testing of whole blood or plasma) and antiviral therapy is initiated only to patients with evidence of CMV replication in the blood.

Ganciclovir and its prodrug valganciclovir are nucleoside analogs that inhibit viral DNA polymerase and were originally approved in 1989 and 2001, respectively. They are the only antiviral agents that are currently FDA approved for CMV prevention in transplant recipients. These agents are associated with significant bone marrow toxicity and are not well-tolerated by HSCT recipients. Therefore, a preemptive approach is more widely used among HSCT recipients. Without prophylaxis, it has been reported that as many as 80% of high-risk HSCT recipients will experience CMV reactivation and approximately 30% of these subjects will develop CMV disease. Letermovir is intended to meet the need for a safe and effective CMV prophylactic agent for use in HSCT recipients. It acts by inhibiting the CMV viral terminase, an enzyme needed for cleavage of CMV DNA and packaging of cleaved CMV DNA into procapsids. Unlike the DNA polymerase targeted by ganciclovir and valganciclovir, the viral terminase does not have an analog in humans. Therefore, letermovir is not expected to exhibit the toxicities associated with agents currently available for CMV prevention. Additionally, as letermovir has a novel mechanism of action, there is no known cross-resistance between letermovir and currently available anti-CMV therapies.

7. Information related to endpoints used in the available clinical data:

The primary efficacy endpoint for the Sponsor's phase 3 trial supporting the BTDR is the development of clinically significant CMV infection at Week 24 post-transplant. This was defined as the occurrence of one of the following outcomes: 1) onset of CMV end-organ disease; or 2) initiation of anti-CMV prophylactic therapy based on documented CMV viremia and the clinical condition of the subject. While CMV end-organ disease is accepted as a clinically meaningful endpoint, CMV viremia is not considered a validated surrogate endpoint at this time. Although CMV viremia has been shown to predict CMV disease, there are not sufficient data at this time to show that suppression of CMV viremia results in improved outcomes such as decreased incidence of CMV disease or decreased mortality. At present, CMV viremia (without end-organ disease) is considered by DAVP as a surrogate endpoint that is reasonably likely to predict clinical benefit in HSCT patients. In addition to this primary efficacy endpoint, several secondary and exploratory endpoints (including all-cause mortality) were included in the Sponsor's trial design.

Based on the use of a surrogate endpoint as the primary efficacy endpoint, it has been the Division's intention to consider this application for accelerated approval, with a need for a confirmatory trial under accelerated approval regulations. However, preliminary data (see question 10 below) suggest that there may be a statistically significant reduction in mortality at 48 weeks post-transplantation among subjects receiving letermovir as compared to those receiving placebo. If the final data confirm this finding, traditional approval may be considered.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

Currently, there are no therapies approved specifically for CMV prophylaxis among HSCT recipients. FDA approved agents with anti-CMV activity include ganciclovir, valganciclovir, foscarnet, and cidofovir. Intravenous (IV) ganciclovir was the first antiviral drug approved for the prevention of CMV disease in transplant patients (in HSCT and solid organ transplant recipients). The need for IV administration and the toxicity profile (primarily hematologic)

of ganciclovir have limited its use for prophylaxis against CMV in transplant patients. Oral ganciclovir was later developed and is approved for the prevention (prophylaxis) of CMV disease in solid organ transplant patients. However, this formulation has poor bioavailability and prophylaxis requires that patients take four capsules three times daily, thus making compliance challenging. Subsequently, valganciclovir, a more orally bioavailable form of ganciclovir, was approved for CMV prophylaxis in solid organ transplant recipients. Valganciclovir replaced oral ganciclovir use and oral ganciclovir is not currently available in the United States. Please see Table 1 for an overview of the agents currently approved for CMV prevention. These agents all received traditional approval (all were approved prior to the introduction of the accelerated approval pathway in 1992).

Table 1. Agents Currently Approved for CMV Prevention

Antiviral Agent	Approved Indications	Efficacy Endpoint	Comments
Ganciclovir (GCV), oral (CYTOVENE)	Prevention of CMV disease in SOT recipients Treatment of CMV retinitis	Reduction in 6-month incidence of CMV disease compared to placebo (4.8% vs. 18.9%, RR 0.22 (0.10, 0.51)) among liver transplant recipients	Oral GCV is currently not available in the United States
Ganciclovir (GCV), IV (CYTOVENE)	Prevention of CMV disease in transplant recipients Treatment of CMV retinitis	Reduction of CMV disease through 120 days post-transplant (16% vs 43% ($p < 0.001$) in GCV and placebo arms, respectively) when administered prophylactically to heart transplant recipients Reduction in CMV disease through 100 days post-transplant (3% vs 43% ($P < 0.001$) in GCV and placebo arms, respectively) when administered preemptively to HSCT recipients	IV GCV has broad indication for CMV prevention among transplant recipients. However, in registrational trials, IV GCV was given preemptively not prophylactically to HSCT recipients.
Valganciclovir (VGCV), oral (VALCYTE)	Prevention of CMV disease in SOT recipients Treatment of CMV retinitis	VGCV was non-inferior to oral GCV for the prevention of CMV disease in the first 6 months after SOT (12% vs 15% (95% CI -0.042, 0.110) ($p = 0.38$)) in the VGCV and GCV arms, respectively)	Heart, liver, kidney, and kidney-pancreas transplant recipients were included in the registrational trial. However, among liver transplant recipients, the rate of CMV disease was higher in the VGCV arm compared to the GCV arm. Therefore, VCGV is approved for CMV prevention specifically in kidney, heart, and kidney-pancreas transplant recipients.
CMV Immune	Prophylaxis of CMV disease	Reduction in the rate of	According to consensus

Globulin, IV (CYTOGAM)	in kidney, lung, liver, pancreas, and heart transplant recipients	"virologically confirmed CMV-associated syndromes" (60% vs 21% ($p < 0.01$) in the placebo and CMV immune globulin arms, respectively) among renal transplant recipients Reduction in the rate of CMV-associated disease (26% vs 12% ($p = 0.02$) in the placebo and CMV immune globulin arms, respectively) among liver transplant recipients	guidelines, CMV immune globulin is no longer recommended for the prevention of CMV disease in adult transplant recipients.

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; ganciclovir, GCV; HSCT, hematopoetic stem cell transplant; IV, intravenous; SOT, solid organ transplant; valganciclovir, VGCV.

In addition to the indications reported in Table 1, valganciclovir and ganciclovir have been used off-label for CMV prophylaxis among HSCT recipients. However, due to the significant myelosuppression and the resultant increase in the incidence of opportunistic infections associated with the use of these agents in HSCT recipients, this practice is uncommon. Foscarnet and cidofovir are approved for the treatment of CMV retinitis in HIV patients. They are also used off-label for the treatment of CMV infections in transplant patients. However, because of greater toxicities relative to other anti-CMV agents (most notably severe renal toxicity and severe electrolyte abnormalities), their role in CMV infections in transplant patients has been limited to patients who are failing ganciclovir/valganciclovir treatment.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Brincidofovir is an antiviral agent with anti-CMV activity that was being developed by Chimerix for the prevention of CMV infection among HSCT recipients. Chimerix requested breakthrough therapy designation (BTD) for this same indication. However, this request was denied on the grounds that the available clinical evidence did not suggest that the drug demonstrated substantial improvement over existing therapies. Brincidofovir is no longer being developed for CMV prevention in HSCT recipients.

10. Information related to the preliminary clinical evidence:

Table 2. Clinical Trials Supporting Breakthrough Therapy Designation for Letermovir for the Prevention of CMV Infection in Hematopoetic Stem Cell Transplant Recipients

Study ID/ Phase	Study Population (N)	Trial Design	Primary Efficacy Endpoint	Results
P020 Phase 2b	CMV seropositive HSCT recipients (N = 131)	Subjects were randomized to letermovir (60 mg QD, 120 mg QD, or 240 mg QD) or placebo within 40 days of transplant. Treatment duration was 12 weeks.	CMV prophylaxis failure (CMV viremia leading to preemptive treatment or CMV disease) within the treatment period.	Prophylaxis failure was significantly reduced in the 240 mg letermovir arm compared to placebo (6% vs. 36%).

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

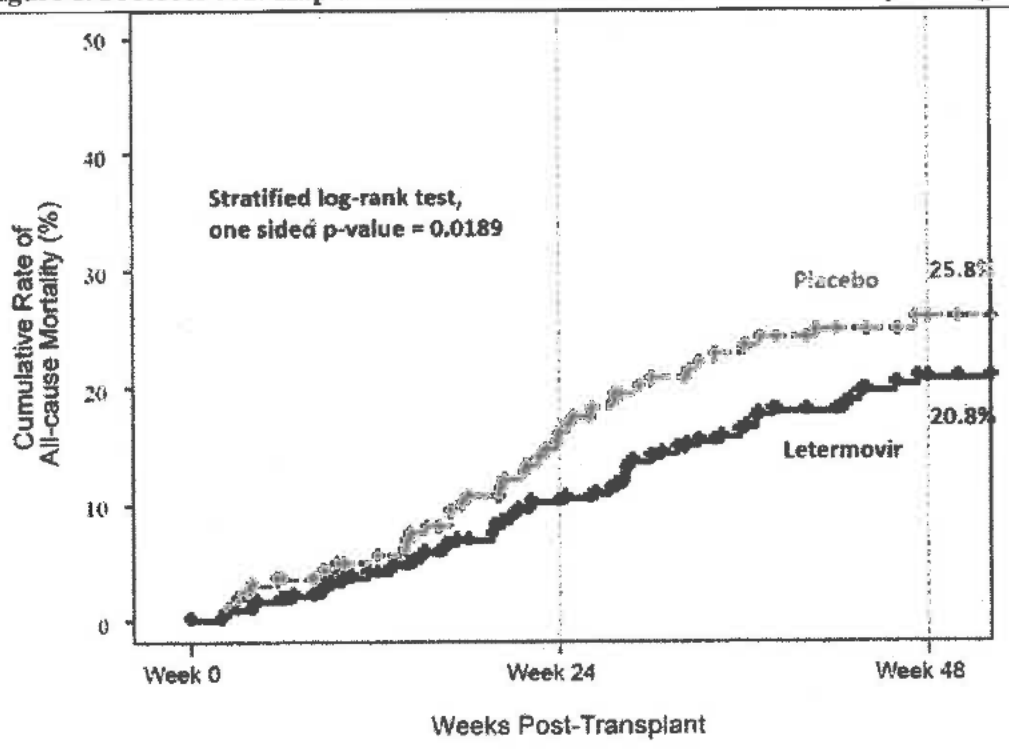
P001 Phase 3	CMV seropositive HSCT recipients (N = 570)	Subjects were randomized to letermovir 480 mg QD (reduced to 240 mg QD if concomitant CsA) or placebo within 28 days of transplant. Treatment continued through 14 weeks post-transplant.	Proportion of subjects with clinically significant CMV infection through week 24 post-transplant. This was defined as: 1) onset of CMV end-organ disease; or 2) initiation of anti-CMV therapy based on documented CMV viremia.	CMV infection* was more common in the placebo arm compared to the letermovir arm (61% vs 38%, $p < 0.0001$). There was a trend towards a reduction in all-cause mortality in the letermovir arm at 24 weeks (10% vs 16%, one-sided p = 0.03). Preliminary data showed that this reduction in mortality reaches statistical significance at 48 weeks (21% vs 26%, one sided p = 0.02)(see Figure 1 below).

*CMV viremia accounted for the majority of CMV infections. End-organ disease rates were similarly low in the letermovir and placebo arms (5(1.5%) and 3(1.8%), respectively).

Abbreviations: CMV, cytomegalovirus; CsA, cyclosporine; HSCT, hematopoetic stem cell transplant; QD, quaque die (daily).

In the Phase 3 trial P001, letermovir met the primary efficacy endpoint of reduction in clinically significant CMV infection as reported in Table 2 above. As cases of CMV end-organ disease were uncommon likely due to initiation of preemptive therapy, this reduction in CMV infection was attributable primarily to a reduction in CMV viremia. As discussed under question 7, CMV viremia is not considered a validated surrogate endpoint at this time. However, in addition to meeting the primary efficacy endpoint, there was a trend in all-cause mortality reduction at week 24 (see Figure 1) and preliminary data suggest a statistically significant reduction in all-cause mortality at week 48 (based on data from approximately 90% of the study population). The final mortality data will be used to help determine if this application is considered for traditional or accelerated approval. Regardless of this, we believe that the preliminary efficacy data from trial P001 provide clear evidence of a substantial improvement over available therapies.

Figure 1. Protocol 001: Kaplan-Meier Plot of Time to All-cause Mortality through Week 48 Post-Transplant



Source: Sponsor Pre-NDA Background Package

In addition to appearing effective in reducing the rate of CMV infection and perhaps in reducing mortality among HSCT recipients, letermovir demonstrated an excellent safety profile in trial P001. Unlike the other currently available anti-CMV therapies, letermovir does not appear to be associated with bone marrow toxicity or nephrotoxicity. Rates and types of adverse events (AEs) were similar in the letermovir and placebo arms.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

BTD should be granted for oral and intravenous letermovir for the prevention of CMV infection among CMV seropositive allogeneic HSCT recipients. Preliminary data suggest that letermovir is effective in reducing the incidence of clinically significant CMV infection, may provide a mortality benefit, and appears to have an excellent safety profile. Presently, there are no drugs approved specifically for CMV prophylaxis in this particular patient population. Therefore, HSCT recipients are currently managed using a preemptive therapy approach which requires frequent monitoring for CMV infection. In subjects in whom CMV infection is detected, treatment with medications associated with significant toxicity is required. Avoiding the direct and indirect sequelae of CMV infection as well as the toxicity associated with currently available CMV therapies is highly desirable in this fragile population.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

The Sponsor has already completed a Phase 3 trial of letermovir for the prevention of clinically significant CMV infection in HSCT recipients. The results of this study and the Sponsor's plans for submitting a New Drug Application (NDA) were discussed at a pre-NDA meeting on December 14, 2016. (b) (4)

(b) (4)

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104706
IND 118361

MEETING MINUTES

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs
351 North Sumneytown Pike, PO Box 1000, UG3C-28
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-8228 (letermovir) tablet (IND 104706) and intravenous formulation (IND 118361).

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2016. The purpose of the meeting was to discuss the acceptability of the proposed filing strategy for MK-8228 for the prevention of CMV infection.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-2567.

Sincerely,

{See appended electronic signature page}

Garrette Martin-Yeboah, PharmD, BCGP, PMP
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 14, 2016, 11:30am to 1:00pm
Meeting Location:	FDA White Oak Campus, Bldg. 22, Room 1311
Application Number:	IND 104706 and IND 118361
Product Name:	MK 8228 (letermovir)
Indication:	Prevention of CMV viremia and disease in at risk populations
Sponsor/Applicant Name:	Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc.
Meeting Chair:	Aimee Hodowanec, MD
Meeting Recorder:	Garrette Martin-Yeboah, PharmD, BCGP, PMP

FDA ATTENDEES

Office of Antimicrobial Products (OAP)

- Edward Cox, MD, MPH, Director
- John Farley, MD, Deputy Director
- Katherine Schumann, MS, Associate Director of Regulatory Affairs

Division of Antiviral Products (DAVP)

- Debra Birnkrant, MD, Director
- Jeffrey Murray, MD, MPH , Deputy Director
- Garrette Martin-Yeboah, PharmD, BCGP, PMP, Regulatory Project Manager
- Elizabeth Thompson, MS, Chief Project Management Staff
- Mary Singer, MD, PhD, Medical Officer, Team Leader
- Aimee Hodowanec, MD, Medical Officer
- Andreas Pikis, MD, Medical Officer
- Julian O'Rear, PhD, Clinical Virology Team Leader
- Takashi Komatsu, PhD, RAC, Clinical Virology Reviewer
- Christopher Ellis, PhD, Pharmacology/Toxicology Team Leader
- David McMillan, PhD, Pharmacology Toxicology Reviewer
- Eric Donaldson, PhD, Clinical Virology Reviewer
- Jeffrey Froude, Clinical Pharmacology Fellow
- Adam Sherwat, MD, Medical Officer, Team Leader
- Stephanie Troy, MD, Clinical Reviewer
- Virginia Sheikh, MD, Clinical Reviewer

Office of Clinical Pharmacology (OCP)

- Islam Younis, PhD, Clinical Pharmacology Team Leader
- Mario Sampson, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics (OB)

- Thamban Valappil, PhD, Statistical Team Leader
- Fraser Smith, PhD, Statistical Reviewer

SPONSOR ATTENDEES

- Cyrus Badshah, MD, PhD, Senior Principal Scientist, Clinical Research
- Yoshihiko Murata, MD, PhD, Senior Principal Scientist, Clinical Research
- Randi Leavitt, MD, PhD, Executive Director, Clinical Research
- Nicholas Kartsonis, MD, Vice President, Clinical Research
- Hong Wan, PhD, Principal Scientist, Biostatistics
- Shailaja Suryawanshi, PhD, Director, Clinical Biostatistics
- Cameron Douglas, PhD, Senior Principal Scientist, Discovery Biology
- Suman K. Mukherjee, PhD, Director, Toxicology
- Sreeraj Macha, PhD, Senior Principal Scientist, Quantitative Pharmacology
- Carolyn Cho, PhD, Senior Principal Scientist, Quantitative Pharmacology
- Marian Iwamoto, MD, PhD, Associate Vice President, Translational Pharmacology
- Walter Straus, MD, Associate Vice President, Clinical Safety and Risk Management
- Catherine Hardalo, MD, Senior Principal Scientist, CSRM
- Joseph Yoon, Associate Director, Regulatory CMC
- Nicole Mahoney, PhD, Director, Global Regulatory Policy
- Anita Shaw, PhD, Director, Regulatory Affairs
- Laurie MacDonald, MD, Executive Director, Regulatory Affairs
- Ercem Atillasoy, MD,Vice President, Regulatory Affairs

1.0 BACKGROUND

Letermovir, a novel inhibitor of CMV viral terminase, is being developed for the prevention of CMV infection in adult CMV seropositive [R+] allogeneic hematopoietic stem cell transplant (HSCT) recipients.

IND 104706 (tablet formulation) was originally submitted by AiCuris GmbH & Co. KG (AiCuris) on February 18, 2009. The FDA granted Fast Track designation on May 25, 2011 and Orphan Product Designation on December 12, 2011. On April 9, 2013, sponsorship of IND 104706 was transferred from AiCuris to Merck. Orphan Product Designation was transferred to Merck on April 29, 2013. IND 118361 (IV formulation) was submitted by Merck on August 22, 2013.

Previous meetings held include a Type C meeting (February 7, 2012) between the FDA and AiCuris to discuss the overall clinical development plan for letermovir, and an End of Phase 2 meeting (September 25, 2013) between the FDA and Merck to discuss the proposed Phase 3 clinical trial program.

Merck Sharp and Dohme Corporation requested a Pre-NDA meeting on October 14, 2016. The primary purpose of this meeting is to discuss the proposed content of the new drug applications (NDAs) for the letermovir tablet and intravenous formulations. The meeting was granted on October 28, 2016.

FDA sent Preliminary Comments to Merck Sharp and Dohme Corporation on December 9, 2016.

2. DISCUSSION

The sponsor's original questions are in ***bold italicized font*** and Division's preliminary responses are in standard font, followed by meeting discussion in standard font. Please note that only questions discussed at the meeting are captured in this document.

2.1. Clinical

Question 2: ***Does the Agency agree that the efficacy and safety data from the pivotal Phase 3 clinical trial (P001) are adequate to support an NDA submission for the proposed indication?***

FDA Response to Question 2: The efficacy and safety data from your pivotal Phase 3 trial combined with the data from your Phase 2b trial appear adequate to support NDA submissions for the indication of CMV prophylaxis among HSCT recipients. Further, we recommend that you submit a request for Breakthrough Therapy Designation (BTD). After reviewing the available information, we think the drug development program for letermovir may meet the criteria for BTD, and the remaining drug development program and review may benefit from the designation.

We would like to further discuss your comments in the meeting background package which states "the robustness of the Phase 3 data together with the now standard practice of initiating anti-CMV pre-emptive therapy based on the clinical endpoint of CMV viremia and the clinical condition of the patient support traditional approval of the application." The available data appear to demonstrate a clear benefit of letermovir over placebo for preventing CMV infection, results driven primarily by CMV viremia rather than tissue-invasive CMV disease. We also note that the Phase 3 trial shows a strong numerical trend towards decreased all-cause mortality in the letermovir arm compared to the placebo arm, although statistical significance was not achieved at week 24 for this secondary endpoint. Please discuss your plans for additional clinical trials with letermovir. We think there are a number of options for confirming clinical benefit of letermovir, including studying longer versus shorter durations of prophylaxis in HSCT recipients and powering a trial for a mortality endpoint, or evaluating letermovir for prophylaxis in the solid organ transplant

population using CMV disease (tissue-invasive disease or CMV syndrome) as the primary endpoint. When will the 48 week data be available for submission?
Please submit the 48 week all-cause mortality data for the current Phase 3 trial when it is available. If a statistically significant mortality benefit over placebo at 48 weeks is confirmed, then we could potentially consider these data as confirmation of clinical benefit.

Meeting Discussion Question 2:

Breakthrough designation (b) (4)

- The sponsor plans to submit a breakthrough therapy designation (BTD) request for (b) (4) HSCT recipients. (b) (4) The sponsor inquired whether this was a reasonable proposal.

- FDA encouraged the Sponsor to apply for breakthrough therapy designation in the HSCT population at this time.

- FDA stated that breakthrough therapy designation could benefit the sponsor by ensuring a dedicated review team, allowing for earlier inspections, potentially expediting the review, and potentially accepting late submissions without extending the review clock. The Sponsor stated that they have planned a CMV prophylaxis

- (b) (4)

Week 48 data (b) (4)

- The Sponsor presented preliminary data showing that at 48 weeks, all-cause mortality was significantly lower in the letermovir arm compared to the placebo arm (20.8% vs 25.8% respectively, one sided p = 0.0189). These preliminary mortality data include approximately 90% of study subjects, and according to the Sponsor were robust in several sensitivity analyses.

- The Sponsor plans to provide a clinical study report (CSR) including Week 48 efficacy and safety data in lieu of the safety update report (SUR). The Sponsor confirmed that this CSR would include all components normally included in the SUR.

- The Sponsor also plans to submit 48 week mortality data with the NDA as a standalone statistical report with corresponding datasets. The mortality data, however, will not be integrated or discussed in the dossier. FDA agreed with the Sponsor's plan.

- The FDA asked the Sponsor to provide an explanation as to how letermovir appeared to impact mortality without directly impacting CMV tissue-invasive disease (rates of CMV disease were low in both the treatment and placebo arms). The Sponsor was not able to provide a concrete mechanism, but suggested that this finding is in line with a recent publication which showed that CMV indirectly impacts mortality and other transplant-related outcomes.
- The Division asked about the proportion of the ITT patients who were included in the analysis of Week 48 data (page 32 of the handout) and the Sponsor stated that 90% of the patients were included in the analysis presented. The Division expressed concern that for the plot of the cumulative rate of all-cause mortality through database lock for study P001, inclusion of all mortality events for subjects who did not have the potential to complete the 48 week study could artificially increase the event rates. Therefore, because the inclusion of mortality events for subjects who had not been enrolled for at least 48 weeks could have an impact on the estimated treatment group difference in mortality rates and the corresponding statistical significance, the Division recommended the Sponsor perform a sensitivity analysis that only includes subjects for whom 48 weeks since randomization had elapsed at the time of database lock. The Sponsor agreed to provide the analyses, as recommended.

2.2. Additional Clinical Comments

Clinical Comment #1

1. Please submit an update on your overall development plan. Please include your plans for a confirmatory trial in the event your applications receive accelerated approval, pending the evaluation of sustained efficacy and safety based on week 48 data. Please note, if a trial in solid organ transplant recipients is not pursued (b) (4), the DAVP may request such a trial as a Postmarketing Commitment, as we feel that data regarding the safety and efficacy of letermovir in this population is of great importance from a clinical and public health perspective. (b) (4)

Meeting Discussion Clinical Comment #1

- The Sponsor confirmed that they intend to study letermovir in the (b) (4) population. Protocol P002 is planned as follows:

  (b) (4)

  - The study will evaluate letermovir in comparison to valganciclovir for prevention of CMV disease in high-risk kidney transplant recipients.

(b) (4)

- Both the FDA and the Sponsor agreed that future studies (b) (4) may be of interest.

(b) (4)

Pediatrics

- The product has orphan drug status and, therefore, does not trigger PREA (b) (4)

(b) (4)

-

Clinical Comment #2

2. Please submit a detailed justification for the approval of the IV formulation of letermovir based on the currently available data. Please incorporate any relevant preclinical and clinical data, such as the number of subjects treated with IV letermovir, number of doses of IV letermovir administered, IV drug exposures (i.e. AUCs) compared to PO exposures and safety and efficacy data. Additionally, please include a justification for any proposed duration of therapy to be included in the indication for IV letermovir. Lastly, please provide details regarding subjects with renal impairment who received the IV formulation of letermovir (number of patients, duration of IV therapy, AEs, baseline degree of renal impairment, and on-treatment changes in renal function). This is of interest given the nonclinical findings of nephrotoxicity associated with hydroxypropyl-β-cyclodextrin as well as clinical information regarding hydroxypropyl-β-cyclodextrin accumulation in the setting of renal impairment.

Meeting Discussion Clinical Comment #2

- According to the Sponsor, a total of 99 subjects received IV letermovir, with 44 receiving > 2 weeks in Trial P001.
    - The PO and IV letermovir formulations exhibited similar safety profiles
    - There were only two infusion reactions (noting that most subjects received the IV formulation via a central line)
    - There was no exposure dependency for the selected AEs (GI, cardiac, and other).

- The FDA raised concerns regarding the beta-cyclodextrin component of the IV formulation and its potential to cause toxicity in subjects with renal impairment. The Sponsor confirmed that only 5 of the subjects who received the IV formulation had renal impairment.

  The Sponsor was asked to clarify their intent regarding the specification of a duration of IV therapy in the label, taking into consideration that only few patients received intravenous therapy for more than 4 weeks. At this time, the Sponsor does not intend to impose a specific duration of IV therapy as this is not how it was studied. The Sponsor will provide more information about the use of the IV formulation in renally impaired subjects and about the occurrence of renal impairment in subjects receiving IV therapy in the NDA.

Clinical Comment #3

3. In addition to the previously agreed upon categories of cases requiring the submission of patient narratives, please provide patient narratives for all cases of tissue-invasive CMV disease and all deaths. This information will be needed especially in view of the emphasis on the mortality endpoint in the Phase 3 trial.

Meeting Discussion Clinical Comment #3

- The Sponsor agreed to provide narratives for all cases of tissue-invasive CMV disease and for all deaths.

Clinical Comment #4

4. Please provide an overall assessment of testicular toxicity in association with letermovir use. Include a summary of preclinical findings, and clinical findings in completed trials, and an analysis of hormonal laboratory findings from the Phase 3 clinical trial.

Meeting Discussion Clinical Comment #4

- Sponsor inquired whether additional studies will be required.

- The FDA confirmed that there may be a PMR related to the issue of testicular toxicity that was evident in the rat study but not in mice. This will ultimately be a review issue and the determination may be made in consultation with the Division of Bone, Reproductive, and Urologic Products.

2.3. Clinical Virology

Question 5: ***Does the Agency agree with the proposed content and format of the NDA as described in the Table of Contents, including the plans for integrated analysis of data from the clinical trials?***

FDA Response to Question 5: The proposed content and format of the NDAs as described in the Table of Contents appears adequate. Further, we agree that the safety and efficacy data from the Phase 2 trials should not be pooled with the data from the Phase 3 trial. However, the safety and efficacy findings from all clinical trials should be incorporated into your overall assessment of the risks and benefits of letermovir.

Clinical Virology Comment: Please confirm that the virology summary is included in Section 2.7.2.4 Special Studies and the virology study reports in Section 5.3.5.4 Other Studies. The line-item virology dataset is generally consistent with the template for submission of CMV resistance data communicated to you on July 26, 2016. However, we note that a few key items are missing (e.g., changes to immunosuppression, previous therapeutic agents (if any), and local laboratory results (if any). Additionally, if data related to other virus infections or CMV-specific immune response (e.g., ELISPOT assays) were collected, please include this information in the line-item virology dataset.

Discussion of Question 5

- The sponsor confirmed the placement of the virology summary and study reports in the appropriate sections of the NDA.
- FDA clarified that the sponsor should include any information where the subject's immune response might change. This would include changes to the immunosuppressive agent, changes to the dose, and the timing of the change.
- The sponsor agreed to include both the local and central laboratory results in the datasets. The sponsor stated that none of the local laboratories used plasma samples to determine HCMV DNAemia.
- The sponsor stated that they were not planning to include other virus infections in the datasets given that letermovir is inactive against other herpes viruses. The virology team clarified that the subjects could be co-infected with other viruses (e.g., EBV, AdV, BKV) that may confound the interpretation of the results. The sponsor agreed to include the data for other virus infections in the datasets

2.4. Additional Clinical Virology Comments

Clinical Virology Comment #5:

5. For your genotypic resistance analysis, please include a method to discriminate between viral DNA polymerase errors and the background of your assay.

Discussion Clinical Virology Comment #5

- The phenotypic resistance analysis will not be available at the time of submission.
- FDA stated that the purpose of this request is to ensure that the sponsor is generating reliable genotypic data. Given the challenges of phenotypic studies in HCMV and that this is a prophylaxis study (i.e., lack of baseline sequence data), it is imperative that the genotypic data are reliable. FDA suggested one method to address this concern would be to take samples where they saw genotypic changes and repeat the genotypic analyses to demonstrate that they are getting reproducible results. The sponsor stated that they are already planning to do what the review team has suggested and will include these data with the NDA submission.

Clinical Virology Comment #6:

6. Overall, the overview of the NGS sample preparation and use of the DDL Athena pipeline is acceptable; however, in the NDA submissions please provide a detailed methods section describing the NGS sample preparation protocol and a detailed NGS analysis protocol providing specific details of the parameters used in the NGS analysis pipeline. In addition, we recommend that you submit any NGS datasets and analyses that you have performed to date or a mock NGS dataset and analysis so that we can confirm that your NGS data are reviewable before an NDA is submitted. In addition, please comment on how your NGS analysis approach will discriminate between errors introduced by the thermostable polymerase used for PCR and mutations introduced by the viral DNA polymerase.

Discussion Clinical Virology Comment #6:

The sponsor confirmed that detailed descriptions of the NGS sample preparation and analysis protocols will be included in the dossier. The sponsor also confirmed that a mock dataset will be submitted

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 3 months after the submission of the original application:

- Week 48 CSR and datasets (note: this would be in lieu of the safety update report).

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - CLINICAL

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

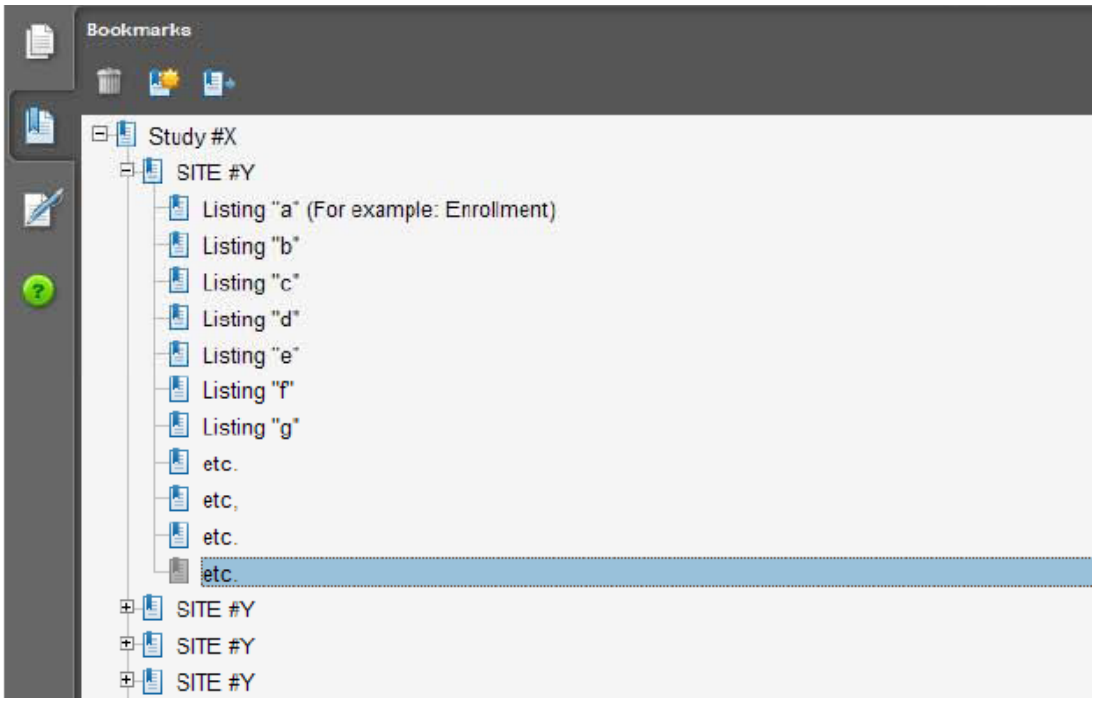
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

4.0 ACTION ITEMS

- Merck will provide a NGS mock dataset

5.0 ATTACHMENTS AND HANDOUTS

- Attachment 1: Technical Instructions for submitting BIMO clinical data in eCTD format
- Attachment 2: Slide set presented by the sponsor at the meeting

6.0 POST MEETING REQUESTS

- Please submit standardized mock datasets for efficacy and safety so we can evaluate their structure and format.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

DEBRA B BIRNKRANT
01/12/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104706

MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Laurie J. MacDonald, MD
Executive Director
351 North Sumneytown Pike, PO Box 1000
UG2D-68
North Wales, PA 19454-2505

Dear Dr. MacDonald:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-8228 (letermovir).

We also refer to the meeting between representatives of your firm and the FDA on September 25, 2013. The purpose of the meeting was to discuss the acceptability of the proposed clinical development program for MK-8228.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sammie Beam, RPh, Regulatory Project Manager at (301) 796-0080 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	September 25, 2013, 12:00pm to 1:30pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 21, Conference Room 1537 Silver Spring, Maryland 20903
Application Number:	IND 104706
Product Name:	MK-8228 (letermovir)
Indication:	Prevention of human cytomegalovirus disease
Sponsor/Applicant Name:	Merck Sharp & Dohme Corp
Meeting Chair:	Debra Birnkrant, MD, Director
Meeting Recorder:	Sammie Beam, RPh, Regulatory Project Manager

FDA ATTENDEES

OND/OAP
Edward Cox, MD, MPH, Director
David Roeder, Associate Director of Regulatory Affairs

OND/OAP/DAVP
Debra Birnkrant, MD, Director, Division of Antiviral Products
Jeffrey Murray, MD, MPH, Deputy Director
Kendall Marcus, MD, Deputy Director for Safety
Mary Singer, MD, PhD, Medical Officer Team Leader
Andreas Pikis, MD, Medical Officer
Christopher Ellis, PhD, Pharmacology/Toxicology Reviewer
Julian O'Rear, PhD, Virology Team Lead
Takashi Komatsu, PhD, Virology Reviewer
Elizabeth Thompson, MS, Chief, Project Management Staff
Sammie Beam, RPh, Regulatory Project Manager

OTS/OCP/DCP4
Leslie Chinn, PhD, Clinical Pharmacology Reviewer

ONDQA

James Vidra, PhD, CMC Reviewer

OTS/OB/DB4
Fraser Smith, PhD, Point of Contact for Statistics Team
Wen Zeng, PhD, Statistician

OSE
George Neyarapally, PharmD, MPH, DRISK reviewer
Morgan Walker, PharmD, MBA, Safety Evaulator
Jamie Wilkins Parker, PharmD, Team Leader, DMEPA

SPONSOR ATTENDEES

Jacqueline Thatcher, BS, MBA, Director, Global Pharmaceutical Commercialization
Suman Mukherjee, PhD, Principal Scientist, Preclinical Toxicology
Hsueh-Cheng Huang, PhD, Principal Scientist, Biology Discovery
Karsten Menzel, PhD, Principal Scientist, Preclinical Pharmacokinetics
Thomas Kerbusch, PhD, Executive Director, Modeling and Simulation
Xiao Sun, MD, MPH, Associate Principal Scientist, Biostatistics
Robert Tipping, MS, Director, Biostatistics
Ellen Hulskotte, PhD, Senior Principal Scientist, Clinical Pharmacology
Cyrus Badshah, MD, Principle Scientist, Clinical Research
Randi Leavitt, MD, PhD, Executive Director, Clinical Research
Nicholas Kartsonis, MD, Executive Director, Clinical Research
Michele Trucksis, MD, PhD, Executive Director, Project Leadership
Laurie MacDonald, MD, Executive Director, Worldwide Regulatory Affairs
Arne van Schanke, PhD, Associate Principal Scientist, Clinical Pharmacokinetics and Pharmacodynamics
Ekopimo Ibia, MD, Director, Regulatory Affairs

AiCuris GmBH & Co. KG
Silvia Riffel-Friedrich
Ibironke Addy

1.0 BACKGROUND

On April 9, 2013 sponsorship of IND 104706 was transferred from AiCuris GmbH & Co. KG to Merck Sharp & Dohme Corp.

Merck Sharp & Dohme Corp. requested a Type B meeting to discuss their planned Phase 3 development program for MK-8228 (letermovir), a novel inhibitor of cytomegalovirus (CMV), for CMV prophylaxis in hematopoietic stem cell transplant (HSCT) (b) (4)

There are two proposed Phase 3 clinical trials with MK-8228. Protocol PN001 (prevention of CMV in HSCT recipients) is a pivotal efficacy study of the safety and efficacy to support the primary indication of prevention of clinically significant CMV infection in adult CMV seropositive allogeneic HSCT recipients. (b) (4)

(b) (4)

The meeting package was submitted August 27, 2013, by Merck Sharp & Dohme Corp. The Division of Antivirals (DAVP) preliminary meeting comments were sent September 23, 2013. Merck Sharp & Dohme Corp. requested (email correspondence dated September 24, 2013,) to focus the meeting discussion on the following questions:

- Question 4c: The recommended viral threshold for initiation of pre-emptive therapy in the low-risk population in the Phase 3 HSCT prophylaxis trial (PN001).
- Question 4d: The statistical analysis approach for evaluating success on the primary efficacy endpoint in the Phase 3 HSCT prophylaxis trial (PN001).
- Question 6: The size of the overall safety database needed to support the initial NDA for a prophylaxis indication in HSCT recipients.
- Question 8: The type and extent of data needed to support registration for a prophylaxis indication (b) (4)

Questions submitted by the Sponsor are in **bold** font, the Agency's preliminary responses are in *italics* and discussion at the meeting is in regular font.

2. DISCUSSION

Merck Sharp & Dohme Corp presented the attached slides before discussion began on the identified issues.

2.1. Clinical Pharmacology

Question 1:
Does the Agency agree that the planned clinical pharmacology trials will be sufficient to support filing and registration for the proposed indications?

FDA's Response to Question 1:
We agree that the planned clinical pharmacology trials will support filing and registration for the proposed indications. The adequacy of the results of the clinical pharmacology trials will be evaluated during the review process.

Meeting Discussion: No further discussion occurred.

Question 2:
Does the Agency agree with the dose selected for the Phase 3 prophylaxis trials?

FDA's Response to Question 2:
Yes, from a clinical pharmacology perspective, the dose selected for the Phase 3 prophylaxis trials is appropriate.

Meeting Discussion: No further discussion occurred.

2.2. Clinical Development

Question 3:
Does the Agency agree that the Phase 2 data are sufficient to support initiation of Phase 3 prophylaxis trials in HSCT (b) (4)

FDA's Response to Question 3:
The Division agrees that you can proceed with the Phase 3 prophylaxis trials in HSCT (b) (4) (b) (4) *However, the Division recommends that the Safety Monitoring Committee meet after 10-20% subjects are enrolled in the trial to assess safety with the proposed letermovir dose because there are inadequate safety data for the selected dose and duration from the Phase 2 study.*

For your Phase 2 studies (AIC001-2-001 & AIC246-01-II-02), please provide all available line-item virology data, including the resistance data in SAS format. Please submit your Virology data using the current template format to be provided by the Division. At this time, you have not demonstrated that your assays can detect MK-8228 resistant virus.

Meeting Discussion: No further discussion occurred.

Question 4:
Does the Agency agree with the proposed design of the Phase 3 prophylaxis trial in HSCT transplant recipients?

a) Does the Agency agree with the patient population?

FDA's Response to Question 4a:
We agree with the selected study population. CMV seropositive recipients of allogeneic HSCT are the group at the highest risk of CMV reactivation and could benefit from CMV prevention.

Meeting Discussion: No further discussion occurred.

b) Does the Agency agree with the timing for initiation of MK-8228; the duration of treatment; and the use of a placebo control arm?

FDA's Response to Question 4b:
We agree that at this time the most straight-forward design for initial registration is the demonstration of superiority in a blinded comparison to placebo. We also agree with the timing of MK-8228 initiation and the proposed duration of treatment.

Meeting Discussion: No further discussion occurred.

c) Does the Agency agree with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint?

FDA's Response to Question 4c:
We agree with the definition of the primary endpoint for the Phase 3 trial in HSCT recipients as the incidence of clinically significant CMV infection within 6 months post-transplant, defined as the occurrence of either CMV disease (end-organ disease) or initiation of anti-CMV pre-emptive treatment based on documented CMV viremia and the clinical condition of the subject. We also agree with the viral threshold of ≥150 copies/mL for initiation of pre-emptive therapy in the high risk population. However, we do not agree with the viral threshold of ≥ 300 copies/mL for initiation of pre-emptive therapy in the low risk population. The recommended viral threshold for initiation of pre-emptive therapy in the low risk population is ≥ 1000 copies/mL.

Meeting Discussion:
Merck proposed a viral threshold of ≥ 300 copies/mL after discussions with consultants. Physicians also use clinical signs of disease in addition to the viral threshold to decide when therapy will begin.

The DAVP agreed that there is not a universally accepted virologic threshold for starting pre-emptive therapy in low risk patients. However, DAVP prefers a threshold of ≥1000 copies/mL for the following reasons:

- In the published literature this threshold has been used frequently, although DAVP acknowledges that there are published papers describing different viral thresholds.
- It has been proposed by other sponsors after consulting with physicians with great expertise in this field; and it is consistent with what is being used by other sponsors in similar trials.

- It may avoid the problem of viral "blips".

In addition, the DAVP pointed out that the 2009 publication by Boeckh and Ljungman (Blood 2009;113:5711-5719) recommends a plasma viral threshold of $\geq$ 500 copies/mL during the first 100 days posttransplantation and $\geq$ 1000 copies thereafter. After hearing Merck's justification to the DAVP's concerns, the DAVP agrees with using 300 copies as the limit recognizing that the cutoff is somewhat arbitrary.

Merck was questioned about which central lab had been chosen for the HCST trial. A decision has not been made. They will be using the approved Roche Assay to measure CMV DNA. It is important for them to find a lab with a quick turnaround time, with 24-48 hours being the desirable time frame, and 5 days being the worst case scenario. Testing will be done in the central lab weekly and will be the only data used by Merck.

Merck noted that in the HCST trial, it is assumed that 50% of the subjects will be high risk and 50% will be low risk for CMV reactivation and disease.

d) Does the Agency agree with the statistical analysis approach and criteria for success on the primary efficacy endpoint?

FDA's Response to Question 4d:

- *Please explain the assumed high discontinuation rate. Can the high rate of discontinuation be reduced?*
- *The Division would prefer that the Sponsor use the stratum-adjusted Mantel-Haenszel (MH) formulae to compute two-sided 95% confidence intervals for the rate difference between two arms in the primary analysis.*

Meeting Discussion:
Merck explained that they will use their standard statistical approach, the stratified Miettinen and Nurminen method for the primary efficacy analysis and agreed to use CMH weighting.

FDA stated that the stratum-adjusted Mantel-Haenszel method is the preferred method for the primary efficacy analysis for this indication, as it provides consistency across sponsors. The sponsor could use their stratified Miettinen and Nurminen method as a sensitivity analysis. If the results from two approaches are similar, there will not be a problem. However, if there is a big discrepancy, the Division will treat the results from the stratum-adjusted Mantel-Haenszel method as the primary efficacy results.

The FDA was also concerned about the number of sites for the study since site is one of stratification factors and the total number of subjects for the study is only 450. If many sites enroll only a few patients, it could create an imbalance between the two arms.

Merck stated that there will be many sites involved in the study and they plan to only allow the sites which can enroll at least 9 patients to avoid the potential imbalance issue.

With an assumed discontinuation rate of 20%, the FDA recommends that the sponsor follows discontinued patients as much as possible.

e) Does the Agency agree with plans for monitoring for testicular toxicity?

FDA's Response to Question 4e:
Although semen analysis remains the only surrogate endpoint for testicular toxicity, the Division agrees with the hormone monitoring plan for the Phase 3 studies. However, in the event of favorable outcome of the Phase 3 studies and an NDA approval, the Division may ask for a post-marketing commitment or requirement to further investigate whether MK-8228 significantly affects spermatogenesis (including semen analysis and hormone monitoring) in adult male transplant recipients.

Meeting Discussion: No further discussion occurred.

Question 5:
Does the Agency agree that a single pivotal Phase 3 prophylaxis trial in HSCT recipients will be sufficient to support an initial NDA for a prophylaxis indication in HSCT recipients?

FDA's Response to Question 5:
In general, we ask for two well-controlled trials for initial NDA submission (e.g., one prophylaxis trial in hematopoietic transplant recipients (b) (4) *, each convincing on its own. However, as we stated in our previous communications, and considering that prevention of CMV disease in HSCT recipients represents an unmet medical need, the Division will accept for an initial NDA submission a large single Phase 3 study supported by Phase 2 study results, if efficacy results are robust.* (b) (4)

Meeting Discussion: No further discussion occurred.

Question 6:
Does the Agency agree that the proposed safety data base will be adequate to support the initial registration of the tablet and intravenous formulations of MK-8228?

FDA's Response to Question 6:
For the initial NDA submission, safety data from 300 to 500 patients (preferably closer to 500 patients) at the selected dose and duration will be needed. Considering mortality, dropouts, and study drug discontinuation because of adverse events or due to CMV viremia

or disease, we believe that Trial 001-00 in HSCT recipients, as proposed, will not be able to provide the required safety data for an initial NDA approval.

Meeting Discussion:
The FDA is concerned that there are limited safety data from the Phase 2 trial and recommends increasing the number of subjects. In addition, some of the 300 subjects randomized to letermovir may drop out for different reasons.

Merck chose 300 subjects because of the unmet medical need and this would optimize time to market. (b) (4) .

The FDA is concerned (b) (4) the proposed New Drug Application for CMV prophylaxis in HSCT recipients, primarily because the data would still be blinded.

Merck understands that the FDA would like to have at least 300 subjects exposed to letermovir for at least 100 days at the proposed dose and duration. Merck will discuss internally.

The FDA has concerns that the IV formulation of letermovir may have a different safety profile from the oral formulation.

Merck expects 20% of the patients will receive letermovir by the IV route for several days to 2 weeks.

The FDA stated that whether there will be sufficient safety data for the IV formulation at the time of NDA submission will be a review issue. One suggestion was to consider including a substudy with subjects who failed prophylaxis. These subjects could be randomized to receive IV letermovir or standard of care as preemptive therapy to provide additional safety and efficacy data.

Merck indicated there would be blinding issues, as well as resistance concerns, especially in subjects from the letermovir arm. Patients would need to be rolled over from the placebo arm. FDA agreed that these issues would need to be considered.

Merck will explore that option, but anticipates operational challenges. They inquired whether enrolling 300 subjects in the HCST study and including an open label, small pre-emptive therapy group would address the safety database issues.

The FDA agreed that this approach may address the safety database issue.

The FDA has concerns about relying on the p-value from only one study, which should be smaller than what is required for two confirmatory studies, i.e., $p \leq 0.05$.

Question 7:
Does the Agency agree that the proposed design of the Phase 3 prophylaxis trial in kidney transplant recipients?

a) Does the Agency agree with the patient population?

FDA's Response to Question 7a:
Yes, we agree with the selected study population.

Meeting Discussion: No further discussion occurred.

b) Dose the Agency agree with the use of valganciclovir as the control arm, the timing for initiation of study medication; and the duration of treatment?

FDA's Response to Question 7b:
Yes, we agree with the use of valganciclovir as the control arm, the timing for initiation of study drug as well as the proposed duration of treatment.

Meeting Discussion: No further discussion occurred.

c) Does the Agency agree with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint?

FDA's Response to Question 7c:
We agree with the proposed definition of the primary endpoint and the time-point for assessment of the primary endpoint. However, the definition of CMV syndrome should be the same as the one used in the IMPACT study rather than the one used in Study PV1600 as shown in Appendices.

Meeting Discussion: No further discussion occurred.

d) Does the Agency agree with the statistical analysis approach; the non-inferiority margin; and planned sample size?

FDA's Response to Question 7d:
The 10% non-inferiority margin seems appropriate for the purpose of designing the study; however, the final non-inferiority margin determination will be a review issue.

Meeting Discussion: No further discussion occurred.

e) Does the Agency agree with plans to plans for monitoring for testicular toxicity?

FDA's Response to Question 7e:
Please see FDA's response to Question 4e.

Meeting Discussion: No further discussion occurred.

Question 8:

(b) (4)

[redacted]

2.3 Chemistry, Manufacturing, and Control

Question 9:

Does the Agency concur that a potential genotoxic impurities (PGI) control level of (b) (4) [redacted] (b) (4) **for individual and total PGIs is acceptable given the proposed indication and duration of therapy?**

FDA's Response to Question 9:
We concur that a limit of (b) (4) *for individual and total impurities which are classified as mutagenic is appropriate. This is based on the draft ICH M7 guidance as released for public comment earlier this year, and our estimate that a reasonable maximum cumulative exposure to letermovir for a given patient will fall in the range of 1-10 years. If a different limit on total mutagenic impurities is recommended in the final M7 guidance, that limit would apply.*

Meeting Discussion: No further discussion occurred.

2.4 PreClinical Safety Assessment

(b) (4)

Meeting Discussion: No further discussion occurred.

3.0 ADDITIONAL COMMENTS

Clinical Virology

1. *When you submit the revised draft protocols for MK-8228 PN001 and PN002, please include a detailed plan to monitor the development of resistance to MK-8228. Please identify the assays that will be used for your resistance analyses and provide the performance characteristics. Of particular interest is the ability to detect minority variants.*
2. *Please consult with DAVP for types of analyses and format of genotypic resistance data prior to submission.*
3. *Please report your HCMV DNAemia results as <LLOQ, not detected; <LLOQ, detected; HCMV titer results in the linear range of the test (as copies/mL, or IU/mL); or >ULOQ (HCMV titer results above the linear range of the test), i.e. consistent with the current label.*
4. *Please include the HCMV gB subtype information in your line-item virology data.*

Clinical Pharmacology

5. *Please evaluate the effect of OATP1B1/3 polymorphisms on letermovir uptake and/or pharmacokinetics.*

ADDITIONAL MEETING DISCUSSION

The DAVP would like to review the final protocols before the trials are initiated. In addition, the DAVP asked Merck to include CMV end-organ disease and/or initiation of anti-CMV pre-emptive therapy based on documented CMV viremia and the clinical condition of the subject at 12 months post-transplantation as a secondary endpoint in the HSCT trial.

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Note: The PREA comments have been revised from the preliminary meeting comments sent on September 23, 2013, as letermovir has orphan drug status.

5.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

6.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

7.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit Protocols well in advance for review before study initiation	Merck Sharp & Dohme Corp	TBD
Include Follow up in HCST protocol at 48 weeks for CMV disease and survival	Merck Sharp & Dohme Corp	TBD
(b) (4)	Merck Sharp & Dohme Corp	TBD
Provide details on serious adverse events and Grade 3 and 4 adverse events and laboratory abnormalities from Study AIC246-01-I-14	Merck Sharp & Dohme Corp	TBD
(b) (4)	Merck Sharp & Dohme Corp	TBD

8.0 ATTACHMENTS AND HANDOUTS

Merck Sharp & Dohme Corp's presentation entitled "MK-8772 (letermovir)"

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/s/

DEBRA B BIRNKRANT
10/16/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

LATE-CYCLE MEETING MINUTES

Merck Sharp & Dohme Corporation,
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Applications (NDAs) dated March 8, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for letermovir 240 mg and 480 mg tablets and 240 mg per 12 mL or 480 mg per 24 mL solution for intravenous infusion.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 8, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Victoria Tyson, Regulatory Project Manager at (301) 796-0827 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andreas Pikis, M.D.
Cross Discipline Team Leader
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time:	September 8, 2017, 10:30 am -12:00 pm
Meeting Location:	Teleconference
Application Numbers:	209939/209940
Product Name:	Letermovir, tablets and injection for intravenous use
Applicant Name:	Merck Sharp & Dohme Corporation, a subsidiary of Merck & Company, Incorporated
Meeting Chair:	Andreas Pikis, M.D., Cross Discipline Team Leader
Meeting Recorder:	Victoria Tyson, Regulatory Project Manager

FDA PARTICIPANTS

Aimee Hodowanec, MD, Medical Officer
Andreas Pikis, MD, Cross Discipline Team Leader
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Mario Sampson, PharmD, Clinical Pharmacology Reviewer
Islam Younis, PhD, Clinical Pharmacology Team Leader
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Jeffrey Murray, MD, MPH, Deputy Director

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Cheryl Emery, MS, Global Regulatory Affairs - CMC
Jennifer Finnegan-McCafferty, PhD, VP, External Quality
Heather Tiscia, MS, Associate Director, Regulatory Affairs
Anita Shaw, PhD, Director, Regulatory Affairs
Laurie MacDonald, MD, Executive Director, Regulatory Affairs
Ercem Atillasoy, MD, Vice President, Regulatory Affairs

1.0 BACKGROUND

NDAs 209939 and 209940 were submitted on March 8, 2017, for letermovir (MK-8228), 240 mg and 480 mg tablets and 240 mg per12 mL and 480 mg per 24 mL solution for intravenous infusion.

Proposed indication:	Prophylaxis of CMV infection and disease in adult CMV-seropositive recipients [R+] of an allogenic hematopoietic stem cell transplant
PDUFA goal date:	November 8, 2017

FDA issued a Background Package in preparation for this meeting on August 25, 2017.

2.0 DISCUSSION

1. Introductory Comments

   FDA stated that the purpose of a Late-Cycle Meeting (LCM) was to share information and to discuss any substantive review issues that have been identified to date and the objectives for the remainder of the review. These applications have not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for these applications. We are sharing this material to promote a collaborative and successful discussion at this meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in the background package prior to this LCM we may not be prepared to discuss that new information at this meeting.

Discussion: *None*

2. Discussion of Substantive Review Issues

Product Quality/Manufacturing Facilities:

At this time the evaluation of manufacturing facilities is on-going.

Discussion: *None*

3. Information Requests

   a. The Division issued an Information request on August 28, 2017, for additional exposure-adjusted safety analyses (similar to what was done for laboratory abnormalities in your labeling response of August 22, 2017). Additionally, we requested an analysis of the timing and distribution of these laboratory abnormalities and certain adverse events during the treatment period.

   b. The Division of Applied Regulatory Science in the Office of Clinical Pharmacology completed a computational assessment and literature review for letermovir to identify potential mechanisms of action for the cardiac events observed in Trial P001. Briefly, these assessments revealed that letermovir may inhibit T-type calcium channels and may bind to adenosine receptors. The computational assessment was sent to the Applicant on August 29, 2017. In this Information Request, the Applicant was asked to inform the Division of any searches they have performed for potential targets for letermovir. The Applicant was also asked to provide a proposal for further investigation of the findings of the computational assessment.

Discussion:

Merck presented the results of additional exposure-adjusted analyses to support their position that the frequency of certain adverse events (AEs) and laboratory abnormalities were similar in the placebo and letermovir arms after accounting for the longer treatment period for subjects in the letermovir arm. Specifically, they presented exposure-adjusted analyses for infection AEs (excluding CMV) and common (≥ 10% of the letermovir subjects) and less common (≥5% but < 10% of letermovir subjects) AEs. They also presented the timing and distribution of these AEs, as well as of creatinine, hemoglobin, and platelet laboratory abnormalities. There appeared to be a clustering of first events early in the treatment period, but a relatively even distribution of all events across the duration of the treatment period, suggesting that exposure-adjusted analyses of the events is appropriate. Further, the rate of infection AEs (excluding CMV) was

found to be similar in both arms after adjusting for exposure duration. For many of the common AEs, the difference in the rates between the arms was no longer notable after adjusting for exposure duration. Exceptions to this were headache, peripheral edema, and vomiting, which remained more common among letermovir subjects. The less common adverse event rates were not impacted as greatly by the adjustment for exposure duration. One specific imbalance that remained after the adjustment for exposure was the higher rate of 'bacteremia' in the letermovir arm. However, Merck noted the exposure-adjusted rate for 'Staphylococcal bacteremia' was actually higher in the placebo arm.

Merck concluded that there is no plausible causal relationship between letermovir and these less common AEs. (b) (4) *Merck was informed that the Division will need to review and discuss the additional exposure-adjusted analyses internally.*

Non-exposure adjusted analyses from the Phase 3 trial (P001) revealed that cardiac AEs were more common in the letermovir arm compared to the placebo arm. Merck was asked if they had also performed exposure-adjusted analyses of the cardiac events. They confirmed that they had and agreed to submit the results of these analyses to the NDA.

In response to the Information Request in which Merck was presented with the report of a computational assessment for potential cardiac targets of letermovir, Merck informed DAVP that they had evaluated the potential for off-target binding and activity for letermovir using 63 radioligand binding assays and there was no meaningful binding at a letermovir concentration of 10 μM. Merck also evaluated letermovir in a GLP hERG assay and did not identify any off-target hERG activity. Further, Merck presented data on the evaluation of the potential mechanisms of action for the cardiac AE's identified by the computation analyses and refuted the proposed targets based on the following:

- *T-type calcium channel inhibition that has been associated with bradycardia, but not tachyarrhythmias. Bradycardia was not commonly reported among subjects receiving letermovir in Trial P001.*
- *Review of other compounds with a 3, 4-dihydroquinazoline sub-structure (idelasib, anagrelide and rifagrelide) showed that the only one associated with cardiac events was idelasib. Merck proposed that the arrhthmias associated with idelasib are attributable to the drug's inhibition of phosphodiesterase 3, rather than to the 3, 4-dihydroquinazoline moiety that the drug shares with letermovir.*
- *No adenosine receptor binding was observed in letermovir screening tests.*
- *Merck has tested other drugs that share the 3, 4-dihydroquinazoline sub-structure with letermovir for phosphoinositide 3 kinase delta inhibition and have found no inhibition.*

Merck, therefore, concluded that further investigation of the potential targets identified by FDA is not warranted. The Division informed Merck that they would review Merck's findings and discuss them internally.

4. Postmarketing Requirements/Postmarketing Commitments

   PMRs/PMCs are under discussion which may include, but are not limited to:

   PMRs:

- Phenotypic analysis of letermovir against CMV mutants carrying pUL56 and/or pUL89 substitutions identified in the Phase 2 or Phase 3 trials

Discussion:

Merck stated that the Phase 2 phenotyping results have been submitted to the NDAs and they do not have any remaining plasma or DNA available for additional analyses. Merck proposed that (b) (4)

The Division acknowledged that while there are no remaining samples from their Phase 2 study for additional analyses, additional phenotypic analyses can still be conducted using bacterial artificial chromosome technology. The Division does not agree with the algorithm that was used to identify the amino acid substitutions of interest from both their Phase 2 and Phase 3 studies. The Division stated that a different algorithm was used:

- *The use of a 5% NGS threshold is arbitrary and the Division has looked at lower thresholds.*
- *While the Division agrees that the resistance-associated substitutions identified to-date have mapped between pUL56 AA231-369, it is premature to set any boundary as there are limited clinical data to support genotyping a specific region. The Division reminded Merck that the region that confers resistance to Valcyte® has expanded over time.*
- *The Division agrees that most of the amino acid substitutions of interest were identified in the pUL56. However, the Division has identified a few amino acid substitutions in the pUL89 of potential interest and reminded Merck that resistance-associated substitutions to Valcyte® map to 2 different proteins.*
- *The Division stated that polymorphic positions should not be automatically ignored as there are several examples where resistance-associated substitutions have mapped to polymorphic substitutions.*

The Division asked Merck to submit the 10 amino acid substitutions identified to the NDA for review and will discuss this issue internally.

PMCs:

- CMV prophylaxis trial in renal transplant recipients (letermovir vs. valganciclovir; trial P002)

Discussion:

Merck agreed to conduct a CMV prophylaxis trial in renal transplant recipients. They submitted a draft protocol in May 2017, and plan to submit a final protocol in January 2018, complete the study in June 2022, and submit the final report in January 2023.

- CMV prophylaxis trial comparing 100 days vs. 200 days of letermovir prophylaxis in HSCT recipients

Discussion:

Merck does not plan to conduct a CMV prophylaxis trial comparing 100 days versus 200 days of letermovir in HSCT recipients. Merck stated the highest risk for CMV reactivation is in the first 100 days post-transplant. Further, when late CMV reactivation does occur, Merck stated that it is generally associated with less severe disease. Because of this, Merck theorized that IRBs may not be willing to approve a study in which subjects were exposed to longer durations of letermovir.

The Division expressed its concerns with Merck's decision not to conduct the proposed trial. The Division stated that there may be a subset of patients who remain at higher risk for CMV reactivation beyond day 100 post-transplant and who would benefit from a longer duration of prophylaxis. Given the survival benefit observed with letermovir prophylaxis, the Division feels strongly that addressing this unanswered question has important safety implications. Should this study not be conducted, the absence of information regarding the optimal duration of prophylaxis and the lack of safety data for letermovir use beyond day 100 post-transplant may be reflected in labeling. (b) (4) *No final agreement was reached between the Applicant and the Division regarding this proposed PMC.*

(b) (4)

Additional data are also needed regarding the safety and efficacy of letermovir in the following patient population subgroups which were underrepresented in Trial P001:

- Black and Hispanic subjects

We strongly recommend that Merck ensure adequate enrollment of subjects from each of these populations in postmarketing clinical trials. In addition, the number of subjects who received

intravenous (IV) letermovir for at least 7 days was limited in Trial P001, and attempts should be made to increase the safety database for this formulation.

Discussion:

Merck agreed to maximize enrollment of Black and Hispanic subjects in postmarketing clinical trials. However, they stated that this may be challenging as fewer Black and Hispanic subjects undergo transplantation (solid organ or HSCT) than white, non-Hispanic subjects.

The Division also stressed the importance of increasing the size of the safety database and the duration of exposure to the IV letermovir formulation. Merck stated that they believe the safety database for the IV formulation to be of adequate size. They plan to continue to evaluate the IV letermovir formulation in the renal transplant trial, though they anticipate that the need for IV therapy will be lower among renal transplant recipients compared to HSCT recipients.

5. Major Labeling Issues

The IV formulation of letermovir contains the excipient hydroxypropyl beta cyclodextrin (HP-β-CD). HP-β-CD is renally excreted and is known to accumulate in persons with impaired renal function. Animal toxicology studies have shown that it is associated with vacuolization of renal tubules. Other IV drugs containing HP-β-CD describe this potential risk in the Warnings and Precautions section of labeling. The Applicant was asked where in the PI they think this information should be presented. If the Applicant does not think a Warning is needed, they were asked to provide a justification for this position.

Discussion

Merck proposed that the theoretical safety concerns associated with HP-β-CD and renal dysfunction be included in Section 8.6 (Use in Specific Populations, Renal Impairment) (b) (4) *They do not think that a Warning is indicated as renal findings in animal studies were generally reversible and were not clearly adverse in nature; and renal toxicity has not been shown in humans. Further, a recently approved antimicrobial agent containing sulfonylbutaether beta-cyclodextrin (delafloxacin) did not include a Warning regarding renal impairment in its PI. The Division stated that they would take this information into consideration.*

6. Wrap-up and Action Items

These applications have not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

ANDREAS PIKIS
09/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209939
NDA 209940

LATE CYCLE MEETING
BACKGROUND PACKAGE

Merck Sharp & Dohme Corporation,
a subsidiary of Merck & Company, Incorporated
Attention: Anita J. Shaw, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike, P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Shaw:

Please refer to your New Drug Application (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for letermovir 240 mg and 480 mg tablets and 240/12 mL or 480 mg/24 mL solution for intravenous infusion.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 8, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your participants at victoria.tyson@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	September 8, 2017, 10:30-12:00 pm
Meeting Location:	Teleconference
Application Numbers:	209939/209940
Product Name:	Letermovir, tablets and injection for intravenous use
Indication:	Prophylaxis of CMV infection and disease in adult CMV-seropositive recipients [R+] of an allogenic hematopoietic stem cell transplant
Applicant Name:	Merck Sharp & Dohme Corporation, a subsidiary of Merck & Company, Incorporated

FDA PARTICIPANTS (tentative)
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Mary Singer, M.D., Ph.D., Medical Team Leader
Mario Sampson, Pharm D., Clinical Pharmacology Reviewer
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Takashi Komatsu, Ph.D., Clinical Virology Reviewer
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Debra Birnkrant, M.D., Director
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INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. These applications have not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for these applications. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issue has been identified to date:

- Product Quality-Facilities

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS/RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Victoria Tyson/Andreas Pikis)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 10 minutes

   Each issue will be introduced by FDA and followed by a discussion.

   - Product Quality:
     Manufacturing Facilities: At this time the evaluation of manufacturing facilities is on-going.

3. Information Requests – 20 minutes

   The following new Information Requests (IR) are currently in preparation:

   a. We will be requesting additional exposure-adjusted safety analyses (similar to what was done for laboratory abnormalities in your labeling response of August 22, 2017). Further, we are interested in the timing and distribution of these laboratory abnormalities and certain adverse events during the treatment period. Additional details will be included in the IR.

   b. The Division of Applied Regulatory Science in the Office of Clinical Pharmacology completed a computational assessment and literature review for letermovir to identify potential mechanisms of action for the cardiac events observed in Trial P001. Briefly, these assessments revealed that letermovir may inhibit T-type calcium channels and may bind to adenosine receptors. We plan to share the computational assessment with you prior to the Late-Cycle teleconference. We would like to know if you have performed any searches for potential targets for letermovir. If so, please submit these findings. Additionally, how do you propose to further investigate the findings of the computational assessment?

4. Postmarketing Requirements/Postmarketing Commitments – 20 minutes

   PMRs/PMCs are under discussion which may include, but are not limited to:

   <u>PMRs:</u>

   - Phenotypic analysis of letermovir against CMV mutants carrying pUL56 and/or pUL89 substitutions identified in the Phase 2 or Phase 3 trials

   <u>PMCs:</u>

   - In vitro study to evaluate whether letermovir is an inducer of CYP2C8 or CYP2C9.
   - CMV prophylaxis trial in renal transplant recipients (letermovir vs. valganciclovir; trial P002)
   - CMV prophylaxis trial comparing 100 days vs. 200 days of letermovir in HSCT recipients

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Additional data are also needed regarding the safety and efficacy of letermovir in the following patient population subgroups which were underrepresented in Trial P001:

- Black and Hispanic subjects

We strongly recommend that you ensure adequate enrollment of subjects from each of these populations in postmarketing clinical trials. In addition, the number of subjects who received intravenous (IV) letermovir for at least 7 days was limited in Trial P001, and attempts should be made to increase the safety database for this formulation.

5. Major labeling issues – 20 minutes

   - There was an increased rate of adverse events in the Infection and Infestation System Organ Class (excluding CMV infection) in the letermovir arm compared to the placebo arm in Trial P001. Please perform and submit an exposure-adjusted analysis of infection adverse events (see item #3 above). Pending the findings of these additional analyses, we would like to discuss potential explanations you may have for this finding as well as any proposals to convey this information in the label.

   - The IV formulation of letermovir contains the excipient hydroxypropyl beta-cyclodextrin (HP-β-CD). HP-β-CD is renally excreted and is known to accumulate in persons with impaired renal function. Animal toxicology studies have shown that it is associated with vacuolization of renal tubules. Other intravenous drugs containing HP-β-CD describe this potential risk in the Warning and Precautions section of labeling, and we are considering a similar Warning for letermovir injection. We would like to discuss your thoughts on the optimal location for this information in the prescribing information. If you do not feel that a Warning is necessary, please justify your position.

   - In labeling, please address the effect of letermovir in combination with cyclosporine on CYP3A substrates. Conduct and submit a summary of a literature search for studies of the combined effect of two moderate CYP3A inhibitors on the PK of CYP3A substrates.

6. Review Plans – 5 minutes

   The review team is working on the following review activities:
   - Complete application review by the Signatory Authority, Division Director, and Cross-Discipline Team Leader
   - Await completion of CMC facility evaluation and address any issues that may arise
   - Finalize labeling
   - Finalize PMR/PMCs: content, dates

7. Wrap-up and Action Items – 5 minutes (Victoria Tyson)

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/s/

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08/25/2017