CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215596Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 051001

MEETING MINUTES

Shire ViroPharma, Incorporated
Attention: Michael A. Cronin, PharmD
Director, Global Regulatory Affairs
650 East Kendall Street
Cambridge, MA 02142

Dear Dr. Cronin:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for maribavir (TAK-620).

We also refer to the teleconference between representatives of your firm and the FDA on January 28, 2021. The purpose of the meeting was to obtain the Agency's alignment on the data package, content and presentation for the planned NDA for maribavir.

A copy of the official minutes of the meeting/telecon 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 (301) 796-5964 or at the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Christine Kim, PharmD, RAC-US
Senior Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	BTD – Pre-NDA
Meeting Date and Time:	January 28, 2021; 9:30 – 11:00 AM
Meeting Location:	Teleconference
Application Number:	IND 051001
Product Name:	maribavir (TAK-620)
Indication:	Treatment of cytomegalovirus (CMV) infection and disease, in transplant patients who are resistant or refractory to prior antiviral therapy
Sponsor Name:	Shire ViroPharma, Incorporated (Shire)
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetics Act
Meeting Chair:	Andreas Pikis, MD
Meeting Recorder:	Christine Kim, PharmD, RAC-US

FDA ATTENDEES

OND/OID/Division of Antivirals (DAV)

- Debra Birnkrant, MD, Director
- Jeffrey Murray, MD, MPH, Deputy Director
- Poonam Mishra, MD, MPH, Deputy Director of Safety
- Yodit Belew, MD, Associate Director for Therapeutics
- Mary Singer, MD, PhD, Medical Team Leader
- Andreas Pikis, MD, Medical Officer
- Julian O'Rear, PhD, Clinical Virology Team Leader
- Takashi Komatsu, PhD, RAC, Clinical Virology Reviewer

Division of Pharm/Tox for Infectious Diseases (DPT-ID)

- Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Division Director
- Ilona Bebenek, PhD, DABT, Pharmacology/Toxicology Reviewer

OND/ORO/Division of Regulatory Operations for Infectious Diseases (DRO-ID)

- Karen Winestock, Chief, Project Management Staff
- Christine Kim, PharmD, Regulatory Project Manager

OTS/OCP/Division of Clinical Pharmacology IV (DCP IV)

- Su-Young Choi, PhD, PharmD, Clinical Pharmacology Team Leader
- Xiaoxia Yang, PhD, Clinical Pharmacology Reviewer

OTS/OB/Division of Biometrics IV (DB IV)
- Thamban Valappil, PhD, Statistics Team Leader
- Fraser Smith, PhD, Statistics Reviewer

SPONSOR ATTENDEES
- Emily Birakdar, PharmD, Fellow, Global Regulatory Affairs
- Robert Bradley, MS, Director, Clinical Operations Lead
- Michael Cronin, PharmD, Director, Global Regulatory Lead
- Martha Fournier, MD, Senior Director, Global Clinical Development Lead
- Alan McEmber, MS, Vice President, Rare Genetic & Hematology Therapeutic Area Head, Global Regulatory Affairs
- Rose Ann Murray, PhD, Director, Global Clinical Development
- Tracy Page, Director, Global Regulatory Project Management
- Ravikumar Peri, PhD, DABT, Director, Drug Safety Research and Evaluation
- Andrew Putney, MBA, Director, Global Program Management
- Ivy Song, PhD, Senior Director, Global Clinical Pharmacology Lead
- Aimee Sundberg, PharmD, Director, Global Clinical Development
- Obi Umeh, MD, MSc, Vice President, Global Program Lead
- Jackie Wu, MS, Director, Biostatistics and Statistical Programming
- Yuna Wu, PhD, Director, Biostatistics and Statistical Programming

1.0 BACKGROUND

Maribavir (TAK-620; formerly SHP620) is an orally bioavailable benzimidazole riboside, and an inhibitor of the CMV pUL97 kinase with a novel mechanism of action against human cytomegalovirus (CMV). Unlike currently available anti-CMV agents that inhibit CMV deoxyribonucleic acid (DNA) polymerase, the predominant inhibitory effect of maribavir is upon viral DNA assembly and egress of viral capsids from the nucleus of infected cells. Shire is developing maribavir for the treatment of CMV infection or disease, including infections resistant or refractory to ganciclovir, valganciclovir, cidofovir, or foscarnet in transplant patients. Maribavir is formulated as an immediate release, (b) (4) tablet of 200 mg strength for oral administration to support a dosing regimen of 400 mg given twice daily.

On October 10, 2017, Shire submitted a Breakthrough Therapy Designation request for maribavir for the treatment of resistant/refractory CMV infection in transplant patients based on data from the Phase 2 study SHP620-202 and supportive data from Study SHP620-203. The request was granted on December 15, 2017, for the treatment of CMV infection and disease in transplant patients resistant or refractory to prior therapy, as it met the criteria for Breakthrough Therapy Designation.

On July 25, 2019, Shire requested a Type B, Breakthrough Therapy Designation meeting to discuss Shire's proposed integrated safety analysis strategy to support a new drug application (NDA) for maribavir as a treatment of CMV infection in transplant recipients that are resistant or refractory to prior therapy. The FDA provided preliminary

comments on October 2, 2019, and subsequently because the Agency's comments were clear, Shire cancelled the teleconference meeting on October 3, 2019.

Shire requested a Type B, Pre-NDA, meeting on November 24, 2020, to discuss and obtain the Agency's alignment on the data package, content and presentation for the planned NDA for maribavir.

The meeting objective includes discussion of the following:
- Nonclinical data package
- Clinical pharmacology data package
- Clinical data package with respect to efficacy, safety and dosing considerations
- Regulatory and other procedural aspects

FDA sent preliminary comments to Shire on January 22, 2021. Upon receiving FDA's preliminary comments, Shire provided a response on January 27, 2021, and requested to focus the meeting discussion on the responses to the following questions:
- Question 3: Clinical
- Question 6: Clinical Virology
- Additional Comments: Clinical Pharmacology comments 3 and 4

2.0 DISCUSSION

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

Question 3: Takeda intends to submit an NDA package for maribavir supported by final data from Phase 3 trial SHP620-303 with additional evidence from Phase 2 studies SHP620-202 and SHP620-203.

Does FDA agree that the proposed NDA clinical data package is acceptable to support the Agency's evaluation of the benefit-risk profile of maribavir?

FDA Response to Question 3: In general, we agree that an NDA package based on the final data from the Phase 3 trial SHP620-303 and supportive data from the two Phase 2 studies is acceptable for submission. In addition, please note that the acceptability of the proposed indication, "Maribavir is indicated for the treatment of adults with post-transplant cytomegalovirus infection and disease, including those infections resistant or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet," will be a review issue.

Please provide the following information for the upcoming pre-NDA meeting:

- *When do you expect the top line data from the Phase 3 trial SHP620-302 to be available?*

- [redacted] (b) (4)
- *The proportion of patients in the IAT arm who had undetectable CMV DNA at Week 8 (23.9%) appears to be much lower than that observed in clinical practice with modification of antiviral medications and immunosuppressive therapy. Please provide an explanation for this difference.*
- *Please clarify how many subjects enrolled in the IAT arm in Trial SHP620-303 had undetectable CMV DNA levels during the first 8 weeks (treatment phase), and discontinued treatment (e.g., for adverse reactions), and then had CMV recurrence before the end of the treatment phase (Week 8) and were thus considered as failures.*
- *Please clarify how many patients in the IAT arm who were refractory to treatment were assigned by the investigator to receive ganciclovir, how many received valganciclovir, foscarnet, etc.*
- *Please provide the efficacy results at Week 20 (maintenance of clearance of CMV viremia at Week 20 (Week 12 post-treatment), if feasible.*
- *Please explain the discrepancy observed between your Phase 2 trial SHP620-202 and the Phase 3 Trial SHP620-303 results. In the phase 2 trial, patients refractory to treatment responded to maribavir better than resistant patients (maribavir all doses: 76% versus 61%). However, in the Phase 3 trial in the maribavir treatment arm, patients resistant to treatment responded to maribavir better than refractory patients (62.8% versus 43.8%).*

Meeting Discussion:

The Sponsor provided a response to the preliminary comments to the IND on January 27, 2021 and asked if the FDA has further clarification or comments. The FDA stated the following:

- No specific questions at this time, but these data will be a review issue.
- Although both Phase 3 studies (SHP620-303 and SHP620-302) will not be included in the NDA package, the FDA understands the delay and will accept the submission based on SHP620-303 and supportive data from the two Phase 2 studies.
- Concerns regarding the low efficacy observed in the investigational-assigned-treatment (IAT) arm of trial SHP620-303 were discussed.

Question 6: Analysis and interpretation of CMV resistance data from SHP620-303 will be provided in the NDA. Resistance analysis data will be provided consistent with the Division of Antiviral Products (DAVP) HCMV Resistance Data Template (May 2018). An initial resistance analysis report prepared in accordance with the RAP will also be submitted in the NDA. The resistance report will be updated in phases as data become available.

FDA Response to Question 6: Your approach appears to be reasonable. Please confirm that the clinical virology study report (in section 5.3.5.4) and the virology summary (in section 2.7.2.4) will be included in the NDA submission. Also, please confirm that the viral load data from both local assessment visit #1 and visit #2 (and any additional prescreening visits, if available) are included in your datasets.

Additionally, please include the resistance data from studies SHP620-202 and SHP620-203 in your dataset. We acknowledge that you may not be able to fill all of the relevant data in the template.

Meeting Discussion:

Shire confirmed that the following will be provided with the NDA:

- The clinical virology study report and the virology summary will be included in the initial NDA as will resistance analysis data for study 303 consistent with the DAVP HCMV Resistance Data Template.
- Resistance analysis data for Study 202 consistent with the DAVP CMV Resistance Data Template.
- Shire proposed to submit the resistance analysis data for Study 203 consistent with the DAVP HCMV Resistance Data Template no later than 30 days after the submission of the original NDA.
- The FDA agreed with Shire's proposal. In addition, the FDA stated that they will provide a formal response to their other recent submission with respect to the CMV viral load assay issue. The FDA agreed that the data submitted are reassuring and that there is a path forward. However, the FDA will be asking for additional quality control analyses to confirm that the CAP/CTM assay data are indeed less reliable than those from the Abbott's test.

Additional Comments:
Clinical Pharmacology

We recommend submitting the following summary documents and supporting datasets to the NDA.

3. *Complete the attached in vitro ADME and in vivo PK study table template and submit as a MS Word document file (.doc or .docx).*
4. *Submit a summary table of bioanalytical method validation report and sample analyses report as outlined in the guidance for industry Bioanalytical Methods Validation[2], table 3.*
5. *We would like to remind you that applicability of PBPK modeling to prospectively estimate the interaction effect of a drug as a perpetrator for efflux transporters has not been fully demonstrated. Please provide a comprehensive validation of the substrate(s) PBPK model(s) for transporter-based DDI, including performance verification of PK and clinical DDIs with other perpetrators.*
6. *Submit key PBPK modeling files (e.g., compound, workspaces and simulation output files) needed for review and reproduction of the analyses. Please refer to the guidance for industry Physiologically-based pharmacokinetic analyses – format and content[3] which provides essential information to be submitted to the FDA for efficient review of your PBPK modeling and simulation. For the submission of PK datasets and population PK analysis/datasets, please refer to Guidelines for submission of model data format and content[4], and Study Data Technical Conformance Guide[5].*

Meeting Discussion:

Shire requested further clarification on the requests outlined above:
3 – in vitro ADME and in vivo PK study table template

- Shire stated that they have a total of 31 in vitro ADME studies and 21 in vivo PK studies and requested if the FDA has a preference on which study to focus on to generate the requested template.
- The FDA noted that the summary tables are not required. If Shire decided to not submit the template, it will not be a review issue. The FDA recommended that Shire modify the table as they think is most appropriate, including all the relevant information. The FDA reiterated that completing the template is not a requirement but is rather to facilitate the review process.
- Shire proposed to submit the template as a minor component to be submitted no later than 30 days after submission of original application.
- The FDA agreed with the proposal.

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[2] https://www.fda.gov/media/70858/download
[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/physiologically-based-pharmacokinetic-analyses-format-and-content-guidance-industry
[4] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/modeldata-format
[5] https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

4 - Bioanalytical method validation report and sample analyses report

- Shire stated that they have a total of 80 summary tables and would like to clarify that relevant information will be included in module 2.7.1. Shire noted that most of the phase 1 studies were conducted more than 15 years ago and that the Agency's guidance has been updated in recent years. Shire proposed to submit a summary table for phase 2 and 3 studies.
- The FDA stated that they are aware that things have changed over the years but is still requesting Shire to provide the summary table for phase 1 studies.
- Shire asked if the summary table is required or is mainly to facilitate the Agency's review.
- The FDA stated that the summary table is not required.
- Shire stated that they will proceed with providing the summary table for phase 2 and 3 studies and will generate additional table for phase 1 studies accordingly. However, Shire proposed to submit the additional summary table as a minor component to be submitted no later than 30 days after submission of original application.
- The FDA agreed with the proposal.

5 - PBPK modeling

- Shire confirmed that a comprehensive validation of the substrate(s) PBPK model(s) for transporter-based DDI, including performance verification of PK and clinical DDIs with other perpetrators will be submitted with the NDA application.

6 - PKPD modeling files

- Shire asked if there is a preferred way to submit the files. Shire explained that some of the files are in a special format and may not comply with the eCTD format.
- The FDA stated that a determination of the appropriate format to be submitted can not be made at this time and requested the Sponsor to submit the inquiry to the IND.

-At the conclusion of the meeting, the FDA provided the following comment:

- The review of this marketing application will most likely be under a priority review; however that will be determined at the time of NDA filing. The FDA anticipates that additional analyses may be requested of the Sponsor during the course of the review.
- Sensitivity Analysis: FDA requested that Shire provide an additional sensitivity analysis of the primary efficacy endpoint, excluding subjects who discontinued by 7, 14, 21, and 28 days and to provide such, if feasible, prior to the submission of the NDA. Shire confirmed that the sensitivity analysis will be included in the NDA package and can arrange to provide such information prior to the submission of the NDA.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Based upon the following:
    - Teleconference discussion,
    - The table of contents submitted in the meeting package dated December 23, 2020,
    - FDA's preliminary comments sent on January 22, 2021,
    - FDA's additional comments (Study Data Standardization Plan and statistics comments) sent on January 22, 2021,
    - Shire's responses to our preliminary comments and additional comment received on January 27, 2021,

  the FDA agreed that the proposed content for a complete application appears acceptable.

- 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.

- A preliminary discussion was held on the need for a REMS, other risk management actions. There is insufficient information to conclusively determine whether a REMs will be needed but based upon the data currently available as well as our response contained in the preliminary comments sent on January 22, 2021, the FDA agreed that the Sponsor did not need to submit a REMS as part of the NDA submission, however, the Agency will make the final determination for the need of a REMS during the review of the NDA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The FDA agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
    - Resistance data from Study 203 consistent with the DAV HCMV Resistance Data Template
    - In vitro ADME and in vivo PK study
    - Summary table of bioanalytical method validation report

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

  NDA NUMBER: LATE COMPONENT - BIOMETRICS
  NDA NUMBER: LATE COMPONENT - CLINICAL
  NDA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY

NDA NUMBER: LATE COMPONENT - NONCLINICAL

In addition, we note that a chemistry pre-submission meeting is scheduled for February 4, 2021. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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[6] and Pregnancy and Lactation Labeling Final Rule[7] 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.

[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* 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 ORA investigators who conduct those inspections. 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

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

- There were no issues requiring further discussion

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	February 25, 2021
Resistance data from Study 202 consistent with the DAV HCMV Resistance Data Template	Sponsor	no later than 30 days after the submission of the original application
• In vitro ADME and in vivo PK study • Summary table of bioanalytical method validation report	Sponsor	no later than 30 days after the submission of the original application

6.0 ATTACHMENTS AND HANDOUTS

- No attachments or handouts were provided for the meeting

[10] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINE KIM
02/04/2021 08:13:47 AM

CDER Breakthrough Therapy Designation Determination Review Template

IND	51001
Request Receipt Date	October 19, 2017
Product	Maribavir (VP 41263, SHP620)
Indication	Treatment of CMV infection and disease, including those resistant/ refractory to ganciclovir, valganciclovir, cidofovir, or foscarnet
Drug Class/Mechanism of Action	CMV antiviral / inhibitor of the CMV pUL97 kinase
Sponsor	Shire ViroPharma Incorporated
ODE/Division	Office of Antimicrobial Products / Division of Antiviral Products (DAVP)
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	December 18, 2017

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)**. Link this review to the incoming 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):**

   Treatment of CMV infection and disease, including those resistant/refractory to ganciclovir, valganciclovir, cidofovir, or foscarnet.

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:

[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

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 adequate 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):

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.

[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

Cytomegalovirus (CMV) is the most frequent opportunistic pathogen in transplant patients, contributing significantly to both patient morbidity and mortality. The risk of developing CMV disease after transplantation depends on a number of different factors, including the CMV serologic status of both donor and recipient, the type of transplant, and the level of immunosuppression. The clinical symptoms of CMV infection range from asymptomatic CMV viremia to tissue-invasive CMV disease. In this submission, the Sponsor is requesting a breakthrough therapy designation for maribavir for the treatment of CMV infection and disease in transplant patients, including those resistant/refractory to ganciclovir, valganciclovir, cidofovir, or foscarnet.

Maribavir, an orally bioavailable benzimidazole riboside, is an inhibitor of the CMV pUL97 kinase with a novel mechanism of action. It inhibits CMV DNA assembly and also inhibits egress of viral capsids from the nucleus of infected cells. In vitro studies showed that maribavir is more potent than ganciclovir against CMV, including strains that are resistant to ganciclovir. Despite encouraging results from a Phase 2 dose-ranging trial in hematopoietic stem cell transplant (HSCT) recipients, the drug failed to demonstrate efficacy in two Phase 3 trials evaluating prophylaxis of CMV; one in allogeneic HSCT recipients and the other in liver transplant recipients at high risk for CMV disease. The dose selection (100 mg BID) was considered a possible explanation for the difference in outcome between the Phase 2 and Phase 3 trials. Although Phase 1 and Phase 2 data indicated that maribavir can be given in much higher doses, the lowest dose that showed efficacy and minimal toxicity profile (dysgeusia and nausea) in the Phase 2 trial was selected for the Phase 3 prophylaxis trials.

Limited data from emergency INDs indicated that maribavir, when used at higher doses (400 to 800 mg BID), may be effective in the treatment of resistant/refractory CMV infection, as 4 of 6 patients had CMV clearance within 6 weeks of treatment. Based on these data, and after discussing with the Division, the Sponsor conducted another Phase 2 trial (SHP620-202) for the treatment of CMV infection resistant/ refractory to prior treatment with ganciclovir/valganciclovir. In fact, this application for breakthrough therapy designation is based on the results from the Phase 2 trial SHP620-202. It is noteworthy that the Sponsor also conducted a non-IND Phase 2, randomized, dose-ranging study to assess the safety and anti-CMV activity of maribavir versus valganciclovir for treatment of CMV infection in transplant patients who did not have CMV end-organ (tissue-invasive) disease (SHP620-203). Safety data from SHP620-203 were also used to support this application.

Of note, on August 13, 2013, ViroPharma (the previous holder of this IND) applied for breakthrough therapy designation for the treatment of resistant/refractory CMV infection in transplant patients based on preliminary data from Study SHP620-202 and supportive data from SHP620-203. The Division and the Medical Policy Council determined that breakthrough therapy designation could not be granted because the submitted data did not indicate that maribavir demonstrated substantial improvement over existing therapies. The decision not to support the breakthrough therapy designation was based on:

- The significant virologic breakthrough observed in 11/26 (42%) patients while on therapy and who completed at least three weeks of treatment raised concerns regarding the potential efficacy of the doses of maribavir evaluated for treatment of CMV infections resistant or refractory to prior treatment with ganciclovir/valganciclovir and/or foscarnet in Study SHP620-202.

- The duration of maribavir treatment for the 15/31 patients who achieved and maintained CMV DNA levels below the level of quantification was not specified in the information provided in th breakthrough therapy designation request; and thus we couldn't assess the durability of treatment response based on these data.

- Importantly, it was not clear from the data provided whether the treatment effect in patients who achieved and maintained CMV DNA levels below the level of quantification was exclusively due to maribavir or to additional factors (e.g., decrease of immunosuppression, addition of other drugs).

- Further, it was not clear from the data provided whether patients who achieved and maintained CMV DNA levels below the level of quantification were infected with CMV resistant to prior ganciclovir/ valganciclovir and/or foscarnet or whether they were refractory to treatment. Specific viral amino acid substitutions associated with resistance to prior treatment were not provided.

In addition, ViroPharma was advised that they could submit a new request if new clinical evidence demonstrated that maribavir provides a substantial improvement in treatment of CMV infection in transplant patients resistant or refractory to prior treatment. The new request should include final report from Study SHP620-202, including resistance data obtained at baseline and at time of breakthrough or relapse.

On May 8, 2017, the Sponsor requested preliminary breakthrough therapy designation advice. Key comments sent to the Sponsor were as follows:

- Confirmed undetectable plasma CMV DNA at week 6 (as included in the May 8, 2017 submission);
- Percentage of patients with CMV-tissue invasive disease, CMV syndrome, or asymptomatic CMV viremia in each treatment arm;
- Percentage of patients at baseline in each treatment arm who were 1) resistant to ganciclovir/ valganciclovir; 2) resistant to foscarnet; 3) refractory to treatment with ganciclovir/ valganciclovir; and 4) refractory to treatment with foscarnet. Additionally, for the patients resistant to ganciclovir/valganciclovir and/or foscarnet, include the breakdown of those who were identified only by the local laboratory and those who were confirmed by the central laboratory as well as the specific resistance-associated substitutions that were identified;
- Available information explaining the discrepancy between the local laboratory and central laboratory baseline resistance analysis results;
- CMV recurrences, including on-treatment and post-treatment recurrences;
- All clinical outcomes assessed in the trial (e.g., deaths, graft rejection);
- Safety data (e.g., serious adverse events, severe adverse events, discontinuations due to adverse events, shifts of 3 or 4 grades from baseline for any laboratory abnormality, neutropenia (ANC <500, 500 - < 750, 750 - < 1000 /μL), anemia (Hgb <6.5, 6.5 - <8.0, 8.9 - <9.5 g/dL), thrombocytopenia (platelets <25000, 25000- < 50000, 50000 - <100000/μL), and elevated creatinine clearance (> 2.5, >1.5 -2.5 mg/dL).
- Please provide evidence for a treatment effect for maribavir that represents substantial improvement over available therapies.
- Provide additional information from the literature for historical controls when resistant/ refractory CMV infection/disease was treated with foscarnet, cidofovir, or high dose ganciclovir. In addition, if available, historical control data showing clearance of viremia and clinical outcomes with no treatment (or continued treatment with ganciclovir/valganciclovir) would provide stronger evidence for a maribavir treatment effect.
- Provide maribavir safety data in comparison with currently available drugs for the treatment of resistant or refractory CMV infection.

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

The primary endpoint in study SHP620-202 was the percentage of patients with undetectable CMV DNA within 6 weeks of treatment. CMV viremia is not considered a validated surrogate endpoint at this time for

treatment of CMV infection/disease, but is considered reasonably likely to predict clinical benefit; however, this was considered acceptable for an exploratory Phase 2 study.

For the ongoing Phase 3 trial in patients with CMV infections that are resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, the Division asked for a composite primary endpoint for patients with tissue-invasive CMV disease (defined by achievement of undetectable CMV DNA and resolution of clinical symptoms).

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.

In general, there are limited therapeutic options for the treatment or prevention of CMV disease in immunocompromised patients. Currently, only five drugs have received FDA approval for systemic use for the treatment or prevention of CMV disease: ganciclovir and its prodrug valganciclovir, foscarnet, cidofovir, and letermovir. However, the only drug approved for the treatment of asymptomatic CMV viremia is ganciclovir. The other treatment indication is that of CMV retinitis in immunocompromised patients, including patients with AIDS (ganciclovir, valganciclovir, foscarnet, and cidofovir). No drug has been approved for the treatment of other CMVend-organ disease or for the treatment of resistant/refractory CMV infection. Further, there have been very few controlled studies of CMV treatment in transplant patients (none of which was performed for registrational purposes) and none for the treatment of refractory/resistant CMV infection.

In clinical practice, intravenous ganciclovir and oral valganciclovir are the first-line treatments (standard of care) for CMV infection or disease. Valganciclovir is the preferred agent for mild to moderate CMV disease in solid organ transplant patients and intravenous ganciclovir for severe and life-threatening cases. IV ganciclovir is also the preferred agent for CMV disease in stem cell transplant patients. Therapeutic options for ganciclovir-resistant CMV are limited. It is highly recommended that the level of immunosuppression be cautiously reduced. The choice of antiviral therapy for treatment of ganciclovir-resistant CMV should be guided by genotypic analysis of the virus. Mutations conferring low level ganciclovir resistance could be overcome by increasing the dose of ganciclovir (i.e., increasing the dose by 50-100%). High-level ganciclovir resistance and suspected resistance in the case of life-threatening disease are best managed with intravenous foscarnet either alone or in combination with ganciclovir. Despite the absence of controlled studies, it appears that the majority of the patients respond to combination treatment. The major adverse reactions associated with foscarnet use are significant nephrotoxicity, and electrolyte abnormalities. Cidofovir is another alternative for the treatment although controlled studies are not available. Cidofovir is also highly nephrotoxic.

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

No other drug has been granted a breakthrough therapy designation for the treatment CMV infection or disease, including those resistant/refractory to prior anti-CMV therapy.

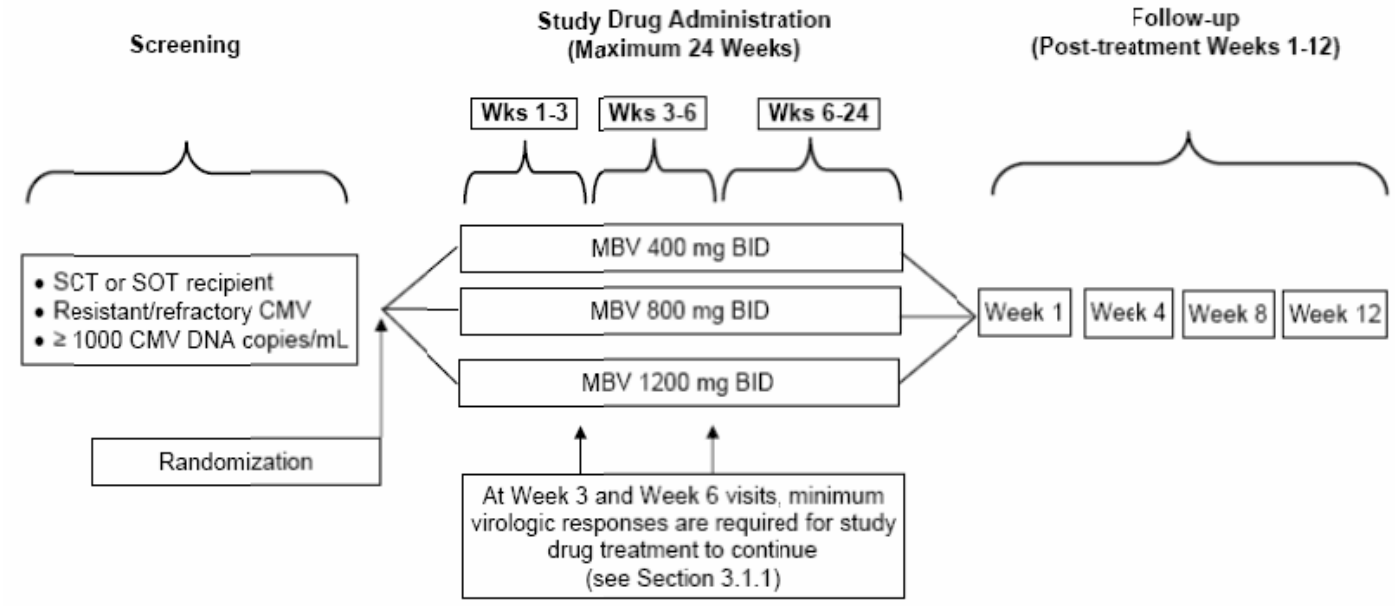
10. Information related to the preliminary clinical evidence:

Protocol SHP620-202: This was an exploratory, Phase 2, randomized study designed to assess the safety and anti-CMV activity of different doses of maribavir for the treatment of CMV infections that were resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet in stem cell or solid organ transplant

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

recipients. The study plan was to enroll 120 subjects. Subjects fulfilling the entry criteria were to be randomized in a 1:1:1 ratio to receive oral maribavir 400 mg BID, 800 mg BID or 1200 mg BID up to 24 weeks after stratification by transplant type (stem cell or solid organ transplantation). All subjects were to receive maribavir, but subjects and investigators were to be blinded to dose. An overview of the study design is shown in the following figure.

Figure 1. Design of Study SHP620-202



At the Week 3 visit, and based on the Week 2 CMV test results, subjects who have demonstrated any decrease in CMV DNA levels were allowed to continue study drug at the discretion of the investigator. Subjects still receiving study drug through Week 6, were to continue treatment with study drug if the Week 5 CMV test results had demonstrated a ≥ 2 $\log_{10}$ decrease from baseline or undetectable CMV DNA levels. For subjects who continued dosing after Week 6 visit, dosing continued at the discretion of the investigator through a maximum of 24 weeks in an attempt to decrease CMV DNA to undetectable and/or to maintain undetectable CMV DNA levels. The primary endpoint was undetectable CMV DNA within 6 weeks of treatment (defined as 2 consecutive post-baseline, on-treatment undetectable results [< 200 copies/mL], separated by at least 5 days). It should be noted that DAVP recommended that an active control treatment arm (standard of care) be added to the trial, leaving the choice of the anti-CMV therapy in the control arm to the discretion of each investigator. This recommendation was not accepted by the Sponsor.

Efficacy results:

The results of the primary endpoint analysis are shown in the following table:

Table 1. Confirmed undetectable plasma CMV DNA within 6 weeks (ITT-S population)*

	Within 6 weeks (N=120)
Subjects with confirmed undetectable plasma CMV DNA, n(%)	80 (67%)
Treatment effect estimate (95% CI)	0.67 (0.57, 0.75)

*Efficacy was similar across the three dosage groups

At the request of the Division, the Sponsor conducted an analysis to determine the proportion of subjects that had undetectable plasma CMV DNA at Week 6. In this analysis, subjects who met the criteria of confirmed undetectable plasma CMV DNA and with non-missing data at Week 6 were counted as responders. In this analysis missing data= failure.

Table 2. Confirmed undetectable plasma CMV DNA at Week 6 week (ITT-S population)

	At Week 6 (N=120)
Subjects with confirmed undetectable plasma CMV DNA, n(%)	64 (53%)
Treatment effect estimate (95% CI)	0.53 (0.44, 0.62)

*Reasons for missing data were reported as follows: adverse event 9 (26%); death 9 (26%), recovery 7 (20%); unknown 7(20%); physician decision 2 (6%), lack of efficacy 2 (6%), withdrawal of consent 1 (3%).

The efficacy of maribavir by type and severity of CMV infection at baseline is shown in Table 3.

Table 3. Confirmed undetectable plasma CMV DNA within 6 weeks by type and severity of CMV infection at baseline (ITT-S Population)

	Maribavir 400 mg BID N = 40	**Maribavir 800 mg BID N = 40**	**Maribavir 1200 mg BID N = 40**	**Maribavir All Doses N = 120**
Proportion of Patients with Asymptomatic CMV Infection, n/N (%)*	24/40 (60.0)	26/40 (65.0)	27/40 (67.5)	77/120 (64.2)
Responder	17 (70.8)	18 (69.2)	22 (81.5)	57 (74.0)
Nonresponder	7 (29.2)	8 (30.8)	5 (18.5)	20 (26.0)
Proportion of Patients with Symptomatic CMV Infection, n/N (%)*	10/40 (25.0)	7/40 (17.5)	8/40 (20.0)	25/120 (20.8)
Responder	6 (60.0)	4 (57.1)	4 (50.0)	14 (56.0)
Nonresponder	4 (40.0)	3 (42.9)	4 (50.0)	11 (44.0)
Proportion of Patients with CMV Organ Disease, n/N (%)*	6/40 (15.0)	7/40 (17.5)	3/40 (7.5)	16/120 (13.3)
Responder	5 (83.3)	3 (42.9)	1 (33.3)	9 (56.3)
Nonresponder	1 (16.7)	4 (57.1)	2 (66.7)	7 (43.8)

Comment: Maribavir appears to be more effective in patients with asymptomatic CMV infection compared to those with symptomatic CMV infection and those with CMV organ disease.

According to the Sponsor, the efficacy of maribavir was lower in patients with any baseline CMV genetic mutations associated with resistance (61%) compared to those without associated resistance mutations (refractory patients, 76%). Further, maribavir appeared to be effective in patients resistant to ganciclovir, foscarnet, cidofovir, or combination of these drugs (relatively less effective in patients with foscarnet mutations (46%) and in patients with a combination of ganciclovir and foscarnet mutations (46%). However, it should be emphasized that the Sponsor has provided limited resistance data despite the repeated requests by the Division.

A total of 30 patients (35%) experienced CMV recurrence during the study. In 25 of the 30 patients, recurrences occurred while on study drug (median observed time from confirmed undetectable CMV DNA to CMV recurrence was 37 days). The results of patients with CMV recurrences are summarized in Table 4.

Table 4. Analysis of time from confirmed undetectable plasma CMV DNA to CMV recurrence through end of study (ITT-S Population)

	Maribavir 400 mg BID N=40	Maribavir 800 mg BID N=40	Maribavir 1200 mg BID N=40	Maribavir All Doses N=120
Number of subjects achieving confirmed undetectable CMV DNA[a]	29/40	27/40	30/40	86/120
Subjects with event, n (%)	7 (24.1)	11 (40.7)	12 (40.0)	30 (34.9)
On study drug, n (%)	6 (20.7)	9 (33.3)	10 (33.3)	25 (29.1)
Post study drug, n (%)	1 (3.4)	2 (7.4)	2 (6.7)	5 (5.8)
Subjects censored, discontinued, n (%)	9 (31.0)	7 (25.9)	7 (23.3)	23 (26.7)
On study drug, n (%)	3 (10.3)	5 (18.5)	4 (13.3)	12 (14.0)
Post study drug, n (%)	6 (20.7)	2 (7.4)	3 (10.0)	11 (12.8)
Subjects censored, ongoing, n (%)	13 (44.8)	9 (33.3)	11 (36.7)	33 (38.4)
Median observed event time (days)				
All	36.0	36.0	82.0	37.0
On study drug	32.5	36.0	63.5	37.0
Post study drug	37.0	57.5	154.0	97.0
Kaplan-Meier estimate (days)[b]				
1st quartile	42.0	37.0	92.0	51.0
Median (95% confidence interval)	NE (NE, NE)	118.0 (37.0, NE)	161.0 (92.0, NE)	NE (118.0, NE)
3rd quartile	NE	NE	NE	NE

In previous submissions the Sponsor stated that maribavir demonstrated substantial improvement in outcomes compared to historical results (67-77% CMV viremia clearance at Week 6 compared to 44-59% in historical studies [Aschan 1992; Avery 2016]). The Sponsor was informed that the comparison with these two studies was not sufficient and was asked to provide additional justification. No additional justification was included in this submission (in the report by Aschan more than 50% of the subjects had end-organ disease compared to 13% in in SHP620-202. In the Avery publication, 28% of subjects had tissue invasive CMV disease, and CMV viremia was cleared in 67% of patients treated with foscarnet, which is somewhat higher than the 53% reported for maribavir in SHP620-202 in the ITT analysis where missing data=failure).

Safety results:

The most common reported treatment-emergent adverse event associated with maribavir was dysgeusia (65% overall), with the reporting frequency showing some evidence of dose dependence (60%, 63%, and 73% in the maribavir 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively. Gastrointestinal adverse events of nausea (34% overall), vomiting (29%), and diarrhea (23%) were the other most commonly reported adverse events.

Serious adverse events: Serious adverse events occurred in 81 of the 120 subjects (68%). Twenty of the 120 subjects (17%) experienced serious adverse events that were considered by investigators as related to study drug.

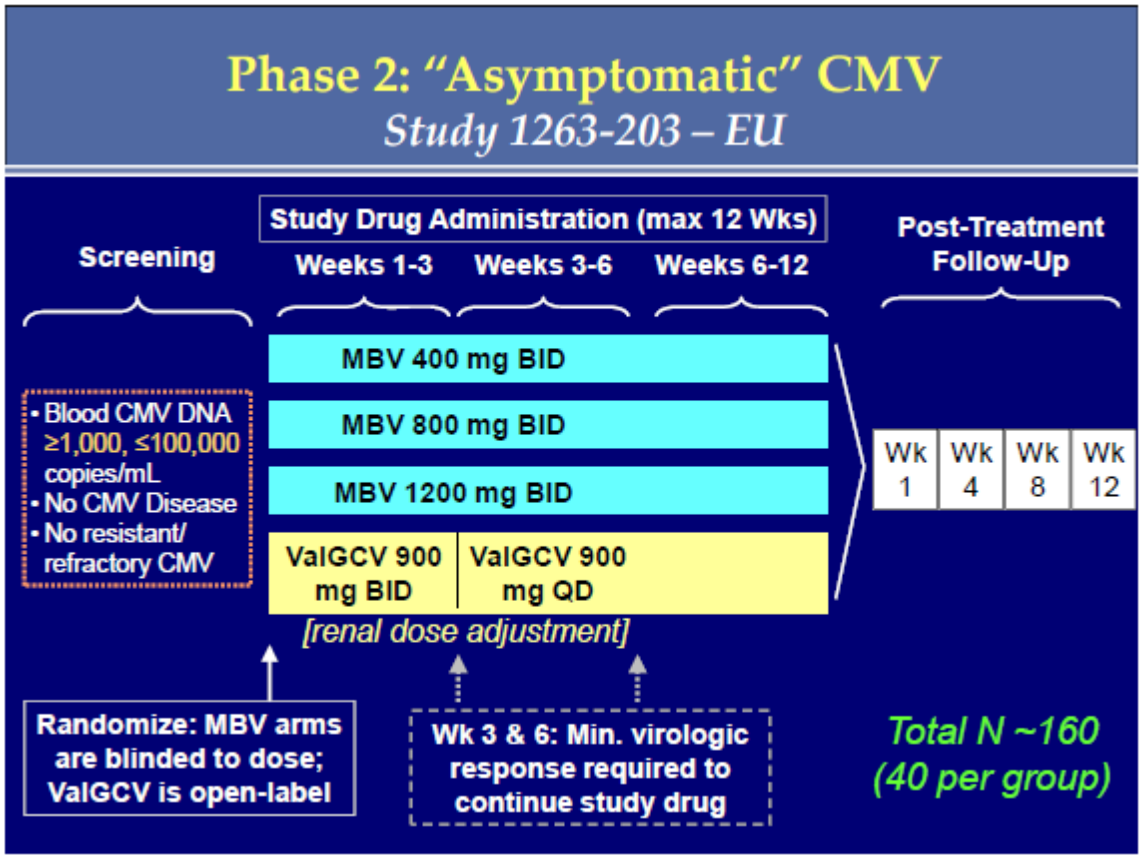
Deaths: A total of 32 deaths (37%) were reported in the study; only one death (multi-organ failure) was considered by the investigator as related to study drug.

Discontinuations due to adverse events: Thirty-four percent of the subjects (41/120) were discontinued from maribavir due to an adverse event. In 15 subjects the adverse events that led to study drug discontinuation were considered by investigators as related to study drug.

Subjects with adverse events causing interruptions of study drug: A total of 20 subjects (17%) experienced an adverse event causing interruption of study drug; in 10 subjects (8%) the adverse event was considered related to study drug.

Supportive safety data:
In the absence of a comparator arm in Study SHP620-202 it is very difficult to assess the safety profile compared to other drugs used for the treatment of patients with CMV resistant/refractory infection. To support a potential benefit of maribavir versus valganciclovir, the Sponsor provided safety data from Study SHP620-203. This was a a non-IND Phase 2, randomized, dose-ranging, parallel-group study of maribavir versus valganciclovir for the treatment of CMV infections in HSCT or solid organ transplant (SOT) recipients. A total of 160 subjects were randomized in a 1:1:1:1 ratio to receive oral maribavir at 1 of 3 dose strengths (400 mg BID, 800 mg BID, or 1200 mg BID) or valganciclovir (Weeks 1-3: 900 mg BID, after Week 3: 900 mg QD; with dose adjustment for renal function) for up to 12 weeks. Eligible subjects did not have CMV end-organ disease or CMV infection that was resistant to anti-CMV drugs. Valganciclovir administration was open-label. Subjects and investigators knew that they were receiving maribavir but they were blinded to the dose strength. A schematic overview of the study is shown in the following figure.

Figure 2. Design of Study SHP620-203



Below is a brief summary of the adverse events observed in Study SHP620-203, as well as a summary of adverse events of special interest.

Consistent with previous studies, the most common reported treatment-emergent adverse event associated with maribavir was dysgeusia (40% in the overall maribavir group versus 3% in the valganciclovir group). Gastrointestinal adverse events of nausea, diarrhea, and vomiting were also reported more frequently in the overall maribavir group than (20 -23%) compared with the valganciclovir group (10-15%).

Serious adverse events: Serious adverse events occurred in 44% (52/119) of subjects in the overall maribavir group compared to 33% (13/33) of subjects in the valganciclovir group. Ten percent (10/119) of the serious adverse events in the maribavir group were considered related to study drug compared to 3% (1/33) in the valganciclovir group.

Deaths: A total of 6 deaths (6/119; 5%) were reported in maribavir subjects and 3 (3/40; 8%) in the valganciclovir group. None of the deaths was considered related to study drugs.

Discontinuations due to adverse events: Twenty-seven (23%; 27/119) subjects in the overall maribavir group discontinued maribavir (related to study drug 13%; 16/119) compared to 5 subjects (13%; 5/40) in the valganciclovir group (related to study drug 10%; 4/40).

Subjects with adverse events causing interruptions of study drug: A total of 10 subjects (8%; 10/119) in the overall maribavir group experienced an adverse event causing interruption of study drug (related to study drug 5%; 6/119) compared to 2 subjects (5%; 2/40) in the valganciclovir group (related to study drug 3%; 1/40).

Laboratory abnormalities of special interest: Laboratory results of special interest are summarized in Table 5.

Table 5. Study SHP620-203 summary of worst post-baseline while on treatment parameters: neutropenia, anemia, thrombocytopenia, and serum creatinine (ITT-S population)

ITT-S Population					
Parameters	Maribavir 400 mg BID N = 40	Maribavir 800 mg BID N = 40	Maribavir 1200 mg BID N = 39	Valganciclovir N = 40	Maribavir All Doses N = 119
ANC					
<500/uL	0	1 (2.5)	0	2 (5.0)	1 (0.8)
500-<750/uL	1 (2.5)	2 (5.0)	1 (2.6)	1 (2.5)	4 (3.4)
750-<1000/uL	1 (2.5)	0	0	3 (7.5)	1 (0.8)
≥1000/uL	36 (90.0)	37 (92.5)	33 (84.6)	29 (72.5)	106 (89.1)
Hemoglobin					
<6.5 g/dL	2 (5.0)	0	0	0	2 (1.7)
6.5-<8.0 g/dL	3 (7.5)	9 (22.5)	7 (17.9)	1 (2.5)	19 (16.0)
8.0-<9.5 g/dL	11 (27.5)	15 (37.5)	12 (30.8)	8 (20.0)	38 (31.9)
≥9.5 g/dL	22 (55.0)	16 (40.0)	15 (38.5)	26 (65.0)	53 (44.5)
Platelets					
<25000/uL	0	0	2 (5.1)	4 (10.0)	2 (1.7)
25000-<50000/uL	3 (7.5)	8 (20.0)	3 (7.7)	3 (7.5)	14 (11.8)
50000-<100000/uL	6 (15.0)	3 (7.5)	3 (7.7)	6 (15.0)	12 (10.1)
≥100000/uL	29 (72.5)	29 (72.5)	26 (66.7)	22 (55.0)	84 (70.6)
Serum Creatinine					
>2.5 mg/dL	4 (10.0)	2 (5.0)	4 (10.3)	1 (2.5)	10 (8.4)
>1.5-2.5 mg/dL	10 (25.0)	16 (40.0)	13 (33.3)	9 (22.5)	39 (32.8)
≤1.5 mg/dL	24 (60.0)	22 (55.0)	17 (43.6)	25 (62.5)	63 (52.9)

Comment: Severe neutropenia and thrombocytopenia favored maribavir; whereas severe anemia and elevated serum creatinine favored valganciclovir.

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

The Division was split to whether a breakthrough therapy designation should be granted and, therefore would appreciate the Medical Council's input on this issue. Below is a brief summary and rationale for the supporters and non-supporters for granting a breakthrough designation of maribavir.

☒ GRANT :

Reasons to support the breakthrough designation request include:

Although the sponsor has not provided the viral genotypic resistance data, as requested, preliminary clinical data show that maribavir may provide an option for treatment of resistant or refractory CMV. Based on the SHP620-202 trial, maribavir at the very least appears to have activity against (de facto) refractory CMV infection (i.e., CMV viremia that has not responded to treatment with ganciclovir or valganciclovir within 2 weeks, but no genotypic resistance was identified). The efficacy of maribavir in that trial was in the same range as that reported by Avery, 2016, for forscarnet (approximately 67%) for treatment of resistant or refractory

CMV infection/disease in a retrospective study. In the Avery study, however, a higher proportion of patients had tissue-invasive CMV disease (28%) in comparison to 13% in the maribavir trial, SHP620-20.

In the Appendix to the breakthrough therapy designation request, the sponsor provided preliminary efficacy data from their non-IND phase 2 trial, 1263- 203, in which several doses of maribavir were compared to valganciclovir for treatment of asymptomatic CMV viremia in HSCT or SOT recipients. At week 6, 26/40 (65%) valganciclovir-treated subjects and 92/118 (77%) maribavir-treated subjects (all doses) achieved undetectable CMV DNA.

No drugs are currently approved for this indication, and very few options exist for treatment in this setting. Foscarnet is the mainstay of therapy (unapproved) for treatment of CMV resistant or refractory to ganciclovir/valganciclovir. However, the toxicities associated with foscarnet (renal impairment, severe electrolyte abnormalities, seizures, QT prolongation and others) frequently limit its use. In a retrospective, single center study of resistant/refractory CMV treatment with foscarnet, Avery (2016) found that renal dysfunction occurred in 51% patient by the end of treatment , and in 28% after 6 months. Ganciclovir, which has been used at higher than approved doses for treatment of resistant/refractory CMV, is associated with severe hematologic abnormalities, including neutropenia and thrombocytopenia. Cidofovir, which is associated with severe nephrotoxicity, is considered a third line agent, an agent of last resort. Thus, there is a significant unmet need for a drug for treatment of resistant/refractory CMV infection/disease.

Thus, preliminary clinical data suggest that maribavir has efficacy for treatment of refractory CMV similar to that of foscarnet and for treatment of non-resistant or non-refractory CMV similar to that of valganciclovir. Preliminary safety data suggest that maribavir may provide a safety advantage over valganciclovir/ganciclovir with respect to neutropenia and thrombocytopenia, and over foscarnet with respect to severe renal impairment. Thus, a case could be made for considering breakthrough designation for maribavir for treatment of refractory CMV or non-resistant/non-refractory CMV infection/disease.

☒DENY:

Reasons to deny the breakthrough designation request include:

The submitted data do not differ substantially from the preliminary data submitted in 2013 when both the Division and the Medical Council agreed that breakthrough therapy designation should not be granted. The decision not to support a breakthrough therapy designation is based on the following:

- The Sponsor has not provided substantial evidence that maribavir is more efficacious or safer than the standard of care.
- It is not clear from the data provided whether patients who achieved and maintained CMV DNA levels below the level of quantification were infected with CMV resistant to prior ganciclovir/valganciclovir and/or foscarnet or whether they were refractory to treatment.
- Specific viral amino acid substitutions associated with resistance to prior treatment were not provided despite numerous requests by the Division.

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

Currently, there are two ongoing Phase 3 trials with maribavir dose higher than that used in the previous Phase 3 trials:

- Protocol SHP620-303: A phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir treatment compared to investigational-assigned treatment in transplant recipients with CMV infections that are refractory or resistant to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir; and

- Protocol SHP620-302: A phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled study to assess the efficacy and safety of maribavir compared to valganciclovir for the treatment of CMV infection in HSCT recipients.

If the recommendation is to deny the request, and in the event of promising results from the two ongoing Phase 3 trials, the Division would like to revisit this issue during the pre-NDA meeting and would like to encourage the Sponsor to re-apply for a breakthrough therapy designation.

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 ☐

* The maribavir breakthrough therapy designation request was presented to the Medical Policy Council on December 13, 2017. The Medical Policy Council decided to grant a a breakthrough therapy designation for the treatment of CMV infection and disease in transplant patients resistant or refractory to prior anti-CMV therapy.

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

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

/s/

ANDREAS PIKIS
12/15/2017

MARY E SINGER
12/15/2017

DEBRA B BIRNKRANT
12/15/2017