NDA 214787

WRITTEN REQUEST – AMENDMENT 1

Gilead Sciences, Inc.
Attention: Madelyn Low, MBS
Senior Regulatory Affairs Associate
333 Lakeside Drive
Foster City, CA 94044

Dear Ms. Low:[1]

Please refer to your correspondence dated May 20, 2022, requesting changes to FDA's October 28, 2021, Written Request (also originally submitted under IND 147753), for pediatric studies for Veklury (remdesivir).

We have reviewed your proposed change and are amending the Written Request. All other terms stated in our Written Request issued on October 28, 2021, remain the same (Text added is underlined. Text deleted is strikethrough).

BACKGROUND:

COVID-19 is a potentially serious or life-threatening disease caused by SARS-CoV-2 virus. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Globally, according to the WHO, 225,024,781 confirmed cases of COVID-19 have been reported as of September 14, 2021, including 4,636,153 deaths. In the US, according to the Centers for Disease Control and Prevention (CDC), 41,262,574 cases of COVID-19 have been reported with 630,380 deaths as of September 14, 2021.

Veklury (remdesivir [RDV] injection) is a nucleotide prodrug that is intracellularly metabolized into its active form GS-441524, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis. Veklury is indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization.

The Division of Antivirals (DAV) has determined that adult and pediatric populations with mild, moderate, or severe COVID-19 generally display similar symptoms, and virologic response to an antiviral drug, such as RDV, is expected to be similar in adult and pediatric patients. These determinations allow extrapolation of efficacy from the adult clinical trials to pediatric patients if they achieve similar drug exposures. Therefore,

[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.

efficacy in pediatric patients will be, in part, supported by and extrapolated from the adult trials that evaluated the efficacy of RDV, and in part by pharmacokinetic/pharmacodynamic and safety data from pediatric patients.

Remdesivir is approved for the treatment of COVID-19 in pediatric patients 12 years and older and weighing at least 40 kg. The efficacy in this pediatric population was established based on extrapolation from adequate and well-controlled studies in adults, including a subset of 30 adult subjects weighing 40-50 kg. The overall safety and efficacy in this group of adults were comparable to adult subjects weighing greater than 50 kg. Safety information from 39 pediatric patients 12 years and older and weighing at least 40 kg who received RDV in a compassionate use program provided additional safety information. Although RDV is labeled for use in pediatric patients 12 years and older weighing at least 40 kg, because there is an ongoing PK and safety study in this age group, the data are requested for submission and review.

To obtain needed pediatric information on RDV, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

REQUESTS

Nonclinical study(ies): Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

Clinical study:

Conduct a study in pediatric patients with COVID-19 to assess the safety, tolerability, pharmacokinetics, and antiviral activity of remdesivir (RDV).

The dose selection and study design must be based on discussions and agreement between the Sponsor and the Agency.

- *Study Objectives:*
  To determine the pharmacokinetics and appropriate dose(s), safety, and antiviral activity of RDV across the age and weight groups in pediatric patients with COVID-19.

- *Patients to be Studied:*
  - Age (or weight) groups to be studied*:*
    - Neonates (<28 days old)
    - Children ages 28 days to less than 18 years, grouped according to the following weight ranges

->40 kg
-at least 20 kg to <40 kg
-at least 12 kg to <20 kg
-at least 3 kg to <12 kg

- *Number of patients to be studied:* At least 52 pediatric subjects, birth to less than 18 years of age must be studied, as described below:
  - A minimum of 4 neonates
  - At least 48 pediatric subjects 4 weeks old or older, reasonably distributed across the weight groups as described above.
  - All 52 subjects must receive remdesivir for treatment of COVID-19 as provided in the protocol.

- *Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
  Primary endpoints
  - Plasma PK of RDV and metabolites (e.g. C_{max}, AUC, C_{trough})
  - Proportion of participants with treatment-emergent adverse events
  - Proportion of participants with treatment-emergent graded laboratory abnormalities

- *Safety Outcomes/Monitoring:*
  Safety outcomes assessments must include adverse events, including laboratory toxicities, and tolerability. Based on available toxicity information about your product, provide in the protocol specific safety parameters that your pediatric program will monitor. Safety monitoring and data collection specified in the protocol must include, but not be limited to: hepatotoxicity, hypersensitivity, or infusion-related reactions. Laboratory monitoring (chemistry [including hepatic, renal parameters], hematology, coagulation) will be as agreed upon in the protocol.

- *Statistical information, including power of study(ies) and statistical assessments:*
  Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in pediatric subjects with COVID-19 is required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection and justification for the sample size selected. Final selection of sample size for each weight group must take into account potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary for adequate

characterization of pharmacokinetics across the intended age (or weight) groups.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*
  - Dosage form: Lyophilized powder for injection
  - Route of administration: Intravenous
  - Regimen: To be determined by development program

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

  (3) you have not marketed the formulation within one year after the Agency publishes such notice,

  The Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If

we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that remdesivir is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all post marketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic*

Safety Update Reports for Marketed Drugs and the guidance addendum.[2] You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017, study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[3] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before August 31, 2023 ~~September 30, 2022~~. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies) but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated October 28, 2021, as amended by this letter must be submitted to the Agency on or before August 31, 2023, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

[2] 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
[3] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[4]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Christine Kim, PharmD, RAC-US, Senior Regulatory Project Manager, at (301) 796-5964 or the Division's mainline at, (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Deputy Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

[4] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

ENCLOSURE:

- Complete Copy of Written Request as Amended

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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Gilead Sciences, Inc.
Attention: Madelyn Low, MBS
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  - Plasma PK of RDV and metabolites (e.g. C_{max}, AUC, C_{trough})
  - Proportion of participants with treatment-emergent adverse events
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- *Safety Outcomes/Monitoring:*
  Safety outcomes assessments must include adverse events, including laboratory toxicities, and tolerability. Based on available toxicity information about your product, provide in the protocol specific safety parameters that your pediatric program will monitor. Safety monitoring and data collection specified in the protocol must include, but not be limited to: hepatotoxicity, hypersensitivity, or infusion-related reactions. Laboratory monitoring (chemistry [including hepatic, renal parameters], hematology, coagulation) will be as agreed upon in the protocol.

- *Statistical information, including power of study(ies) and statistical assessments:*
  Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in pediatric subjects with COVID-19 is required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection and justification for the sample size selected. Final selection of sample size for each weight group must take into account potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary for adequate characterization of pharmacokinetics across the intended age (or weight) groups.

The following information pertains to all clinical studies in the Written Request.

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- *Drug information:*
  - Dosage form: Lyophilized powder for injection
  - Route of administration: Intravenous
  - Regimen: To be determined by development program

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  In accordance with section 505A(e)(2), if

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

  (3) you have not marketed the formulation within one year after the Agency publishes such notice,

  The Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the

product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that remdesivir is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all post marketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[2] You are encouraged to contact the reviewing Division for further guidance.

  For studies started after December 17, 2017, study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the

[2] 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

document “Study Data Specifications,” which is posted on FDA.gov[3] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before August 31, 2023. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies) but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.
In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written

[3] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[4]

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found on the Clinical Trials website.[5]

If you have any questions, call Christine Kim, PharmD, RAC-US, Senior Regulatory Project Manager, at (301) 796-5964 or the Division's mainline at, (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Deputy Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

[4] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[5] www.ClinicalTrials.gov

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/

ADAM I SHERWAT
05/26/2022 07:19:08 AM