DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205834

WRITTEN REQUEST

Gilead Sciences, Inc.
Attention: Linda Lintao, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Lintao:

Reference is made to your February 10, 2014 Proposed Pediatric Study Request (PPSR). We have determined that a Written Request is appropriate.

The studies in this Written Request investigate the potential use of a ledipasvir in an agreed upon combination regimen by the Agency for the treatment of pediatric patients 3 to less than 18 years of age with chronic hepatitis C virus (HCV) infection with genotypes 1, 4, 5 or 6 and compensated liver disease.

BACKGROUND

No systematic surveillance of chronic HCV infection among pediatric patients is available making an accurate assessment of prevalence and severity in this age group difficult. In developed countries, the HCV seroprevalence is estimated to be 0.1% to 0.53%. In US, the estimated seroprevalence is approximately 0.2% in children less than 12 years of age and 0.4% among children 12 to 19 years of age. The primary mode of HCV transmission to children is via vertical transmission. The rate of vertical transmission is estimated to be about 5% but may be increased in the presence of HIV infection. Among vertically infected patients, an estimated 20-30% will have spontaneous clearance of HCV and clearance is more likely in the first 2-3 years of life. Although most pediatric patients with chronic HCV infection will remain asymptomatic for many years, up to 30% will have chronic active infection during the pediatric period and an unknown proportion will go on to develop serious complications of chronic HCV including cirrhosis, hepatocellular carcinoma, or need for liver transplantation.

The goal of treatment is to delay or prevent long-term complications of chronic HCV infection. The current standard of care in treatment of chronic HCV in pediatric patients includes a regimen of subcutaneous injections of pegylated interferon alfa + oral ribavirin (PR) for a period of 6 to 12 months depending on genotype of HCV. Based on meta-analysis of prospective trials that evaluated PR, the rates of sustained virologic response (SVR) in pediatric patients were 51% in genotype 1 and 93% in genotype 2/3. Pediatric patients with chronic HCV with genotype 4 treated with PR have lower SVR

rate (41%) compared to genotypes 1, 2 or 3. There are insufficient data to describe the SVR rates with PR for genotypes 5 or 6 in children.

SVR rates have been significantly improved with introduction of direct acting antivirals (DAAs) for the treatment of chronic HCV infection in adults. Sofosbuvir (SOF) is a DAA nucleotide analog drug designed to inhibit the NS5B polymerase of HCV. Several SOF-containing regimens have been developed for the treatment of HCV infections. Ledipasvir (LDV) is also a DAA, designed to inhibit the NS5A protein of HCV. Currently, LDV is only available as part of a fixed dose combination product with SOF. Based on the available adult data, LDV/SOF appears to offer health benefits without requiring additional therapy with PR in chronically HCV-infected children with genotypes 1, 4, 5 or 6, and with compensated liver disease.

The Division of Antiviral Products (DAVP) has determined the course of chronic HCV in pediatric patients is sufficiently similar to chronic HCV infection in adults to allow extrapolation of efficacy from the adult clinical trials to pediatric patients. As SOF and LDV are both DAA agents (i.e., inhibits viral replication directly), pediatric patients with chronic HCV infection are expected to respond similarly to adults treated with LDV/SOF if they achieve similar drug exposures. Therefore, efficacy in pediatric patients between the ages of 3 to less than 18 years old will be in part supported by the adult trials that evaluated the efficacy of LDV/SOF, including trials conducted in treatment-naïve subjects and those who had previously failed HCV treatment, and by pharmacokinetic/pharmacodynamic and safety data from pediatric patients. LDV/SOF is expected to replace the standard PR regimen in pediatric patients infected with genotypes 1, 4, 5 or 6.

A trial evaluating the safety and effectiveness (i.e., SVR assessed 12 weeks following cessation of treatment, SVR12) of LDV/SOF regimens in pediatric patients ages birth to less than 3 years is not requested because such trials are impossible or highly impracticable to conduct because it is not uncommon for this age group to spontaneously clear the virus.

TYPES OF STUDIES

To obtain needed pediatric information on LDV/SOF, the Food and Drug Administration (FDA) is hereby making a 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.

- *Nonclinical study(ies)*:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

Study 1: Clinical pharmacology trials must be performed to assess the multiple dose pharmacokinetics (PK) of SOF, GS-331007, and LDV in pediatric patients with chronic HCV infection with genotypes 1, 4, 5 or 6, and compensated liver disease.

The necessary PK data must be obtained from Study 1 to inform dosing before the efficacy trial(s) is initiated. Study 1 may be conducted as the initial part of a multifunctional safety, PK, effectiveness trial (i.e., as part of Study 2).

The dose selection, duration of treatment, and HCV genotypes for Study 2 must be based on discussions and agreement between the sponsor and the Agency following review of the pediatric PK data and the results of the adult efficacy trials.

Note: SOF and GS-331007 PK evaluations for submission under the LDV/SOF NDA must be performed when SOF is combined with LDV, and not when SOF is given with ribavirin or other agents.

Study 2: Clinical trials must be performed to assess safety and effectiveness (SVR12 rate) of LDV/SOF in pediatric patients with chronic HCV infection with genotype 1, 4, 5 or 6 and compensated liver disease.

The *study design* may be open-label, single arm trial. The trial may enroll both treatment-naïve and interferon-experienced pediatric patients with chronic HCV infection. The latter group, however, may be enrolled as a separate cohort.

Measurement of SVR12 in pediatric subjects enrolled in Study 2 will provide additional supportive evidence that the correct dose has been selected and that pediatric patients respond similarly to treatment in adults with this new class of DAAs.

- *Objective of each study:*
  - *Study 1:* To determine the optimal dose of LDV and SOF across the pediatric age range based on achieving drug exposure similar to that shown to be safe and effective in adult patients.

  - *Study 2:* To determine the safety and effectiveness as measured by SVR12 of LDV/SOF in pediatric patients with chronic HCV infection with genotype 1, 4, 5, or 6 and compensated liver disease.

- *Patients to be Studied:*
  - Subjects in Study 1 and 2 must have evidence of chronic HCV infection with genotypes 1, 4, 5 or 6 as documented by positive HCV antibody for at least 6 months, measurable HCV RNA in the blood, and evidence of liver inflammation documented by persistently abnormal liver transaminases or liver biopsy. Subjects with genotypes 2 or 3 must be excluded from the study.

  - *Age group in which study(ies) will be performed*:
    Studies 1 and 2 must include pediatric patients 3 to < 18 years of age to evaluate the PK of SOF, GS-331007, LDV, and the safety and SVR12 of LDV/SOF.

  - *Number of patients to be studied:*

Study 1 must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance with 80% power for each of the following age cohorts: 3 to <6 years, 6 to <12 years, and 12 to <18 years.

Study 2 must include at least 100 subjects receiving LDV/SOF at the to-be-marketed dose and duration or higher. Study 2 must include the following number of patients in each age range:

- 12 to less than 18 years old: at least 35 subjects
- 6 to less than 12 years old: at least 35 subjects
- 3 to less than 6 years old: at least 30 subjects

- *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:
  - *Pharmacokinetic endpoints*:

The PK endpoints for Study 1 must include determination of PK parameters, including Cmax, Tmax, Cmin, t1/2, AUC, volume of distribution and clearance, to support selection of a dose for Study 2.

- *Pharmacokinetic/Pharmacodynamic Endpoints*

The PK and pharmacodynamic endpoints for Study 2 must include collection of sparse PK samples and plasma HCV RNA levels. Plasma HCV RNA must be measured at Weeks 12 and 24 during treatment, at end of treatment, and at Weeks 12 and 24 after completion of treatment.

- *Efficacy Endpoints*

The primary efficacy endpoint must be SVR and must be assessed by undetectable HCV RNA level 12 weeks after completion of treatment, measured using an agreed upon PCR assay.

Important secondary endpoints include normalization of ALT assessed by measurement of serum ALT levels, decline in serum HCV RNA from baseline, and proportion of patients with undetectable HCV RNA at weeks 12 and 24 on treatment, at end of treatment, and at week 24 post treatment as assessed by measurement of HCV RNA levels.

HCV resistance data must be analyzed in all studies. Collect and submit resistance data from baseline and on-treatment clinical isolates from pediatric subjects receiving LDV/SOF who experience breakthrough, or rebound in HCV RNA during treatment or relapse after completing treatment. Analyze resistance data for correlates to loss of efficacy, cross-resistance with other drugs, and persistence of resistant viral populations after completion of treatment. Submit data in the HCV Resistance Format provided by the Division of Antiviral Products.

- *Safety Endpoints*

Safety outcomes during the trial must include recording of: adverse events/serious adverse events, deaths, discontinuations due to adverse events, tolerability, vital signs, routine hematologic and biochemical laboratory monitoring, growth parameters and development. Outcomes suggestive of progression of liver disease must be monitored, such as development of cirrhosis and its complications, need for liver transplantation, hepatocellular carcinoma, and liver-related deaths.

- *Monitoring*
  The following are known drug safety concerns and must be actively monitored:
  1. Creatine kinase and lipase elevations – laboratory monitoring
  2. Progression of liver disease during the course of treatment and at the time of SVR12 and SVR24 assessment.

  All other clinically significant adverse events not mentioned specifically above must be captured when spontaneously reported.

  All adverse events must be monitored until symptom resolution or until the condition stabilizes. Patients who prematurely discontinue treatment with LDV/SOF must be followed for 12 weeks.

  A Data Monitoring Committee (DMC) may be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees
  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *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, we remind you that you must contact the Agency to seek an amendment as would be the case for any circumstances prompting you to deviate from the Written Request. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Statistical information, including power of study(ies) and statistical assessments:*
  The PK study (Study 1) must include an adequate number of subjects to characterize PK for dose selection. The study must be prospectively powered to target a 95% CI within 60 and 140% of the point estimate for the geometric mean estimates of clearance for SOF and LDV in the following age groups: 3 years to < 6 years, 6 years to < 12 years and 12 years to <18 years.. Final selection of sample size for each age group must take into account all 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 characterization of PK across the intended age range.

  For Study 2, the statistical plan must be based on discussions and agreement between the sponsor and the Agency. The study design may be a single arm, open-label trial using descriptive statistics to summarize the efficacy (SVR12) of LDV/SOF.

- *Drug information:*
  - *dosage form*: age appropriate formulations for each combination studied
  - *route of administration*: oral
  - *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 LDV/SOF 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 postmarketing 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. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data 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 the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before February 28, 2019. 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the 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 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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

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 Public Health Service Act (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 at www.ClinicalTrials.gov.

If you have any questions, call Linda C. Onaga, MPH, Senior Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

EDWARD M COX
09/02/2016