DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209394

WRITTEN REQUEST – AMENDMENT 2

AbbVie, Inc.
Attention: Sejal Emerson, Pharm.D.
Director, Regulatory Affairs
1 North Waukegan Road
Dept. PA 77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. Emerson:

Please refer to your correspondence dated June 30, 2017, requesting changes to FDA's February 3, 2017 Written Request for pediatric studies for Glecaprevir and Pibrentasvir.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on February 3, 2017, and as amended on May 10, 2017, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Clinical studies:*

Study 1: A clinical pharmacology trial must be performed to assess the multiple dose pharmacokinetics (PK) of Glecaprevir (ABT-493)/Pibrentasvir (ABT-530) in pediatric patients with chronic HCV infection 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 safety, PK, effectiveness trial (i.e., as part of Study 2).

Prior to enrolling children under 12 years of age in Study 2, the Applicant must obtain the Agency's agreement ~~Prior to the initiation of Study 2, the Agency must be in agreement~~ on final dose selection, duration of treatment, and HCV genotypes.

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 February 3, 2017, as amended by this letter and by the previous amendment dated May 10, 2017, must be submitted to

the Agency on or before December 31, 2021, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a 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 addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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 Alicia Moruf, PharmD, MPH, Regulatory Project Manager, at 301-796-3953.

Sincerely,

{See appended electronic signature page}

Ed Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

BACKGROUND:

The studies proposed in the PPSR investigate the potential use of Glecaprevir (GLE) and Pibrentasvir (PIB) in pediatric patients 3 to less than 18 years of age with chronic hepatitis C virus infection.

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 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 a lower SVR rate (41%) compared to genotypes (GT) 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.

There are several ongoing pediatric trials evaluating interferon-free, DAA regimens with or without RBV; but none have released results.

AbbVie's next-generation combination is expected to be an active antiviral therapy in subjects infected with HCV GTs 1-6, with treatment durations of 8 to 16 weeks, few drug-drug interactions, a convenient once daily dosage, without concomitant Ribavirin (RBV). Better tolerated all-oral interferon-free regimens that provide high sustained virologic response (SVR) rates with shortened treatment durations could substantially improve the benefit-risk ratio for treating HCV in children as it has in adults.

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 GLE and PIB are both DAA agents (i.e., inhibit viral replication directly), pediatric patients with chronic HCV infection are expected to respond similarly to adults treated with GLE/PIB 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 GLE/PIB, including trials conducted in treatment-naïve subjects and in those who had previously failed HCV treatment, and by pharmacokinetic/pharmacodynamic and safety data from pediatric patients. GLE/PIB is expected to act as a replacement of the standard PR regimen in pediatric patients infected with HCV.

Studies in neonates are not requested as clinical trials in this age group are impractical because the number of patients requiring treatments is very small. Additionally chronicity of HCV infection is difficult to establish in children younger than 3 years of age.

TYPES OF STUDIES

To obtain needed pediatric information on Glecaprevir (ABT-493) and Pibrentasvir (ABT-530), 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.

- *Non-Clinical 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: A clinical pharmacology trial must be performed to assess the multiple dose pharmacokinetics (PK) of Glecaprevir (ABT-493)/Pibrentasvir (ABT-530) in pediatric patients with chronic HCV infection 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 safety, PK, effectiveness trial (i.e., as part of Study 2).

Prior to enrolling children under 12 years of age in Study 2, the Applicant must obtain the Agency's agreement on final dose selection, duration of treatment, and HCV genotypes.

Study 2: Clinical trial must be performed to assess safety and effectiveness (SVR12 rate) of GLE/PIB in pediatric patients with chronic HCV infection and compensated liver disease.

The study design may be an open-label, single arm trial. The trial may enroll both treatment-naïve and interferon- and/or sofosbuvir 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 DAAs.

- *Objective of each study:*

Study 1: To determine the appropriate dose of GLE and PIB across the pediatric age range based on achieving drug exposures 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 GLE/PIB in pediatric patients with chronic HCV infection and compensated liver disease.

- *Patients to be Studied:*

Subjects in Studies 1 and 2 must have evidence of chronic HCV infection as documented by positive HCV antibody and measurable HCV RNA in the blood.

  - *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, efficacy and safety of GLE and PIB.

  - *Number of patients to be studied:*

    Study 1 must include at least:
    • 12 to less than 18 years old: at least 12 subjects
    • 3 to less than 12 years old: at least 24 subjects, 12 of which must be 3 to less than 6 years old
    Additional subjects must be enrolled, as needed, to adequately characterize pharmacokinetics for dose selection.

Study 2 must include at least 100 subjects receiving GLE/PIB 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
- 3 to less than 12 years old: at least 50 subjects of which at least 12 subjects must be 3 to less than 6 years old

- *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* (*Study 1*)*:*

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 (Study 2):*

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 every 4 weeks during treatment, at end of treatment, and at Weeks 12 and 24 after completion of treatment.

- *Efficacy Endpoints (Study 2):*

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

Other endpoints include characterization of virologic failures, including those with on-treatment failure, post-treatment relapse, and percentages of new HCV infection. Additional endpoints include decline in serum HCV RNA from baseline, and proportion of patients with undetectable HCV RNA at weeks 4, 8 and 12 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 GLE/PIB 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. Bilirubin (direct and indirect) elevation, liver enzyme elevation – 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 GLE/PIB 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 pharmacokinetic study (Study 1) must include an adequate number of subjects to characterize pharmacokinetics for dose selection. At least 12 patients with intensive PK must be obtained for GLE and PIB 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 GLE/PIB.

- *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 Glecaprevir (ABT-493) and Pibrentasvir (ABT-530)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 December 31, 2021. 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 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.

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/s/

EDWARD M COX
10/13/2017