NDA 205832
IND 129333

WRITTEN REQUEST – AMENDMENT 1

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Attention: Lorraine Sachs, MS, RAC
Senior Associate Director, Regulatory Affairs

Dear Ms. Sachs:

Please refer to your correspondence dated December 15, 2020, requesting changes to FDA's October 27, 2020, Written Request for pediatric studies for for Ofev (nintedanib).

We have reviewed your proposed changes and are amending the Written Request. All terms stated in our Written Request issued on October 27, 2020, remain the same with the exception of three items noted below and some minor editorial changes: (Text added is underlined. Text deleted is strikethrough.)

1. In the *Background* section the following changes have been made:

   "… there is reason to believe that the disease process may be similar between adults and children. However, given the differences in the distribution of underlying etiologies, controlled efficacy data will be required. ~~it is uncertain if efficacy in adults can be extrapolated to pediatric patients.~~

   In light of the above, the study outlined in this Written Request is designed to provide evidence for dosing, safety, and efficacy for nintedanib in patients aged 6 to <18 years. Given the rarity of pediatric ILD, the study design also takes into account feasibility. To aid in the interpretation of the study, additional statistical analysis methods that leverage the data collected in adults, including Bayesian analysis methods with informative priors must be prospectively planned. ~~and is not powered to demonstrate efficacy~~."

2. In the *Patients to be Studied* section, the following changes have been made:

   "The majority of patients must be followed for 52 weeks. Follow up data of patients may be obtained in a separate open label trial."

3. In the *Statistical information* section, the following changes have been made:

> ~~"Statistical analyses for safety and efficacy will be descriptive.~~ Bayesian analyses with informative priors, should be considered and must be described in a future version of the WR when agreed upon with the Agency. The statistical analysis plan should be submitted and agreed upon before the unblinding of the study."

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 27, 2020, as amended by this letter must be submitted to the Agency on or before March 31, 2024, 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 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.[1]

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.

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

If you have any questions, call Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Complete Copy of Written Request as Amended

AMENDED WRITTEN REQUEST

BACKGROUND

This study will investigate the potential use of nintedanib in the treatment of chronic fibrosing interstitial lung diseases (ILD) with a progressive phenotype in patients ages 6 to <18 years old.

Chronic fibrosing interstitial lung diseases with a progressive phenotype, can also be referred to as progressive fibrosing ILD (PF-ILD). PF-ILD is a recently termed entity which represents ILDs from a variety of etiologies that share the common characteristics of fibrosis and rapid progression[1]. Once the defining PF-ILD characteristics are present (fibrosis and rapid progression), the prognosis, no matter the underlying ILD diagnosis, is generally poor[2]. Nintedanib is approved for the treatment of PF-ILD in adults.

Pediatric ILD is rare[3, 4] and there are no approved therapies. In some pediatric patients, pediatric ILD can manifest with characteristics similar to PF-ILD (i.e., fibrosis and progression). While the underlying etiologies in adults and children can differ and/or vary in frequency between adults and children, there is overlap for some etiologies. As such, there is reason to believe that the disease process may be similar between adults and children. However, given the differences in the distribution of underlying etiologies, controlled efficacy data will be required.

In light of the above, the study outlined in this Written Request is designed to provide evidence for dosing, safety, and efficacy for nintedanib in patients aged 6 to <18 years. Given the rarity of pediatric ILD, the study design also takes into account feasibility. To aid in the interpretation of the study, additional statistical analysis methods that leverage the data collected in adults, including Bayesian analysis methods with informative priors must be prospectively planned. Studies in patients <6 years of age, including neonates, are not included given safety concerns regarding bone growth and dentition which may be more pronounced in the younger population.

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,

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[1] Harari S. Beyond idiopathic pulmonary fibrosis: the world of progressive-fibrosing interstitial lung disease. Eur Respir Rev 2018, 27(150)

[2] Wijsenbeek M et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Current Medical Research and Opinion, 35:11, 2015-2024. https://doi.org/10.1080/03007995.2019.1647040

[3] Dinwiddie R et al. Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. Pediatr Pulmonol 2002;34(1):23–29.

[4] Saddi V et al. Childhood interstitial lung diseases in immunocompetent children in Australia and New Zealand: a decade's experience. Orphanet J Rare Dis 2017;12:133.

provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on nintedanib, 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.

- *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:*

  A randomized, double-blind, placebo-controlled, parallel-group study of 24-weeks duration to evaluate safety and efficacy of weight-based dosing of oral nintedanib capsules compared to placebo as add-on therapy to standard-of-care in pediatric patients aged 6 to <18 years with chronic fibrosing interstitial lung disease with a progressive phenotype. Following the 24-week placebo-controlled period, patients will continue to be followed for safety in an open-label manner for a total exposure of ≥52 weeks.

  - *Study Objectives:*

    To evaluate the safety, pharmacokinetics, and efficacy of oral weight-based nintedanib dosing compared to placebo in pediatric patients aged 6 to <18 years with pediatric ILDs.

  - *Patients to be Studied:*

    - *Age groups to be studied:* Pediatric patients with ILD aged 6 to <18 years

    - *Number of patients to be studied:*

      The study will include ≥30 total patients with the following:
      - ≥10 patients ages 6 to <12 years of age
      - ≥20 patients ages 12 to <18 years of age
      - The majority of patients must be followed for 52 weeks. Follow up data of patients may be obtained in a separate open label trial.

- *Study endpoints:*

  - Pharmacokinetic Endpoints:
    Primary pharmacokinetic endpoints must include steady state area under the concentration versus time curve (AUC). Other pharmacokinetic endpoints that should be included are oral clearance (CL/F) and Cmax. PK sampling must enable estimation of primary PK parameters with reasonable precision.

  - Pharmacodynamic/Efficacy Endpoints:
    The pharmacodynamic/efficacy endpoints must include the change from baseline in forced vital capacity, quality of life questionnaires, oximetry measurements (at rest and with exertion), six minute walk distances, and hospitalization information (length of stay). All endpoints must be assessed at 24 and 52 weeks.

- *Safety Endpoints/Monitoring:*

  Safety concerns with nintedanib include hepatobiliary adverse events (AE) (hepatic impairment, elevated liver enzymes, drug induced liver injury), gastrointestinal AEs (gastrointestinal perforation, diarrhea, nausea, and vomiting), and hematologic AEs (risk of bleeding and arterial thromboembolic events). There are also concerns for adverse bone and dental effects for the pediatric population.

  Regarding these concerns, safety monitoring in the study must include adverse event recording, vital signs (blood pressure and pulse), physical examinations, growth assessments (height, weight, leg length), clinical labs (including but not limited to liver function), and dental examinations (performed by a qualified dentist at baseline prior to initiation of nintedanib and every 6-months).

  All adverse events must be monitored until symptom resolution or until the condition stabilizes. Monitoring for safety concerns must be performed in the clinical trials.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Bayesian analyses with informative priors, should be considered and must be described in a future version of the WR when agreed upon with the Agency. The statistical analysis plan should be submitted and agreed upon before the unblinding of the study.

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:* capsule
  - *route of administration:* oral
  - *regimen:* twice daily

  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 nintedanib 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 postmarketing 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 postmarketing 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.[5] 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 FDA.gov[6] 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 March 31, 2024. 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.

[5] 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
[6] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

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 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.[7]

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.[8]

[7] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[8] 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/

JULIE G BEITZ
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