CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217759Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 124045

MEETING REQUEST-
WRITTEN RESPONSES

Pharming Technologies B.V.
10 Independence Boulevard
Suite 401
Warren, NJ 07059

Attention: Jennifer Knicley
Director, Regulatory Affairs

Dear Ms. Knicley:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CDZ173 (leniolisib).

We also refer to your submission dated January 28, 2022, containing a meeting request. The purpose of the requested meeting was to provide an overview of nonclinical, clinical, and quality data for leniolisib and to reach agreement with the FDA on the approach for NDA filing and review.

Further reference is made to our Meeting Granted letter dated February 3, 2022, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 23, 2022, background package.

If you have any questions, please call me at (240) 402-4483.

Sincerely,

{See appended electronic signature page}

Linda Ebonine, PA-C
Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Application Number:	124045
Product Name:	CDZ173 (leniolisib)
Indication:	Treatment of APDS/PASLI
Sponsor Name:	Pharming Technologies B.V.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Pharming Technologies B.V. (Pharming) submitted a Type B meeting request on January 28, 2022. The purpose of the requested meeting was to provide an overview of nonclinical, clinical, and quality data for leniolisib and to reach agreement with the FDA on the approach for NDA filing and review. The proposed indication for leniolisib is the treatment of activated phosphoinositide 3-kinase-delta (PI3K-δ) syndrome (APDS) in adolescent and adult patients.

The Division granted the meeting as a Written Response on February 3, 2022, and the Sponsor provided a meeting briefing package on March 23, 2022. The Sponsor's questions from the package are provided in *italics* followed by FDA responses in normal font.

2.0 QUESTIONS AND RESPONSES

2.1. Clinical

Question 1:
Does the Agency agree that the safety data from the single Phase II/III APDS study (CCDZ173X2201) in conjunction with the additional safety data from the interim analysis of the long-term extension study (CCDZ173X2201E1) provide sufficient exposures to leniolisib for an NDA filing?

FDA Response:
Your safety database includes 38 patients treated with leniolisib across studies CCDZ173X2201 and CCDZ173X2201E1. The duration of exposure for controlled safety data is roughly 12 weeks, while the duration for uncontrolled data is a median of 102 weeks. Given the feasibility challenges in this rare disease, the size of the safety database appears reasonable. Ultimately, the adequacy of the data to support review and the proposed indication will be a review issue.

Question 2:
Does the Agency agree that the single, adequate and well-controlled study (CCDZ173X2201) will support NDA approval of leniolisib as therapy for adolescent and adult patients with APDS, provided that the results for the primary efficacy measure(s) are statistically significant and there is directional consistency across the secondary efficacy measures?

FDA Response:
As communicated in previous interactions between the IND Sponsor and the Agency, conceptually, a single adequate and well-controlled study may be sufficient to support approval of leniolisib for APDS. The adequacy of the data to support the proposed indication will be determined during application review, as approval is based on the full benefit-risk analysis of the provided evidence. See FDA Response to Question 4.

Question 3:
Does the Agency agree that a 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety are sufficient and a separate Integrated Summary of Efficacy and Integrated Summary of Safety in 5.3.5.3 are not required to be included in the NDA?

FDA Response:
The Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) are detailed integrated analyses of all relevant data from clinical study reports. In general, an ISE and an ISS are necessary when submitting applications in the common technical document (CTD) or the electronic common technical document (eCTD) format. These summaries should be submitted in Module 5.3.5.3. If you believe that section 2.7.3 (Summary of Clinical Efficacy) and section 2.7.4 (Summary of Clinical Safety) would respectively be sufficiently detailed to serve as the summary portion of the ISE and ISS, then, size permitting, the summary portion of the integrated assessment may be placed in Module 2 and the appendices of tables, figures, and datasets may be placed in section 5.3.5.3. In this case, electronic links in Module 2 to the tables in Module 5 and figures in Module 5 should be provided.

For additional information about the location of ISS and ISE in the CTD, refer to the *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.[1]

Question 4:
Does the Agency agree that in totality, together with the studies described in the briefing package, all available literature studies, results from the Phase II/III clinical study and consequent population PK analysis, and results from the interim analysis of the long-term open-label extension study (CCDZ173X2201E1) are adequate for NDA submission?

[1]https://www fda.gov/media/75783/download

FDA Response:
The clinical program you have outlined is adequate to characterize the safety and efficacy of leniolisib to support an NDA filing. However, our ability to review the NDA submission will depend on the completeness of your submission with thorough analyses of all clinically relevant efficacy and safety outcomes, including those we specify in this response, such that timely, efficient, and complete review by all relevant disciplines is permitted. If the requested analyses are not included, the NDA submission could be considered incomplete.

Include in your submission how substantial evidence of effectiveness is demonstrated through the single adequate and well-controlled clinical investigation of leniolisib and clearly identify the element(s) of confirmatory evidence. Explain which endpoints demonstrate direct clinical benefit to the patient population.

The original application is expected to include all major components. In addition, we have the following comments:

1. Include the following assessments of important clinical outcomes: use of recent/concomitant therapies, including immunosuppressants, antibiotics, and IVIG; incidence and type of infections; fatigue (if assessed); and autoimmune diseases, including cytopenias.

2. Analyze supportive medical literature in a written discussion and provide copies of all referenced publications. Include a detailed description of the expected natural history of the disease as currently understood, including with respect to each efficacy endpoint.

3. Provide available pre-trial clinical history on enrolled subjects to assist in determining natural history.

4. Include a comprehensive, readily located list of all clinical sites and manufacturing facilities.

5. Provide the imaging charters for studies CCDZ173X2201 and CCDZ173X2201E1, and in your discussion of efficacy, describe all clinically relevant details of the selection and analysis of index lesions.

6. Provide all relevant contextual information for analysis of endpoints. For example, for immunophenotyping data, include the age-appropriate normal range for each laboratory value, when available.

7. We recommend an exploratory analysis linking longitudinal data of the subjects who participated in both studies CCDZ173X2201 and CCDZ173X2201E1 to

analyze washout-related changes if there was a gap in leniolisib administration when rolling from the first study into the open-label extension study.

8. For each subject, provide information on the predicted immunologic and clinical phenotype associated with their specific genetic mutation, as current scientific knowledge permits.

9. Provide subgroup analysis of efficacy endpoints by age group (adolescents and adults).

10. SF-36, WPAI-CIQ, PGA and PtGA were included in your trials. Include the following information to support the review of these PROs to support efficacy of leniolisib for your proposed indication:

    a. Conceptual framework of the instrument
    b. Evidence of content validity (e.g., qualitative research with patients and/or expert clinicians) obtained for this specific context of use
    c. Exact copy of the instrument as it was administered during the clinical trial (e.g., electronic screen shots) and any associated training materials and user manuals
    d. Scoring algorithm(s) with rationale and corresponding information on how the instrument's scores were analyzed as part of an endpoint
    e. Results from and evaluation of the psychometric properties and performance of the instrument (i.e., reliability, validity, and ability to detect change) after content validity has been established
    f. Pre-specified plans for handling missing data
    g. An *a priori* threshold (or range of thresholds) representing clinically meaningful within-patient improvement in the instrument's scores.

Adequacy of the data to support review and the proposed indication will be determined during application review. To facilitate timely filing and review of your application, if you require further clarification of the data and analyses needed to facilitate our review, you may wish to request clarification or a teleconference to discuss these items in advance of a planned NDA filing.

Additional Clinical Pharmacology Comments:

a) We acknowledge that the relative bioavailability (BA) between the film-coated tablet (FCT) and hard-gelatin capsule (HGC) of CDZ173 is to be assessed in study CCDZ173X2201E1. We have the following comments:

- The PK endpoints to assess the relative BA of CDZ173 are AUC0-12,ss and Cmax,ss. Table 8-1 (assessment schedule) reports that the last PK sample will be collected at 8 hours following administration of FCT and HGC. Clarify the discrepancy between AUC0-12,ss and the 8-hour post-dose sample.

- The effect of food for the FCT of CDZ173 has not been assessed in your clinical program. Specify how you plan to address the food effect issue in your clinical program.

b) You report that leniolisib shows pH dependent solubility and that concomitant medications that increase pH in the stomach could potentially impact the absorption of leniolisib. Specify how you plan to address this potential drug-drug interaction (DDI) issue, including future DDI clinical study, in the NDA submission.

c) In vitro studies have identified CDZ173 to be an inhibitor of the OATP1B1/1B3, BCRP, OAT3, OCT2, MATE1, and MATE2K transporters. Specify how you plan to address these potential drug-drug interaction (DDI) issues, including future DDI clinical studies, in the NDA submission.

d) The major route of elimination of CDZ173 is via metabolism. Despite this, a hepatic impairment study has not been conducted in the clinical program. Specify how you plan to address this issue, including future PK study in subjects with hepatic impairment, in your NDA submission.

Question 5:
An analysis was conducted to characterize the relationship between QTc and leniolisib exposure utilizing the data from the first-in-human (FIH) healthy volunteer Study CCDZ173X2101, which concluded that leniolisib treatment was not associated with prolongation of the QTcF interval. Based on the totality of concentration-QTc data, does the Agency agree that a thorough QT study is not required to support the NDA submission?

FDA Response:
Yes, we agree. The proposed study design and analysis plan appear adequate to characterize the potential for leniolisib to prolong the QTc and can potentially serve as an alternative to the TQT study (See ICH14 Q&A (R3) 5.1). Whether these data exclude a 10-ms mean QTc effect at the high clinical exposure scenario will be a review issue when the data are submitted.

We have the following additional comments:

1. It is not clear whether digital ECGs were obtained. There is increased uncertainty in QT characterization when high-quality 12-lead digital ECGs are not available. The process of scanning/redigitizating may increase the variance in the QT, which would reduce the power to detect a small treatment effect (Stockbridge, N., J Electrocardiol 2005; 38, 319-20). Furthermore, it is not possible to evaluate the presence of bias in the QT measurements resulting from the assessment of the digitized/scanned ECG waveforms. In the absence of high-quality 12-lead digital

ECG waveforms, we recommend that the automatic QT measurements provided by the device recording the ECG at the clinical site are used for QT assessment.

2. When you submit your QT evaluation report, please include a completed version of the most recent "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-researchcder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt).

2.2. Nonclinical

Question 6:
Does the Agency agree that the completed nonclinical studies described in the briefing package are adequate to support NDA submission?

FDA Response:
Yes, we agree the studies are adequate.

Question 7:
As agreed during the Type C meeting in November 2020, Pharming plans to conduct the 2-year rat carcinogenicity and rat pre/postnatal development studies post approval. Although originally proposed to include the ongoing 6-month mouse carcinogenicity study in the original NDA, the study has encountered delays. Would the Agency agree to also accept the 6-month transgenic (rasH2) mouse carcinogenicity study report post approval?

FDA Response:
Yes, we agree based on the indication for APDS/PASLI.

2.3. Chemistry, Manufacturing, and Controls

Question 8:
As an update to the discussion at the Type C meeting of November 2020, Pharming intends to submit 9 months stability data on 1 primary drug product batch and 6 months stability data on 2 primary drug product batches. As each batch has met acceptance criteria and no trends have been observed, does the Agency agree that 9 months stability data on 1 primary drug product batch and 6 months stability data on 2 primary drug product batches in addition to supporting data from batches manufactured throughout clinical development are adequate to support a 24-month expiration dating period?

FDA Response:
We generally recommend a minimum of 12 months of long-term data for the primary stability batches as per ICH Q1A and that applicants follow Q1E for the determination of the expiration dating period. You may submit your NDA with less than 12 months of stability data as proposed and we would not refuse to file it based on that condition

alone. However, unsolicited stability updates, especially those arriving late in the review cycle, may not be evaluated due to limited resources, which may lead to the Agency granting a limited expiration dating period that may not be commercially viable.

Question 9:

(b) (4)

FDA Response:

(b) (4)

2.4. Procedural

Question 10:

Does the Agency agree that the NDA for leniolisib (an orphan designated drug), which provides significant improvement in safety and efficacy in APDS patients when compared with existing therapies, will qualify for priority review under PDUFA, resulting in a shorter review of the marketing application (8 months versus 12 months for NME)?

FDA Response:
You may request priority review when you submit the original NDA. Based on your submission, it appears that this application would meet the requirements for priority review designation, but this decision will be a review issue upon receipt of the NDA submission.

Question 11:
Given the mechanism of action, lack of safety signal, and strength of the data proposed to be included within the registration submission, does the Agency anticipate requesting an advisory committee?

FDA Response:
Given that leniolisib is a new molecular entity for a novel indication, and that surrogate endpoints provide the primary support for effectiveness, a Pulmonary-Allergy Drug Advisory Committee meeting may be warranted; however, a final decision will be made upon receipt of the NDA submission.

Question 12:
Does the Agency agree that a Risk Evaluation and Mitigation Strategy (REMS) will not be required to inform health care stakeholders about medication risks with leniolisib in the adolescent and adult APDS population based on the benefit-risk assessment?

FDA Response:
It is premature to comment on the need for a REMS at this time; this will be a review issue.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory

authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned

criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

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

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

commercial production and those used for product and manufacturing process development.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

/s/

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