CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761161Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 110161

MEETING MINUTES

Protalix Ltd.
c/o Target Health Inc.
Mary Shatzoff, MS, RAC
Sr. Director of Regulatory Affairs
261 Madison Avenue 24th Floor
New York, NY 10016

Dear Ms. Shatzoff:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pegunigalsidase alfa (PRX-102).

We also refer to the meeting between representatives of your firm and the FDA on October 15, 2019. The purpose of the meeting was to seek the agency's input on the data package needed to support submission of a BLA under the accelerated approval regulatory pathway.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Nicolas Kong, Regulatory Manager at Nicolas.Kong@fda.hhs.gov or 240-402-0269.

Sincerely,

{See appended electronic signature page}

Nicolas Kong
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: October 15, 2019
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

Application Number: 110161
Product Name: PRX-102; pegunigalsidase alfa
Indication: Fabry Disease
Sponsor: Protalix

Meeting Chair: Patroula Smpokou M.D.
Meeting Recorder: Nicolas Kong

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products
Dragos G. Roman, MD., Acting Director
Patroula Smpokou, MD., FACMG, Medical Team Leader
Anita Zaidi, MD, Medical Officer
Nicolas Kong, MD, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics IV
Quing Zhou, PhD, Biometrics Reviewer
Yan Wang, PhD, Biometrics Team Leader

Office of Clinical Pharmacology/Division of Clinical Pharmacology III
Insook Kim, PhD., Clinical Pharmacology Team Leader
Christine Hon, PhD., Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality
Ying-Xin Fan, PhD, Office of Biotechnology Products, Reviewer
Haoheng Yan, MD PhD, Office of Biotechnology Products
Frederick Mills, PhD, Office of Biotechnology Products
Kelly Burridge, PhD, Office of Biotechnology Products, Team Lead
Virginia Carroll, Division of Microbiology Assessment, Reviewer
Reyes Candau-Chacon, Quality Assessment Lead

Division of Cardiovascular and Renal Products (DCaRP)

Aliza Thompson, MD, Deputy Director
Kimberly Smith, MD, DCaRP Reviewer

SPONSOR ATTENDEES

Dror Bashan, CEO Protalix Ltd.
Einat Almon, PhD. Sr. Vice President Product Development Protalix Ltd.
Yoseph Shaaltiel, PhD. Executive Vice President Product R&D Protalix Ltd.
Raul Chertkoff, MD., Vice President Medical Affairs Protalix Ltd.
Sari Alon, MSc., Director, Product Development Protalix Ltd.
(b) (4) Consultant (b) (4)
(b) (4) consultant (b) (4)
(b) (4)
Mary Shatzoff, MS, RAC Sr. Director of Regulatory Affairs Target Health Inc.
Erin Stokes, PhD. Manager of Clinical and Scientific Affairs Target Health Inc.
Jules Mitchel, PhD. President Target Health Inc.
Colleen Johnson, MS, D.A.B.T. Nonclinical consultant Target Health Inc.
Giovanni Milazzo, MD., PhD. Chiesi Farmaceutici S.p.A.
Marta Toschi, MS Regulatory Manager Biotechnologicals Chiesi Farmaceutici
Federica Cattaneo, MD. Rare Disease Unit Chiesi Farmaceutici S.p.A.
Matt Medlin, PhD, RAC Sr. Regulatory Manager Chiesi USA. Inc
Giorgio Iotti, PhD. Rare Disease Unit Chiesi Farmaceutici S.p.A.
Martin Linhult Technical Leader, Rare Disease Unit Chiesi Farmaceutici S.p.A.
Claes Anderson, Early Research Head, Rare Disease Unit Chiesi Farmaceutici
(b) (4) consultant (b) (4)
(b) (4) Consultant (b) (4)

1.0 BACKGROUND

Pegunigalsidase alfa (PRX-102) is a PEGylated, covalently cross-linked plant cell-expressed recombinant human alpha-galactosidase indicated in the treatment of Fabry disease.

The proposed regulatory pathway for approval of pegunigalsidase alfa is application submission under §351(a) of the Public Health Service Act [42 U.S.C. 262(a), 262(k)].

The Sponsor intends to pursue expedited approval of pegunigalsidase alfa under the Accelerated Approval pathway as described in §356(c) of the U.S.C. and codified in 21 CFR Part 601 Subpart E § 601.41.

The purpose of this Type B, Pre-BLA meeting is discuss the clinical, nonclinical and CMC data packages needed to support submission of a BLA under the Accelerated Approval regulatory pathway (21 CFR 601 Subpart E).

The meeting request was granted, and an Acknowledgment Letter was submitted to the sponsor on July 11, 2019.

2.0 DISCUSSION

2.1. Nonclinical Question

Question 1: **Overall Adequacy of Nonclinical Data Package**
Does the Agency agree that the listed studies, as well as the agreement to conduct the pre- and post-natal toxicity study in rats as a post-approval commitment, fulfill the nonclinical requirements for this BLA and that no additional nonclinical studies are needed?

FDA Response:
The listed studies and the planned pre- and postnatal development study in rats (the latter to be conducted as a post-marketing requirement), appear adequate to fulfill the nonclinical requirement for this BLA.

Meeting Discussion:
No discussion

2.2. Clinical Questions

Question 2: Agreement with the Presentation of Surrogate Endpoint and Additional Outcome Data in the BLA Under Subpart E
Does the FDA agree with the planned scope and presentation of the surrogate endpoint and additional outcome data to support the BLA submission?

FDA Response:
In general, we agree with your proposed presentation of the efficacy data. Also submit the following:

1. **graphical patient profiles for each patient enrolled trial PB-102-F01/F02/F03. For each graphical patient profile, present the following variables from baseline to the last available assessment (x-axis should be time): renal Gb3 inclusions, plasma lyso-Gb3, wbc α-gal A enzyme activity. You should also provide gender, genotype, and classic vs non-classic subtype for each patient (please see FDA Draft Guidance for Industry Fabry Disease: Developing Drugs for Treatment https://www.fda.gov/media/129690/download for definitions).**

2. **analysis of the change in renal Gb3 inclusions, subdivided by classic vs non-classic FD and also by gender.**

3. **analyses of potential correlations of α-gal-A residual enzyme activity with the change from baseline in renal Gb3 inclusions.**

Meeting Discussion:
The Agency asked that the sponsor submit results of the baseline alpha Gal A enzyme activity including details of the assay used to assess it. In addition, the Agency reiterated that the sponsor should also submit genotype data for all patients including the associated clinical interpretation of pathogenicity of each alpha Gal A gene variant. The Sponsor agreed to submit both in the BLA. The Agency asked how the sponsor will define classic vs non-classic FD patients for purposes of subgroup efficacy and safety analyses in the BLA; the sponsor stated that they plan to define "classic" FD using specific criteria including residual alpha Gal A enzyme activity (<5%) and clinical information (presence of cornea verticillata, angiokeratomas, and neuropathic pain at baseline).

The sponsor will provide the validation reports for all assays including those used for assessment of residual alpha Gal A enzyme activity and plasma lyso-gb3.

Question 3: Safety Data in the Integrated Summary of Safety (ISS) and Summary of Clinical Safety (2.7.4)
a) Does FDA agree with the planned scope and presentation of safety data in Module 2.7.4?

FDA Response:
In general, we agree with your proposed presentation of safety data. However, you should also provide available safety data from trial F20 as it is the only trial that is blinded and contains a control group for comparison.

We remind you that immunogenicity assessment is a fundamental component in evaluating every biological product, and the application needs to include enough information regarding both duration and number of patients with informative immunogenicity assessments to provide reassurance that the product is safe for chronic administration.

b) Does FDA agree with the planned scope and presentation of safety data in Module 5.3.5.3 (ISS)?

FDA Response:
In general, we agree. However, we do not believe that comparisons of safety and immunogenicity data of your product in the completed clinical trials to those contained in the Fabrazyme label would be informative. We remind you that

comparisons of safety/immunogenicity data between your product and Fabrazyme may be misleading, due to potential influences and confounding by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Refer to the following FDA Guidance for more information.

https://www.fda.gov/media/119788/download

Question 4: Specification for Datasets
Does FDA agree that this approach meets the submission requirements?

FDA Response:
Clarify what is meant by the statement "statistical data packages (datasets)." We recommend submission of for all analysis data in ADaM format.

Question 5: Overall Adequacy of Immunogenicity Testing to Support the BLA
Does the Agency agree that the proposed immunogenicity assessment package is adequate to support an Accelerated Approval BLA submission under Subpart E?

FDA Response:
Your proposal to submit an Integrated Immunogenicity Summary Report in Module 5.3.5.3 of the BLA is acceptable. We have the following comments regarding your proposed immunogenicity assessment package.

- **We note that you plan to submit safety data from FD patients treated with 1 mg/kg pegunigalsidase alfa EOW in Studies PB-102-F01/F02, PB-102-F03, PB-102-F30, and PB-102-F60 as of the database lock date August 8, 2019. However, you plan to submit immunogenicity data from Studies PB-102-F01/F02, PB-102-F03, and PB-102-F30 only. We recommend that you also include immunogenicity data from PB-102-F60 and provide the impact assessment of immunogenicity on long-term safety in PB-102-F06. Provide the impact assessment of immunogenicity on PD in Study PB-102-F60 as well.**

- **You plan to assess patient-related factors that could affect immunogenicity risk of your drug product. We recommend that you assess the (1) incidence of immunogenicity and (2) impact of immunogenicity on PK, PD, safety, and efficacy between classic and non-classic FD patients, between males and females, and among subject's residual enzyme activity.**

- **We note that you have developed assays to detect anti-PRX-102 IgM antibodies, anti-PEG antibodies, and anti-plant glycans antibodies. You also plan to submit the study reports for the measurement of these antibodies in human serum samples to the BLA. However, you have not described in the meeting package how the study results for these**

antibodies will be evaluated. We recommend that you develop an immunogenicity assessment plan for evaluating these antibodies and provide such evaluations in the BLA.

- **In Study PB-102-F30 in which patients were switched from Replagal to pegunigalsidase alfa, you propose to evaluate the presence of pre-existing anti-Replagal antibodies prior to the switchover but not after the switchover. We recommend that you continue immunogenicity testing for anti-Replagal antibodies in clinical samples after the switchover because anti-Replagal antibodies can potentially cross react with pegunigalsidase alfa and impact its efficacy. In addition, submit the assay validation report for the assay testing of anti-Replagal antibodies.**

Meeting Discussion:
The sponsor stated that out of the 22 patients enrolled into the PB-102-F30 study, only one patient was found to have pre-existing anti-Replagal antibodies. The sponsor asked whether the Agency agrees that additional assessment of anti-Replagal ADAs is unnecessary after the switch-over to pegunigalsidase alfa for the BLA. The sponsor confirmed that all samples in PB-102-F30 will be tested for anti- PRX-102 antibodies. FDA agreed that the sponsor does not need to test anti-Replagal ADAs after the switchover in the F30 study.

In regards to your immunogenicity assay validation package, we do not agree with the proposed approach to evaluate immunogenicity in the PRX-102 studies. You did not include an assay to test ADA to pre-PEGylated alpha-galactosidase A (prh-alpha-GAL-A) protein. In addition to the characterization of ADA for anti-glycan and anti-PEG, you should include an assay to detect anti-prh-alpha-GAL-A antibody in the patient samples. Submit the assay validation report and testing results in the BLA.
In addition, we have the following comments on immunogenicity assay validation which should be addressed in you upcoming BLA.

Regarding the anti-drug IgG assay:

1. **It appears that you did not perform outlier analysis and exclusion prior to the screening cut point calculation. Recalculate the screening cut point (after the outliers were appropriately excluded) or provide scientific justification to support the proposed screening cut point.**
2. **Provide normality and skewness analysis for the screening and confirmatory cut point determination.**
3. **You determined screening and confirmatory cut point using commercial normal human serum. In order to ensure that these cut points are appropriate for the specific study population, these cut points need to be verified using serum samples from treatment-naïve study subjects. Confirm the screening and confirmatory cut points using available pretreatment in-study samples.**

4. **Provide data to justify the minimal required dilution (MRD) of 60-fold used in the immunogenicity assays.**
5. **You stated that the assay specificity was tested by immunodepletion studies using an excess of free drug PRX-102 versus irrelevant proteins but did not included data for the specificity evaluation. Provide data that supports the specificity of the anti-drug IgG assay.**
6. **You did not evaluate the robustness for the anti-drug IgG assay. Evaluate the impacts of variations in the method and instrument on the assay performance, especially on different batches of drug-coated plates, if applicable.**
7. **The sensitivity of the assay has been determined to be** (b) (4) **The FDA guidance recommends that in order to control the assay at low signal levels, the LPC should be near the sensitivity of the assay. Revise the LPC to be near assay sensitivity and provide appropriate scientific justification.**
8. **Provide assay selectivity data.**
9. **Your method validation results for the anti-drug IgG assay demonstrated a drug tolerance of 500 ng/ml for the low level of positivity control anti-PRX-102 antibody. Since PRX-102 is PEGylated and crosslinked, it has a long plasma half-life of approximately 80 hours. As shown in Figure 1 and 2 in your meeting package, when administered at the proposed dose of 1 mg/kg once every two weeks, free drug concentration in the patient plasma will be higher than or near the drug tolerance level of the assay. Provide a strategy to accurately assess anti-drug antibody in the presence of on-board drug levels exceeding your assay's defined drug tolerance level.**

Regarding the Enzymatic Activity Assay for the Detection of Neutralizing Antibodies:

1. **Your NAb assay has a very low sensitivity of 16.7 ug/ ml, which will make it difficult to accurately assess Nabs in patient sera. You should attempt to improve the sensitivity of this assay.**
2. **It is not clear how you performed the inter-run precision evaluation for the neutralizing antibody assay. Provide detailed information for the inter-run evaluation, including how many analysts performed the test and on how many days the test was performed.**
3. **The assay cutpoint was established using healthy subject donor serum. You state that "the cutpoint may be re-evaluated based on the disease population while testing study samples and may be adjusted accordingly". The cutpoint for your assay should be verified using pre-treatment sera of the study population. Confirm the NAb assay cutpoint using available pretreatment in-study samples.**
4. **Provide assay drug tolerance and selectivity.**

Regarding the Assay for anti-PEG Antibodies:

1. **To ensure that your assay can detect anti-PEG in patients who are being treated with PRX-102, determine the drug tolerance of your anti-PEG Antibodies assay.**

Regarding the Assay for antibodies specific to plant glycans:

1. [redacted] (b) (4) **Provide scientific justification to support the use the** (b) (4) **as competitive agent in the assay.**
2. [redacted] (b) (4) **Provide data to support the suitability of the positive control.**
3. **You used an outlier exclusion criterion of "> the 95% percentile" in the cut point determination. Provide statistical analysis, including data distribution analysis to support the outlier exclusion criterion.**

Regarding the Assays for Anti-PRX-102 IgM and IgE:

The assay validations are inadequate because you did not include proper positive control, i.e. anti-PRX-102 IgM and anti-PRX-102 IgE to demonstrate the performance of the assays. Nevertheless, you should still submit the testing results from the anti-PRX-102 IgM and IgE assays in the BLA submission.

Meeting Discussion:
The sponsor stated that current data show that patient exposed to PRX-102 can develop anti-prh-alpha-GAL-A antibody, and some developed neutralizing antibody. The sponsor believes that based on the current testing results, the proposed immunogenicity assay validation package allows for full evaluation. The agency stated that the protein moiety, its glycan, and the PEG moiety of PRX-102 are all potentially immunogenic. Patients treated with PRX-102 can develop antibodies against the protein, its glycan and/or PEG. Since anti-protein, anti-glycan and anti-PEG are not mutually exclusive in each individual patient, lack of specific anti- prh-alpha-GAL-A antibody results may create difficulty and uncertainty for interpreting immunogenicity data. Therefore, FDA strongly suggested the sponsor develop and validate an assay to test ADA to prh-alpha-GAL-A protein. The agency further clarified that this is a requirement for all pegylated protein products. The sponsor stated there might not be enough time to develop a new assay for the BLA submission planned for 1Q next year, and asked if the FDA would agree to a post marketing commitment for the assay. FDA would discuss the question internally and provide answer as post meeting

comments. FDA suggested that the sponsor explore the possibility of using the existing anti-Replagal assay to serve the purpose of testing antibody against the protein part of PRX-102. FDA stated that the suggestion was not meant to be prescriptive, but rather an idea that sponsor may choose to explore. The sponsor asked whether a competitive inhibition assay would be acceptable for testing anti-prh-alpha-GAL-A antibody. FDA states that a competitive inhibition assay is acceptable.

Post Meeting Comments:
For pegylated protein biologics that have an endogenous counterpart, antibodies to the protein moiety may also react with the endogenous protein, and potentially worsen a patient's disease. Moreover, because your NAb assay has low sensitivity, sensitive measurement of anti-protein antibodies and titer to some degree can serve as a surrogate for a NAb assay. Finally, it is the FDA's experience that immunogenicity assessment of pegylated biologics includes measurement of antibodies to the protein moiety.
Therefore, we strongly suggest you implement a validated assay to test ADA to prh-alpha-GAL-A protein and include the testing results in your evaluation of clinical impact of ADA for BLA submission. Whether it is acceptable to submit the assay validation and testing results as post marketing requirement/or commitment depends on the review of the BLA.

2.3. Clinical/ Statistics Question

Question 6: Statistical Analysis Plan (SAP) to Support the Analysis of the PB-102-F20 Confirmatory Study

a) Does the Agency agree that the PB-102-F20 study, as currently designed, is adequate and well-controlled and thus has the potential to fulfill the requirements of a confirmatory trial under 21 CFR 601 Subpart E providing full approval of pegunigalsidase alfa?

FDA Response:
No, we cannot agree at this time as we still have the following concerns regarding your proposal:

1. **You need to justify your assumptions regarding your power calculation for trial PB-102-F20. Provide the references to justify the proposed quantitative relationship between renal interstitial capillary GL-3 inclusions and eGFR slope that your power calculation was based on.**
2. **You should confirm that the "full set of measurements available" includes all eGFR measurements regardless of whether the patient remains on study drug or not.**
3. **You should submit a summary of the rules that will guide decision-making by individuals tasked with identifying AKI events (e.g., a committee charter)**

and address what documentation will be provided regarding these assessments and the values that are excluded from key efficacy analyses.

4. **It is generally not reasonable to assume eGFR data are missing at random for key efficacy analyses; imputation rules should consider the reasons eGFR data are missing (e.g., adverse outcome).**
5. **Provide additional details regarding the proposed sensitivity analyses to address the impact of missing data.**
6. **Clarify the meaning of "dropout rate." We note that you state that the original sample size calculations assumed a 15% dropout rate resulting in a sample size of 78 but due to a lower than anticipated dropout rate of <10%, the projected enrollment was lowered to 73. Given that efficacy analyses will include the "full set of measurements available" and patients are to be followed regardless of whether they remain on study drug, it is not clear what is meant by "dropout rate."**

b) Does the Agency agree with the proposed model and the proposed sensitivity analyses for missing data for the primary endpoint analysis?

FDA Response:

Although you have specified the fixed effects in your proposed longitudinal mixed model, you have not provided sufficient information on the remaining parts of the model. For example, you did not specify the random effects and the underlying assumptions regarding the random effects. Additionally, you proposed a number of covariance structures depending on the convergence of the model. Thus, it is not clear how the estimated fixed effects will be impacted by the selected covariance structures. Furthermore, the SAP stated that the primary analysis will be implemented using SAS PROC MIXED and the code and additional details are provided in a separate programming convention document. However, we cannot locate this document in the submission. Please clarify.

Your first sensitivity analysis for the primary endpoint is the analysis of the individual slopes (fitting slope for each subject and then comparing treatment groups using the ANCOVA). We find this method intuitive because it is based on patient-level slopes which are needed to understand the estimated population slope for each treatment group. We also expect that this analysis relies on fewer assumptions than your proposed primary analysis method. Thus, we recommend this analysis as the primary analysis.

The proposed sensitivity analyses for missing data appears to be reasonable; however, the revised SAP needs to provide details regarding these sensitivity analyses

c) Does the Agency agree with the proposed plan to maintain the blinding of the results and treatment assignments after Stage 1 analysis and the period prior to the Stage 2 analysis at Year 2?

FDA Response:
Your proposal to maintain blinding of the patients and personnel directly involved with the treatment of the patients throughout stage 1 and stage 2 and unblinding of a select team that will not be directly involved directly with treatment- and who will be directly involved with the regulators from the EMA appears reasonable.

d) ***Does the Agency agree with the proposed approach to control for multiplicity based upon the Stage 1 analysis?***

FDA Response:

Regarding multiplicity control, your SAP states that, "since there is no intention to stop the study for futility or efficacy and no plan for study adaptations based on outcomes of the stage 1 analysis, no alpha penalty for the final superiority analysis is needed." This proposal is acceptable.

Meeting Discussion:
The sponsor stated that they have completed enrollment of 78 patients for the F20 trial. The sponsor stated the 1.1mL/min/1.73m2 eGFR rate difference between PRX102 and Fabrazyme is based on a 30% improvement in the slope of eGFR (accepted previously as a clinically meaningful difference for drug approval in renal disease indications) and also based on data from their open-label trial in patients switched from Replagal to PRX-102. The Agency stated that overall the power calculations appear reasonable but may provide further comments after review of the revised SAP.

The sponsor will submit a revised SAP and the AKI charter with the adjudication procedures.

2.4. Regulatory Questions

Question 7: BLA Table of Contents and Technical Specifications
a) Does the Agency find the proposed structure, format and content of the BLA to be acceptable?

FDA Response:
Your proposed plan appears reasonable.

b) Does the Agency have any additional comments or questions regarding the proposed structure, format, and content of the BLA?

FDA Response:
The manufacturing process [redacted] (b) (4) **Clarify how the 3.2.S section will be organized for the drug substance intermediate and the drug substance. See additional CMC microbiology comments at the end of the document.**

We note that you plan to submit the Summary of Clinical Pharmacology Studies in Module 2.7.2 of the BLA. We recommend that you include in this Module (1) summary of performance characteristics for the PK and PD (i.e., plasma lyso-Gb3) assays, (2) summary results of the PK/PD assessments and exposure-response analysis, (3) evaluations of intrinsic and extrinsic factors that impact PK/exposure, and (4) rationale for the dose selection. Provide working hyperlinks referring to the corresponding study results in Module 5 of the BLA.

Submit the assay validation reports for the measurement of pegunigalsidase alfa, lyso-Gb3, and other biomarker concentrations in Module 5.3.1.4 of the BLA.

Provide the original PK, PD, and immunogenicity datasets, the PK/PD analysis datasets, and PK/PD parameter datasets for the study(ies).

Post Meeting Comment:

We recommended that you submit all PK and PD bioanalytical method validation reports and bioanalytical study reports for PK and PD assessments used in clinical studies which may support labeling claims. In addition, we recommend that you submit tables summarizing the bioanalytical methods used and the life-cycle information using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document (https://go.usa.gov/xVsdJ) and submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

Question 8: Question 8 – Risk Evaluation Mitigation Strategy (REMS)
Does the Agency agree that a REMS is not appropriate for this submission?

FDA Response:
Based on the submitted safety information, a REMS is unlikely to be needed. However, final determination of the need for a REMS will be made during review of your application.

2.5. CMC Questions

[redacted] (b) (4)

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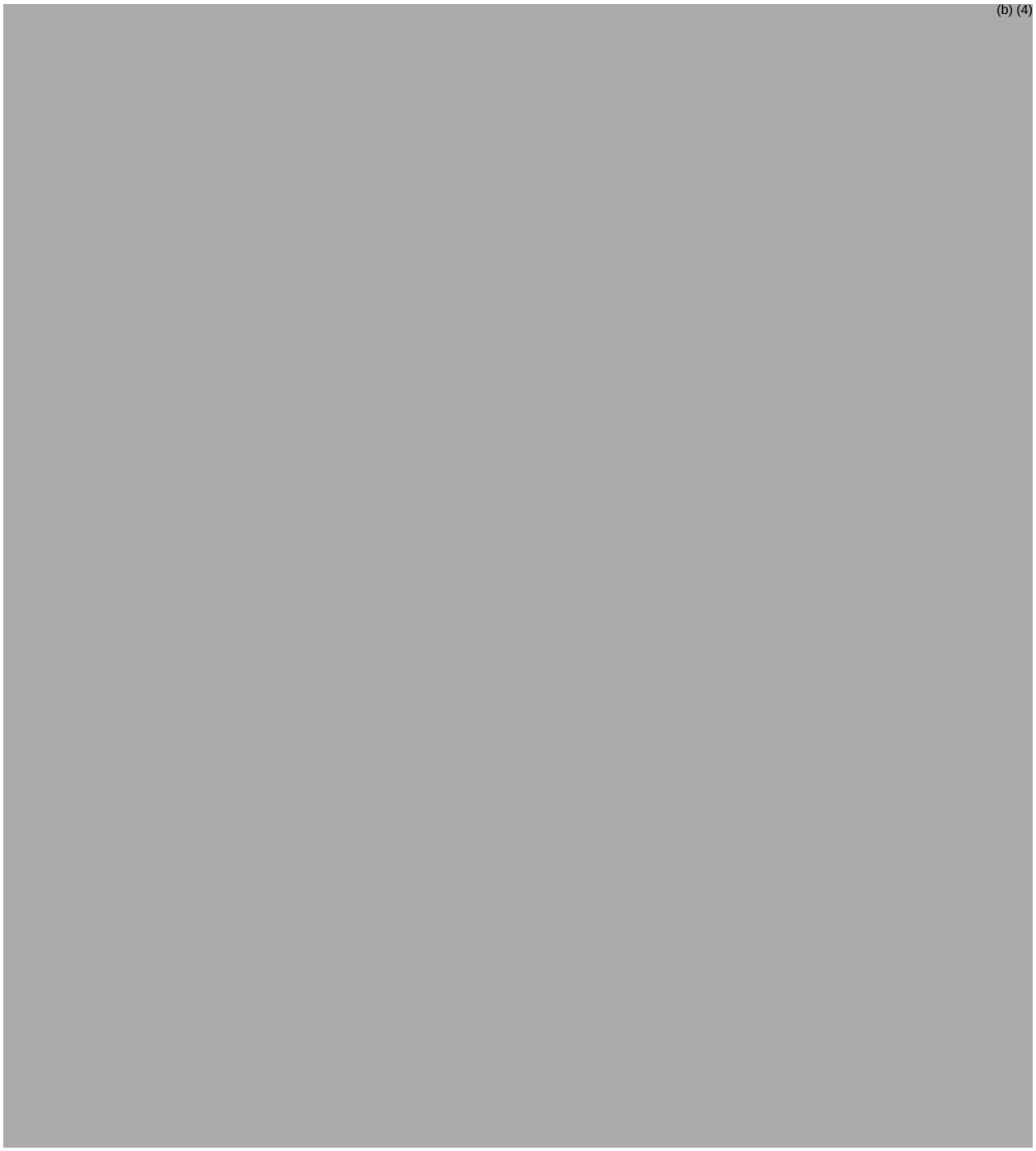

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 11, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with

FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

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:*

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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]

6.0 ATTACHMENTS AND HANDOUTS

Sponsor responses to Meeting Preliminiary Comments received 10/11/2019.

[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

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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/

NICOLAS KONG
11/12/2019 10:24:17 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110161

MEETING MINUTES

Protalix Biotherapeutics c/o Target Health, Inc.
Attention: Glenn D. Park, PharmD, FCCP
Senior Director, Clinical and Regulatory Affairs
261 Madison Avenue 24th Floor
New York, New York 10016

Dear Dr. Park:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PRX-102 (Plant Cell Expressed Recombinant, Pegylated,Cross-linked Alpha-galactosidase A).

We also refer to the meeting between representatives of your firm and the FDA on November 3, 2015. The purpose of the meeting was to discuss the adequacy of the proposed program to support a future Biologics Licensing Application (BLA) for PRX-102 for the treatment of Fabry Disease.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-9651.

Sincerely,

{See appended electronic signature page}

Lisa N. Pitt, PharmD, MSJ
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: November 3, 2015, 2:00-3:00 PM
Meeting Location: White Oak, Building 22 Conference Room 1315

Application Number: 110161
Product Name: PRX-102
Indication: Fabry Disease
Sponsor/Applicant Name: Protalix BioTherapeutics

Meeting Chair: Laurie Muldowney
Meeting Recorder: Lisa Pitt

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, MD, Director
Dragos Roman, MD, Acting Associate Director
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1.0 BACKGROUND

Protalix Biotherapeutics requested a Type B, End-of-Phase-2 meeting to discuss the adequacy of the proposed Chemistry, Manufacturing and Controls (CMC), nonclinical and clinical development programs to support a future Biologics Licensing Application (BLA) for PRX-102 for the treatment of Fabry Disease.

FDA sent Preliminary Comments to Protalix on October 29, 2015.

2. DISCUSSION

Protalix indicated via email November 2, 2015 that the meeting discussion on Clinical Question 12, Nonclinical Question 10 and Quality Question 2a and 6a, time permitting.

2.1. Quality

(b) (4)

5 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

2.2. Nonclinical

Question 10: Does the Agency agree that the nonclinical studies summarized in Section 12.2 (Chronic Toxicity Studies and Reproductive Toxicity Studies) are sufficient to support the BLA and that no additional nonclinical studies are needed?

FDA Response to Question 10: ***No. We do not agree. In addition to the studies listed in the briefing package (Table 24, page 95), you need to conduct a pre- and post-natal developmental study in rats.***

Discussion:
The Sponsor proposed an (b) (4) ***in lieu of a Segment 3 study. The FDA stated that this proposal will not fulfill the requirement. The Sponsor needs to conduct a Segment 3 study, if not pre-market then as a PMR.***

2.3. Clinical Pharmacology and Biopharmaceutics

Question 11: Does the Agency agree that the Phase 1/2 clinical study will provide sufficient pharmacokinetic data for the BLA?

FDA Response to Question 11: ***No, we do not agree. We recommend that you also collect pharmacokinetic (PK) samples in the proposed phase 3 trials.***

In general, characterization of the PK profile of the to-be-marketed formulation in the target patient population will be needed to support the review of your BLA. We acknowledge that your phase 1/2 Studies (PB-102-F01 and PB-102-F02) have evaluated the PK of PRX-102 (0.2, 1, 2 mg/kg) in adult naïve patients with Fabry disease. Your proposed two phase 3 pivotal studies will evaluate the efficacy and safety of PRX-102 (1 mg/kg) in patients with Fabry disease previously treated with Fabrazyme or Replagal. It is not clear whether or not previous Fabrazyme or Replagal treatment would have an impact on PK of PRX-102. In addition, collecting PK data in your proposed phase 3 studies will be necessary in order to explore the exposure-response relationships for efficacy and safety of PRX-102 for the treatment of Fabry disease. Therefore, we recommend that you collect PK samples in the proposed phase 3 trials.

We may have additional comments on your phase 3 PK blood sampling scheme after review of your phase 3 protocols when they are submitted under the IND.

2.4. Clinical

Question 12: Does the Agency agree that the two Phase 3 switch over clinical studies planned for PRX-102 in the Fabry disease adult population are appropriate to support the BLA?

FDA Response to Question 12: ***No, we do not agree that the 2 phase 3 studies, as proposed, are adequate to support a BLA. Please see our comments below for each of the proposed studies.***

The switch-over study as proposed may be appropriate to provide supportive information on the safety of your product but would not provide efficacy data for labeling claims.

We have concerns regarding your choice of comparator group for the proposed head-to-head study. The current labeling for Fabrazyme does not include a claim of clinical benefit based on eGFR. Therefore, your proposed study which primarily plans to demonstrate non-inferiority to Fabrazyme, will not provide sufficient evidence of clinical benefit because you are not studying PRX-102 against a comparator that has demonstrated a clear clinical benefit. Specifically, for a non-inferiority study to be interpretable, one would need to know that Fabrazyme was effective in slowing the loss of renal function and have a reliable estimate of the size of the treatment effect. Instead, a study design to demonstrate superiority to Fabrazyme could be acceptable to support regular approval with a clinically meaningful endpoint. Alternatively, we recommend you consider a trial in treatment-naïve Fabry patients comparing PRX-102 with either an active or placebo control, with a clinically meaningful endpoint.

We have the following additional comments regarding your selection of endpoints for your phase 3 program:

eGFR: ***An endpoint based on the annualized change in eGFR may be reasonable for an uncommon, slowly progressive renal disease that has a high likelihood of progressing to end-stage kidney disease, such as Fabry. However, since patients do not perceive changes in eGFR per se, you would ultimately need to be able to demonstrate that the magnitude of the treatment effect on eGFR is clinically meaningful (i.e., will translate into a clinically relevant effect on progression to end-stage kidney disease). As an alternative to using a continuous variable to define the endpoint, you could consider assessing the proportion of subjects who developed a decline in renal function of a pre-specified magnitude (e.g., the proportion of subjects with a 30% decline in eGFR). Showing a treatment effect on the need for dialysis or renal replacement therapy provides the most obvious evidence of a drug's efficacy in the treatment of chronic kidney disease but may not be feasible given the size of the population and slow rate of disease progression. It would be important to collect information on whether the treatment effect continues to accrue across the various stages of the disease and over time. Based on the results of the phase 1/2 study, it is unlikely that a 9 to 12 month treatment period will be sufficient to demonstrate a treatment effect on the rate of eGFR decline. Moreover, a 9 to 12 month treatment period is not sufficient to address whether the treatment effect continues to accrue over time in this slowly progressive disease. For this reason, a trial duration of at least 2-3 years may be necessary; justify the duration based on available natural history data and the anticipated magnitude of the treatment effect over time.***

LVMi: ***The Agency has not previously accepted changes in left ventricular mass as a potential surrogate marker for efficacy of a treatment for Fabry disease. It should also be noted that the Agency has not previously used treatment induced effects on left ventricular mass (LVM)as a surrogate endpoint and basis for approval of a therapy developed to treat a cardiac disease. Based on the natural history of Fabry disease, LVH occurs in most, but not all male patients over time. Additionally, it is not clear what level, if any, of slowing the rate of increase of LVMi would be considered clinically meaningful. Therefore, we do not agree that LVMi alone is an appropriate clinical marker for Fabry patients (either as a surrogate endpoint or as a clinical benefit endpoint).***

GI Symptoms: ***In addition, you have reported interim analysis results from your phase 1/2 study that preliminarily show a favorable trend in the severity and frequency of abdominal pain and frequency of diarrhea after 6 months of treatment with your product. We encourage you to further evaluate the effect of PRX-102 on gastrointestinal (GI) signs and symptoms in a new Fabry disease controlled trial. These signs and symptoms commonly occur in Fabry patients, and among pediatric patients, GI signs and symptoms due to Fabry disease may be more prevalent than renal or cardiac disease. During a recent ERT shortage, patients who reduced or discontinued ERT dosing developed worsening of GI signs and symptoms within a few weeks to months. Thus, the effects of a novel treatment on GI signs and symptoms could be demonstrated relatively rapidly. Evaluating GI signs and symptoms as endpoints in a Fabry disease trial (in addition to clearance of GL-3 from renal tissue) may represent a path forward, as improvement in GI signs and symptoms could provide evidence of clinical benefit and could support regular approval. For regular approval, a clinically meaningful improvement in Fabry signs and/or symptoms would need to be demonstrated.***

Dose Selection: ***We recommend that you provide rationale for the selection of the 1 mg/kg dose for the proposed phase 3 trials.***

Discussion:

The discussion centered on possible clinical development approaches to support PRX-102 approval either under Subpart E or via a standard approval pathway. At this time the FDA does not support using renal Gb3 clearance as an option for either Subpart E or standard approval because of the uncertainty regarding the relationship between this histological endpoint and clinical outcome(s).

The Sponsor proposed two phase 3 clinical trials. The first study would be a short-term, placebo-controlled "GI study" in treatment-naïve patients, in which renal function would be assessed as a secondary endpoint. The second study would be a long-term (e.g. 2 years or more) parallel-arm, superiority "renal study" comparing PRX-102 with Fabrazyme in patients previously treated with Fabrazyme. The primary endpoint would be eGFR assessed as either a change from baseline to the last visit or comparing eGFR slopes. If the Sponsor proposes the primary analysis based on the slope change, FDA will carefully examine the validity of the linear assumption. In either case, the Sponsor will need to demonstrate that the treatment

effect is clinically meaningful. To this end, the Sponsor plans to submit a new proposal for a revised clinical development plan, with supporting evidence that the anticipated treatment effect relative to Fabrazyme is expected to be associated with a predictable clinical benefit (such as delay in time to reaching end-stage renal disease). The Sponsor indicated that they were interested in submitting a BLA upon completion of the GI study and interim data from the head-to-head study. The BLA will also include the safety data from the ongoing extension of the phase 1-2 study at the dose intended for labeling and marketing. The FDA indicated that the next proposal will have to address and justify the specific size of the safety database that the Sponsor anticipates at the time of BLA submission. The FDA finds it acceptable to submit the BLA upon successful completion of the GI study.

Post-meeting comment:
FDA would like to clarify that given the fact that the Sponsor believes that 1 year is insufficient to demonstrate a treatment effect based on eGFR, an interim look at the efficacy data may not be necessary for BLA submission. However, consideration should be given to unblinding the safety data from this trial for analyses to support the safety of the product in patients who switch from Fabrazyme to PRX-102.

Question 13: Does the Agency agree that no further studies in the naïve adult patient population are required?

FDA Response to Question 13: Please see response to Question 12.

Question 14: Does the Agency agree? […that the overall planned clinical development is suitable basis for a BLA]

FDA Response to Question 14: Please see response to Question 12.

Question 15: Does the Agency agree with this immunogenicity testing approach?

FDA Response to Question 15: The immunogenicity testing approach appears adequate. In addition, you should determine whether anti-drug antibodies have cross-reactivity to Fabrazyme. As per the Agency's advice letter dated August 18, 2014, all assays used should be qualified and appropriately sensitive and specific for their intended purposes. We recommend that you submit your assay validation packages to the Agency for review prior to use with clinical trial samples, to help ensure the suitability of the test results. Therefore, provide detailed information regarding the development status of your immunogenicity assays as an IND amendment. Describe clearly your proposed sampling schedule for your pivotal clinical studies.

2.5. Biostatistics

Question 16: Dose the Agency agree with the statistical basis of the head-to-head study referenced in Section 13.2 Proposed Phase 3 Study, PRX-102 versus Fabrazyme?

FDA Response to Question 16: ***In addition to the design concerns that were pointed out in our response to Question 12, we have the following comments:***

- ***For both pivotal studies, you should provide the detailed justification for the assumptions, including treatment effect as well as the anticipated dropout rates, used for the sample size calculation.***

- ***We remind you that in a pivotal trial, the efficacy evaluation should be conducted based on formal statistical tests using two sided significance level of 0.05 or one-sided significance level of 0.025.***

- ***For the switch-over study, you indicate that the sample size of 22 patients is adequate to evaluate safety of subjects who would transition from Replagal to PRX-102. Please clarify the basis for your proposed sample size calculation to support that it would be adequate to describe the safety in this patient group (including the specific safety concern that you powered for).***

2.6. Regulatory

Question 17: Does the Agency agree the study design could provide appropriate data to support a Breakthrough Therapy Designation Request?

FDA Response to Question 17: ***Please refer to Question 12. You would need to provide preliminary clinical evidence that your drug provides substantial improvement on a clinically significant endpoint(s) over available therapies. If superiority of your product were to be demonstrated to an available therapy (i.e. Fabrazyme), appropriate data might be provided to meet the criteria for Breakthrough Designation.*** (b) (4) ***A study designed to demonstrate the superiority of your product on a clinically significant endpoint compared to placebo or an active control may provide the needed data to support a Breakthrough Designation.***

Please see the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics for additional information.

Question 18: Does the Agency agree with Protalix approach to meet PREA requirements?

FDA Response to Question 18: ***Yes, you must submit an iPSP within 60 days of this meeting to request a deferral or waiver of pediatric studies.*** (b) (4)

Question 19: Does the Agency agree that re-importation of an approved drug as the comparator is acceptable?

FDA Response to Question 19: ***A non-U.S.-licensed comparator product is considered an investigational new drug in the United States, and thus would require an IND for importation and use in the United States (see 21 CFR 312.110(a)). If you intend to conduct a clinical investigation in the United States using a non-U.S.-licensed comparator product, the IND requirements in 21 CFR part 312 also would apply to this product (see, e.g., 21 CFR 312.2). Importation may be acceptable, provided that there is documentation regarding the non-US-licensed Fabrazyme (purchased in the United Kingdom) that is submitted to the IND, and the IND is in effect per 21 CFR§ 312.40. Additionally, the non-US-licensed Fabrazyme should be labeled according to 21 CFR 312.6. We also suggest referring to the following regulation for import requirements of INDs: 21 CFR 312.110 Import and export requirements.***
With respect to Chemistry, Manufacturing, and Controls (CMC) information, you should submit to the IND as much of the CMC information required by 21 CFR 312.23(a)(7) as is available. However, we recognize that you may not be able to obtain all of the CMC information required by 21 CFR 312.23(a)(7) for a non-U.S.-licensed comparator product for which you are not the manufacturer. In these circumstances, a sponsor can request that FDA waive the requirement for complete CMC information on the non-U.S.-licensed comparator product (21 CFR 312.10). The IND must include, as part of the waiver request, at least one of the following:

- ***A sufficient explanation why compliance with the complete requirements of 21 CFR 312.23(a)(7) is unnecessary or cannot be achieved,***

- ***Information that will satisfy the purpose of the requirement by helping to ensure that the investigational drug will have the proper identity, strength, quality, and purity, or***

- ***Other information justifying a waiver.***

Information that is relevant to whether the investigational drug will have the proper identity, strength, quality, and purity may include, for example, information indicating whether the investigational drug has been licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonization (ICH) countries). This should include, to the extent possible, summary approval information and current product labeling made public by the foreign regulatory authority. In addition, you should also provide information on the conditions and containers that will be used to transport the drug product to the US clinical site(s) and information on the relabeling and repackaging operations that will be used to relabel the drug product vials for investigational use. (This should include information on how exposure of the product to light and temperature conditions outside of the recommended storage conditions will be prevented. A risk assessment

on the impact the relabeling operations may have on drug product stability should also be included.)

As you move forward in your development program, you should consult with the FDA regarding the CMC information necessary to support a proposed clinical trial.

While we agree that it may be acceptable to use a non-US-licensed active comparator product in a clinical trial, there may be additional considerations regarding the use of such a comparator product depending on the details of the clinical trial design. Based on the comments provided in the response to Question 12 and the lack of agreement on the design of your proposed clinical trial, we defer further comment at this time. As the details of your clinical program are discussed further, we encourage you to revisit this issue with the FDA.

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a

clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

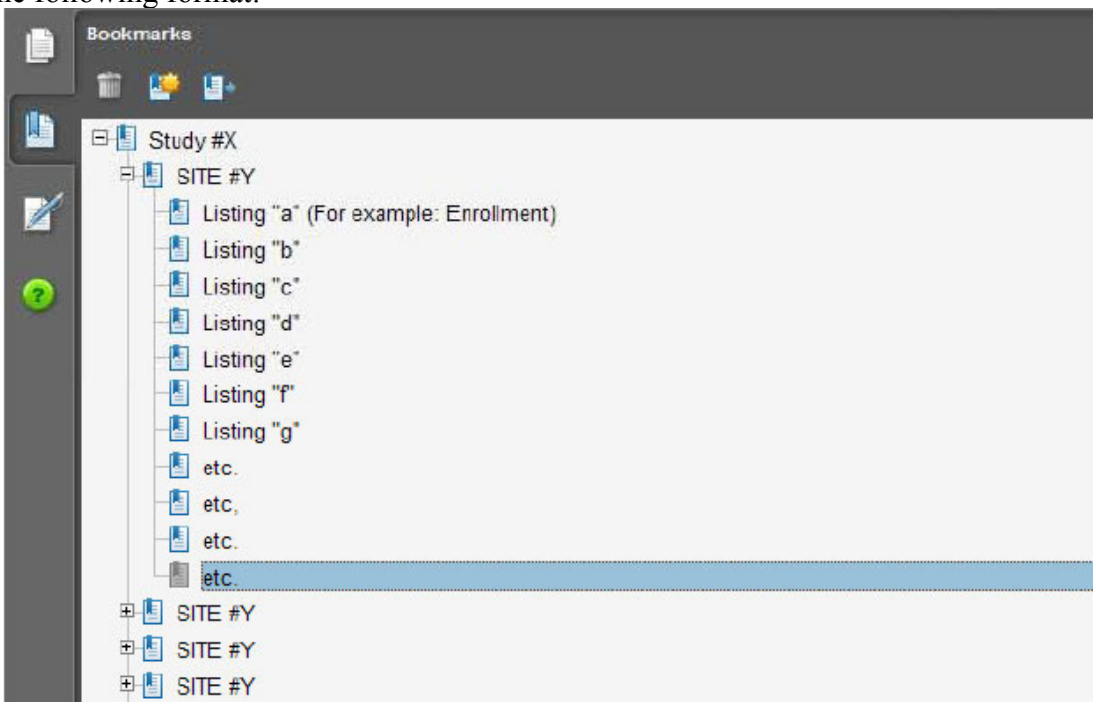
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

4.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

DRAGOS G ROMAN
11/06/2015