CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761184Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 132494

MEETING MINUTES

Pfizer Inc.
Attention: Randi Albin, PhD
Senior Director, Pfizer Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Dr. Albin:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MOD-4023 injection.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2019. The purpose of the meeting was to discuss the content and format of the planned BLA.

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 Sejal Kiani, Regulatory Project Manager, at (301) 796-6445.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	Monday, December 16, 2019 9:30 AM to 10:30 AM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 132494
Product Name:	MOD-4023
Indication:	Treatment of pediatric growth hormone deficiency
Sponsor/Applicant Name:	Pfizer Inc.
Meeting Chair:	Marina Zemskova, MD
Meeting Recorder:	Sejal Kiani, MS

FDA ATTENDEES

Division of Metabolism and Endocrinology Products
Lisa Yanoff, MD, Director (Acting)
Sonia Doi, MD, Clinical Reviewer
Marina Zemskova, MD, Clinical Team Lead
Elena Braithwaite, PhD, Nonclinical Reviewer
Feleke Eshete, PhD, Nonclinical Reviewer
Sejal Kiani, MS, Regulatory Project Manager
Julie Van der Waag, MPH, Chief, Project Management Staff

Office of Clinical Pharmacology
Sang Chung, PhD, Clinical Pharmacology Reviewer
Jaya Vaidyanathan, PhD, Clinical Pharmacology Team Lead

Office of Biostatistics
Jennifer Clark, PhD, Biometrics Reviewer
Feng Li, PhD, Biometrics Team Leader

Office of Product Quality
Montserrat Puig, PhD, Laboratory of Immunology Reviewer, Office of Biotechnology Products

Daniela Verthelyi, PhD, Chief of Laboratory of Immunology, Office of Biotechnology Products
Kavita Vyas, PhD, Office of Policy for Pharmaceutical Quality

Office of Surveillance and Epidemiology
Deveonne Hamilton-Stokes, RN, BSN, MA, Safety Regulatory Project Manager

Office of Scientific Investigations
Cynthia Kleppinger, MD, Medical Officer

Office of Regulatory Policy
Daniel Ritterbeck, JD, Regulatory Counsel
Anuj Shah, JD, Senior Regulatory Counsel

Office of Therapeutic Biologics and Biosimilars
Sarah Brown, PharmD, Science Policy Analyst
Tyree Newman, Senior Regulatory Health Project Manager

Center for Devices and Radiological Health
Rumi Young, Team Lead, Injection Team

Office of Combination Products
Maryam Mokhtarzadeh, MD, Medical Officer

SPONSOR ATTENDEES

Randi Albin, Senior Director, Regulatory Strategy, Pfizer
Vincent Amoruccio, Senior Director, Statistical Programming and Analysis, Pfizer
Jose Cara, Medicines Team Lead and Global Clinical Lead, Pfizer
Tony Cruz, Chief Executive Officer, Transition Therapeutics
Samantha Davis, Co-Development Team Lead – Large Molecules, Pfizer
Jane Hsiao, Vice Chairman, Chief Technology Officer, OPKO Health
Joan Korth-Bradley, Senior Director, Clinical Pharmacology, Pfizer
Allison Manners, Senior. Director, Chemistry and Regulatory Affairs, OPKO Pharmaceuticals
Sandra Martin, Director, Global CMC, Pfizer
Amanda Matthews, Senior Director, Global CMC, Pfizer
Daniel Meyer, Executive Director, Global Biometrics and Data Management, Pfizer
Aleksandra Pastrak, Vice President, Clinical Development, Transition Therapeutics
Diane Rocco, Global Regulatory Portfolio Lead, Pfizer
Carl Roland, Senior Director, Clinician, Pfizer
Carrie Turich Taylor, Senior Director, Safety and Risk Management, Pfizer
Srinivas Valluri, Director, Biostatistics, Pfizer
David Wright, Associate Research Fellow, Nonclinical Drug Safety

1.0 BACKGROUND

MOD-4023 is a C-terminal peptide-modified recombinant human growth hormone (hGH). MOD-4023 is provided as a single-patient use, disposable, prefilled pen containing ready to be administered solution for injection at a concentration of 20 mg/mL (24 mg presentation) or 50 mg/mL (60 mg presentation) with a nominal volume of 1.2 mL.

MOD-4023 is intended for once weekly self-administration via subcutaneous (SC) injection. The prefilled pen has the capability for setting and delivering variable doses, which is determined based on patient weight. The 24 mg/1.2 mL pen presentation delivers a dose in increments of 0.2 mg and the 60 mg/1.2 mL pen in increments of 0.5 mg.

The proposed indication is the treatment of children with growth disturbance due to insufficient secretion of growth hormone.

Pfizer states that MOD-4023 is expected to have a safety and efficacy profile comparable to daily rhGH therapy. MOD-4023 has been granted orphan drug designation (ODD) by the Office of Orphan Drug Products (OODP) for the treatment of growth hormone deficiency (GHD) (ODD 10-3134).

(b) (4)

Pfizer Inc. plans on submitting the BLA in third quarter 2020. In the planned BLA, data supporting the safety and efficacy of MOD-4023 in the pediatric population will be provided by a single pediatric Phase 3 registration study (CP-4-006), a supportive pediatric Phase 2 study (CP-4-004), and data from the ongoing open-label extensions (OLE) of both studies. (b) (4)

FDA sent Preliminary Comments to Pfizer on December 13, 2019.

2.0 DISCUSSION

Your questions are repeated below with our responses followed in bold.

2.1. Chemistry, Manufacturing and Controls

Question 1: *Does the Agency agree with the proposed structure for Module 3.2,*

including a drug substance node, 2 separate nodes for the drug product solution filled into cartridges and the fully assembled prefilled pen, in addition to appendices and regional information nodes?

FDA Response to Question 1: **The section organization for Module 3.2, including 2 nodes for the DP solution and the pen injector is adequate. However, ensure that your 3.2.P.3 Manufacture section of the prefilled pen includes the following information as recommended by the eCTD Technical Conformance Guide[1]: Lot Distribution Data, Manufacturers, Batch Formula, and Description of Manufacturing Process and Process Controls sections. Additionally, it is unclear from your structure if you will provide all the content needed for review if the device constituent. See Additional Device Comments below for details.**

Discussion: *Pfizer sought clarification on the expectations of the Lot Distribution Data, since they have not provided such information before. FDA stated that it may be acceptable to not include this information but will verify with colleagues and provide post-meeting comments.*

POST-MEETING COMMENT: *FDA confirmed that Pfizer does not need to provide lot distribution data in their premarket submission.*

Question 2: *In place of a traditional Module 2.3 Quality Overall Summary (QOS) that separately summarizes each section of the Common Technical Document, the Applicant proposes to submit a comprehensive QOS designed to summarize the overall control strategy and quality considerations for MOD-4023. A high-level outline of the proposed content is provided in the briefing document. Does the Agency agree with this proposal?*

FDA Response to Question 2: **You propose to organize Module 2.3 with different subsections from those suggested by the International Council on Harmonization (ICH) M4, with the intention to facilitate the review process. We agree to the proposed content sections as long as all the information required in the QOS is included and all the data is clearly indexed.**

Discussion: *No discussion occurred.*

Question 3: *To facilitate the Agency's review of the manufacturing processes and control strategy for MOD-4023 drug substance and drug product solution (filled cartridge) in Module 3:*

[1] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf

a. *The Applicant proposes to summarize information for process parameters and in-process controls in the following tabular format with a separate table for each unit operation. Does the Agency agree with the table format as outlined?*
b. *The Applicant proposes to summarize information for quality attributes, and product and process related impurities for the drug substance and drug product solution in the following tabular format. Does the Agency agree with the table format as outlined?*

FDA Response to Question 3: **The proposed format of the tables for both process parameters and in-process controls (Table in Question 3a), and quality attributes and product and process related impurities (Table in Question 3b) are adequate to summarize the data. However, the summary tables should supplement rather than replace information typically provided in Module 3.**

Discussion: *No discussion occurred.*

Question 4: *The Applicant proposes to provide established conditions (ECs) and a Product Lifecycle Management (PLCM) document in the 3.2.R Regional as part of the initial BLA. Does the Agency agree with this approach?*

FDA Response to Question 4: **Yes, we concur with your proposal to include EC and PLCM document in the 3.2.R Regional section of Module 3.**

Discussion: *No discussion occurred.*

Question 5: *The Applicant proposes to include one full set of executed batch records and master batch records for drug substance and a single to-be-registered strength of drug product solution and prefilled pen in the planned BLA. Does the Agency agree with this approach?*

FDA Response to Question 5: **We are not clear what you mean by "one full set" of batch records for DS. Please explain.**

Also, confirm that the commercial lots of DS will be solely manufactured in Grange Castle (Ireland) and not in Rentschler Biotechnologie (Germany). Otherwise, you will need to submit full records for DS from each manufacturing site.

It is unclear if you mean you only intend to provide functional data to support the lower concentration and strength prefilled pen configuration (20mg/ml; 24mg) in your BLA. Please note that we will expect you to provide data to support both prefilled pens (20mg/ml and 50mg/ml) as the concentration can impact the functional performance testing. You may choose to provide data for only one configuration for drug product agnostic functional testing.

Discussion: *Pfizer confirmed that the commercial lots of DS will be solely manufactured in Grange Castle (Ireland).*

Pfizer proposed to only provide batch records for the 20mg/ml prefilled pen configuration. FDA agreed with this proposal noted that if they identify device performance anomalies, they may request batch records from the other concentration interactively during our review.

Pfizer confirmed that they intend to provide verification data for both the 20mg/ml and 50mg/ml prefilled pens.

Question 6: *The Applicant proposes to provide information on* (b) (4) (b) (4) *Puurs site information (drug product solution [filled cartridge] manufacturing and prefilled pen assembly site) as outlined in the Company Position. Does the Agency agree with the proposal for where information will be provided in support of the planned BLA and maintenance of the information post approval?*

FDA Response to Question 6: **Information regarding equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters should be submitted as part of the BLA Study protocols and summary validation study data for sterilization and depyrogenation of product contact equipment and components must also be included in the BLA. Information regarding the prefilled pen assembly facility and process should be provided in the BLA.**

We also remind you that a BLA applicant is expected to have knowledge of and control over the manufacturing process for the biological product to comply with applicable regulatory requirements. As such, we generally would not expect a BLA for a biological product to reference a master file for drug substance, drug substance intermediate, or drug product information.

Additional Product Quality Microbiology Comments:

These are additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product manufacture should be provided in the BLA submission to facilitate the

planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

1. **The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:**

   a. **Endotoxin removal steps should be clearly identified in the manufacturing process description (3.2.S.2.2). Endotoxin removal validation data obtained during manufacture of the process performance qualification lots (PPQ) should be provided in section 3.2.S.2.5.**

   b. **If antibiotics are added to the fermentation bioreactors, justify the presence of any antibiotics that are used in the growth media for the drug substance fermentation production phases. Use of antibiotics during fermentation production is not recommended unless justified and should be removed from fermentation media, if feasible.**

   c. **Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided in section (3.2.S.2.4).**

   d. **Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots should be summarized in (3.2.S.2.5).**

   e. **Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits should be provided in section (3.2.S.2.5).**

   f. **Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization and summarized in section (3.2.S.2.5).**

g. Information and summary results from the shipping validation studies should be summarized in (3.2.S.2.5).

h. Drug substance bioburden and endotoxin release specifications should be summarized in (3.2.S.4).

i. Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, a brief description of the methods should be provided in addition to the compendial reference numbers summarized in section (3.2.S.4).

2. The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*[2].

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

a. Identification of the manufacturing areas and type of fill line (e.g., open, RABS, isolator), including area classifications.

b. Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

c. Parameters for filling and plunger placement for the cartridge.

d. Parameters for filling and capping for the vials.

e. A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.

f. Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.

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[2] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

g. **Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 ml.**

3. **The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:**

   a. **Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.**

   b. **Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.**

   c. **In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.**

   d. **Isolator decontamination summary data and information, if applicable.**

   e. **Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.**

   f. **Information and summary results from shipping validation studies. For autoinjectors (pen), the effects of varying air pressure on pre-filled cartridge plunger stopper movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled cartridge plunger stopper movement during air transportation does not impact product sterility.**

   g. **Validation of capping parameters, using a container closure integrity test for cartridge manufacture.**

4. **The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:**

a. **Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled cartridge and autoinjector (pen) should be included. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.**

b. **Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.**

c. **Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).**

d. **Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time. Low endotoxin recovery studies may not be necessary for products that do not contain polysorbate.**

Discussion: *Pfizer understood that the requested information was a guidance to the information that the BLA should contain; however, they clarified they were not planning to include in the BLA submission information contained in the DMFs to avoid redundancy.*

Regarding comment 4d, Pfizer sought clarification on whether this was a requirement, and whether the comment is specific for MOD-4023. They also sought clarification on whether they should perform the low endotoxin recovery studies given the DPI formulation.

FDA stated that it would clarify these questions with the Product Quality Microbiology staff and include a post-meeting comment in the meeting minutes.

POST-MEETING COMMENT: *Regarding the DMF, study protocols and validation data for product contact components and equipment should be included in the BLA.*

Please also refer to our initial response to Question 6 regarding the referencing of master files, including DMFs.

Given that the drug product [redacted] (b) (4) *low endotoxin recovery studies should be performed.*

2.2. Nonclinical

Question 7: *Does the Agency agree that nonclinical development program fulfills the nonclinical requirements for the planned BLA and that no additional nonclinical studies are required?*

FDA Response to Question 7: **Yes, we agree that the nonclinical studies submitted are sufficient to support filing of a BLA. Whether the nonclinical studies are adequate to support marketing approval will be determined during review of the BLA.**

In the BLA, provide a carcinogenicity assessment document to support your proposed labeling of MOD-4023 in Section 13.

Discussion: *No discussion occurred.*

2.3. Clinical Pharmacology

Question 8: *Does the Agency agree that the proposed clinical pharmacology data package as outlined in this briefing document fulfills the requirements for the planned BLA and no additional clinical pharmacology studies are required?*

FDA Response to Question 8: **Yes, we agree that the proposed clinical pharmacology data package is sufficient to support the filing of planned BLA.**

Discussion: *No discussion occurred.*

Question 9: *Does the Agency agree that the proposed clinical data package as outlined in this briefing document fulfills the requirements for approval of the planned commercial pen presentation and that no additional studies are required?*

FDA Response to Question 9: **Yes, we agree that the proposed data package for the planned commercial presentation (formulation and device) is sufficient to support filing of the planned BLA. Whether the proposed clinical data for the planned commercial presentation (formulation and device) is sufficient to support marketing approval will be determined during review of the BLA.**

While the clinical studies were performed with the intended patient population (i.e., pediatric) and same prefilled pen design, they may not have validated the limits of your prefilled pen functional specifications (e.g., dial torque force, injection force). Please ensure that your BLA discusses how the clinical studies validated the specification limits. Alternatively, you can use literature or anthropometric studies to validate these specifications for the pediatric patient population.

Discussion: *Pfizer agrees and will provide this information in the BLA.*

2.4. Clinical

Question 10: *Does the Agency agree that the proposed presentation of efficacy information within the Summary of Clinical Efficacy (SCE, Module 2.7.3) as outlined in the draft TOC is appropriate to support the review of the planned BLA?*

FDA Response to Question 10: **Your proposed presentation of efficacy information in the SCE consisting of data from a primary 12-month Phase 3 pediatric study (CP-4-006) period, a supportive data from 12-month Phase 2 pediatric study (CP-4-004) period and data from open-label extension (OLE) periods for both studies with a cut-off date of 1 November 2019 is sufficient to support a BLA submission.**

Additional Comments:

1. **Please specify how many patients enrolled in both studies are expected to achieve final height by cut-off date.**

2. **We also request that you clarify your using [redacted] (b) (4) as opposed to [redacted] (b) (4) for the proposed pediatric indication of MOD-4023.**

Discussion: *In reference to the additional comments:*

1. *Pfizer indicated they will not have any patients achieve final height as measured by chronological age at the data cut-off point. Pfizer also sought clarification on the definition of "final height". Pfizer proposed to define final height as height velocity <1cm per year, measured within 6 months prior to cut-off date. FDA indicated that overall this proposal is acceptable and asked Pfizer to provide the total number of patients who achieve final height based on this proposed definition, the age, and the duration of exposure with MOD-4023.*

POST-MEETING COMMENT: *Please also provide bone age, Tanner stage and neutralizing antibody titers (if available) in those patients who achieve "final height" during the study.*

2. *In response to the Additional Comment on the use of* [redacted] (b) (4) *Pfizer indicated that the labeling will use language* [redacted] (b) (4) [redacted] (b) (4)

Question 11: *The Applicant plans to submit a complete textual presentation of the efficacy data analyses in Module 2.7.3, Summary of Clinical Efficacy. The Integrated Summary of Efficacy (ISE) in Module 5.3.5.3 will contain supportive tables, listings, and figures with hyperlinking between the 2 modules as appropriate. Does the Agency agree with this approach to the placement of efficacy analyses in the submission?*

FDA Response to Question 11: **Your proposed approach to the placement of efficacy analyses in the BLA that include a complete textual presentation of efficacy data in the Summary of Clinical Efficacy (SCE) and supportive tables, listings and figures in the Integrated of Summary of Efficacy (ISE) is acceptable.**

Discussion: *No discussion occurred.*

Question 12: *Does the Agency agree that the proposed structure of the Summary of Clinical Safety (SCS) is appropriate and sufficient to evaluate the overall safety profile of MOD-4023?*

FDA Response to Question 12: **Your proposed structure of the SCS that include safety data from a primary 12-month Phase 3 study (CP-4-006) period, 12-month Phase 2 pediatric study (CP-4-004) period and data from open-label extension (OLE) periods for both studies with a cut-off date of November 1, 2019 appears appropriate to support BLA submission.**

Discussion: *No discussion occurred.*

Question 13: *Does the Agency agree that the planned strategy for the safety database is appropriate and sufficient to evaluate the overall safety profile of MOD-4023?*

In particular, please comment on the adequacy of the following:

a. *Proposed size of the safety database.*
b. *Proposed data cut-offs for on-going OLEs for the pediatric Phase 2 and Phase 3 studies.*
c. *Proposed pooling strategy for the safety data.*
d. *Proposed Medical Dictionary for Regulatory Activity (MedDRA) versions for provided data.*

FDA Response to Question 13:

a. Your proposed size of the safety database which will include 109 patients (out of 214 patients) in the main study period (1 year) of Study CP-4-006, and approximately 10 patients from the OLE period with 1-year exposure and 90 patients with 6-month exposure to MOD-4023, with additional safety data provided by the Phase 2 Study CP-4-004 consisting of 42 patients treated with MOD-4023 in the main period and 40 patients from the 53 patients with a 4-year OLE data appears reasonable for filing.

b. Your proposed data cut-offs for on-going pediatric studies CP-4-006 and CP-04-004 might be sufficient to support BLA submission, providing there are no new or unexpected safety findings associated with use of your drug in the intended population. We may request additional data if safety concerns are identified during the review for which additional data may be informative.

c. While we agree in general that the you may include additional pooled analyses sets assessing long-term safety of MOD-4023, the interpretability of these analyses will be complicated, due to differences in studies design, previous exposure to different somatropin agents, differences in the drug presentation being studied, etc. Thus, we do not agree that it is appropriate to combine the data from studies CP-4-006 and CP-4-004 from the point in time when patients begun MOD-4023 treatment through the cutoff date noted above due to the different exposure, use of vial vs. pen, etc. for the overall safety analysis. A simple pooling of data from these studies would not be informative and can be misleading and your BLA submission should include separate summaries of safety for the individual studies.

d. While coding using a single MedDRA version would be preferable, your plan to present data from individual studies using MedDRA versions in which the database was locked for each individual study may be acceptable. In your BLA, please include a discussion of any relevant adverse event analyses that may have been impacted by the use of differing versions of MedDRA. For example, identify any preferred terms reported in your studies that would have been coded differently based on the MedDRA version.

Discussion: *Regarding FDA response for 13b, Pfizer confirmed understanding of FDA's request, and stated that the data from studies CP-4-006 and CP-4-004 will not be combined. FDA stated that if Pfizer wants to pool any data, they should get FDA feedback.*

Pfizer also sought clarification on how this applies to the main study and the extension study. FDA stated that they would like to see the data separately for the main study and for the extension open-label periods.

Pfizer requested clarification on the content of ISE and ISS for submission. FDA clarified that the ISE and ISS are required modules for the BLA submission. However, the sponsor should not interpret ISE or ISS as analyses that must be based on simply pooled data. The ISE and ISS should generally provide an overview of results from relevant studies by examining study-to-study differences in results and discussing how these studies collectively support the efficacy and safety of the proposed product.

Question 14: *Does the Agency agree that the planned analyses are sufficient to evaluate the overall safety profile of MOD-4023?*

In particular, please comment on the adequacy of the following:

a. Proposed MedDRA queries for the events of special interest
b. Proposed definitions for subgroup analyses

FDA Response to Question 14: **The planned analyses appear sufficient to evaluate the overall safety profile. Refer also to the response to Question 13.**

a. You primarily selected the AEs of special interest (AESIs) from the class-based potential or identified risks related to somatropin-containing products, and the selected AESIs include: glucose metabolism impairment, thyroid function impairment, cortisol changes, intracranial hypertension, neoplasia, intracranial hemorrhage, intracranial aneurysm, immunogenicity, injection site reactions, and consecutive IGF-1 SDS >2. Consider also including slipped capital femoral epiphysis and pancreatitis as AEs of special interest. We recommend that you use a single MedDRA version for the proposed analysis. Please see also the response to Question 13.d

b. Your definitions for subgroups appear acceptable. However, we recommend you conduct subgroup analyses for Study CP-4-006 and Study CP-4-004 separately. Also see our response to Question 13b.

Discussion: *No discussion occurred.*

Question 15: *The Applicant plans to provide a complete textual presentation of the safety data analyses in Module 2.7.4, Summary of Clinical Safety. The Integrated Summary of Safety (ISS) in Module 5.3.5.3 will contain supportive tables, listings and figures with hyperlinking between the 2 modules as appropriate. Does the Agency agree with this approach?*

FDA Response to Question 15: **Your proposed approach to provide textual presentation of safety data analyses in SCS and supportive tables, listings and figures in ISS is acceptable.**

Discussion: *No discussion occurred.*

Question 16: *The Applicant proposes to include case report forms (CRFs) and narratives for all serious adverse events (SAE)s, deaths, discontinuations due to AEs, non-serious AEs of special interest, and pregnancies for all completed and ongoing MOD-4023 clinical studies. Does the Agency agree with the proposed narrative plan and that the presentation of safety narratives for the MOD-4023 studies supports the safety review of the planned BLA?*

FDA Response to Question 16: **Your proposed plan for CRF and narratives appears reasonable to support BLA submission.**

Discussion: *No discussion occurred.*

Question 17: *The Applicant intends to provide listings of deaths, non-fatal SAEs and adverse events (AEs) leading to discontinuation for the 4-Month Safety Update (4MSU). Does the Agency agree that this is sufficient scope for the 4MSU?*

FDA Response to Question 17: **No, we do not agree with providing death, SAEs and AEs leading to discontinuation in listings format only. In addition to listing, we request you to include narratives for all deaths, serious adverse events, and adverse events leading to discontinuation from the pediatric clinical development program in the 4-Month Safety Update.**

Discussion: *Pfizer will provide the narratives as requested.*

2.5. Immunogenicity Assessments

Question 18: *Does the Agency agree that the proposed summary and presentation of the immunogenicity assessments are sufficient to support review of the planned BLA?*

FDA Response to Question 18: **Overall your proposed immunogenicity assessment appears adequate to support review of the planned BLA. Refer also to the response to Question 12.**

Note that changes were recommended in guidance for Industry *Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection*[3] regarding the immunogenicity assessment section. For your BLA submission, include an Integrated Summary of Immunogenicity (ISI) that describes the totality of the ACP-011 immunogenicity program, as recommended in the Guidance Section

[3] https://www.fda.gov/media/119788/download

VIII Documentation. Submit the ISI report to eCTD Section 5.3.5.3 Reports of Analysis of Data from More than One Study. In the ISI include: summary of validated binding antidrug antibody assay (BADA) and neutralizing anti-drug antibody assays (NADA), the complete immunogenicity data set, information on the drug product lots administered to each patient, the BADA status and titers, the NADA status and the level of drug in each patient's test sample at the specific sampling point.

Discussion: *No discussion occurred.*

2.6. Datasets

Question 19: *Complete CSRs will be provided for the Phase 2 and Phase 3 studies of MOD-4023* (b) (4) (b) (4) *although Data Tabulation Datasets and Analysis Datasets and Programs for these studies will not be included in Module 5. Does the Agency agree with this approach?*

FDA Response to Question 19: **Your proposed approach for datasets presentation for the studies** (b) (4) **appears acceptable.**

Discussion: *No discussion occurred.*

2.7. Submission Format and Organization

Question 20: *Does the Agency agree with the proposed placement of information in the eCTD structure and that this appears acceptable and complete?*

FDA Response to Question 20: **From technical perspective (and not content related), the organization of information in the eCTD structure is acceptable.**

Discussion: *No discussion occurred.*

2.8. Bioresearch Monitoring (BIMO) Clinical Data

Question 21: *For BIMO inspections of clinical data for the planned BLA, the Applicant will provide the list of investigators, data listings and datasets for the Phase 3 registration study (CP-4-006). Does the Division agree that the proposed scope of the BIMO is adequate to support the clinical review of the planned BLA?*

FDA Response to Question 21: **Yes, the proposed scope to include the Phase 3 registration study CP-4-006 only regarding the requested information for BIMO inspections is acceptable.**

Discussion: *No discussion occurred.*

2.9. Regulatory/Administrative

Question 22: *It is the Applicant's understanding that since MOD-4023 has been granted orphan drug designation for the treatment of growth hormone deficiency, in accordance with 21 CFR 314.55(d) submission of a pediatric assessment is not required for the planned BLA, and that a waiver is not needed. Does the Agency agree?*

FDA Response to Question 22: **Yes, we agree. Please refer to section 4.0 PREA Requirements below.**

Discussion: *No discussion occurred.*

Additional Device Comments:

Device content for marketing application
Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications".

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1. **Device Description Documentation**

    a. **Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.**

    b. **Describe the principles of operation of your device.**

    c. **Describe any accessories or other devices labeled for use with your device.**

2. **Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the**

FDA Design Control Guidance for Medical Device Manufacturers[4]. We recommend that the design control information provided in your application include the following:

a. **Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)**

b. **Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)**

c. **Design Verification Plan/Summary Report, supporting data and traceability**

d. **Design Validation Plan/Summary Report, supporting data and traceability**

e. **Risk Management File**

3. **Essential Performance – Identify essential performance requirements (EPR) for the device.**

   For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. The final set of essential performance requirements should be based on your design control process. Further guidance on this topic is limited as your device design is not included. We are providing the following example EPRs for the two devices we believe you may be referencing. This is not an exhaustive list and product specific factors should influence your EPR selection.

   Example pen injector EPRs:
   - **Delivered Volume Accuracy**
   - **Injection Force**
   - **Injection Time (if applicable)**

   Please refer to guidance for industry and FDA staff: *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* for more details.

4. **Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may**

[4] https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf
U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.

5. **Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.**

6. **Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.**

7. **Quality System**
   The marketing application should contain a complete summary of your base operating system as described in guidance for industry and FDA staff: *Current Good Manufacturing Practice Requirements for Combination Products.*

Discussion: *No discussion occurred.*

Additional Combination Product Comments:

1. **Combination product manufacturing**

   Please note that Part 3 combination products are subject to 21 CFR Part 4 Current Good Manufacturing Practice Requirements for Combination Products[5]. Also refer to guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products*.

2. **eCTD Location of combination product information**

   For information on the location of device related information, see Section 5 of the agency eCTD Technical Conformance Guide: Technical Specifications Document: Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications November, 2018.

Discussion: *No discussion occurred.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

[5] https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

- The content of a complete application was discussed. The application is expected to be complete at the time of submission.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. There are no agreements for late submission of application components.

4.0 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

5.0 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[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

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.

6.0 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* (February 2018) and the associated *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*.[8]

7.0 NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

[8] 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/

LISA B YANOFF
01/15/2020 11:32:39 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 079745

MEETING MINUTES

CBR International Corp.
U.S. Agent for OPKO Biologics Ltd.
Attention: Jeanne M. Novak, PhD
CEO and Principal Consultant
2905 Wilderness Pl., Ste. 202
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MOD-4023 (CTP modified hGH injection).

We also refer to the meeting between representatives of your firm and the FDA on March 23, 2015. The purpose of the meeting was to discuss the design of a pivotal Phase 3 clinical trial to evaluate the safety and efficacy of MOD-4023 for the treatment of children with growth hormone deficiency (GHD).

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 Linda Galgay, Regulatory Project Manager, at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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:	March 23, 2015, 3:00 - 4:00 p.m. ET
Meeting Location:	Bldg. 22, Rm. 1415
Application Number:	IND 079745
Product Name:	MOD-4023 (CTP modified hGH injection)
Indication:	Treatment of children with growth failure due to inadequate secretion of endogenous growth hormone.
Sponsor:	OPKO Biologics Ltd. (OBL) (Israel)
U.S. Agent:	CBR International Corp.
Meeting Chair:	Jean-Marc Guettier, MD
Meeting Recorder:	Linda Galgay, RN, MSN

FDA ATTENDEES

Office of Drug Evaluation II, Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, MD	Director
Marina Zemskova, MD	Clinical Team Leader (Acting)
Ronald Wange, PhD	Pharmacology/Toxicology Supervisor
Federica Basso, PhD	Pharmacology/Toxicology Reviewer
Julie Van der Waag, MPH	Chief, Project Management Staff
Linda Galgay, RN, MSN	Regulatory Project Manager

Office of Translational Sciences, Office of Biostatistics

Mark Rothmann, PhD	Lead Mathematical Statistician, Division of Biometrics II
Cynthia Liu, MS	Mathematical Statistician

Office of Translational Sciences, Office of Clinical Pharmacology

Jaya Vaidyanathan, PhD	Team Leader (Acting), Division of Clinical Pharmacology 2
Johnny Lau, PhD	Clinical Pharmacology Reviewer

Office of Biotechnology Products, Division of Therapeutic Proteins (DTP)

Daniela Verthelyi, PhD	Supervisory Biologist, Laboratory of Immunology
Montserrat Puig, PhD	Reviewer, Laboratory of Immunology

Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis (DMEPA)

Yelena Maslov, PharmD	Safety Team Leader
Mishale Mistry, PharmD, MPH	Safety Evaluator

Office of Surveillance and Epidemiology/Division of Risk Management (DRISK)

Carolyn L. Yancey, MD	Senior Medical Officer

Office of Combination Products

Bindi Nikhar, MD	Associate Clinical Director

SPONSOR ATTENDEES

Jane Hsiao, PhD	Vice Chairman, OPKO Health, Inc.
Leanne Amitzi, MSc	Head of Clinical Affairs, OPKO Biologics Ltd.
Ronit Koren, PhD	Clinical Director, OPKO Biologics Ltd.
Gili Hart, PhD	General Manager, OPKO Biologics Ltd.
Oren Hershkovitz, PhD	General Manager, OPKO Biologics Ltd.
Rivka Zaibel	QA/RA Director, OPKO Biologics Ltd.
(b) (4)	(b) (4) Medical Consultant, OPKO Biologics Ltd.
(b) (4)	(b) (4) Pharmacometric consultant
Jose Cara	Medical Affairs Product Lead, Rare Disease, Global Medical Affairs; Global Innovative Pharma Business, Pfizer Inc.
Iwona Jeske DuPont	Global Regulatory Portfolio Lead, Worldwide Safety & Regulatory GIPB – Regulatory – Rare Disease, Pfizer Inc.
Amanda Matthews	Pharmaceutical Sciences, Global CMC, Pfizer Inc.

1.0 BACKGROUND

OPKO Biologics Ltd. (OBL) is developing MOD-4023 (CTP-modified hGH injection), a long-acting recombinant human growth hormone analog, for the treatment of children with growth failure due to inadequate endogenous growth hormone secretion (b) (4) (b) (4) MOD-4023 active substance is a single-chain polypeptide (rDNA origin) molecule whose amino acid sequence contains the 191 amino acid sequence of human growth hormone (hGH) and three copies of the CTP of the beta chain of hCG.

OBL proposes to demonstrate the efficacy and safety of MOD-4023 for use as a once weekly injection treatment for (b) (4) pediatric patients with GHD.

Clinical development is currently underway [redacted] for the treatment of children with growth failure associated with GHD [redacted]

The purpose of the March 23, 2015, meeting was to discuss the following:

- The design of a pivotal Phase 3 clinical trial to evaluate the efficacy and safety of MOD-4023 for the treatment of GHD in the pediatric population
- The overall clinical development plan [redacted] for the treatment of GHD in children
- The nonclinical development plan [redacted] for the treatment of GHD in children

The briefing document received February 9, 2015, provided the background and questions to be addressed at the meeting. Preliminary Comments were sent to OBL on March 10, 2015. OBL responded on March 20, 2015, via an email communication to the project manager.
On March 31, 2015, OBL submitted a copy of the March 20, 2015, email, sponsor's minutes, and the sponsor's slides from the March 23, 2015 meeting.

2.0 DISCUSSION

Questions are in regular text. Preliminary responses are in **bolded** text. Discussion is in *italicized* text. Additional comments are in **bolded**, *italicized* text.

2.1 NONCLINICAL

OBL Question 1:

Can the Agency confirm that the panel of completed non-clinical studies is adequate to support the planned Phase 3 pediatric study [redacted] for pediatric use of MOD-4023?

FDA Response to Question 1:
We agree that the nonclinical studies conducted are adequate to support the planned Phase 3 pediatric study [redacted] for pediatric use of MOD-4023. Significant changes in drug formulation or impurities may require additional nonclinical assessment.

OBL comment (March 20, 2015 email): Accept.

Discussion: *There was no discussion regarding Question 1.*

2.2 CLINICAL

OBL Question 2a:
Can the Agency comment on the design of the proposed clinical trial, specifically in regard to the duration of the pivotal study for [redacted] (b) (4) inclusion and exclusion criteria, the parameters for stratification, the timing of assessment of the primary endpoint, and the additional efficacy and safety parameters to be evaluated?

FDA Response to Question 2a:

i. **The study design (randomized, active control, open-label) is acceptable.**

OBL comment (March 20, 2015 email): Accept.

ii. **The inclusion/exclusion criteria are, in general, acceptable. However, we do not agree with** [redacted] (b) (4)

OBL comments (March 20, 2015 email): Agree. [redacted] (b) (4) The revised protocol will provide monitoring requirement and rescue criteria.

iii. **The proposed safety parameters to be evaluated in the Phase 3 study appear acceptable.**

OBL comment (March 20, 2015 email): Accept.

iv. **At this time, however, we are not convinced that 12 months of treatment is enough to evaluate the long-term safety and efficacy of the product. Your GH product is not an immediate-release GH. While there is ample efficacy and safety experience with recombinant immediate-release GH products which has been accumulated over three decades, this is not the case with continuous-release, long-acting GH products. Clarify how you plan to bridge short-term efficacy data (12 months) with long-term improvement including final height.**

Discussion regarding Question 2aiv:
The sponsor stated that MOD-4023 exerts the same mechanism of action as rhGH, and thus, the long-term safety and efficacy of MOD-4023 is expected to be the same as of daily rhGH. The sponsor also indicated that, based on the 12-month data from the Phase 2 study of MOD-4023 in children, the efficacy and safety of MOD-4023 administered weekly is comparable to the efficacy and safety of daily rhGH. (b) (4)

(b) (4)

The Division asked about comparability of the product used in the Phase 2 study with the product to be used in the Phase 3 study and the to-be-marketed product. The sponsor indicated that manufacturing process changes will be implemented for the Phase 3 and the to-be-marketed product. Details of the changes and characterization that these changes have on product quality attributes will be discussed during a separate CMC meeting with the Agency. The Division emphasized the importance of the need to adequately characterize differences between products used in Phase 2 and the product used in Phase 3 and the to-be-marketed product. The Division asked if the sponsor considered using blind switching between the products to compare the safety and efficacy of these products. The Division agreed that the adequacy of the bridging strategy should be discussed with the Agency during a future meeting.

OBL Question 2b: Does the Agency agree with the duration of 12 months safety and efficacy assessment of the pivotal study?

FDA Response to Question 2b:
Refer to the response to question 2a.

Discussion: *There was no discussion regarding Question 2b.*

OBL Question 2c: Does the Agency agree with the proposed safety assessment during the long term extension study as described in section 7.2 of the BP?

FDA Response to Question 2c:
The proposed safety assessment during the long-term extension study seems acceptable.

OBL comment (March 20, 2015 email): Accept.

Discussion: *There was no discussion regarding Question 2c.*

OBL Question 2d: Does the Agency have other comments regarding the design of the proposed Phase 3 study or the long term extension study?

FDA Response to Question 2d:
We have the following recommendations regarding the conduct of this Phase 3 trial:

i. **Use measurements of serum cortisol level as the test of choice for the evaluation of the status of the HPA axis during MOD-4023 treatment, because salivary cortisol is not a fully validated test.**

OBL comment (March 20, 2015 email): Accept.

ii. **Develop criteria for MOD-4023 dose discontinuation in the proposed study should IGF-I levels exceed +2 SDS on treatment and incorporate these criteria in the stopping rules of the study.**

Discussion regarding Question 2dii:

The sponsor stated that they do not plan to discontinue treatment with MOD-4023 in patients who have IGF-1 SDS values greater than 2 without clinical symptoms, indicating that clinical guidelines on the treatment of GHD in children do not recommend the discontinuation of treatment based solely on elevated serum IGF-1 levels. The sponsor also stated that multiple published clinical trials using daily rhGH demonstrated that approximately 30% of patients had IGF-1 SDS values greater than 2 at the end of the 2- year treatment period without clinical consequences (refer to slides 6-8). However, the sponsor also indicated that the dose will be reduced in those patients who have IGF-1 SDS values greater than 2. The sponsor plans to reduce the dose if the IGF-1 SDS value is greater than 3 on two consecutive measurements one month apart or if the IGF-1 SDS value is within the range of plus 2.5 to plus 3 on two consecutive measurements three months apart. The Division inquired as to whether it will be safe to allow patients not to have a dose adjustment earlier than the proposed time intervals between two identified high IGF-1 SDS values. The sponsor replied that the lab testing turn-around time is at least 2 to 3 weeks and that normally during that time the patient will grow into the dose. The sponsor also stated that results from the Phase 2 study demonstrated that IGF-1 peaks around day 2 post dosing and then declines before the next dose; no IGF-1 accumulation was observed in this study. When asked for the plan if the dose reduction does not decrease IGF-1 levels the sponsor stated that it is very rare that the dose reduction will not affect IGF-1 levels; the expectation is that 90% of patients will respond properly to the dose adjustments. The sponsor also indicated that occasionally such adverse events as persistent headaches and pains may lead to the discontinuation of GH treatment in the pediatric population; however, such cases are rare.

The sponsor will incorporate the dose titration scheme and discontinuation criteria in the final protocol.

iii. **Perform a baseline ophtalmoscopic evaluation in all patients prior to the first MOD-4023 dose administration.**

OBL comment (March 20, 2015 email): Accept.

Discussion: *There was no discussion regarding Question diii.*

iv. **Present bone age change vs. chronological change and/or bone age /chronological age ratio analyses as appropriate.**

OBL comment (March 20, 2015 email): Accept.

Discussion: *There was no discussion regarding Question 2div.*

OBL Question 2e: Since GHD in pediatric population is an orphan indication, does the Agency agree that the proposed Phase 3 clinical study in pediatric GHD patients can be sufficient to support licensure of MOD-4023 for treatment of growth failure in children due to growth hormone deficiency?

FDA Response to Question 2e:
Your proposal to submit data from a single Phase 3 trial (Study CP-4-006) is acceptable. The Phase 2 trial CP-4-004 can be regarded as supportive evidence of effectiveness. However, whether the results of the pivotal study will support approval of MOD-4023 for the treatment of children with the GHD indication depends on the quality of the data, the treatment effect size, and the overall safety profile, among others. Unanswered questions or residual uncertainties at the end of the review process may require additional data.

OBL comment (March 20, 2015 email): Accept.

Discussion: *There was no discussion regarding Question 2e.*

OBL Question 3:
Does the Agency agree with the dose selected for evaluation in the Phase 3 clinical trial?

FDA Response to Question 3:

i. **Your proposed dose of 0.66 mg/kg/week of MOD-4023 and 34 mcg/kg/day of Genotropin appear reasonable to be studied in the Phase 3 clinical trial to evaluate the efficacy and safety of MOD-4023. However, we recommend that you consider evaluating the efficacy and safety of an additional lower dose of 0.48 mg/kg/week of MOD-4023 in the proposed Phase 3 clinical trial in case any safety concerns arise with the 0.66 mg/kg/week dose.**

ii. **Provide the dose titration algorithm for the safety reasons.**

Discussion regarding Questions 3i and 3ii:
The sponsor acknowledged the Agency's recommendation regarding the utility of an additional dose (0.48 mg/kg/week) in the proposed Phase 3 trial. The sponsor further indicated that the final Phase 3 study design will be confirmed following the completion of the Phase 2 study. The sponsor provided the proposal for dose titration *(refer to slides 6-9 and to the discussion regarding Question 2dii).*

OBL Question 4a: Does the Agency agree with the proposed analytical approach to immunogenicity sample analysis?

FDA Response to Question 4a:
In general, we agree with the immunogenicity paradigm that you propose for the sample analysis. Regarding the immunogenicity assays, your justification for revalidating the assays (b) (4) is acceptable. The assays are in general adequate for the assessment of immunogenicity on the pediatric patients undergoing MOD-4023 treatment however the following comments should be addressed:

i. **Regarding the validation of your assay's robustness: provide data assessing the impact of parameters such as lipemia, hemolysis, and bilirubin content on the assay performance as recommended in the FDA immunogenicity guidance for industry "Assay development for Immunogenicity testing of therapeutic proteins", at http://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf.**

OBL comment (March 20, 2015 email): Accept.

Discussion: *There was no discussion regarding Question 4ai.*

ii. **We noticed that you established the cut point of the confirmatory assay considering (b) (4)% instead of 1% of false positive rate. This is not the recommended practice since it could lead to false negative results. Modify or justify.**

Discussion regarding Question 4aii:
The sponsor agreed to establish the cut point of the confirmatory assay considering a 1% false positive rate as currently recommended by the Agency.

iii. **We also noted an apparent gender bias in the confirmatory neutralization assay for hGH. Clarify whether the sensitivity of the assay is modified by the age, gender or hormonal status of the patients and adjust your controls accordingly.**

OBL comment (March 20, 2015 email): Accept.

Discussion regarding Question 4aiii:
The Agency discussed the gender bias observed in the validation of the confirmatory neutralization assay for hGH. The sponsor stated that the bias observed is unlikely to represent a true bias and committed to follow up possible positive samples for hGH NAb in the next Phase 3 studies and investigate the cause of the data bias if observed.

OBL Question 4b: Does the Agency agree with the proposed frequency and timing of sample collection for immunogenicity assessment during the pivotal and extension periods?

FDA Response to Question 4b:
No, we do not agree with the proposed serum sampling schedule for the proposed Phase 3 clinical studies. Your early studies indicated that MOD-4023 elicits an immune response in a large fraction of the pediatric patients. Understanding the natural history of the antibody response and pairing antibody responses with safety and efficacy data will be important at the time of evaluating your product. For the pivotal studies, sample at 10-14 days, at 1 month and then at month 3, 6, 9, and 12 months. In addition, increase the testing frequency at least during the first year of the extension study to every 3 months.

OBL comments (March 20, 2015 email): Agree. The pivotal protocol will be modified as suggested to, sample at 10-14 days, at 1 month and then at month 3, 6, 9, and 12 months. The testing frequency for the extension study will be every 3 months during the first year of the extension study.

Discussion: *There was no discussion regarding Question 4b.*

OBL Question 5:
Does the Agency agree that the proposed size of the safety database in children is adequate for submission (b) (4)

FDA Response to Question 5:
(b) (4)

Discussion: *There was no discussion regarding Question 5.*

2.3 CLINICAL STATISTICAL

OBL Question 6a: Does the Agency agree with the proposed approach to assessing the non-inferiority of MOD-4023 compared to Genotropin?

FDA Response to Question 6a:
No, we do not agree. The Division's efficacy standard uses a two-sided significance level of 0.05. Non-inferiority in this context will be established when the lower bound of the two-sided 95% CI (not one-sided as stated in your briefing package) for the treatment difference (MOD-4023 minus r-hGH) is greater than a pre-specified margin.
The primary efficacy analysis population should follow the intention-to-treat principle and comprise all randomized patients. All patients should be followed for their heights through 12 months and all data should be used regardless of adherence to therapy or study protocol. Considerable efforts should be made in order to avoid any missing data since a sizable amount of missing data will impact our confidence in study findings. The primary analysis methodology should take missing data into consideration.

See the 2010 report on missing data by the National Academy of Sciences, "The Prevention and Treatment of Missing Data in Clinical Trials," for additional discussion. A version of the report can be found online at, http://www.nap.edu/catalog.php?record_id=12955.
Refer to the minutes from the March 11, 2013, End-of-Phase 2 meeting (b) (4) (b) (4)

In addition, missing data may attenuate differences, thus making it easier to conclude non-inferiority when non-inferiority does not exist. The primary non-inferiority analysis should consider imputation under the non-inferiority null (see page 341 of Koch Stat Med. 27, 333-342, 2008). Sensitivity analyses should study limitations of the data. For each sensitivity analysis, a description should be provided as to what limitation(s) of the data or assumption(s) of the primary analysis is/are being evaluated and how the sensitivity analysis achieves this. The most appropriate analysis in describing the treatment effect will be a review issue.

The informed consent forms must clearly differentiate treatment discontinuation from study withdrawal, and we recommend that the forms also include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early.

OBL Question 6b: Does the Agency agree that the proposed sample size is adequate to assess the non-inferiority of MOD-4023 to r-hGH?

FDA Response to Question 6b:
Your sample size calculation seems to be based (b) (4)

Re-calculate the sample size based on a two-sided alpha of 0.05 with various power assumptions.

OBL comments regarding Questions 6a and 6b (March 20, 2015 email):
Primary Analysis
OBL accepts the FDA's suggestion to use a two-sided significant level of 0.05 and will amend the sample size accordingly. We seek clarification on methods of handling missing data. We expect the missing data to be missing at random and that a mixed models approach for modeling growth curve would be appropriate. Additional approaches include: LOCF, imputation (either for each patient or for all patients pooled) based on predicted patient growth curves, or a logistic regression model based on propensity score for each patient.
We would appreciate feedback if the Division recommends a preferred method of handling missing data. A detailed Statistical Analysis Plan will be submitted to the Division for review and approval once the protocol is finalized.

Discussion: *There was no discussion regarding Questions 6a and 6b.*

OBL Question 6c: Can the Agency comment on the proposed interim analysis to evaluate the need for a larger sample size in the event that the variability in response to treatment is greater than anticipated?

FDA Response to Question 6c:
Sample size re-estimation must be in a blinded fashion, i.e., no interim efficacy results should be communicated to the sponsor and investigators.

OBL comments regarding Question 6c (March 20, 2015 email):
Interim Analysis
Sponsor confirms that the statistician will perform the sample size re-estimation based on the observed standard deviation, using blinded data pooled across study groups. Neither the sponsor nor investigators will be informed of the efficacy data or individual patient data. We seek clarification whether the Division recommends the sample size increase to be pre-defined in the statistical analysis plan.

Discussion: *There was no discussion regarding Question 6c.*

2.4 CLINICAL PHARMACOLOGY

OBL Question 7a: Does the Agency agree that the provided information is adequate to support the BLA of MOD- 4023 and no further DDI studies are needed?

FDA Response to Question 7a:
Your literature review of drug interaction pertains to human growth hormone. However, MOD-4023 is a C-terminal peptide modified human growth hormone and a different molecular entity from human growth hormone. Also, the disposition of MOD-4023 is not characterized. Conduct in vitro drug-drug interaction studies to rule out significant interactions between MOD-4023 and other drugs known to be cytochrome P450 substrates. Also monitor the patients who will receive concomitant medications that are cytochrome P450 substrates in the proposed Phase 3 trial for any safety concerns.

Additional clinical studies may be necessary based on the outcome of the in vitro studies and the proposed Phase 3 trial.

OBL comments (March 20, 2015 email):
Agree. An in-vitro drug-drug interaction study will be conducted to rule out significant interactions between MOD-4023 and other drugs known to be cytochrome P450 substrates. OBL will also monitor the patients who receive concomitant medications that are cytochrome P450 substrates in the proposed Phase 3 trial for any safety concerns.

Discussion: *There was no discussion regarding Question 7a.*

OBL Question 7b: Can the Agency confirm that no additional clinical pharmacology studies are needed to support BLA of MOD-4023?

FDA Response to Question 7b:

i. **Ascertain that the clinically-tested formulation of MOD-4023 for the pivotal efficacy/safety trial is identical to the to-be-marketed (TBM) MOD-4023 formulation. Otherwise, you will have to address the bioequivalence between these two formulations before final regulatory submission of MOD-4023.**

Discussion regarding Question 7bi: *Refer to the discussion regarding 2.6 DEVICE.*

ii. **Address the effect of renal impairment on the exposure of MOD-4023 before the final regulatory submission. Renal excretion may likely be a key route of elimination for MOD-4023 since its molecular weight is about 32 kDa and thus filterable by the glomerulus.**

Discussion regarding Question 7bii (refer to slides 12-13):
The sponsor responded that although the measured molecular weight of MOD-4023 is approximately 38 kDa, the apparent molecular weight is substantially higher. The sponsor is planning to submit the molecular weight information to the IND. OBL speculated that as MOD-4023 is highly glycosylated and this increases the hydrodynamic volume, the renal excretion will be minimal. The sponsor further stated that all the patients participating in the proposed trial will have a normal renal function (based on calculated eGFR). The Agency recommended that the sponsor include the justification at the time of the BLA submission.

iii. **The need of a thorough QT/QTc study is being discussed internally and will be communicated at a later time.**

OBL comments (March 20, 2015 email): Noted. Sponsor would appreciate if additional guidance based on FDA internal discussions on QTc is included as part of the Minutes.

Discussion: *There was no discussion regarding Question 7biii.*

Post-meeting note:
The Agency agrees that no thorough QT study (TQT) is required for your product at this time. However, collect ECG in all the ongoing Phase2 and Phase 3 studies at the time when the maximum plasma concentrations (Cmax) of your product are expected. Confirm that you are collecting ECG at the time of Cmax in these studies or modify the study(s) protocol accordingly.

2.5 REGULATORY

OBL Question 8a:
Can the Agency provide feedback on the suggested abbreviated clinical development plan for (b) (4)

FDA Response to Question 8a:
We cannot provide comments regarding the proposed study (b) (4) We need to review additional data from your clinical program prior to answering this question. Refer to the comments made in response to Clinical Question 2a.

OBL Question 8b: Would the Agency permit licensure of MOD-4023 (b) (4) (b) (4) based on proof of concept established in Phase 3 studies in GHD (b) (4)

FDA Response to Question 8b:
Questions regarding the licensure of MOD-4023 (b) (4) are premature at this time. We would like to review the results of the Phase 3 program before discussing specifics of the future clinical program for MOD-4023. Refer to the comments made in response to Clinical Question 2a.

(b) (4)

OBL comments regarding Questions 8a and 8b (March 20, 2015 email): Sponsor will seek additional FDA interaction (b) (4)

Discussion: *There was no discussion regarding Questions 8a and 8b.*

2.6 DEVICE

Additional Comments

Your MOD-4023 (CTP modified hGH injection) drug product proposed to be used with a pen-device injector would be a drug-device combination product subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at: https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products.

Pursuant to your briefing package, an open-label multi-dose actual use study is being proposed to support licensure of the autoinjector to deliver MOD-4023.

There is concern that as such, the proposed combination product is not being used in pivotal clinical trials, and there is inadequate bridging data to support use of the autoinjector. Ideally, the final TBM combination product should be used in pivotal Phase 3 clinical trials. In addition, the final TBM combination product and its Instructions for Use (IFU) should be assessed in Human Factors validation studies conducted prior to pivotal clinical trials; this helps assure safe and effective use of a validated combination product in these trials. Human Factors studies should include representative pediatric age groups that may be expected to self-inject, as well as caregivers and healthcare providers. Additionally, given that you intend to seek approval for MOD-4023 (b) (4) ***Overall, Human Factors and pivotal clinical studies should be in keeping with anticipated labeling for the proposed combination product. Details regarding Human Factors studies are provided below.***

Given the above, in lieu of the proposed open-label, multi-dose actual use study that assesses use of the autoinjector, the final TBM drug-device combination product needs to be used in the pivotal Phase 3 clinical trial in pediatric patients, i.e., Study CP-4-006.

Provide details regarding the autoinjector. The details you provide will be discussed in conjunction with CMC issues in a separate Type C meeting.

Human Factors studies:

i. ***We recommend reviewing the following Human Factors Guidance documents to help you understand what the Agency is looking for in terms of Human Factors testing:***

- ***Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm***

- ***Applying Human Factors and Usability Engineering to Optimize Medical Device Design, available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm***

- ***Safety Considerations for Product Design to Minimize Medication Errors, available online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf***

ii. Submit your draft protocol in advance for our review and evaluation in order to ensure that your methods and the resulting data will be acceptable.

OBL comments regarding 2.6 DEVICE Additional Comments and Question 7bi (March 20, 2015 email):
Agree. It is our intent that the Human Factors draft protocol for the Summative Validation of the TBM product ahead of licensure of the product will be submitted for review.

The Sponsor's current intention is to initiate the pivotal study with the to-be-marketed (TBM) drug-device combination product. An appropriate formulation is being developed with the aim to support multi-dose requirements and enable drug product storage at 2-8 °C (intended formulation of the commercial product). A multi-use pre-filled pen is being selected and will represent the intended combination product for the commercial product. We intend to complete Handling Studies prior to Phase 3 initiation. Lastly, a real use evaluation is planned as part of a sub-study of the proposed pediatric Phase 3 trial.

- The existing (Combination Product) Guidances do not fully address real use evaluation. Our understanding is that collecting user experience in a proportion of patients in the Phase 3 trial would be satisfactory, and would appreciate discussion at the Clinical EOP2 Meeting to confirm participant numbers for the Phase 3 use / evaluation.

Further details relating to this product will be provided in conjunction with the separate EOP2 CMC meeting request as well as the plan for Human Factor / IFU development.

- We appreciate the guidance already provided in the preliminary comments on device and human factors considerations. In addition, it would be useful for planning to understand requirements for expected bridging studies in the alternative scenario if the device had to be studied in parallel with (not as part of) a pivotal Phase 3 study.

Discussion regarding 2.6 DEVICE:
At the meeting, the sponsor proposed options for introducing the device into the clinical development program, but overall the sponsor's strategy was not clear.

The Agency reiterated its strong recommendation that the final to-be-marketed version of the drug and device parts of the drug-device combination product be used in pivotal clinical trials, preferably after the device has been validated in summative Human Factors studies. This allows for the most robust assessment of the safety and efficacy of the combination product, and characterizes in-use device malfunction and other device-related adverse events.

If the sponsor intends that once marketed patients self-inject at home, the clinical development plan should address this.

No agreements between the sponsor and the Agency regarding the above were reached at the meeting; however, based on the meeting discussion, the sponsor will submit a proposal for review prior to initiating pivotal clinical trials. In addition, the sponsor acknowledged that it will submit device details during a separate Type C meeting.

Post-meeting note:

Patient self-injection at home in appropriate age groups should be assessed by having representative patients self-inject throughout the duration of the clinical trial, or a major duration of the trial after initial injections have been conducted under supervision of a health-care provider. If this is not possible, self-injection could be assessed in a proportion of patients that could be rolled over from the pivotal clinical trial into the open-label extension study. For the latter scenario, provide rationale, and propose the number of patients to be included in the open-label study.

2.7 RISK EVALUATION AND MITIGATION STRATEGY

Additional Comments
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of CTP modified hGH injection outweigh the risks, and if it is necessary, what the required elements will be. It will be important to consider the benefit-risk profile of CTP modified hGH injection for the proposed new indication for the treatment of children with growth failure due to GHD.

Discussion: *There was no discussion regarding 2.7 RISK EVALUATION AND MITIGATION STRATEGY.*

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

5.0 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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

6.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

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).

A. **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).**

Include the following information in a tabular format in the license application for each of the completed pivotal clinical trials:
Site number
Principal investigator
Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

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.

Include the following information in a tabular format, by site, in the license application 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

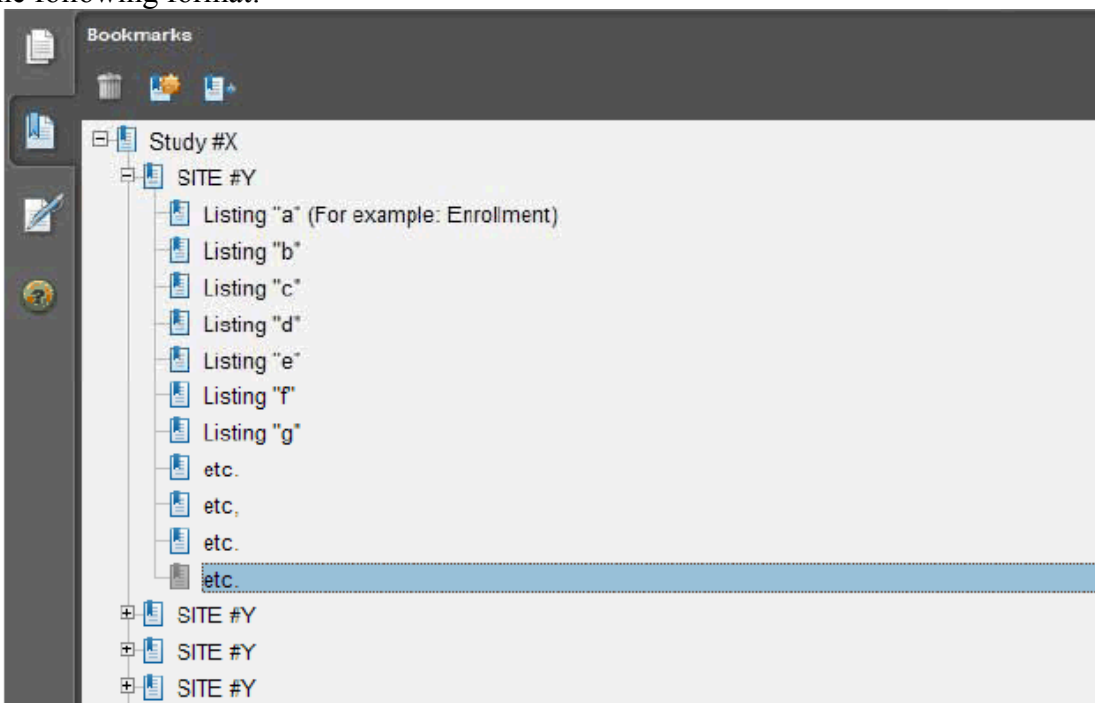
1. Include the following information in a tabular format in the license application for each of the completed pivotal clinical trials:
    a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability 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.

2. 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).
3. 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).

B. 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:



C. 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.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

JEAN-MARC P GUETTIER
04/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 79745

MEETING MINUTES

CBR International Corporation
Agent for PROLOR-Biotech Ltd.
Attention: Judy Ruckman, PhD
2905 Wilderness Place, Suite 202
Boulder, CO 80301

Dear Dr. Ruckman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MOD-4023 (CTP modified hGH injection).

We also refer to the meeting between representatives of your firm and the FDA on March 11, 2013. The purpose of the meeting was to discuss questions related to:

1. Design of a Phase 3 clinical trial to evaluate the efficacy and safety of MOD-4023
2. Adequacy of the overall clinical development plan
3. Adequacy of the nonclinical development plan
4. Manufacture and testing of the Phase 3 clinical trial material
5. Regulatory requirements for submission of a Biologics License Application (BLA).

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 Linda Galgay at (301) 796-5383.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	Monday, March 11, 2013, 1:00 – 2:00 pm ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 79745
Product Name:	MOD-4023 (CTP modified hGH injection)
Indication:	Treatment of growth hormone deficiency (b) (4)
Sponsor Name/Agent:	PROLOR-Biotech Ltd. (PROLOR)/CBR International Corporation
Meeting Chair:	Mary Parks, MD
Meeting Recorder:	Linda Galgay, RN, MSN

FDA ATTENDEES

Office of New Drugs – Therapeutic Biologics and Biosimilars Team

Leah Christl, PhD	Associate Director for Therapeutic Biologics

Office of Drug Evaluation II, Division of Metabolism and Endocrinology Products

Mary Parks, MD	Director
Dragos Roman, MD	Clinical Team Leader
Marina Zemskova, MD	Clinical Reviewer
Todd Bourcier, PhD	Pharmacology/Toxicology Supervisor
Federica Basso, PhD	Pharmacology/Toxicology Reviewer
Julie Marchick, MPH	Chief, Project Management Staff
Linda Galgay, RN, MSN	Regulatory Project Manager

Office of Translational Sciences, Office of Biostatistics

Jon T. Sahlroot, PhD	Deputy Director, Division of Biometrics II
Cynthia Liu, MS	Mathematical Statistician

Office of Translational Sciences, Office of Clinical Pharmacology

Immo Zadezensky, PhD	Team Leader, Division of Clinical Pharmacology 2
Zhihong Li, PhD	Clinical Pharmacology Reviewer

Office of Business Informatics / eData Management Solutions

Douglas Warfield, Ph.D.	Interdisciplinary Scientist

Office of Biotechnology Products, Division of Therapeutic Proteins (DTP)

Susan Kirshner, PhD	Associate Chief, Laboratory of Immunology,
Montserrat Puig, PhD	Reviewer, Laboratory of Immunology

PROLOR-BIOTECH LTD ATTENDEES (PROLOR)

Abraham Havron, PhD	CEO, PROLOR-Biotech Ltd.
Eyal Fima, PhD	COO, PROLOR-Biotech Ltd.
Leanne Amitzi, MSc	Director, Clinical Affairs, PROLOR-Biotech Ltd.
Gili Hart, PhD	Director, Preclinical, PROLOR-Biotech Ltd.
Rivka Zaibel	QA/RA Consulting Director, PROLOR-Biotech Ltd.
Ronit Koren, PhD	Clinical Consulting Director, PROLOR-Biotech Ltd.
Oren Hershkovitz	Director, CMC Operations, PROLOR-Biotech Ltd.
(b) (4)	Clinical Consultant, (b) (4)
Jeanne Novak, PhD	Principal Consultant, CBR International Corp.
Judy Ruckman, PhD	Senior Consultant, CBR International Corp.
Miles Brennan, PhD	Scientific Consultant, CBR International Corp.
Jennifer Schlegel, PhD	Scientific Consultant, CBR International Corp.
Jessica Egner, BS	Technical Associate, CBR International Corp.

1.0 BACKGROUND

PROLOR-Biotech Ltd. (PROLOR) is developing MOD-4023, a long-acting recombinant human growth hormone analog, (b) (4) for treatment of children with growth failure due to inadequate endogenous growth hormone secretion.

PROLOR has stated that MOD-4023 is designed to enable fewer injections than is currently needed for other hGH products (b) (4) (b) (4) The product consists of hGH fused to three copies of the C-terminal peptide (CTP) of the beta chain of human Chorionic Gonadotropin (hCG): one copy at the N-terminus and two copies (in tandem) at the C-terminus.

(b) (4)

The FDA and PROLOR have met twice previously during the development of MOD-4023. The PIND Meeting was held on December 10, 2007. The September 13, 2011, Type C meeting, addressed the design of the initial Phase 2 clinical trial in pediatric patients with GHD, the design and validation of the immunogenicity test methods, the scope of nonclinical testing (b) (4) (b) (4) and the firm's questions related to product manufacturing and testing.

The purpose of the March 11, 2013, meeting was to discuss questions related to:

A. Design of a Phase 3 clinical trial to evaluate the efficacy and safety of MOD-4023
B. Adequacy of the overall clinical development plan
C. Adequacy of nonclinical development plan
D. Manufacture and testing of the Phase 3 clinical trial material
E. Regulatory requirements for submission of a Biologics License Application (BLA)

Preliminary comments were sent to PROLOR via email on March 4, 2013.

In a March 7, 2013, email to the project manager, PROLOR requested that the following responses form the basis for discussion at the meeting:

1. FDA response to question #3b, item ii (rationale for IGF-I sampling time points)
2. FDA response to question #3b, item iii (immunogenicity sampling plan)
3. Additional comments on clinical pharmacology (interaction with P450)
4. FDA response to question #9 (proposed specifications)
5. FDA response to question #1a (Phase 3 sample size)
6. Additional comments on clinical statistics
7. Additional comments on data standards for studies
8. FDA response to question #8 (comparability of Phase 3 clinical trial material).

PROLOR submitted their version of the meeting minutes on March 22, 2013.

2.0 DISCUSSION

Questions are in regular text. Preliminary responses are in **bolded** text. Discussion is in *italicized* text. Additional comments are in **bolded**, *italicized* text.

2.1. CLINICAL

(b) (4)

2.2. NONCLINICAL

Question 7: PROLOR has completed a panel of nonclinical studies addressing MOD-4023 local, systemic, reproductive and developmental toxicity, as well as in vitro studies of hGH receptor binding, intracellular signaling, and potential off-target binding. The company has also submitted a report addressing potential interference by MOD-4023 in pregnancy tests that rely on detection of the beta subunit of hCG. A list of the completed and ongoing nonclinical studies is provided in the meeting briefing package.

In minutes from a Type C meeting held on 13 September 2011 (response to Question 6, page 8 of 11), the Agency indicated that the nonclinical study package appeared to be adequate to support a license application for MOD-4023, barring any significant changes in product quality or unexpected results in nonclinical and clinical studies. To date, no unexpected results have been observed.

Does the Agency concur that the nonclinical study package is adequate to support a license application for MOD-4023?

FDA Response to Question 7: **Yes, we agree that the nonclinical studies completed to date and the planned pre- and post-natal development study in rats are adequate to support a license application for MOD-4023.**

Discussion regarding Question 7:
Question 7 was not discussed at the meeting.

2.3 CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

(b) (4)

Additional CMC discussion:

We recommended that you meet with the Office of Compliance Biotech Manufacturing and Assessment Branch (BMAB) during Phase 3. BMAB is responsible for facilities evaluation, bioburden control (including hold time qualification studies), and most aspects of shipping validation.

2.4 REGULATORY

Question 11: PROLOR acknowledges the Agency's request for submission of a Pediatric Study Plan (reference End of Phase 2 Meeting Request Granted letter, dated 18 December 2012), required under the Pediatric Research Equity Act (PREA) as amended by the FDA Safety and Innovation Act of 2012. The Sponsor notes that the requirements of PREA are not applicable to product submissions seeking licensure for an orphan indication (21 USC 355(c)(k)), as in the case of MOD-4023 (reference Office of Orphan Products Development response to Designation Request #10-3134, dated 29 September 2010). Nevertheless, PROLOR is actively pursuing development of MOD-4023 in the pediatric population (b) (4)

Does the Agency agree that PROLOR is not required to submit a Pediatric Study Plan or to request a waiver or deferral of the pediatric study requirements under PREA (b) (4) (b) (4)

FDA Response to Question 11: **Indications that have received orphan designation do not trigger PREA. You do not need to submit a pediatric study plan or to request a waiver or deferral of the pediatric study requirements under PREA.**

Discussion regarding Question 11:
Question 11 was not discussed at the meeting.

Additional regulatory comments: ***It should be noted that a BLA submitted under section 351(a) of the PHS Act must contain all required data and information necessary to demonstrate the safety, purity, and potency of the proposed biological product. A BLA submitted under section 351(a) of the PHS Act is a "stand-alone" application and may not rely on published literature describing studies of other biological products to fulfill a requirement for licensure.***

Discussion regarding additional regulatory comments:

We restated that a BLA is a "stand-alone" application and may not rely on published literature to fulfill a requirement for licensure.

2.5 CLINICAL STATISTICS

Additional statistical comments for the Phase 3 Pivotal Trial:

A. The primary efficacy analysis model should include terms for any factors used to stratify the randomization.

Discussion regarding statistical comment (A):
You agreed to incorporate any factors used to stratify the randomization and also include baseline as a covariate.

B. All efficacy endpoints, primary and secondary, should be tested at a two-sided significance level. You should apply type I error control to address any / all statistical statements intended for the product label including secondary endpoints and statements generated by secondary hypotheses. This procedure will provide us some assurance that a result being considered for labeling can be attributed to the drug and is not due to chance. However, the content of the final label is ultimately a review issue.

Discussion regarding statistical comment (B):
Statistical comment B was not discussed at the meeting.

C. The proposed primary efficacy analysis population is essentially a completers population. You must use a primary efficacy analysis population that includes all patients who are randomized and have at least one post-randomization measurement of the primary endpoint (not just completers). This analysis population will likely include patients with missing data. Therefore, you should use a primary analysis methodology that accounts for missing data. Please note that the Last Observation Carried Forward (LOCF) method for imputing missing values is discouraged by the Division following the 2010 publication of the National Academy of Sciences (NAS) report on missing data, The Prevention and Treatment of Missing Data in Clinical Trials. The FDA commissioned this report. The report states "The panel believes that in nearly all cases, there are better alternatives to [LOCF]…which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects". A version of the report can be found online at http://www.nap.edu/catalog.php?record_id=12955.

Discussion regarding statistical comment (C):
We clarified that the NAS report is not official FDA guidance but does represent the Division's current thinking on missing data. We stated that a guiding principle for the imputation of missing data from the NAS report is to impute outcomes for missing data that are generally unfavorable to the test drug. Mixed model repeated measure analysis was given as an example for use as the primary analysis method. You were also advised that analyses based on LOCF for missing data and analyses based on completers population can be used as supportive analyses.

We stated that the Agency is currently drafting a guidance on missing data. It is not known at this time when the guidance will be finalized.

2.6 CLINICAL PHARMACOLOGY

Additional clinical pharmacology comment and request: ***It has been shown in literature that somatropin may interact with cytochrome P450. Justify why you have not planned to address this drug-drug interaction potential in your development program.***

Discussion regarding additional clinical pharmacology comment and request:
We stated that other somatropin product labels included literature information regarding somatropin interaction with cytochrome P450 substrates. You were advised to conduct a literature review on the drug-drug interaction potential, summarize the findings, and provide a justification as to why a drug-drug interaction study is not necessary. You were encouraged to submit the literature review prior to the submission of the application. We clarified that literature results cannot take the place of necessary data or studies in a BLA submitted under 351(a) of PHS Act.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Discussion regarding data standards for studies:

You indicated that you plan to use Clinical Data Interchange Standards Consortium (CDISC) models to collect and represent your studies data for the BLA submission. The models mentioned include the Clinical Data Acquisition Standards Harmonization (CDASH) data collection methodology for case report form (eCRF/CRF) design and implementation of the CDISC models to include the data definitions (define.xml) and data models (Study Data Tabulations Model (SDTM), Standard for Exchange of Nonclinical Data (SEND), and Analysis Data Model (ADaM).

Post-meeting comments regarding data submission:

We prefer that sponsors submit datasets based on the Study Data Specifications version published at the time of submission (currently 2.0). However, in general, we accept datasets which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance, based on the timing of protocol design, protocol initiation, and data collection.

We expect sponsors to evaluate the risk involved converting study data collected to standardized data, if applicable. We prefer that sponsors submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario: decision rationale for not converting or decision rationale for converting. We expect that the sponsor's evaluation and rationale includes study data scientifically relevant to the application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017 guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. You should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. You should use the CDISC Technical Road Map to design end-to-end harmonized data standardization, including the CDASH standard for design and implementation of data collection instruments.

Our methodology and submission structure supports research study design, as indicated in the Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications and the Study Data Specifications. Our methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits.
You should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See SEND, SDTM and ADaM as referenced in Study Data Specifications). Study analyses datasets should be traceable to the tabulations datasets.

In addition, please reference the CDER Common Data Standards Issues Document for further information on data standardization in submissions.

Additional Links:
Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)
Study Data Standards Resources

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts.

Reference ID: 5200111

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

/s/

MARY H PARKS
04/09/2013