CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208171Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107331

MEETING MINUTES

Pharmacosmos A/S
c/o PAREXEL International
Attention: Elizabeth Ferguson
U.S. Agent
4600 East-West Highway, Suite 350
Bethesda, MD 20814

Dear Ms. Ferguson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Monofer® [Iron (III) Hydroxide Isomaltoside 1000 Complex].

We also refer to the meeting between representatives of your firm and the FDA on January 12, 2015. The purpose of the meeting was to discuss the proposed organization and content of the proposed NDA as well as a panel of questions related to clinical and CMC issues.

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

If you have any questions, call me at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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:	Pre-NDA
Meeting Date and Time:	January 12, 2015; 2:00 PM - 3:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 107331
Product Name:	Monofer® [Iron (III) Hydroxide Isomaltoside 1000 Complex]
Indication:	MONOFER (iron isomaltoside 1000) is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in adult patients with chronic kidney disease (nondialysis dependent and hemodialysis dependent).
Sponsor/Applicant Name:	Pharmacosmos A/S
Meeting Chair:	Kathy Robie Suh, MD, PhD
Meeting Recorder:	Jessica Boehmer, MBA

FDA ATTENDEES

Division of Hematology Products (DHP)
Edvardas Kaminskas, MD, Deputy Division Director
Robert Kane, MD, Deputy Director of Safety
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Min Lu, MD, MPH, Clinical Reviewer
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Clinical Pharmacology (OCP)
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader

Office of Biostatistics
Kyung Y. Lee, PhD, Statistical Reviewer

Division of Hematology Oncology Toxicology
Haw-Jyh Chiu, PhD, Supervisory Pharmacologist
Brenda Gehrke, PhD, Pharmacologist

Office of New Drug Quality Assessment
Janice Brown, MS, CMC Lead

Office of Pharmaceutical Science / Product Quality Microbiology
Robert Mello, PhD, Microbiologist

Office of Surveillance and Epidemiology (OSE)/ Division of Risk Management (DRISK)
Naomi Redd, PharmD, Acting Team Leader

SPONSOR ATTENDEES

Pharmacosmos A/S Attendees:
Kim Nordfjeld, PhD, Vice President, Quality and Regulatory Affairs
Lars Lykke Thomsen, MD, PhD, Vice President & Chief Medical Officer
Ruben Giorgino, MD, PhD, Director of Drug Development at Helsinn Healthcare
John Friend, MD, Senior Vice President R&D, Helsinn Therapeutics US Inc.

(b) (4)

1.0 BACKGROUND

The purpose of this meeting is to discuss the proposed organization and content of the proposed NDA as well as a panel of questions related to clinical and CMC issues.

Pharmacosmos is developing iron isomaltoside 1000 (Monofer) as an intravenous iron replacement product for the treatment of iron deficiency anemia in multiple patient populations. This pre-NDA meeting is intended to discuss iron isomaltoside 1000 (Monofer) as an intravenous iron replacement product for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (non-dialysis dependent and hemodialysis dependent).

Iron isomaltoside 1000 is a complex between iron and a carbohydrate moiety and consists of (b) (4) particles. The chemical name is Iron (III) hydroxide isomaltoside 1000α-D-Glucan, (1-6)-, reduced, reaction products with iron hydroxide (Fe(OH)3) (CA index name).

IND 107331 was submitted as a new IND on December 30, 2009 with a proposal for a phase 3 study. The IND was placed on full clinical hold January 28, 2010 due to insufficient safety

information to support the proposed study. The sponsor subsequently withdrew the Phase 3 protocol and submitted a protocol for a Phase 1 pharmacokinetic study and the clinical hold was removed on January 13, 2011. The Sponsor met with FDA on December 17, 2012 for an End-of-Phase 2 Meeting (Meeting Minutes dated December 19, 2012). The Sponsor requested that the Agency cancel the End-of-Phase 2 Meeting scheduled for February 4, 2014 for CMC and Non-clinical discussion, as they stated the Preliminary Comments dated January 31, 2014 adequately addressed their questions and the meeting was no longer deemed necessary.

FDA sent Preliminary Comments to Pharmacosmos A/S on January 8, 2015.

2. DISCUSSION

Question 1:

Does FDA agree that data from clinical trials of iron deficiency anemia in CKD, IBD, CIA. CHF, PP, and CABG can be pooled to develop an integrated summary of safety to support an indication for the treatment of iron deficiency anemia associated with CKD?

FDA Response to Question 1:

No. To evaluate the benefit and risk of iron isomaltoside 1000 for the proposed indication for the treatment of iron deficiency anemia in patients with CKD, you need to provide sufficient safety and efficacy data in patients with CKD in clinical trials. The safety data from other populations will be reviewed as additional safety data for the application. The proposed number of patients exposed in the CKD population (i.e., N=674) is insufficient to evaluate the hypersensitivity reactions of iron isomaltoside 1000 in this population. Also, considering the large size of the target population for the indication, the inclusion of both patients with non-dialysis dependent and dialysis dependent CKD, and several different dose and administration options, the proposed number of patients exposed in the CKD population is insufficient to establish adequate safety for labeling.

Discussion:

See Discussion of Question 2.

Question 2:

Assuming that there are no signals of concern arising out of the data, does FDA agree that the sample size for assessment of safety of iron isomaltoside 1000 compared to oral iron sulfate is sufficient?

FDA Response to Question 2:

No. See response to Question 1. The current sample size is insufficient to evaluate the risk of hypersensitivity reactions of iron isomaltoside 1000 for the proposed indication. We recommend you conduct a study to evaluate the risk of hypersensitivity reactions of iron

isomaltoside 1000 as compared to a currently approved intravenous iron product for the proposed indication and dose regimens. You should propose a sample size adequate to enable a safety comparison with other IV products. Considering the large size of the target population, you should propose a sample size sufficient to provide comparative safety data compared to a currently approved product. The needed sample size would likely be several thousand patients. Comparison to oral iron is not appropriate for safety evaluation.

Discussion:

The Sponsor expressed a desire to broaden the indication for initial NDA submission to two indications: (1) NDD-CKD and (2) IDA. There was extensive and wide ranging discussion on what would constitute an acceptable data package for the NDA (e.g., number of studies, number of patients needed for safety database). FDA commented that because of the large size of the target population, the availability of multiple approved products (i.e., other parenteral iron products) for the indications, and the known safety risks for these products (e.g, hypersensitivity/ anaphylaxis, cardiovascular), it is imperative that there be sufficient data on this risk for Monofer to allow a meaningful quantitation and assessment of that risk. The FDA stated that there would need to be a sufficient safety database for each indication. There would be a need for a large safety study for the IDA indication. There would need to be a sufficient study to support the dose for each population. The information must be adequate to allow meaningful benefit-risk evaluation for the product for the proposed indications. FDA commented that generally two adequate and well-controlled studies are needed for each indication and referred sponsor to guidance on demonstration of efficacy. Sponsor indicated they were aware of the guidance. FDA recommended that the sponsor should consider FDA concerns and advice and provide a proposal including rationale for the data package and include specific questions for written response. The Sponsor will consider FDA advice and provide a proposal and specific questions for written response.

Question 3:

Does FDA agree with the proposed approach to provide data from ongoing studies in postpartum hemorrhage and inflammatory bowel disease in the NDA and final study reports during the NDA review period prior to 90 days before the action due date?

FDA Response to Question 3:

See responses to Question 1 and 2. For the ongoing non-CKD studies, all available safety data should be submitted with the initial NDA submission and additional accrued safety data should be submitted in the 120-Day Safety Update.

Discussion:

No discussion occurred.

Question 4:

Does the Agency agree with the study grouping proposal and the pooling/integration of IBD, CKD, CIA, CHF, PP and CABG data based on defined exposure regimes for presenting safety results?

Is the proposal for presenting safety results as summarized in Table 2 and further analysis evaluating the effect of dose groups, subject characteristics (age group, sex, race and ethnicity), patient type, duration, region and other treatment conditions acceptable?

FDA Response to Question 4:

No. See responses to Question 1 and 2. Pooling for all patients with CKD and by dose regimen for these patients should be provided to evaluate the safety of iron isomaltoside 1000 for the proposed indication. Additional safety data in other populations should be presented separately for each patient population. You may pool all studies to evaluate the risk of hypersensitivity reactions and cardiovascular events of iron isomaltoside 1000 provided that these events are defined and collected in the studies.

Discussion:

See Discussion of Question 2.

Question 5:

Does FDA agree that interim safety data from the IDA-01 study be included in the NDA as a safety report separate from the ISS?

FDA Response to Question 5:

See responses to Question 1, 2 and 3.

Discussion:

No discussion occurred.

Question 6:

Does FDA agree that data from the observational study may be used to support the safety of iron isomaltoside 1000 in the treatment of iron deficiency anemia in patients with CKD?

FDA Response to Question 6:

Safety data from the uncontrolled observational study should not be considered as pivotal safety data for the proposed indication. The data should be submitted as additional safety information in the application.

Discussion:

No discussion occurred.

Question 7:

For the Integrated Summary of Efficacy, does FDA agree with the proposal:

- **to integrate/pool P-CKD-01, P-CKD-02 and P-CKD-03**
- **to integrate/ pool P-IBD-01 and P-IBD-02**
- **to present the results for CKD, IBD and CHF patients side-by-side?**

Is the proposal for further efficacy analysis evaluating the effect of dose groups, subject characteristics (age group, sex, race and ethnicity), duration, region and other treatment conditions acceptable?

Does FDA agree with the proposal to integrate efficacy data across all studies performed in iron deficiency anemia including CKD, IBD, CHF, and CIA?

FDA Response to Question 7:

No. Efficacy data and analysis should be presented by individual study for primary assessment of efficacy evaluation. Any additional analyses, such as pooled, would be considered supportive. Efficacy data from clinical trials in CKD population will be evaluated to determine efficacy of iron isomaltoside 1000 for the proposed indication.

Please provide statistical analysis plans.

Discussion:

No discussion occurred.

Question 8:

Does FDA agree that the proposal for dose/exposure response analysis sufficient to support the target dosing regimen for iron isomaltoside 1000?

FDA Response to Question 8:

No. See responses to Question 1 and 2. For the proposed dose regimens, you need to provide safety data to evaluate the risk of hypersensitivity reactions of iron isomaltoside 1000.
We do not agree with your proposal to integrate efficacy data across all studies performed in iron deficiency anemia including CKD, IBD, CHF, and CIA. For your proposed dosing regimen, you will need to provide sufficient dose justification information for each disease state. We do not have sufficient information to comment on the population PK analyses or what supportive information it will provide in the context of the exposure-response relationship. In addition, consider conducting integrated dose/exposure safety analyses using pooled data from all disease states.

Discussion:

See Discussion of Question 2.

Question 9:

Does the Agency find the proposed data submission format acceptable?

FDA Response to Question 9:

The proposed format is acceptable. Please put all the tabulation datasets (including SDTM and legacy data) under legacy folder since they are not completely CDISC SDTM compliant. Please ensure traceability from analysis data to tabulation data to eCRF.

Submit all the programs for study analysis data derivation and ISS/ISE analysis data derivation.

Discussion:

No discussion occurred.

Question 10:

Does FDA find the data submission package adequate and acceptable?

FDA Response to Question 10:

Yes, it is acceptable. Since tabulation data consists of SDTM data and legacy data, please place all of them under legacy folder with define.pdf. Reviewer's guides should include additional information/ explanation for all datasets, including legacy datasest. Please refer to Study Data Reviewer Guide at http://www.phusewiki.org/wiki/images/2/2d/SDRG_v1.1_2013-05-13.zip and ADaM Data

Reviewer Guide at http://www.phusewiki.org/wiki/images/2/2a/ADRG_V1.01_2014-05-20.zip

Discussion:

No discussion occurred.

Question 11:

Does FDA agree with the compliance requirement for submitted datasets and their metadata?

FDA Response to Question 11:

Yes, it is acceptable.

Discussion:

No discussion occurred.

Question 12:

Does FDA agree with the proposal to include an ISE with full text, tables, and datasets in module 5 of the eCTD, with text and abbreviated in-text tables of the main efficacy results in m2.7.3?

FDA Response to Question 12:

Yes. Also, see responses to Question 7. Full study report of each individual study with datasets should be submitted under Module 5.

You should also submit the program files and associated datasets for any population PK or PK-PD models conducted. Refer to the following guidelines regarding general expectations of submitting pharmacometric data and models: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

Discussion:

No discussion occurred.

Question 13:

Pharmacosmos intends to provide a Summary of Clinical Safety based on the CTD M4E Guidance for the Summary of Clinical Safety (m2.7.4). In addition, in m5.3.5.3, an Integrated Summary of Safety (ISS) will be provided. The format of the ISS will follow the same outline as m2.7.4. We intend to provide an ISS in the format of the clinical safety summary (m2.7.4).

Is this acceptable to the Agency?

FDA Response to Question 13:

Yes. The proposed sections are acceptable. Also, see responses to Question 1 and 2.

Discussion:

No discussion occurred.

Question 14:

Does FDA find the proposed recoding of Adverse Events, Concomitant Medications and Medical History data acceptable?

FDA Response to Question 14:

Clarify the coding system used in the studies. You need to use the most current version of MedDRA if recoding is needed.

Discussion:

No discussion occurred.

Question 15:

Is the proposal for the provision of listings as described above acceptable to the Agency?

FDA Response to Question 15:

Yes. The proposal is acceptable.

Discussion:

No discussion occurred.

Question 16:

Is the proposal for the provision of narratives as described above acceptable to the Agency?

FDA Response to Question 16:

Yes. You should also provide patient narratives for anaphylaxis reactions.

Discussion:

No discussion occurred.

Question 17:

Is the proposal for the provision of CRFs as described above acceptable to the Agency?

FDA Response to Question 17:

No. CFRs for SAEs and anaphylaxis reactions should also be provided.

Discussion:

No discussion occurred.

Question 18:

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Does FDA agree?

FDA Response to Question 18:

No. According to Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMPs), all NDAs are to be complete in the original submission.

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Discussion:

No discussion occurred.

3.0 OTHER IMPORTANT MEETING LANGUAGE

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.

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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

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

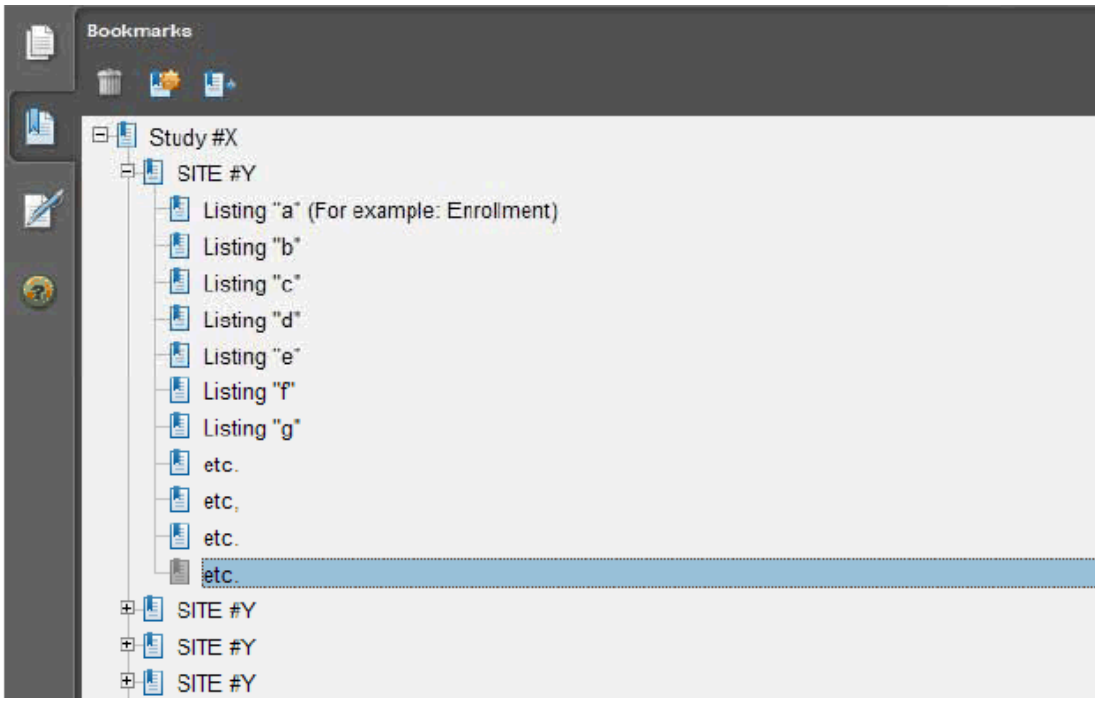
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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



III. Request for Site Level Dataset:

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

KATHY M ROBIE SUH
01/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107331

MEETING MINUTES

Pharmacosmos A/S
Attention: Donald P. Cox, Ph.D.
Vice President, Regulatory Affairs
ClinSmart LLC
2080 Cabot Boulevard West, Suite 201
Langhorne, PA 19047

Dear Dear Dr. Cox:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Monofer® [Iron (III) Hydroxide Oligosaccharide Complex].

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2012. The purpose of the meeting was to discuss the pre-approval safety assessment strategy and full clinical development program for Monofer® to support an indication for treatment of patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible.

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 Jessica Boehmer, Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, M.D., Ph.D.
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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:	December 17, 2012, 1:00 PM – 2:00 PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1417 Silver Spring, Maryland 20903
Application Number:	IND 107331
Product Name:	Monofer
Indication:	Treatment of patients with documented iron deficiency in whom oral iron administration is unsatisfactory, impossible, or where there is a clinical need to deliver iron rapidly
Sponsor/Applicant Name:	Pharmacosmos A/S
Meeting Chair:	Kathy Robie Suh
Meeting Recorder:	Jessica Boehmer

FDA ATTENDEES

Division of Hematology Products (DHP)
Edvardas Kaminskas, M.D., Deputy Director
Kathy Robie Suh M.D., Ph.D., Clinical Team Leader
Min Lu, M.D., Ph.D., Medical Officer
Karen Bengtson, B.A., Regulatory Project Manager
Jessica Boehmer, M.B.A., Regulatory Project Manager

Division of Hematology Oncology Toxicology (DHOT)
Haleh Saber, Ph.D., Pharmacology/Toxicology Supervisor
Brenda Gehrke, Ph.D., Pharmacology/Toxicology Reviewer

Office of New Drug Quality Assessment (ONDQA)
Janice Brown, M.S., CMC Lead
Joyce Crich, Ph.D., Review Chemist

Office of Biostatistics (OB), Division of Biometrics (DB)
Mark D. Rothmann, Ph.D., Statistical Team Leader
Kyung Yul Lee, Ph.D., Statistical Reviewer

Office of Surveillance and Epidemiology (OSE)
Kevin Wright, Pharm.D., Safety Evaluator
Cristina Makela, B.S., Team Lead, Project Management

SPONSOR ATTENDEES

Pharmacosmos A/S
Kim Nordfjeld Ph.D., Pharmacy Vice President, Quality and Regulatory Affairs
Lars Lykke Thomsen, M.D., Ph.D., Vice President & Chief Medical Officer
Claes Christian Stroem, M.D., Ph.D., Vice President Medical Affairs

(b) (4) [redacted]

(b) (4) [redacted]

1.0 BACKGROUND

The purpose of meeting is to:

- To allow FDA to review the full Clinical Development Plan for Monofer® aiming at continuing into Phase III in the USA
- To allow FDA to review the progress in the development of Monofer® in the treatment of iron deficiency.
- To obtain FDA endorsement of the full clinical development program for Monofer® for the US Market.

The chemical name of Monofer is Iron (III) hydroxide isomaltoside 1000 complex. The chemical structure of Monofer is proposed spheroidal matrix structure for Iron Isomaltoside 1000 in which iron atoms are bound and dispersed (approximately 10 iron atoms per Isomaltoside 1000 molecule).

IND 107331 was submitted as a new IND December 30, 2009. The IND was placed on full clinical hold January 28, 2010. A Meeting Request for an End-of-Phase 2 Meeting was submitted by the Sponsor on March 30, 2010, and was denied because the IND was on clinical hold at the time. The clinical hold was removed on January 13, 2011. The Sponsor submitted a Meeting Request for a pre-NDA meeting on August 16, 2012. The meeting request was denied because it was deemed premature. The Sponsor subsequently submitted a request for this End-of-Phase 2 meeting.

The clinical development of iron isomaltoside 1000 (Monofer®) builds on the accumulating experience including:

Phase I – Clinical Pharmacology: Three finalized pharmacokinetic (PK) studies in patients with inflammatory bowel disease (IBD), chronic kidney disease (CKD), and cancer patients with chemotherapy induced anemia (CIA). Three additional ongoing PK studies (Phase I) of which one is conducted in the US – data analyses of this later trial is currently ongoing.

Phase II/III – safety and efficacy of different dosages: Two finalized open label non-comparative international clinical studies in patients with CKD and chronic heart failure (CHF) with a total of 202 patients and one comparative international phase II/III study including 338 patients with IBD.

Phase III – Confirmatory efficacy and safety: Three ongoing comparative international clinical studies including approximately 350 patients each in anemic patients with erythropoiesis stimulating agent (ESA) treated CKD on dialysis, patients with chemotherapy induced anemia (CIA), and non-dialysis dependent-chronic kidney disease (NDD-CKD) patients

The Sponsor's objectives for this meeting are:

- To obtain FDA agreement on the selected doses for Monofer® in iron deficiency.
- To obtain FDA agreement on the clinical strategy in Phase III to support an NDA filing of the proposed claim (indication(s)).

2. DISCUSSION

2.1. CMC

Question 1:

Does the Agency agree that the CMC documentation is sufficient for continuing in Phase III?

FDA Response to Question 1:

The referenced CMC information serial No. 015, dated 14-Nov-2012 in your meeting package could not be found. You may continue your investigations based on the information currently in the IND. However, it is not clear that the available CMC information would be sufficient to support an NDA application.

We recommend that you request a CMC specific end-of-phase-2 (EOP2) meeting with the Agency to update your CMC package. Prior to the meeting, provide a background document which includes summary CMC information along with specific questions. Provide a description of any changes to the CMC information since your original IND submission.

For detailed CMC information recommended for Phase 3 studies, please refer to FDA's Guidance for Industry, INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls Information (May 2003), Section IV.

Discussion:

No Discussion occurred.

2.2. Nonclinical

Question 2:

Does the Agency agree that there is no need for additional non-clinical studies?

FDA Response to Question 2:

As stated in your meeting package, published literature of the activity and toxicity of iron compounds in nonclinical studies has been submitted to the IND. It appears that nonclinical studies have not been conducted with iron (III) hydroxide isomaltoside 1000 complex and that you plan to use published literature to support your NDA. Your proposal to rely on published literature for nonclinical studies is acceptable should you intend to submit your NDA as a 505(b)(2) application. However, please note that the articles

provided in the NDA submission should adequately address the safety of your product and all nonclinical sections of the label for your drug product. Adequacy and relevance of the references you provide is a review issue. Where the literature you provide does not cite studies using your product you will need to provide a "bridge" that supports the scientific appropriateness of such reliance.

Sponsor Comment Question 2:

The sponsor wishes to have further clarification regarding the Division's response. We believe that the considerable non-clinical data on iron oligosaccharide complexes in addition to the extensive clinical safety data generated from completed and ongoing studies of Monofer should preclude the need for any further non-clinical studies.

Discussion:

The Sponsor sought clarification on applicability of literature data (*e.g.*, from the carbohydrate and iron separately) for their product. The Agency commented that the Sponsor would need to make the case and justification for the applicability of the literature information to their product. The Agency recommended that the Sponsor submit additional information to the IND and request a specific Preclinical Meeting to further discuss the available literature. The Agency commented that a clear link between the Sponsor's product and reference products would need to be made for a 505(b)(2). The Sponsor mentioned that (b) (4) **The Agency commented that the Sponsor has to make the case.**

2.3. Clinical

Question 3:

Does the Agency agree that the Clinical Development Plan and the overall estimated size of the safety data base will be sufficient for NDA submission?

FDA Response to Question 3:

No. We disagree. You need to conduct Phase 3 clinical trials in patients who have documented iron deficiency anemia and who are intolerant to oral iron or have had unsatisfactory response to oral iron for the proposed indication.

Sponsor Comment Question 3:

The sponsor wishes further clarification regarding this response. We have provided an extensive table of clinical studies ranging from Phase I through Phase III that are either

completed or ongoing that are intended to support the development and ultimate approval of this product for the US market. (Reference Table 1 on page 6, 7 of meeting background package).

Discussion:

The Agency clarified its concern for safety of parenteral iron products in general and emphasized that parenteral iron should be used in iron deficiency situations where use of oral iron is known to be ineffective (*e.g.*, in patients on dialysis). However, in cases where oral iron can be used it is preferred. Therefore, patients being offered parenteral iron should have documented intolerance and/or lack of responsiveness to oral iron. The Sponsor could pursue use for a specific indication such as in dialysis patients. However, for the broad indication of iron deficiency, the study population needs to include adequate representation of the breadth of patients treated for iron deficiency in clinical practice (*e.g.*, patients with abnormal uterine bleeding).

Question 4:

Does the Agency agree that based upon IND 107,331 and the additional information provided that the dose regimen for Monofer® is acceptable?

FDA Response to Question 4:

No. We disagree. We have safety concerns for the proposed dosing regimen and administration. You need to provide data to support the proposed dosing regimen. Clinical studies with pre-specified safety endpoints to demonstrate an acceptable safety profile including hypersensitivity reactions as compared to other approved iron products will be needed for the proposed dosing regimen.

Sponsor Comment Question 4:

The sponsor wishes further clarification regarding this response. We believe that we provided extensive evidence to support the dosage regimen from completed and ongoing Phase I/II studies.

Discussion:

The Agency clarified that it has a specific concern regarding the rate of administration (mg/min) as well as the total dose administration for parenteral iron products. The Sponsor will need to provide data assuring that administration of higher amounts and rates does not confer additional safety risk as compared to lower amounts and rates.

Question 5:

Considering the proposed indication, does the agency concur with the current clinical development plan for Monofer®?

FDA Response to Question 5:

No. See responses to Question 3 and 4.

Discussion:

No Discussion occurred.

Additional Comments:

Clinical Pharmacology

1. Evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of Monofer or total serum iron in humans.
2. Submit your overall QT risk evaluation plan for FDA review. For more information, refer to the Guidance for Industry entitled E14 Clinical Evaluation of QT/QTc Interval Prolongation.

FDA Post-Meeting Regulatory Comment:

3. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

   If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)) . We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

3.0 PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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 ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

6.0 ISSUES REQUIRING FURTHER DISCUSSION

None

7.0 ACTION ITEMS

None

8.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

KATHY M ROBIE SUH
12/19/2012