CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214373Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 103822

MEETING MINUTES

Theracos Sub, LLC
Attention: Mark E. Lostrom, M.S., RAC
Regulatory Advisor to Theracos Sub, LLC
15554 Virginia Point Road NE
Poulsbo, WA 98370

Dear Mr. Lostrom:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for bexagliflozin tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2019. The purpose of the meeting was to discuss your proposed statistical analysis plans and dataset structure to support filing a new drug application for bexagliflozin.

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

If you have any questions, call Michael G. White, Ph.D., Senior Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Deputy 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: B
Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, December 5, 2019; 10:00 AM to 11:00 AM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: IND 103822
Product Name: bexagliflozin tablets

Indication: treatment of Type 2 diabetes mellitus
Sponsor Name: Theracos Sub, LLC

Meeting Chair: Lisa B. Yanoff, M.D.
Meeting Recorder: Michael G. White, Ph.D.

FDA ATTENDEES

Office of Drug Evaluation II

Mary T. Thanh Hai, M.D.	Director (Acting)

Division of Metabolism and Endocrinology Products

Lisa B. Yanoff, M.D.	Director (Acting)
Mitra Rauschecker, M.D.	Clinical Team Lead (Acting)
Suchitra Balakrishnan, M.D., Ph.D.	Clinical Reviewer
Federica Basso, Ph.D.	Lead Pharmacologist (Acting)
Michael G. White, Ph.D.	Senior Regulatory Project Manager

Division of Clinical Pharmacology II

Manoj Khurana, Ph.D.	Clinical Pharmacology Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics II

Yun Wang, Ph.D.	Lead Mathematical Statistician
Alexander Cambon, Ph.D.	Mathematical Statistician

Division of Biometrics VII

Eugenio Andraca-Carrera, Ph.D.	Lead Mathematical Statistician
Bo Li, Ph.D.	Mathematical Statistician

Division of Medication Error Prevention and Analysis

Hina Mehta, Pharm.D.	Team Leader

Ariane Conrad, Pharm.D.	Safety Evaluator
Office of Scientific Investigations	
Cynthia Kleppinger, M.D.	Medical Officer

SPONSOR ATTENDEES

(b) (4)	
Mark Lostrom	Regulatory Affairs Advisor
(b) (4)	

1.0 BACKGROUND

Theracos Sub, LLC (Theracos) is developing bexagliflozin, a selective inhibitor of human sodium-glucose linked transporter 2 (SGLT2), as agent for the treatment of Type 2 Diabetes Mellitus (T2DM) (b) (4). The Division of Metabolism and Endocrinology Products (DMEP) received Theracos' Investigational New Drug (IND) 103822 for bexagliflozin proposed as a treatment for adult patients with T2DM on January 7, 2009. (b) (4). The following background highlights the regulatory interaction between Theracos and the FDA as it pertains to the development of bexagliflozin for the treatment of T2DM.

Carcinogenicity special protocol assessments (SPAs) for bexagliflozin were received on April 14, 2010, and June 17, 2010, with the FDA's responses transmitted on May 26, 2010, and July 28, 2010, respectively.

On November 30, 2012, a Type C meeting was requested by Theracos to discuss starting materials for the synthesis of bexagliflozin for which FDA issued written responses on January 18, 2013. On June 11, 2014, a Type C meeting was requested to discuss (b) (4), for which the FDA provided written responses on August 24, 2014. An End-of-Phase 2 Meeting was held with Theracos on January 15, 2015, with final meeting minutes issued on February 12, 2015.

On March 12, 2015, Theracos submitted an Initial Pediatric Study Plan (iPSP) for which the FDA issued an initial agreement letter on October 27, 2015.

On July 8, 2016, the FDA received a request for a Type C guidance meeting to follow-up on the clinical discussions that occurred during the End-of-Phase 2 meeting. Written responses were issued on September 21, 2016.

On April 16, 2018, Theracos submitted both a CMC-only, End of Phase (EOP) meeting request to discuss the manufacturing program for bexagliflozin and a Type C meeting request and final meeting package to discuss their rationale to complete the bexagliflozin clinical pharmacology evaluation without conducting a dedicated absolute bioavailability study. The meetings were granted, and Written Responses for the two meetings were issued on June 15, 2018, and June 19, 2018, respectively.

(b) (4)

Additionally, FDA issued advice on May 28, 2019, pertaining to a juvenile rat toxicity protocol that had been submitted by Theracos.

On October 1, 2019, FDA received a request from Theracos for a Pre-NDA meeting to discuss their proposed statistical analysis plans and dataset structure to support a new drug application (NDA) for bexagliflozin. The meeting was granted on October 4, 2019, and the meeting background package was received form Theracos on November 4, 2019. FDA sent Preliminary Comments to Theracos on December 3, 2019.

2. DISCUSSION

Theracos' questions are repeated below in regular text, followed by the FDA's preliminary responses (**bolded**), which are followed by any applicable discussion for that question if it occurred (***bolded and italicized***, and indented).

2.1. Non-clinical

Question 1: Does FDA agree that the non-clinical pharmacology and safety assessment is complete and the information adequate to support the NDA?

FDA Response to Question 1:
Yes, we agree that the non-clinical pharmacology and safety assessment is complete and the information adequate to support the NDA. However, additional toxicology studies might be needed if unexpected safety issues arise during the review process.

Discussion for Question 1:
No discussion occurred.

2.2. Clinical Pharmacology

Question 2: Does the agency agree that the clinical pharmacology studies are adequate to support an NDA?

FDA Response to Question 2:
Yes, we agree. Please submit the population PK analysis datasets (in SAS transport format) and codes/scripts for reviewers to recreate all the results and figures in the study report in the NDA submission. All model codes or control streams, output listings and scripts used to generate plots should be provided for all modeling performed. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_R.txt, myfile_ctl.txt, myfile_out.txt).

Discussion for Question 2:
No discussion occurred.

Question 3: The sponsor proposes that the label will state that bexagliflozin tablets, 20 mg, are to be consumed once daily with or without food and that adjustments to dosage are not required for concomitantly administered medications. No dose adjustment will be recommended for patients with mild or moderate renal disease, or with moderate hepatic disease. Does the agency agree with the proposed dosing instructions?

FDA Response to Question 3:
It is premature to agree on proposed dosing instructions as this is a review issue.

Discussion for Question 3:
No discussion occurred.

2.3. Clinical

Question 4: Does FDA agree that the proposed integrated analyses will be sufficient for assessing the effectiveness of bexagliflozin tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus?

FDA Response to Question 4:
Please note that integrated analyses for efficacy are not needed for labeling or approval. If you plan to use integrated analysis to support approval or Drug Trial Snapshot, then studies that are pooled/integrated should have similar designs and study populations. In conducting integrated analyses (including subgroup analyses across multiple studies), you should account for study differences, (e.g. randomization ratios, study duration, etc.) by stratifying by study to ensure avoidance of Simpson's paradox.

Discussion for Question 4:
Theracos clarified that they intended to pool two or more monotherapy diabetes studies. FDA agreed with the strategy to pool monotherapy studies together if the studies were sufficiently similar and Theracos was able to provide adequate justification for the pooling in their NDA submission.

Question 5: Does FDA agree with the proposed primary endpoint analysis and sensitivity analyses to support the proposed indication for the treatment of T2DM?

FDA Response to Question 5:
We do not agree with your proposal to use MMRM (Mixed Model Repeated Measures) for your primary analysis for the primary or secondary endpoints, or for the tipping point analysis. We also do not agree with your sensitivity analyses. The MMRM in your proposed primary analyses likely does not appropriately address missing data, as it treats the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are on-treatment in the same treatment group. Our preferred estimand is the treatment policy (de facto) estimand. To estimate the treatment estimand, efficacy data should be collected and utilized in analyses on all randomized treated patients regardless of treatment adherence, rescue status, or other post baseline status (e.g. post bariatric surgery status). Missing data should be imputed in a fashion consistent with what the measurement would have been, had it been measured. In cases where there are a sufficient number of retrieved dropouts (patients who discontinued treatment before the final assessment window but still had an efficacy measurement in the final assessment window), we prefer a multiple imputation approach that models the missing final assessment of non-retrieved dropouts (patients who discontinued treatment before the final assessment window and did not have a measurement in this assessment window) based on known measurements from the retrieved dropouts. We suggest that, for the non-retrieved dropouts, you multiply impute the change from the last measurement before treatment discontinuation to the final assessment, using this information from the retrieved dropouts. You may consider using time on treatment as either a continuous variable or a factor for this multiple imputation model. If you choose to use this variable as a factor, you may use the median value as a cut-off.

Note that patients who did not discontinue treatment early, but did have a missing final assessment, can be treated as missing at random (MAR). They can be represented by patients who did not discontinue early and did have a final assessment.

An appropriate analysis method for each fully imputed data set would be, for continuous endpoints, an ANCOVA model with pre-specified fixed factors and covariates. These should include baseline value as a covariate, and stratification factors as factors. As mentioned above in response to question #4, an

appropriate method such as stratification should be used to account for study differences. Rubin's rule should be used to properly combine the analysis results from the multiple imputed datasets.

The above approach should also be used for your subgroup analyses.

If there are not enough retrieved dropouts to do a retrieved dropout analysis, we recommend a return-to-baseline analysis. In this analysis a patient's final assessment is multiply imputed based on the patient's baseline value. Variance for the multiple imputation can be based on residual variance from an ANCOVA model, using the non-missing final assessments as the response variable.

We do note from your Table 4 in Section 7.5 that you use windowing for assessments. The final assessment should be windowed using variable ADY (analysis relative day - days from randomization). For a Week 24 final assessment for HbA1c, typically a +/- 3 week window is used: i.e. - 24*7 +/- 21 (in terms of analysis relative day variable – ADY).

Discussion for Question 5:
Theracos clarified that they expected less than 10% drop out and that they were agreeable to implementing FDA's recommendation of a return-to-baseline analysis. Theracos inquired that if significance was lost using return-to-baseline, whether FDA would be open to discuss the use of other conservative imputation methods. FDA indicated it would be open to proposals for sensitivity analysis using other imputation methods if adequately justified.

Theracos also inquired about the FDA's suggested 3-week windowing for assessments and stated that they only have one off-treatment follow-up visit scheduled for 7 days following receipt of the last treatment. Therefore, there would only be a 7-day window. Theracos also stated that they did not intend to include data from the off-treatment follow-up visit. FDA stated that a 7-day window would be adequate given their follow-up visit schedule, but encouraged Theracos to collect and use as much data as possible, including from the off-treatment follow-up visit.

Question 6: Does the agency agree that the analysis and objective is an appropriate undertaking?

FDA Response to Question 6:
In addition to the results from your dedicated renal impairment study (C-448), you propose to conduct a meta-analysis of the treatment effect in subjects with stage 3a and 3b CKD from all randomized placebo-controlled trials to inform labeling in patients with renal impairment. The agency would like to review the statistical protocol/analysis plan for this meta-analysis before agreeing to this approach. Also refer to Agency general statistical comments regarding integrated analysis

under Question 4. You may want to consider stratifying by chronic kidney disease stage. Final labeling language in patients with renal impairment will be a review issue based on the results of Study C-448 and the results of the meta-analyses.

Discussion for Question 6:
Theracos informed that they intended to pool just two studies for the meta-analysis. FDA stated that the previously provided comments on meta-analysis apply even if only two studies are pooled. FDA also indicated that it may be hard to support an efficacy claim for an SGLT-2 inhibitor in subjects with stage 3b chronic kidney disease, given the findings for other members of the class. In regards to possible proposed labeling for use in patients with lower eGFRs, FDA recommend that Theracos be prepared to provide an overall argument why a recommendation to avoid use of their product in patients with an eGFR less than 45 mL/min/1.73 m^2 would not be present in a proposed bexagliflozin label since this recommendation is present in the label of other products in this class. Upon inquiry by Theracos, FDA stated that study results that may support such a potential labeling difference would not need to be submitted for review prior to the NDA, but if submitted with their NDA, they would be considered during the normal course of their NDA's review. FDA suggested a meeting could be requested if Theracos deemed one to be necessary before submission of their NDA.

Question 7A: Does FDA agree that the pooling strategy will encompass the various characteristics of patients affected and will provide appropriate information for risk assessment to support an indication for treatment of type 2 diabetes?

FDA Response to Question 7A:
The proposed pooling strategy is acceptable for review of the NDA and assessment of risk. Determination of adequacy to support an indication for treatment of Type 2 DM will be made during the NDA review.

Discussion for Question 7A:
No discussion occurred.

Question 7B: Does FDA agree with the methodology for identification and analysis of adverse events of special interest outlined in the statistical analysis plan for the integrated summary of safety?

FDA Response to Question 7B:
In general, studies that are integrated should have similar designs and study populations. In conducting integrated analyses, you should account for study differences, (e.g. randomization ratios, study duration, etc.) by stratifying by study to ensure avoidance of Simpson's paradox, as previously discussed.

We also have the following recommendations related to your identification of adverse events. We note that your DKA definitions are based on the monitoring and adjudication plan dated July 24, 2017. We recommend that you broaden your approach to capture DKA events to improve sensitivity. In addition, you should specify the SMQs or customized queries of PT's you will use to identify adverse events of special interest.

Please note that we had also recommended that you capture amputations as an adverse event of interest in our written responses dated September 21, 2016. Necrotizing fasciitis of the perineum is an additional adverse event of interest for the SGLT2 inhibitor class.

Discussion for Question 7B:
Theracos clarified that in addition to the case report form being provided with defined DKA events, any adjudicated DKA event would be provided with additional information as stated in their monitoring plan. FDA clarified that although it was not asking Theracos to change its methodology for identifying or adjudicating adverse events, the FDA is requesting additional analysis in order to capture as many DKA events, or events associated with potential DKA, as possible. FDA suggested additional analyses by custom MedDRA preferred terms or SMQ for a broader analysis of non-adjudicated events in the safety database. For example, the FDA indicated it was interested in potential ketosis events, and would be interested in analyses of all these events, rather than restricting analyses to only ketosis events based on lab value cut-offs such as BHB levels.

Theracos informed that thus far it had only identified 19 DKA events and FDA indicated that these events could be individually evaluated, but reiterated that it also desired to see a broader search of terms than those that resulted in events referred for adjudication or identified as SAEs. This would include capturing events that weren't necessarily clinically meaningful and would allow for analyses of such items as trends in serum bicarbonate levels or ketones. FDA explained that such information wasn't necessarily an impediment to eventual approval of bexagliflozin, but that it had a general interest in collecting more information on the general physiological effects of SGLT-2 inhibitors.

Question 7C: Does FDA still want the eGFR from the Cockcroft-Gault equation? If so, can FDA clarify that this should be presented as an additional summary of eGFR change from baseline over time?

FDA Response to Question 7C:
We agree that summaries of eGFR change using the Cockcroft-Gault equation would not be required.

Discussion for Question 7C:
No discussion occurred.

Question 8: Does FDA agree with the updated meta-analysis plan for bexagliflozin cardiovascular risk assessment?

FDA Response to Question 8:
We have the following comments regarding your proposed plan to assess cardiovascular risk:

a) **Your plan to rule out non-excessive risk of 4-point MACE+ with a risk margin of 1.8 through a meta-analysis is generally acceptable. Your plan to use a dichotomous categorization (THR-1442-C-476 versus all other studies) to stratify the Cox regression model in your meta-analysis is acceptable. However, we request that you also provide results of analyses stratified by each individual trial.**

b) **We recommend that you remove the test for a risk margin of 1.3 for 3-point MACE from your testing hierarchy.**

c) **We recommend that tests for superiority, or risk reduction, of cardiovascular endpoints associated with bexagliflozin are based on trial THR-1442-C-476 alone, not on a meta-analysis. We recommend that you update the documentation of your testing hierarchy accordingly.**

d) **If you wish to include tests for superiority for heart failure and/or CV death from trial THR-1442-C-476 alone in your testing hierarchy, we recommend that you provide an estimate of the pooled (blinded) number of events expected in the trial and the corresponding power to conclude superiority.**

Discussion for Question 8:
Regarding point a), FDA agreed with Theracos' proposal to use two strata for the primary analysis: the trial with the majority of events (THR-1442-C-476) and all other trials combined. The FDA would also want to see sensitivity analyses stratified by each individual trial.

Regarding point b), Theracos indicated that data lock for the study had already occurred on November 22, 2019, and that treatments were unblinded, so that it would not be able to make changes to the testing hierarchy in order to remove the risk margin. FDA agreed that no changes could be made in the pre-specified testing hierarchy after treatment unblinding.

FDA also indicated that results based on trial THR-1442-C-476 alone will be considered during the review process due to it containing the most events.

2.4. Study Data Standardization Plan

Question 9: Theracos will prepare and submit integrated ADaM datasets and the corresponding reviewer's guide and define.xml. Theracos would like to seek clarification on whether integrated SDTMs will be required for the NDA.

FDA Response to Question 9:
Integrated SDTM datasets would not be required.

Discussion for Question 9:
No discussion occurred.

Question 10: Theracos will submit study reports and datasets that support a new drug application for bexagliflozin tablets, 20 mg. Studies THR-1474-C328, THR-1474-C-396, THR-1442-C-429 and THR-1442-C-402 were conducted in early development to determine the PK and PD properties of bexagliflozin capsules or tablets that did not perform as required. Theracos will not include the study reports or the data sets in the NDA. Does FDA agree with this plan and rationale?

FDA Response to Question 10:
Your plan is generally acceptable if you do not intend to rely on the results of the aforementioned studies to support any component of the proposed label or any Clinical Pharmacology assessments in the submission. However, we encourage you to submit, at minimum, the PDF reports of these studies. Note that we may request additional data from these studies if results of aforementioned studies are needed for the agency's assessment of bexagliflozin PK and PD during the review. In addition, clarify if there will be any changes to the to-be-marketed formulation referencing formulations used in the pivotal clinical trials.

Discussion for Question 10:
FDA asked Theracos to comment on the agency's request for clarification in the responses above whether there have been or will be any further changes to the formulation used in pivotal trials and it is indeed the to-be-marketed product. Theracos confirmed that there had been no further changes and none were planned.

Question 11: Does FDA agree with the revised SDSP for terminology standards update to a newer version?

FDA Response to Question 11:
The proposal for the revised SDSP terminology standards update to a newer version is acceptable.

Discussion for Question 11:
No discussion occurred.

2.5. Office of Scientific Investigations

Question 12: Does FDA agree with the selection of pivotal studies for BIMO inspection?

FDA Response to Question 12:
Yes, FDA is in agreement with the selection of pivotal studies THR-1442-C-450, -C-423, -C-448, -C-419, -C-480 and -C-476 for BIMO inspection.

Discussion for Question 12:
No discussion occurred.

2.6. General Review

Question 13: Will FDA convene an Advisory Committee for this program?

FDA Response to Question 13:
It is premature to comment on the need for an advisory committee at this point; this will be determined after submission of the NDA.

Discussion for Question 13:
No discussion occurred.

3.0 ADDITIONAL FDA COMMENTS

Statistics

Please provide or point to the location of details of your justification for the non-inferiority margin of 0.35%. Please refer to statistical comments sent to you on 5/20/2017 and on 12/18/2017.

Provide a Kaplan Meier plot for treatment discontinuation for each study. Identify adverse events that led to discontinuation on each arm for each study, along with severity rating (mild/moderate/severe, SAE). Please provide, for each study, the following table for subjects that discontinued treatment. Also provide the programs used to create the tables, using the same guidelines provided above.

Subject ID Number	Treatment Group	Time of Discontinuation (ADY)	Adverse Event Leading to Discontinuation	Period in which Discontinuation Occurred	Severity (mild/ moderate/ severe, SAE)	Seriousness Criteria	Causality Status	How long was patient followed up after treatment discontinuation; were there any other events/ adverse events

In general, please make sure that the datasets, and the define and adrg files conform to all applicable CDISC STDM and CDISC ADaM data and metadata standards that were applicable at the time of study start date. Please also refer to the Technical Conformance Guide[1,2] and the Data Standards Catalog.[3] Please describe (or point to the location of) the format you are using for data collection.

In addition, each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. For the electronic submission, include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables in the analysis dataset documentation (Define.pdf). Provide the location of the dataset, the names of the variables, and the programs used to get every new value that you plan to include in the label.

Also include the programs that are used to create the derived datasets for the efficacy endpoints, and the programs that are used for efficacy data analysis. Please incorporate this information in the footnote of each table in the report. Include comments and clarifications in your programs/codes. For example, indicate where paths need to be changed for the code to successfully execute in a different environment. If there are sub-macros/programs referenced in the program that are needed for the code to successfully execute in a different environment, please provide them.

Discussion for ADDITIONAL FDA COMMENTS, Statistics:
Theracos indicated that it had responded to the above referenced statistical comments, issued by FDA on May 20, 2017 and December 22, 2017, on August 29, 2017 and March 9, 2018, respectively. FDA stated that it would review these submissions and provide post-meeting comments which follow:

Thank you for providing the locations of the details for your justification for the non-inferiority margin of 0.35% for the HbA1c endpoint. Your response is acceptable.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM624939.pdf
[3] https://www.fda.gov/forindustry/datastandards/studydatastandards/default htm

4.0 ADDITIONAL FDA POST-MEETING COMMENTS

FDA recommended that any questions concerning [redacted] (b) (4)

5.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Theracos indicated that it intended to provide a complete application at the time of their NDA submission which is currently anticipated in the second half of June, 2020. It did not anticipate any late components; however the timing of CMC components might be discussed at an intended future CMC-specific Pre-NDA meeting.

- 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. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the

draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[4] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[5]

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.
- 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.

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[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

- 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[8]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[9]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters),

[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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 guidance for industry *Assessment of Abuse Potential of Drugs*.[10]

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.”

[10] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 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*.[11]

[11] 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
12/17/2019 08:59:22 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103822

MEETING MINUTES

Theracos, Inc.
Attention: Mark Lostrom, M.S., RAC
Regulatory Affairs Consultant to Theracos, Inc.
4901 Wailapa Road
Kilauea, HI 96754

Dear Mr. Lostrom:

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

We also refer to the meeting between representatives of your firm and the FDA on January 15, 2015. The purpose of the meeting was to discuss clinical and nonclinical plans for Phase 3 trials of bexagliflozin for type 2 diabetes mellitus.

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 Michael White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

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:	Thursday, January 15, 2015; 3:00-4:00 PM ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 103822
Product Name:	bexagliflozin
Indication:	An adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 diabetes mellitus
Sponsor/Applicant Name:	Theracos, Inc.
Meeting Chair:	Jean-Marc Guettier, M.D.
Meeting Recorder:	Michael G. White, Ph.D.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products
- Jean-Marc Guettier, M.D., Director
- William Chong, M.D., Clinical Team Leader
- Suchitra Balakrishnan, M.D., Ph.D., Clinical Reviewer
- Ronald Wange, Ph.D., Supervisory Pharmacologist
- Mukesh Summan, Ph.D., D.A.B.T., Nonclinical Reviewer
- Pamela Lucarelli, Chief, Project Management Staff
- Michael G. White, Ph.D., Regulatory Project Manager
- Martin White, M.S., Regulatory Project Manager

Division of Clinical Pharmacology II
- Manoj Khurana, Ph.D., Clinical Pharmacology Team Leader
- Sang Chung, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics II
- Bradley McEvoy, M.S., Dr.P.H., for Statistical Team Leader
- Shuxian Sinks, Ph.D., Statistical Reviewer

Office of Biostatistics, Division of Biometrics VII
- Matthew Soukup, Ph.D., Safety Statistical Team Leader, Safety Statistical Reviewer

SPONSOR ATTENDEES

Albert Collinson, Ph.D., President and CEO of Theracos, Inc.
(b) (4)
(b) (4)
Mark Lostrom, M.S., Merchant Taylor International, Regulatory Affairs consultant
(b) (4)
(b) (4)

1.0 BACKGROUND

Bexagliflozin (EGT0001442) was identified during a synthetic program to create highly selective and potent inhibitors of human sodium-glucose linked transporter 2 (SGLT2). Inhibition of SGLT2, which is responsible for reabsorption of excreted glucose in the proximal tubule, results in the diversion of blood glucose into urine. Because insulin and insulin therapies promote the uptake of glucose hypertrophic adipose reservoirs, an underling factor in T2DM emergence and progression, the sponsor is developing bexagliflozin as an oral adjunct to diet and exercise to improve glycemic control in adult patients with T2DM, either as a monotherapy or in combination with other approved therapies.

The Division of Metabolism and Endocrinology Products received Theracos' IND on January 7, 2009. In response, the FDA issued letters on February 13, April 8, and June 16, 2009, containing advice and information requests related to pharmacology/toxicology issues. A response to these letters was received on June 29, 2009.

A clinical pharmacology advice and request for information was sent on September 11, 2009, in response to an amendment received May 21, 2009. A response received on October 19, 2009.

A request for a carcinogenicity special protocol assessment (SPA), "104-Week Oral Carcinogenicity Study of EGT0001442 in CD-1 Mice," was received on March 17, 2010, and denied. It was resubmitted with a requested full report of the mouse toxicity study, and received by the Agency on April 14, 2010. The FDA's response was transmitted on May 26, 2010. Another carcinogenicity SPA request for the protocol, "26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with EGT0001442 in Rats with a 4-Week Recovery Phase," was received on June 17, 2010, with an Agency response transmitted on July 28, 2010.

In response to amendment received on May 19, 2011, the Agency sent an advice letter on July, 26, 2011, that included a request for review of the Thorough QT study (TQT) protocol synopsis, entitled, "*THR-1442-C-428: A Partially Double-blind, Randomized, Crossover Study to Assess the Effects of EGT0001442 on QTc Interval Compared to Placebo in Healthy Adult Subjects.*" A response to the agency was received in an amendment on February 8, 2013, and a clinical study report for the TQT was received on August 20, 2013.

On February 1, 2012, the Agency received carcinogenicity SPA amendment containing dosing and vehicle changes with which ECAC did not concur. The Agency responded with advice on February 3, 2012. Further carcinogenicity protocol amendments and advice requests were received on February 17, 2012, and April 6, 2012 (the latter was first received informally via email on April 4, 2012). The Agency responded on February 29, and April 5, 2012, respectively. An additional amendment was received on August 14, 2012, with the Agency again responding on September 5, 2012, with ECAC reiterating their lack of concurrence with dosing and vehicle changes.

A Type C meeting request was received November 30, 2012, that sought agreement from CMC on starting materials for the synthesis of EGT0001442. The Agency communicated its agreement on January 18, 2013.

On May 10, 2013, the Agency received nonclinical study reports for 104-Week Oral Carcinogenicity Studies THR-1442-T-405 and THR-1442-T-406, along with a request for comments on carcinogenicity studies. The Agency's reply on July 18, 2013, again reiterated ECAC's lack of concurrence with doses and vehicle change, along with a need for a complete study review. A response from the sponsor containing the requested study data was received on November 12, 2013.

(b) (4)

The current meeting was requested was received on November 5, 2014. The purpose of the meeting is to elicit the Agency's views of Theracos' proposed design and conduct of phase 3 clinical investigations of bexagliflozin in order to support a New Drug Application.

FDA sent Preliminary Comments to Theracos on January 13, 2015.

2. DISCUSSION

2.1. Clinical

Question 1: Clinical Dose Selection

Theracos plans to evaluate bexagliflozin tablets, 10 mg and 20 mg, in the phase 3 clinical program and will determine the commercial dosage strength(s) based on the final risk-benefit assessment resulting from an integrated analysis of the entire development program. Does the Division agree with this plan?

FDA Response to Question 1:

We do not agree with your plan to select phase 3 doses based on data from studies of the immediate release formulation. We recommend that you conduct an adequate dose-finding

study utilizing your new extended release formulation prior to initiating the proposed phase 3 evaluations. This recommendation is based on the following observations:

- **We note that the available PK data do not demonstrate bioequivalence between the immediate-release and extended release formulations and do not provide an adequate bridge between these formulations. You have not adequately addressed how PK/PD differences between the two formulations will impact efficacy and tolerability. Thus we feel that the available data are not sufficient to guide dose selection for the formulation you wish to study in phase 3.**

- **While the dose-pharmacodynamic data (i.e., UGE) seem supportive of the proposed doses, we are concerned that the primary glycemic data (i.e., HbA1c and percent achieving HbA1c goal [<7%]) do not fully support a benefit of the proposed doses. Compared to other approved therapies, the 20 mg dose of immediate release bexagliflozin had only a marginal treatment effect (change from baseline in HbA1c of -0.28%). Though the placebo-adjusted change is larger, this appears to be due primarily to worsening control in the placebo arm (change from baseline in HbA1c of +0.51%). The change in the placebo arm is markedly worse than historical change in placebo from studies in other drugs of the same class (see approved labeling for canagliflozin and empagliflozin). The percentage of patients achieving HbA1c goals was also worse in the placebo and bexagliflozin 20 mg arms compared to historical data from other drugs of the same class. It is unclear whether this is an issue of study design/conduct or a potential efficacy issue with bexagliflozin.**

Together, these findings raise questions regarding the adequacy of the two proposed doses utilizing an entirely different formulation for evaluation in phase 3.

Discussion for Question 1:

The sponsor indicated that it was in general agreement with the Agency's comments and recommendations and presented a table of monotherapy study design comparison (see Attachment 1). The Agency reiterated that, prior to proceeding to Phase 3 studies, it recommended conducting an additional dose range finding study with the extended release formulation using HbA1c as the primary glycemic endpoint to evaluate the impact of dose on tolerability and efficacy so that the sponsor can validate its dose selection. The sponsor agreed to consider these recommendations when designing a new study with the 5, 10, and 20 mg doses, and will submit that study protocol to the agency for feedback.

The unexpected placebo response was also discussed and a graph illustrating bexagliflozin's effect on HbA1c compared to placebo was presented (see Attachment 2). The sponsor suggested that the study design, specifically the lack of washout, was likely responsible for the difference in patients on bexagliflozin achieving HbA1c goals compared to historical data from drugs of the same class. The sponsor reported that that around 90% of patients were not treatment-naive, the majority of whom were receiving 1000-1500 mg of metformin prior to study enrollment, and that insulin users were disallowed. To improve the study design, the sponsor commented that they will implement a longer washout period in its next protocol.

Question 2: Efficacy and Safety Assessment

a. The efficacy and safety of bexagliflozin tablets as a monotherapy will be demonstrated in study THR-1442-C-450. Data from the phase 2 studies THR-1442-C-418 and THR-1442-C-402 will be considered supportive. Does the Division agree?

FDA Response to Question 2a:

Please refer to our response to Question 1. Given the lack of established bioequivalence between the immediate and extended release formulations as well as other issues raised above, it is unlikely that the findings from studies THR-1442-C-402 and THR-1442-C-418 will be relevant to the formulation you intend to evaluate in phase 3.

We have the following additional comment with regard to the general design of Study THR-1442-C-450:

Based on your outline for study THR-1442-C-450, it appears that you plan to enroll patients with type 2 diabetes who are either treatment-naïve, or treated with one or two oral antidiabetic drugs. We recommend you restrict enrollment to subjects who are treatment naïve or who are not well controlled on submaximal doses of only one oral antidiabetic drug for patient safety.

b. The efficacy and safety of bexagliflozin tablets in the context of combination therapy will be explored in studies THR-1442-C-419, THR-1442-C-423, and THR-1442-C-480, in which metformin will be coadministered, in study C-420, in which sulfonylureas will be coadministered, in study THR-1442-C-470 in which insulins are coadministered, and in studies THR-1442-C-448 and THR-1442-C-476, in which all approved anti-diabetic therapies will be candidates for coadministration. Studies THR-1442-C-423 and THR-1442-C-480 are designed to demonstrate that bexagliflozin will be as effective as sitagliptin or glimepiride. Does the Division agree that these trials, if meeting their desired endpoints and with adequate documentation of safety and tolerability, will support a label indication for the use of bexagliflozin in individuals with T2DM that will not be restricted by type, number, or duration of additional anti-diabetic therapies?

FDA Response to Question 2b:

If supported by the clinical trial data, we anticipate that the labeled indication would be "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." This is the current indications for all anti-diabetic medications approved for the treatment of adult patients with type 2 diabetes mellitus.

Additional clinical comments on the phase 3 clinical studies:

1. **In addition to the events you list in section 7.4.4 of the background document (i.e. hypoglycemia, hypovolemia, falls, fractures, urosepsis, pyelonephritis, urinary tract infections, genital infections, hepatic adverse events, and malignancies), you should**

also prospectively collect and evaluate hypersensitivity reactions, hypotension episodes, acid-base disorders, and renal failure events as adverse events of special interest.

2. **Serum creatinine should be measured in a central lab using an IDMS traceable assay and you should perform central tendency and categorical analyses for eGFR and serum creatinine compared to baseline.**

3. **Orthostatic BP measurements should include supine, sitting and standing measurements. Changes in baseline anti-hypertensive therapy and need for additional anti-hypertensive therapy should be recorded and analyzed.**

Additional statistical comments on the phase 3 clinical studies:

4. **Please justify any non-inferiority margin based on the effect of the active control from previous clinical trials studying the active control therapy (see the draft FDA Guidance on Noninferiority Trials for further information).**

5. **The description of studies, as it was presented in the background package, did not address issues of missing data. Considerable effort should be made to avoid missing data. A sizable amount of missing data will impact our confidence in study findings. The behavior of the missing data will also not be the same as the observed data since missing data tend to be associated with changes in adherence to randomized therapy. Additionally, your analyses do not account for differences in the distributions of patient characteristics (e.g., baseline HbA1c) that may be effect modifiers between patients with data on the primary endpoint and patients whose data are missing on the primary endpoint. It is therefore critical that extensive effort is made to prevent missing data.**

   To this end, the full protocol should: (1) describe procedures that will be in place to prevent missing data which should include training site investigators, (2) collect the reason for missing data, when it does occur, and (3) describe the assumptions that went into the choice of the primary analysis method.

   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.

   We also recommend that the informed consent forms for your phase 3 trials clearly differentiate treatment discontinuation from study withdrawal, and that the forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early.

6. **You should include sensitivity analyses to study the limitation of the missing data, and the assumptions made about the missing data for the primary analysis. It**

should also be explained what assumptions or limitations are being addressed or evaluated by a sensitivity analysis.

7. **Additionally, missing data may attenuate differences making it easier to conclude non-inferiority when non-inferiority does not exist. An imputation under the non-inferiority null method should be considered for the primary non-inferiority analysis (see page 341 of Koch Stat Med. 27, 333-342 2008).**

8. **As details were not provided on the analysis plan, we cannot comment on many issues including the analysis population and multiplicity.**

c. At launch Theracos plans to list in the prescribing information (b) (4) effects are elicited by bexagliflozin administration. Does the Division agree?

FDA Response to Question 2c:

It is premature to discuss labeling at this time.

Discussion for Question 2:

The sponsor indicated it would like to calculate glomerular filtration rate using the MDRD GFR equation. The Agency responded that this was reasonable. Clinical Pharmacology requested that they also provide creatinine clearance estimates using the Cockcroft Gault equation and the sponsor agreed to do so.

Question 3: Efficacy and safety in patients with renal impairment

In the proposed study no dose adjustment is planned. Does the Division agree with this proposal?

FDA Response to Question 3:

See our response to Question 1. We do not believe the data submitted support your selection of the extended release formulation dose you intend to study in phase 3.

For the study in patients with moderate renal impairment you will need to adequately characterize the effect of bexagliflozin across the complete moderate eGFR range . In addition to stratifying randomization, we recommend that you enroll an adequate number of patients within each moderate eGFR categories (e.g., from 45 to 60 ml/min/1.73 m^2, < 45 ml/min/1.73 m^2) and cap enrollment to allow sufficient representation of each sub-group.

Discussion for Question 3:

No discussion.

Question 4: Clinical Studies in Special Populations

a. Theracos proposes to defer a study in populations of subjects from 10 to 18 years of age to the post-market program and will submit a Pediatric Study Plan within 60 days of the EOP2 meeting. Theracos further requests that a study in subjects from ages 0 to 10 years be waived due to the low incidence of T2DM in this population. Is the Division in agreement with these proposals?

FDA Response to Question 4a:

Your proposals will be considered when you submit your PSP and will provide comments regarding your proposals at that time.

b. No stand-alone clinical pharmacokinetic study in elderly patients is planned to be conducted prior to submission of the NDA. Is the Division in agreement with this proposal?

FDA Response to Question 4b:

Your plan to conduct population PK analyses appears reasonable as long as the age range is adequately represented. We recommend that your clinical program have sufficient representation of patients over 65 and 75 years of age to adequately characterize the safety of your product in this population.

Discussion for Question 4:

No discussion.

2.2. Statistics

Question 5: Cardiovascular Safety Study Design and Analysis Plan

a. Is the Agency in agreement with the proposed patient population to be recruited in this study and would data excluding a MACE risk elevated by 1.8-fold or greater in these groups be accepted by the Division for submission of an NDA?

FDA Response to Question 5a:

For your proposed study of patients with elevated risk of MACE, you propose to enroll patients who satisfy at least one of your prespecified risk factors (Age > 40 with known atherosclerotic disease, age > 50 with 2 or more risk factors but without known atherosclerotic disease, or age > 20 with NYHA Class II or III heart failure). Clarify why you intend to enrich your study population with patients with heart failure as most patients

with heart failure due to ischemic events would be eligible for participation based on your first two criteria. If you intend to use this enrichment strategy we recommend capping enrollment to 400. We also request that you clarify the recruitment you expect from the each of the prespecified risk groups. We are concerned that if the study population is predominantly patients from the second, relatively lower risk population (i.e. patients with risk factors but no known CAD) that this may impact the ability to capture a sufficient number of events. We note that you will carry out a multinational trial. We recommend that 25-30% of the patients in your study be recruited from the US to ensure results are reasonably reflective of the US standard of care.

b. Study THR-1442-C-476 is designed to collect cardiovascular endpoints to address the Division's questions relating to the cardiac safety of novel medicines for T2DM as well as to provide efficacy data relating to improvements in hyperglycemia, blood pressure (BP), and body mass. Does the Division agree that these efficacy data could be summarized under the Clinical Trials Section of the Prescribing Information?

FDA Response to Question 5b:

It is premature to discuss labeling at this time. In general, an endpoint will only be considered for inclusion in labeling if statistical testing for the endpoint is pre-specified and adjusted for multiplicity. Final determination of whether an endpoint is or is not included in labeling is made after review of the application.

c. In the planned meta-analysis, a four point MACE+ criterion, defined as CV death, nonfatal MI, non-fatal stroke, and hospitalization for unstable angina, is the composite primary endpoint for CV risk assessment. Does the Division agree that this criterion is appropriate for the assessment of the cardiovascular hazard posed by bexagliflozin treatment?

FDA Response to Question 5c:

The MACE+ primary composite endpoint as defined is acceptable for the pre-marketing assessment of CV safety to exclude an excess risk of over 80%. The MACE endpoint (defined as CV death, nonfatal MI, non-fatal stroke) should be the primary composite for post-marketing exclusion of CV risk over 30%.

We recommend that you refer to the updated draft standardized definitions for cardiovascular and stroke endpoint events in clinical trials (see CDISC Draft Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials [August 20, 2014]).

d. The primary CV risk assessment of the adjudicated MACE+ will be conducted using the Full Analysis Set. The Full Analysis Set includes all patients that are randomized in the phase 2 and phase 3 studies who will have received at least one dose of study medication. Patients will be analyzed according to their randomized treatment. Does the Division agree with this analysis plan?

FDA Response to Question 5d:

For the planned meta-analysis of time to first occurrence of MACE+, the use of the full analysis set (FAS) is acceptable. We have the following additional comments on the planned meta-analysis of MACE+:

- **Using the FAS, multiple ascertainment windows (i.e. censoring schemes) are recommended to be included in the analysis. The primary analysis should be based on an on-study censoring scheme which includes MACE+ that occur while exposed to treatment and those that occur after treatment discontinuation. As such, it is important that all trials planned to be included in the analysis continue to obtain MACE+ status after treatment discontinuation. Sensitivity analysis should incorporate an on-treatment censoring scheme where only MACE+ that occur while on treatment plus ascertainment windows of 7 and 30 days are included in the analysis.**

- **As it is expected that the majority of events will be observed in Trial THR-1442-C-476, analysis of this trial alone should also be presented in your NDA submission.**

- **The meta-analysis plan also states that if the 1.8 risk margin is excluded, then the 1.3 risk margin will be tested. It should be noted that the assessment of the 1.3 risk margin is commonly based on the findings from a large cardiovascular outcome trial (CVOT) and this risk margin has associated with it its own two-sided Type I error rate of 0.05. As your development program to date does not include a sufficiently powered CVOT for the 1.3 risk margin, testing of the 1.3 risk margin based on a meta-analysis would need to be at a stringent alpha level, such as 0.001, for the meta-analysis. If the test for the 1.3 risk margin is not excluded using the stringent alpha level, a separate CVOT would be required in the post-market setting. Also, note as described above, assessment of the 1.3 risk margin should be based on the MACE endpoint.**

Discussion for Question 5:

The sponsor indicated general agreement with the Agency's comments and recommendations for cardiovascular safety studies, including capping enrollment of patients with CHF at 400, and that they will review and clarify patient enrichment strategies. The sponsor also acknowledged the Agency's concern about the possibility that a high percentage of patients from the lower risk stratum (i.e. over 50 years with two risk factors) may be recruited. The Agency reiterated that it was concerned that the sponsor may not be able to capture an adequate number of cardiovascular events to meet pre-submission requirements for exclusion of excess cardiovascular risk, and that inclusion criteria should be geared towards ensuring a sufficient number of ischemic events. The Agency reiterated that 25-30% of patient recruitment should come from the United States in order that the study reflects the US standard of care. The sponsor indicated it intended to capture such a population. The sponsor indicated that a revised protocol would be submitted for Agency feedback.

2.3. Clinical Pharmacology

Question 6: Clinical Pharmacology and Drug-Drug Interaction Studies

a. Theracos proposes not to provide explicit instructions for dosing in the fasted or fed states. Does the Division agree with this proposal?

FDA Response to Question 6a:

It is premature to discuss the specifics of labeling. We recommend that you perform a food effect study with the intended commercial extended release formulation to allow for adequate labeling of your product. Refer to the food-effect (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126833.pdf) and general bioavailability and bioequivalence (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf) Guidances.

b. Theracos plans to conduct additional clinical pharmacology studies outlined [in the meeting packet] to evaluate potential drug-drug interactions based on the known pathways for absorption, distribution, metabolism and excretion (ADME) of the compound. Does the Division consider that these studies will be sufficient to support an NDA?

FDA Response to Question 6b:

In general, your plans seem reasonable. However, it should be noted that findings of dose-response and/or final proposed doses may have an impact on the interpretation of drug-drug interaction study results and require additional assessment.

Discussion for Question 6:

No discussion.

2.4. Non-clinical

Question 7: Non-clinical Toxicity and Safety Evaluation

Theracos believes the nonclinical studies will be sufficient to support an NDA. Does the Division agree?

FDA Response to Question 7:

We agree that the completed and planned toxicity studies appear to be sufficient to support the phase III clinical studies and filing of the NDA, but additional studies may be needed if there are unexpected results in the clinical or nonclinical studies that merit further nonclinical investigation.

Discussion for Question 7:

No discussion.

2.5. General Discussion

Administration Question:

The sponsor inquired as to when datasets needed to be submitted. The Agency responded that datasets are required to be submitted at the time of NDA submission, but could be submitted earlier if desired (e.g. with submission of clinical study reports).

3.0. OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

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).

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.

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 3, 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

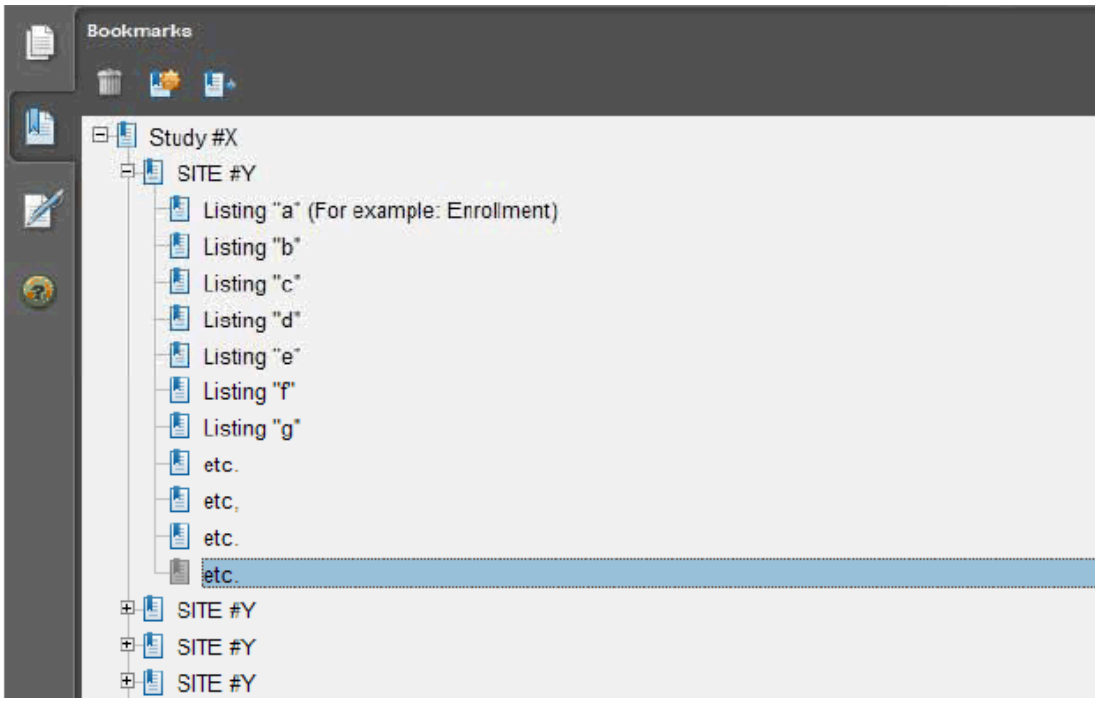
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

The Agency reiterated its suggestion for the sponsor to conduct an adequate dose ranging study for the extended release formulation of bexagliflozin in order for the sponsor to construct a data-driven rationale for dose selection prior to moving forward with Phase 3 studies. The agency stated its desire for the sponsor to communicate those studies results to the Agency so that it might review the data and the resulting rationale for dose selection.

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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
02/12/2015