CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216951Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 101291

MEETING MINUTES

GlaxoSmithKline Intellectual Property Development Ltd. England
Attention: Susan Nolt
US Agent
1250 S Collegeville Road
Collegeville, PA 19426

Dear Ms. Nolt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for daprodustat (GSK1278863).

We also refer to the telecon between representatives of your firm and the FDA on September 7, 2021. The purpose of the meeting was to obtain agreement between the Agency and GSK on proposals for the content and format of the planned New Drug Application (NDA) and to provide high level results from the daprodustat phase 3 ASCEND program (204837/ASCEND TD, 205270/ASCEND-NHQ, 201410/ASCENDID, 200807/ASCEND-D, and 200808/ASCEND-ND).

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

If you have any questions, contact Caden Brennen, Regulatory Project Manager, at 301-796-6591 or at Caden.Brennen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Associate Director of Therapeutic Review
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 7, 2021, 9:00-10:00AM (ET)
Meeting Location: Teleconference

Application Number: IND 101291
Product Name: daprodustat (GSK 1278863)
Indication: Treatment of anemia associated with chronic kidney disease (CKD)
Sponsor Name: GlaxoSmithKline Intellectual Property Development Ltd. England
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Caden Brennen, MS

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Lisa Yanoff, MD, Deputy Director (Acting)

OCHEN, Division of Nonmalignant Hematology (DNH)
Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Deputy Director
Tanya Wroblewski, MD, Clinical Team Lead
Patricia Oneal, MD, Clinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistical Team Lead
Lola Luo, PhD, Statistical Reviewer

Office of Biostatistics (OB), Division of Biometrics VII
Clara Kim, PhD, Statistical Team Lead
(Thanh) Van Tran, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Leader
Anusha Ande, PhD, Clinical Pharmacology Reviewer

Office of New Drug Products (ONDP)
Mohan Sapru, PhD, Branch Chief, Division of New Drug Products III

Dhanalakshmi Kasi, PhD, Quality Reviewer

Office of Regulatory Operations
Julie Van Der Waag, Director of Project Management Staff
Charlene Wheeler, MSHS, Chief, Project Management Staff
Caden Brennen, MS, Regulatory Project Manager

SPONSOR ATTENDEES
GSK

Janet van Adelsberg, MD	VP, Medicine Development Leader, GSK
Alex Cobitz, MD, PhD	Senior Director, Clinical Development, GSK
Mark DeSiato	Vice President, Global Regulatory Affairs, GSK
George Kummeth	Senior Director, Global Regulatory Affairs, GSK
Susan Nolt	Manager, Global Regulatory Affairs, GSK
Alex West	Senior Director, Global Regulatory Affairs, GSK
Allison Blackorby, MS	Statistics Director, Development Biostatistics, GSK
Sara Hughes	SVP & Head of Biostatistics
Nandita Biswas, PhD	Statistics Leader, Development Biostatistics, GSK
David Wade, MS	Programming Leader, Development Biostatistics, GSK
Tara Barker, MS	Senior Director, Global Safety, GSK
Susanna Cuadripani, MD	Medical Director, Global Safety, GSK
Kelly Mahar, PhD	Director, Clinical Pharmacology Modeling & Simulation, GSK
Misba Beerahee, PhD	Senior Director, Clinical Pharmacology Modeling & Simulation, GSK
Joe Sisko, PhD	Medicine and Process Delivery Leader, GSK
Donna Ferguson	Manager, CMC Development Projects, Global Regulatory Affairs, GSK
Dave Adams	Scientific Leader, Toxicology Project Specialist, Translation Platform Project Specialists Group (TPPS), In Vitro/In Vivo Translation (IVIVT) - Research, GSK
Liangfu Chen, PhD	Director, DMPK Project Specialist, Drug Metabolism and Pharmacokinetics, GSK
William Prichett	Regulatory Project Manager, Nonclinical Regulatory Affairs, GSK
Rodrigo Refoios Camejo	Senior Director, Value Evidence and Outcomes, GSK
Tom Keeley	Director, Patient-Centered Outcomes - Value Evidence and Outcomes, GSK
Michelle Carfagno	Director, Labeling Development & Strategy, GSK
Jo Dole, PhD	Director, Clinical Development, GSK
Jody Breneman	Manager, Clinical Data Management, GSK

1.0 BACKGROUND

Daprodustat is an inhibitor of hypoxia inducible factor (HIF)-prolyl-4-hydroxylases (PHD)1, PHD2 and PHD3. The proposed indication for daprodustat is for the treatment of anemia due to chronic kidney disease in adult patients on dialysis and not on dialysis. Daprodustat 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablets are being developed for once

daily [redacted] (b) (4)

The purpose of this Type B Pre-NDA meeting is to obtain agreement between the Agency and the Sponsor on proposals for the content and format of the planned NDA and to provide the results of the 5 daprodustat ASCEND studies:

- 204837/ASCEND-TD: One year, double-blind, double-dummy, active-comparator controlled study in HD patient which will provide evidence of efficacy and safety for 3-times a week dosing of daprodustat.

- 205270/ASCEND-NHQ: One 6-month double-blind, placebo-controlled study in ND patients to provide evidence of efficacy and safety and quality-of-life versus placebo.

- 201410/ASCEND-ID-one year, open-label, active-comparator controlled study to provide evidence for efficacy and safety in incident dialysis patients.

- 200807/ASCEND-D/200808/ASCEND-ND: Event driven, open-label (sponsor-blind), active-comparator-controlled cardiovascular outcome studies (CVOTs) which provide the primary evidence for non-inferiority of daprodustat versus rhEPO for hemoglobin and CV outcomes in dialysis (ASCEND-D) and non-dialysis (ASCEND-ND).

The Sponsor plans to submit the New Drug Application in December 2021.

Four of the 5 global phase 3 studies (except the 200808/ASCEND-ND) have full data outputs and in process of being reported. Preliminary data has become available for 200808/ASCEND-ND and were included in the meeting package (Section 3.3.2 and 3.3.3). For all 4 of the active-controlled studies, the primary Hgb efficacy endpoints were evaluated for non-inferiority of daprodustat using the pre-defined margin of -0.75g/dL with targets of 10-11g/dL. The primary Hgb efficacy endpoint in the placebo-controlled 205270/ASCEND-NHQ study was evaluated for superiority and utilized a Hgb target of 11-12g/dL.

The CVOTs, 200807/ASCEND-D and 200808/ASCEND-ND, have co-primary endpoints of efficacy as described above and primary cardiovascular (CV) safety endpoints (time to first adjudicated MACE, a composite of all-cause mortality, non-fatal myocardial infarction or non-fatal stroke). In the sponsor's analysis of time to first occurrence of MACE, the upper bound for the 95% confidence interval of the hazard ratio was below the pre-specified non-inferiority margin of 1.25 in both studies. The analysis of time to first occurrence of adjudicated MACE in the ASCEND-D study demonstrated a HR 0.96; 95% CI (0.81, 1.14). In the ASCEND-ND study, the analysis of the first occurrence of MACE demonstrated a HR 1.03; 95% CI (0.895, 1.192).

FDA sent Preliminary Comments to Sponsor on August 31, 2021.

2.0 DISCUSSION

2.1. Category/Discipline A

Question 1: Does the Agency agree that the content of Modules 1, 2, 3, 4 and 5 of the dossier as outlined in the proposed draft electronic Common Technical Document (eCTD) table of contents (TOC) constitute a complete application? Does the Agency agree the proposed Dossier supports the intended indication?

FDA Response: In the meeting background, you state that 200808/ASCEND-ND recently has preliminary data available. Please clarify if you intend to submit the proposed NDA application with full data from 200808/ASCEND-ND. In order to have a complete application, we recommend that you submit full data from 200808/ASCEND-ND along with full data from the other four studies (ASCEND-NHQ, ASCEND-ID, ASCEND-D, ASCEND-TD).

We have the following technical recommendations:

> **Issue #1 - The Proposed eCTD Table of Contents for the planned submission contains" List of Clinical Sites (PDUFA)" in Section 1.1. All Study Sites Lists should be placed in Section 5.3 under the specific study.**
>
> **Issue #2 - The Proposed eCTD Table of Contents for the planned submission contains "FDA Form 3674" in Section 1.2. All Forms should be placed in Section 1.1.**
>
> **Issue #3 - The Proposed eCTD Table of Contents for the planned submission contains "Agreed Initial Pediatric Study Plan (iPSP)" and "Written Request" in Sections 1.9.6.1 and 1.9.6.2. These documents should be placed in Section 1.9.6 under "Other Correspondence Regarding Pediatric Exclusivity or Study Plans".**

Refer to the Comprehensive Table of Contents Headings and Hierarchy for more details on each section referred in the FDA Response.

From a technical perspective (and not content related), all other sections proposed in the eCTD-IND Table of Contents are acceptable.

Meeting Discussion: No discussion took place during the meeting.

Question 2: Does the Agency agree with the proposal for submission of batch records for Daprodustat Tablets in the NDA?

FDA Response: Your proposal to submit in the NDA, the executed batch records for each of the 5 tablet strengths (1 mg, 2 mg, 4 mg, 6 mg, and 8 mg) produced by

each process (continuous process and batch process) for the 10 batches used in Study 213022 Part B (Bioequivalence Study) seems reasonable while also noting that master batch records will be provided in the NDA for intended commercial scale manufacturing for both the processes. Adequacy of information provided is a review issue and will be evaluated in the context of entirety of the CMC submission.

Meeting Discussion: No discussion took place during the meeting.

Question 3: GSK proposes to utilize the in vitro drug-drug interaction (DDI) studies, clinical pharmacology studies, dose/concentration-PD assessments, and phase III studies, population PK and exposure-safety analyses to support the submission and review of the daprodustat NDA. Does the Agency agree this approach will be sufficient?

FDA Response: Your approach is reasonable with the following exceptions:

- **Daprodustat is a BCRP substrate based on your in vitro studies. There is potential for increase in its systemic exposure when co-administered with BCRP inhibitors. We recommend that you conduct a clinical drug interaction study between daprodustat and a BCRP inhibitor e.g., cyclosporine, to provide dosing recommendations for patients who are taking BCRP inhibitors.**

- **You plan to evaluate the effect of co-administration of iron and non-iron phosphate binders and acid reducing agents on daprodustat PK in the planned extrinsic effect covariate analyses. We recommend that you evaluate drug interactions with important and clinically relevant concomitant medications such as phosphate binders in dedicated studies rather than with popPK methods, because the dose and duration of use of concomitant medications, time of administration, etc. are neither collected nor controlled as they would be in a dedicated drug interaction study.**

Meeting Discussion: The Sponsor responded to our preliminary comment regarding the potential for DDI with a BCRP inhibitor. The Sponsor **believes the clinically relevant victim DDI risk (increased exposure) of daprodustat when co-administered with a BCRP inhibitor is likely low due to the following reasons:**

- **Oral daprodustat is well-absorbed, with a calculated fraction absorbed (Fabs) of 80% with good oral bioavailability (65%).**

- **Intestinal BCRP inhibition would not be expected to have increased Fabs and systemic exposure greater than 25% (within upper bioequivalence margin of 125%).**

- **Systemic daprodustat has limited hepatobiliary clearance and is cleared almost exclusively by oxidative metabolism.**

The Division agreed with the Sponsor's rationale that the risk of clinically significant DDI based off BCRP inhibition is low. For interactions with phosphate binders and acid reducing agents, the Division commented that the Sponsor's strategy (as outlined in the slides) for addressing these potential interactions seemed reasonable. However, the final decision on dose adjustment or lack thereof, will be a review issue.

Question 4: GSK proposes to devote the Integrated Summary of Safety and the Summary of Clinical Safety (m 2.7.4) to summarize the safety data from the 5 global phase III studies, as detailed within the background information in Section 3.3.3, to provide a thorough assessment of the safety of daprodustat, both in comparison with placebo and recombinant human erythropoietin and its analogs. Does the Agency agree with this approach?

FDA Response: We agree with use of the Integrated Summary of Safety and Summary of Clinical Safety to summarize safety data according to the Summary Document Analysis Plan that you submitted and for which we provided comments on May 4, 2021.

Meeting Discussion: No discussion took place during the meeting.

Question 5: Does the FDA agree with GSK's proposal regarding the inclusion of case report forms (CRFs) and presentation of patient data?

FDA Response: Your proposal regarding the inclusion of case report forms (CRFs) for those subjects who died during the study or discontinued from the study due to an AE is acceptable along with the complete adjudication package from studies 200807/ASCEND-D and 200808/ASCEND-ND on patients with a positively adjudicated event(s).

We also recommend that you include narratives for all patients in the trials to be included in the NDA who experience SAEs (including MACE only adjudicated SAEs, potential and confirmed Hy's law cases, and patients who developed any malignancy during trial conduct and deaths). In addition, CRFs must be provided for every patient for whom a narrative is written.

Meeting Discussion: The Sponsor clarified that positively adjudicated endpoint events of MACE in the ASCEND-D/200807 and ASCEND ND/200808 studies will be reported separately and complete adjudication packages for each positively adjudicated event identified as MACE would be provided in place of patient narratives. Narratives will be provided for SAEs, including negatively adjudicated events, Hy's law cases, and patients who developed any malignancy, and TEAEs

leading to treatment discontinuation. The Division has no objections to the proposal regarding inclusion of case report forms and presentation of data.

Question 6: Does the Agency agree that the Patient Reported Outcome efficacy evidence that GSK are planning to submit will be sufficient for review?

FDA Response: In principle, the described patient-reported outcome (PRO) efficacy evidence appears to be reasonable to include in the planned NDA submission. However, we may have additional information requests during our review.

Per the FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims[1], PRO evidence should be placed in section 5.3.5.3 of the electronic common technical document.

Meeting Discussion: No discussion took place during the meeting.

Question 7: Does the FDA have any comments on the evidence planned to be included in the PRO dossier to support endpoints assessing fatigue and Quality of Life in the ASCEND clinical development program?

FDA Response: At this time we do not have comments on your planned PRO evidence dossier. We will review all components of the evidence dossier during our review, which may generate additional information requests.

Meeting Discussion: No discussion took place during the meeting.

Question 8: Does the FDA agree with GSK's proposal for providing information for the Office of Scientific Investigations?

FDA Response: Your proposal appears acceptable. Additionally, in your clinical study reports (201410/ASCEND-ID, 204837/ASCEND-TD, 205270/ASCEND-NHQ, 200807/ASCEND-D, and 200808/ASCEND-ND), provide a physical address and contact information where the Trial Master Files (TMFs) are stored or located.

Meeting Discussion: No discussion took place during the meeting.

Question 9: Does the Agency agree with the complementary use of post-hoc ascertainment windows for on-treatment MACE and treatment emergent AE data that adjust for the dosing exposure associated with different dosing frequencies?

FDA Response: We agree with your proposal to conduct additional analyses using the post-hoc ascertainment windows for on-treatment MACE and treatment

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf

emergent AEs. Given that these analyses are post-hoc, the regulatory utility of the results would be a review issue when you submit your NDA. Additionally, conduct analyses using the post-hoc ascertainment windows for adjudicated safety outcomes (see the full list of outcomes in Appendix 1).

Additional Statistics Comments: Please conduct the additional analyses listed below. As part of your NDA submission, submit the analysis code, relevant data with clear definitions of all variables, and results. Conduct the analyses separately for the non-dialysis-dependent population (ASCEND-ND) and the dialysis-dependent population (ASCEND-D).

1. **Time to first event analysis using an ascertainment window of on-treatment plus 7 days (OT+7), defined as the period starting from the treatment start date to the earlier of the date of study completion/withdrawal or last non-zero dose date + 7 days.**
    - **For each adjudicated safety outcome (see Appendix 1), fit a Cox proportional hazard model.**
    - **Adjust the model with the same covariates used in the primary analysis model of each outcome.**
    - **Provide Kaplan-Meier curves for each outcome.**

2. **Examine potential associations between dose/hemoglobin level and each adverse event (adjudicated safety outcomes and adverse events from datafiles) listed in Appendix 1. For patients who experience more than one adverse event with the same preferred term or more than one adverse event within a grouping of preferred terms (i.e., a query), the first adverse event should be used for analysis. Use ascertainment windows of on-treatment plus 7 days (OT+7) and on-treatment plus 28 days (OT+28), defined as the period starting from the treatment start date to the earlier of the date of study completion/withdrawal or last non-zero dose date + 7/28 days.**

    2.1 Adverse events in relation to average weekly dose

    2.1.1 Adverse events by average dose while receiving treatment

    - **For each subject, calculate the overall average dose while receiving treatment. Place each patient in a quintile based on their average dose, separately for each treatment arm.**
    - **Tabulate the numbers of adverse events for each dose quintile by treatment arm. Express the results as adverse events per 100**

patients (i.e., percent of patients with adverse events, within each quintile and by treatment group). See example in Appendix 2 Table 1.

2.1.2 Adverse events by average dose quintiles based on the dose received during the *4 weeks preceding the adverse event*

- **Calculate the average dose through the 4 weeks preceding the adverse event. For example, the average dose at Week 16 should be the average dose during weeks 12 through 16. The average dose at Week 3 would be the average dose during weeks 0 through 3. Place each patient in a quintile based on their average dose, separately for each treatment arm.**

- **Calculate the number of patient-years for each dose quintile by treatment arm. Tabulate the numbers of adverse events for each dose quintile by treatment arm. Express the results as adverse events per patient-year. See example in Appendix 2 Table 2.**

2.1.3 Adverse events by average dose quintiles based on the dose received during the *2 weeks preceding the adverse event*

- **Conduct analyses as per 2.1.2, except that the dose should be calculated through the preceding 2 weeks rather than 4 weeks.**

2.1.4 Adverse events by dose *at the time of the adverse event*

- **Determine the dose at the time of the adverse event. Place each patient in a quintile based on their dose, separately for each treatment arm.**

- **Calculate the number of patient-years for each dose quintile by treatment arm. Tabulate the number of adverse events for each dose quintile by treatment arm. Express the results as adverse events per patient-year.**

2.2 Adverse events in relation to hemoglobin (Hb) concentration

2.2.1 Adverse events by Hb just prior to the adverse event

- **While a subject was on treatment, determine the last known Hb value prior to the adverse event or during the onset of the adverse event.**

Place each patient in a quintile based on their Hb, separately for each treatment arm.

- **Calculate the number of patient-years for each Hb quintile by treatment arm. Tabulate the number of adverse events for each Hb quintile by treatment arm. Express the results as adverse events per patient-year. See example in Appendix 2 Table 3.**

2.2.2 Adverse events by Hb rate of change

- **While a patient was on treatment, estimate the Hb rate of change (g/dL/week) over the 4 weeks, inclusive, preceding the adverse event by fitting a linear regression line through the Hb values obtained during that interval. For example, the slope at Week 8 would be calculated from Hb values obtained on Weeks 4, 5, 6, 7, 8. For intervals during which Hb was assessed only once or not assessed, it will not be possible to calculate a slope. Such patient-years will not be included in the analyses.**

2.2.2.1 Adverse events by Hb rate of increase

- **For each patient with an Hb rate of change ≥0, place each patient in an Hb slope quintile.**

- **Calculate the number of patient-years for each Hb slope quintile by treatment arm. Tabulate the number of adverse events for each Hb slope quintile by treatment arm. Each adverse event should be linked to the Hb slope that preceded it. Express the results as adverse events per patient-year. See example in Appendix 2 Table 4.**

2.2.2.2 Adverse events by Hb rate of decrease

- **The analysis is the same as described in 2.2.2.1, except that only negative slopes are considered. For each patient with an Hb rate of change <0, place each patient in an Hb slope quintile.**

- **Calculate the number of patient-years for each Hb slope quintile by treatment arm. Tabulate the number of adverse events for each Hb slope quintile by treatment arm. Each adverse event should be linked to the Hb slope that preceded it. Express the results as adverse events per patient-year. See example in Appendix 2 Table 5.**

<u>Meeting Discussion:</u> Sponsor had follow-up questions for several of the Additional Statistics Comments. Listed below is a summary for each of Sponsor's proposal/question followed by a summarized discussion.

- Sponsor proposed OT+7/28 be defined as the period starting from the treatment start date to the earlier of the date of study completion/withdrawal or last non-zero dose date + dosing exposure+ 7/28 days, where dosing exposure is defined as 1 day for daily doses, 2 days for TIW doses, 7 days for weekly doses, 14 days for every 2-weekly doses, 28 days for 4-weekly doses.

  FDA agreed that Sponsor may use OT+28 as proposed above. FDA requested that Sponsor conduct analyses using an ascertainment window that does not account for variable dosing, i.e., defined as the period starting from the treatment start date to the earlier of the date of study completion/withdrawal or last non-zero dose date + 28 days, as requested in Additional Statistics Comment 1, because this ascertainment window was originally proposed for the supportive while on treatment analysis. FDA stated that Sponsor does not need to conduct analyses using OT+7.

- Appendix 1 includes an adverse event query labelled 'Thrombosis (includes stroke; excludes hemorrhagic stroke)', however the attached table provides a list of preferred terms for 'Thrombosis (includes all stroke)'. Which list of preferred terms should be used for the Appendix 1 query?

  During the meeting, FDA recommended that analyses be conducted for both thrombosis preferred terms (with and without hemorrhagic stroke). However, after internal discussion, FDA recommends that Sponsor conduct analyses for thrombosis (includes all stroke) only. FDA may ask Sponsor to conduct additional analyses for thrombosis during the review of NDA submission. Refer to the updated Appendix 1 and the Excel sheet containing the preferred terms.

- Additional Statistics Comments 2 requests exploration AE groupings and adjudicated safety outcomes by dose and Hgb quintiles. Is there a threshold for the minimum number of events in each treatment group that should be applied at which the decision would be made not to conduct these summaries?

  FDA stated that there is no threshold for the minimum number of events to conduct analysis.

- For the patient-year (PY) summaries by dose outlined in Additional Statistics Comments 2.1, the request has been made to tabulate rates per PY separately for

each treatment arm. In the ASCEND-D/200807 study, the rhEPO control arm includes both epoetin alfa for hemodialysis (HD) patients and darbepoetin alfa for peritoneal dialysis (PD) patients. For the requested PY summaries by dose, should the two rhEPO control treatments be combined into a single rhEPO control group by algorithmically converting the darbepoetin alfa doses to epoetin alfa doses, or should HD and PD patients be presented separately (allowing epoetin alfa and darbepoetin alfa doses to be presented separately) for these summaries in this study?

Sponsor had a follow-up question on September 8, 2021 that stated: Given that peritoneal dialysis patients (who receive darbepoetin alfa) make up only 169 (11%) of the 1,477 patients in the control arm, algorithmically converting the darbepoetin alfa doses to epoetin alfa doses will provide more robust support for the dose quintile summaries than the approach of providing separate summaries for hemodialysis and peritoneal dialysis patients. Consequently GSK are proposing to only use the algorithmic conversion approach to generate results for a single control arm. Does the FDA agree with this proposal?"

FDA agrees that the results can be generated for a single (combined) control arm.

- When calculating rates per PY by dose, if a patient first experiences the AE of interest after the end of the OT period, but still within the 7 or 28-day ascertainment window, should the patient's dose at the time of the adverse event considered to be 0 mg/ug/U or should the patient's last dose be carried forward?

  FDA stated that 0 mg/ug/U should be used for these subjects during the meeting. However, we have clarified our analysis request for Additional Statistics Comment 2.1 (see next bullet) and recommended the Sponsor use the average weekly dose closest to time of the AE.

- Can we confirm the calculation of AEs per PY by dose quintile from Additional Statistics Comment 2.1?

  FDA written response: We acknowledged the limitations that the Sponsor raised during the meeting regarding the exclusion of subjects without AEs in our previous analysis request. We have revised the analysis request for AE by dose (2.1) below, which uses average weekly dose. Given the variable dosing frequency in the control arm, propose how you would calculate average weekly dose for the combined control arm.

  2.1 Adverse events in relation to average <u>weekly</u> dose

  2.1.1 Adverse events by average weekly dose while receiving treatment

Step 1. Separately for each treatment arm: For each week, while the subject is receiving treatment until the occurrence of first AE for subjects with AE or until the end of treatment for subjects with no AE

1.1. Calculate the average weekly dose

1.2. Categorize the average dose in 1.1 based on your pre-defined dose categories

Step 2. Determine the number AEs for each dose category

Step 3: For each dose category, express the results as adverse events per 100 patients (i.e., percent of patients with adverse events)

2.1.2 Adverse events by average dose categories based on the dose received during the *4 weeks preceding the adverse event*

Step 1. Separately for each treatment arm: For each week, while the subject is receiving treatment until the occurrence of first AE for subjects with AE or until the end of treatment for subjects with no AE

1.1. Calculate average dose over every 4 weeks (e.g., for week 16, average over weeks 12-16)

1.3. Categorize the average dose in 1.1 based on your pre-defined dose categories

Step 2. Determine the number AEs for each dose category

Step 3. Determine the number of weeks that subjects spend in each dose category

Step 4: For each dose category, express the results as adverse events per 52 patient weeks.

2.1.3 Adverse events by average dose categories based on the dose received during the *2 weeks preceding the adverse event*

- **Conduct analyses as per 2.1.2, except that the dose should be calculated through the preceding 2 weeks rather than 4 weeks.**

In general, we agree with your use of pre-defined dose categories. We have the following specific comments.

- **Your dose categories might need to be updated to reflect average weekly dose to accommodate the revised analysis request above. Additionally, consider defining the categories such that there is an**

adequate number of person-time in each, while avoiding categorization based on the size of the estimates obtained from the categorization.

- **For the control arm, specify dose categories that are similar in magnitude to the daprodustat arm.**

- **Your pre-defined dose categories are based on possible doses in the study and do not appear to be quintiles. Consider changing the shell table column headers to not state "Quintile" if you are using a different dose categorization.**

- **Update the shell table to contain a single control arm as proposed above.**

- Can we confirm the calculation of AEs per PY by Hgb quintile from Additional Statistics Comment 2.2?

  FDA written response: In general, we agree with your proposed approach for tabulating the AEs and PYs for Hgb rate of change, which appear to be calculated for each subject at every 4-week interval. We have the following specific comments.

  - **For the analysis of AEs by Hgb just prior to the adverse event, the Hgb value should be determined for <u>each week that the subject was on treatment</u>. You may use the last known Hgb value.**

  - **For subjects who do not have an AE, use only the time that the subject is on treatment, not the entire ascertainment period.**

  - **We recommend that you use all unscheduled Hgb values in the analysis, which would provide additional valuable information for the analysis.**

  - **Update the shell table to contain a single control arm as proposed above.**

- In the daprodustat program, Hgb assessments were scheduled once every 4 weeks during the first year of the study. In the subsequent years of the study, visits could be as infrequent as once every 3 months, so it is anticipated that the visit schedule will create a meaningful amount of missing data for these summaries. Is there a threshold for missing data that should be applied at which the decision would be made not to conduct these summaries, or to use a 12-week interval instead of a 4-week interval?

FDA recommended that the Sponsor conduct analyses using the 4-week interval and, separately, the 12-week interval.

APPENDIX 1: Adverse events

Note: The individual preferred terms that should be included in queries are provided in attached table.

Adjudicated safety outcomes

MACE
All-cause mortality
CV mortality
Fatal or non-fatal myocardial infarction (MI)
Fatal or non-fatal stroke
Hospitalization for heart failure (HF)
Thromboembolic event

Adverse events from datafiles

Thrombosis (includes all stroke)
Device/shunt thrombosis
Device/shunt thrombosis, occlusion, malfunction, stenosis
Deep venous thrombosis
Pulmonary embolism
Acute coronary syndrome
MI

Sepsis
Bacteremia
Bacterial infectious disorders HLGT

Nausea or vomiting
Dyspepsia
Increased bilirubin or alkaline phosphatase
EPS, potential EPS, tardive dyskinesia
Memory loss, impairment
Seizure
Insomnia
Paresthesia

APPENDIX 2: Shell Tables

Table 1. Adverse events and dose of study agents (% of patients with events)

	Overall Average Dose - Quintiles									
	Daprodustat					rhEPO				
	1	2	3	4	5	1	2	3	4	5
AE1 AE2 …										

Abbreviation: AE = Adverse Event.

Table 2. Adverse events by dose quintiles based on the dose received during the 4 weeks preceding the event (events per patient-year)

	Average Dose - 4 Weeks Preceding Event - Quintiles									
	Daprodustat					rhEPO				
	1	2	3	4	5	1	2	3	4	5
AE1 AE2 …										

Abbreviation: AE = Adverse Event.

Table 3. Adverse events by hemoglobin (Hb) quintiles based on the Hb value just prior to the event (events per patient-year)

	Hb value just prior to the event - Quintiles									
	Daprodustat					rhEPO				
	1	2	3	4	5	1	2	3	4	5
AE1 AE2 …										

Abbreviation: AE = Adverse Event.

Table 4. Adverse events by hemoglobin (Hb) rate of increase quintiles based on the Hb rate of increase (g/dL/week) over the 4 weeks preceding the event (events per patient-year)

	Hb rate of increase (g/dL/week) over the 4 weeks preceding the event - Quintiles									
	Daprodustat					rhEPO				
	1	2	3	4	5	1	2	3	4	5
AE1 AE2 …										

Abbreviation: AE = Adverse Event.

Table 5. Adverse events by hemoglobin (Hb) rate of decrease quintiles based on the Hb rate of decrease (g/dL/week) over the 4 weeks preceding the event (events per patient-year)

	Hb rate of decrease (g/dL/week) over the 4 weeks preceding the event - Quintiles									
	Daprodustat					rhEPO				
	1	2	3	4	5	1	2	3	4	5
AE1 AE2 …										

Abbreviation: AE = Adverse Event.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Agency acknowledged and agreed with the Sponsor's responses at the meeting but had additional statical comments for the Sponsor. Please refer to the meeting discission section in Question 9.

  - 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.

  - A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan, and it was concluded that decision for the need for a REMS will be determined during the review of 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.

PREA REQUIREMENTS

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

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

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

PRESCRIBING INFORMATION

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

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

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

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

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

SUBMISSION FORMAT REQUIREMENTS

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

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

SECURE EMAIL COMMUNICATIONS

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

[6] http://www.fda.gov/ectd
[7] 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*.[8]

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)				

[8] 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)				

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

[9] https://www.fda.gov/media/84223/download
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[11] https://www.fda.gov/media/85061/download

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

See attached.

18 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

TANYA M WROBLEWSKI
09/22/2021 10:02:51 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101291

MEETING MINUTES

Glaxo Smith Kline LLC
Attention: Margaret M Kreider, PhD
Senior Director, Global Regulatory Affairs
2301 Renaissance Blvd, PO Box 61540
RN0420
King of Prussia, PA 19406-2772

Dear Dr. Kreider:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1278863.

We also refer to the meeting between representatives of your firm and the FDA on February 22, 2016. The purpose of the meeting was to discuss the non-clinical and clinical program conducted to date and the Phase 3 clinical development plan for GSK1278863 in the context of a future registration package.

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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
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:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	February 22, 2016; 3:00PM-4:00PM (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 101291
Product Name:	GSK1278863
Indication:	Treatment of anemia of chronic kidney disease
Sponsor/Applicant Name:	Glaxo Smith Kline LLC
Meeting Chair:	Tanya Wroblewski, MD, Clinical Reviewer
Meeting Recorder:	Rachel McMullen, MPH, MHA, Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products
Ann Farrell, MD, Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Medical Officer
Rachel McMullen, MPH, MHA, Regulatory Project Manager

Division of Hematology Oncology Toxicology Staff
Christopher Sheth, PhD, Supervisory Pharmacologist

Office of Clinical Pharmacology/ Division of Pharmacometrics
Nitin Mehrotra, PhD, Lead Pharmacologist
Jee Eun Lee, PhD, Clinical Pharmacology Reviewer

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics
Yuan Li Shen, PhD, Lead Statistician
Lola Luo, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology/Division of Risk Management
Carolyn L. Yancey, MD, Clinical Reviewer

SPONSOR ATTENDEES
Glaxo Smith Kline
John Lepore, Medicines Development Leader for GSK12788863
Alexander Cobitz, Physician Lead for anemia
Lata Kler - Director, Clinical Development
Steven Caltabiano, Director, Clinical Pharmacology
Kelly Mahar, Manager, Clinical Pharmacology
Deborah Kelly, Medical Director, Global Clinical Safety and Pharmacovigilance
David Adams, Investigator, Nonclinical Safety Assessment
Stephen Newsholme, Director, WW Nonclinical Safety Assessment
Delyth Jones, Director, Clinical Statistics
Richard Davies, Director, Clinical Statistics
Margaret Kreider, Director, Global Regulatory Affairs
Elvis Osei-Tutu, Post-Doctoral Fellow, Global Regulatory Affairs
Jennifer Dudinak, Vice President, Global Regulatory Affairs
Ajay Singh, Chair of the Steering Committee for the GSK1278863 Phase 3 Program, Harvard Medical School

1.0 BACKGROUND

Glaxo Smith Kline LLC (Sponsor) has developed GSK1278863, a small molecule inhibitor of hypoxia-inducible factor (HIF) prolyl-4-hydroxylases for the treatment of anemia associated with chronic kidney disease (CKD). According to the Sponsor, GSK1278863 stimulates erythropoiesis by activating pathways involved in tissue responses to hypoxia. The development of GSK1278863 as a treatment for anemia associated with CKD has progressed through the completion of Phase 2 studies in patients on dialysis and patients not on dialysis.

On December 17, 2015, the Sponsor requested an End of Phase 2 meeting with the Agency to discuss the non-clinical and clinical program conducted to date and the Phase 3 clinical development plan for GSK1278863 in the context of a future registration package. The completed and planned non-clinical and clinical programs are intended to support approval of GSK1278863 as a treatment of anemia associated with CKD.

FDA sent Preliminary Comments to Glaxo Smith Kline on February 19, 2016.

2. DISCUSSION

NON-CLINICAL

Question 1:
GSK considers that the completed, ongoing, and planned nonclinical studies for GSK1278863 and its 3 major circulating human metabolites provide an appropriate nonclinical package for

registration. Does the Agency agree?

FDA Response:
The number and types of nonclinical studies are appropriate; however, a decision regarding their adequacy can only be made upon review of data submitted with your NDA. We note that your rat and mouse carcinogenicity studies (in which all male rats had to be terminated at Week 97 due to low survival in control males) were conducted inconsistent with the agreed upon SPA based on the adjustment in vehicles. This will be a review issue.

DISCUSSION: ***There was no discussion.***

CLINICAL

Question 2:
Does the agency agree that the data from the completed phase 1 and phase 2 studies provide an appropriate basis for progression into phase 3?

FDA Response:
Overall, your efficacy and safety data from your Phase 1 and Phase 2 studies appears sufficient to proceed into Phase 3 development for GSK 1278863.

DISCUSSION: ***There was no discussion.***

Question 3:
Does the Agency agree that the proposed study populations for the Phase 3 trials are appropriately representative of the proposed indicated patient population?

FDA Response:
We do not agree with the inclusion criteria for the non-dialysis population with regard to baseline serum ferritin and TSAT levels. We recommend that all CKD patients have a TSAT > 20% (both dialysis and non-dialysis) and that ferritin levels > 100ng/mL for all CKD non-dialysis patients.
We agree with alignment to a single target hemoglobin range (10-11g/dL) between the US, EU and rest of world for your dialysis dependent populations (both initiation and maintenance) and non-dialysis populations.

DISCUSSION: ***There was no discussion.***

Question 4:
Does the Agency agree that the plan to identify and analyze the subgroup of subjects hyporesponsive to rhEPO could support inclusion of the efficacy of GSK1278863 (b) (4)

FDA Response:
No, the Division expresses several concerns over the analysis of a subpopulation of patients with rhEPO hyporesponsiveness in your trial design. There are many confounders with the inclusion

of this population that will make interpretation of efficacy and safety results difficult. These include no widely accepted definition of ESA hyporesponsiveness and a myriad of etiologies for suboptimal responses to ESAs (e.g. chronic inflammatory states, inadequate dialysis, hyperparathyroidism, clinical and subclinical iron deficiency).

We recommend conducting a separate randomized trial in subjects who are ESA hyporesponsive. Further discussion with the Agency is recommended to determine an acceptable definition of ESA hyporesponsiveness for this population.

DISCUSSION: ***The Agency and the Sponsor had a discussion regarding the analysis of a subgroup with hyporesponsiveness to rhEPO. The Agency considers the analysis of this population to be exploratory only and requested a justification of the proposed definition of rhEPO hyporesponsiveness.***

Question 5:
Does the Agency agree that the proposed dosing scheme for study medication for the Phase 3 trials (GSK1278863 and rhEPO) provides an appropriate basis for comparative assessment of efficacy and safety?

FDA Response:
Your approach to selecting the starting doses appears to be reasonable. However, the effect of body weight on dose selection should be more clearly illustrated to be able to accept the proposed doses regardless of body weight. Perform a simulation for subgroups of body weight with more than 4 levels so that the doses for underweight patients (low BMI) could be compared to normal or overweight patients.

In addition, you should also conduct simulations to predict the time course of Hgb to determine the proportion of patients that are expected to be within the target Hgb range at different time points.

DISCUSSION: ***The Agency reiterated that the effect of body weight on dose selection be clearly articulated. Adequate justification should be provided that the start dose and dosing regimens proposed are appropriate for patients across a range of body weights.***

Question 6:
(b) (4)

FDA Response:
(b) (4)
The modeling and simulation were utilized to support the starting dose for once daily dosing regimen. You can utilize modeling and simulation to justify the proposed starting dose in PHI204837.

DISCUSSION: ***The Agency stated that the data obtained will be reflected in the labeling.***

Question 7:
Does the Agency agree that the Phase 3 PK sampling plans will provide sufficient data to evaluate the exposure response relationship for safety and effectiveness?

FDA Response:

- We recommend that the final population PK/PD analysis include data obtained from Phase 3 studies.
- The planned exposure-response analyses for efficacy and safety should be performed with the revised PK/PD model.

DISCUSSION: There was no discussion.

Question 8:
Does the Agency agree with the proposal to exclude adjudicated events that are determined by the CEC to be study endpoints from serious adverse event reporting requirements?

FDA Response:
No, all serious adverse events regardless if they are adjudicated safety events for an endpoint need to be reported to the Agency.

DISCUSSION: The Agency and the Sponsor discussed submission of adverse event reporting for the Phase 3 trials. The Agency requested that the Sponsor pre-specify in the protocol the events which will be adjudicated by the CEC and reviewed by the IDMC, and to submit the IDMC charter.

Question 9:
Does the agency agree that the plans for safety monitoring in the phase 3 studies will provide adequate assessment of the safety of enrolled subjects?

FDA Response:
No, we do not agree with the timing of your laboratory assessments. During the initiation phase of therapy assessment of haemoglobin needs to be undertaken at least every 2 weeks. During the maintenance phase of therapy, we recommend that hemoglobin concentrations be measured at least monthly. TSAT and ferritin levels should be monitored at least every 3 months during therapy with GSK 1278863 and more frequent testing may be indicated in situations of blood loss or increasing or decreasing doses of GSK 1278863.

In addition, if there is a change in dose of study drugs during the maintenance period, haemoglobin measurements and iron status needs to be reassessed.

We recommend including safety stopping rules in your dialysis-dependent and non-dialysis trials.

Your protocols need to specify patient stopping rules for lack of efficacy. In order to ensure comparability, the patient stopping rules for lack of efficacy need to be similar between the two treatment arms.

DISCUSSION: The Agency and the Sponsor had a discussion regarding the timing of hemoglobin levels during the initiation phase and during the first 52 weeks. The Sponsor is proposing to measure hemoglobin every 4 weeks during the first 52 weeks, and then every 12 weeks thereafter. The Agency acknowledges the Sponsor's proposal and will review it when the final protocol is submitted.

Question 10:
Does the agency agree that the plan to assess the effects of gsk1278863 treatment vs rhepo on blood pressure (including exacerbations of hypertension) (b) (4)

FDA Response:
CDER's Division of Cardiovascular and Renal Products is still considering this question. We will forward their response when it is available.

DISCUSSION: There was no discussion.

STATISTICS

Question 11:
Does the Agency agree that the analysis strategy for the proposed co-primary endpoints could support registration in each population (Dialysis and Non-Dialysis)?

FDA Response:
Your proposed change in the MACE NI to 1.2 appears reasonable based on our current understanding.

FDA acknowledges your consideration of the new ICH E9 (R1) (2014) guidance. However, FDA recommends the primary efficacy analysis population should still be based on the intent-to-treat (ITT) population, since randomization ensures fair assignment of treatments. The proposed modified-ITT population may be used as a sensitivity analysis. Any difference in the results of these analyses should be explained and could be indicative of poor study conduct/quality.

Every subject should be accounted for in the analysis by either being measured for the primary endpoint or properly accounted for if not measured for the primary endpoint. The number of subjects not measured for the primary endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results. Imputation under the non-inferiority null should be considered.

Please provide more details of timing and censoring schemes for time-to-event analysis based on MACE.

DISCUSSION: The sponsor explained that the ITT analysis will include all observable data with no imputation occurring during the evaluation assessment period. The Agency stated that the approach appears to be acceptable. However, sensitivity analysis should be performed to

demonstrate the robustness of the results.

Question 12:
Does the Agency agree that the plan to assess and analyze the principal secondary endpoints would support inclusion of successful principal secondary endpoints (b) (4) *?*

FDA Response:
No, we do not agree with the inclusion of your principal secondary endpoints.
Your trials are designed as a non-inferiority or superiority trial for MACE and non-inferior for Hgb change from baseline. You are attempting to assess a variety of secondary endpoints that will be difficult to control for and adequately balance in your trials. We consider the inclusion of the secondary endpoints to be exploratory only and may aid with the design of future trials to adequately assess these endpoints.

DISCUSSION: The Agency and the Sponsor discussed the plan for the principal secondary endpoints. The Agency commented on the difficulty and challenges of assessing principal secondary endpoints and recommended submitting a hypothesis for each endpoint and a statistical analysis plan to control multiplicity.

Additional Clinical Comments

FDA considers US-licensed Epogen/Procrit as product that carries the US-licensed Epogen/Procrit label and license number. Products that do not carry the US-licensed Epogen/Procrit label and license number are not considered US-licensed Epogen/Procrit regardless of the origin of such products.

We encourage the use of US-licensed Epogen/Procrit for your comparator arm because we know the safety, purity and potency of US-licensed Epogen/Procrit.

If you choose to use US-licensed Epogen/Procrit at certain study sites and non-US-licensed epoetin alfa at other study sites for the active comparator arm of your clinical trial(s), you will need to establish an adequate scientific bridge to justify the relevance of data obtained with the non-US –licensed epoetin alfa. With respect to your development program, they type of bridging data that may be needed to provide adequate scientific justification for this approach would include data from direct, comparative analytic studies (e.g. structural and functional data) of US-licensed Epogen/Procrit and non-US licensed epoetin alfa and is likely to also include bridging clinical PK study data. The comparisons should meet the pre-specified acceptance criteria for analytical and PK similarity. You may submit publicly available information regarding non-US-licensed epoetin alfa to justify the extent of comparative data needed to establish a bridge to US-licensed Epogen/Procrit. The complexity of the product, particularly with respect to higher order structure, post-translational modifications (e.g. glycosylation) and the degree of heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. You should address any other factors that may affect the extent of bridging data to support such an approach.

In addition, we recommend that you compare the safety, efficacy and dosing of US-licensed Epogen/Procrit with non-US-licensed epoetin alfa products used in the clinical trial. Differences in the safety, efficacy, and dosing profile of US-licensed Epogen/Procrit with other non-US-licensed epoetin alfa products may affect the Agency's ability to interpret the results of your clinical trial. The adequacy of this scientific justification and bridge would be a review issue.

Please note, however, that the use of US-licensed Epogen/Procrit and non-US-licensed epoetin alfa as active comparators in a clinical trial may have labeling implications should the data generated using multiple comparator products are necessary to support approval.

DISCUSSION: The sponsor indicated that they will use US-licensed product globally.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

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

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

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

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

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide

feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

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 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

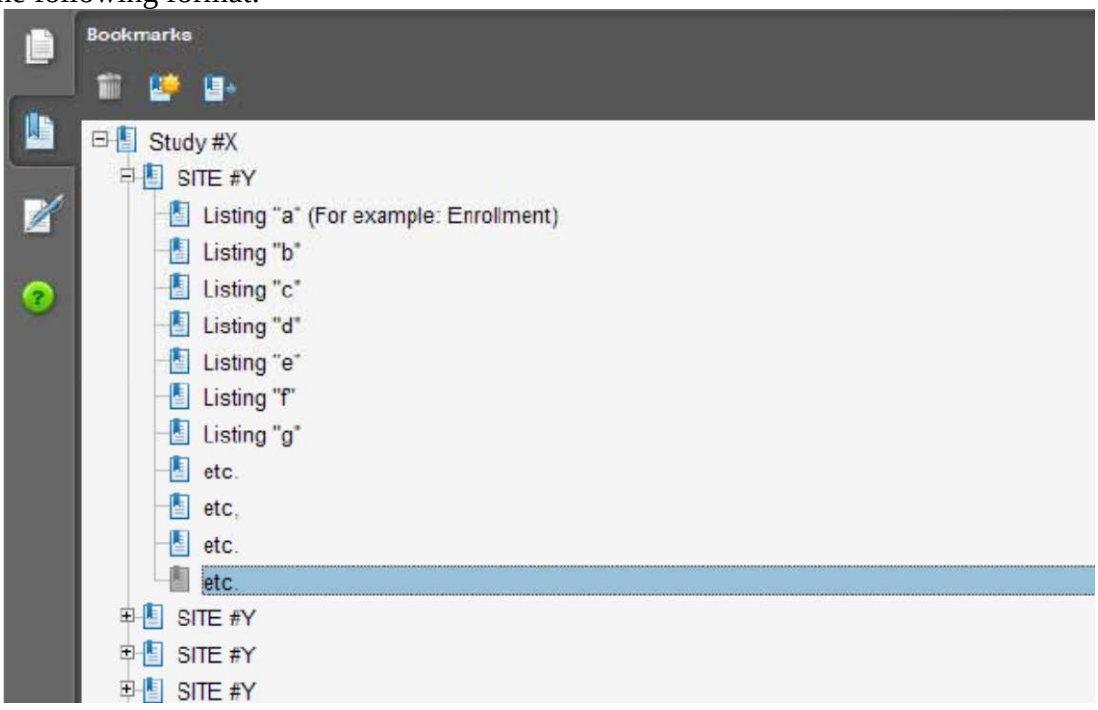
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

Attachment 1

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

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

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

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

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

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

References:

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

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

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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the sponsor's response is attached.

Confidential

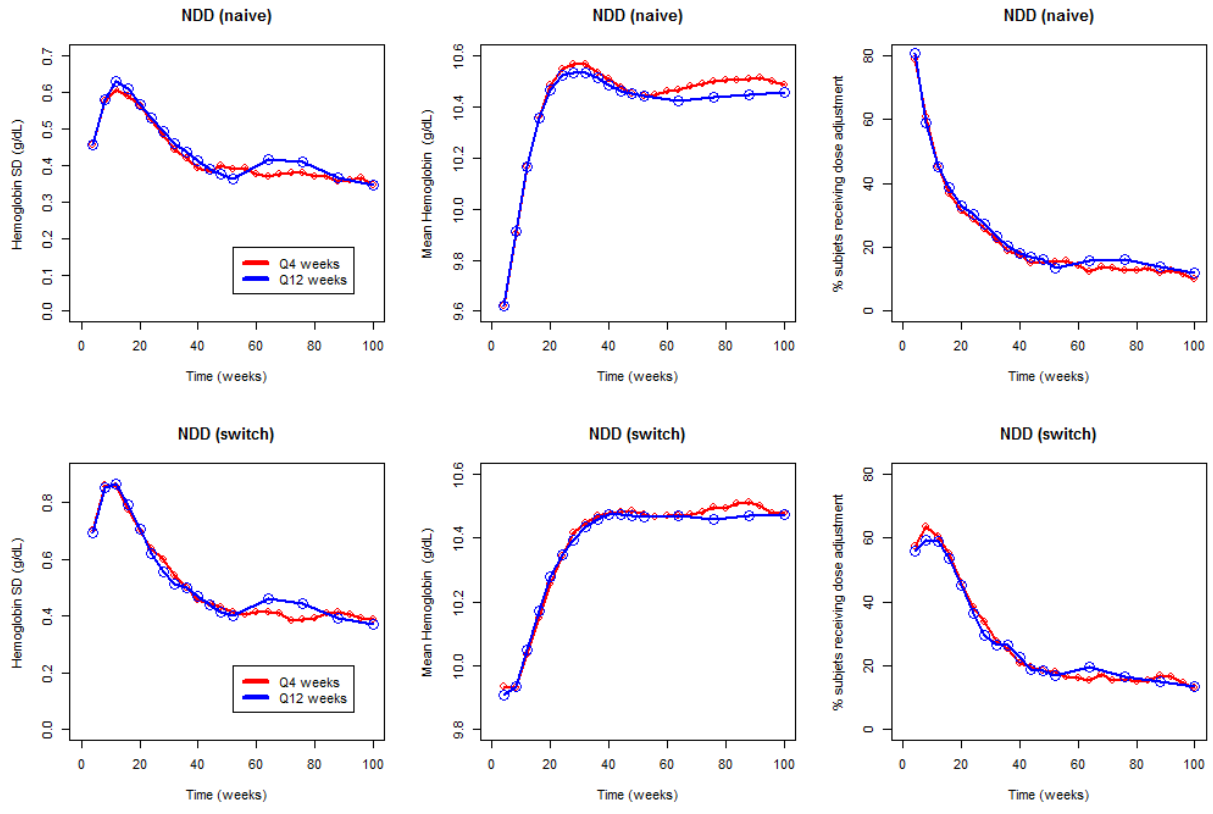
GSK1278863 – FDA Meeting February 22, 2016

Information for Question 9

Year 2 Simulations: Assessing maintenance phase hemoglobin assessments

Simulations of 1000 anemic patients with CKD patients were performed for both hemodialysis-dependent (HDD) non dialysis-dependent (NDD) naïve to ESA and NDD switching from ESA to GSK1278863. Only patients from the NDD naïve and switch simulations are presented here as they would be the most impacted by a more frequent clinic visit schedule, because dialysis patients have Hgb measured more frequently in the dialysis centers.

Figure 1. Simulations of the impact of 4 weeks visits vs. 12 week visits in the second year of treatment with GSK1278863 on Hgb variability (SD, 1st panels), mean Hgb (middle panels) and % of patients requiring dose adjustments (3rd panels) at each visit, by population.



When evaluating the impact of a 4 week visit frequency, Hgb standard deviation (SD), mean Hgb and percentage of patients requiring dose adjustments were assessed over a 2 year time frame. There does not appear to be any considerable differences in Hgb variability, mean Hgb or the proportion of subjects receiving dose adjustment in the second year, with visits every 12 weeks as compared to visits every 4 weeks. This suggests most subjects have titrated to a stable dose of GSK1278863 by the end of year 1.

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

/s/

ROMEO A DE CLARO
02/24/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101291

MEETING MINUTES

GlaxoSmithKline
Attention: Margaret M. Kreider, Ph.D.
Global Regulatory Affairs
2301 Renaissance Boulevard
P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Dr. Kreider:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK 12778863, a hypoxia inducible factor (HIF)-prolyl hydroxylase inhibitor.

We also refer to the meeting between representatives of your firm and the FDA on July 23, 2012. The purpose of the meeting was to discuss the proposed development plan for GSK1276883 in the Phase 2b program for informing the selection of a starting dose in the Phase 3 clinical trials.

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 Theresa Ferrara, Regulatory Project Manager at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, 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:	C
Meeting Category:	End of Phase 2a
Meeting Date and Time:	July 23, 2012 3:00 – 4:00 PM EST
Meeting Location:	FDA While Oak Building 22, Room 1309
Application Number:	IND 101291
Product Name:	GSK1278863
Indication:	A treatment for anemia of chronic kidney disease (CKD)
Sponsor/Applicant Name:	GlaxoSmithKline
Meeting Chair:	Albert Deisseroth, MD, PhD
Meeting Recorder:	Theresa Ferrara, MPH

FDA ATTENDEES

Ann Farrell, MD	Division Director, DHP
Edvardas Kaminskas, MD	Deputy Director, DHP
Albert Deisseroth, MD, PhD	Clinical Team Leader DHP
Saleh Ayache, MD	Medical Officer, DHP
Angelo de Claro, MD	Medical Officer, DHP
Yun Wang, PhD	Statistical Reviewer, Office of Biostatistics
Mark Rothmann, PhD	Statistical Team Leader, Office of Biostatistics
Rachelle Lubin, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Bahru Habtemariam, PhD	Clinical Pharmacology Acting Team Leader, Office of Clinical Pharmacology
Anshu Marathe, PhD	Pharmacometric Reviewer, Office of Clinical Pharmacology
Nitin Mehrotra, PhD	Pharmacometric Acting Team Leader, Office of Clinical Pharmacology
Theresa Ferrara, MPH	Regulatory Project Manager, DHP

SPONSOR ATTENDEES

John Lepore, MD	Medicines Development Leader for GSK1278863
Alexander Cobitz, MD, PhD	Physician Lead for anemia
Amy Meadowcroft, PharmD	Director Clinical Development
Steve Caltabiano, PhD	Director, Clinical Pharmacology
Brendan Director, PhD	Clinical Pharmacology, Modeling and Simulation
Delyth Jones, MS	Director Clinical Statistics
Margaret Kreider, PhD	Director Regulatory Affairs

1.0 BACKGROUND

The sponsor requested a Type C meeting on April 30, 2012 to discuss the clinical development of GSK1278863 as a treatment of anemia associated with CKD in patients requiring hemodialysis (HDD) and patients not requiring hemodialysis (NDD). The type C meeting was scheduled for July 23, 2012.

IND 101291 for GSK 1278863, a prolyl hydroxylase inhibitor, was originally submitted on June 2, 2008 for the treatment of anemia associated with chronic kidney disease and was found to be safe to proceed on July 3, 2009.

GSK1278863 is a potent time dependant inhibitor of hypoxia inducible factor prolyl hydroxylases (HIF-PH), EGLN1, EGLN2 and EGLN3 (egg-laying deficiency protein nine-like proteins [EGLNs]). GSK1278863 stimulates erythropoiesis by triggering the pathways involved in innate hypoxia.

GSK has designed a Phase 2b program to characterize the dose response relationship of fixed starting doses and to evaluate whether the starting dose should be adjusted based on subject characteristics. In addition, the Phase 2b program is designed to evaluate a dose adjustment algorithm for achieving and maintaining target Hgb levels. GSK also proposes to conduct separate Phase 3 trials to assess efficacy in two groups – the HDD and NDD populations. Furthermore, the sponsor plans to assess cardiovascular safety in prospectively defined meta-analysis across the Phase 3 trials.

2.0 DISCUSSION

PHARMACOMETRICS

1. Does the FDA agree that the proposed modelling approach to inform the selection of starting doses in the Phase 2B trials is reasonable?

FDA Response to Question 1: Yes, your modeling approach to inform the selection of starting doses in the Phase 2B trials seems reasonable. However, we have the following comment: Because of the known delayed effect in the pharmacodynamics and the long life span of red blood cells, besides the QD regimen, you should evaluate less frequent dosing regimen in your modeling and simulation.

Meeting Discussion July 23, 2012: The sponsor will explore less frequent dosing regimen in their modelling exercise.

2. Does the FDA agree that the proposed modelling approach to determine the dose adjustment algorithm for investigation in the Phase 2B trials is reasonable?

FDA Response to Question 2: Yes, your modeling approach to determine the dose adjustment algorithm seems reasonable. See response to question 1.

Meeting Discussion July 23, 2012: No further discussion needed.

3. Does the FDA agree that the proposed design of the Phase 2B trials and the Bayesian approach to utilize information from Phase 2A in the analysis of Phase 2B will provide sufficiently robust characterization of the dose response relationship of GSK1278863 for each population and that the approach is sufficient for informing starting dose selections for Phase 3?

FDA Response to Question 3: Your approach may be reasonable, provided you justify the use of Bayesian approach for your model. We recommend that you pool data across trials and use mixed effects modeling. The adequacy of the characterization of the dose response relationship of GSK1278863 for each population would be a review issue. We recommend that you provide results from your model and data from your Phase 2 studies in order to justify your Phase 3 dose and titration scheme.

Furthermore, we encourage you to consider an End of Phase 2A meeting with the Agency to discuss the details of your modeling approaches to select the appropriate dose for your Phase 3 trial.
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079690.pdf)

Meeting Discussion July 23, 2012: FDA clarified that the data may be pooled across phase 2a and 2b for the same population.

CLINICAL

4. Does the FDA agree that exploration of Hgb targets up to 12 g/dL for non-dialysis and up (b) (4) for hemodialysis with GSK1278863 is appropriate for the Phase 2B trials?

FDA Response to Question 4: No. We do not agree with your Hgb target for the phase 2B trial. The proposed target of Hgb of 12 g/dL in non dialysis patients (b) (4) in hemodialysis patients should be revised to a change in hemoglobin level from baseline and not a specific hemoglobin level. We advise you to review the most recent labeling for darbepoetin and epoetin for preferred limit for hemoglobin (e.g., dose adjustments for hemoglobin exceeding 11 g/dL).

Meeting Discussion July 23, 2012: The Agency and GSK discussed a drug development plan that would involve a two stage approach. Stage 1 would be comprised of a phase 3 randomized comparison of the test drug, GSK1278863, to ESAs in terms of their effect on Hgb levels within the recommendations of the existing ESA labels. Stage 2 could explore hypotheses that relate to the relative safety of ESAs given within the guidelines of ESA labeling, as compared to schedules and doses of administration GSK1278863 that might be outside those existing recommendations for Hgb levels.

5. Does the FDA agree that valid safety comparisons can be made between blinded GSK1278863 treatment arms and open-label rhEPO in the Phase 2B trials?

FDA Response to Question 5: No. The suggested period of 4 weeks for a blinded comparator arm is not sufficient to compare the safety between the GSK1278863 and rhEPO. In addition, the duration of study in phase 2B trials in general is not adequate to provide a valid safety comparison.

Meeting Discussion July 23, 2012: No further discussion needed.

6. Does the FDA agree that the extent of patient exposure and the frequency and extent of safety monitoring proposed for Phase 2B program is adequate to progress into Phase 3 trials of approximately 5500-6000 patients with a median duration of exposure anticipated to be approximately 15 months?

FDA Response to Question 6: The extent of patients' exposure and extent of safety monitoring proposed for phase 2 B appear to be adequate to support the initiation of the proposed phase 3 trials. However, additional safety monitoring steps may be required in the Phase 3 trials based on the results from the phase 2 B trials.

Meeting Discussion July 23, 2012: No further discussion needed.

CLINICAL/ LABELING

7. Does the FDA consider that demonstration of non-inferiority of GSK1278863 on a composite cardiovascular endpoint across the pooled Phase 3 trials is necessary and sufficient to support registration of GSK1278863?

FDA Response to Question 7: No. The demonstration of non inferiority of GSK1278863 on a composite cardiovascular endpoint across the phase 3 trials is not sufficient to support registration of GSK1278863.
Separate meta-analyses should be performed for NDD and HDD patients, instead of combining both settings.
We recommend you consider a superiority design for cardiovascular safety.
MACE or MACE+ should be used as the composite safety endpoint. The MACE+ endpoint will require adjudication of hospitalization events.

Meeting Discussion July 23, 2012: The Agency reiterated its concerns regarding question 7.

8. Does the FDA agree that demonstration of non-inferior CV risk for GSK1278863 when treating to higher Hgb targets (12 g/dL for NDD and Hgb (b) (4) for HDD) compared to rhEPO (b) (4) recommendations that GSK1278863 can be used to those higher Hgb targets?

FDA Response to Question 8: No we do not agree. See responses to questions 4 and 7 above.

Meeting Discussion July 23, 2012: Please refer to discussion captured under questions 4 and 7.

9. Does the FDA agree that demonstration of superiority of GSK1278863 on CV outcomes in a meta-analysis of the pooled Phase 3 trials, with appropriate internal consistency and pre-defined alpha spending strategy, (b) (4) a reduction in CV risk relative to rhEPOs?

FDA Response to Question 9: (b) (4) a reduction in CV risk of GSK1278863 relative to a specific product requires a strength of evidence consistent with achieving favorable one-sided p-values less than 0.025 from two independent studies. See response to question 7.

Meeting Discussion July 23, 2012: To answer this question, it would require further discussion.

10. Does the FDA agree that rhEPO hyporesponders represent a medically important subgroup (b) (4)

FDA Response to Question 10: Hyporesponders represent a medically important subgroup. (b) (4) you must define this population clearly and establish a pre-specified statistical analysis plan for testing hypotheses about this population prior to the start of the phase 3 trials.

Meeting Discussion July 23, 2012: The Agency and GSK agree that a multi-step process that involves repeated communications between the Agency and GSK relevant to trial design, definition of patient population, and statistical analysis plan will maximize the chances of success of the drug development plan for GSK1278863.

Additional Clinical Pharmacology comments:

1. GSK1278863 is primarily metabolized by CYP2C8 and to some extent by CYP3A4. We recommend you document concomitant use of strong and moderate inhibitors/inducers of CYP3A4 in your planned trials.

2. We recommend you collecting ECG samples at baseline and at around T_{max} of GSK1278863 and metabolites after the first dose and periodically thereafter, during all ongoing and proposed clinical trials until a thorough QT study has been completed and reviewed by the Agency.

Meeting Discussion July 23, 2012: The Agency stated this is just a recommendation that GSK may follow as necessary.

3. As part of your phase 2a/2b, we recommend that you explore the relationship between exposure and safety pharmacodynamic markers such as EPO, VEGF, hsCRP, ferritin, transferrin and total iron.

During the development of GSK1278863, address the following:

1. **Evaluate QT/QTc interval prolongation potential of GSK1278863. 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**

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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/

ALBERT B DEISSEROTH
07/27/2012