# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 217900Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131423

**MEETING MINUTES**

Concert Pharmaceuticals, Inc.
Attention: Thomas M. Koperniak, Ph.D., RAC
Director, Regulatory Affairs
65 Hayden Avenue, Suite 3000N
Lexington, MA 02421

Dear Dr. Koperniak:

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

We also refer to the teleconference between representatives of your firm and the FDA on December 12, 2022. The purpose of the meeting was to discuss plans for an initial NDA submission.

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

If you have any questions, call Qianyiren Song, Regulatory Project Manager at 301-796-2581.

Sincerely,

*{See appended electronic signature page}*

Gordana Diglisic, MD
Associate Director for Therapeutic Review
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** December 12, 2022; 1:30 p.m. – 2:30 p.m. EDT
**Meeting Location:** Teleconference

**Application Number:** IND 131423
**Product Name:** deuruxolitinib phosphate tablets, 8 mg, 12 mg (CTP-543)

**Proposed Indication:** treatment of adults with moderate to severe alopecia areata

**Sponsor:** Concert Pharmaceuticals, Inc.
**Regulatory Pathway:** 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

**Meeting Chair:** Gordana Diglisic, MD
**Meeting Recorder:** Qianyiren Song, PharmD

## FDA ATTENDEES

Gordana Diglisic, MD, Associate Director for Therapeutic Review, Division of Dermatology and Dentistry (DDD)
Melinda McCord, MD, Clinical Team Leader, DDD
Kapil (Dev) Verma, MD, Clinical Reviewer, DDD
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Soo Hyeon Shin, PharmD, PhD, Clinical Pharmacology Reviewer, DIIP
Joseph G. Toerner, MD, MPH, Deputy Director (Acting), Office of Immunology and Inflammation

## SPONSOR ATTENDEES

Christine Boisclair, Senior Vice President, Regulatory Affairs and Quality Assurance
Christopher L. Brummel, Ph.D., Vice President, DMPK, Pharmacology and Bioanalysis
James V. Cassella, Ph.D., Chief Development Officer
Cameron Cowden, Ph.D., Vice President, Pharmaceutical Development
Joseph M. Farella, Manager, Regulatory Affairs
Brett Grotbeck, Senior Director, Formulation Development
Colleen Hamilton, Senior Director, Clinical Operations
Thomas M. Koperniak, Ph.D., RAC, Director, Regulatory Affairs

## 1.0 BACKGROUND

Deuruxolitinib (CTP-543) is a JAK inhibitor being developed for the treatment of adult patients with moderate to severe alopecia areata. The purpose of the Pre-NDA meeting was to discuss the plans and reach agreement between Concert Pharmaceuticals and the Division of Dermatology and Dentistry for the NDA submission.

FDA sent Preliminary Comments to Concert Pharmaceuticals on December 9, 2022.

## 2.1. Chemistry, Manufacturing, and Controls (CMC)

***Question 1:***
The NDA will include two commercial manufacturers of Drug Substance (DS). Does the Agency agree with the proposed content and format for the data to support both manufacturers?

***FDA Response to Question 1:***
The proposed drug substance content appears reasonable, but final determination is an NDA review issue. However, the planned layout of the DS CMC sections in the NDA filing should be changed so that one module 3.2.S. does not contain the documentation related to both drug substance manufacturing sites.

Use one module 3.2.S. for each DS manufacturing site. Within each module, one section may reference the corresponding section so that duplication of documentation is minimized. For example, in the module for the first site, the section for S.3 Characterization may contain the documentation and the corresponding section in the module for the second site to reference it. However, for the section S.4 Control of Drug Substance, both modules should provide site-specific batch analysis for the respective sections.

## 2.2. Biopharmaceutics

**Question 2:**
Does the Agency agree that the clinical study demonstrating bioequivalence between the tablet formulation used in Phase 3 studies and the to-be-marketed formulation (Study CP543.1009), along with the supportive comparative dissolution data, will satisfy the requirements for bridging between formulations?

**FDA Response to Question 2:**
Your approach appears reasonable. The adequacy of the data will be determined during the review of the NDA.

**Additional Clinical Pharmacology Comments:**
Address the potential for drug interaction with gastric acid reducing agents (e.g., antacids, histamine H2-receptor antagonists, and proton pump inhibitors). Refer to the

FDA Guidance – Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications for details.

**MEETING DISCUSSION:**
The Sponsor proposed to provide a justification for not conducting the drug interaction study with gastric acid-reducing agents using the drug solubility data. The Agency responded that their rationale is reasonable. The supporting data will be reviewed after NDA submission.

## 2.3. Clinical

**Introductory Clinical Comments:**
You are developing deuruxolitinib phosphate tablets, 8 mg and 12 mg, for the proposed indication of the treatment of adult patients with moderate to severe alopecia areata (AA) under the 505(b)(1) regulatory pathway. Deuruxolitinib (CTP-543) is a Janus Kinase (JAK) 1/2 inhibitor which is intended for oral administration twice daily. In your NDA planned for submission in the second quarter of 2023, you propose to provide data from the following clinical trials:

**Phase 3**

a. CP543.3001: double-blind (DB), randomized (R), placebo-controlled (PC), 24-week trial to evaluate the efficacy and safety of CTP-543 8 mg and 12 mg in 706 adult subjects with moderate to severe AA. North America (NA) and the European Union (EU) (completed)

b. CP543.3002: DB, R, PC, 24-week trial to evaluate the efficacy and safety of CTP-543 in 517 adult subjects with moderate to severe AA. NA and EU (completed)

c. CP543.5001: open-label (OL), extension trial to assess long-term (220 weeks) safety and efficacy of CTP-543 in 1064 adult subjects from NA with moderate to severe AA [eligible subjects from 2001 (12 mg arm), 2002, 2003, 2004, 3001 and 3002 who completed 24 weeks of treatment] (ongoing)

d. CP543.5002: OL extension trial to assess long-term (52 weeks) safety and efficacy of CTP-543 in 407 adult subjects from the EU with moderate to severe AA (eligible subjects from 3001 and 3002 who completed 24 weeks of treatment) (ongoing)

**Phase 2**

a. CP543.2001: DB, R, PC, 24- week trial to evaluate the efficacy and safety of CTP-543 (4 mg, 8 mg, 12 mg) in 149 adult subjects with moderate to severe AA (completed)

b. CP543.2002: R, parallel-group, 24- week trial to evaluate the efficacy and safety of 2 dosing regimens [daily (QD) vs twice daily (BID)] of CTP-543 (8 mg BID vs 16 mg QD) in 57 adult subjects with moderate to severe AA (completed)

c. CP543.2003: R, parallel-group, 24- week trial to evaluate the efficacy and safety of 2 dosing regimens (QD vs BID) of CTP-543 (12 mg BID vs 24 mg QD) in 66 adult subjects with moderate to severe AA (completed)

d. CP543.2004: DB, R trial to evaluate maintenance of hair regrowth following dose reduction or discontinuation of CTP-543 in adult subjects with moderate to severe AA (Part A: duration of effect on hair regrowth after dose reduction or discontinuation in 403 subjects for up to 24 weeks and Part B: response after re-treatment with 8 mg BID or 12 mg BID for 24 weeks) (ongoing) (only part A to be submitted with NDA)

**Question 3:**
Does the Agency agree that the efficacy and safety data from the two adequate and well-controlled Phase 3 studies (Study CP543.3001 and Study CP543.3002) support the submission of the planned NDA for deuruxolitinib as a treatment of adults with moderate to severe alopecia areata?

**FDA Response to Question 3:**
To support filing, submit the results for Study CP543.3001 and Study CP543.3002 with data from the open label extension trial (CP543.5002) for 52 weeks of follow up and the results from Study CP543.2004 (Part A) with data from the open label extension trial (CP543.5001) for at least 52 weeks of follow up.

The decision regarding whether your application is fileable will be made within 60 days of the NDA submission.

For the clinical trials included in your submission:

a) Submit the datasets in Clinical Data Interchange Standards Consortium (CDISC) [both Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] format. Submit datasets in SAS transport format (.xpt). The analysis datasets should include all variables needed for conducting the analyses included in the study report.

b) Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

c) Include statistical programs for the key primary and secondary analyses, including programs for data imputations.

d) Include all protocols (including protocol amendments) and statistical analysis plans.

e) Include an annotated case report form (CRF). If any data is collected via electronic data capture rather than directly on the CRF, include annotated screen shots of the electronic data capture system.

**Question 4:**
Does the Agency agree with the composition and size of the safety database to support the initial NDA submission and proposed content of the 120-day safety report?

**FDA Response to Question 4:**

**Size of the safety database**
You state that at the time of NDA filing, you intend to submit safety data from an estimated 1500 subjects with moderate to severe AA who have been exposed to any dosage of deuruxolitinib, with at least 950 subjects who have been exposed to any dosage of deuruxolitinib for at least 1 year. Of these, approximately 400 subjects will have been exposed to the highest dosage of deuruxolitinib (12 mg BID) for at least 1 year. You will submit safety data on over 100 subjects who have received any dosage of deuruxolitinib for 2 years and 3 years.

As previously communicated (Advice Letter dated May 25, 2021), the size of the safety database must provide reasonable assurance that serious adverse events could be observed in a 52-week trial and be sufficient to inform long term safety. The acceptable size of the safety database will depend on the safety signals identified during the development program and the epidemiology of the disease. Because you have evaluated two doses (8 mg and 12 mg), the safety database must have sufficient numbers of subjects at each to-be-marketed dose to allow adequate safety evaluation. The safety data obtained from a lower dose will not support approval at a higher dose.

**120-day safety report**
In the 120-day safety report, you propose to include "additional safety data" from ongoing trials CP543.5001 and CP543.5002 [open-label extension (OLE) trials] and CP543.2004 Part B (response after re-treatment). At the time of NDA submission, provide data for at least 52 weeks of follow-up from ongoing open label extension trials CP543.5001 and CP543.5002 to inform the long-term safety of your product. See FDA Response to Question 3.

Per 21 CFR 314.50, the safety update report must provide new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any

Medication Guide. Include the same kinds of information (from clinical trials and other sources) in the same format as the integrated summary. Provide narratives for all subjects who died, experienced serious adverse events (SAEs), pregnancy, and reported treatment emergent adverse events of special interest (TEAESI).

**Question 5:**
At the Type B Meeting held on 08 August 2022 to discuss the analysis plan for the ISS, the Agency requested narratives for all TEAESIs. With regard to the TEAESI of all infections, Concert proposes to submit narratives only for infections assessed as being ≥ Grade 3 severity (CTCAE v5.0 criteria), unless the infection meets the criteria for another TEAESI category. All infections (regardless of Grade) will still be tabulated in the ISS as a TEAESI category for inclusion in the ISS. Does the Agency agree with this approach for the narratives?

**FDA Response to Question 5:**
In general, we agree with your approach.

However, in addition to submitting narratives for the treatment emergent adverse events of special interest (TEAESI) of all infections assessed as ≥ Grade 3 in severity according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria, submit narratives for all infections assessed as being serious per the International Council for Harmonisation (ICH) serious adverse event (SAE) criteria regardless of severity.

Also, submit narratives for:

a. all other TEASIs regardless of severity [serious infections, opportunistic infections, herpes zoster, herpes simplex, tuberculosis (TB), all malignancies, malignancies excluding non-melanoma skin cancer (NMSC), NMSC, major adverse cardiovascular event (MACE), thrombosis, gastrointestinal perforation, hypersensitivity reactions, anaphylaxis, angioedema, and laboratory abnormalities (neutropenia, lymphopenia, anemia, lipid elevation, thrombocytosis, thrombocytopenia, creatine phosphokinase elevations (CPK), liver enzyme elevations and drug induced liver injury (DILI)]

b. all TEAEs related to retinal detachment regardless of severity

Additional case report forms and narratives should be available upon request.

**Question 6:**
The Agency noted at the Type B Meeting held on 08 August 2022 that narratives for TEAESIs should be included in the NDA as discussed above in Question 5. As also discussed at the Type B Meeting, Concert plans to include narratives and case report forms for deaths, discontinuations due to AEs, SAEs, MACE, malignancies, increases in CK (≥10,000 U/L), neutropenia (<500 cells/µL), platelet increases (≥650,000 cells/µL),

thrombocytosis, and potential drug-induced liver injury (DILI). Does the Agency agree that mild (Grade 1) and moderate (Grade 2) TEAESI case report forms are not needed to support the NDA?

**FDA Response to Question 6:**
Yes, we agree that CRFs for mild and moderate TEAESI are not needed. All CRFs should be available upon request. However, provide narratives for all TEAESI regardless of severity in your NDA submission as discussed in the FDA Response to Question 5.

**Question 7:**
Does the Agency agree with the Bioresearch Monitoring (BIMO) proposal to include the two pivotal Phase 3 studies (Study CP543.3001 and Study CP543.3002) in the summary level clinical site dataset?

**FDA Response to Question 7:**
Yes.

Additional Clinical Comments:

a. In the Clinical Study Report for Trial CP543.3001 submitted on November 22, 2022, you provided tabulations of TEAESI reported for ≥2% of subjects in any treatment arm. We reiterate our advice to provide tabulations in the Integrated Summary of Safety (ISS) of TEAEs, adverse reactions (ARs), adverse events (AEs) leading to discontinuation, and SAEs greater than **≥1%** of subjects in any treatment arm, not ≥2% in your NDA submission (August 8, 2022, Type B Meeting).

b. Submit (evaluation of Drug-Induced Serious Hepatotoxicity) eDISH plots, an analysis of potential Hy's Law and Temple's Corollary cases, narratives, tabulations, and discussions of abnormal liver enzyme findings.

c. Provide representative photosets for subjects who achieved Severity of Alopecia Tool (SALT) ≤20 in your phase 3 trials. For each subject, provide photographs taken at Baseline, Week 24, and Week 52. Include photographs for the following subgroups:

    a. 10 subjects with partial scalp hair loss at Baseline (SALT score 50-94)

    b. 10 subjects with complete or near-complete scale hair loss at Baseline (SALT score 95-100)

d. Refer to the August 8, 2022, Type B Meeting Minutes for additional comments regarding data presentation (e.g., pooling, shift tables, demographics tables).

**MEETING DISCUSSION:**
The Agency agreed that Sponsor's proposal to include photosets up to Week 24 is acceptable. The Agency advised the Sponsor that the photographs should be placed in Module 5 in the Appendix (Section 16) of each clinical study report.

## 2.4. Regulatory

**Question 8:**
Does the Agency agree that the proposed content and format as outlined in the proposed Table of Contents meets the requirements for a Complete Application?

**FDA Response to Question 8:**
The proposed eCTD Table of Contents contains Form FDA 3455: Financial Disclosure located in Section 1.1 Forms. This Form (FDA 3455) should be placed in Section 1.3.4 - Financial certification and disclosure.

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

The overall content of the proposed Table of Contents (TOC) appears reasonable. In addition, include the following:

a. In Module 1, provide available data (e.g., from published literature, pharmacovigilance database, and clinical trials) to support the content of Section 8 of labeling, 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential sections.

b. In Module 2.5 Clinical Overview include a benefit-risk analysis, a statement of Good Clinical Practice that all clinical studies were conducted under the supervision of an Institutional Review Board (IRB) and with adequate informed consent procedures and a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.

c. In Module 5, provide interim results from open-label Trials CP543.5001 and CP543-5002 (not included in current TOC).

**MEETING DISCUSSION:**
Given the documented safety profile for JAK inhibitor class products and the chronic indication (AA), the Agency reiterated the need to understand both the short- and long-term safety of the product in the treatment of AA. Therefore, the Agency stated that safety data for 52 weeks will be needed to establish the risk and benefit in the target population.

The Agency reiterated the FDA Response to Question 3 that we expect the Sponsor to submit data for 52 weeks of follow-up for the ongoing open- label extension trials

CP543.5001 and CP543.5002. The Agency reiterated that the adequacy of the safety database will depend on safety signals seen in the development program. The Agency emphasized that data from the open-label trials should include data from the highest dose to help inform safety because safety findings from the lower dose will not support safety of the higher dose.

Regarding the need for interim reports, the Agency agreed that the Sponsor can include safety and efficacy data from these extension trials in the ISS and ISE. The data should be presented side by side for each open- label trial individually and provide the disposition of subjects, the number of dropouts and missing data, reasons for discontinuation, and safety findings (including adverse events).

**Question 8a:**
Does the Agency agree (in accordance with PDUFA VII), if needed, Concert may submit additional stability data no later than 30 days of the original NDA Application?

**FDA Response to Question 8a:**
Your approach of submitting additional stability data no later than 30 days of the original NDA application appears reasonable.

**Question 9:**
Based on current information from the ongoing evaluation of the clinical safety of deuruxolitinib, and in line with recent approvals of other JAK inhibitors for dermatology indications, including alopecia areata, Concert believes that labeling will adequately communicate safety risks to prescribers. Therefore, Concert does not propose to submit a Risk Evaluation Mitigation Strategy (REMS) at the time of the initial NDA submission, but will include a Patient Medication Guide to ensure patient education about the potential risk of deuruxolitinib. Does the Agency agree with this proposal?

**FDA Response to Question 9:**
The need for REMS will be determined during the NDA review.

**Question 10:**
Does the Agency agree with the clinical studies for which financial disclosure information will be provided?

**FDA Response to Question 10:**
Yes, we agree. Per 21 CFR 54.2 (e) and 54.3, the two phase 3 trials are “covered clinical studies” and the open-label extension trials do not serve to support the effectiveness of a product or include a single investigator who makes a significant contribution to the demonstration of safety. Refer to Section G in the *Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators (2013)* for additional information on trials qualifying as “covered clinical studies.”

## 3.0 ADMINISTRATIVE COMMENTS

### 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. 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.

### 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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

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

human drug and biological products.

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

- Regulations and related guidance documents.

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

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

- 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.

## MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

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[3] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[4]. 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.

## 4.0 SPONSOR'S RESPONSE TO FDA PRELIMINARY COMMENTS

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

**Section 2.2 Biopharmaceutics:**

**Additional Clinical Pharmacology Comments (Page 2):**

Regarding the FDA Guidance on Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents, we believe that deuruxolitinib, which is an immediate-release dosage form, is unlikely to have *in vivo* drug interactions with acid reducing agents. Deuruxolitinib meets the definition of a high solubility compound with the highest marketed dose strength soluble in 250 mL of water over the pH range of 1.0–6.8 at 37°C. Specifically, the solubility of deuruxolitinib is at least 0.12 mg/mL in the relevant physiological pH range (pH 1.0–6.8), which is greater than the maximum single dose, 12 mg, divided by 250 mL (0.05 mg/mL).

Based on this assessment, a DDI clinical study has not been conducted and pivotal clinical studies did not restrict use of any acid reducing agents.

Concert plans to include this rationale for not conducting this DDI study, as well as the relevant solubility data in the application. Does the Agency agree with our proposal?

**Section 2.3 Clinical:**

**Additional Clinical Comments (c) (Page 7):**

Photographs were collected at each study visit when SALT assessments were performed in the Phase 3 studies CP543.3001 and CP543.3002; however, photographs were not collected in the open label extension studies. Therefore, we will not be able to provide the requested representative photosets beyond the first 24 weeks of dosing. However, for the requested representative photosets, we can provide photos for the subgroups described at Baseline, Week 12 and Week 24.

Would this be acceptable to the Agency?

Could the Agency advise on where these photographs should be included in Module 5?

**Section 2.4 Regulatory:**

**Question 8 (c) (top of Page 8):**

As the Open Label Extension studies CP543.5001 and CP543.5002 will still be on-going at the time of the initial filing, as discussed at the ISS/ISE Meeting on 08 August 2022, we are planning to include a data-cut from these studies in the ISS and ISE. We were not planning to submit interim reports because there will be a summary and discussion of the interim data from these studies in specific sections (long-term exposure) of the ISS and ISE. Does the Agency agree that these summaries in the ISS and ISE will address this request for "interim results"?

---

**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/

---

GORDANA DIGLISIC
12/15/2022 08:37:04 AM

IND 131423

**MEETING MINUTES**

Concert Pharmaceuticals, Inc.
Attention: Christine Boisclair
Vice President, Regulatory Affairs & Quality Assurance
65 Hayden Avenue, Suite 3000N
Lexington, MA 02421

Dear Ms. Boisclair:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CTP-543 tablets, 4mg, 8 mg, and 12 mg.

We also refer to the telecon between representatives of your firm and the FDA on March 30, 2020. The purpose of the meeting was to discuss the development program for CTP-543.

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

If you have any questions, call Qianyiren Song, Regulatory Project Manager at 301-796-2581.

Sincerely,

*{See appended electronic signature page}*

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** March 30, 2020 9:00 a.m. – 10:00 a.m. DST
**Meeting Location:** Teleconference

**Application Number:** 131423
**Product Name:** CTP-543 tablets, 4 mg, 8 mg, 12 mg

**Proposed Indication:** For the treatment of moderate to severe alopecia areata
**Sponsor Name:** Concert Pharmaceuticals, Inc.

**Meeting Chair:** Kendall A. Marcus, MD
**Meeting Recorder:** Qianyiren Song, PharmD

## FDA ATTENDEES

- Kendall Marcus, MD, Director, DDD
- Gordana Diglisic, MD, Clinical Team Leader, DDD
- Melinda McCord, MD, Clinical Reviewer, DDD
- Mohamed Alosh, PhD, Biometrics Team Leader, DB III
- Kathleen Fritsch, PhD, Biometrics Reviewer, DB III
- Onyekachukwu Illoh, MPH, OD, Acting Team Leader, Clinical Outcome Assessment (COA)
- Yasmin Choudhry, MD, Reviewer, COA
- Barbara Gould, MBAHCM, Chief of Project Management Staff, DDD
- Qianyiren “Cicy” Song, PharmD, Regulatory Project Manager, DDD

## SPONSOR ATTENDEES

- Christine Boisclair, Vice President, Regulatory Affairs and Quality Assurance
- Virginia Braman, Vice President, Clinical Development
- James V. Cassella, Ph.D.  Chief Development Officer
- Colleen Hamilton, Associate Director, Clinical Operations
- Thomas M. Koperniak, Ph.D., RAC, Associate Director, Regulatory Affairs
- (b) (4) Statistics and Clinical Writing Consultant (b) (4)
- (b) (4) Clinical Consultant (b) (4)

## 1.0 BACKGROUND

**Purpose of Meeting:**
The purpose of this meeting is to discuss the adequacy of the proposed developmental plan of CTP-543.

**Regulatory Correspondence History**

We have had the following meetings/teleconferences with you:

- October 5, 2016 Pre-IND

We have sent the following correspondences:

- December 19, 2017 Grant Fast Track
- July 7, 2017 Remove Full Clinical Hold
- May 22, 2017 Full Clinical Hold
- December 7, 2016 Study May Proceed

## 2.0 DISCUSSION

**General Comments**

You are developing an oral Janus kinase inhibitor (JAK), CTP-543 tablets, for the treatment of moderate to severe alopecia areata (AA). We continue to be concerned about the exposure of vulnerable populations to a deuterated form of ruxolitinib. Ruxolitinib tablets, marketed as JAKAFI® is indicated for the treatment of patients with: intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis, polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea and steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older. Serious adverse reactions described in labeling for JAKAFI® include the risk of thrombocytopenia, anemia requiring transfusion, neutropenia, serious infections [such as tuberculosis, herpes zoster, hepatitis B, Progressive Multifocal Leukoencephalopathy (PML)], non-melanoma skin cancer, and lipid elevation (Warnings & Precautions section of labeling).

To date, you have completed 6 clinical trials in your development program that enrolled 315 adult subjects. Four trials evaluated healthy volunteers and two trials evaluated subjects with moderate to severe AA.

Phase 1 Trials in Healthy Adult Volunteers (HV)

1. **CP543.1001**: Randomized, dose escalation trial evaluated the pharmacokinetics (PK), pharmacodynamics (PD) and safety of single doses (8,16, 32 and 48 mg) and multiple doses (8, 24, 32 mg QD X 7 days; 8 or 16 mg BID X 7 days) of CTP-543 or placebo in 77 HV (non-IND trial).

2. **CP543.1002**: Open- label, single dose, PK trial compared the systemic exposure of 16 mg of CTP-543 to the systemic exposure of 15 mg of Jakafi® in 12 HV.

3. **CP543.1003**: Open- label trial evaluated the bioavailability of 16 mg of CTP-543 under fed and fasting conditions using a crossover design in 14 HV.

4. **CP543.1004**: Open- label trial evaluated the absorption, metabolism, excretion, and mass balance of CTP-543 in 6 HV.

Phase 2 Trials in adults with moderate to severe AA (age 18 to 65 years with ≥ 50% hair loss according to SALT and current episode lasting 6 months to 10 years)

1. **CP543.2001**: Randomized, double-blind, placebo-controlled, 24 -week dose ranging trial to evaluate the safety and efficacy of CTP-543 (4, 8, or 12 mg BID) in 149 subjects with AA. The study design included 3 sequential cohorts. Most subjects were female, White and had patchy AA (46%) or alopecia universalis (36%) with a mean SALT score of 87-89 at Baseline.

    a. Subjects who received either 8 mg BID or 12 mg BID of CTP-543 met the primary efficacy endpoint (percentage of patients achieving a ≥ 50% relative change from baseline at 24 weeks).

    b. There were no deaths and one serious adverse event (SAE) which was assessed as possibly related in the 12 BID dosing group (cellulitis.)

    c. The most common treatment emergent adverse events (TEAEs) in the CTP-543 dosing groups were headache, upper respiratory tract infection, acne and nasopharyngitis. Investigators observed decreases in red blood cell parameters and neutrophil counts in the CTP-543 groups. One subject withdrew due to grade 1 anemia in the 8 mg BID group. Increased platelet counts of unknown significance occurred in all CTP-543 groups compared to placebo but there were no reports of associated bleeding or thrombosis.

2. **CP543.2002**: Randomized, multi-center, 24 -week trial of double dummy design to evaluate the efficacy and safety of 2 dosing regimens of CTP-543 (8 mg BID or 16 mg QD) in 57 subjects with AA. Most subjects had patchy or universalis pattern alopecia. The primary outcome was the relative change in SALT score for each dose regimen from baseline at Week 24.

    a. Following 24 weeks of dosing, subjects in the 8 mg BID dose group had a 46% relative change from Baseline in Total SALT score at Week 24 compared to 18% in the 16 mg QD dose group.

    b. There were no deaths, serious adverse events or TEAEs that lead to study discontinuation. Dose interruption occurred in one subject with elevated creatinine. There were slightly more TEAE in the 16 mg QD cohort.

**Ongoing Trials in Adult Subjects with Alopecia Areata (AA)**

1. **CP543.2003**: Randomized, multi-center, 24 -week trial of double dummy design to evaluate the efficacy and safety of 2 dosing regimens of CTP-543 (12 mg BID or 24 mg QD) in 66 subjects with AA.

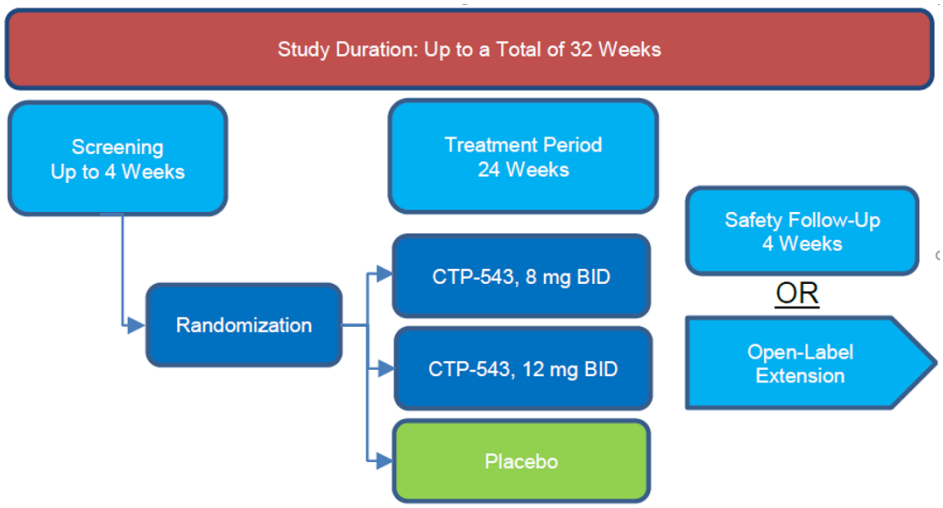
    o There were no deaths and one SAE of syncope associated with an elevated troponin level assessed as possible related which lead to dose interruption. To date, the most common TEAEs reported across the two treatment groups are headache (18%), upper respiratory tract infection (18%), and nasopharyngitis (12%) with the higher incidence of treatment emergent adverse events occurring in the 24 mg QD dose group.

2. **CP543.5001**: Open-label extension study enrolling completers from Trials CP543.2001 (Cohort 3), CP543.2002, and CP543.2003. Subjects will receive 8 mg BID or 12 mg BID of CTP-543 for up to 108 weeks. You plan to evaluate approximately 150 subjects for safety. To date, you reported two SAEs: near syncope from atrial fibrillation and colon cancer in a subject with a family history of colon cancer which were assessed as possible related and unlikely related, respectively.

**Proposed Phase 3 Trial(s)**

- **CP543.3001:**

You proposed to conduct replicate double-blind, randomized, placebo-controlled, multicenter trials to evaluate the efficacy and safety of 2 doses of CTP-543 (8 mg or 12 mg BID) in adult subjects age 18 to 65 years with moderate to severe AA. Subjects will be randomized in a 3:3:1 ratio (8 mg:12 mg: placebo) and stratified by degree of hair loss (partial: SALT ≥ 50 and < 95 or near complete: SALT ≥ 95). After the 24-week treatment period, subjects may enroll in the open-label extension trial or participate in a 4-week follow-up period.



You plan to enroll approximately 630 subjects with a current episode of scalp hair loss persisting ≥ 6 months to ≤ 10 years and ≥ 50% scalp hair loss according to Severity of Alopecia Tool (SALT) scoring at Screening and Baseline. No more than approximately 75% of subjects may have severe hair loss (SALT ≥ 95). Subjects with concomitant moderate to severe androgenic alopecia, systemic infection, malignancy, organ transplantation and laboratory findings at screening suggestive of thyroid, hematologic, hepatic, renal metabolic disfunction will be excluded.

Safety monitoring will include AEs, vital signs, physical examinations, concomitant medications, and clinical laboratory parameters (chemistry/hematology bi-weekly for 1 month and then monthly; lipids monthly.)

Other assessments: sparse pharmacokinetic (PK) sampling for population PK analysis, patient and clinician global impression of disease severity (CGI-S and PGI-S), patient and clinician global impression of improvement (CGI-I and PGI-I), Patient Reported Outcome for Satisfaction (SPRO) and Hair Quality (QPRO), and the Hospital Anxiety and Depression Scale (HADS).

**Endpoints**

Primary Efficacy Endpoint

- The primary efficacy endpoint will be the percentage of patients achieving an absolute SALT ≤20 at Week 24.

Key Secondary Endpoints

1. Percentage of responders (defined as “much improved” or “very much improved”) using the CGI-I at Week 24
2. Percentage of responders (defined as “much improved” or “very much improved”) using the PGI-I at Week 24
3. Mean change from baseline in the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Week 24
4. Percentage of patients achieving an absolute SALT score of ≤20 at Week 20, 16, 12, 8, and 4

**Development Plan**

1. **Phase 3 trial in adolescent subjects (12-17)** to be conducted concurrently with the second Phase 3 trial in adults.
2. **Trials in special populations** (subjects with renal and hepatic impairment; subjects receiving concomitant CYP3A4 inducers, inhibitors and oral contraceptives)
3. **Effects of CTP-543 on QT/QTc intervals** (single dose, 12 and 48 mg, placebo, moxifloxacin)

## 2.1. Regulatory

***Question 9***
Concert plans to submit a formal initial Pediatric Study Plan separately and within 60 days of this EOP2 meeting for review but does the Division have any comments on the brief summary of the proposed plan included in the Briefing Document?

***FDA Response to Question 9***
In your initial Pediatric Study Plan, you propose to request the following:

1. a partial waiver of assessments for the pediatric age group 0 to < 6 years of age on the grounds that studies would be impossible or highly impracticable because of the rarity of alopecia areata in this age group

2. a deferral of pediatric studies [redacted] (b) (4) to allow for the collection of additional safety and efficacy data.

Given the documented safety profile of the moiety, we recommend that you request a deferral of assessments in the pediatric population until the efficacy (including durability of response, maintenance of response and response after retreatment) and safety of your product have been determined in the adult population.

For future trials in the pediatric population, if you plan to use the same instruments (e.g., SPRO, QPRO) from Study CP543.3001, confirm the content relevance of these instruments in this target population. It will also be important to assess the readability and comprehensibility of the instruments in this subpopulation.

Additional considerations specific to pediatric populations should be taken into account when selecting an appropriate clinical outcome assessment, including using an instrument that is content and psychometrically valid for assessment in the patient population of interest. You may refer to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force paper for further clarification on pediatric clinical outcome assessment considerations.

***Meeting Discussion:***
*The sponsor requested clarification regarding deferral of assessments in the pediatric population age 6 to 17 years. The FDA recommended that iPSP include deferral of assessment in pediatric population (6 to 17 years of age) until the efficacy and safety is established in the adult population.*

## 2.2. Chemistry, Manufacturing and Controls (CMC)

No CMC questions were provided for this meeting.

## 2.3. Nonclinical

***Question 1a***
Does the FDA agree that the available toxicology data are sufficient to support the proposed Phase 3 studies in adult patients, and in conjunction with ongoing and planned studies, are sufficient to support the NDA filing for the treatment of moderate to severe alopecia areata, specifically:

1. Repeat-dose toxicology studies
2. Reproductive toxicology studies
3. Genotoxicity studies
4. Carcinogenicity studies

***FDA Response to Question 1a***
We agree that your proposed nonclinical program appears reasonable to support the proposed Phase 3 trials in adult subjects and NDA filing.

***Question 1b***
Does the FDA agree that a 26-week carcinogenicity study in Tg.rasH2 mice, in combination with the 2-year rat carcinogenicity study, is sufficient to support an NDA filing?

***FDA Response to Question 1b***
We agree that your proposed carcinogenicity testing appears reasonable to support NDA filing.

***Question 1c***
Does the FDA agree that additional nonclinical CNS, cardiovascular, and pulmonary safety pharmacology studies are not required to support an NDA filing?

***FDA Response to Question 1c***
We agree that additional nonclinical CNS, cardiovascular and pulmonary safety pharmacology studies are not needed to support NDA filing.

***Question 1d***
Does the FDA agree that in light of the immunomodulatory mechanism of action of CTP-543 a separate immunotoxicity study is not required to support an NDA filing?

***FDA Response to Question 1d***
We agree that a separate immunotoxicity study is not needed to support NDA filing since repeat-dose toxicity studies have demonstrated the immunosuppressive effects associated with CTP-543.

**Question 2**
Does the FDA agree that the available toxicology data are sufficient to support the inclusion of patients aged between 12 and 17 years in the Phase 3 program?

***FDA Response to Question 2***
We agree that the available toxicology data support inclusion of subjects 12 – 17 years old in Phase 3 clinical trials.

## 2.4. Clinical Pharmacology/Clinical/Biostatistics

***Question 3***
Does the FDA agree that the metabolite profile data generated to date are sufficient to support an NDA filing?

***FDA Response to Question 3***
We acknowledge that your two main metabolites (C-21214 and C-21217) do not need additional toxicology studies as you indicated that the levels of metabolites did not exceed 10% of parent concentration. The adequacy of your metabolite profile data will be a review issue at the time of NDA submission.

***Question 4***
Does the FDA agree that the available and planned Clinical Pharmacology studies are sufficient to support an NDA filing?

***FDA Response to Question 4***
Your overall planned Clinical Pharmacology studies appear reasonable; however, the adequacy of the studies will be determined at the time of your NDA review. We may have additional comments when you submit full study protocols.

***Question 5***
Does the FDA agree that the proposed drug-drug interaction (DDI) studies are sufficient to support an NDA filing?

***FDA Response to Question 5***
Your proposed DDI study outlines appears reasonable. We may have additional comments when you submit full study protocols. The adequacy of your DDI studies will be a review issue at the time of NDA submission.

***Question 6***
Does the FDA agree with the key study design parameters for the proposed Phase 3 trials in adult patients (refer to draft CP543.3001 clinical trial protocol in Appendix 1) in order to support an indication for the treatment of moderate to severe alopecia areata, including:

A. Eligibility Criteria
B. Primary and Key Secondary Endpoints
C. Statistical Analysis
D. Sample Size
E. Dose Selection and Dosing Regimen

F. Treatment Duration
G. Safety Monitoring and Data Monitoring Committee

***Question 6a***
Does the FDA agree with the key Eligibility Criteria for patient participation in the proposed Phase 3 trial (CP543.3001), including extent and duration of current episode of hair loss at baseline, in order to support an indication for the treatment of moderate to severe alopecia areata?

***FDA Response to Question 6a***
Your key eligibility criteria (adult subjects with moderate to severe AA with ≥ 50% hair loss as measured by the SALT and a current episode of hair loss with a duration of 6 months to ≤ 10 years) are reasonable. In addition, the demographics of your study population should be consistent with your target population and potential real-world use (e.g. age >65 years, hemoglobin A1c ≥6.5% etc.)

***Question 6b***
Does the FDA agree with the primary and key secondary endpoints for the proposed Phase 3 trial (CP543.3001)?

***FDA Response to Question 6b***
Your proposed primary efficacy endpoint of the percentage of subjects achieving an absolute SALT ≤20 at Week 24 appears reasonable.

We have the following comments regarding your proposed secondary endpoints:

1. In Phase 3 trials, secondary endpoints intended for labeling need to be limited in number, clinically meaningful and analyzed within a framework that controls for multiplicity.

2. Your proposed secondary endpoint of the percentage of subjects achieving an absolute SALT score of ≤20 at Week 20, 16, 12, 8, and 4" is clinically meaningful and supportive of the primary efficacy endpoint.

3. You propose to evaluate mean change from baseline in the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Week 24. A single satisfaction item is a reasonable option to assess overall satisfaction of the scalp hair in the proposed context of use. However, the results of the SPRO overall satisfaction item will be expected to be consistent with the results of the Quality of Hair in Patient-Reported Outcome (QPRO) to strengthen the support of a satisfaction claim. We have the following additional comments regarding the SPRO:

    a. Submit evidence of other measurement properties (reliability, construct validity, ability to detect change), including what constitutes a meaningful within-patient score change (i.e., responder), to further support the

adequacy of this instrument. Plan to provide a justification for a threshold of meaningful within-patient score change.

b. Consider the most appropriate endpoint definition [redacted] (b) (4) Currently, the change from baseline analysis may be difficult to interpret as a mere change in magnitude of satisfaction might not translate to a clinically meaningful benefit. Consider measuring the percentage of subjects achieving "satisfied" or "very satisfied" at prespecified timepoints.

c. The administration of the SPRO at three time points (Baseline, Weeks 12 and 24) may be insufficient and may miss important information on the benefits of the product throughout the trial. We recommend administering the SPRO and QPRO at intervals throughout the treatment period to see whether there are steady increases in SPRO and QPRO scores over time as this provides useful evidence that scores are determined by experience and are not simply an initially hopeful response to a new treatment, which subsequently declines.

4. For the context of this development program, we view the Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Improvement (PGI-I) as exploratory measures that can be used as anchors to determine what constitutes a clinically meaningful change in another clinical outcome assessment (COA). Further, the CGI-I and PGI-I have limitations, as they are susceptible to recall error and lacks assessment of change from baseline.

5. Based on your qualitative data, eyelash and eyebrow hair loss is important to patients. Consider modifying your secondary endpoint hierarchy to evaluate these outcomes as key secondary endpoints using appropriate scales. However, in the absence of the copies of the Brigham Eyebrow Tool for Alopecia (BETA) and Brigham Eyelash Tool for Alopecia (BELA), we cannot fully comment on the adequacy of these instruments. Submit exact copies of these instruments, including information regarding its development history, for review and comment.

***Question 6c***

Does the FDA agree with the statistical analysis strategy, including missing value and multiple comparison approach, for the proposed Phase 3 trial (CP543.3001)?

***FDA Response to Question 6c***

1. *Analysis Population:* We recommend defining the efficacy population as all subjects randomized and dispensed medication, rather than all subjects who have at least 1 post-treatment SALT assessment.

2. *Analysis Method:* Analyzing the primary efficacy endpoint with the Cochran-Mantel-Haenszel test stratified on baseline scalp hair loss (SALT ≥50 to <95 vs. SALT ≥95) appears reasonable.

3. *Missing Data Handling:* We do not agree with your approach towards missing data handling. You have proposed using LOCF as the primary method of handling missing data with sensitivity analyses conducted using observed cases and Worst Observation Carried Forward. You have proposed only single imputation methods, and LOCF and WOCF are likely to lead to very similar results. In addition, an observed case analysis does not follow the intent-to-treat principle. To account for additional variability introduced by missing data, we recommend using a multiple imputation approach (full details of the approach should be included in the protocol, including the number of imputations, analysis and imputation models, randomization seeds, and any needed transformations). To ensure that the results are not driven by the missing data handling method, we recommend that the sensitivity analyses for the handling of missing data use alternative assumptions from the primary method. We also recommend including a tipping point analysis.

***Meeting Discussion:***
*The sponsor acknowledged the Agency's recommendations regarding using missing data handling methods that use a variety of methods and assumptions. The sponsor inquired whether it would be acceptable to use LOCF as the primary method and multiple imputation and tipping point analysis as sensitivity analyses. The Agency stated that while it is difficult to recommend specific procedures because all procedures have challenges, multiple imputation procedures have some advantages over single imputation methods and may be preferable over LOCF for the primary method.*

4. *Multiple Comparisons:* Your proposed hierarchical approach for analyzing the primary and key secondary endpoints across two doses will not adequately control the type I error rate. You propose to compare the 12 mg dose vs. placebo for the primary efficacy endpoint. If this comparison is statistically significant at 0.05 you plan to proceed to both the 8 mg dose vs. placebo comparison for the primary endpoint and to the first key secondary endpoint listed in your hierarchy, regardless of whether the 8 mg dose vs. placebo comparison is statistically significant. Such a proposal inflates the overall type I error rate, because it does not propose any method of splitting the alpha across the two potential paths (proceed to the primary endpoint for 8 mg vs. placebo or the first key secondary endpoint for the 12 mg vs. placebo comparison). One approach that would control the overall type I error rate across your set of primary and key secondary endpoints is to allocate $\alpha$=0.025 to each set of dose comparison endpoints (12 mg vs. placebo and 8 mg vs. placebo). As the secondary endpoints should be supportive of the primary endpoint, the secondary endpoints for a dose level should only be evaluated if the primary endpoint for that dose level is statistically significant.

***Meeting Discussion:***
*The sponsor clarified that in their planned hierarchical method, the proposed hierarchy would be to test the primary endpoint for the 8 mg dose, only if the primary endpoint for the 12 mg dose was significant, and then only test the secondary endpoints for the 12 mg dose if the primary endpoint was significant for the 8 mg dose. The secondary endpoints for the 8 mg dose would only be tested if all secondary endpoints for the 12 mg dose were significant. The Agency acknowledged that the while the clarified procedure would control multiplicity, it may cause challenges with interpreting the results, as whether the secondary endpoints could be tested for a particular dose would depend on the results for endpoints from the other dose. The proposed procedure may not be able to provide complete supportive information regarding the efficacy of each dose, as the hierarchical procedure may stop before getting the opportunity to evaluate some endpoints. Thus, we recommend proposing a procedure that permits assessment of the secondary endpoints for the doses that demonstrate significance for the primary endpoint and controls multiplicity across all of the primary and secondary endpoints, such as a procedure that allocates 0.025 to each dose family.*

***Question 6d***
Does the FDA agree with the sample size determination for the proposed Phase 3 trial (CP543.3001)?

***FDA Response to Question 6d***
Your sample size calculations are based on an analysis proposal that does not adequately take into account the multiplicity introduced by two doses and multiple key secondary endpoints. Once you specify a method that adequately controls the overall type I error rate for the study, you will need to take the design modifications into account with your sample size calculations (for example, using $\alpha=0.025$ for your calculations rather than $\alpha=0.05$).

***Question 6e***
Does the FDA agree with the Dose Selection and Dosing Regimen for the proposed Phase 3 trial (CP543.3001)?

***FDA Response to Question 6e***
The decision to pursue further development of a given dose and dosing regimen are based on the assessment of the benefit and risk of a product in the target population. The reason for the substantial disparity in efficacy between once daily and twice daily dosing regimens is not clear.

***Question 6f***
Does the FDA agree with the treatment duration for the proposed Phase 3 trial (CP543.3001)?

***FDA Response to Question 6f***

The primary timepoint to evaluate the efficacy of a product for the treatment of AA depends on the rate of growth of the hair (impacted by the stage in the growth cycle, location, sex, ethnicity and age) and the performance of the product (e.g. informed by a dose ranging study). Based on the data from Phase 2 Trial CP543.2001, the proposed time point for the primary efficacy evaluation (Week 24) may be reasonable However, efficacy data from later timepoints are not provided.

***Meeting Discussion:***

*The sponsor clarified that the primary time point for the efficacy assessment was based on data collected in Phase 2 trial. The Agency responded that the sponsor's approach appears reasonable.*

***Question 6g***

Does the FDA agree with the scope of the safety monitoring and establishment of a Data Monitoring Committee for the proposed Phase 3 trial (CP543.3001)?

***FDA Response to Question 6g***

We agree with your plan to include an Independent Data Monitoring Committee in your Phase 3 trials. Your proposed safety monitoring which includes periodic evaluation of adverse events, vital signs, physical examinations, concomitant medications, and clinical laboratory parameters appears reasonable. In view of the 2 recent reports of syncope/near-syncope which appear to be of cardiac origin, you may consider conducting your evaluation of the effects of CTP-543 on QT/QTc prior to the Phase 3 trials.

Progressive Multifocal Leukoencephalopathy (PML) has been reported with the use of Janus Kinase Inhibitors including ruxolitinib. We recommend that you propose acceptable safety monitoring, stopping criteria and follow-up assessments for potential cases of PML.

***Meeting Discussion:***

*The sponsor indicated that the drug-and-drug interaction studies that they intended to conduct prior to the QT/QTc would be delayed. Therefore, they intend to conduct QT/QTc concurrently with the first Phase 3 trial. The Agency agreed that the proposal was reasonable.*

***Question 7***

Does the FDA agree that the overall projected safety database will be sufficient to support the proposed NDA filing for the treatment of moderate to severe alopecia areata?

***FDA Response to Question 7***

An adequate safety database to support NDA filing should include at least the number of subjects described in ICH E1A using the to-be-marketed formulation and dosing

regimen (concentration and frequency). The size of the safety database will be driven by the adverse events of interest expected to be observed in your clinical trial. You should design your trial to able to observe such adverse events with a reasonable probability (example 0.95).

However, the adequacy of the data to support approval of CTP-543 for the treatment of moderate to severe AA will be a review issue.

***Question 8***
Does the FDA agree that the proposed Phase 3 program will be sufficient for the proposed NDA filing for the treatment of moderate to severe alopecia areata, assuming the primary efficacy endpoints are met, and the secondary endpoints similarly support efficacy and safety?

***FDA Response to Question 8***
We have the following comments regarding your Phase 3 development program:

1. Given the safety profile of your product and the chronic conditions of use, we need to understand both the short- term and long- term effects of treatment in the target population. To understand the performance of your product, you will need to address how you will determine maintenance dosing (which may differ from the dosing regimen that induced the response), durability of effect, and response after retreatment (e.g. potential for tachyphylaxis).

***Meeting Discussion:***
*The sponsor inquired about the need to evaluate durability of the effect. They cited clinical experience with other Janus Kinase products, that the loss of treatment effect occurs rapidly (within 1 to 3 months) following the discontinuation of treatment. The Agency responded that evaluation of the durability of the effect, as well as treatment effect after retreatment, is needed in the clinical development program to inform product labeling. The Agency advised that loss of response should be assessed using the same scale used for efficacy assessment, and that, disease severity does not need to return to baseline. Additionally, the Agency reiterated that evaluation of maintenance dosing and minimal effective dose are important objectives of development programs that may be addressed through different strategies.*

*The Agency noted the dose for maintenance is usually driven by safety and efficacy considerations. The sponsor may explore whether a lower dose than those used in the induction period would be reasonable for maintenance can be done by randomizing responders to their dose during the induction and to a lower dose. Results from the maintenance trial can be described without formal statistical testing. The Agency will provide comments to proposal when the sponsor submit their protocol.*

2. An open-label extension trial with a duration of 2 years or less may be insufficient to characterize the potential risk of some rare events that have been observed

with Janus Kinase inhibitors (e.g. effects on cardiovascular, immune and skeletal systems. In addition, you may consider implementing a registry to capture adverse events which occur in the postmarket setting.

***Meeting Discussion:***
*The Agency clarified that implementing a registry is intended to occur in post-marketing setting and not during the conduct of Phase 3 clinical trials.*

**Additional comments:**

1. Similar to the SPRO and QPRO, the BETA, and BELA should be administered more frequently throughout the treatment period.

2. COAs will need to be culturally adapted and adequately translated for all intended study populations for use in multinational trials. We refer you to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) principles for the translation and cultural adaptation process[1].

3. COA measurement should be obtained before or shortly after patient withdrawal from treatment should early withdrawal be unpreventable.

## 3.0 ADMINISTRATIVE COMMENTS

**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

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

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]

## 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.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[5] 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[6] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The

---

[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] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[5] https://www.fda.gov/media/88173/download

[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[7] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[8] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[9] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

## 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

[7] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[8] https://www.fda.gov/media/88173/download
[9] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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.[10]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[11] 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[12] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

---

[10] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[11] https://www.fda.gov/media/88173/download
[12] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[13] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[14] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[15] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[16]

## 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:

---

[13] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[14] https://www.fda.gov/media/88173/download
[15] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[16] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

- 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.

## 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[17] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[18]

## 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.[19]

[17] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[18] https://www.fda.gov/media/109533/download
[19] http://www.fda.gov/ectd

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.[20]

**Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[21]

[20] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[21] https://www.fda.gov/media/85061/download

---

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

---

/s/

---

KENDALL A MARCUS
04/03/2020 06:15:45 PM