CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219155Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135351

MEETING MINUTES

LEO Pharma A/S
Attention: Theresa Tran
Director, Regulatory Affairs
7 Giralda Farms, 2nd Floor
Madison, NJ 07940

Dear Theresa Tran:[1]

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

We also refer to the video conference between representatives of your firm and the FDA on September 27,2023. The purpose of the meeting was to discuss the development program for delgocitinib cream.

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

If you have any questions, call Kimberle Searcy, Regulatory Project Manager at 240-402-4454.

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 and Power Point

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 27, 2023 at 11:00am-12:00pm EST
Meeting Location:	Video Teleconference
Application Number:	IND 135351
Product Name:	delgocitinib cream, 20 mg/g
Indication:	For the treatment of moderate to severe chronic hand eczema
Sponsor Name:	LEO Pharma A/S
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Gordana Diglisic, MD
Meeting Recorder:	Kimberle Searcy, MPH

FDA ATTENDEES

Gordana Diglisic, MD Associate Director for Therapeutic Review, Division of Dermatology and Dentistry (DDD)
Melinda McCord, MD, Clinical Team Leader, DDD
Jessica Nguyen, MD, Clinical Reviewer, DDD
Kevin Ebert, PhD, Pharmacologist, DDD
Kathleen Fritsch, PhD, Biometrics Reviewer, Division of Biometrics III (DB III)
Daeyoung Lim, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Prakash Bhagav, PhD, PharmD, PhD, Clinical Pharmacology Reviewer, DIIP
Kimberle Searcy, MPH, Regulatory Project Manager, Office of Regulatory Operations

SPONSOR ATTENDEES

Jacob Thyseen, MD, PHD, Chief Science Officer
Brett Turner Watson, PhD, VP Global Program Head
Keith Baranowski, MD, Medical Lead
Kristine Noergaard Strandfelt, MSc, PhD Safety Lead
Jens Strodl Andersen, MSc Eng, PhD, Biostatistics Lead
Daniel Elenius Madsen, MSc, PhD, Clinical Pharmacology Lead
Shannon Schneider, PhD, Senior Medical Director, US Medical Affairs
Sheetal Alur, PharmD, MS Executive Director, Head of North America Regulatory Affairs
Vivi Worm, MSc Pharm, Senior Global Regulatory Lead, Global Regulatory Affairs
Theresa Tran, PharmD, Director, US Lead Director, US Lead, Global Regulatory Affairs

David Cohen, MD, MPH (external), New York University Grossman School of Medicine
Jonathan Silverberg, MD, PhD, MPH (external), George Washington University School of Medicine and Health Sciences

1.0 BACKGROUND

Purpose:
To discuss the development program of delgocitinib cream and the adequacy of the sponsor's proposed New Drug Application for delgocitinib cream for the treatment of moderate to severe chronic hand eczema (CHE).

FDA sent Preliminary Comments to Leo Pharma A/S on September 25, 2023. Discussions from the video conference held on September 27, 2023, are indicated below.

2.0 DISCUSSION

2.1. Clinical

Introductory Comments:
You are developing delgocitinib cream 20 mg/g for the proposed indication of the treatment of adult patients with moderate to severe chronic hand eczema (CHE) under the 505(b)(1) regulatory pathway. Delgocitinib is a pan-Janus Kinase (JAK) inhibitor which is intended for topical administration twice daily.

Delgocitinib ointment, Corectim Ointment 0.5%, is marketed in Japan for treatment of atopic dermatitis (initially approved on January 27, 2020 for ≥16 years of age, then in March 23, 2021 for ≥2 years of age). A marketing authorization application (MAA) for delgocitinib cream 20 mg/g has been submitted to the European Medicines Agency (EMA) in July 2023 and to Swissmedic in August 2023.

At the end of phase 2 (EoP2) meeting in September 2020, the FDA did not agree with the study design of phase 3 trials LP0133-1401/1402 and LP0133-1403 (long-term extension). Specifically, the FDA recommended: a "run-in period" to define the study population with regard to an "inadequate response" to topical corticosteroids (TCS); evaluating "loss of response" (IGA-CHE = 2 not "relapse" defined as IGA-CHE =1); and the development of static, parallel scales for assessments by the investigator (IGA-CHE) and subject (PaGA) with removal of descriptors for pain and pruritus. You submitted your iPSP in November 2020 but later withdrew it and stated that you planned to conduct phase 3 trials as non-IND trials in Canada and Europe (Letter dated April 16, 2021). You did not submit your phase 3 protocols for review. You also intended to resubmit iPSP for CHE within 210 days prior to NDA submission.

In your planned NDA submission, you propose to provide data from the following clinical trials:

Phase 3: completed

- LP0133-1401, DELTA 1: double-blind (DB), randomized (R) 2:1, parallel-group (PG), vehicle-controlled (VC) trial to evaluate the efficacy, safety, and pharmacodynamics (PD) of delgocitinib topical cream 20 mg/g twice-daily (BID) for 16 weeks [conducted in Canada (CA) and the European Union (EU)].
  - Study population: a total of 487 adult subjects with moderate to severe chronic hand eczema (CHE) based on duration of ≥ 3 months or recurrent ≥2 times within the last 12 months, Investigator's Global Assessment (IGA-CHE) of 3 or 4, and a recent history of inadequate response to treatment with topical corticosteroid (TCS) at any time within 1 year before the screening visit or for whom TCS treatment are otherwise medically inadvisable (e.g. due to important side effects or safety risk).
  - Primary endpoint was IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement (IGA-CHE TS) from Baseline to Week 16. The primary endpoint was achieved by 19.7% in the delgocitinib group and 9.9% in the vehicle group at Week 16.
  - Secondary endpoints (unclear if adjusted for multiplicity) included:
    - 75% improvement in Hand Eczema Severity Index (HECSI) score at Week 16 and Week 8;
    - 90% improvement in HECSI score at Week 16;
    - IGA-CHE TS at Week 8 and Week 4;
    - percentage change in HECSI score from Baseline to Week 16;
    - reduction in Hand Eczema Symptom Diary (HESD) itch score (weekly average) of ≥4 points from baseline at Week 16, 8, 4, 2;
    - reduction in HESD score (weekly average) of ≥4 points from baseline at Week 16, 8, 4;
    - reduction in HESD pain score (weekly average) of ≥4 points from baseline at Week 16, 8, 4;
    - The remainder of the 23 secondary endpoints were based on Dermatology Life Quality Index (DLQI), HESD, Hand Eczema Impact Scale (HEIS), and HEIS Proximal Daily Activity Limitations (PDAL).

  - Safety: Adverse events (AEs) and severe AEs (SAEs) were reported by 45.2% and 1.8%, respectively, of subjects who received delgocitinib, and 50.6% and 1.9%, respectively, of subjects who received vehicle. No AEs of special interest **(**AESI: serious infections, non-melanoma skin cancers, thrombosis, cytopenias (thrombocytopenia, anemia, neutropenia), major adverse cardiovascular events (MACE such as cardiovascular death, myocardial infarction, and stroke), were reported during the trial. The most frequently reported SOC was infections and infestations. There were no deaths or pregnancies.

- **LP0133-1402**, DELTA 2: DB, R 2:1, PG, VC, trial to evaluate the efficacy, safety, and PD of delgocitinib cream 20 mg/g BID for 16 weeks conducted in CA & EU (similar trial design to Trial 1401).
  - Study population: a total of 473 adult subjects with moderate to severe CHE
  - Primary endpoint: IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement (IGA-CHE TS) from Baseline to Week 16. The primary endpoint was achieved by 29.1% in the delgocitinib group and 6.9% in the vehicle group at Week 16.
  - Secondary endpoints included:
    - 75% improvement in Hand Eczema Severity Index (HECSI) score at Week 16 and Week 8;
    - 90% improvement in HECSI score at Week 16;
    - IGA-CHE TS at Week 8 and Week 4;
    - percentage change in HECSI score from Baseline to Week 16;
    - reduction in HESD itch score (weekly average) of ≥4 points from baseline at Week 16, 8, 4, 2;
    - reduction in HESD score (weekly average) of ≥4 points from baseline at Week 16, 8, 4;
    - reduction in HESD pain score (weekly average) of ≥4 points from baseline at Week 16, 8, 4;
    - The remainder of the 23 secondary endpoints were based on DLQI, HESD, HEIS, and HEIS PDAL.

  - Pharmacokinetics (PK): There was minimal systemic delgocitinib exposure levels observed per the Sponsor, and the geometric mean delgocitinib plasma concentration was lower at Week 16 (0.11 ng/mL) compared with Weeks 1 (0.21 ng/mL) and 4 (0.21 ng/mL).
  - Safety: Adverse events (AEs) and severe AEs (SAEs) were reported by 45.7% and 1.6%, respectively, of subjects who received delgocitinib, and 44.7% and 1.9%, respectively, of subjects who received vehicle. No AESIs were reported during the trial. The most frequently reported SOC was infections and infestations. Three pregnancies were reported with 2 elective abortions and 1 of unknown outcome at time of reporting. There were no deaths reported in both groups.

Phase 3: ongoing

- **LP0133-1403**, DELTA 3: Open-label (OL) extension of trials LP0133-1401 and LP0133-1402 to assess long-term (36 weeks) safety and efficacy of delgocitinib cream 20 mg/g BID for treatment of CHE. Subjects received delgocitinib cream 20mg/g BID as needed for flares for up to 36 weeks when IGA-CHE ≥2. Up through 12/30/2022, 392 subjects have had 26 weeks of continuous delgocitinib treatment and 79 subjects have had 52 weeks of continuous delgocitinib treatment.
- Study population: a total of 801 adult subjects with CHE. Eligible subjects from LP0133-1401 and LP0133-1402 who completed 16-weeks of treatment in both

delgocitinib- and vehicle-treated groups were included in this trial. At entry, subjects with IGA-CHE score of 0 ('clear') or 1 ('almost clear') will be "off treatment" and subjects with IGA-CHE score ≥2 will receive "flare treatment" with delgocitinib cream 20 mg/g twice daily until IGA-CHE score of 0 or 1 is achieved at the scheduled visits.

- Primary endpoint-safety: number of treatment-emergent AEs (TEAEs) from baseline up to Week 38. Adverse events (AEs) and severe AEs (SAEs) were reported by 48.4% and 2.5%, respectively, for subjects who were receiving delgocitinib cream, and 20.6% and 0.9%, respectively, for subjects who were off treatment. One AE of special interest (eczema herpeticum of neck and eyelids) was reported during an on-treatment period. The most frequently reported SOC was infections and infestations, most notably COVID-19 infection. Four pregnancies were reported with 2 spontaneous abortions, 1 elective abortion, and 1 of unknown outcome at time of reporting. **Two deaths assessed as not related**: a 63-year-old subject with metastatic esophageal cancer who was previously treated with vehicle in the parent trial and received a single dose of delgocitinib cream in Trial 1403 (cause of death not provided) and a 72-year-old subject with a history of multiple comorbidities (hypertension, epilepsy, renal cell carcinoma, spinal stenosis, prior alcohol abuse, hepatitis B, liver cirrhosis) who had fallen and died during hospitalization with cause of death unknown during an off-treatment period. (Preliminary clinical trial report with data through 12/30/22; final expected 2/2024).

- **LP0133-1426**, DELTA TEEN: DB, R 3:1, PG, VC, 16-week trial to evaluate the efficacy and safety of delgocitinib cream, 20 mg/g BID in approximately **92** adolescents 12 to 17 years of age with moderate to severe CHE. Primary endpoint is IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement (IGA-CHE TS) from Baseline to Week 16. Key secondary endpoints (eight total) include 90% improvement in HECSI score at Week 16; IGA-CHE TS at Weeks 2, 4, 8 and 12; reduction in HESD itch, pain, and total score (weekly average) of ≥4 points from baseline at Week 16; and change in children's DLQI score from baseline to Week 16. No additional information provided.
- **LP0133-1528**, DELTA FORCE: R 1:1, PG, assessor-blind, active-controlled 24-week trial to evaluate the efficacy and safety of delgocitinib cream 8 mg/g BID compared with alitretinoin capsules 30 mg once daily (QD), not approved in the United States, in 510 adult subjects with severe CHE. No additional information provided.

Phase 2

- **LP0133-1180**: DB, R 2:1, VC, Phase 2a, proof-of-concept 8-week trial (non-IND) to evaluate the efficacy, safety, and PK/PD of delgocitinib topical ointment, 30 mg/g BID in **91** adult subjects with mild to severe CHE. Sixty (60) subjects applied delgocitinib ointment and 31 subjects applied vehicle twice daily for 8 weeks to a treatment area ≤ 4% BSA. Subjects treated with delgocitinib ointment showed greater improvement on PGA than subjects treated with vehicle. Per

Sponsor, the study products were well tolerated with no reports of SAEs or AR; the mean exposure was 0.385 ng/mL.

- **LP0133-1273**: DB, R, VC, dose-finding, Phase 2b trial to evaluate the dose-response, safety, efficacy and change in quality of life of delgocitinib cream 1, 3, 8, and 20 mg/g BID for 16 weeks.
  Study population: a total of 258 adult subjects with persistent mild to severe CHE (≥ 3 months or recurrent ≥2 times within the last 12 months) with a recent history (within 1 year prior to screening) of inadequate response to topical corticosteroid treatment or topical corticosteroid treatment being medically inadvisable.
  Primary endpoint: Primary endpoint was Investigator Global Assessment (IGA-CHE) score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement (IGA-CHE TS) from Baseline to Week 16. Secondary endpoints included the "Change in Hand Eczema Severity Index (HECSI) score from Baseline to Week 16" and "Time to IGA-CHE TS". Among the subset of subjects with moderate to severe CHE, the primary endpoint was achieved by 41.5% in the delgocitinib 8 mg/g group, 39.0% in the delgocitinib 20 mg/g group, and 10.5% in the vehicle group at Week 16.
  Safety: Treatment emergent adverse events (TEAEs) were reported by 61-77% of subjects who received any dose of delgocitinib cream and 60% of subjects who received vehicle. The most common adverse events were nasopharyngitis, eczema and headache in all treatment group. TEAEs did not appear to be dose related.

- **LP0133-1275**: DB, R, VC, dose-finding 8-week trial to evaluate the efficacy, safety, and PK of delgocitinib cream, 1, 3, 8, and 20 mg/g BID in adult subjects with mild to severe atopic dermatitis (AD). Primary endpoint was change in EASI score from Baseline to Week 8. (Completed- results not provided).

Phase 1

- **LP0133-1408:** DB, R, controlled, single dose, within subject comparison of the **phototoxicity** potential of multiple concentrations of delgocitinib cream (1, 3, 8, and 20 mg/g) in 35 healthy adult subjects. Primary endpoint was positive skin reaction at 24 or 48 hours after irradiation. (Completed- results not provided).

- **LP0133-1409**: DB, R, PG, placebo-controlled (PC) trial to evaluate the potential for **QT/QTcF** interval prolongation/arrhythmia of delgocitinib capsules (1, 5, 3, 6, and 12 mg) in 40 healthy adult subjects. Primary endpoint was change in QTcF predose to 24 hours postdose. (Completed- results not provided).

- **LP0133-1411**: R, VC, within subject comparison of the photo- allergenicity potential of delgocitinib cream 8 mg/g in 50 healthy adult subjects. Primary endpoint was positive skin reaction at 72 hours after irradiation. (Completed- results not provided).

- **LP0133-2285:** OL, single-arm, 1-week trial conducted in Germany to assess the PK and safety of delgocitinib cream 20 mg/g BID in 15 adult subjects with moderate to severe CHE.
  - Results: Geometric mean value for AUC on Day 1 was 2.5h*ng/mL and on Day 8 was 3.7 h*ng/mL, while arithmetic mean for AUC on Day 1 was 6.1 h*ng/mL and on Day 8 was 4.2 h*ng/mL. Geometric mean value for C_{max} on Day 1 was 0.50 ng/mL and on Day 8 was 0.46 ng/mL, while the arithmetic mean value for C_{max} on Day 1 was 1.53 ng/mL and on Day 8 was 0.53 ng/mL. The Sponsor concluded that the systemic exposure of delgocitinib observed in subjects with CHE was low after topical administration of delgocitinib cream 20 mg/g. There were no AEs, deaths, or other serious AEs reported.

- **LP0133-1181**: OL 8-week trial to evaluate the safety and PK of delgocitinib cream 20 mg/g BID in 46 adults and pediatric subjects with moderate to severe AD. The trial consisted of 2 parts. Part 1 enrolled 12 adolescents (12-17 years) and 14 adults (≥18 years). Part 2 enrolled 20 subjects (2-11 years) and was a maximal usage trial (MUsT) that included children with a body surface area of ≥ 35% at Screening and at Baseline. PK results are as shown in table below (briefing package page 40). This trial did not evaluate the to-be-marketed formulation.

Panel 11 Pharmacokinetic parameters at Day 1 and Day 8 (per protocol analysis set) - Trial 1181

Population	Children 2-11 years (N = 18)		Adolescents 12-17 years (N = 11)		Adults ≥ 18 years (N = 14)	
	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
C_{max} (ng/mL)						
n	17	16	10	10	12	13
Geometric mean	3.94	3.26	0.89	0.70	1.28	1.20
CV (%)	1312.50	369.32	1147.57	216.42	372.50	188.27
AUC (h×ng/mL)						
n	17	16	10	8	12	13
Geometric mean	18.23	23.30	6.21	5.93	8.69	8.39
CV (%)	2478.94	313.27	1601.06	289.39	515.13	231.48
t_{max} (h)						
n	17	16	10	10	12	13
Geometric mean	2.04	2.59	2.15	3.44	3.16	1.88
CV (%)	95.19	126.17	88.73	137.61	113.93	103.56

Abbreviations: AUC = area under the curve from time 0 to last quantifiable observation; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects in age cohort; n = number of subjects with data; t_{max} = time of which maximum plasma conentration occurs.

Per the Sponsor, the mean systemic exposure following twice-daily administration of delgocitinib cream 20 mg/g for 8 days in subjects with moderate to severe AD was low with no accumulation of delgocitinib between Day 1 and

Day 8. The systemic exposure was comparable between adolescents and adults. However, there was a trend of higher exposure in children attributed by the Sponsor to a higher % BSA in children compared with adolescents and adults (due to the different inclusion criterion regarding AD involvement in children compared with adults and adolescents). Delgocitinib cream 20 mg/g BID for 8 weeks was well-tolerated and no safety concerns were identified per the Sponsor.

Sponsor provided only high-level summary safety information. Per annual safety report (ASR) dated January 13, 2023, approximately 2007 subjects (1872 patients and 135 healthy volunteers) have been enrolled while an estimated 1719 of these subjects have received delgocitinib. Notable SAEs listed in 2019 to 2023 ASR included infections and malignancies (1 case of melanoma, 2 cases of pancreatic cancer). Lymphocytopenia was cited as an important potential risk for delgocitinib from nonclinical oral toxicity data, though cumulatively there have been no serious cases of lymphocytopenia reported in the trials but it remains under continuous surveillance.

Additionally, the Sponsor notes the post-marketing safety data for delgocitinib ointment (Corectim) did not reveal any new safety concerns or risks considered relevant for delgocitinib cream in CHE including no deaths, skin malignancies (including NMSC), embolic or thrombotic events, or cardiovascular events of interest.

Question 1:
At the EoP2 meeting with FDA in September 2020, LEO Pharma asked whether the clinical development program could be sufficient to support an indication for topical treatment of moderate to severe CHE in adults. The FDA responded that the planned development program may support the proposed indication.

Since the EoP2 meeting, results from a dedicated phase 1 PK trial (Trial 2285), 2 pivotal phase 3 trials (Trials 1401 and 1402), and a long-term extension trial (Trial 1403) in subjects with CHE became available.

Based on the results from these trials, does the FDA agree that the clinical development program is adequate to support the filing and review of an NDA?

FDA Response to Question 1:
The decision regarding whether your application is fileable will be made by the filing date, which is 60 days from the day of the NDA submission.

Your application is required to be complete at the time of filing. For approval, you will need to provide sufficient information including all trial data and long-term safety data to establish that your drug product is safe and effective for the proposed indication.

Your phase 3 development program was not conducted under the IND. Therefore, we did not review your phase 3 protocols. However, it appears that the study designs of

your phase 3 protocols were not consistent with our recommendations from the EoP2 meeting. Adequacy of the data to support approval of the NDA will be a review issue. We continue to have concerns regarding your efficacy evaluation based on the 5 -point IGA-CHE scale used in your phase 3 trials to define study population and to assess efficacy. The categories of "mild", "moderate" and "severe" were not sufficiently distinct. Defining the appropriate study population with moderate to severe CHE using this scale may be problematic. Provide justification in your NDA that the results from your phase 3 trials using IGA-CHE scale are interpretable. Refer to comments from theEoP2 meeting minutes dated October 23, 2020.

Meeting Discussion:
The Sponsor requested that the Agency identify specific concerns related to the distinction between categories in the IGA-CHE scale. Although the categories for "clear" and "almost clear" in the IGA-CHE scale are distinct, the "mild" and "moderate" categories have overlapping descriptors. For example, the category of "mild", is described as slight but definite hyperkeratosis/lichenification and superficial fissures versus the category of "moderate" is described as clearly perceptible hyperkeratosis/lichenification and definite fissures. Therefore, it is difficult to distinguish the study population with moderate disease compared to mild disease.

The Agency acknowledged the photo guide for the IGA-CHE instrument that the Sponsor provided. However, even with this photo guide, it is still difficult to distinguish mild from moderate disease.

The Agency recommended that the Sponsor provide photos of subjects with moderate disease at baseline with the NDA submission.

Question 2:
The proposed indication is: "PROPRIETARY NAME is indicated for the topical treatment of moderate to severe chronic hand eczema (CHE) in adults".

Does the FDA agree with the proposed indication?

FDA Response to Question 2:
In your phase 3 trials (LP0133-1401 and LP0133-1402), your study population was defined as subjects with a documented history of inadequate response to TCS at any time within 1 year before the screening visit or a documented rationale for TCS to be medically inadvisable (e.g., due to adverse effects or safety risks). With your proposed indication, you intend to capture a broad population of all subjects with moderate to severe CHE, regardless of their history of response to TCS. You have not studied the safety and efficacy of your product in subjects without a history of TCS use. Provide the justification for the proposed indication in your NDA submission. Include the method by which the history of topical corticosteroid usage was obtained for each individual subject such as through history, chart review or any other method in your NDA submission.

As previously communicated (Pre-IND meeting minutes dated May 17, 2017), the indication granted will reflect the population studied during the development program. Subjects with failure to respond adequately to treatment with TCS may define a different population than subjects not treated with TCS. Safety and efficacy in this population could be different.

Question 3:
Based on the results from the pivotal trials (Trials 1401 and 1402), does the FDA agree that the population enrolled (without a TCS run-in period) in LEO Pharma's pivotal program is adequate to support the target indication in US?

FDA Response to Question 3:
Refer to FDA response to Question 2 regarding proposed indication.

You provided a rationale for your decision to define the study population in your phase 3 trials without a run-in period. You state that in your phase 3 trials, 374 out of 959 subjects were enrolled under 'run-in-like' conditions such that subjects received daily TCS treatment. Among these subjects, 24% used very potent TCS, with approximately 90% of these subjects discontinuing TCS treatment within 2 weeks of screening due to inadequate response at Screening and Baseline visits based on IGA-CHE scale. In addition, you state that post-hoc analysis did not demonstrate any "meaningful differences" between the efficacy of delgocitinib cream 20 mg/g observed in this subset of subjects compared with the overall population across endpoints. You do not state if there were any differences in safety findings.

We acknowledge your rationale. However, it is premature to agree with your conclusions until trial data from 1401, 1402, and 1403 are submitted and reviewed. Include your rationale in the NDA submission.

Question 4:
The pivotal phase 3 trials were conducted at several sites in Canada and Europe. Does the FDA agree that the foreign data is applicable to the US population?

FDA Response to Question 4:
In your NDA submission, you will need to provide justification for applicability of foreign clinical data to the US population.

Refer to *the ICH guidance for industry, E5 Ethnic factors in the Acceptability of Foreign Clinical Data, September 2006*.

Question 5:
Does the FDA agree that Trials 2285 and 1402 adequately characterize PK of delgocitinib cream 20 mg/g and therefore a MUsT in CHE is not needed?

FDA Response to Question 5:

It is premature to provide any agreement at this stage. Provide the following information in the NDA for review.

1. We noted that you used the proposed to-be marketed formulation for the trial 2285 (phase 1) and trial 1402 (phase 3) and an early formulation for trial 1181(MUsT). We also note that the MUsT (trial 1181) was conducted in the AD indication. If you intend to use the PK data from the MUsT that was conducted with a different formulation in the AD indication, provide a scientific justification and/or supporting data to justify the establishment of a clinical bridge between the 2 formulations in your NDA submission for review.

2. In the NDA submission, in addition to the full study reports, submit a summary of PK assessment in the Clinical Pharmacology section which includes information on, for example, PK sampling timepoints, number of subjects PK was assessed in, %BSA the drug was applied to in each of the subjects, mean daily dose used in subjects that underwent PK assessment as well as subjects that did not undergo PK assessment, summary of PK parameters, and also include information on when the systemic concentrations are expected to be at steady state.

3. For your trial 2285 (phase 1), submit information on the % BSA the drug was applied to in each subject in the NDA.

4. In the NDA submission, submit bioanalytical method validation as well as bioanalysis reports for review.

Question 6:
Does the FDA agree that the projected overall safety database and the total number of subjects exposed to delgocitinib provides sufficient evidence to support an NDA for the proposed indication?

FDA Response to Question 6:
You state that your safety database will include 392 subjects who will have received continuous treatment with delgocitinib for more than 6 months. You expect at least 200 subjects (79 subjects since December 30, 2022, and an additional 153 subjects by February 28, 2024) to receive continuous treatment with delgocitinib for 52 weeks.

At the End of Phase 2 (EoP2) meeting (September 23, 2020), the Agency emphasized the need for sufficient safety data from continuous long-term exposure (e.g., 200 subjects for 12 months) to the proposed product in the target population due to the known safety profile of Janus Kinase Inhibitors. At the time of NDA submission, the Agency expects that the safety database will include data from at least 300 subjects continuously exposed for 6 months and at least 200 subjects continuously exposed for 12 months. At the time of submission, your New Drug Application should be complete including 12 months of the long-term safety data.

Ultimately the adequacy of the safety database for the proposed indication and the intended population will be a review issue.

Question 7:
LEO Pharma is currently conducting a trial in adolescents with CHE (Trial 1426) similar in design as the pivotal trials (Trials 1401 and 1402) in adults. If the FDA agrees to the adequacy of LEO Pharma's clinical development program to support an NDA filing (Question 1Section 11.1.1), does the FDA agree that LEO Pharma may resubmit the iPSP including the ongoing adolescent trial with its current trial design prior to the NDA submission?

FDA Response to Question 7:
You state that you are conducting a randomized, double-blind, parallel-group, vehicle-controlled trial in approximately 92 adolescents (69 subjects exposed to delgocitinib cream) 12 to 17 years of age with moderate to severe CHE. The primary endpoint is IGA-CHE score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement (IGA-CHE TS) from Baseline to Week 16. From your brief summary, the overall study design appears reasonable. However, the number of adolescent subjects proposed is not sufficient to characterize the safety and efficacy of your product in this population. Support the proposed sample size with epidemiologic data.

As previously communicated, per PREA requirements, your iPSP must be resubmitted at least 210 days before any potential NDA submission.

Meeting Discussion:
The Sponsor inquired if the Agency agrees that a Bayesian methodology supports the sample size in assessing efficacy from the adolescent trial and stated that they are considering modifying the proposed analysis plan for their ongoing pediatric study to incorporate a Bayesian analysis that would leverage adult data. The Agency noted that changes to analysis methods after a study has commenced may be a significant concern regarding interpretability of the study. The Agency also noted that we have had limited interactions regarding specific protocol designs in the development program; therefore, whether the existing study as designed would support the efficacy in the pediatric population would depend on the appropriateness of the design, power, and conduct of the study. It is beyond the scope of the meeting to discuss significant changes to the planned analysis for an ongoing trial.

The Sponsor requested clarification regarding what epidemiologic data would be needed to inform the sample size.

Delgocitinib cream is a pan JAK inhibitor that may be associated with potentially serious adverse events. The Sponsor should establish the safety of this product in the pediatric population age 12 to 17 years old. The size of the safety database for

pediatric patients should be justified by epidemiological data (prevalence of chronic hand eczema in the adolescent population).

The Agency inquired whether the Sponsor intended to seek the indication for treatment of chronic hand eczema to include the adolescent population with the original NDA submission. The Sponsor responded that they did not.

Additional Comments:

- For any clinical outcome assessment (COA) tool intended to support regulatory decision-making and labeling claims, provide the following:

  a. Exact copies of the instrument(s) as they were administered during the clinical trial (e.g., copy of paper version, electronic screen shots) and any associated training materials and user manuals

  b. Conceptual framework of the instrument(s), where applicable. This includes a description of the items comprising each of the instrument's domains.

  c. Evidence of content validity and other measurement properties (e.g., reliability, construct validity, ability to detect change) obtained for the specific context of use, including final qualitative and quantitative summary reports if available. Literature related to the development history would be acceptable; however, submit copies of publications.

  d. Proposed scoring algorithm(s) with rationale and corresponding information on how the instruments' scores were analyzed as part of an endpoint, including what constitutes meaningful within-patient score changes.

  e. Strategy for handling missing data

  f. Information regarding translation and cultural adaptation for the target patient population(s), if applicable. Refer to the ISPOR principles for the translation and cultural validation process[2].

  We recommend that you compile this information into an evidence dossier for the target COAs for your NDA submission.

- We have the following comments regarding specific assessment scales:

[2] 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

- **Investigator's Global Assessment Scale** (IGA-CHE):
  Refer to FDA Response to Question 1.
  Clarify whether you used a photographic guide to illustrate disease severity categories. Any photographic guide used to reduce inter- and intra-rater variability should be included in your NDA submission.

- **Hand Eczema Severity Index** (HECSI):
  As previously communicated (EoP2 meeting minutes dated September 23, 2020), we have concerns regarding the HECSI. The HECSI scale is a calculated scale that represents the summation of the extent, location and severity of different cutaneous signs into a single score. All signs are equally important in scoring. The same HECSI score may represent a different combination of signs and severities. As such, this data is difficult to interpret and translate into labeling. Provide accompanying instructions, training materials and /or a user manual for the HECSI and evidence of the inter-rater reliability.

- **Hand Eczema Symptom Diary** (HESD)**, Dermatology Life Quality Index** (DLQI)**, Hand Eczema Impact Scale** (HEIS), and **HEIS Proximal Daily Activity Limitations** (PDAL).
  - Refer to the comments provided at the EoP2 meeting (meeting minutes dated September 23, 2020). As previously communicated, these instruments have measurement challenges that may make it difficult to inform regulatory decision-making (b) (4)

- You did not include any information in your briefing package regarding the proposed content and format of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) which are required in applications submitted to the FDA in accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively).

  Comments regarding the content of the ISS

- In view of the differences in formulation of your drug product that were evaluated in your phase 2 and phase 3 trials, conduct your primary safety evaluation using pooled data from Trials LP0133-1401 and LP0133-1402. Provide a discussion of any differences in the safety monitoring between the pooled trials and a comparison of safety results from the individual trials and pooled data.

- With regard to the analysis of the safety data, we have the following comments:

  - Provide a tabulation of treatment-emergent adverse events (TEAEs) ≥1% in any treatment arm, treatment related TEAEs (adverse reactions [AR] with

possible or probable causality) ≥1% in any treatment arm, adverse events (AEs) leading to discontinuation, and serious adverse events (SAEs) from Baseline to Week 16. In addition, provide crude percentages and exposure-adjusted incidence rates (EAIRs) of TEAEs, ARs, SAEs and AEs leading to discontinuation from Baseline to Week 52.

We recommend that you pool related preferred terms in your tables (e.g., pool upper respiratory tract infection with nasopharyngitis, viral upper respiratory tract infection etc.)

- Provide shift tables for all laboratory values and vital signs from Baseline to end of treatment for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

- Provide Case Report Forms (CRF) with electronic links for all deaths, serious adverse events, hypersensitivity reactions, and discontinuations due to adverse events. Other eCRFs should be readily available upon request. However, if the eCRFs are located in the Clinical Study Report (CSR), then provide links to the eCRFs in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety.

- Provide narratives with electronic links for all deaths, serious adverse events (SAEs), and subjects who discontinued the study agent due to adverse events (AEs). Narratives may be included in the CSRs with links to these narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety. Additional case report forms and narratives should be available upon request.

- Based on adverse events associated with class of JAK inhibitors, conduct an issue-based safety review of your product. Submit narratives for all treatment emergent adverse events of special interest (TEASIs) regardless of severity including 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 including anaphylaxis and angioedema, and laboratory abnormalities (neutropenia, lymphopenia, anemia, lipid elevation, thrombocytosis, thrombocytopenia, creatine phosphokinase elevations (CPK), liver enzyme elevations and drug induced liver injury (DILI)].

- Provide evaluation and discussion of uncommon, rare or unexpected events in your submission that may be possibly related to the study drug

- Provide safety analyses for the following subgroups:
  - ✓ Race categories include Caucasian, African American, Asian and Other
  - ✓ Age categories (12 to 17, 18 to 64, >65)
  - ✓ Ethnicity (Hispanic/Latino or not Hispanic/Latino)
  - ✓ Sex
  - ✓ Baseline severity

- Labeling for your proposed product is required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, provide a review of available information for your product and the moiety regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., from published literature, pharmacovigilance database, etc.)

  - Provide narratives for all pregnancies that occurred during the development program
  - Provide summary table or tables that include
    - Pregnancy outcomes:
      - ✓ gestational age of stillbirths and miscarriage and whether congenital anomalies were described
      - ✓ gestational age of live births with a table describing type and numbers of cases of adverse infant outcomes that were observed, including congenital anomalies, preterm birth, small-for-gestational age and other adverse pregnancy outcomes.
    - Perinatal complications (the number and type), such as gestational diabetes, preeclampsia, postpartum hemorrhage, pregnancy-induced hypertension, etc.
    - Adverse effects on breastfed infants exposed to your product via lactation reported in the pharmacovigilance database and the number of cases for each type of reported adverse event. Please provide the case report forms for any lactation cases that were reported as fatal.
    - Adverse events (the number and type) related to male and female fertility in the pharmacovigilance database.

  In the 120-day safety update report (SUR), per section 505(i) of the act, you should update the NDA application with new safety information learned about the product that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Provide narratives in the SUR for all subjects who died, experienced SAEs, pregnancies and AEs of special interest.

- Provide a worldwide safety update, since the moiety is approved in other jurisdictions

- Include the full text version of any referenced articles.

- As part of our review of your original drug, the Agency will conduct a comprehensive assessment of the benefits and risks of your drug product. The information needed to complete this analysis is described in the Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation Plan which is available at: https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm.

  In your NDA submission, we recommend that you consider/ discuss why your product provides an advantage with regard to benefit/risk compared with other products used in the treatment of moderate to severe chronic hand eczema.

- Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). The Agency can provide recommendations regarding the pooling of certain preferred terms (e.g., viral upper respiratory tract infection and upper respiratory tract infection) to enhance your safety analysis if you submit your coding dictionary prior to completion of the safety analysis for your BLA.

Comments regarding datasets and trial documentation

For the clinical studies included in your submission we request the following:

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. 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.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Please be advised that if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan

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*.[3] 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.[4]

PRESCRIBING INFORMATION

[3] 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.
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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

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

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

- Regulations and related guidance documents.

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

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

- 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.

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

4.0 ATTACHMENTS AND HANDOUTS

- Agenda and Power Point

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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/

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IND 135351

MEETING MINUTES

Leo Pharma A/S
Attention: Emily Burd, PharmD
Manager, Regulatory Strategy, Global Regulatory Affairs
7 Giralda Farms, 2nd Floor
Madison, NJ 07940

Dear Dr. Burd:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for delgocitinib cream, 8 mg/g.

We also refer to the telecon between representatives of your firm and the FDA on September 23, 2020. The purpose of the meeting was to discuss the development program for delgocitinib cream, 8 mg/g.

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 Kimberle Searcy, Regulatory Project Manager, at 240-402-4454.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
- Meeting Minutes
- Sponsor Agenda

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	September 23, 2020, 9:30 –10:30 a.m. DST
Meeting Location:	Teleconference
Application Number:	IND 135351
Product Name:	delgocitinib cream, 8 mg/g
Proposed Indication:	For the treatment of moderate to severe chronic hand eczema in adults
Sponsor Name:	Leo Pharma A/S
Regulatory Pathway:	505(b)(1) of the Food, Drug, and Cosmetics Act
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Kimberle Searcy, MPH

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDD
Gordana Diglisic, MD, Clinical Team Leader, DDD
Melinda McCord, MD, Clinical Reviewer, DDD
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics (DB) III
Kathleen Fritsch, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Soo Hyeon Shin, PhD, PharmD, PhD, Clinical Pharmacology Reviewer, DIIP
Selena Daniels, Pharm D, MS, Team Leader, Clinical Outcomes Assessment (COA)
Yasmin Choudry, MD, Reviewer, COA
Barbara Gould, MBAHCM, Chief, Project Management Staff, Division of Regulatory Operations for Dermatology and Dentistry (DRO-DDD)
Kimberle Searcy, MPH, Regulatory Project Manager, DRO-DDD

SPONSOR ATTENDEES

Antonella Lozito-Heerschap, PharmD, Head of Global Regulatory Strategy, Global Regulatory Affairs, Innovative Portfolio
Emily Burd, PharmD, Manager Regulatory Strategy, Global Regulatory Affairs, Innovative Portfolio

Paul Barclay, PhD, Vice President Global Program Head, Global Development Delgocitinib
Anne Birk Osterskov, MD, Senior Medical Director, Medical Department
Per Sørensen, MSc Stat, Biostatistics Lead, Medical Sciences
Thor Schütt Svane Nielsen, MSc Principal Statistician, Biostatistics
Michala Gauguin, MD, Manager Delgocitinib, Global Safety Surveillance, Innovative Portfolio
Lotte Seiding Larsen, MSc PharmPrincipal Scientific Adviser PROs, Clinical Pharmacology
Robert Arbuckle, MSc, Adelphi Values Ltd, UK Managing Director, Patient-Centered Outcomes
(b) (4)

1.0 BACKGROUND

Purpose of meeting:
The purpose of this meeting is to discuss the development program for delgocitinib cream, 8 mg/g.

CORONAVIRUS – 19 (COVID 19) CLINICAL TRIAL GUIDANCE

During the COVID-19 public health emergency, ensuring the safety of study participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of study participants, and modify study conduct accordingly. It is critical that study participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*. 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

Introductory Comments:
The sponsor responded on September 21, 2020 with a list of questions to be discussed during the September 23, 2020 teleconference. The focused agenda for the meeting included clarification regarding the following questions: 6a, 2, 7, 12, and 1. The sponsor submitted additional questions within their meeting agenda document that were not discussed during the teleconference; however, a FDA response is included in the meeting minutes. Additionally, the sponsor submitted a post meeting clarification question on September 28, 2020 for Question 6a.

In view of your comprehensive comments and revisions to your proposals, we are not able to provide agreements with all of the elements of your study designs. Additional comments will be provided upon submission of the protocols.

2.0 DISCUSSION

2.1. Regulatory

No regulatory questions were submitted for this meeting.

2.2. Chemistry, Manufacturing, and Controls (CMC)

No CMC questions were submitted for this meeting.

2.3. Nonclinical

No nonclinical questions were submitted for this meeting.

2.4. Clinical Pharmacology

Question 8:
Does the Agency agree with the proposed plan to address drug interaction potential with delgocitinib?

FDA Response to Question 8:
We acknowledge your in vitro drug interaction studies that have been conducted. The decision to conduct clinical drug interaction assessment should be based on the systemic exposure of delgocitinib under maximal use conditions. Since your maximal use PK study is ongoing, it is premature to comment on the adequacy of drug interaction assessment.

Post-Meeting Response:
At the IND stage, we typically do not review full study reports as we review them along with the bioanalytical method validation under the NDA submission. However, you are welcome to submit the study reports along with a summary and scientific justification. We will provide you with our comments, if any.

For the drug-drug interaction (DDI) assessment, we encourage you to refer to the FDA Guidance to help with the decision making and if you plan to submit your position, you should include DDI assessment based on the systemic exposure you observe from the completed maximal use PK study.

Question 9:
Does the Agency agree that conduct of an ADME trial is not required, given the low systemic exposure to delgocitinib in subjects with CHE?

FDA Response to Question 9:
Since your maximal use study (MUsT, Study LP0133-1181) is ongoing and we have not received and reviewed the systemic exposure data from the study, it is premature to respond to this question. It will be a review issue during NDA submission.

Post-Meeting Response:
Refer to FDA Response to Question 8.

Question 10:
Does the Agency agree that a MUsT in subjects with CHE is not required to assess the bioavailability of delgocitinib?

FDA Response to Question 10:
The systemic exposure data to be obtained from a MUsT in subjects with AD, LP0133-1181, could be used to address the systemic safety of delgocitinib in subjects with CHE. However, we note your plan to change the formulation by changing the concentration of (b) (4). Hence you will need to provide a scientific rationale to support how the PK data obtained using the old formulation would be applicable to the new formulation.

Question 11:
Based on FDA's guidance 'Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products', LEO Pharma plans to conduct a fit-for-purpose validation of biomarkers intended to describe the principal PD effects of delgocitinib in CHE under the PD subsection of the label.

Does the Agency agree that the proposed fit-for-purpose validation suffices in this regard?

FDA Response to Question 11:
We acknowledge your plan to evaluate several biomarkers to describe the PD effects of delgocitinib as exploratory endpoints. The acceptance of your validation of biomarkers and the PD effects that you would like to include in the labeling will be a review issue.

2.5. Clinical

General Comments:
You are developing a novel pan-JAK inhibitor, delgocitinib cream, for the proposed indication of the topical treatment of moderate to severe chronic hand eczema (CHE) in adults. You are also investigating the proposed product for the treatment of atopic dermatitis (AD) and discoid lupus erythematosus (DLE).

To date, you have completed the following trials in subjects with CHE:

Phase 2

- **LP0133-1180**: a randomized, double-blind, vehicle-controlled, Phase 2a proof-of-concept, trial (non-IND) to evaluate the safety and treatment effects of delgocitinib **ointment**, 30 mg/g (initial dosage form) in 91 adult subjects with mild to severe CHE. Sixty (60) subjects applied delgocitinib ointment and 31 subjects applied vehicle twice daily for 8 weeks to a treatment area ≤ 4% BSA. Subjects treated with delgocitinib ointment showed greater improvement

on PGA than subjects treated with vehicle. Per sponsor, the study products were well tolerated with no reports of SAEs or AR; the mean exposure was 0.385 ng/mL

- **LP0133-1273**: a randomized, double-blind, vehicle-controlled, dose-finding Phase 2b trial to evaluate the dose- response, safety, efficacy and change in quality of life of twice daily applications of delgocitinib **cream** 1, 3, 8, and 20 mg/g for 16 weeks. A total of 258 adult subjects with persistent mild to severe CHE (≥ 3 months or recurrent ≥2 times within the last 12 months) with a recent history (within 1 year prior to screening) of inadequate response to topical corticosteroid treatment or topical corticosteroid treatment being medically inadvisable. Primary endpoint was Investigator Global Assessment (IGA-CHE) score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement (IGA-CHE TS) from Baseline to Week 16. Secondary endpoints included the "Change in Hand Eczema Severity Index (HECSI) score from Baseline to Week 16" and "Time to IGA-CHE TS".

  Among the subset of subjects with moderate to severe CHE, the primary endpoint was achieved by 41.5% in the delgocitinib 8 mg/g group, 39.0% in the delgocitinib 20 mg/g group, and 10.5% in the vehicle group at Week 16. Treatment emergent adverse events (TEAEs) were reported by 61-77% of subjects who received any dose of delgocitinib cream and 60% of subjects who received vehicle. The most common adverse events were nasopharyngitis, eczema and headache in all treatment group. TEAEs did not appear to be dose related.

Ongoing Trials (evaluating the same formulation as Phase 2b trial)

- **LP0133-1408**: Randomized, double-blind, controlled, single dose, within subject comparison of the phototoxicity potential of multiple concentrations of delgocitinib cream 1, 3, 8, and 20 mg/g in 35 healthy adult subjects.

- **LP0133-1181**: Open-label, safety, PK maximal usage trial (MUsT) of delgocitinib cream 20 mg/g applied twice daily for 8 weeks in 44 subjects with moderate to severe AD. The trial is conducted in 2 parts: Part 1- 24 subjects age 12-17 years; Part 2- 20 subjects age 2-11 years. Dose and duration of Part 2 to be determined. Proposed to be applicable to CHE program because systemic exposure in the study population with AD is likely to exceed maximal use conditions achievable in subjects with CHE.

Planned Trials (In an amendment to the briefing package, you proposed to pursue the development of the 20 mg/g dose rather than the 8 mg/g dose as proposed in the briefing package.)

Phase 3

- **LP0133-1401/ LP0133-1402**: **Randomized, double-blind**, parallel-group, vehicle-controlled Phase 3 trials to evaluate the efficacy and safety of delgocitinib cream for the treatment of chronic hand eczema (CHE).

    - Approximately 450 adult subjects will be randomized 2:1 to receive delgocitinib cream 8 mg/g or vehicle applied twice daily for 16 weeks.1

    - Eligible subjects will have a disease severity graded as moderate to severe according to IGA-CHE and a recent history of inadequate response to treatment with TCS (at any time within 1 year before the screening visit) or for whom topical corticosteroid (TCS) treatment are otherwise medically inadvisable (e.g. due to important side effects or safety risk).

    - Scheduled visits will occur at Weeks 1,2,4,8,12,16 and 18 (if not participating in the extension trial.)

    - The primary endpoint is a score of 0 (clear) or 1 (almost clear) with a ≥ 2 step improvement from Baseline at Week 16 on IGA-CHE (IGA-CHE-TS).

- **LP0133-1403**: **Open-label** extension of trials LP0133-1401 and LP0133-1402 to evaluate the long -term safety of delgocitinib cream for the treatment of CHE.

  Approximately 480 subjects will apply delgocitinib cream 8 mg/g twice daily for up to 36 weeks as needed for the treatment of flares. At entry, subjects with IGA-CHE score is 0 (‘clear’) will be “off treatment” and subjects with IGA-CHE score is ≥1 (‘almost clear’ or above), the subject will receive “flare treatment” with delgocitinib cream 8 mg/g twice daily until PaGA score of 0 is achieved between the scheduled visits or an IGA-CHE score of 0 is achieved at the scheduled visits. Subjects who fail to achieve IGA-CHE score of 0 may be discontinued. The trial is intended to address the regulatory requirement of ICH E1A guideline to evaluate a minimum of 300 subjects for 26 week and 100 subjects for 52 weeks.

Phase 1

- **LP0133-1409:** Randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the potential for **QT/QTcF** interval prolongation/ arrhythmia of delgocitinib capsules (1, 5, 3, 6, and 12 mg) in 40 healthy adult subjects.

- **LP0133-1411**: Randomized, vehicle-controlled, within-subject comparison of the **photo allergenicity** potential of delgocitinib cream 8 mg/g in 50 healthy adult subjects. The study products will be applied twice weekly during the induction phase, followed by a 2 week rest period and then a single application during the challenge phase.

Planned but not intended for submission with the NDA:

Phase 3

- LP0133-1426: Randomized, double-blind, parallel-group, vehicle-controlled trial to evaluate the efficacy and safety of delgocitinib cream for the treatment of moderate to severe chronic hand eczema (CHE) in adolescents. Approximately 92 subjects age 12 to 17 years will be randomized 3:1 to receive delgocitinib cream 8 mg/g or vehicle applied twice daily for 16 weeks.

- LP0133-1528: Randomized, assessor-blind, parallel-group, active-controlled trial to evaluate the efficacy and safety of delgocitinib cream 8 mg/g applied twice daily compared with Alitretinoin capsules 30 mg once daily (dose reduction to 10 mg if needed) for 24 weeks. Approximately 510 subjects who are eligible for treatment with alitretinoin will be randomized 1:1 to one of the two active products.

Question 1:
Does the Agency agree that the proposed clinical development program could be sufficient to support an indication for 'Topical treatment of moderate to severe chronic hand eczema in adults'?

FDA Response to Question 1:
Yes. In general, we agree that your planned development program may support the proposed indication.

We acknowledge your intent to conduct an assessment of your product in the pediatric population age 12 to 17 years after review of your marketing application. Unless there is a safety concern, you are encouraged to include the relevant pediatric populations in your Phase 3 trials rather than delay assessments until after marketing approval.

In addition, as CHE is a chronic disease, we recommend that you consider evaluating the duration of effect following discontinuation of therapy with your product as well as efficacy after retreatment.

See FDA Response to Question 10 regarding the MUsT.

Sponsor Response:

- As evidenced by Fast Track Designation granted to delgocitinib, the unmet medical need in adults with moderate to severe CHE is acknowledged. We also acknowledge the unmet medical need in adolescents with moderate to severe CHE given the absence of available therapy to treat this condition. In the Phase 2b trial LP0133-1273 (in adults with CHE), only about 20% of the subjects had an age of onset of CHE before the age of 18, which corroborates that the prevalence of CHE in adolescents is lower than in adults (Mortz et al.

2014; Mortz et al. 2001). As a result, we anticipate that recruitment of adolescents with CHE into the adult Phase 3 program may pose a challenge to the ability to register delgocitinib in the adult indication if adult data are available before adolescent subjects have completed treatment. Therefore, we propose to defer the pediatric assessment in an effort to facilitate timely registration in adults. We understand this is subject to the initial PSP review, and we seek Agency advice as to how to best address the unmet needs of adults and adolescents with CHE while facilitating timely registration of delgocitinib for the adult indication.

- Based on the FDA's preliminary comments and based on precedent in dermatology, we understand that such data on duration of effect following discontinuation and efficacy after retreatment are not necessary to support approval of the proposed indication. We also understand that such data would be informative to prescribers in labeling to be able to optimally manage CHE as a chronic condition.

  As designed, study LP0133-1403 (long-term extension) will provide data on duration of effect upon discontinuation of treatment as well as efficacy of retreatment among subjects who had achieved IGA-CHE of 0 ('clear') on delgocitinib in the parent trials (LP0133-1401/1402). As stated under Section 10.1.6 of the End of Phase 2 briefing package, if a subject's IGA-CHE score is 0 ('clear') at baseline of LP0133-1403, then the subject will continue in the trial but will be 'off-treatment', i.e. the subject will not commence or continue treatment with delgocitinib.

  Duration of effect following discontinuation of treatment will be evaluated by assessing the time to first relapse (defined as IGA-CHE or PaGA ≥1) for subjects who were randomized to delgocitinib treatment and had achieved an IGA-CHE score of 0 (i.e. 'clear') at the end of week 16 of the parent trials (LP0133-1401/1402) (i.e., baseline in study LP0133-1403).

  When a subject's IGA-CHE or PaGA becomes ≥1 while off delgocitinib treatment in study LP0133-1403, the subject will then be "retreated" with delgocitinib 20 m g/g BID until IGA-CHE or PaGA reaches 0. Efficacy of retreatment will then be evaluated by a cross tabulation of proportion of responders at baseline (i.e. IGA-CHE=0) and proportion of responders at the end of the first flare (i.e. achieving IGA-CHE=0 or PaGA=0), for subjects experiencing at least one additional flare during LP0133-1403.

  Does the Agency agree with the Sponsor's proposal to evaluate duration of effect following discontinuation of delgocitinib treatment

after achieving IGA-CHE of 0 (clear) as well as efficacy after retreatment?

Meeting Discussion:
The Agency encouraged the sponsor to allow enrollment of pediatric subjects in their Phase 3 trials. Alternatively, the sponsor may consider a separate open-label trial in adolescent subjects conducted concurrently with the Phase 3 trials that allows all subjects to receive active treatment.

The adequacy of data will be a review issue.

The Agency agreed that assessments of the duration of effect following discontinuation of therapy and efficacy after retreatment were not required components of the NDA submission. The Agency did not agree with the proposed definition of "relapse" (i.e.IGA-CHE ≥ 1) provided by the sponsor. The Agency recommended using the term "loss of response" (i.e. "loss of treatment success "-IGA-CHE ≥ 2). However, it is difficult to assess the time to loss of response because the event is not well defined, and assessments are infrequent. The sponsor may follow subjects' treatment response over time and present such data descriptively (i.e. plot) in labeling. In order to make specific claims about loss of response over time, the study design would need to be altered to include a comparison against a control or specify a specific threshold that the loss of response could be compared to at a specific time; however, such design elements are not required components of the NDA submission.

Question 7:
Does the Agency agree to the proposed strategy for assessing skin irritation and sensitization in the pivotal phase 3 trials and photoallergenicity in a phase 1 trial in healthy subjects?

FDA Response to Question 7:
For the assessment of dermal safety, you propose to conduct studies of photoallergenicity (planned) and phototoxicity (ongoing Trial LP0133-1408) and evaluate the cumulative irritation and sensitization potential of delgocitinib cream under the intended conditions of use. Your plan to evaluate cumulative irritation and sensitization during the Phase 3 trials (LP0133-1401, LP0133-1402, and LP0133-1403) is reasonable. However, you suggest that you intend to evaluate the signs of reactions at the application site using the global scales, IGA-CHE, Hand Eczema Severity Index (HECSI) and Chronic Hand Eczema Symptom Diary (HESD). You indicate that subjects will evaluate symptoms of "tolerability" (i.e. stinging/ burning) associated with study product application. You state that "Unless the investigator suspects contact dermatitis...the outcome of the subject assessment of local tolerability is reported as an AE(s) at the discretion of the investigator."

We are concerned that data regarding stinging / burning from a retrospective assessment of "the worst sensation at the application site since the last visit" may be

confounded by recall bias. In addition, in order to estimate the frequency of local reactions of irritation and sensitization, you will need to document findings for all subjects who had an assessment. We prefer that you evaluate irritation and sensitization using a dedicated scale such as the Berger and Bauman system and document findings at all visits.

The initial consideration for assessment of photoreactive potential is whether a compound absorbs photons at any wavelength between 290 and 700 nm. A compound that does not have a molar extinction coefficient (MEC) greater than 1000 L mol-1 cm-1 at any wavelength between 290 and 700 nm is not considered to be sufficiently photoreactive to result in direct phototoxicity or photoallergenicity.

For topical products where the active pharmaceutical ingredients (APIs), or any new excipient has an MEC value greater than 1000 L mol-1 cm-1 at any wavelength between 290 and 700 nm, a photoallergy assessment is generally warranted in addition to phototoxicity testing. As you indicated, because the predictivity of nonclinical photoallergy tests is unknown, this would typically be a clinical assessment using the to-be-marketed formulation and conducted in a sufficient number of healthy, adult subjects (e.g. 45 evaluable subjects).

Submit the absorption spectrum of your final to-be-marketed product and the protocol for the photoallergenicity trial with sufficient time for review. Additional comments may be provided in response. For further information, refer to the ICH guidance for industry *S10 Photosafety Evaluation of Pharmaceuticals.*

Sponsor Response:
The Sponsor herein clarifies the approach whereby local tolerability and suspicion of contact dermatitis will be assessed in the Phase 3 program.

Subjects assessment of local tolerability:
As noted in the ‘schedule of trial procedures’ of each trial outline (Appendices 2, 3 and 4 of the briefing package), subjects will be asked by the investigator at each visit to retrospectively assess stinging/burning in connection with the IMP application since their last visit. The assessment will be done using the 4-point scale as noted in the aforementioned appendices. The highest (worst) skin reaction score across treatment area(s) will be recorded in the eCRF and the subjects assessments of local tolerability will be summarised by visit. The subject assessment of local tolerability will be reported as an AE at the discretion of the Investigator.

The Sponsor would like to clarify whether FDA’s concerns on recall bias are related to the format by which the data is collected and reported or related to the timing of data collection, and therefore seek FDA’s guidance on how to best address the concern on recall bias.

Investigator scoring of local skin reaction related to IMP application with suspicion of contact dermatitis

As noted in the 'schedule of trial procedures' of each trial outline (Appendices 2, 3 and 4 of the briefing package), at each visit the investigator will evaluate whether there is a reason to suspect a local skin reaction (contact dermatitis) related to IMP application. This evaluation will be based on the investigator's initial inspection of the subject's hands and the subject's own assessment of stinging and burning in connection with IMP application and will be independent of the global scales (IGA-CHE, HECSI) and HESD. If the investigator suspects a local skin reaction related to IMP, the investigator will score the suspected application site reaction using the Berger and Bauman system (as recommended by the Agency in preliminary comments) rather than the scoring noted in Panel 7 of each trial outline).

The investigator will then perform an IMP patch test in order to confirm a diagnosis of allergic contact dermatitis caused by the IMP. The patch will be removed after 2 days and the investigator will perform readings of any apparent patch test reaction at 3-4 days and then 5-7 days after applying the patch. The patch test reaction will be documented by photography and scored according to guidelines (Johansen, 2015).

Therefore, the Sponsor herein clarifies that the following will be captured in the eCRF for suspected contact dermatitis related to IMP application:

- the highest (worst) score (according to the Berger and Bauman system)
- for the IMP patch test: the date and time of each reading and the patch test reaction scores (negative reaction, doubtful reaction, weak positive reaction, strong positive reaction, extreme positive reaction, or irritant reaction)
- etiology (diagnosis) of the local skin reaction will be recorded (irritation/toxicity, allergic or other (specified)
- The final diagnosis will also be captured as an AE

Does FDA agree with the revised proposal for the investigator evaluation of suspected local skin reaction?

Meeting Discussion:

In general, the Agency agreed with the strategy for the assessment of irritation and sensitization in the short-term Phase 3 trials. However, the Agency suggested that the use of an electronic diary may allow subjects to capture symptoms of stinging and

burning with greater reliability. The use of this tool may minimize recall bias resulting from assessments of remote events (i.e. up to 30 days ago). In addition, the Agency emphasized the importance of evaluating irritation and sensitization in the long- term, extension trial assessing continuous treatment for ≥ 6 months.

Question 2:
Does the Agency agree to the proposed patient population in the pivotal phase 3 trials?

FDA Response to Question 2:
In your Phase 3 trials, you propose to evaluate adult subjects with moderate to severe CHE as defined by the following key entry criteria:

a. persistent for ≥ 3 months or ≥ 2 episodes within the preceding 12 months

b. a score of 3 or 4 on the 5- point Investigator's Global Assessment for chronic hand eczema (IGA-CHE) scale at screening and baseline

c. a score of ≥2 (mild to severe) on the 5-point Patient's Global Assessment of disease severity (PaGA) scale

d. have a recent history of inadequate response to treatment with topical corticosteroid (within 1 year prior to screening) or for whom topical corticosteroids are otherwise medically inadvisable (e.g. due to important side effects or safety risks)

We have the following comments regarding your proposed study population:

e. You propose to limit your study population to subjects with "a recent history of inadequate response to treatment with topical corticosteroid (at any time within 1 year before the screening visit) or for whom topical corticosteroids are otherwise medically inadvisable (e.g. due to important side effects or safety risks)." The labeled indication will reflect the population studied. In addition, as previously communicated, it may not be possible to confirm an "inadequate response" to topical corticosteroid therapy by history alone. To ensure that your study population meets this entry criterion, consider adding a "run-in period" to your study design with implementation of a comprehensive program of standard measures (e.g., moisturizers and irritant avoidance) combined with topical corticosteroid therapy.

f. It is important to identify the subtypes of CHE at enrollment. We recommend you perform patch testing on all subjects without recent results. We also recommend that you conduct testing to exclude subjects with treatable conditions (e.g., mycologic testing to exclude the diagnosis of tinea manuum).

g. You proposed to define your study population on both the Investigator's Global Assessment for chronic hand eczema (IGA-CHE) scale and Patient's Global

Assessment of disease severity (PaGA) scale at screening. We continue to have concerns about these proposed scales and assessments. Refer to the Pre-IND Meeting Minutes dated August 2, 2017.

i. We reiterate that the IGA-CHE and PaGA should be parallel and describe similar measurement concepts. While you have revised the IGA-CHE scale, it is not clear whether you have revised the PaGA scale. We recommend that you exclude symptoms (i.e. pruritus) from PaGA scale. Pruritus and pain are clinically meaningful symptoms that need to be evaluated separately. See FDA Response to Question 4a.

ii. The descriptors in the proposed the IGA-CHE do not articulate clear, non-overlapping, non-comparative categories. The category of "mild" is not sufficiently distinct from the category of "moderate". In both severity categories, subjects may have faint erythema, slight flaking and mild thickening. In the "mild" category, subjects may have scattered vesicles, slight dermal swelling and superficial fissures; in the "moderate" category, subjects may have clustered vesicles, definite dermal swelling and definite fissures. For example, a subject may have "faint erythema" and "slight" versus "definite dermal swelling". Therefore, the assessment of disease severity based on proposed scale may not allow subjects of the appropriate severity to be enrolled in your Phase 3 trials.

iii. We recommend you include representative photographs for each category of IGA-CHE scale to improve consistency of assessment of disease severity (including in investigator training materials).

Sponsor Response:

- The IGA-CHE scale as provided in the briefing package was utilized in the Phase 2b trial LP0133-1273 in adults with mild to severe CHE. Given the consistency in treatment effect versus vehicle in both the mild to severe and moderate to severe populations in the Phase 2b trial LP0133-1273, the Sponsor asserts that the effect of delgocitinib is robust and reliable despite the overlapping descriptors for IGA-CHE and PaGA.

  The Sponsor acknowledges the Agency's comments provided to the IGA-CHE scale. We therefore propose the following changes to the IGA-CHE scale for Phase 3 to ensure clear and non-overlapping categories (shown in tracked changes and clean version):

**Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) - tracked changes and proposed text in red color:*

IGA severity	IGA score	Sign/symptom	Intensity and description
Clear	0	Erythema, scaling, hyperkeratosis/lichenification	Absent
		Vesiculation, oedema, fissures	Absent
Almost clear	1	Erythema	Faint erythema
		Scaling, hyperkeratosis/ lichenification, vesiculation, oedema, fissures	Absent
Mild	2	Erythema, scaling, hyperkeratosis/lichenification	At least one: • Faint erythema • Slight flaking (mostly fine scales) • Slightly perceptible ~~Mild~~ thickening with exaggerated skin lines
		Vesiculation, oedema, fissures	At least one: • Scattered vesicles, without erosion • Barely palpable ~~Slight~~ dermal swelling • Superficial fissures
Moderate	3	Erythema, scaling, hyperkeratosis/lichenification	At least one: • ~~Faint erythema, or p~~Prominent redness • ~~Slight flaking (mostly fine scales), or f~~Flaking (thicker scales) • ~~Mild thickening with exaggerated skin lines, or p~~Palpable thickening
		Vesiculation, oedema, fissures	At least one: • Clustered vesicles, without visible erosion or excoriation • Definite dermal swelling • Definite fissures
Severe	4	Erythema, scaling, hyperkeratosis/lichenification	At least one: • ~~Prominent redness, or d~~Deep intense red colour • ~~Flaking (thicker scales), or d~~Desquamation with thick scales • ~~Palpable thickening, or p~~Prominent thickening with exaggeration of normal skin markings
		Vesiculation, oedema, fissures	At least one: • High density of vesicles, or with erosion or excoriation • Dermal swelling with skin induration • One or more deep fissures with/without bleeding

*Tables provided by sponsor prior to teleconference in Sponsor's Response to FDA Preliminary Comments

**Investigator's Global Assessment for Chronic Hand Eczema (IGA-CHE) – clean version:*

IGA severity	IGA score	Sign/symptom	Intensity and description
Clear	0	Erythema, scaling, hyperkeratosis/lichenification	Absent
		Vesiculation, oedema, fissures	Absent
Almost clear	1	Erythema	Faint erythema
		Scaling, hyperkeratosis/ lichenification, vesiculation, oedema, fissures	Absent
Mild	2	Erythema, scaling, hyperkeratosis/lichenification	At least one: • Faint erythema • Slight flaking (mostly fine scales) • Slightly perceptible thickening with exaggerated skin lines
		Vesiculation, oedema, fissures	At least one: • Scattered vesicles, without erosion • Barely palpable dermal swelling • Superficial fissures
Moderate	3	Erythema, scaling, hyperkeratosis/lichenification	At least one: • Prominent redness • Flaking (thicker scales) • Palpable thickening
		Vesiculation, oedema, fissures	At least one: • Clustered vesicles, without visible erosion or excoriation • Definite dermal swelling • Definite fissures
Severe	4	Erythema, scaling, hyperkeratosis/lichenification	At least one: • Deep intense red colour • Desquamation with thick scales • Prominent thickening with exaggeration of normal skin markings
		Vesiculation, oedema, fissures	At least one: • High density of vesicles, or with erosion or excoriation • Dermal swelling with skin induration • One or more deep fissures with/without bleeding

*Tables provided by sponsor prior to teleconference in Sponsor's Response to FDA Preliminary Comments

In order to ensure consistency of assessment of disease severity, all investigators will be provided with a photo guide illustrating representative

photographs for each category of the IGA-CHE scale. Furthermore, all investigators will receive training in the assessment of IGA including photo examples depicting the different IGA-CHE disease severity grades. All principal investigators must be either a dermatologist or allergist and only investigators with experience in treating CHE and documented experience and/or training in use of the assessment will participate in the Phase 3 trials.

Does the Agency agree with the Sponsor's proposed revision to the IGA-CHE scale, as well as the plan to ensure consistency?

Meeting Discussion:

The Agency recommended that the sponsor revise the descriptors in the Investigator's Global Assessment for chronic hand eczema (IGA-CHE) scale. The categories of " mild", "moderate" and "severe" were not sufficiently distinct. Defining the appropriate study population with moderate to severe CHE using this scale would be problematic. In particular, the category of "moderate" does not appear to reflect CHE of adequate disease severity (i.e. some subjects may have mild disease according to the scale). The sponsor planned to develop a photographic guide to illustrate the disease severity categories. The Agency advised the sponsor to submit the photographic guide with the Phase 3 protocols for review. The Agency indicated that the following review by Coenraads et al.[2] might be informative:

Sponsor Response:

The Sponsor acknowledges the Agency's comment that the IGA-CHE and PaGA should be parallel and describe similar measurement concepts. Therefore, we agree to exclude itch from the PaGA scale and propose the following changes to PaGA to reflect the changes proposed for the IGA-CHE (above).

Does the Agency agree with this proposed revision of the PaGA scale?

**PaGA - tracked changes:*

Clear	No symptoms	No symptoms of hand eczema at all. No redness, ~~itching,~~ scaling, skin thickening, blistering, swelling or cracking at all.
Almost clear	Only redness	Only slight redness.
	No other symptoms	No scaling, ~~itching,~~ skin thickening, blistering, swelling or cracking) of hand eczema

[2] Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. British Journal of Dermatology 2005 152, pp296–301. DOI 10.1111/J.1365-2133.2004.06270.X.

Mild	At least one mild	Redness, scaling or skin thickening
	Al least one mild	~~Itching,~~ blistering, swelling or cracking
Moderate	At least one ~~mild or~~ moderate	Redness, scaling or skin thickening
	At least one moderate	~~Itching,~~ blistering, swelling or cracking
Severe	At least one ~~moderate or~~ severe	Redness, scaling or skin thickening
	At least one severe	~~Itching,~~ blistering, swelling or cracking

**PaGA - clean version:*

Clear	No symptoms	No symptoms of hand eczema at all. No redness, scaling, skin thickening, blistering, swelling or cracking at all.
Almost clear	Only redness	Only slight redness.
	No other symptoms	No scaling, skin thickening, blistering, swelling or cracking) of hand eczema
Mild	At least one mild	Redness, scaling or skin thickening
	Al least one mild	Blistering, swelling or cracking
Moderate	At least one moderate	Redness, scaling or skin thickening
	At least one moderate	Blistering, swelling or cracking
Severe	At least one severe	Redness, scaling or skin thickening
	At least one severe	Blistering, swelling or cracking

*Tables provided by sponsor prior to teleconference in Sponsor's Response to FDA Preliminary Comments

Meeting Discussion:

The Agency acknowledged the proposed revisions to the PaGA scale. However, the Agency clarified that prespecified scores on the PaGA scale are not necessary for

defining the study population and recommended excluding the PaGA in the inclusion criterion to characterize disease severity. A simplified version of the PaGA may have utility as an external anchor scale.

Question 3:
Does the Agency agree with the proposed alternate dosing regimen of 20 mg/g twice daily in the pivotal phase 3 trials?

FDA Response to Question 3:
From the data provided, it appears that the originally planned dose and dosing regimen for your proposed product, delgocitinib cream, 8 mg/g twice daily, is reasonable. In your amendment you stated that based on data from a limited number of subjects (9 to 12 subjects with severe disease in each treatment group), you propose to develop the high concentration (20 mg/g) because you have concluded that for subjects with severe disease, there may be additional benefit from the higher concentration. In addition, you stated that there were no dose-related adverse events. However, the dose response trend was not clear or consistent in your dose-ranging study, as subjects with moderate disease had better response rates on the 8 mg/g dose than the 20 mg/g dose. It is also possible that the observed differences based on baseline severity are due to chance or other subject characteristics that might be confounded with baseline severity. If the observed difference in response rates based on baseline severity is a real effect, then which dose is better for the intended population may depend on the relative prevalence of the disease severity categories in the population.

The decision to pursue further development of a given concentration of delgocitinib cream lies with you.

Question 4a:
Does the Agency agree with the proposed primary and key secondary endpoints, as well as the statistical testing procedure for these endpoints?

FDA Response to Question 4a:
The proposed primary efficacy endpoint, Investigator Global Assessment (IGA-CHE) score of 0 (clear) or 1 (almost clear) with at least a 2-step improvement (IGA-CHE TS) from Baseline to Week 16 on an acceptable scale is reasonable.

The proposed key secondary endpoints with which you seek agreement include:

- HECSI90 at Week 16.
- Reduction of HESD itch score (weekly average) of ≥3-points from baseline at Week 16.
- Reduction of HESD score (weekly average2) ≥3-points from baseline at Week 16.
- IGA-CHE TS at Week 8.
- IGA-CHE TS at Week 4.

- HECSI75 at Week 8.
- Reduction of HESD itch score (weekly average) ≥3-points from baseline at Week 8.
- Reduction of HESD itch score (weekly average) ≥3-points from baseline at Week 4.
- Reduction of HESD itch score (weekly average) ≥3-point from baseline at Week 2.
- Reduction of HESD score (weekly average) ≥3-points from baseline at Week 8.
- Reduction of HESD score (weekly average) ≥3-points from baseline at Week 4.
- Reduction of HESD pain score (weekly average) ≥3-points from baseline at Week 4.

You propose to evaluate more than 20 key secondary efficacy endpoints based on IGA-CHE, HECSI and Chronic Hand Eczema Symptom Diary (HESD) and include them all in your multiplicity adjustment scheme. Secondary endpoints that are intended for labeling should be limited in number, clinically meaningful and supportive of the primary efficacy endpoint. Thus, we recommend limiting the number of key secondary endpoints in your multiplicity adjustment scheme to those that are supportive of the primary efficacy endpoint and clinically meaningful. The proposed key secondary endpoints based on IGA-CHE are supportive of the primary efficacy endpoint and clinically meaningful. The evaluation of pruritus and pain in subjects with CHE is clinically meaningful.

However, we have concerns about the HECSI and HESD scales. The HECSI scale is a calculated scale that represents the summation of the extent, location and severity of different cutaneous signs into a single score. All signs are equally important in scoring. The same HECSI score may represent a different combination of signs and severities. As such, this data is difficult to interpret (b) (4). While it may be possible to evaluate pruritus and pain in subjects with CHE using HESD, you need to establish an appropriate threshold that would constitute a clinically meaningful change in the target population. Refer to FDA Response to Question 12c for comments regarding your proposed responder thresholds (i.e.≥3-points) for HESD itch and pain scores.

We have the following comments regarding the secondary COA endpoints:

HECSI:

1. The item content of the HECSI appears somewhat relevant to CHE. However, there are some concepts that are not supported by patient input based on your qualitative data. For example, swelling, blisters, and thickened skin are concepts that were probed and not experienced in a good proportion of patients (i.e., >50% of sample, see Figure 12 of Appendix 7), suggesting that these concepts may not be important to CHE patients. Further the item response distribution data at baseline (Figure 9 in Appendix 5) in the phase 2b trial (Study LP0133-1273) demonstrates

that a good proportion of subjects' hands were rated with a None/Absent severity score. Provide a rationale for including these concepts in the HECSI.

2. Clarify whether there are accompanying instructions, training materials and /or a user manual for the HECSI. The copy of the instrument included in the briefing package lacks instructions, so it is unclear whether standardized training and instructions for administration is provided for all respondents (i.e., clinicians) across sites. Additionally, in the absence of category descriptions for the intensity ratings (i.e., severity score) of the clinical signs (none/absent, mild, moderate, severe), there is concern regarding potential variability and measurement error within and across respondents. Provide evidence of the inter-rater reliability of the HECSI.

HESD:

3. Refer to FDA Responses to Questions 12a and 12b.

PaGA, DLQI, and HEIS:

4. These instruments have measurement challenges that may make it difficult to inform regulatory decision-making (b) (4). However, we acknowledge that these instruments may be necessary for other regulatory authorities and/or payers. Refer to Additional Comments for specific comments regarding some of these instruments.

Question 4b:

Does the Agency agree with the proposed primary and supplementary estimands, the handling of missing data, and the statistical analysis methods?

FDA Response to Question 4b:

Your proposal to analyze the primary endpoint and other binary endpoints using the Cochran-Mantel-Haenszel test stratified by region and baseline IGA-CHE and calculate confidence intervals with the Mantel-Haenszel method appears reasonable.

Your proposal to use the composite strategy for your primary estimand appears reasonable. However, for subjects with missing data from sources other than the specified intercurrent events, we recommend using a missing data approach that also captures the statistical uncertainty due to data missingness, such as through multiple imputation, rather than imputing all missing data as non-response. Whether or not a single imputation procedure is conservative may depend on the pattern of dropout on the different treatment arms. Your supplementary estimand using the treatment policy strategy with a multiple imputation strategy and your tipping point analysis appear reasonable. We recommend that you fully pre-specify the details of the multiple imputation analyses, including the randomization seeds, in your protocol or SAP.

Meeting Discussion:
We have had insufficient time to evaluate your proposal regarding the estimand and handling of missing data due to COVID-19. The Agency will provide a response after the sponsor provides details in their protocol about these issues.

Question 5a:
Does the Agency agree that the psychometric evidence for the HECSI score in CHE is adequate and supports its use in assessing disease severity and evaluating treatment benefit in adults with moderate to severe CHE?

Question 5b:
Based on the evidence provided, does the Agency agree with the proposed within-patient responder definition(s) for the HECSI score(s) and that this is clinically meaningful?

FDA Response to Questions 5a & 5b:
We continue to have concerns regarding the HECSI scoring algorithm as previously communicated in the FDA Meeting Minutes dated August 2, 2017.

You indicate that "the inter-item correlation heat map and the exploratory bi-factor factor analysis provide evidence that the items of the HECSI assessing clinical signs for each area of the hand should be grouped together to form domain scores, which can then be grouped to form a total score." Based on your item-level analyses, it appears that there are specific locations (Figure 14 of Appendix 5) and components (Figure 15 of Appendix 5) that are overly influencing changes observed in the total score. For example, the areas of fingers and palms contribute more to the total score than other areas of the hand. Similarly, the erythema, scaling, and infiltration/papulation components contribute more to the total score than other clinical signs. Provide a rationale to justify that the six components of the HECSI have equal clinical impact.

Further provide a rationale for generating a score for each location (total of both hands) of the affected area. You indicate that "In general, patients described the locations of their signs/symptoms as a whole rather than describing different locations for different signs/symptoms. The location of the various signs and symptoms were variable and not necessarily related to the location where patients may have come into contact with an allergen or irritant in those with the allergic and irritant subtypes."

Question 6a:
Does the Agency agree that the proposed exposure database would be sufficient to evaluate the safety of delgocitinib?

FDA Response to Question 6a:
The number of subjects needed to demonstrate safety may be substantially higher than the number of subjects needed to demonstrate efficacy. The size of the safety database depends on known safety signals for the drug class, data regarding systemic

bioavailability and any safety signals observed during the development of your drug product.

You propose to submit data from an estimated 808 subjects with CHE exposed to any concentration of delgocitinib cream which includes approximately 600 subjects exposed to the target dose of delgocitinib cream (8 mg/g or 20 mg/g) for 16 weeks in Phase 3 trials and approximately 52 subjects exposed to the target dose of delgocitinib cream for 16 weeks in the Phase 2 trial (LP0133-1273). Subjects completing the Phase 3 trials (LP0133-1401 and LP0133-1402) will have the option to participate in the 36- week, long- term extension trial (LP0133-1403). You anticipate that ≥ 300 subjects will receive delgocitinib cream for 6 months and ≥ 100 subjects will receive delgocitinib cream for 12 months. You plan to include data from subjects who received delgocitinib cream for 6 months with your NDA submission and provide data from subjects who received delgocitinib cream for 12 months in the Safety Update Report.

In view of the known adverse reaction observed with Janus Kinase Inhibitors drug products and without a known systemic exposure threshold for these adverse reactions in the target population, we recommend that you propose a larger safety database, including the number of subjects with short- term exposure (see guideline) and long-term exposure (e.g. 200 subjects for 12 months.) Refer to the guideline for industry “The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions.”

At the time of submission, your New Drug Application must be substantially complete including 12 months of the long- term safety data. The adequacy of the safety database for the proposed indication and the intended population will be a review issue.

Sponsor Response:
In addition to the Phase 2b and Phase 3 trials in CHE, the Sponsor proposes to include subjects with CHE and AD exposed to delgocitinib in studies LP0133-1180, LP0133-1181 and LP0133-1275 in the total safety database because the safety profile from completed studies in both formulations and indications have shown to be similar. As a result, the total safety base proposed for the NDA submission is 1,115 and includes the following additional subjects.

- 60 subjects with CHE exposed to delgocitinib ointment 30mg/g for 8 weeks in study LP0133-1180
- 46 subjects with AD exposed to delgocitinib cream 20mg/g for 8 weeks in LP0133-1181
- 201 subjects with AD exposed to delgocitinib cream (1, 3, 8 and 20 mg/g) for 8 weeks in LP0133-1275

Although in the briefing package (under Section 10.1.6) we stated that 480 subjects will be rolled over from the parent trials to the LTE, we will now

plan to offer all 900 subjects from the parent trials (n=600 on active plus n=300 vehicle) to roll over into the LTE. As a result, approximately 550 subjects are expected to roll over into the LTE.

Therefore, in accordance with ICH E1 guidance, at time of NDA submission, ≥300 subjects will receive delgocitinib cream for 6 months and ≥ 100 subjects will receive delgocitinib cream for 12 months. At the time of the Day 120 Safety Update, ≥200 subjects will be exposed for 12 months.

Does the Agency agree that the revised proposal for exposure database would be sufficient to evaluate the safety of delgocitinib in CHE?

Meeting Discussion:
The Agency could not provide agreement with the overall size of the safety database without further consideration of the proposal submitted by the sponsor. In view of adverse event profile associated with the product class, the Agency emphasized the need for sufficient safety data from continuous long- term exposure (i.e. ≥ 6 months) to the proposed product in the target population. At the time of NDA submission, the Agency expects that the safety database will include data from at least 300 subjects continuously exposed for 6 months and 200 subjects continuously exposed for 12 months. The safety update report should include data from 100 additional subjects continuously exposed for 12 months.

Post-Meeting Question:
We would like the Agency's clarification and agreement on the definition of "continuous treatment" and proposes the following subjects to be considered as having received continuous treatment with delgocitinib for purposes of exposure requirements:
subjects treated with delgocitinib 20 mg/g twice daily in the parent trials (LP0133-1401/1402) and treated with delgocitinib 20 mg/g twice daily in periods with IGA-CHE ≥ 2 (i.e. non-responders) in the LTE trial (LP0133-1403).

Does the Agency agree with this proposal?

Post-Meeting Response:
No, we do not agree. Under real world conditions, some patients will apply delgocitinib cream continuously, not just for loss of response. Therefore, the long- term extension trial (LP0133-1403). should evaluate subjects who are exposed to delgocitinib cream continuously, not intermittently for loss of response (IGA-CHE ≥ 2.)

Question 6b:
Does the Agency agree with the proposed strategies for cardiac safety and the long-

term safety assessment plan in the phase 3 trials?

FDA Response to Question 6b:

Cardiac Safety:
You state that the results of the cardiac safety monitoring from the Phase 2b LP0133-1273 in subjects with CHE and Part 1 of Trial LP0133-1181 in subjects with atopic dermatitis (AD) indicated no clinically meaningful QTc-prolongation from exposure to delgocitinib. In addition, you indicate that a single oral dose of delgocitinib (up to 3 mg/kg) in the dog study, resulted in no effect on ECG parameters. Currently, you are planning to conduct a Phase 1 trial (LP0133-1409) to evaluate the QTcF prolongation and proarrhythmic potential of delgocitinib after oral administration in healthy subjects based on the anticipated higher exposure in subjects with AD.

In view of the anticipated low exposure (< 1 nM) in subjects with CHE, you propose to conduct cardiac safety monitoring at Baseline and end- of- treatment (EOT) in the Phase 3 trials. Based on the available safety and exposure data from the Phase 2 trial (results from the MuST are pending), your plan is reasonable. However, consider performing an ECG at steady -state.

Long-term Safety:
You propose to enroll approximately 480 adult subjects from Phase 3 trials LP0133-1401 and LP0133-1402 into open-label, long-term, safety Trial LP0133-1403. In general, your safety monitoring for Trial LP0133-1403 which includes physical examinations (Baseline and EOT), vital signs (Baseline, Week 8, Week 16, Week 24 and EOT), ECG (Baseline and EOT), chemistry/hematology (Screening/Baseline, Week 8, Week 16, Week 24 and EOT), urinalysis (Screening/Baseline, Week 4, Week 6, Week 8 and EOT), AEs (all visits after Screening), pregnancy testing (monthly) and local tolerability (all visits after Baseline) is reasonable.

Refer to FDA Response to Question 7 for comments regarding local safety assessments.

Post-Meeting Response:

Comments regarding the proposed TQT study design are pending internal consultation.

Question 12a:

Does the Agency agree that a PRO assessing severity of key CHE symptoms of itch, pain, cracking of the skin, redness, dryness, swelling, thickening of the skin, and flaking of the skin is relevant to include as part of the evaluation of treatment benefit in adults with moderate to severe CHE?

FDA Response to Question 12a:

The concepts of itch, pain, cracking of the skin, redness, dryness, and flaking appear content relevant to the target population. However, swelling and thickened skin are concepts that were probed and not experienced in a good proportion of patients (i.e., >50% of sample, see Figure 12 of Appendix 7), suggesting that these concepts may not be important to CHE patients. Further, the response distributions of the HESD daily scores at Baseline indicate that >15% of patients reported "No sign or symptom (0)" for the concepts of swelling and thickened skin (see Table 42 in Appendix 9). Provide a rationale for including these two concepts in the HESD.

Question 12b:
Does the Agency agree that evidence of content validity and measurement properties for the HESD is adequate and supports its use in assessing the severity of the CHE symptoms of itch, pain, cracking of the skin, redness, dryness, swelling, thickening of the skin, and flaking of the skin in adults with moderate to severe CHE?

FDA Response to Question 12b:
See FDA Response to Question 12a regarding the content relevance of the HESD. Regarding the other measurement properties, the results appear reasonable, in general. Provide the distribution of change on the HESD itch score, pain score, and total score by change on the IGA-CHE and PaGA scales, separately, by providing descriptive statistics for improvement in these scores for each level of categorical improvement in the anchors [N (total number), mean, median, standard deviation, range, and confidence intervals] versus collapsed categories (i.e., >1 grade improvement).

Question 12c:
Does the Agency agree that the responder definitions for HESD itch score (weekly average), HESD pain score (weekly average), and the HESD score (weekly average; including itch, pain, cracking, redness, dryness, swelling, thickening of the skin, and flaking of the skin) are clinically relevant?

FDA Response to Question 12c:
We cannot fully comment on your proposed responder definitions as your external anchors have limitations. Refer to the Additional Comments regarding considerations for use of external anchors.

While the PaGA may be a reasonable anchor for the HESD total score, it does not measure the concept of interest for the HESD itch and pain scores, but CHE signs and symptoms as a whole. The anchor's concept should be the same as the specific concept being assessed by the COA endpoint of interest. Similarly, the IGA-CHE, PGI-C, DLQI, and QOLHEQ does not measure the concept of interest for the HESD itch, pain, and total scores. Plan to use appropriate external anchors in Studies 1401 and -1402 to confirm the responder definitions for the HESD itch score, pain score, and total score.

We acknowledge that the responder thresholds were supported by patient input,

however, anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in instruments. Qualitative methods should be used to complement anchor-based methods.

Sponsor Response:

We acknowledge the comments that for the HESD itch score (weekly average) and HESD pain score (weekly average) the Agency would prefer anchors more closely aligned to the concepts being assessed by the COA endpoints of interest. We also acknowledge the 'Additional Comments' made by the Agency regarding the properties that external anchors should have. Based on those comments, and also taking account the examples suggested in the FDA 'Patient Focused Drug Development' guidance, new PGI-S and PGI-C items that are specific to itch and pain on the hands have been developed. In addition, new PGI-S and PGI-C items specific to hand eczema symptoms have been developed for use in place of the PaGA as an anchor.

As per the Agency feedback, the new PGI items are focused on the same specific concepts as the concepts being assessed by the COA endpoints of interest. They are easier to interpret than the COA measure itself and use the suggested none, mild, moderate and severe response scale. The PGI-S items also have a recall period of "the past week", thus aligning with the recall period of endpoints on the HESD itch score, HESD pain score and HESD total score, which are averaged over a week.

We propose including these new PGI-S and PGI-C items in the Phase 3 trials (studies LP0133-1401 and -1402) to support further anchor-based analyses for the HESD itch score (weekly average), HESD pain score (weekly average) and HESD total score (weekly average). These new PGI-S and PGI-C items are provided below:

New itch PGI-S: Please choose the response below that best describes the severity of any **itch** on your hands over the **past week**

Response scale: 'None' – 'Mild' – 'Moderate' – 'Severe'

New itch PGI-C: Please choose the response below that best describes the overall change in any **itch** on your hands since you started taking the study medication

Response scale: 'Much better' – 'A little better' – 'No change' – 'A little worse' – 'Much worse'

New pain PGI-S: Please choose the response below that best describes the severity of any **pain** on your hands over the **past week**

Response scale: ‘None’ – ‘Mild’ – ‘Moderate’ – ‘Severe’
New pain PGI-C: Please choose the response below that best describes the overall change in any **pain** on your hands since you started taking the study medication

Response scale: ‘Much better’ – ‘A little better’ – ‘No change’ – ‘A little worse’ – ‘Much worse’

New HESD score PGI-S: Please choose the response below that best describes the severity of your **hand eczema symptoms** over the **past week**

Response scale: ‘None’ – ‘Mild’ – ‘Moderate’ – ‘Severe’

New HESD score PGI-C: Please choose the response below that best describes the overall change in your **hand eczema symptoms** since you started taking the study medication

Response scale: ‘Much better’ – ‘A little better’ – ‘No change’ – ‘A little worse’ – ‘Much worse’

Does the Agency agree with the wording of the itch, pain and the general hand eczema symptoms PGI-S and PGI-C anchor items? Does the Agency have any further comments or suggestions regarding wording of the new PGI items?

As stated above, and as requested by the Agency, we plan to include these new external anchors in Phase 3 studies LP0133-1401 and -1402 to confirm the responder definitions for the HESD Itch score (weekly average), HESD Pain score (weekly average) and HESD score (weekly average). Psychometric measurement properties and responder definition analyses will be reassessed using these new anchors using methods consistent with those used with the Phase 2b data, using blinded data from Phase 3 pooled across treatment groups. As part of these analyses that will use the Phase 3 data we will be sure to calculate the distribution of change on the HESD Itch score, HESD Pain score, and HESD score by change on the updated IGA-CHE, PaGA and these new PGI-S and PGI-C scales, separately, by providing descriptive statistics for improvement in these scores for each level of categorical improvement in the anchors [N (total number), mean, median, standard deviation, range, and confidence intervals] versus collapsed categories (i.e., >1 grade improvement) - as requested in response to Question 12b.

We propose to perform these anchor-based responder definition analyses, and also further confirm the psychometric properties of the HESD Itch

score, HESD Pain score and HESD score using blinded data, pooled across treatment groups, from Phase 3. The analyses will be performed on an early cut of the blinded data as soon as an adequate sample has completed the trials to support adequate analysis and interpretation.

As summarised in the briefing package, based on the analyses conducted to date, the Sponsor propose pre-specifying endpoints with responder definition thresholds of 3-point change for the HESD Itch score (weekly average), HESD Pain score (weekly average) and HESD score (weekly average). If the findings of the responder definition analyses performed using an early cut of the blinded data from Phase 3 suggest that a responder definition threshold other than 3-point change is more appropriate for any of these endpoints, then the responder definition in the trial protocols will be modified via protocol amendments prior to unblinding of the trials.

Does the Agency agree to the plans for re-assessment of the psychometric measurement properties as well as confirming the responder definition threshold, using blinded data from Phase 3, for the HESD Itch score (weekly average), HESD Pain score (weekly average) and HESD score (weekly average)?

Does the Agency agree to modify the endpoints on HESD Itch score, HESD Pain score and HESD score via trial protocol amendments, prior to unblinding the trials, in case the responder definition analyses suggest other than a 3-point change?

Meeting Discussion:

The Agency noted that a threshold improvement of at least 4 when assessing itch has been used in other applications.

The Agency does not concur with the sponsor's proposal to determine a threshold level for pain based on analysis of blinded data from Phase 3 trials and to modify the proposed threshold improvement level of at least 3, if needed, prior to unblinding the data. There are several details that need to be worked out including ensuring the blinding is maintained and determining who carries such analysis. Furthermore, holding out the possibility of changing the threshold prior to breaking the blind may impact the integrity of the trial.

*The sponsor inquired whether all subjects need to meet a threshold the level for itch at study enrollment. The Agency responded that we would expect a good proportion of subjects to meet such threshold level (*i.e. ≥ 4*) to be able to interpret the results and potentially include in labeling. The sponsor noted that over 70% of the subjects enrolled in their Phase 2 trials met such criteria and inquired whether such a proportion is*

acceptable for Phase 3 trials. The Agency noted that a proportion of 70% or higher should be reasonable.

Post Meeting Comments:

1. *The new proposed anchor scales appear reasonable, in principle. Consider including "hand eczema signs" in addition to "hand eczema symptoms" to the item stem in the proposed New HESD score of PGI-S and PGI-C (i.e., "hand eczema signs and symptoms"), as the HESD includes items related to hand eczema signs (e.g., flaking, dryness). However, refer to Additional comment #1.*

2. *Regarding the use of the Phase 3 data to derive threshold(s) for meaningful within-patient score changes in the HESD, there is a potential concern with overfitting and generalizability because you are using the same set of patients to determine the responder threshold as well as demonstrate efficacy. To lessen this concern, we recommend that you blindly pool a subset (e.g., 100) of subjects in each trial to establish a meaningful change threshold(s), or a range of threshold(s), and then confirm using blinded, pooled data from remaining subjects in each study. The proposed meaningful change threshold(s) (e.g., a range of score changes) should be submitted to the IND prior to data unblinding. We also recommend that you utilize a blinded, independent (external) statistician to conduct the analysis in order to maintain the integrity of the trial conduct prior to unblinding.*

3. *You will need to provide evidence to support the proposed responder thresholds for the HESD. Anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints. You should plan to incorporate these methods for the proposed COAs in your protocol and analyses. Anchor-based methods should be supplemented with anchor-based empirical cumulative distribution function and probability density function curves. Other methods may be explored to complement the anchor-based methods or when anchor-based methods are not feasible (i.e., when no adequate anchor measure(s) are available, small sample size). For example, patients can be queried via cognitive interviews, exit interviews, or surveys to help inform the improvement threshold.*

Additional Comments:

1. *External anchors should have the following properties:*

    a. *The anchor's concept should be the same as the specific concept being assessed by the COA endpoint of interest. For example, for an endpoint measuring a specific aspect of the disease, an anchor measuring a global status of the disease may not be helpful.*

b. *Easier to interpret than the COA measure itself and meaningful to patients; an anchor measure that uses a 0-10 numeric rating scale would not be easy to interpret and would not be an appropriate anchor scale. A commonly used response scale for rating severity is none, mild, moderate, or severe.*

c. *The anchor's recall period should be consistent with the assessment time period of the prespecified endpoint. For example, if the target endpoint measure is the number of incontinence episodes collected in incontinence diaries averaged over 7 days, a verbal rating scale assessing the bother of incontinence with a 7-day recall period would serve as an easily interpretable anchor scale for interpretation of meaningful within-patient change in mean incontinence episodes.*

d. *Anchor scales should be plainly understood by respondents in the context of use; sponsors could consider testing the draft anchor item(s) in their cognitive interviews.*

2. *We have the following comments regarding the PaGA, DLQI, and HEIS:*

PaGA

a. *For the context of this development program, we view this global assessment as an exploratory anchor scale to aid in determination of what constitutes a clinically meaningful within-patient change in another COA instrument's score(s), rather than as standalone secondary endpoint.*

b. *We recommend using the simplified version of the PaGA. While your qualitative supports both the original and simplified versions, your qualitative sample was skewed in relation to educational level. There may be patients in the clinical trial that are at a lower educational level (e.g., literacy) who may have difficulty with the formatting of this item in the original version.*

DLQI

c. *The DLQI is a generic instrument that contains questions that ask about various concepts related to a skin problem and treatment, which may lack clinical relevance and may be insensitive in detecting potential treatment effects in your patient population. Further, there are issues with the inclusion of multi-barreled questions (questions measuring more than one concept, e.g., one item asks how "itchy, sore, painful or stinging" the skin has been; another item asks about the skin's interference with "going shopping or looking after [one's] home or garden") which can lead to unwanted variability in the data. If you are interested in assessment of disease-related impacts, we encourage you to use a more disease-specific instrument that evaluates the impacts of those symptoms on patients' daily lives in order to provide meaningful information regarding the clinical benefit of your treatment.*

HEIS

d. The HEIS includes broad concepts (e.g., sleep quality, dislike the appearance of hands, feel frustrated), that might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect.

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*.[3] 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.[4]

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

[3] 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.

[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[5]

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*, 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 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. 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

[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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 (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. 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.[7]

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[8] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[9]

SECURE EMAIL COMMUNICATIONS

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

4.0 SPONSOR AGENDA

[7] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[8] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] https://www.fda.gov/media/109533/download

Items for Discussion:

- Question 6a
- Question 2
- Question 7
- Question 12
- Question 1

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
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