

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212801Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117489

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Victoria Papademas, Pharm.D., R.Ph.
Associate Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Papademas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for osilodrostat (LCI699).

We also refer to the meeting between representatives of your firm and the FDA on August 20, 2018. The purpose of the meeting was to discuss the data to support your planned new drug application (NDA) for the treatment of patients with [REDACTED] ^{(b) (4)}.

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

If you have any questions, call Jennifer Johnson, Regulatory Project Manager at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: Monday, August 20, 2018; 1:00 – 2:00 pm EST
Meeting Location: FDA White Oak Campus
Application Number: IND 117489
Product Name: osilodrostat (LCI699)
Indication: Treatment of patients with [REDACTED] (b) (4)
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation
Meeting Chair: William Chong, M.D.
Meeting Recorder: Jennifer Johnson

FDA ATTENDEES

Office of Drug Evaluation II

Mary T. Thanh-Hai, M.D. Acting Director

Division of Metabolism and Endocrinology Products

William Chong, M.D. Acting Director
Marina Zemskova, M.D. Clinical Team Leader
Shannon Sullivan, M.D. Acting Clinical Team Leader
Diala El-Maouche, M.D. Clinical Reviewer
Todd Bourcier, Ph.D. Pharmacology/Toxicology Supervisor
Pam Lucarelli Chief, Project Management Staff
Jennifer Johnson Regulatory Health Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology 2

Jaya Vaidyanathan, Ph.D. Clinical Pharmacology Team Leader

Office of Biostatistics, Division of Biometrics 2

Jiwei He, Ph.D. Statistics Reviewer
Jennifer Clark, Ph.D. Statistics Team Leader

SPONSOR ATTENDEES

Representing Novartis Pharmaceuticals Corporation

Oliver Jung, Ph.D. Global Program Head
Alberto Pedroncelli, M.D. Global Program Clinical Head
Tianxiang (Kevin) Han, Ph.D. Investigator, Pharmacokinetic Sciences
Michael Roughton, M.Sc. Trial Statistician, Global Biostatistics
Shantha Rao, Ph.D. Director, Global Biostatistics

Shoba Ravichandran M.D.
Matthias Jauslin, Ph.D.

Executive Director, US Medical
Global Therapeutic Area Lead, Regulatory
Affairs

Victoria Papademas, Pharm.D.
Pio Donizete Zapella, Ph.D.

Senior Global Program Regulatory Manager
Global Head, Regulatory Affairs

(b) (4)

1.0 BACKGROUND

Osilodrostat is an orally-administered inhibitor of 11 beta-hydroxylase (CYP11B1). It is manufactured as a phosphate salt and available as 1 mg, 5 mg, and 10 mg, and 20 mg filmcoated tablets. (b) (4)

(b) (4)

Given the mechanism of action to inhibit cortisol synthesis at the adrenal glands, osilodrostat has therapeutic potential in all forms of endogenous Cushing syndrome (i.e., pituitary Cushing's disease, adrenal Cushing's syndrome and ectopic ACTH syndrome). Osilodrostat is a new molecular entity and has not yet been approved in any country, and was granted orphan drug status for the treatment of Cushing's disease on September 13, 2013.

An End-of-Phase 2 meeting was held on October 9, 2013, and minutes issued on November 8, 2013. A guidance meeting (written responses only) was requested on October 10, 2017, to confirm with FDA that (b) (4) are not required to be submitted as part of the Cushing's disease New Drug Application (NDA). A Written Responses letter issued on December 22, 2017. A CMC-only guidance meeting was requested on April 9, 2018, to discuss the sponsor's proposal to designate (b) (4) as starting materials for the commercial manufacture of LCI699 phosphate drug substance. A Written Responses letter issued on May 18, 2018.

To support approval of an eventual NDA, the sponsor is conducting pivotal study CLCI699C2301, entitled "A Phase III, multicenter, double-blind, (b) (4) randomized withdrawal study of LCI699 following a 24-week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease (b) (4)." The data from study C2301 is to be supplemented by data from studies C2201 and C1201.

The sponsor requested a Pre-NDA meeting on May 25, 2018. A Meeting Granted letter issued on June 15, 2018, and a meeting package was submitted on July 19, 2018.

FDA sent Preliminary Comments to Novartis on August 17, 2018.

2. DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded) and meeting discussion (bolded/italicized).

Question 1: Novartis is of the opinion that the robust results from the pivotal, randomized, Phase III Study C2301 (LINC-3) in patients with Cushing's disease, in conjunction with supportive studies C2201 and C1201, are adequate and sufficient to substantiate the safety and efficacy of osilodrostat and support a NDA filing in the proposed indication. Does the Agency agree?

FDA Response to Question 1: We agree that Study C2301 in conjunction with studies C2301 and C1201 conducted in patients with Cushing's disease will support an NDA filing. The adequacy of the efficacy and safety data generated in the phase 3 study C2301 to support approval will require a full review of the NDA.

As phase 3 study C2301 is a randomized withdrawal trial and randomization was carried out only in those who were responders during an open label single arm treatment, interpretability of efficacy and safety data from such a trial will be challenging. Address the following at the meeting and in detail in any future NDA submission:

1. Clarify whether patients with pseudo-Cushing's and cyclic Cushing's syndrome were excluded from the study.

Novartis response sent via email on August 20, 2018: Novartis will address this during the meeting.

2. Clarify why the majority of patients (~ 70%) who were responders at the end of week 26 and entered the randomization period had UFC normalization on the lowest dose (2 mg bid) without dose escalation after week 12. In addition, we note that patients who were randomized in period 3 had lower UFCs at baseline compared to non-randomized patients. This might represent preselection of patients with mild disease. Patients with more severe disease may require longer titration (> 12 weeks) to achieve effective dose.

Novartis response sent via email on August 20, 2018: Novartis will address this during the meeting.

3. We note that 19 patients had normal UFCs at the end of period 2, but were not randomized in Period 3 because they required longer than 12 weeks titration. Provide the doses and duration of the titration in these patients.

Novartis response sent via email on August 20, 2018: We will provide the details of these patients as part of the NDA.

No further discussion is planned at the meeting.

4. **Clarify how many non-randomized patients had normal UFCs at the end of the study; comment on their baseline UFCs, doses required and duration of the titration.**

Novartis response sent via email on August 20, 2018: Please see response below. No further discussion is proposed at the meeting.

At Week 48, 32/66 (48.5%) of non-randomized patients had normal mUFC.

Proportion of non-randomized patients with normal mUFC at Week 48 by baseline mUFC category

Baseline mUFC category	n/N(%)
<2xULN	5/11 (45.5)
2 to <5xULN	12/28 (42.9)
>=5xULN	15/27 (55.6)

Doses required and duration of the titration will be provided in the NDA.

5. **We note that by the end of Period 3 for study C2301, 86.1% of patients in the active treatment arm with normal UFCs (down from 100% at entry in the randomized period), and 29.4% of patients treated with placebo with normal UFCs. Please comment on the reasons for the patients with apparent loss of efficacy in the treatment arm, and also on the reasons for the patients that continued to have normal UFCs in the placebo group.**

Novartis response sent via email on August 20, 2018: Please see summary response below. A more detailed discussion will be included in the NDA. No further discussion is proposed at the meeting.

Randomized to osilodrostat: There were 36 patients randomized to osilodrostat. For the primary analysis, 31 (86.1%) patients were considered responders.

Of the 5 patients who were classified as non-responders for the primary analysis:

- 2 patients had normal mUFC at the end of the RW period, but had a dose increase during the RW period, so per protocol were classified as non-responders
- 3 patients that had a mUFC greater than the ULN. 2/3 of these patients had marginally elevated mUFC at the end of the RW period.

Randomized to placebo: There were 34 patients treated with placebo from Week 26-Week 34. 10 (29.4%) of these patients had normal mUFC by end of the 8 week RW period (Period 3). Novartis is carefully evaluating these data and will include a discussion of potential reasons in the NDA.

6. Clarify how many UFC samples were required for the calculation of mUFC for the primary and secondary analysis.

Novartis response sent via email on August 20, 2018: Please see summary response below. No further discussion is proposed at the meeting.

UFC was assessed centrally and measured in three 24-hour urine samples averaged to obtain the mUFC level. To compute the mUFC for a patient at any particular visit, at least two UFC specimens were required at that visit, otherwise the value was considered missing.

7. Clarify how many responders at the end of randomized period had pituitary surgery within last 6 months. Comment how other potential confounders (i.e., latent effect of radiation, surgery, cyclic disease, etc.) which may affect efficacy result interpretation were handled.

Please note that we continue to believe that use of a traditional placebo-controlled study would have provided a more straightforward assessment of efficacy and would likely have addressed many of the above uncertainties.

Novartis response sent via email on August 20, 2018: Please see summary response below. More details about these patients will be provided in the NDA. No further discussion is proposed at the meeting.

120/137(87.6%) patients had pituitary surgery and 18/120 (15.0%) patients had surgery within 6 months prior to study entry. 6/18 (33.3%) of patients who had surgery within the last 6 months prior to study entry were responders at week 34.

Per protocol, patients with a history of pituitary irradiation were eligible provided at least 2 years (stereotactic radiosurgery) or 3 years (conventional radiation) had elapsed from the time of last radiation treatment to study entry. 22/137 patients (16.1%) had received radiation prior to study entry. Randomization at Week 26 was stratified by prior irradiation status. At Week 34, 11/22 (50%) patients achieved normal mUFC.

Cyclic disease will be addressed as part of Question 1. Other potential confounders will be discussed in the NDA submission.

Discussion during meeting: The sponsor indicated that in order to minimize a chance of enrolling patients with cyclic and pseudo Cushing's syndromes (CS) in the study, patients who had surgery were required to have positive staining of the tumor post-surgery; and patients with pituitary adenomas < 6 mm were required to have bilateral inferior petrosal sampling for the confirmation of the tumor. Additionally, the sponsor used a cut-off of mUFC $\geq 1.5 \times ULN$ (3 UFC samples collected at screening and an additional three at baseline, which spans a period of 6 weeks and 2 weeks,

respectively). The sponsor believes that this proposed cut-off and duration of UFC collections further minimize a chance of enrolling patients with cyclic and pseudo-CS. FDA noted that there is a chance that mUFC values might be driven by a single large UFC value and indicated that Novartis should include absolute UFC values as well as mUFC in the NDA. Novartis confirmed that all absolute UFC values will be included in the NDA. FDA also asked the sponsor what is the incidence of cyclic CS and indicated that there are published reports of 15-20% rate. The sponsor stated that based on the published literature cyclic CS is very rare.

FDA reiterated their concern that patients who were randomized in period 3 had lower UFCs at baseline compared to non-randomized patients. The sponsor presented the data to respond to this question (refer to slides 3 and 4 of sponsor presentation). Novartis agreed that because of the study design (mUFCs > 1.5xULN for the inclusion criteria), the majority of patients enrolled in the study had milder disease. The sponsor will include the absolute values of UFCs for each patient in the NDA submission.

FDA asked Novartis whether all patients were enrolled in the study based on their first set of UFC values at screening. Novartis stated that there are a few patients in the study who did not meet the inclusion criteria for mUFC at the first set of screening values. These patients were re-tested and included in the study based on their second set of screening values. FDA expressed the concern that this approach may result in more patients with fluctuating borderline UFC values being included in the study. Novartis said that they will look further into this. The sponsor also referred to slide 4 and indicated that there were patients with high UFCs who also responded to the treatment and were randomized into Period 3; they consider that the disease control in these patients is representative of the expected disease control in patients with high UFCs.

FDA also indicated that the majority of patients who were randomized to Period 3 were responders to the lower dose of the drug and that patients with more severe disease may require longer titration (> 12 weeks) to achieve effective dose. The sponsor agreed that the design of the study did not allow longer titration.

FDA asked the sponsor to comment on efficacy of the drug, noting that it seems that the drug was effective in 50% of patients at week 12, and that this response was maintained in 80% of responders at the end of the study. The sponsor agreed that the study demonstrated that 50% of patients responded to the drug at the end of 12 weeks and 80% of these patients demonstrated maintenance of response at week 48.

FDA also asked Novartis to comment on why 30% of patients who were randomized to placebo maintained the normal UFCs at the end of the study. The sponsor indicated that they are currently analyzing this issue.

Lastly FDA reiterated that upfront randomization would have addressed many of the discussed uncertainties. The sponsor acknowledged this and stated that the available data from the ongoing randomized placebo-control study will be also included in NDA.

Question 2: Novartis also has conducted Study C1201 (b) (4)

Novartis plans to include data from Japanese patients with Cushing's syndrome from Study C1201 in the NDA.

Does the Agency agree with the inclusion of Study C1201 to support the filing of the new drug application (b) (4)

FDA Response to Question 2: No, we do not agree (b) (4)

Data from study C1201
should be included to support assessment of safety, (b) (4)

(b) (4)

Novartis response sent via email on August 20, 2018: Novartis acknowledges FDA comments. No further discussion is proposed for the meeting.

Question 3: Novartis has previously aligned with the Agency on the acceptability of the clinical pharmacology program during the End of Phase 2 (EOP2) meeting. Based on the results of human ADME study and additional metabolism pathway analyses, Novartis does not believe that a drug-drug interaction study specifically investigating osilodrostat as a victim drug is warranted.

Does the Agency agree that the current clinical pharmacology program is sufficient to support the proposed indication?

FDA Response to Question 3: Your clinical pharmacology program seems reasonable to support filing.

Osilodrostat is metabolized by multiple CYP enzymes. In patients with Cushing's disease/syndrome, ketoconazole and mifepristone, which are CYP inhibitors, could be used as concomitant medications. Address this drug interaction potential with osilodrostat.

Additionally, multiple UGT enzymes are involved in the metabolism of osilodrostat. Address the drug interaction potential due to inhibition of UGT enzymes.

Novartis response sent via email on August 20, 2018: Please see summary response below. More details about these patients will be provided in the NDA. No further discussion is proposed at the meeting.

In response to the Agency's comment regarding the DDI potential for Osilodrostat as a victim to with CYP and UGT inhibitors, the DDI potential for osilodrostat due to CYP inhibition (such as concomitant use of ketoconazole and mifepristone), or UGT inhibition is likely to be low.

Firstly, a systematic review of the clearance pathways of osilodrostat from the human ADME study (LCI699C2101) and in vitro enzyme reaction phenotyping showed that multiple metabolic enzymes contribute to osilodrostat metabolism, and no single enzyme contributes greater than 25% to total clearance. Simultaneous and complete inhibition of three CYP enzymes (CYP3A, CYP2D6 and CYP2B6) would potentially result in an increase in AUC by 26%. Assuming simultaneous and complete inhibition of three UGT enzymes (UGT1A4, UGT2B7 and UGT2B10) an increase in AUC by 19% would be expected. This is within the reported clinical variability of osilodrostat exposure (8-41%), and likely not clinically meaningful. Detailed results can be found in Report [DMPK-DDI-R1600650] and [Study LCI699C2101 CSR].

Contributions of clearance pathways from the human ADME study (Study LCI699C2101 and DMPK-DDI-R1600650)

Metabolite/ LCI699	Proposed reaction	Proposed enzyme/pathway involved	Amount excreted (mean % of dose)	Amount excreted (normalized to 100%) ^a
<u>Urine</u>				
<i>Non-CYP mediated:</i>				
M10	oxidation, +3O, +4H	likely non-CYP; not seen in HLM or by individual rhCYPs	2.47	2.68
M6	secondary to <u>M16.4B</u>	non-CYP	3.37	3.66
M16	secondary to <u>M16.4B</u>	non-CYP	1.77	1.92
M16.4B	metabolism on imidazole ring (opening)	likely non-CYP; not seen in HLM or by individual rhCYPs	2.87	3.11
M16.5	direct <i>N</i> -glucuronide	UGT1A4, UGT2B7, UGT2B10	17.3	18.8
M18B	ribose conjugate +O	non-CYP ^b	7.87	8.54
M20.8	ribose conjugate	non-CYP	2.28	2.47
M23.1	<i>N</i> -methylation	non-CYP	4.35	4.72
M22	glucuronide of M34.5	non-CYP	12.6	13.7
M34.5	di-oxygenated LCI699	non-CYP; not seen in HLM or by individual rhCYPs	0.81	0.879
LCI699	n.a.	n.a.	5.19	5.63

Metabolite/ LCI699	Proposed reaction	Proposed enzyme/pathway involved	Amount excreted (mean % of dose)	Amount excreted (normalized to 100%) ^a
<i>CYP mediated:</i>				
M15	secondary to <u>M24.9</u>	The primary reaction was CYP-mediated	7.23	7.84
M19.9	Possibly secondary to M24.9; glucuronic acid conjugate of mono-hydroxy LCI699	Likely the primary reaction was CYP-mediated	5.97	6.48
M24.9	hydroxylation of the pyrrolidine- ring system	CYP3A4 (45%), CYP2D6 (31%), CYP2B6 (24%)	10.8	11.7
<u>Feces</u>	Uncharacterized	Assumed non-CYP	1.58	1.71
<u>Other</u>	Uncharacterized	Non-assigned radioactivity	5.74	6.23
TOTAL %			92.2	100
TOTAL % UGT			UGT1A4, UGT2B7, UGT2B10	
			18.8	
			26.0 =	
TOTAL % CYP			CYP3A4 (45%), CYP2B6 (24%), CYP2D6 (31%)	
			11.7 CYP3A4	
			8.07 CYP2D6	
			6.25 CYP2B6	

n.a., not applicable

^abased upon a mean dose recovery of 92.2%

^bbased upon LC-MS/MS data, the position of the additional oxygen is not at the same position as M24.9, therefore is unlikely to have been derived by a CYP-mediated reaction

Source data: [\[CLCI699C2101 Table 11-9\]](#) and [\[CLCI699C2101 Table 11-11\]](#)

Secondly, in clinical practice, osilodrostat will be taken at low starting dose and followed by individual dose titration according to clinical outcome. mUFC will be periodically monitored and dose can be adjusted if needed.

Finally, during Phase III study, concomitant use of substrate, inhibitors and inducers of CYP enzymes as well as inhibitors of UGT enzymes were not prohibited.

In conclusion, the DDI potential for osilodrostat due to CYP inhibition (such as concomitant use of ketoconazole and mifepristone), or UGT inhibition is likely to be low.

Question 4: Novartis believes that the completed nonclinical safety program is adequate to support the filing of osilodrostat in the proposed indication. Does the Agency agree?

FDA Response to Question 4: We agree that the scope of the nonclinical program appears adequate to support filing. Given your summary description of liver neoplasia in both rat and mouse carcinogenicity studies, there is an expectation that the NDA will include a robust dataset supporting your proposed CAR-mediated tumorigenic mode of action. Of particular interest is demonstrating the essentiality of CAR activation in the gene

expression profile obtained with osilodrostat in rodents. Refer to Peffer et al for further discussion of datasets considered critical for establishing a CAR-based mode of action. (Peffer et al (2018) Minimum datasets to establish a CAR-mediated mode of action for rodent liver tumors. Reg Tox Pharm, 96; 106-120.)

Novartis response sent via email on August 20, 2018: Novartis acknowledges FDA comments. No further discussion is proposed for the meeting.

Question 5: Novartis considers that the proposed electronic datasets and analysis programs to be included in the submission are adequate. Does the Agency agree?

FDA Response to Question 5: The proposed dataset structures seem acceptable. Make sure the data conversion for SDTM and ADaM structures follows regulatory guidelines (see <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

We have the following general comments for datasets and analysis programs:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting the primary and important sensitivity analyses included in the study report.
- Provide analysis programs that are used to create the derived datasets for the efficacy endpoints and the analysis programs that are used for key efficacy analysis.
- Please submit one analysis program for each analysis.
- Please separate the code used for analysis and the code used for generating tables and figures.

Novartis response sent via email on August 20, 2018: Novartis acknowledges FDA comments. No further discussion is proposed for the meeting.

Question 6: Does the Agency agree with the patient narratives and CRFs proposed to be included in the submission?

FDA Response to Question 6: Yes, your proposal is acceptable. Refer also to the response to question 7.

Novartis response sent via email on August 20, 2018: Novartis acknowledges FDA comments. No further discussion is proposed for the meeting.

Question 7: Novartis believes that the proposed the proposed content and format of the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS), presenting safety and efficacy data from Study C2301 and supportive studies C2201 and C1201, are adequate to allow for a proper evaluation of the application by the Agency.

Does the Agency agree?

FDA Response to Question 7: Yes, the inclusion of safety and efficacy data from the studies C2301, C2201 and 1201 in the SCE and SCS is acceptable.

Additionally, as indicated in the Agency’s Advice Letter from December 22, 2017, include in your NDA the summaries of the safety findings in tabular format and narratives for all deaths, serious adverse reactions or adverse reactions leading to discontinuation from phase 2 studies conducted in hypertensive patients.

Lastly, we request that you also include in your NDA a summary of the safety findings in tabular format, narratives for all deaths, serious adverse events, and adverse events leading to discontinuation from ongoing study C2302. We acknowledge that this will be an ongoing, blinded trial, but safety data from this trial should be submitted with the NDA for review. Unblinding of the trial for purposes of presenting the safety should not occur, and data should be presented by treatment arm without identification of the treatment (e.g., treatment A, treatment B). We may discuss unblinding of the trial if a significant safety concern is identified.

Novartis response sent via email on August 20, 2018: Novartis will address this during the meeting.

Study C2302 is a randomized double blind placebo controlled trial with 2:1 randomization. Therefore, presenting the data by treatment arm without identification of treatment (as in the Agency’s example) would still lead to unblinding and compromise the integrity of the study. Please note that the safety is monitored by DMC on a 6 month basis per the DMC charter and the DMC advises Novartis of any potential safety concern. At this time, the DMC has not reported any patient safety concerns in the study.

Discussion during meeting: Novartis expressed the concern of breaking the blind if they were to present the data by treatment arm. FDA agreed with the sponsor’s plan not to present the data by treatment arms and asked Novartis to provide the safety data in one table with the corresponding total number of patients (without stratifying by treatment arm) so the integrity of the data is not compromised. FDA also asked to include in NDA patient narratives of deaths, serious adverse events, adverse events leading to discontinuation and adverse events of special interest. FDA asked if Novartis could provide DMC minutes to FDA without jeopardizing scientific integrity, and Novartis said they can provide the redacted minutes, but not the data. FDA asked if Novartis expects to continue collecting safety data during the NDA review; Novartis replied that FDA can anticipate an additional 6 months of safety data from study C2301. FDA asked when Novartis plans on submitting their NDA; Novartis anticipates submission during the first quarter of 2019.

Question 8: Novartis considers that Study C2301, C2201, and C1201 constitute the ‘covered studies’ under the ‘Financial Disclosure for Clinical Investigators’ rule. Does the Agency agree?

FDA Response to Question 8: Any clinical pharmacology study that is critical to an efficacy determination is also a covered study. You will need to make this determination.

Although financial disclosure information is not required to be submitted to the FDA for studies under your IND until a marketing application is submitted containing the results of the covered clinical study, under 21 CFR 312.53(c), a sponsor is required to obtain clinical investigator financial information before allowing the clinical investigator to participate in a covered clinical study. This would include the additional phase 3 Study CLIC699C2302 (Study C2302, “LINC-4”) that is currently ongoing.

Novartis response sent via email on August 20, 2018: Novartis acknowledges the Agency’s comment. No further discussion is proposed.

Question 9: Does the Agency agree that the contents of the NDA as outlined in the proposed electronic Common Technical Document (eCTD) table of contents (TOC) constitute a complete application?

FDA Response to Question 9: Your eCTD TOC seems acceptable.

Novartis response sent via email on August 20, 2018: Novartis acknowledges the Agency’s comment. No further discussion is proposed.

Additional FDA comments:

- 1. In your early drug development, a capsule formulation was used. The relative bioavailability between the capsule formulation and the to-be-marketed tablet formulation remains unknown. Clarify what information you plan to include in your package insert from the early clinical trials using capsule formulation.**

Novartis response sent via email on August 20, 2018: Please see summary response below. No further discussion is proposed at the meeting.

Data generated with the capsule formulation will mostly support clinical pharmacology parameters discussed in the USPI.

The comparison between Clinical Service Form (CSF) capsule and Final Market Image (FMI) tablet formulations was evaluated in the results across healthy volunteer studies A2101 (first-in-human study), C2103 (hepatic impairment study) and C2104 (renal impairment study). The observed AUCs and C_{max} after a single osilodrostat dose of 30 mg from these three studies are presented in below Table 1-2.

As expected for a [REDACTED]^{(b) (4)}, osilodrostat exposure was similar for FMI tablet and CSF capsule formulations. The formulation used to characterize the safety and efficacy of osilodrostat in the Phase III Study C2301 was the FMI tablets.

Table 1-2 Summary statistics of PK parameters of osilodrostat FMI tablet versus CSF capsule formulation after a single 30mg dose

Parameter	Statistics	CSF Capsule (A2101) N=6	FMI Tablet (C2103) N=9	FMI Tablet (C2104) N=6
AUCinf (ng*h/mL)	n	6	9	6
	Mean (SD)	1800 (200)	1570 (435)	1820 (555)
	CV%	11.1	27.7	30.4
	Geo-mean	1790	1520	1760
	Geo-CV%	11.5	27.9	29.7
	Median	1830	1740	1810
	Min- Max	1490-2010	1080-2400	1270-2790
AUClast (ng*h/mL)	n	6	9	6
	Mean (SD)	1780 (199)	1520 (422)	1800 (556)
	CV%	11.2	27.7	30.8
	Geo-mean	1770	1470	1740
	Geo-CV%	11.7	28.0	30.3
	Median	1830	1660	1790
	Min- Max	1460-1960	1060-2310	1250-2760
Cmax (ng/mL)	n	6	9	6
	Mean (SD)	250 (41.6)	209 (38.1)	214 (65.0)
	CV%	16.7	18.2	30.4
	Geo-mean	247	206	207
	Geo-CV%	16.9	18.9	28.6
	Median	257	213	202
	Min- Max	196-313	156-266	153-332

n = number of subjects with corresponding evaluable PK parameters.
Included in the table were healthy subjects taken a single osilodrostat dose of 30mg.
Geometric mean (Geo-mean) and geometric CV% (Geo-CV%) were not reported in LCI699A2101 study.
Subjects with normal hepatic function in LCI699C2103 and normal renal function in LCI699C2104 study were included in the table.

- 2. Osilodrostat phosphate has one chiral center and is used as single isomer (R-enantiomer). We acknowledge the chiral analysis of rat plasma indicated that the concentration of the (-)-enantiomer, LCI698, relative to osilodrostat, was less than 0.053% in oral dose samples and not detectable in i.v. plasma samples. Please also address chiral conversion in human.**

Novartis response sent via email on August 20, 2018: Please see summary response below. No further discussion is proposed at the meeting.

- 3. Please provide the number and percentage of patients with missing mUFC values for the primary and key secondary objectives in Study C2301, and clarify whether they are considered non-responders in these analyses.**

Novartis response sent via email on August 20, 2018: Please see summary response below. No further discussion is proposed at the meeting.

All patients with missing mUFC values were considered non-responders for the primary and key secondary objectives in Study C2301.

There was only one patient (placebo) who had a missing mUFC assessment for the primary analysis at Week 34.

There were 12/137 patients who had a missing mUFC assessment for the key secondary analysis at Week 24. All of these 12 patients were part of the non-randomized group.

- 4. In the SAP, it stated “during the randomized withdrawal study period, the patient must be discontinued from the randomized withdrawal period, declared a non-responder, if the mUFC increases to $> 1.5 \times \text{ULN}$, and at least 2 individual urine samples show $\text{UFC} > 1.5 \text{ ULN}$ at a single visit.” Clarify what happened to these discontinued patients and whether they are included in the patient disposition table 4-23 from the meeting package.**

Novartis response sent via email on August 20, 2018: Please see summary response below. No further discussion is proposed at the meeting.

The disposition table 4-23 shows patients who permanently discontinued from the entire study.

Patients with $\text{mUFC} > 1.5 \times \text{ULN}$ (with at least 2 individual UFC results $> 1.5 \times \text{ULN}$) at any time during randomized withdrawal were discontinued from the randomized treatment but not from the entire study. Per protocol, these patients were to continue in the study and resumed treatment with open-label LCI699 at a dose selected by the investigator.

- 5. In the future NDA submission, provide a plot showing individual change in mUFC from baseline to Week 24 in the full analysis set (Study C2301).**

Novartis response sent via email on August 20, 2018: Novartis acknowledges FDA comment. No further discussion is proposed.

- 6. Clarify what information will be included in 120-Day Safety Update.**

Novartis response sent via email on August 20, 2018: We anticipate being able to provide an additional 6 months of safety data from Study C2301 by the timing of the 120-Day Safety Update.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 15, 2018, communication granting this meeting, 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 VI. 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. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the

Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) 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* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for

CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

- PowerPoint slide presentation by Novartis Pharmaceuticals

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

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/

WILLIAM H CHONG
10/02/2018



IND 117489

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Sandip Roy, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. Roy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LCI699 capsules.

We also refer to the meeting between representatives of your firm and the FDA on October 9, 2013. The purpose of the meeting was to discuss your proposed Phase 3 study, CLCI699C2301, "A Phase III, multicenter, double-blind, (b) (4) randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease (b) (4) ."

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

If you have any questions, call Elisabeth Hanan, Regulatory Project Manager, at (240) 402-0350.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: Wednesday, October 9, 2013; 12:00 – 1:00 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1315
Silver Spring, Maryland 20903

Application Number: IND 117489
Product Name: LCI699 capsules
Indication: Treatment of Cushing's disease
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Elisabeth Hanan, M.S.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director (Acting)
Dragos Roman, M.D.	Clinical Team Leader
Marina Zemsanova, M.D.	Clinical Reviewer
Naomi Lowy, M.D.	Clinical Reviewer
Smita Abraham, M.D.	Clinical Reviewer
Todd Bourcier, Ph.D.	Supervisor, Pharmacology/Toxicology
Jessica Hawes, Ph.D.	Nonclinical Reviewer
Julie Van der Waag, M.P.H.	Chief, Project Management Staff
Elisabeth Hanan, M.S.	Regulatory Project Manager
Jennifer Johnson	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Immo Zadezensky, Ph.D.	Clinical Pharmacology Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics II

Mark Rothmann, Ph.D.	Team Leader
Bradley McEvoy, Ph.D.	Biometrics Reviewer

Office of Orphan Products Development

Henry Startzman, M.D.	Medical Officer
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SPONSOR ATTENDEES

Germo Gericke, M.D.	Global Program Head
Nicholas Sauter, M.D.	Global Clinical Program Head, LCI699
William Ludlam, M.D.	U.S. Clinical Development & Medical Affairs
Li Li, Ph.D.	Pre-Clinical Safety
Lillian Ting, Ph.D.	Clinical Pharmacology Lead, LCI699
Antonella Maniero, Ph.D.	Executive Director, Global Biostatistics
Eric Xin Zhi, Ph.D.	Biostatistics, LCI699
Shanthi Ganeshan, Ph.D.	North America Head, Drug Regulatory Affairs
Sandip Roy, Ph.D.	Global Program Regulatory Manager

1.0 BACKGROUND

LCI699 is a new chemical entity that is an orally-administered 11 β -hydroxylase inhibitor. It is manufactured as a phosphate salt and available in hard gelatin capsule strengths of 0.25, 0.5, 1, 5, and 50 mg. LCI699 is being developed for the treatment of (b) (4)

As part of the initial filing of IND 117489, the Agency reviewed the thorough QT study of LCI699 in healthy volunteers, Protocol CLCI699C2105, "A randomized, double-blind, placebo- and active-controlled, four-way crossover study to investigate the ECG effects of therapeutic and suprathreshold doses of LCI699 in healthy volunteers." The Agency issued non-hold comments for this protocol on July 18, 2013, to which Novartis submitted a response on September 6, 2013. Novartis submitted Protocol CLCI699C2102, "An open-label, fixed sequence investigation of the effects of LCI699 on the pharmacokinetics of CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5 substrates using a modified Cooperstown cocktail in healthy adult subjects" for review on August 14, 2013. LCI699 was granted orphan drug status for the treatment of Cushing's disease on September 13, 2013.

Novartis submitted a meeting briefing document on August 14, 2013. The Agency issued preliminary comments responding to the questions contained in this submission on October 7, 2013. Based on these preliminary comments, the sponsor reduced the agenda to primarily discuss the Agency comments regarding the Phase 3 study design (see Question 2a below). In addition, the sponsor provided a brief background presentation regarding Cushing's disease and the LCI699 product, results of their Phase 2 study, and their rationale for their Phase 3 study design (see attached slides following these minutes). This revised agenda and slide presentation were provided to the Agency via email on October 8, 2013.

2.0 DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA preliminary response (bolded), followed by the sponsor response and meeting discussion (italicized), and where applicable, the post-meeting comments (bolded/italicized).

2.1. Non-Clinical

Question 1: Novartis believes that the proposed nonclinical safety program supports entry into a pivotal study and registration of LCI699 in Cushing's disease in adult patients. Does the Agency agree?

FDA Response to Question 1: We agree that the proposed nonclinical safety program appears sufficient to support the Phase 3 clinical studies and filing of the NDA. Additional studies may be needed if there are unexpected results in the clinical or nonclinical studies that merit further nonclinical investigation.

Please clarify your approach to further investigate potential interactions of LCI699 with cardiac ion channels, and provide an approximate timeline for submission of results.

Sponsor Response / Meeting Discussion: No discussion at the meeting; the sponsor's response was provided in the attached slides.

Post Meeting Comments:

- a. **Please also include voltage-gated sodium channels (i.e. Nav1.5) in your assessments of cardiac ion channels.**
- b. **Measurements of functional channel activity are preferred over binding studies.**

2.2. Clinical

Question 2: Novartis plans to conduct a phase III pivotal trial, LCI699C2301, entitled "A Phase III, multicenter, double-blind, (b) (4) randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease (b) (4)." Does the Agency agree with the overall design in general and the following design elements in particular?

- a) Double-blind, (b) (4) randomized withdrawal study design, following a 24-week, single-arm, open-label dose titration and treatment period
- b) Adequacy of the eligibility criteria to define the target population on which safety and efficacy will be established
- c) Inclusion of patients with a history of pituitary irradiation
- d) Duration of the withdrawal period and the overall duration of the study
- e) Dose titration scheme
- f) Adequacy of the primary and secondary end-points to assess the efficacy and safety of LCI699 in the target population, including the proposed timing for the assessments
- g) Stratification factors for randomization
- h) Adequacy of the proposed efficacy analysis to support the registration
- i) Adequacy of the sample size

FDA Response to Question 2:

- a) **We do not agree. We believe that a randomized, double-blind, placebo-controlled study to establish efficacy (8-12 Week) of LCI699, followed by a controlled extension phase, to establish durability of effect and obtain long-term comparative safety data, would be more scientifically useful, is feasible and would be ethically acceptable.**

We believe this trial design would be more scientifically useful in that it would be double-blind, that efficacy would be unequivocally demonstrated, and that controlled safety data would be available from the start of intervention to rigorously evaluate the safety profile of LCI699 at the proposed doses and in the population for whom the drug is intended. In our review of other recent Cushing's programs, the lack of this important information led to substantial challenges during the review.

We believe that a short-term placebo-control period to establish efficacy would be ethical provided adequate safeguards are in place in the protocol. Our rationale is as follows:

- **No drug treatment for Cushing's disease (including LCI699) to date has been shown to increase survival or prevent irreversible morbidity.**
- **Robust clinical safety data for LCI699 at the proposed doses and duration in this population is lacking.**
- **The placebo-control would be added to standard of care blood pressure, glucose, electrolyte, and lipid management.**
- **Many adverse clinical consequences of hypercortisolism can be monitored in the trial setting. Some risks can be mitigated by use of appropriate rescue medications (e.g., spironolactone and potassium replacement therapy for hypokalemia, anti-diabetic drugs for glucose abnormalities, ACE inhibitors and spironolactone for hypertension) and others by appropriate eligibility criteria.**
- **Short-term (12-26 weeks) placebo-controlled trials are routinely used in the evaluation of anti-hypertensive¹ and anti-diabetic drugs.**
- **Cushing's disease patients regularly undergo wash-out periods from adrenolytic and/or other therapies which may confound interpretability of dynamic testing (e.g., Inferior Petrosal Sinus Sampling) for diagnostic purposes.**
- **Finally, orphan drugs developed for other serious conditions including, homozygous familial hypercholesterolemia, acute respiratory distress syndrome, and lysosomal storage disorder have made use of randomized, double-blind, placebo-controlled designs.**

¹ DeFelice, Willard, et al. The risks associated with short-term placebo-controlled anti-hypertensive trials: a descriptive meta-analysis. *J Human Hypertension* 2008; 22:659-668
Al-Khatib, Califf, et. al. Placebo-controls in short-term clinical trials of hypertension *Science* 2001 292:2013-2015

Sponsor Response / Meeting Discussion: The sponsor reiterated the considerations and scientific arguments detailed in the briefing package to justify their selection of a randomized withdrawal design for the single pivotal Phase 3 clinical trial (see attached slides). The Agency re-affirmed the position communicated in the pre-meeting responses in favor of a traditional short-term, placebo-controlled trial followed by a longer term safety extension. In the discussion that followed, both sides clarified the detailed reasoning behind their respective choices and recommendations. The discussion explored the strengths and weaknesses of both approaches, but no agreement on the design of the pivotal study was reached.

Discussion focused around several key points as outlined below:

i. General trial design issues:

- Novartis's position was that a traditional placebo-controlled trial will require allocating some of the participants to placebo. They stated it is preferable to obtain safety data on as many patients as possible, given that Cushing's disease is a rare disease. In their current trial design, 100% of participants (i.e., ~132 patients) would be exposed to the investigational drug at some point.*
- The Agency was not entirely convinced of this argument. Although more precision around common safety issues can be gained with more patients exposed, the benefit in terms of identifying a new 'rare' event by exposing an additional ~60 patients to the investigational agent is expected to be small. The Agency pointed out that adequate and well-controlled efficacy or safety data in this patient population are lacking. The lack of blinding, randomization and adequate control has led to substantial challenges in the review of two recent applications due to potential confounding and in the drafting of a truly informative label.*
- The Agency believes that establishing safety and efficacy using a traditional placebo-controlled study would resolve these issues. Blinding and randomization would, in addition, remove known and unknown factors that could bias efficacy and safety outcomes.*
- Furthermore, the Agency believes that this would be an ethical trial to conduct because Cushing's severity spans a wide spectrum and the morbidity and mortality associated with Cushing's arises over the long term and is linked to factors that can be reasonably well controlled through means other than cortisol normalization in a short term study. To ensure patient safety in such a trial, eligibility criteria can be optimized and a run-in period can be used to select patients with relatively stable disease (i.e., those with CV risk factors controlled). During the intervention, patients on placebo would be receiving standard-of-care treatment for Cushing's disease complications, including optimization of therapies for hypertension, glucose intolerance/diabetes, electrolyte disturbances and dyslipidemia. In addition, patients whose control is inadequate in spite of these measures could be rescued.*
- The Sponsor argued that efficacy information collected at a later time in the trial (i.e., after drug titration is completed) is likely to be more relevant; in a traditional placebo-controlled trial most patients, in time, will likely require to be rescued with other anti-Cushing's medications.*

- ii. *Safety assessment after study drug withdrawal*
 - *The Sponsor's position was that randomized withdrawal allows for assessment of rebound and withdrawal effects in responder patients and that such information is important for adrenolytic therapy and requested by investigators.*
 - *The Agency agreed that this was important safety information. The Agency pointed out that the randomized withdrawal design will provide information for responders only and that in a trial that uses a placebo control durability of response and effect of drug withdrawal can also be assessed in the subgroup of responders.*
- iii. *Duration on experimental therapeutic dose, timing of key endpoints, and long-term safety assessment*
 - *Novartis's position was that a later time point for primary efficacy will be more informative, as they already have Phase 2 data on efficacy and safety at shorter treatment intervals, and a short placebo-controlled trial will only evaluate efficacy at the end of the titration period. Assessing drug effect using a short titration period would be extremely difficult because the trial will be an international study, urine free cortisol will be centrally measured and the rapidity of dose titration would depend on the turnaround of these centrally measured outcomes. In addition, potential adverse events related to adrenal blockade would not be expected to appear until later in the treatment phase due to build-up of precursor molecules and their feedback effect.*
 - *The Agency understands that implementation of a shorter term trial would be difficult if centrally measured values are used to guide dose titration. The Agency is open to having a longer term controlled trial provided safety measures are in place, or to basing titration decision on local laboratory measures. The Agency indicated that durability of effect can be assessed in an extension, perhaps actively controlled, to the traditional placebo-controlled trial. In such an extension the sponsor still has the option to perform a randomized withdrawal. The merits and the challenges of using several active comparators (pasireotide, mifepristone, and ketoconazole) were also discussed. There was consensus that use of mifepristone as an active comparator for efficacy would be very difficult because of the inability to use urinary free cortisol for efficacy comparisons.*
- iv. *Duration on placebo treatment*
 - *Novartis's position was that less time on placebo treatment would be preferred by investigators and patients. Patients in a placebo-controlled study would need to remain on placebo for the entire 12-week titration phase of the study. Novartis believes that investigators and patients will be resistant to enrolling patients if they know they could potentially be randomized to placebo. Novartis expressed concerns that a placebo-controlled trial may render patient enrollment challenging.*
 - *The Agency is particularly interested in trial designs that can handle potential sources of biases such as the ones mentioned above (e.g., those introduced as a result of investigator and patient expectations).*
 - *The Agency acknowledged that some investigators involved in developing drug treatments for Cushing's may be resistant to enrolling patients in a placebo-*

controlled trial. However, the Agency feels a strong argument can be made regarding the importance of using an adequate and well-controlled trial to obtain the most rigorous data to gain important scientific knowledge which will be used to inform and guide medical practice.

- *The Agency acknowledged that randomization to placebo may lead to difficulty in recruitment. The Agency however stated that the treatment options for Cushing's disease when surgery is not an option are limited, that no gold-standard treatment exists, and that LCI699 remains an investigational agent that has not been determined to be safe or effective. The informed consent document should clearly reflect this to ensure patients understand that exposure to LCI699 does not automatically guarantee benefit and carries with it certain risks. In addition, patients randomized to placebo would be expected to benefit from participating in the trial with regards to optimization of therapies and with regards to closer monitoring than would otherwise occur in standard practice. For these reasons and those mentioned above (see meeting discussion [i] fourth bullet point), the Agency believes there would be equipoise and that a placebo-controlled data would be feasible and ethical. Finally, the Agency pointed out that in clinical practice patients with Cushing's disease may have their cortisol lowering therapies held temporarily (2-6 weeks) for the purpose of diagnostic testing. It was requested that Novartis solicit feedback from investigators as well as European and Japanese regulatory bodies regarding the proposed placebo-controlled study design.*
- *Placebo-controlled trials in rare diseases are not unusual and the Agency has had experience with such designs in other disease areas. The reason for asking for a placebo-controlled trial is two-fold; the Agency wants the best possible data, and experience with uncontrolled studies in Cushing's disease has taught us about how critical it is to have a controlled arm.*

v. *Controlled assessment of safety versus placebo*

- *Novartis's position was that they have not encountered a new safety signal with short-term LCI699 use in their Phase 2 study. They believe that comparison of a placebo versus an efficacious dose (as in their randomized-withdrawal study design) would be more informative than comparison of placebo versus patients in a titration phase. They asked if submitting*

(b) (4)

(b) (4)

- *The Agency re-affirmed its preference that controlled safety data should be available from the start of the study.*
- *The Agency asked if Novartis is confident that the proposed starting dose is low enough. The Agency is aware of many drug development programs that focus on maximum efficacious dose with little attention paid to establishing the lowest safe and effective dose, only to recognize such omission when the Phase 3 program is complete. The sponsor indicated that they feel confident with the dose selection for the Phase 3 program.*

Post Meeting Comments: *The Division reviewed the Agency's experience with regards to non-oncology orphan drug programs and use of placebo-controlled design. We found many examples of drug programs aiming to address unmet therapeutic needs for orphan diseases that utilized a randomized double blind placebo-controlled design in their pivotal trial (s) (e.g., Duchenne Muscular Dystrophy, homozygous familial hypercholesterolemia, acute respiratory distress syndrome, and lysosomal storage disorders). In these examples, the placebo control is usually added to available standard of care and the duration of the placebo control period is longer than proposed above. The conditions listed in the example, similar to Cushing's disease, are serious and are associated with substantial morbidity and mortality.*

To understand the impact of trial design on sample size requirements, the Agency analyzed various theoretical scenarios. For example, assuming a 2:1 randomization, a response rate of 50% in LCI699 and 5% in placebo, 43 patients would be required to have 90% power to detect a significant difference based on UFC. Alternatively, if the response rate is 30% in LCI699 and 5% in placebo respectively, 108 participants would be required for 90% power. These sample sizes are smaller than the currently proposed sample size.

The Agency continues to believe a placebo-controlled trial would be needed to support filing of a new drug application for LCI699 for the treatment of Cushing's disease.

FDA Response to Question 2: (continued)

- b) The study population (patients with confirmed Cushing's disease and elevated urinary free cortisol levels $\geq 1.5 \times$ UNL) is acceptable.**

Sponsor Response / Meeting Discussion: *None.*

- c) Inclusion of patients with a history of pituitary irradiation is acceptable. Please specify the time interval that should elapse after pituitary irradiation for Cushing's disease before patients are considered radiation-treatment failures and become eligible to participate in the trial. Treatment groups may need to be stratified also by the post- radiation interval.**

Sponsor Response / Meeting Discussion: *No discussion at the meeting; the sponsor's response was provided in the attached slides.*

- d) Refer to our response to Question 2(a).**

Sponsor Response / Meeting Discussion: *None.*

- e) We have no objections with your approach for starting dose selection and dose escalation scheme for the pivotal Phase 3 study. Please specify the time interval that should elapse between dose escalations.**

Sponsor Response / Meeting Discussion: No discussion at the meeting; the sponsor's response was provided in the attached slides.

- f) The proposed primary endpoint (i.e., the proportion of patients with UFC \leq ULN), is acceptable. Secondary endpoints will need to be modified to account for the new trial design. We recommend adding evaluation of changes to antidiabetic and antihypertensive medications when analyzing efficacy.**

Sponsor Response / Meeting Discussion: No discussion at the meeting; the sponsor's response was provided in the attached slides.

- g) Refer to our response to Question 2(a).**

Sponsor Response / Meeting Discussion: None.

- h) Refer to our response to Question 2(a).**

Sponsor Response / Meeting Discussion: None.

- i) Refer to our response to Question 2(a).**

Sponsor Response / Meeting Discussion: None.

Question 3: Novartis believes that the evidence provided by a single registration trial, LCI699C2301, supported by the PoC trial LCI699C2201 pre-Amendment 4, and post-Amendment 4, is sufficient and adequate to demonstrate the efficacy and safety of LCI699 in the proposed indication. Does the Agency agree?

FDA Response to Question 3: Your plan to submit data from a single Phase 3 trial (Study LCI699C2301) supported by the results from the Phase 2 trial LCI699C2201 is acceptable. Whether the results of these studies will support registration of LCI699 for treatment of adults with Cushing's disease indication will be a review issue.

Sponsor Response / Meeting Discussion: None.

Question 4: Based on the nonclinical cardiac safety data, as well as exploratory *post-hoc* analysis of clinical data from the first-in-human study (LCI599A2101), LCI699 potentially causes QT prolongation in a dose-dependent manner in humans. Therefore, a thorough QT (TQT) study (LCI699C2105) is planned to evaluate the effect of LCI699 on QTcF and other cardiac intervals in healthy volunteers. In addition, intensive ECG monitoring is currently being implemented into the phase II study (LCI699C2201), and is similarly planned for the proposed phase III study (LCI699C2301). Does the Agency agree that cardiac safety program outlined for LCI699 is sufficient for registration?

FDA Response to Question 4: Your plan for evaluating the effects of LCI699 on the QT interval is acceptable. Whether these will be supportive of registration will depend on the results of those studies and will be a review issue.

Sponsor Response / Meeting Discussion: None.

2.3. Clinical Pharmacology

Question 5: Novartis believes that the proposed clinical pharmacology program is sufficient to support registration of LCI699 in Cushing's disease. Does the Agency agree?

FDA Response to Question 5: In general, your proposed clinical pharmacology program seems acceptable. We recommend conducting a drug interaction study (i.e., effect of other drug(s) on LCI699) if there will be significant exposure changes of LCI699 and/or its major metabolites in the proposed hepatic impairment study. Whether the proposed clinical pharmacology program will be supportive of registration will be a review issue.

Sponsor Response / Meeting Discussion: No discussion at the meeting; the sponsor's response was provided in the attached slides.

2.4. Regulatory

Question 6: Novartis believes that based on preliminary clinical evidence LCI699 represents ^{(b) (4)} for patients with Cushing's disease. Does the Agency agree?

FDA Response to Question 6: We refer you to the FDA Guidance for Industry:

^{(b) (4)}

Sponsor Response / Meeting Discussion: None.

2.5. Additional Clinical Comments

1. Regarding secondary endpoints:

- a. Define in the protocol the signs and symptoms of Cushing's syndrome that will be evaluated at baseline and subsequent visits to assess the disease progression or improvement.**
- b. We note your intention to use the general Health Related QoL instrument EQ-5D-5L, Beck Depression Inventory and Cushing's quality of life (QoL) questionnaire in the clinical trial. We advise you to consult the**

FDA Guidance for Industry – Patient-Reported Outcome [PRO] Measures: Use in Medical Product Development to Support Labeling Claims

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>) in order to familiarize yourself with FDA's current requirements in using health-related quality of life questionnaires. Use of a non-validated PRO is purely exploratory. If you intend to develop and validate a PRO for labeling claims, we advise you to contact the Study Endpoint and Labeling Development (SEALD) team for concurrence prior to conducting your Phase 3 program.

2. Regarding inclusion and exclusion criteria:

- a. Please specify the time interval that should elapse after surgery for Cushing's disease before patients are considered treatment failure and become eligible to participate in the trial.**
- b. We recommend excluding patients with uncontrolled hypertension since LCI699 increases levels of steroid hormone precursors and, thus, may worsen blood pressure control.**

Sponsor Response / Meeting Discussion: No discussion at the meeting; the sponsor's response was provided in the attached slides.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

5.0 ACTION ITEMS

Novartis has provided the Agency, via email, with feedback received from investigators and European/Japanese regulatory agencies regarding the proposed placebo-controlled study design. Novartis will also submit this information as an IND amendment.

6.0 ATTACHMENTS AND HANDOUTS

The slide presentation prepared by Novartis for this meeting is attached. This presentation includes introductory/background information presented at the meeting (slides 1-9), discussion points for the meeting (slides 10-11), responses to the Agency preliminary comments that were not discussed at the meeting (slides 12-20), and back-up slides presented at the meeting during the discussion phase (slides 21-23).

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/s/

JEAN-MARC P GUETTIER
11/08/2013