CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212801Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	3/2/2020
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 212801
Applicant	Novartis
Date of Submission	3/7/2019
PDUFA Goal Date	3/7/2020
Proprietary Name	Isturisa
Established or Proper Name	Osilodrostat
Dosage Form(s)	film-coated tablets for oral use
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with Cushing's disease
Applicant Proposed Dosing Regimen(s)	2 mg-30 mg to be administered orally twice a day
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Cushing's Disease (CD) is a rare disease caused by an ACTH-secreting pituitary adenoma, which results in excess cortisol secretion and is associated with increased morbidity and mortality. CD is the most common cause of endogenous Cushing's syndrome (CS) and accounts for approximately 70% of cases of endogenous CS. Because of the significant morbidity associated with CD, early therapy is fundamental. Surgical resection of the adenoma is first-line therapy and the treatment of choice. Surgery is successful in 60-80% patients with CD caused by pituitary microadenoma (less than 1 cm in diameter). However, even in patients who respond to surgery, up to 25% will experience recurrence within 10 years. Second-line therapy of CD includes pituitary radiation, medical therapy to reduce serum cortisol concentrations or block cortisol action, and bilateral adrenalectomy. Although not curative, medical therapy plays an important role in the management of CD. Medical therapy is employed in patients with persistence or recurrence of CD despite having undergone surgery, in patients with CD who undergo radiotherapy to control hypercortisolemia until the results of radiotherapy become effective, and in patients who are not candidates for radiation or surgery due to poor health. Lifelong medical treatment to suppress cortisol levels may be required if the primary cause of Cushing's syndrome (CS) cannot be treated successfully with surgery and/or radiation.

The U.S.-approved drugs indicated to treat one or more manifestations of CS/CD are: two injectable formulations of pasireotide, a somatostatin analog (Signifor, NDA 200677 and Signifor LAR, NDA 203255, Novartis), and mifepristone, a glucocorticoid receptor antagonist (Korlym, NDA 202107, Corcept Therapeutics). Pasireotide is approved for the treatment of patients with CD for whom surgery is not an option or has not been curative. Mifepristone is approved for the control of hyperglycemia in adult patients with endogenous CS with type 2 diabetes mellitus (T2DM) or glucose intolerance who have failed surgery or are not candidates for surgery. These drugs are associated with adverse events including QT interval prolongation, gastrointestinal adverse reactions, and adrenal insufficiency. For pasireotide, the need for injections can affect compliance or acceptability of the treatment. Registration trials have shown that pasireotide normalized or decreased urine cortisol by 50% in □ 40% of patients. As already mentioned, mifepristone is approved only for a subgroup of CS patients - patients who have abnormalities in glucose metabolism - which include about 50-60% of all CS patients. Therefore, there is an unmet need for additional approved therapies for CS/CD.

Current guidelines from professional societies list several unapproved drugs as part of the medical management of patients with CS or CD[1] [2]. According to these guidelines, steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane and etomidate) are recommended and are the most widely used agents in the treatment of CS of any etiology; these drugs are effective in 75- 80% of patients[3]. Treatment with these drugs is

[1] Biller BM, Grossman AB, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2008 Jul;93(7):2454-62.
[2] Nieman LK, Biller BM, et al. Endocrine Society Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31.
[3] Feelders RA, Hofland LJ, de Herder WW. Medical treatment of Cushing's syndrome: adrenal-blocking drugs and ketaconazole. Neuroendocrinology. 2010;92 Suppl 1:111-5

associated with such adverse reactions as gastrointestinal adverse effects, adrenal insufficiency, liver toxicity (ketoconazole), edema, hypertension and hirsutism (metyrapone), etc. Thus, extensive clinical monitoring is required which may limit their use in patients with CS. Overall, therapeutic options for treatment of CS remain limited and many patients with CS remain undertreated.

The Applicant has demonstrated in a single, multi-center, double-blind, randomized withdrawal (RW) study of osilodrostat following a 24-week, single arm, open-label dose titration period (study C2301) that treatment with osilodrostat in patients with non-surgical or recurrent CD is effective in reducing mean 24-hour urinary free cortisol (mUFC) levels from baseline. In this study, 137 patients were initially treated with osilodrostat for 24 weeks in a dose titration open-label single arm period. The starting dose was 2 mg BID; the dose was titrated based on mUFC levels every 2 weeks to maximum dose 30 mg bid to achieve normalization of mUFC. The prespecified titration schedule was 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg; however, some subjects were titrated more slowly than was prespecified or had doses decreased during the study because of drug tolerability and adverse events including adrenal insufficiency. After the first 24 weeks of treatment, 70/137 patients who were responders at week 24 (defined as patients who had normal mUFC and did not require a dose increase during the previous 12 weeks) were randomized to receive osilodrostat or placebo in the RW period. Those who were not eligible for randomization continued the study with open-label osilodrostat.

The primary endpoint was the proportion of patients whose mUFCs remained in the normal range after withdrawal of treatment between the osilodrostat and placebo groups. The key secondary efficacy endpoint was the proportion of complete responders in the 24 week open label period. To be considered successful, the lower bound of the 95% CI for the proportion of patients who had normalization of mUFC at week 24 was to exclude 30%, representing the minimum threshold demonstrating a clinically significant response to therapy in all treatment-naïve patients without any insight as to whether the patient will be a responder to osilodrostat or not (i.e. how the drug will be used in clinical practice). The primary analysis demonstrated that osilodrostat was superior to placebo at Week 34, the end of the RW period: 86.1% (95% CI: 70.5, 95.3) of patients in the osilodrostat group maintained normal mUFC without dose change compared to 29.4% (95% CI: 15.1, 47.48) of patients in the placebo group. The response rate was not affected by the dose or history of pituitary radiation and ranged from 83.9% to 100%, based on the randomization stratification factor (dose at week 24 -> 5 mg bid and ≤5 mg bid and history of pituitary radiation). Therefore, the primary analysis confirmed that the UFC lowering effect was attributable to the drug itself and not to the other factors such as inactive disease, cyclic CS, etc. (as demonstrated by significant difference in the proportion of responders in active drug versus placebo groups). The key secondary efficacy endpoint achieved the pre-specified goal: 72 of 137 (52.6%; 95% CI: 43.9, 61.1) of patients met the definition for complete responder at week 24; lower bound excludes 30%.

The most common adverse events (AE) in the 48-week Core Phase of the pivotal study C2301 were hypocortisolism related AEs (51%), nausea (37%), headache (30%), insomnia (26.3%) fatigue (24%), vomiting (19.7%), nasopharyngitis (19.7%). The high rate of hypocortisolism related AEs was most likely overestimated due to poor definition of the term of ‘adrenal insufficiency (AI)’ in the protocol that was based on non-specific signs and symptoms (nausea, fatigue, etc.) of the condition without concurrent serum cortisol levels. As such, some patients who poorly tolerated rapidly decreasing cortisol levels were defined as having adrenal insufficiency; however, their cortisol levels remained within normal range. There was no death due to AI in the study, and all events improved/resolved with osilodrostat dose adjustment and/or treatment with glucocorticoids. Overall, hypocortisolism-related AEs are expected events based on the mechanism of action of osilodrostat. Monitoring and

dose adjustment/interruption and treatment with glucocorticoids will be recommended in the WARNING and PRECAUTION section of the USPI to mitigate this risk. In addition, the pre-specified titration schedule used in the clinical study may also account for this risk, and I recommend a more conservative approach to titration in the postmarketing setting. Thus, the risk will be further mitigated by the labeled dosing recommendations which will advise not to increase the dose more frequently than every 2 weeks, to consider using smaller dose increments and to base the decision of whether to increase the dose not only on absolute cortisol values, but also on the rate of cortisol change and individual patient signs and symptoms.

Other potential safety issues associated with the use of osilodrostat include the risk of QT prolongation and adrenal hormone precursor accumulation-related adverse reactions (hypertension, hypokalemia, hirsutism, acne). All these risks will be mitigated through product labeling which will include recommendations on appropriate patient selection, on monitoring for occurrence of these reactions and on interventions to address these reactions including but not limited to osilodrostat dose adjustment and/or temporary interruption. A WARNING and PRECUATION section discussing these safety concern will be included in labeling to ensure prescribers recognize that osilodrostat may be associated with these risks and can take appropriate precautions in patients at risk.

In conclusion, safety and efficacy data from the single, double blind randomized withdrawal phase 3 study conducted to support the approval of osilodrostat for the treatment of recurrent or non-surgical Cushing's disease have demonstrated that the benefits outweigh the risks in this population. Thus, I recommend approval of osilodrostat for the treatment of adult patients with CD. However, I recommend restricting the indication to adult patients with CD for whom pituitary surgery is not an option or has not been curative reflecting the patient population evaluated in the clinical program.
All identified safety issues can be mitigated by communicating risks in the product label and recommending appropriate patient selection, monitoring and dose adjustment if required.

The following postmarketing requirements should be issued to further characterize the safety profile of osilodrostat.

- To complete the ongoing Phase 3 multi-center, randomized, double-blind, 48-week study with an initial 12-week placebo-controlled period (study C2302). This study will evaluate the safety profile of osilodrostat, including rate of hypocortisolism-related AEs using a dosing regimen that dose titration every 3 weeks)

These safety issues may be assessed postmarketing because they do not adversely impact the overall benefit risk assessment at this time.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CD is a rare disease, caused by an ACTH secreting-pituitary adenoma, which results in excess cortisol secretion. • CD is a serious and life-threatening disease. Hypercortisolemia leads to decreased quality of life and increased morbidity and mortality, primarily due to cardiovascular complications. • The 2015 Endocrine Society Guideline on treatment of Cushing's Syndrome recommends normalizing UFC levels in subjects with Cushing's Syndrome as a means of preventing hypercortisolemia-related complications (hypertension, hyperglycemia, obesity, psychiatric abnormalities, bone loss, etc.), and thus improving morbidity and mortality in this population.	• Prolonged hypercortisolemia is associated with increased morbidity and mortality in patients with CD, including decreased overall quality of life (QOL) and increased death due to cardiovascular complications. • Normalization of UFC is the goal of treatment and is associated with improvement in the signs and symptoms of the disease and amelioration of complications such as diabetes and obesity.
Current Treatment Options	• Transsphenoidal surgery is a first-line treatment for CD. • Medical therapy is a second-line treatment option in patients not suitable for surgery and in patients with persistent or recurrent disease after TSS. • Two drugs are approved in the US for treatment of CS; pasireotide and mifepristone. Injectable formulations of pasireotide are approved for the treatment of CD and effective in 40% of patients. Oral formulation of mifepristone (Korlym) is approved for the subgroup of patients with CS-patients who have cortisol-induced hyperglycemia. • Therapies used 'off-label' to treat hypercortisolemia include steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, etomidate) and dopamine agonists (cabergoline, bromocriptine) are effective in 70-80 % and recommended for the treatment of patients with CS by current guidelines from professional societies.	• There are a limited number of alternative therapies available for the treatment of CS and CD, some of which are approved (pasireotide and mifepristone) and some of which are used off-label • Therapeutic options for treatment of CS remain limited and many patients with CS remain undertreated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Osilodrostat is effective in reducing mUFC levels from baseline in patients with CD as demonstrated in a single pivotal, multi-center, double blind, randomized withdrawal (RW) study of osilodrostat following a 24-week, single arm, open-label dose titration period (study C2301). • Osilodrostat was superior to placebo at the end of the randomized withdrawal period: 86.1% (95% CI: 70.5, 95.3) of patients in the osilodrostat group maintained normal mUFC without dose change compared to 29.4% (95% CI: 15.1, 47.48) of patients in placebo group. • The primary analysis (in the RW period) confirmed that the UFC lowering effect was attributable to the drug itself and not to other factors such as inactive disease, cyclic CS, etc. (as demonstrated by a significant difference in the proportion of responders in the active drug and placebo groups). • Osilodrostat normalized UFCs in approximately 52% of all treatment-naïve patients after 24 weeks of treatment in the open label, single arm period of the study (key secondary endpoint). • By the end of the study, week 48, 66.4% of all patients had normal mUFC. • Improvements in other secondary efficacy endpoints (e.g., decrease in mUFC and serum cortisol levels) in all patients are supportive of the efficacy of osilodrostat in treating of hypercortisolemia in patients with CD.	• Treatment with osilodrostat should normalize UFC and reduce morbidity and mortality and improve quality of life in treatment-naïve patients with hypercortisolemia secondary to Cushing's disease. • Osilodrostat is effective in approximately 52% of all treatment-naïve patients after 6 months of treatment (key secondary endpoint) • The response can be maintained in approximately 80% of patients who responded to the drug and tolerated the drug during the first 6 months of treatment • The magnitude of the effect observed in the open-label, single arm periods of the study and in the RW period may not reflect the magnitude of the effect that will be seen in clinical practice in all treatment-naïve patients.
Risk and Risk Management	• The safety profile of osilodrostat in patients with CD was well characterized in the overall clinical program. • The most frequent AEs were hypocortisolism related AEs, nausea, vomiting, headache, insomnia and fatigue. • Hypocortisolism-related AEs, including AI, are expected adverse events based on osilodrostat's mechanism of action. There was a high rate of such events observed in study C2301 (50%). However, only approximately 1/2 of these events were associated with low UFC levels or required glucocorticoid treatment, indicating that the reported rate was overestimated. No deaths were reported, and all cases of AEs resolved with osilodrostat dose decrease/interruption and/or treatment with	• Treatment with osilodrostat is associated with nausea, vomiting, fatigue, hypocortisolism related AEs, AEs associated with accumulation of adrenal precursors and androgens. • The high rate of hypocortisolism-related AEs was overestimated in the pivotal study and/or was due to aggressive dose titration. The risk of hypocortisolemia will be communicated through labeling and mitigated through proper monitoring and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	glucocorticoids. The clinical data also raised a possibility that these events may be due to fast dose titration, as evident by the fact that the majority of these events occurred during first 12 weeks of drug titration. • Osilodrostat blocks cortisol synthesis; an increase in levels of steroid hormone precursors (11-DOC and DOC) and androgen precursors was observed during treatment with osilodrostat. AEs associated with accumulation of these precursors (hypertension, hypokalemia, edema, hirsutism acne) were observed in up to 12% of patients. Hypertension and hypokalemia resolved in all patients without or with dose adjustments and/or treatment with potassium supplements and antihypertensive drugs. • Osilodrostat is associated with QT interval prolongation at supratherapeutic doses. • No clinically meaningful changes in tumor volume were identified in the study to date. • Changes in hemoglobin, absolute neutrophil count, LFTs were small and of unknown clinical significance. • Labeling will be used to mitigate against the serious risks of hypocortisolemia, QTc interval prolongation, and adrenal hormone precursor accumulation-related AEs. • A post-marketing requirement to complete the ongoing Phase 3 study C2302 to further evaluate the safety profile of osilodrostat with slower titration schedule will be issued. • No risks identified require risk management beyond labeling to warrant consideration of a Risk Evaluation and Mitigation Strategy (REMS).	dose adjustment. To further mitigate this risk, titration not more frequently than every 2 weeks using small increments of 1-2 mg will be recommended. • The risks of AEs associated with accumulation of adrenal precursors including hypokalemia, hypertension, hirsutism acne, etc. are expected AEs based on the drug's mechanism of action, monitorable AEs and will be mitigated through appropriate labeling. • The risk of QTc prolongation will be mitigated by proper patient selection, monitoring and dose adjustment if required. • The potential improvement in the safety profile of osilodrostat with slower titration regimen (i.e. every 3 weeks) will be further evaluated in study C2302 (postmarketing requirement). • The potential safety risk of change in osilodrostat exposure when co-administered with strong CYP3A4 inhibitors will be further characterized in a post-marketing requirement (i.e., drug-drug interaction study).

2. Background

On March 7, 2019 Novartis submitted a New Drug Application (NDA) for osilodrostat under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following indication:

Treatment of patients with Cushing's disease.

Osilodrostat is a novel inhibitor of cortisol (via inhibition of 11-β-hydroxylase) and of aldosterone (via inhibitions of aldosterone synthase) synthesis formulated for oral administration.

Endogenous Cushing's syndrome (CS) is a serious, multisystem disorder that results from the overproduction of cortisol by the adrenal glands. CS is a rare disease, with an incidence of 0.7 to 2.4 per million per year[4]. Most cases of Cushing's syndrome (80%) are ACTH-dependent and due to oversecretion of adrenocorticotropic hormone (ACTH): the source of ACTH may be pituitary (Cushing's Disease) or ectopic. Cushing's Disease (CD) is the most common cause of endogenous CS, and accounts for approximately 70% of all cases of endogenous CS.

The clinical manifestations of CD are variable, often times severe and are related to the local growth of the tumor (headache, loss of vision) and to systemic symptoms of hypercortisolism. Systemic symptoms include impaired glucose tolerance or diabetes, hypertension, myopathy, bone loss which can lead to fracture, compromised immune function, and psychiatric disturbances, among others. CS (and CD) is associated with decreased quality of life and an increased mortality rate. The mortality rate in patients with CS is 5-fold higher than that of that of the general population [5]. Cardiovascular complications are the main cause of death in CS, and the risk of death is independently increased by co-existing diabetes mellitus and/or hypertension[6].

Because of the significant morbidity associated with CS, early therapy is fundamental. In general, surgery is first-line therapy and the treatment of choice for all causes of CS. Surgery is successful in 60-80% patients with CD caused by pituitary microadenoma[7]. However, even in patients who respond to surgery, up to 25 % will experience recurrence within 10 years. Second-line therapy of CS includes radiation, medical therapy, and bilateral adrenalectomy.

Although not curative, medical therapy plays an important role in the management of CS. Medical therapy is employed pre-operatively for control of severe hypercortisolemia, in patients with persistence or recurrence of CS despite having undergone surgery, in patients

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[4] Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006 May 13;367(9522):1605-17.

[5] Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf). 1994 Apr;40(4):479-84.

[6]Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. J Clin Endocrinol Metab. 2011 Mar;96(3):632-42

[7] Pivonello R, De Martino MC, De Leo M, Lombardi G, Colao A. .Endocrinol Metab Clin North Am. 2008 Mar;37(1):135-49

with CD who undergo radiotherapy to control hypercortisolemia until the results of radiotherapy become effective, and in patients who are not candidates for radiation or surgery due to poor health. Lifelong medical treatment to suppress cortisol levels may be required if the primary cause of CS cannot be treated successfully with surgery and/or radiation.

Availability of medical therapies for the treatment of CS and CD

- Approved therapies

FDA approved two drugs for treatment of CS/CD: Korlym (mifepristone) and Signifor (pasireotide):

- Mifepristone, a glucocorticoid receptor antagonist, was approved on February 17, 2012 for the treatment of cortisol-induced hyperglycemia in patients with CS. Mifepristone does not reduce cortisol levels but, by blocking the glucocorticoid receptor in peripheral tissues, it also blocks the action of cortisol.

- Pasireotide is a somatostatin analog that binds to somatostatin receptors on the surface of ACTH-secreting pituitary tumors and reduces ACTH output with subsequent decline in cortisol levels. Two injectable pasireotide formulations (Signifor and Signifor LAR) were approved in 2012 and 2018, respectively, for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Both drugs are associated with adverse reactions including vaginal bleeding and risk of pregnancy termination (mifepristone), hyperglycemia, diabetes, QT interval prolongation, cholestasis, gastrointestinal AEs (pasireotide) and adrenal insufficiency (associated with both drugs). For pasireotide, the need of injections can affect compliance or acceptability of the treatment. In addition, neither mifepristone nor pasireotide is expected to be effective in all patients. Registration trials have shown that pasireotide normalized or decreased urine cortisol by 50% in 40% of patients. As already mentioned, mifepristone is approved only for a subgroup of Cushing's syndrome patients - patients who have abnormalities in glucose metabolism - which include about 50-60% of all Cushing's syndrome patients.

- Off label therapies

Current guidelines from professional societies list several unapproved drugs as part of the medical management of patients with Cushing syndrome or Cushing disease[8] [9]. According to these guidelines, steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane and etomidate) are recommended and the most widely used agents in the treatment of CS of any etiology: these drugs are effective in 75- 80% of patients 80%[10]. Treatment with these drugs is

[8] Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ, Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JA, Boscaro M. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2008 Jul;93(7):2454-62.

[9] Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Endocrine Society Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31.

[10] Feelders RA, Hofland LJ, de Herder WW. Medical treatment of Cushing's syndrome: adrenal-blocking drugs and ketaconazole. Neuroendocrinology. 2010;92 Suppl 1:111-5

associated with such adverse events as gastrointestinal adverse effects, adrenal insufficiency, liver toxicity (ketoconazole), edema, hypertension and hirsutism (metyrapone), etc. Thus, extensive clinical monitoring is required which may limit their use in patients with CS.

Overall, there are several alternative therapies available for the treatment of CS and CD, some of which are approved and some of which are used off-label, however, therapeutic options for treatment of CS remain limited and many patients with CS remain undertreated.

Regulatory History

Osilodrostat has been in clinical development under [redacted] (b) (4) DMEP.

[redacted] (b) (4) However, because osilodrostat inhibits cortisol synthesis, the Sponsor decided to continue development of this drug for treatment of CD. This review is focused on use of osilodrostat for the treatment of patients with CD; the [redacted] (b) (4) will not be discussed further in details in this review, unless otherwise specified.

The major regulatory interactions between the Sponsor (Novartis) and DMEP for the CD indication are summarized below.

1) IND 117489 in DMEP was opened on 6/18/2013 with a protocol for a thorough QT study (TQT) in healthy volunteers (CLCI699C2105, referred to as study C2105 hereafter).

2) Osilodrostat was granted Orphan Drug designation for "the treatment of Cushing's disease" on 9/13/2013 by the Office of Orphan Products Development.

3) End-of-Phase 2 meeting (EOP2), 10/09/2013

- Several issues and uncertainties regarding the proposed Phase 3 clinical program were raised during this meeting.

The Division stated disagreement with the Sponsor's design of the pivotal Phase 3 study (LCI699C2301), i.e. double-blind, [redacted] (b) (4), randomized withdrawal study. The Division recommended the conduct of a randomized, double-blind, placebo-controlled study to establish efficacy (8-12 weeks) followed by an extension phase to establish durability of effect and obtain long-term comparative safety data. The Division indicated that such a trial would be ethical provided adequate safeguard are in place in the protocol. The Sponsor disagreed with the proposed trial design and indicated that randomized withdrawal allows for assessment of rebound and withdrawal effect in responders and that such information is important for adrenolytic therapy and that the efficacy information collected at a later time of the trial (i.e. after the drug titration is completed) is likely to be more relevant. Additionally, the Sponsor also expressed the concern that use of placebo may lead to difficulty in recruitment. The Division was also concerned that the randomized withdrawal study would provide information for the responders only. Lastly, the Division also indicated that the study with the up-front randomized design will require smaller sample size based on various power calculations to

detect a significant difference based on UFC (43-108 patients) compared to the sample size proposed in the randomized withdrawal study.
The Division also expressed the concern that the proposed study is lacking a comparator for safety assessment. The Sponsor indicated that comparison of a placebo versus efficacious dose (as in proposed randomized withdrawal study) will be more informative than comparison of placebo versus patients in a titration phase (as in the Division's proposed study). However, the Sponsor proposed to submit controlled data from (b) (4) to relieve the Division's concern. The Division disagreed with the proposed (b) (4) .
No agreement on the design of the pivotal study was reached during the meeting.

- The Division and the Sponsor reached an agreement on other points of the discussion including study population (patients with CD and elevated UFC> 1.5XULN), proposed doses and proposed primary endpoint (i.e. the proportion of patients with UFC < ULN).

In addition, the Division asked the Sponsor to stratify by the post-radiation interval, to include evaluation of changes to antidiabetic and antihypertensive medications and provide the time interval that should elapse between dose escalations.

- Lastly, the Division agreed with the Sponsor's plan to submit data from a single Phase 3 trial (LCI699C2301, referred to as Study C2301 hereafter) supported by the results from Phase 2 trial LCI699C2201 (referred to as Study C2201 hereafter) for NDA filling.

4) The design of a Phase 3 up-front randomized, double-blind placebo-controlled study (LCI699C2302, referred to as Study C2302 hereafter) was further discussed between the Agency and the Sponsor.

- On 1/9/2014 the Sponsor requested for further clarification on design of an up-front randomized placebo-controlled study and on the number of studies to be included in NDA submission (refer to email communication in DARRTS). On 1/16/2014, the Agency provided the following recommendations via email:

- The Agency agreed with the duration of C2302 study of 12 weeks, however, recommended that after completion of the 12-week double-blind, placebo-controlled phase of the trial, LCI699 responders should continue to be treated in an open-label extension phase for up to 12 months in order to gather additional safety data and to document durability of effect. Patients in the placebo arm should be switched to LCI699 at the end of the 3-month controlled phase in order to provide additional safety (and efficacy) data.
- The Sponsor was recommended to increase the number of patients to be enrolled in the study from 43 to 100 to further evaluate the safety of the drug.
- Treatment of complications (glucose, blood pressure (BP), electrolyte management) should be optimized prior to randomization.
- In the randomized, double-blind phase, rescue criteria should be implemented based on clinical complications of the disease rather than on a biochemical response criterion to ensure subject retention.
- Lastly, the Agency agreed that results of new study C2302 (as a pivotal study instead of study C2301) together with results from supportive Phase 2 study LCI699C2201 should be included in NDA.

- The Sponsor responded to the Agency's comments by email on 2/5/2014 and indicated that it will be difficult to conduct a large (100 patients) study with upfront placebo-controlled design as the only registration trial. Therefore, the Sponsor decided to conduct 2 pivotal

studies, a planned randomized withdrawal study (C2301) and an upfront placebo-controlled study (C2302).

- On 7/17/2014, the Sponsor submitted the revised plan for Study C2302, addressing the majority of the Agency's recommendations from 1/16/2014. The Agency agreed, in general, with the Sponsor's revised plan for study C2302 (refer to Clinical review in DARRTS from 9/29/2014 for details):

- The Sponsor agreed to enroll patients with controlled disease complications, to conduct the open-label extension phase, and to switch placebo patients to osilodrostat in the follow-up phase, and to follow patients who were discontinued in the randomized phase until trial end.
- The proposed inclusion criterion of mean UFC value > 1.3xULN was found to be acceptable.
- The Sponsor's plan to enroll 69 patients instead of 100 patients was found to be reasonable assuming the safety database provided in NDA will include approximately 180 patients with CD from 2 pivotal trials.
- Lastly, the Agency agreed with the Sponsor's proposed duration of placebo-controlled period of 10 weeks instead of initially planned 12 weeks, however, indicated that it will be a review issue of whether the proposed duration is adequate for the approval. The Sponsor's decision was based on the results from Phase 2 C2201 study and on the assumption that 10 weeks will be enough to allow for safe dose titration and for establishing the adverse event profile of drug compared to placebo.

5) (b) (4)

6) The protocol for the pivotal Phase 3 double-blind randomized withdrawal study C2301 was submitted on 3/25/2014. The protocol was reviewed and found to be safe to proceed (refer to the review in DARRTS from 4/9/2014).

The study was amended 4 times since the original submission:

- Version 1 (submitted on 7/28/2014 and reviewed on 9/25/2014).

In this amendment, the Sponsor clarified that the extension period will be of 1-year duration, the definition of time-to escape period, and safety monitoring for QT prolongation.

- Version 2 (submitted on 4/10/2105 and reviewed on 4/13/2015).

In this amendment the Sponsor proposed to decrease the time period of elapsed time since the last radiation treatment from 3 years to 2 years, to include intermediate dose levels, 3 mg, 7 mg, and 15 mg bid, to include monitoring of renin, androstenedione, DHEAS levels, and to allow use of spironolactone, cyproterone or finasteride for hirsutism.

- Version 3 (submitted on 4/25/2016 and reviewed on 8/9/2016).

The Sponsor included specific criteria for the identification and management of patients with potential drug-induced liver injury (DILI), added the recommendations regarding dose modification for symptomatic adrenal insufficiency and increased the duration of the extension phase until the approval of the drug.

- Version 4 (submitted on 11/14/2017 and reviewed on 4/20/2018)

In this version, the risk of neutropenia was included in the protocol (based on a single 15-day report of neutropenia that occurred during the study).

7) The protocol for Phase 3 up-front randomized placebo-controlled double-blind study, C2302, was submitted to the Agency on 1/29/2016 and reviewed on 5/2/2017.
The protocol incorporated all the Agency's recommendations discussed above, however, the Sponsor agreed to extend randomized period to 12 weeks. The Sponsor also proposed to adjust the dose based on the average of two UFC samples and to collect three UFC samples only for the determination of patient eligibility and evaluation of primary endpoint (week 12 visit).

8) The statistical sections of the phase 3 protocols, C2301 (submitted 4/10/2015) and C2302 (submitted 1/29/2016) were reviewed by biostatistician Dr. Yoonhee Kim, on 6/30/2017. The reviewer recommended that for each sensitivity analysis the Sponsor plans to conduct, to describe the limitations of the data or assumptions of the primary analysis being evaluated and how the sensitivity analysis evaluates this and asked the Sponsor to also include the tipping point analysis using the primary analysis population. In addition, for Study C2302, Dr. Kim recommended including data collected from patients who discontinued the study earlier than week 12 but continued to be followed up.

9) Type C meeting (10/10/2017)
The Sponsor and the Agency discussed safety data to be included in the NDA submission. The Sponsor indicated that the results from four Phase 2 studies conducted in patients with hypertension provide very limited assessment of risk-benefit of the drug in patients with CS and proposed not to include the full dataset from these studies in the NDA submission. The Agency agreed with this plan, however asked the Sponsor to submit the summary of safety findings from these studies.

10) Pre-NDA meeting (8/20/2018)
During this meeting, content and format of the NDA, the osilodrostat clinical program for CD, and the Division's concerns regarding the interpretability of the results of Phase 3 study C2301 were discussed:

- Novartis indicated that the results from the single pivotal study, C2301, and from 2 supportive studies C2201 (Phase 2 study in patients with CD) and C1201 (Phase 1 study in healthy volunteers) will be included in the NDA. The Phase 3 study with up-front randomized design, C2302, is still ongoing and the results from this study will not be included in the submission. Given the rarity of the disease, the Agency agreed with the proposed plan but indicated that the interpretability of efficacy results will be challenging due to the C2301 study design. The Applicant and the Agency also agreed that this submission will include data from the completed Core Phase (48 weeks) and from the ongoing extension phase up to the data cut-off date of 2/21/2018 (the extension phase will be still ongoing at time of NDA submission).
- The preliminary results of efficacy were discussed during the meeting. The Agency reiterated the concerns raised during EOP2 meeting that the C2301 trial was a randomized withdrawal trial, and, thus, it was carried out only in those who were responders during the open label period of the trial. The Agency also noted that the patients who responded to the treatment during the study had less severe disease at baseline (lower UFCs) and/or required lower doses to respond to the treatment and indicated that patients with more severe disease might require longer titration (> 12 weeks). Novartis agreed that the design of the study did not allow longer titration. The Agency also expressed a concern that 30% of patients on

placebo remained responders and, reiterated that upfront randomization would have addressed many uncertainties.
Novartis also agreed that the drug demonstrated efficacy in 50% of drug-naïve patients at the end of 12 week, and that the results from the randomized withdrawal period demonstrated efficacy only in pre-selected patients who responded to the drug earlier, i.e. maintenance rate of the response (80% of patients who responded during the initial periods of treatment maintained the response at the end of this period)

(b) (4)

- Lastly, because of liver neoplasia findings in nonclinical carcinogenicity studies, the Agency requested to include in the NDA a robust dataset supporting the proposed CAR-mediated tumorigenic mode of action.

11) NDA submission: March 7, 2019.

3. Product Quality

The CMC reviewers recommend approval of this application (refer to Dr's. Dhanalakshmi Kasi executive summary). There are no outstanding issues that preclude approval. The Office of Pharmaceutical Quality and Office of Compliance has determined the manufacturing facilities are acceptable (refer to review dated 1/2/2020).

The drug product is an inhibitor of 11 β-hydroxylase (CYP11B1), the enzyme that catalyzes the final step in the synthesis of cortisol in the adrenal cortex. The molecular weight is 325.24 g/mol.

The drug substance is osilodrostat phosphate in the form of a powder, white to off-white in color. The CMC reviewer indicated that the data presented in this submission establishes the identity, purity, and quality of the drug substance and that the impurities (process or degradants) have been adequately described with respect to the origin, identification, and characterization of actual and potential impurities for the drug substance. Residual solvents met ICH requirements.

Osilodrostat is manufactured as 1 mg, 5 mg and 10 mg film-coated tablets, and it is an immediate release dosage form for oral administration. The 5 mg and 10 mg strengths are dose-proportional. The excipients used in the tablet core are microcrystalline cellulose, mannitol, magnesium stearate, croscarmellose sodium and colloidal silica. The excipients used in film coating are hydroxypropylmethyl cellulose, titanium (b) (4), iron oxide yellow, iron oxide red, iron oxide black, polyethylene glycol 4000 and talc. The reviewer concluded that "all excipients are well within the II G limits".

An expiry of 36 months was granted when stored at ambient temperature (kept below 30 ºC) and humidity.

The proposed commercial primary packaging for osilodrostat film-coated tablets consists of double-sided aluminum blisters with (b) (4) foil as forming foil and aluminum foil with a (b) (4) as backing foil. Stability data indicates that the proposed packaging is compatible with the osilodrostat film-coated tablets. Each carton will contain 3 blisters /pack.

(b) (4)

The applicant also provided the following commitment: (b) (4)

Lastly, the CMC team requested the Applicant to provide stability data for at least one batch of commercial drug product packaged in the proposed commercial container and closures under long term and accelerated storage conditions for three months post action. The Applicant committed to submit the required data.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues, and the pharmacology/toxicology reviewers recommend approval of osilodrostat with no requirements for post-approval nonclinical studies (refer to Pharmacology/toxicology review in DARRTS from 12/12/2019).

The applicant conducted all the required non-clinical studies, including pharmacokinetic and toxicokinetic studies to support the chronic use of osilodrostat in patients with CD.

Nonclinical and in-vitro studies have demonstrated that osilodrostat inhibits 11b-hydroxylase (CYP11B1), the enzyme that catalyzes the last step in the biosynthesis of cortisol in the adrenal gland (IC_{50} = 2.5 nM). Osilodrostat is also potent inhibitor of aldosterone synthase (IC_{50} = 0.7 nM). Osilodrostat also inhibits aromatase, but at a higher concentration (IC50 = 1.7 μM) than that necessary to inhibit CYP11B1 and CYP11B2. However, this activity is still within 2-fold of Cmax.

The toxicity of osilodrostat was assessed in series of repeat-dose toxicity studies in mice, rats, and dogs. The primary target organs were the adrenal gland, liver, and female reproductive tissues. In the adrenal glands, increased weights, cortical hypertrophy, and/or vacuolation occurred in all species. The reviewers concluded that the effects on the adrenal gland is related to the pharmacologic activity of the drug and may reflect an adaptive response, with the vacuoles possibly forming as a result of accumulation of precursor lipids secondary to the inhibition of cortisol synthesis.

Effects on rodent's, but not dog's, livers included increased weights, hypertrophy, and

vacuolation at significantly higher exposure than at Maximum Recommended Human Dose (MRHD), all of which were reversible. In the repeat dose rodent toxicity studies, there were no effects on liver enzymes until exposures were in excess of 100-fold the exposure at the MRHD.

The reversible effects on the ovary (increased weights, follicular degeneration, prominent corpora lutea) and uterus (increased or decreased weights, atrophy) were noted at the exposures >0.3-fold those at the MRHD across species. The reviewers concluded that the observed effects may be due to the inhibition of aromatase by osilodrostat.

Cardiovascular studies in dogs and nonhuman primates (NHP) revealed the following adverse effects at high exposures: inhibition of the hERG current at > 50-fold the MRHD, prolongation of the QRS, QT, and QTc levels at 11- > 15-fold the MRHD, Torsades de Pointes and ventricular tachycardia (in NHPs) at 100-fold the exposure at the MRHD. Refer to the Safety section below for further discussion of the QT-prolonging effect of osilodrostat in humans.

The carcinogenicity studies revealed an increase in the incidences of hepatocellular adenomas, and/or carcinomas in mice and rats and in thyroid follicular adenomas and/or carcinomas in rats (again, at supraphysiologic exposures of osilodrostat). The reviewers concluded that the hepatocellular tumors likely were induced by non-genotoxic mechanisms and that the overall weight of evidence indicates that the rodent liver neoplasms were most likely mediated by rodent-specific CAR activation which is not relevant in humans. Overall, there is not a significant concern for human-relevant liver neoplasms at clinically relevant exposures.

Fertility studies performed in rats demonstrated evidence of impaired fertility (increased time to mating, decreased mating and fertility, decreased implantation sites, increased resorptions, etc.) at supratherapeutic osilodrostat exposures (> 100-fold those at the MRHD). Embryofetal development studies revealed increased fetal resorptions and altered morphological development in rats and rabbits, again, at very high exposures (> 100-fold and 7-fold the exposure at the MRHD, respectively). The reviewers indicated that considering the role of cortisol in human fetal development, fetal exposure to osilodrostat may present a risk. However, the reviewers concluded that the overall risk of embryofetal development in patients with CD is very low (based on the findings in healthy animals at supratherapeutic exposure) and do not recommend including this risk in the WARNING and PRECAUTION section of the USPI. I agree with the reviewers' recommendations. For the same reasons, a pregnancy test is not required prior to the initiation of the treatment with osilodrostat in patients with CD. The drug will not be used by patients with normal cortisol levels, and patients with CD have very low rate of fertility in general due to hypercortisolemia.

5. Clinical Pharmacology

The clinical pharmacology review was completed by Dr. Sang M Chung, and Pharmacometrics review was completed by Dr. Jianghong Fan. Both reviewers recommended approval of osilodrostat for the proposed indication.

For a detailed discussion, please refer to their Clinical Pharmacology review in DARRTS dated 1/16/2020.

The clinical pharmacology review concluded that PK of osilodrostat has been adequately characterized in Novartis's studies in healthy volunteers and in patients with CD. The reviewers confirmed that PK of osilodrostat was comparable between patients and healthy volunteers.

(b) (4)

T_{max} is 1 hour and is increased by 25% with food following 30 mg dose. The $T_{1/2}$ of osilodrostat is 4 hours after a single dose and 3-5 hours after multiple dose administration. Once absorbed, osilodrostat is metabolized by CYP enzymes (total CYP contribution 26%: ~11.7% by CYP3A4, ~6.25% by CYP2B6, and ~8.07% by CYP2D6) and by UDP-glucuronosyltransferase (UGT) enzymes (total UGT contribution 19%). Other non-CYP, non-UGT mediated metabolism (such as other oxidative metabolism by unknown enzymes, ribose conjugation etc.) was shown to contribute to ~50% of total clearance. Primary metabolite (M34.5) was not pharmacologically active. Metabolism was extensive as urinary elimination of osilodrostat was minor (5/19% of dose). Plasma protein binding of osilodrostat is 36.4%.

The review indicates that the PK of osilodrostat was more than proportional to dose: exposure (AUC_{inf} and C_{max}) slightly increases over the therapeutic dose range of 2-30 mg. A time-dependent non-linearity was noted and was most likely due to potential auto-induction in metabolism. The reviewers concluded that:

- the potential of a time-dependent PK is not significant since there was no significant difference between AUC_{inf} following single dose and AUC_{tau} following multiple doses
- there was is no apparent accumulation following multiple doses
- although there was non-linearity in PK following single doses, the degree of non-linearity was comparable following multiple doses
- there were no apparent changes in C_{trough} at apparent steady-state in Phase 2 and 3 trials
- dose was individualized with adjustment to clinical responses; until normalization of mUFC or intolerable as protocol-specified. It indicates that exposure-response is confounded as dose is adjusted to clinical responses without exposure consideration.

The reviewers concluded that uncertainty introduced by non-linear PK can be "managed within the proposed dosing regimen and labeling". Finally, the reviewers agreed with a starting dose of 2 mg orally twice daily with increments 1-2 mg based on the individual response with the goal to achieve normal cortisol levels. The reviewers noted that between-subject variability in response is expected to be high as responses are confounded by individual status of the HPA axis and its feedback sensitivity.

Intrinsic factors (e.g. weight, age, gender) that could influence exposure and activity were evaluated using Population PK analyses. Age, gender, race, and body weight had no clinically relevant effect on the PK of osilodrostat.

No clinically significant changes were found in the food effect studies conducted with 30 mg single dose in healthy volunteers. Thus, osilodrostat can be administered with or without food.

Results from a study conducted in patients with normal and severe renal impairment showed no significant change in PK of osilodrostat. There was an increase in AUC in subjects with moderate and severe hepatic impairment (geo-mean ratio 1.44 and 2.66, respectively) without significant changes in C_{max}. Thus, reviewers recommend osilodrostat starting dose of 1 mg twice daily in patients with moderate hepatic impairment (Child-Pugh B) and 1 mg once daily in subjects with severe hepatic impairment (Child-Pugh C).

Osilodrostat was evaluated for potential QT prolongation in a single thorough QT study, CLCI699C2105. The study design and its results were reviewed and discussed in detail by the FDA Interdisciplinary Review Team (IRT) for QT Studies (refer to the full reviews in DARRTS from 8/2/2019). Briefly, the study was conducted in 86 healthy volunteers with one of the therapeutic doses (10 mg) and with a supratherapeutic dose of 150 mg. As per the IRT reviewer, the 150 mg dose is 5-fold the Cmax for the therapeutic dose (30 mg bid) and covers ~2-fold of the worst-case exposure scenario (severe hepatic impairment). In this study, significant QTc prolonging effect of osilodrostat was observed only at the supratherapeutic dose studied (150 mg), and the trial did not suggest that the drug is associated with significant QTc prolonging effect at the proposed therapeutic doses. The study demonstrated a maximum mean placebo-corrected QTcF interval increase of 1.73 ms [90% confidence interval (CI): 0.15, 3.31] at a 10 mg single dose, and 25.38 ms (90% CI: 23.53, 27.22) at a supratherapeutic 150 mg single dose. The mean placebo-corrected QTcF change from baseline at the highest recommended dose (30 mg twice daily) was estimated by the exposure response analysis and was predicted to be 5.27 ms (90% CI: 4.12, 6.42). The IRT reviewer also noted that the results of the study indicate that patients without risk factors for QT prolongation are unlikely to experience a clinically significant QTc effects and recommended to monitor ECG only in patients with risk factors for QT prolongation, and not in all patients. At the end, IRT concluded that the study was overall informative and made specific labeling recommendations.

Finally, based on the known metabolism of osilodrostat, on the results of conducted drug-drug interaction studies and on the results of PBPK modeling and simulation, the Clinical Pharmacology reviewers provided the following conclusions and recommendations:

- osilodrostat is a moderate inhibitor of CYP1A2, a weak to moderate inhibitor of CYP2C19, and a weak inhibitor of CYP2D6 and CYP3A4/5, and thus should be used with caution when administered with CYP1A2 and CYP2C19 substrates with narrow therapeutic index (such as theophylline, tizanidine, and S-mephenytoin)
- there was no significant impact of osilodrostat on PK of oral contraceptives.
- there was a significant uncertainty in the osilodrostat-strong CYP3A4 inhibitors interaction according to the assessment in PBPK modeling.

Because of the above uncertainties regarding interaction between osilodrostat and CYP3A4 inhibitors and because there is a potential for off-label use of ketoconazole (a strong CYP3A4) inhibitor) with osilodrostat in patients with CD, reviewers conducted further analyses to assess the DDI liability of osilodrostat with ketoconazole without auto-induction incorporated in the model (refer to the Applicant's response to the Agency's Information Request from 2/12/2020 and Agency's Information Request sent to the Sponsor on 1/21/2020). Based on the results of these analyses, the reviewers recommend the following labeling changes:

- For co-administration with a strong CYP3A inhibitor, reducing the dose to one-half of the usual dose in patient without co-medication of a strong CYP3A4 inhibitor**.**

- For strong CYP3A inducer, [redacted] (b) (4)

I agree with the proposed labeling changes.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Drs. Alexander Cambon (biostatistician) and Diala El-Maouche (clinical reviewer) reviewed the efficacy results and recommend Approval (refer to the reviews in DARRTS from 12/19/2019 and 1/14/2020, respectively). The statistical and clinical reviewers concluded that the results of the Phase 3 program provided sufficient evidence to support the efficacy claims proposed in this NDA, i.e. treatment of CD patients.

The osilodrostat clinical program for CD includes 4 clinical studies. Two of these studies are Phase 3 studies evaluating efficacy and safety of osilodrostat in patients with CD (Study C2301- randomized withdrawal study and Study C2302 -up-front randomized placebo-controlled double-blind study). The primary study to support efficacy of osilodrostat is the completed Core phase (48 weeks) of study C2301. This study was the largest in the intended population, included the most diverse range of efficacy assessments in the clinical program, and used randomization (refer to the discussion regarding randomization to *Efficacy results* below). Study 2302 is still ongoing and blinded; thus, the results of this study will not be discussed further in detail in this review. Study 2302 is not considered necessary to establish efficacy and support the favorable benefit risk assessment for this NDA (see Efficacy Conclusions and Benefit Risk Assessment).

I will also briefly summarize the results of Phase 2 study in patients with CD (study C2201), since the efficacy results from this study were submitted as supportive evidence of the efficacy of osilodrostat in patients with CD. All other study(s) will be referenced as needed.
For the full list of studies refer to the clinical review in DARRTS from 1/14/2020.

Study C2301

This study was a Phase 3, multi-center (66 centers across 19 countries), double blind, randomized withdrawal (RW) study of osilodrostat following a 24-week, single arm, open-label dose titration period that investigated the use of osilodrostat in 137 adult patients with CD.
The primary objective of the trial was to assess the complete response rate at the end of the 8-week RW period (Week 34) between patients randomized to continue osilodrostat therapy vs. placebo.

The Agency and the Applicant discussed the design of study C2301 and overall Phase 3 program on several occasions (refer to regulatory history above). Since the randomized withdrawal study is not as informative as an upfront randomized controlled study, the Applicant also agreed to conduct a second upfront randomized placebo-controlled study (C2302) in order to support the substantial evidence of effectiveness of osilodrostat and to characterize the safety of the product for its intended use. However, at the end, given the rarity of the disease and the fact that study C2302 was still ongoing and would be completed in 2020, the Agency found the submission of a single pivotal Phase 3 clinical study using a randomized withdrawal design to be acceptable for an NDA submission. The Applicant and the Agency also agreed that this submission will include data from the completed Core Phase (48 weeks) and from the ongoing extension phase up to the data cut-off date of 2/21/2018 (the extension phase is still ongoing). The Division accepted the NDA submission that includes the results from the ongoing extension phase, since the main evidence of efficacy for osilodrostat in patients with CD comes from the Core Phase (48-week study) that was completed prior to the NDA submission and the results from the Core Phase are included in the submission.

Patient population

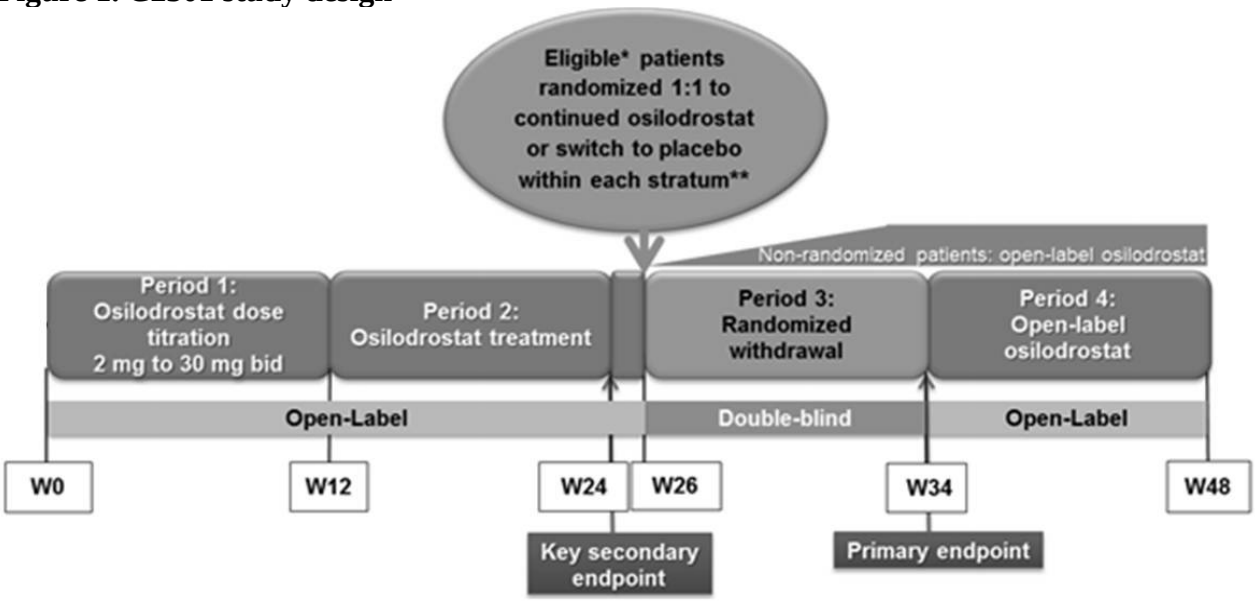
Consistent with the indication sought in this application (medical treatment of CD) the study enrolled only CD patients who were candidates for medical therapy according to current medical practice, i.e. primarily patients with persistence or recurrence of hypercortisolism despite prior pituitary surgery, and some patients with *de novo* Cushing's disease who were poor surgical candidates or who refused surgery. The study had clear and rigorous inclusion criteria to confirm the diagnosis of CD, confirm the presence of hypercortisolism at enrollment and exclude conditions that may overlap clinically or biochemically with Cushing's disease (see Dr. El-Maouche's clinical review for details). Any potential carry-over effect of previous medications was minimized by a washout of previous medical therapies which took into consideration the half-lives of specific drugs. Patients who received pituitary radiotherapy within 2-3 years prior to screening were excluded from the study in order to eliminate the residual effect of these therapeutic modalities on the response rate. In addition, a chance of enrolling patients with cyclic disease (that may affect efficacy results due to the spontaneous fluctuations in cortisol levels) was minimized by the following prespecified UFC cutoff (s) and duration of UFC collection required: a cut-off of mUFC > 1.5 x ULN (3 UFC samples collected at screening and an additional three at baseline, which spans a period of 6 weeks and 2 weeks. Dr. El-Maouche's review of protocol violators did not identify any significant deviations in the way the inclusion/exclusion criteria were applied in the clinical trial. This is important since CD is not expected to improve spontaneously except in very rare situations.

Study design

The schematic of the trial is displayed below.

C2301 included four major periods, three of these 4 periods were open-label, single-arm periods and one was an 8-week RW period. As evident from this design, the efficacy and safety of the drug was evaluated mostly in an open-label, single-arm fashion; only the 8-week RW period used randomization and blinding.

Figure 1. C2301 study design



To be eligible for randomization, the patient must have mUFC ≤ULN at Week 24, and no further dose increase after Week 12.
** Strata were determined by the combination of two stratification factors at randomization; 1) Osilodrostat dose at Week 24 (≤5 mg bid vs. >5 mg bid) and 2) history of pituitary irradiation (yes/no).
Source: Statistical review, figure 1, p.9.

Period 1, dose-titration period
Period 1 was a 12-week, open-label, single-arm period. All patients were started on osilodrostat 2 mg bid; the dose was allowed to be increased based on mUFC results (calculated from 3 samples) every 2 weeks and decreased for safety at any time (see discussion of the regimen below). The goal of titration was to achieve normal mUFC levels.

Period 2, dose-titration and treatment period
Period 2 was also an open-label, single-arm period of another 12 weeks duration.
At the end of this period, those patients who had mUFC < ULN (i.e. at week 24) and the dose of the drug was not increased above that established in Period 1 were defined as 'complete responders' and were randomized in Period 3 (described below). The decrease/interruption in dose for safety reason and subsequent increase in dose to less than that established in Period 1 did not preclude the possibility of being classified as a 'complete responder' at week 24. Those patients who had elevated mUFC in this period were not randomized in Period 3 but continued open-label dose titration and treatment until the end of the Core period of the study. During this period the efficacy of osilodrostat at therapeutic doses determined in Period 1 was assessed (secondary key point; refer to the efficacy results below).

Period 3, RW period
Complete responders at the end of Period 2 were randomized in a 1:1 ratio to osilodrostat or placebo treatment at week 26 (patients remained on the stable dose of osilodrostat during week 24-26 to allow sufficient time to receive lab results from central laboratory). Patients were stratified at randomization according to: osilodrostat dose at Week 24 (≤ 5 mg bid vs. >5 mg bid) and history of pituitary irradiation (yes/no).

Patients who had normal mUFC at week 34 and did not have an increase in the dose of the drug during the RW period were considered complete responders (see discussion of primary endpoint below). Again, similar to Period 2, the decrease/interruption in dose for safety reasons and subsequent increase in dose to the level less than established in Period 2 did not preclude the possibility of complete response at week 34. Patients were to discontinue the RW period if both, mUFC and 2 of 3 individual UFC samples were > 1.5X ULN at a single visit. These patients were considered to be non-responders.

Period 4, open-label treatment
All enrolled patients continued open-label treatment with osilodrostat drug in this period: patients who were not randomized during Period 2, patients who were randomized and completed Period 3, and those patients who were withdrawn during period 3. The titration of the drug for efficacy and/or safety was continued/resumed in this period.

Extension Phase
All patients who completed the 48-week treatment with the study drug in the Core Phase and received clinical benefit as per the Investigator's discretion, entered the optional extension period without drug interruption. The extension period is still ongoing at the time of this review and will end after all patients have completed Week 72 or have been discontinued earlier.

Dosing regimen
As per the protocol, the starting dose was 2 mg BID and was allowed to be increased every 2 weeks to 5 mg, 10 mg, 20, and 30 mg BID based on absolute mUFC values > ULN (calculated from 3 subsequent samples). The dose was allowed to be decreased at any time and by any decrements for safety reasons. There are two major concerns with the dose titration regimen used in the study:

- Aggressive uptitration (every 2 weeks and using large increments) which appeared to result in many patients having symptoms of hypocortisolism

The Sponsor stated that such fast titration using large dose increments was implemented to achieve the normalization of UFCs as soon as possible. However, it should be noted, that even though hypercortisolemia is associated with symptoms of CD, there are no data to date demonstrating a clear relationship between the degree of UFC elevation and symptoms. As such, the magnitude of hypercortisolemia does not always correlate with severity of the disease. Moreover, symptoms of CD can be successfully controlled with other medications including antidiabetic, antihypertensive, etc. medications while hypocortisolemia itself is being controlled.
In addition, because 3 UFC samples collected prior to the next visit were required for dose uptitration, and because of the UFC central laboratory turnaround time and multiple dose changes for safety between UFC collections, the full effect of the last dose escalation was not captured in the next urine collection and the mean duration between dose change and next UFC collection was approximately 8 days (instead of 2 weeks as per protocol; refer to Novartis's response to Information Request (IR) from 10/25/2019).

- Downtitration schedule for safety and subsequent uptitration of the drug was not clearly defined in the protocol.

The dose was allowed to be reduced/interrupted at any time if mUFC was <LLN (even in asymptomatic patients), or if the patient was symptomatic and mUFC was in the lower part of the normal range. The dose decrements for safety and the subsequent dose increments (after resolution of adverse events and for elevated UFC) were not specified in the protocol. It should be also noted that adrenal insufficiency as an adverse event was not clearly defined in the protocol and was mainly based on non-specific symptoms such as nausea, fatigue (that may be due to the rapid decrease in cortisol levels and not due to the low absolute cortisol values and/or to the drug itself) and not on absolute serum cortisol threshold (required criterion for the diagnosis of AI) (refer to safety section below). Of note, only AI is a life-threatening condition that requires prompt interruption of dosing and treatment with glucocorticoids. All other conditions, i.e. "relative hypocortisolism" that are due to the rapid decrease in cortisol and/or fatigue/nausea due to the drug itself, are not-life-threatening conditions (since cortisol values remain within normal range) and are usually self-limiting and/or improve with slower titration.

Thus, because of the above uncertainties, the actual titration scheme implemented in the study was flexible and was ultimately left at the discretion of the Investigator. The actual dose titration schedule during the study conduct used some smaller dose increments, i.e. 1 mg, 2 mg, 3 mg, 5 mg, 7 mg, 10 mg, 15 mg, 20 mg, and 30 mg bid. In addition, some Investigators based their decision to increase the dose not on the absolute UFC values but on the rate of UFC decrease (due to safety issues).

In conclusion, retrospectively, the trial could have benefited from a better structured prespecified titration schedule (e.g., using smaller increments or going slower) allowing more time to respond to the previous dose and the better defined algorithm for up and/or down dose titration based not only on the absolute UFC values but also on the UFC rate of changes and improvement in signs and symptoms of CD to achieve control of the disease and to minimize risk of AI (see safety section).

Primary Efficacy Outcome

The primary efficacy endpoint was assessed at the end of the RW period, Week 34, in the randomized analysis set (RAS) population (defined as all randomized subjects who received at least one dose of randomized drug). The primary endpoint was the proportion of randomized treated patients who were complete responders at the end of the RW period. In order to be categorized as a complete responder, a patient had to meet all of the following conditions:

- mUFC≤ ULN at the end of the RW period
- no dose increase during the RW period above the level established at Week 26. The dose was allowed to be decreased for safety.

Patients who were discontinued during the RW period (refer to the description of the trial design above) or had a missing mUFC assessment at the end of the RW period were considered as nonresponders. If a patient had only one of 3 required UFC collection for particular visit, the mUFC for this visit was considered missing.

Secondary endpoints

The key secondary endpoint was the proportion of patients who were complete responders at the end of the Period 2, the osilodrostat treatment period. A complete responder for this endpoint was defined as an enrolled patient who had mUFC ≤ ULN at Week 24 and had no

dose increase during the Study Period 2 above the level established at the end of Period 1. Dose reductions and temporary dose interruptions for safety reasons did not preclude patients from being complete responders for the key secondary endpoint. Patients with missing mUFC data (as above) at Week 24 were counted as non-responders.

Other secondary endpoints were: time to last control of mUFC during the RW period, the proportion of complete and partial responders (defined as a patient with mUFC decrease by > 50% from baseline) at the end of each period, change from baseline in mUFC during the study, change in cardiovascular-related metabolic parameters, change from baseline in physical features of CD, in bone mineral density, time to escape, change in health related quality of life.

The secondary endpoints were assessed in the full analysis set (FAS) population (defined as all enrolled subjects who received at least one dose of osilodrostat) and in RAS population (randomized and received at least one dose during the RW period) when appropriate.

Efficacy results

Baseline demographic and disease characteristics

The patients' characteristics at enrollment in Study C2301 were generally consistent with those of patients with CD seen routinely in clinical practice. The mean age at baseline was 41.2 years (range 19 to 70 years). 106/137 (77.4%) of all patients were female, consistent with the higher prevalence of CD in women.

For enrolled patients, medical treatment was initiated because of persistence/recurrence of hypercortisolism despite pituitary surgery (i.e. failed pituitary surgery) in 120 (87.6%) patients, and *de novo* CD diagnosis in 17 (12.4%) patients. 22 (16.1%) patients had received radiation to the pituitary in past. The mean baseline mUFC level was 1006 nmol/24h which corresponds to approximately 7x ULN (median mUFC 476.4 nmol/24h; range 35.6-9611.6 nmol/24h) and approximately 33% of patients (45/137) had UFC > 5x ULN.

The demographic and disease characteristics were balanced between the patients who were later randomized to osilodrostat or placebo groups in the RW period: the mean age was 44.3 years in the osilodrostat group and 42 years in the placebo group; 6 patients in the osilodrostat group and 5 patients in the placebo group had previous history of radiation treatment.

Patient disposition and completion rate

A total of 137 patients with CD were enrolled in the study and received at least one dose of osilodrostat. Of these, 72 patients (50%) were responders at the end of Period 2, and 71/72 patients were randomized in the RW period (1 patient was withdrawn between week 24 and 26 due to the Investigator's decision and was not randomized). 70/71 randomized patients received osilodrostat (36 patients) or placebo (34 patients); 1 patient who was randomized to placebo did not receive treatment in the RW period (patient had to interrupt the treatment through the entire RW period due to AI; and was restarted on osilodrostat in Period 4). 66/137 patients were not randomized (65 patients were not responders at the end of Period 2 and one patient was not randomized in RW period-see above), but continued treatment with osilodrostat beyond week 26.

Completion rate in the Core period (week 48) was approximately 82.5% (113/137 patients). 24 patients discontinued the Core Period prematurely; the majority of these patients (19/24 patients) discontinued the study early, prior to week 26. The most common reasons for discontinuation during the Core Period were AEs (15/24 patients; 4 patients discontinued during Period 1, 8 -during period 2, 1- during the RW period, and 2 nonrandomized patients- after week 26). 106/137 patients (77.4%) entered the optional extension period. An additional 11 patients discontinued the study during the Extension Period; 5 of these 11 patients discontinued the study due to AEs.

Primary analysis

Dr. Alexander Cambon reviewed the primary statistical analysis methods used to support the establishment of efficacy. Efficacy findings are also reviewed and discussed in Dr. El-Maouche's review. For detailed discussions of the efficacy findings, see these reviews. My memorandum provides a summary of the main efficacy findings.

The Applicant conducted the primary efficacy analysis in 70 patients who were randomized and received at least one dose of osilodrostat in the RW period (RAS population) using Cochran-Mantel-Haenzel exact test (CMH) stratified by dose at week 24 (> 5 mg bid or ≤5 mg bid) and history of pituitary radiation. As per the Applicant, the study met its primary endpoint: the complete response rate in the osilodrostat group was higher (86.1%) compared to placebo (29.4%), and the results were statistically significant (Table 1).

Dr. Cambon independently verified the Applicant's results for the primary analysis using the sponsor's stratified CMH and confirmed that the primary endpoint of proportion of responders at the end of the RW period demonstrated superiority. The primary efficacy analysis was repeated using Dr. Cambon's preferred method, i.e. the difference of proportions. The analysis still demonstrated superiority, with an overall difference in proportions of 57% (Table 1a). Lastly, a sensitivity analysis was also conducted excluding six patients who had dose increase in Period 2; the odds ratio was still 13.7 with these patients excluded. The response rate was not affected by the stratified dose ((> 5 mg bid or ≤5 mg bid) and history of pituitary radiation and ranged from 83.9% to 100%, based on the randomization stratification factor.

Table 1. Primary and Secondary Endpoint Results-Sponsor's Primary Analysis Method

Endpoint	Exp	Ctrl	OR	LCL	UCL	P-Val
Responder* (mUFC<ULN)	31/36 (86.1%)	10/34 (29.4%)	13.7	3.7	53.4	<.001
Responder ** (mUFC<ULN)	72/137 (52.6%)	NA	NA	43.9%	61.1%	

Table 1a. Primary endpoint results- FDA approach (difference in proportions, using 95% Miettinen-Nurminen)

Responder	Exp	Ctrl	% Diff.	LCL	UCL	P-Val
(mUFC≤ ULN)	31/36 (86.1%)	10/34 (29.4%)	57			
Strat. #1	5/5	1/5	80	18	97	
Strat. #2	17/21	7/21	48	18	69	
Strat. #3	9/10	2/8	65	19	88	

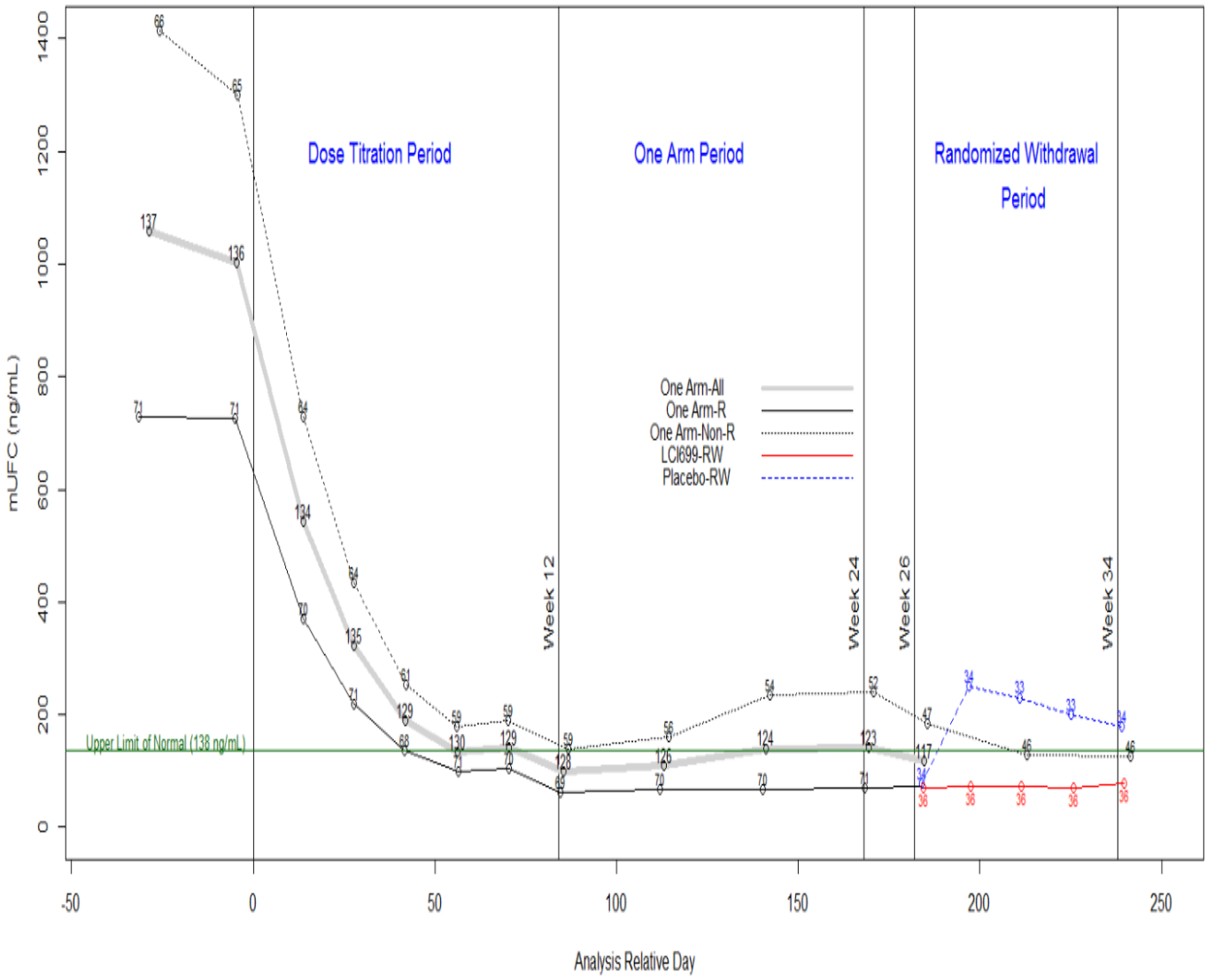
Exp.-Experimental Arm; Ctr.-Control Arm (Placebo); OR-Odds Ratio; P-Val-P-Value; Strat. – Stratification level according to order shown in Table 3; NA- Not applicable (since the secondary endpoint did not include a control arm) *Primary Endpoint; mUFC-mean urinary free cortisol; ULN-Upper Limit of Normal (138 ng/mL); ** Secondary endpoint.; complete responder. Source, biostatistician's review, table 4, modified

Interestingly, approximately 30% of patients randomized to placebo maintained UFC levels within the normal range at the end of RW period, although there was a trend in cortisol level increase. This may be explained by multiple factors including the short duration of the RW period (8 weeks) and prolonged suppression of cortisol synthesis (long biological t1/2 and impaired HPA axis feedback recovery due to the disease itself), and most likely not due to inactive disease (spontaneous improvement in CS is rare, majority of randomized patients, had UFC> ULN at baseline, the use of double blind randomization for the primary endpoint).

Overall, Dr. Cambon agreed that the study met the primary endpoint, and the results demonstrated that osilodrostat is effective in decreasing UFC. However, he also noted that multiple limitations with the study design complicate the overall interpretation of the results. Some of these limitations are: 1) the study "was not designed to directly evaluate the treatment effect in comparison to placebo in treatment-naïve patients (patients that have not already been exposed to the experimental drug). Instead it addresses the question of maintenance: whether the drug should continue to be taken by patients who are still using it after 24 weeks, and what the treatment difference will be if the patients stop treatment after 24 weeks; 2) the primary endpoint was assessed in only 70 (51%) of the 137 patients that were enrolled and treated in the study; 3) the key secondary endpoint lacks a comparator arm by design; 3) the aggressive dose titration (based on absolute UFC values rather than on slope of UFC decrease, use high dose increments, etc.) used in the study may not be reflective of what would be used in clinical practice; 4) the UFC samples were collected shortly after each dosing and measurements did not have time to stabilize before the response to the dose.

Thus, in order to understand the results of the study using the pre-specified titration schedule and in the absence of the comparator arm (see biostatistician's concerns above), Dr. Cambon conducted additional analyses evaluating mean UFC trajectories in different patient groups: all patients with non-missing assessments at each time point, randomized patients in RW period (71 patient), patients who were not randomized (66/137 patients), patients randomized to osilodrostat in the RW period (36 patients) and patients randomized to placebo in RW period (34 patients). The results of this analysis are summarized on Figure 2 and in Table 2 below.

Figure 2: Mean Group mUFC Trajectories during Screening, Dose Titration, One-Arm, and RW Periods



mUFC – mean urinary free cortisol in ng/mL (nanograms per milliliter); RW-Randomized Withdrawal; One-Arm-All – Group consisting of all 137 patients – trajectory shown from screening and dose titration to time of randomization at Week 26; One-Arm-R – this group was not pre-defined at time 0 - this group consists of all patients that ended up being randomized at week 26 (n=71); the mean trajectory for this group is shown up to time of randomization; only 70 of the 71 patients in this group were included in the RW analysis; one patient was randomized but did not receive at least one dose of randomized treatment; One-Arm-Non-R - Group consisting of all 66 patients that ended up not being randomized; LCI699-RWpatients randomized to drug during RW period; Placebo-RW – patients randomized to placebo during RW period; numbers above trajectory lines are the number of patients assessed at the time point.
Source-Biostatistician's review, figure 2.

Table 2: Descriptive Statistics for mUFC by Visit for Dose Titration and One Arm Period

Week	Day	N	Mean	Std. Dev.	% Not Missing
-4	-29	137	1059	1903	100%
-1	-5	136	1001	1595	99.3%
2	14	134	542	754	97.8%
4	28	135	322	446	98.5%
6	42	129	191	267	94.2%
8	56	130	134	171	94.9%
10	70	129	143	270	94.2%
12	85	128	98	120	93.4%
16	113	126	109	125	92.0%
20	141	124	141	235	90.5%
24	169	123	143	292	89.8%
26	185	117	118	205	85.4%

N – number of patients with assessments for the week; St. Dev. – standard deviation.
Source: biostatistician's review, table 5.

This analysis demonstrated that there was a steep drop in UFC over time in all groups of patients, randomized and non-randomized, responders and non-responders. Moreover, Dr. Cambon's analysis also demonstrated that the decrease in mUFCs was consistent across patients with various severity of the disease at baseline: even though the nonrandomized group had higher baseline mUFCs (1414 ng/ml) compared to randomized group, the average mUFC decrease for the nonrandomized group was 139 mg/mL at week 12, just over the ULN.

Secondary analyses

I will discuss results of some secondary and exploratory analyses conducted in the FAS population, mainly those that provide evidence of the efficacy of the drug in all drug-naïve patients and those that were supportive of the primary analysis. The FAS population represents the population that will use the drug in clinical practice. However, the results of these analyses should be interpreted with caution due to the absence of the comparator arm. For discussion of the results of all secondary analyses, refer to Drs. Cambon and Dr. El-Maouche.

Lastly, the results of secondary/exploratory analyses in the RAS population and/or conducted in the RW period will not be discussed in this memorandum, since these results do not provide useful insight regarding efficacy of the drug in all patients with CD due to the multiple study limitations discussed above (e.g., a preselected and small population, and a short duration of treatment of 8 weeks).

Key secondary endpoint

The key secondary endpoint, the proportion of complete responders at week 24, was significant, with 72 of 137 (52.6%; 95% CI: 43.9, 61.1) patients meeting the definition for complete responder (Table 1). The 95% lower confidence limit was greater than 30%, which met the pre-specified criteria. The results of this analysis are important (even in the absence of

the comparator arm) since they demonstrate the efficacy of the drug in patients who are naïve to osilodrostat without any insight as to whether the patient will be a responder to osilodrostat or not (i.e. how the drug will be used in clinical practice).

Other secondary endpoints

- Change in cortisol levels (mUFC and serum cortisol) during the study

The median mUFC levels declined relative to baseline (476 nmol/24h) in all patient groups, randomized and non-randomized at weeks 12 (62.5 nmol/24h), 24 (75.5 nmol/24h), and 48 (63.3 nmol/24h), respectively. These results are consistent with the results obtained by Dr. Cambon as described above. These changes were accompanied by a reduction in serum cortisol levels.

- Proportion of complete and partial responders (defined as a patient with mUFC decrease by > 50% from baseline) at the end of each period

Patients responded quickly to osilodrostat treatment: at Week 8: 68.6% of patients (94/137) had normalization of UFCs and 16.8% (23/137) had decrease in UFC > 50%. The median time to first controlled mUFC response was 41 days and was similar in randomized and nonrandomized patients. At week 12, 71.5% of patients (98/137) had mUFC ≤ ULN and 13.9% (19/137) had decrease in mUFC by > 50%. The proportion of the responders remained relatively constant by the end of the Core Period, and the majority of patients had normalization or at least reduction in mUFC by 50% by the end of the Core Period (91/137 (66.4%) patients had normal mUFC and 13/137 (9.5%) had decrease in mUFC by > 50%, respectively).

Although all these analyses are conducted without a comparator, they provide compelling evidence that the drug is effective in all treatment-naive patients treated with osilodrostat for 12 months as evident by the substantial number of patients who had normal or decreased mUFC at each prespecified timepoint and that the response rate is generally maintained over time. As noted above, spontaneous remission is unexpected.

- Change in cardiovascular-related metabolic parameters

Improvements in cardio-metabolic parameters in patients with CD were also seen during the study: decrease in systolic (by 4% at week 24 and by 7% at week 48) and diastolic (by 4% and 6.6%, respectively) blood pressure, decrease in weight (by 3% at week 24 and 4.6% at week 48, respectively), decrease in BMI, waist circumference, fasting glucose and HbA1C.

Although the improvement in BP and glucose control may be due to the changes in antihypertensive and antidiabetic medications, the Applicant indicated that the changes in BP from baseline were analyzed with and without adjustment for increased usage in corrective medications.

To evaluate further clinically relevant HbA1C changes, the Applicant was asked to analyze changes in HbA1C in patients with a history of DM separately. The applicant identified 48 subjects with DM enrolled in the study (the Applicant's response to the Agency's IR from 9/24/2019). The mean baseline HbA1C value was 6.9% in these subjects and decreased to 6% at week 12; mean HBA1C was 6% at week 24. However, this subgroup analysis is a post-hoc analysis in a small group of patients without the controlled arm and needs to be interpreted with caution.

- Change from baseline in physical features of CD

Study subjects also reported improvements in physical signs related to cortisol excess by the end of the Core Period, including facial rubor (improved in 46% of patients), supraclavicular

fat (51% of patients), dorsal fat (52% of patients), striae (32% of patients), bruising (35% of patients), muscle wasting (38% of patients), and hirsutism in women (34% of female patients); both randomized and non-randomized patients reported similar improvements in physical signs of hypercortisolemia. However, interpretability of these results is complicated due to the subjective nature of the assessment.

- Improvement in Cushing QoL scores was also observed during the treatment with osilodrostat. Of note, none of the PRO questionnaires have been validated for patients with CD by the Agency's Clinical Outcomes Assessment (COA) committee to date, which limits interpretability of these data and does not allow for any labeling claims based on the PRO data.

Overall, the improvements in other signs and symptoms of CD occurred concurrently with decreasing mUFC levels as expected (improvement in hypercortisolemia leads ultimately to the improvement in cortisol-induced signs and symptoms of CD).

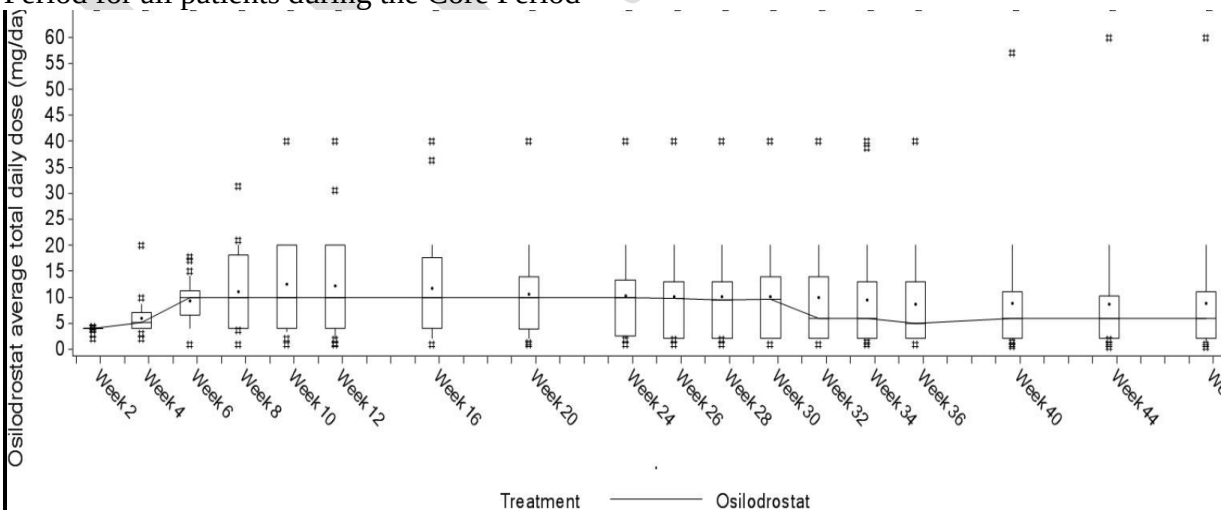
Dose-response

Dr. El-Maouche concluded that the proposed starting dose of 2 mg bid and maximum dose of 30 mg bid are acceptable. I agree with this assessment.

It should be noted that the overall conclusion regarding the predictability of reducing of cortisol levels in patients with CD based on osilodrostat exposure is complicated since the dose titration scheme implemented in the study was affected by cortisol levels. Indeed, because of the patient's individual and unpredictable response to the drug, the titration in the study resulted in use of wide range of dose/ dose increments during the study, ranging from 1-2 mg to the increments pre-specified in the protocol (i.e., to 5, 10,15 and 20 mg) with no discernable pattern in the study.

The average doses required by patient at each visit are depicted below (Figure 3).

Figure 3. Box plot of osilodrostat average total daily dose (mg/day) by visit during the Core Period for all patients during the Core Period



#-outliers. Source, Applicant's figure 12-1, CSR study C2302.

As evident from this figure and the table below (Table 3), the majority of patients required doses ≤ 30 mg. The mean dose at which the subject spent the longest time was 10.6 mg/day. The average dose used in the study was 2 mg - 7 mg bid and the most frequently received daily dose was also in the range of 4 to 6 mg. However, some patients required higher doses to normalize mUFC, > 30 mg/day, and 1 patient at week 12, 2 patients at week 24, and 2 patients at week 48 required doses ≥ 20-30 mg bid.

Table 3. Number of patients (n) with normal mUFC at the end of each visit by dose level

Total daily dose, mg	0-2	>2- 4	>4-6	>8-10	>10-20	>20-30	>30
Week 12, n (N=130)	19	14	10	18	27	0	10
Week 24 (N=125)	19	14	11	1	16	21	9
Week 48 (N=113)	27	14	10	1	10	22	7

N= number of patients remained on the treatment at the end of the period; mUFC at the time of last collection for the visit
Source" Applicant's table from the response to IR from 8/9/2019, modified.

Additional analysis: impact of the severity of the disease on the response rate
It was hypothesized that patients with more severe disease at baseline might be more resistant to treatment and may require a different titration scheme to respond to the drug (e.g. require higher doses or longer titration to achieve the response). In addition, it was noted that patients who responded to the drug earlier (at week 24 and were randomized in RW period) had lower mean mUFC at baseline (890 nmol/24 h and 560 nmol/24h, in osilodrostat and placebo groups, respectively) compared to mUFC of patients who were not randomized and responded to the drug later, after week 26 (1006 nmol/24h). Thus, the Applicant conducted an additional post hoc analysis with regard to dose and severity of mUFC elevation at baseline.

Although the results of this analysis provide some insight regarding how patients with different severity of the disease respond to the treatment with osilodrostat, the results of these analyses should be interpreted with caution and should not be included in the label since the study overall was not designed to evaluate the difference in the response rate in these patient subgroups and this subgroup analysis was not prespecified, the subgroups were small and not balanced by other demographic and disease characteristics.

The Applicant compared the response rates between three group of patients with different disease severity at baseline (mUFC <2XULN, 2-5 XULN, > 5 ULN). There was no evidence that patients with higher mUFC at baseline require higher osilodrostat dose. Patients with more severe disease also responded to the low to average doses during the study: at the end of Week 12 and week 24 the majority of patient were on doses < 10 mg bid regardless of baseline UFC values (89-94% at week 12, and 90-100% at week 24). However, as evident from Table 3, patients with more severe disease at baseline may require longer titration to achieve normalization of mUFC. More patients with lower mUFC at baseline responded to the drug

earlier, at week 12-24 (Table 4). At week 12 and 24, there were more responders among patients with mUFC < 5X ULN (73%-84%) compared to the group of patients with higher mUFC (50-60% responders), however, at week 48 the majority of patients in each group had normal mUFC at the end of this period.

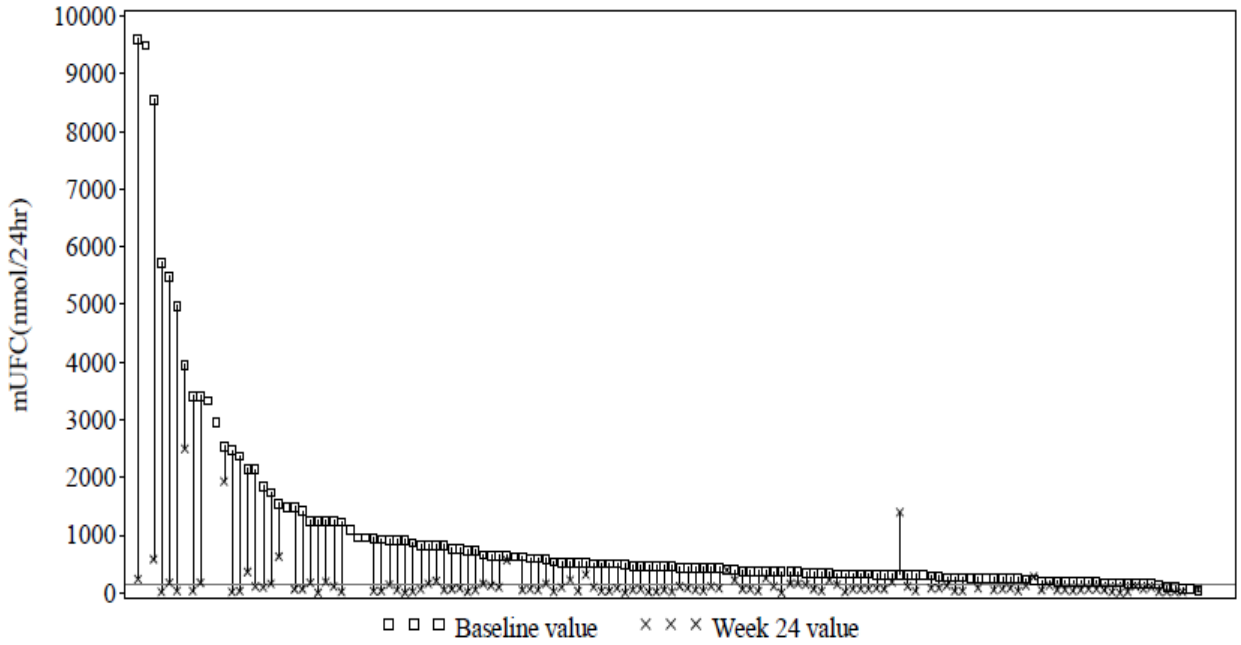
Table 5. Number of patients with normal mUFC in each subgroup by UFC elevation at the end of each study period, FAS population (137 patients)

mUFC	< 2 x ULN	2-5 X ULN	> 5 XULN
N, baseline (n=137)	32	60	45
N, Week 12	26 (84%)	44 (73%)	28 (62%)
N, Week 24	27 (84%)	43 (73%)	23 (51%)
N, Week 48	23 (72%)	39 (65%)	45 (100%)

N=number of patients, Source, Applicant's table 4.2-1.7, CSR, modified.

Lastly, it is also important to note that UFC decreased from baseline in the majority of patients regardless of the disease severity at baseline (Figure 4).

Figure 4. Individual patient mUFC values at baseline and Week 48 (FAS)



□ -baseline values, X- Week 48 values.
Source: Applicant's SCE, figure 5-1.

Durability of the response

As demonstrated in the single arm, open-label extension period of study C2301, at the last available assessment, 88.3% of patients had improvement in hypercortisolemia: 98/137 patients had normal UFC and 23/137 patients had UFC decreased by > 50% from baseline. Although data from extension trials provide some evidence of persistence of the osilodrostat effect beyond 1st year of treatment, the quantitative efficacy data obtained from such an open-

label, uncontrolled trial should not be used for labeling because by the very nature of its design, the trial selected a patient population likely to have benefited from the drug, and a control group is lacking.

Efficacy conclusions

In their totality, the efficacy analyses conducted in study C2301 demonstrated that osilodrostat effectively decreased and ultimately normalized UFC levels in all patients with CD in the trial. The primary efficacy analysis met its prespecified goal and demonstrated that 80% of patients who responded to osilodrostat during first 24 weeks of treatment, maintained normal mUFC levels for 8 weeks in the RW period. The primary analysis confirmed that osilodrostat was superior to placebo in controlling of mUFC, the UFC lowering effect was attributable to the drug itself and not to the other factors such as inactive disease, cyclic CS, etc. (as demonstrated by significant difference in the proportion of responders in active drug and placebo groups). In general, spontaneous improvement in hypercortisolemia is not expected in CD patients enrolled in this trial, nor can the results be attributed to previously received pituitary radiation therapy (since patients were stratified according to status of previous radiation treatment) and, very importantly, ACTH levels remained high during the trial (the expectation would be that, if radiation therapy were to be effective, ACTH secretion would diminish). Finally, Study C2301 did not enroll patients with cyclic Cushing's syndrome or pseudo-Cushing's syndrome, and the clinical diagnosis and descriptions of the patients enrolled did not match any of these conditions.

Importantly, the results of the key secondary analysis demonstrated that osilodrostat was effective in patients without any insight into whether these patients will be responders to the drug and normalized UFCs in approximately 52% of all treatment-naïve patients after 6 months of treatment.

The other secondary analyses were supportive of efficacy of osilodrostat for the proposed indication. A decrease in the mean mUFC in all patients regardless of the disease severity at baseline was observed during the study; changes in serum cortisol and salivary cortisol were consistent with UFC changes.

Patients generally responded quickly to osilodrostat: at Week 8: 68.6% of patients (94/137) had normalization of UFCs and 16.8% (23/137) had decrease in UFC > 50%. There was a substantial proportion of patients who had normal or decreased mUFCs at each prespecified timepoint (at 12, 24 and 48 weeks). The proportion of responders remained relatively constant by the end of the Core Period: 66.4% of patients had mUFC in the normal range. There was no evidence that patients with higher mUFC at baseline do not respond to treatment with osilodrostat or require higher doses; the majority of patients with more severe disease required doses < 10 mg bid. However, it seems that patients with higher UFC at baseline may require longer titration time to achieve treatment goals.
The trend toward the improvement in signs and symptoms of CD (blood pressure, body composition measures, glucose parameters, physical signs of CD) and quality of life measures were observed during the study. Although interpretability of these secondary and exploratory outcome data is difficult in a non-controlled study using several subjective measures, these

data provide further support for the efficacy of osilodrostat in the CD population but are not rigorous enough to support labeling claims.

Lastly, mechanistical rationale (the drug blocks cortisol synthesis) supports the observed efficacy of osilodrostat in patients with CD to control hypercortisolemia.

However, I also agree with Dr. Cambon's conclusion that the magnitude of the effect observed in the open-label, single arm periods of the study may not reflect the magnitude of the effect that will be seen in clinical practice in all treatment-naïve patients. In addition, the use of a randomized-withdrawal phase is not reflective of how the product will be used in clinical practice; in clinical practice, prescribers will offer the product to patients who are naïve to osilodrostat without any insight as to whether the patient will be a responder to osilodrostat or not. Thus, the efficacy estimate with use of a randomized-withdrawal phase might be overestimated in treatment-naïve patients. For these reasons, I agree with Dr. Cambon's recommendations that the efficacy results for study C2301 should be presented descriptively in Section 14 of the label due to the study limitations discussed in this section.

Supportive evidence of effectiveness of osilodrostat in patients with CD from study C2201

Study C2201 is a multicenter, single-arm, proof of concept study that evaluated efficacy and safety of a forced titration of osilodrostat (2 mg bid starting dose with titration every 2 weeks up to maximum of 30 mg bid) in adult patients with CD. The study consists of two parts: Part I and Part II. Part I evaluated safety and efficacy of osilodrostat in 12 patients treated for 10 weeks followed by 14- day washout period. Part II was initially designed as a 12-week study; however, the study was extended later and is still ongoing (data cut-off date is 11/14/2017). A total of 19 patients were enrolled in Part II: 4 patients who completed Part I (follow-up cohort) and 15 newly enrolled patients (expansion cohort). The same titration regimen that was used in study C2301 was also used in both parts of this study. Patients were started on 2 mg bid; the dose was allowed to be increased every 2 weeks to 5, 10, 15, 20 and 30 mg bid based on the mean of three 24-hour urinary free cortisol collections (mUFC). The dose was allowed to be decreased or discontinued for safety at any time during the study.

The patients' characteristics at enrollment in Study C2201 Parts I and II were similar to those of patients enrolled in pivotal study C2301. In Part I, the mean age at baseline was 39 years. 69% of all patients were female, and mean mUFC was 390 nmol/24h. In Part II, the mean age was 37 years, and mean mUFC was 1630 nmol/24h (median 387 nmol/24h) in the expansion cohort, and 398 nmol/24h in the follow-up cohort (median 454 nmol/24h). All 12 patients completed Part I. Of the 19 patients enrolled in Part II, 17/19 patients completed initial 12-week treatment, 16/19 (84%) of patients continued into the extension period of Part II (1 subject discontinued due to AE), and 10/19 patients are still on treatment (2/16 subjects in the extension phase discontinued due to AEs).

Overall, this study has provided proof that osilodrostat in doses 2-30 mg bid can normalize mUFC. This observation was made at the end of the 10-week treatment period with osilodrostat in 9/12 (75%) of patients that participated in the Part 1 study (3/12 patients were excluded from the analysis because of single UFC collection). In Part II, the response rate (%

of patients with mUFC< ULN at the end of 12-week treatment) was consistent with the response rate observed in the Part I study: 80% in treatment naïve patients (12/15 patients) and 75% in previously treated patients (3/4 patients).

In conclusion, the efficacy results from study C2201were consistent with the efficacy results observed in the pivotal study C2301, providing additional evidence that osilodrostat is effective in reducing UFC from baseline in patients with CD.

8. Safety

The primary safety data in support of the proposed indication of osilodrostat in patients with CD is derived from the pivotal study C2301. Supportive safety data is provided from the Phase 2 study, C2201 (mainly from Part II because of the long exposure to the drug; up to the data cutoff date of 11/14/2017). The Applicant also provided additional safety data in patients with CD from the ongoing Phase 3 study C2302 (up to cut-off date 8/30/2018) and the C1201 Study in Japanese patients with CS (up to the data cut-off date of 6/7/2018). It should be noted that the two last studies provide only limited data on the safety of the product in patients with CD, since study C2302 is still ongoing and blinded, and study C1201 is small (9 patients) and conducted in a different patient population: patients with non-pituitary CS. Lastly, the Applicant included the results of the TQT study (discussed in the Clinical Pharmacology section above), and from the Phase 1 drug-drug interaction study in healthy females, C2108 (to evaluate the risk of cortisol suppression).

This memorandum will focus on the safety observations made in the pivotal study, C2301, Findings from study C2201 (mostly from Part II) will be summarized only briefly and as needed. The additional sources will be mentioned only when relevant. It should be mentioned that, to a large extent, the adverse reaction profile of osilodrostat can be anticipated from its mechanism of action (e.g., hypocortisolism-rated AEs, AEs due to increase in adrenal precursors) and nonclinical findings (e.g., embryo-fetal toxicity).

This memorandum will discuss safety findings that occurred in the study C2301 in all patients regardless of the group assignment in the RW period. The Applicant's original submission included some safety analysis that excluded AEs that occurred in patients during placebo treatment in the RW period. However, all patients were exposed to the drug during the first 24-week open-label, single-arm period. In addition, the duration of the RW period was short - 8 weeks, with a potential carry-over effect from the previous osilodrostat treatment. Thus, all AEs observed in the placebo group during the withdrawal period can still be drug-induced and it is not possible to make a safety comparison between treated subjects and treatment naïve-subjects due to the study design. Therefore, the Applicant was asked to submit all safety data that occurred in all patients (including patients who were on placebo during RW period) during treatment with osilodrostat in study C2301 (refer to the Applicant's response to the Agency's IRs from 7/9/2019 and 1/8/20).
In addition, this memorandum will focus on AEs that occurred in the safety analysis set (SAS) population that comprises all of the enrolled patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment. The AEs that occurred in the safety analysis set for the RW Period (SASR) population (only randomized patients who received at least one dose of the randomized treatment (osilodrostat or placebo)) will not be discussed separately.

Overall exposure

In the overall clinical program of osilodrostat, more than 1000 subjects received at least one dose of osilodrostat (patients with CD, with CS, with hypertension and healthy volunteers). Of these subjects, 156 patients with CD received at least 1 dose of osilodrostat in 2 long-term studies (C2301-137 patients and C2201, Part II- 19 patients); 107/156 patients received the drug for > 12 months, and 17/156 patients received treatment for > 36 months.

In study C2301, the overall median duration of exposure to osilodrostat was 74.7 weeks (range: 0.9 to 165.3 weeks); 137 patients received at least one dose of the study drug, 118 patients received the drug for > 6 months, 92 patients received the drug for > 12 months and 65 patients received the drug for > 36 months. The most frequently received daily dose was in the range of 4 to 6 mg, the mean dose at which subjects spent the longest time was 10.6 mg/day, with the mean highest dose of 18.4 mg/day.

In study C2201, Part II, median duration of exposure was 226 weeks; the mean daily dose was 12 mg/day.

Overall, the level of exposure is adequate for a chronically administered drug in the orphan population of patients with CD.

Major safety results

Death

There was one death in study C2301 not related to the study drug. The narrative was reviewed. Briefly, this patient was 55-year old female with CD who committed suicide in the extension period of the study. I agree with the Applicant's conclusion that the death was most likely unrelated to the study drug (the last dose was 1 mg bid, patient's last UFC was normal 72.5 nmol/day), and most likely related to underlying and poorly controlled psychiatric disorders (anxiety, depression, panic disorder).

Nonfatal SAEs

In the Core Phase of study C2301, 35/137 (25.5%) of patients experienced 69 SAEs. As expected, the highest rate of SAEs was observed during dose titration Period 1: 16/137 patients developed 32 SAEs (11.7%); 13 patients in Period 2 (10%) developed 19 SAEs and 7 patients in period 4 developed 19 SAEs. The lowest rate of SAEs was observed in the RW period (3 patients;, however, only pre-selected patients who tolerated the drug in the previous two periods and responded to the treatment were enrolled in this period and this period was only of 8-week duration, thus this low rate of SAEs is not informative. SAEs were most frequently observed in Endocrine Disorders, Infections and Infestations, and Neoplasms (SOC). The most frequent SAEs by PT were AI (a total of 9 subjects: AI- 6 subjects, glucocorticoid deficiency-2 subject and AI acute- 1 subject) followed by pituitary tumor (a total of 4 patients: pituitary tumor -2 patients and pituitary tumor benign 2 patients), cholelithiasis, gastroenteritis, and influenza (in 2 patients, each). All other SAEs occurred in 1 patient each.
Frequencies for all SAEs that occurred in the Core Period are summarized below.

Table 6. SAEs by SOC, PT and periods of the study, Core Period.

System Organ Class/ Preferred Term	Period 1 (N=137) n (%)	Period 2 (N=130) n (%)	Period 3, randomized patients (N=70) n (%)	Period 3, non-randomized patients (N=47) n (%)	Period 4 (N=116) n (%)	Entire Core Study (N=137) n (%)
Blood and lymphatic system disorders	1 (0.7)	1 (0.8)	1* (2.8)			3 (2.2)
Anemia#		1 (0.8)				1 (0.7)
Lymphadenopathy	1 (0.7)					1 (0.7)
Neutropenia#			1* (2.8)			1 (0.7)
Endocrine disorders	5 (3.6)	5 (3.8)			1 (0.9)	10 (8)
AI#	3 (2.2)	2 (1.5)-3 events			1 (0.9)	6 (4.4)
Glucocorticoid deficiency#	2 (1.5)	1 (0.8)				2 (1.5)
AI acute#		1 (0.8)				1 (0.7)
Pituitary dependent Cushing's syndrome		1 (0.8)				1 (0.7)
Eye disorders	1 (0.7)					1 (0.7)
Visual Impairment[1]	1 (0.7)					1 (0.7)
Gastrointestinal disorders	2 (1.5)	1 (0.8)				3 (2.2)
Abdominal pain		1 (0.8)				1 (0.7)
Nausea	1 (0.7)					1 (0.7)
Vomiting	1 (0.7)					1 (0.7)
General disorders and administration site conditions (occurred in a single patient)	1 (0.7)					1 (0.7)
Chills	1 (0.7)					1 (0.7)
Pain	1 (0.7)					1 (0.7)
Pyrexia	1 (0.7)					1 (0.7)
Hepatobiliary disorders	1 (0.7)	1* (2.8)				3 (2.2)
Cholelithiasis		1* (2.8)-2 events				2 (1.5)
Cholecystitis**						1 (0.7)^

Immune system disorders	1 (0.7)					1 (0.7)
Anaphylactic shock[2]	1 (0.7)					
Infections and infestations	4 (2.9)	2 (1.5)			1 (0.9)	6 (4.4)
Gastroenteritis	1 (0.7)				1 (0.9)	2 (1.5)
Influenza	1 (0.7)	1 (0.8)				2 (1.5)
Cellulitis	1 (0.7)					1 (0.7)
Pneumonia	1 (0.7)					1 (0.7)
Urinary tract infection		1 (0.8)				1 (0.7)
Injury, poisoning and procedural complications	1 (0.7)					1 (0.7)
Overdose	1 (0.7)					1 (0.7)
Investigations	2 (1.5)		1 (2.9)			3 (2.2)
Blood corticotrophin increased			1 (2.9)			1 (0.7)
Hemoglobin decreased[#]	1 (0.7)					1 (0.7)
Transaminase increased	1 (0.7)					1 (0.7)
Metabolism and nutrition disorders	1 (0.7)	2 (1.5)				3 (2.2)
Decreased appetite	1 (0.7)					1 (0.7)
Dehydration	1 (0.7)					1 (0.7)
Hypercalcemia		1 (0.8)				1 (0.7)
Hypokalemia[#]		1 (0.8)				1 (0.7)
Musculoskeletal and connective tissue disorders	1 (0.7)					1 (0.7)
Groin pain	1 (0.7)					1 (0.7)
Pain in extremity	1 (0.7)					1 (0.7)
Neoplasm benign, malignant and unspecified		2 (1.5)		1 (2.1)	2 (1.7)	5 (3.6)
Pituitary tumor[#]				1 (2.1)	1 (0.9)	2 (1.5)
Pituitary tumor benign[#]		1 (0.8)			1 (0.9)	2 (1.5)
Malignant pituitary tumor[#]		1 (0.8)				1 (0.7)
Nervous system disorders	2 (1.5)			1 (2.1)	1 (0.9)	4 (2.9)
Cranial nerve disorders[3]					1 (0.9)	1 (0.7)
Migraine	1 (0.7)					1 (0.7)

Syncope#	1 (0.7)					1 (0.7)
6th nerve paralysis#				1 (2.1)		1 (0.7)
Psychiatric disorders		2 (1.5)			1 (0.9)	3 (2.2)
Anxiety		1 (0.8)			1 (0.9)	2 (1.5)
Depression		1 (0.8)				1 (0.7)
Renal and urinary disorders					1 (0.9)	1 (0.7)
Cystitis granularis					1 (0.9)	1 (0.7)
Reproductive system and breast disorders					1 (0.9)	2 (1.5)
Metrorrhagia					1 (0.9)-2 events	1 (0.7)
Vaginal hemorrhage		1 (0.8)				1 (0.7)
Respiratory, thoracic and mediastinal disorders	1 (0.7)-2 events	2 (1.5)		2 (4.3)		4 (2.9)
Cough	1 (0.7)					1 (0.7)
Dyspnea	1 (0.7)					1 (0.7)
Epistaxis				1 (2.1)		1 (0.7)
Pulmonary edema		1 (0.8)				1 (0.7)
Respiratory disorders		1 (0.8)				1 (0.7)
Vocal cord polyp				1 (2.1)		1 (0.7)
Skin and subcutaneous tissue disorders	2 (1.5)					2 (1.5)
Hidradenitis	1 (0.7)					1 (0.7)
Urticaria	1 (0.7)					1 (0.7)
Vascular disorders	1 (0.7)					1 (0.7)
Venous thrombosis	1 (0.7)					1 (0.7)

Source: The Applicant's response to Agency's IR from 7/9/2019. SAEs that occurred in > 1 subject are highlighted in yellow.
*Patient on active drug during RW period; ^The event occurred during period 3 in patient who was randomized to placebo but did not receive any placebo, therefore not included in safety set for period 3. This patient was withdrawn from period 3 due to non-serious AI, but restarted treatment in period 4.
**Patient had normal LFTs
#Adverse events discussed in respective sections below.
[1]Visual impairment was most likely not pituitary tumor-related due to short duration of treatment (6 days) and stable tumor size on follow-up MRI
[2] The narratives were reviewed: the anaphylactic shock was due to use of antibiotics
[3] SAEs of cranial nerve disorder was not related to the study drug and was most likely caused by viral infection.

An additional 15 subjects in the extension period of study C2301 experienced SAEs: acute kidney injury and acute AI occurred in 2 subjects, each; all others SAEs occurred in 1 subject each (pneumonia, 6th cranial nerve paralysis, autoimmune neutropenia, completed suicide, foot

deformity, headache, head injury, influenza like illness, metastasis to liver, non-cardiac chest pain, acute pancreatitis, respiratory failure, uterine polyp, seizure, suicidal ideation, tumor invasion).

In study C2201, 1 subject experienced 4 SAEs (hemoglobin decrease, tachycardia, palpitations and chest pain) in Part I and 5 subjects experienced SAEs in Part II, up to data cut-off date: pituitary dependent CS in 2 patients; AI, gastroenteritis, and pituitary tumor benign in 1 patient, each up to data cutoff date.

Overall, these AEs are common in patients with CD and the majority of the events are due to the mechanism of action (e.g., adrenal insufficiency), or the disease itself (e.g., pituitary tumor, venous thrombosis, infections).

AEs leading to Discontinuations

Eighteen of 137 subjects (13.1%) discontinued C2301 study prematurely due to the AEs; the majority of these subjects discontinued the study within the first 26 weeks (15 subjects). The most frequent AEs that led to study discontinuation were in Endocrine disorders SOC (adrenal insufficiency- 4 patients) and Neoplasms benign, malignant SOC (pituitary tumor-related AEs- 6 patients). Other AEs that led to study discontinuation occurred in one patient each: visual impairment, asthenia, fatigue, BP diastolic increase, BP systolic increase, hypokalemia, pain in extremity, headache, paresis cranial nerve, 6th nerve paralysis, rash.

Three subjects in study C2201 discounted the study due to AEs: 1 patient due to pituitary tumor benign (microadenoma), 1 patient due to papule, diarrhea, muscular weakness, malaise, nausea, and 1 patient due to neoplasm progression (pituitary tumor), blood corticotroph increased.

Common AEs

The observed types of AEs were similar across the two clinical studies, C2301, the Core Period and C2201, Part II, with nausea, headache, insomnia, adrenal insufficiency, fatigue, vomiting and nasopharyngitis being the most frequent AEs in both studies. By SOC, gastrointestinal disorders were the most frequently reported AE in both studies (60% in each study) followed by infections and infestations (58% and 73%, respectively), general disorders and administrative conditions (60% and 79%, respectively), investigations (44% and 89%), musculoskeletal and connective tissue disorders (47% and 68%, respectively), nervous system disorders (49% and 63%, respectively), skin and subcutaneous tissue disorders (50% and 63%, respectively), endocrine disorders (43% and 47%, respectively). There was no trend of increasing frequency in AEs based on the data from the extension phase of study C2301 up to data cutoff date and from the 120-day safety update.

The common AEs that occurred in the pivotal study C2301, the Core Phase are briefly summarized below. In the Core Phase, all subjects experienced at least one AE (Table 6).

Table 6. AEs by PT that occurred in > 5% of patients in Core Period, study C2301, Safety Set (137 patients).

Preferred Terms	**N (%)**
Nausea	51 (37.2)
Headache	42 (30.7)
Insomnia	36 (26.3)
Adrenal insufficiency	33 (24.1)
Fatigue	33 (24.1)
Vomiting	27 (19.7)
Nasopharyngitis	27 (19.7)
Arthralgia	24 (17.5)
Glucocorticoid deficiency	22 (16.1)
Oedema peripheral	21 (15.3)
Back pain	21 (15.3)
Blood corticotropin increased	20 (14.6)
Diarrhea	20 (14.6)
Asthenia	20 (14.6)
Dizziness	19 (13.9)
Hormone level abnormal	17 (12.4)
Rash	17 (12.4)
Myalgia	17 (12.4)
Urinary tract infection	16 (11.7)
Decreased appetite	16 (11.7)
Pyrexia	15 (10.9)
Hypokalemia	15 (10.9)
Anemia	14 (10.2)
Cough	14 (10.2)
Influenza	14 (10.2)
Hypertension	14 (10.2)
Blood testosterone increased	14 (10.2)
Abdominal pain	12 (8.8)
Acne	12 (8.8)
Hirsutism	12 (8.8)
Hypotension	12 (8.8)
Dyspepsia	11 (8)
Pain in extremity	11 (8)
Insomnia	11 (8)
Gastroenteritis	10 (7.3)
Anxiety	10 (7.3)
Dry skin	10 (7.3)

Abdominal pain upper	9 (6.6)
Malaise	9 (6.6)
Edema	9 (6.6)
Depression	9 (6.6)
Rhinorrhea	8 (5.8)
Alopecia	8 (5.8)
Upper respiratory tract infection	7 (5.1)
Contusion	7 (5.1)
Cortisol free urine decrease	7 (5.1)
Muscle spasm	7 (5.1)
Hyperhidrosis	7 (5.1)
Pruritus	7 (5.1)

Source: Applicant's Table HA3-Q12_1, Response to Agency's IR from1/7/2020, modified.
AEs are ranked by frequency, with the most frequent reactions listed first.

Other notable AEs which occurred with a frequency less than 5% were: ALT increase, AST increase (4 patients, each); steroid withdrawal, BP diastolic increase, BP increase. BP diastolic increase (2 patients, each), neutropenia, neutrophilia, hyperandrogenisms, generalized edema, localized edema, hepatic functions abnormal, androstenedione, potassium decrease, testosterone abnormal, Hb decrease, LFTs abnormal, neutrophil count decrease, oxycorticosteriods increase (in 1 patient each).

No AEs of tumors other than pituitary tumors were reported in any of the studies (refer to nonclinical section regarding carcinogenicity findings)

Clearly, a number of these would be expected in patients with CD; however, a lack of comparator for this analysis limits overall conclusions about AEs and also limits an analysis of AEs as related to dose. Since all patients were exposed to the drug, I recommend including in labeling all AEs that occurred in the study regardless group assignment in the RW period and that were reported in more than 10 % of subjects.

Analyses of Submission-specific safety issues (AESI)

A total of five AEs of special interest were analyzed. They were intended to capture events based on osilodrostat mechanism of action or observed in nonclinical program. Some of these AEs are already reviewed by Dr. El-Maouche in her review, others are summarized below.

The majority of patients developed these AEs during the first 26 weeks of the study (79/92 patients with AESI).

Hypocortisolism-related AEs.

Hypocortisolism-related AEs including AI are well-known safety issues with all steroidogenesis inhibitors and are based on their mechanism of action. Osilodrostat suppresses cortisol synthesis, thus, these events are anticipated with its use.

It is important to recognize that the diagnosis of adrenal insufficiency in patients with CD is complicated. In general, patients who are treated for CD may experience two types of hypocortisolism- related AEs. The first hypocortisolism-related adverse event is the true serious event of AI. AI is a life-threatening condition and is associated with such serious symptoms as hypotension, electrolyte disturbances, dehydration, loss of consciousness and ultimately death if left unrecognized and untreated. This condition is usually characterized by low absolute cortisol levels. The treatment is immediate discontinuation of the drug and treatment with glucocorticoids. The second AE is better described as "relative AI" and is due to the fact that most patients with hypercortisolemia poorly tolerate low normal levels of cortisol or rapid decrease in cortisol levels (rather than due to low absolute cortisol levels). The signs and symptoms associated with rapid decrease in cortisol levels are similar to symptoms of true AI (e.g., nausea, vomiting, fatigue); however, this condition is non-life-threatening because the absolute levels of cortisol remain within normal limits. This condition is usually self-limiting or require dose decrease/interruption; treatment with glucocorticoids is rarely required. Thus, due to the non-specific symptoms of both conditions (these symptoms may also be due to the drug itself, to uncontrolled CD itself or to underlying medical conditions/ concomitant drugs), serum cortisol levels are universally required for the diagnosis of AI.

Thus, Endocrine Society treatment guidelines[11] recommend treatment target for patients with CS is either UFC in the normal range or mean serum cortisol levels that are between 5.4 and 10.8 mcg/dL (150 –300 nmol/L) to avoid overtreatment and decrease the risk of adrenal insufficiency.

There was a high rate of hypocortisolism-related AEs reported in the pivotal C2301 study: 70/137 (51%) patients. The highest incidence of AI (42/70 patients) was reported during the initial dose titration period (week 1-12). There was no dose-dependency for the events; the median dose was 10 mg bid at time of the event. Of those who had AEs of hypocortisolism, the majority of patients had 1 or 2 events (36 (50%) and 17 (25%) patients, respectively), and 3 patients had a total of 6 hypocortisolism-related events, each. The majority of patients were symptomatic (e.g., headache, vomiting, nausea, fatigue, decreased appetite), some patients had no symptoms or symptoms that were not reported, and only few patients had hypotension and electrolyte disturbances at the time of the event. In addition, some patients with cortisol levels < 5.4 were reported as "asymptomatic", and other patients with normal serum cortisol and UFC levels had headache, nausea, vomiting, hypotension. Most of the cases resolved with dose decrease and/or temporary interruption (30 patients); 19 patients required glucocorticoid treatment.

[11] Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Endocrine Society Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31.

There was no death due to these AEs, and 9 patients in the Core Phase and 2 patients in the extension phase experienced at least one SAEs of AI. Four patients were discontinued from the trial because of the event. Four patients had two SAEs of AI, and 7 had one SAE of AI, each. All patients were symptomatic (e.g., nausea, vomiting, hypotension), and the majority of patients were hospitalized due to the event. Precipitating factors were reported in the majority of patients with SAEs of AI including right adrenal venous thrombosis (1 patient), influenza (2 patients), gastroenteritis (2 patients), pneumonia, respiratory tract infection (in 1 patient, each). All SAEs of AI resolved.

It is important to note that serum cortisol levels (as required for the diagnosis of AI) and/or time of the sample collection (morning or afternoon) were not reported at the time of the event in the majority of patients, and some patients had cortisol levels > 5.4 mcg/dl at the time of the event. 38/72 patients (25%) with AEs of AI had mUFC < LLN, all other patients had normal mUFC values or > UNL. It should be noted that UFC below normal level is not the recommended test for AI due to its high variability; accuracy of UFC is also affected by urine volume and creatinine clearance. Thus, low UFC concentrations may be misleading in the diagnosis of AI. At the same time, it is highly unlikely that patients with normal/elevated UFC levels have true AI.

In conclusion, the absence of serum cortisol levels significantly complicates the assessment of the true rate of AI and the reported high rate of AI was most likely overestimated because of the poor definition of the event of "adrenal insufficiency" in the protocol. The protocol instructed Investigators to monitor patients for AI by "questioning on the signs and symptoms of glucocorticoid withdrawal/hypocortisolism/adrenal insufficiency". The prespecified hypocortisolism-related symptoms included gastrointestinal symptoms (nausea, vomiting), fatigue, weakness, failure to thrive, morning headache, symptoms consistent with hypoglycemia, or dizziness. As explained above, these symptoms are not specific and may be due to the drug itself or due to uncontrolled CD or other conditions/concomitant medications and do not distinguish between absolute and relative AI without serum cortisol levels at time of the event. In addition, the Applicant recommended to decrease the dose (for presumed AI) if mUFC was < LLN or if patient was symptomatic and mUFC was in the low normal range. Again, as stated above, UFC levels may be misleading in the diagnosis of AI. The conclusion that the rate of AI was overestimated is supported further by the following facts: 1) the majority of patients with "AI" had normal or elevated UFC values; 2) only 25% of patients required glucocorticoid treatment; 3) the majority of patients had normal BP and normal electrolytes values.

However, the high rate of hypocortisolism may be due, in part, to the aggressive titration schedule (as described above). Interestingly, for this drug, hypocortisolism can also be seen as evidence of efficacy (based on its mechanism of action). Thus, the Applicant's intent in the trial to normalize cortisol levels as soon as possible in order to control hypercortisolism by fast titration (every 2 weeks) and by large increments with giving very little consideration to the rate of cortisol decrease as well as to the improvement in signs and symptoms of CD may be another reason for the high rate of hypocortisolism-related events observed in this trial. This conclusion is further supported by the observation that the majority of hypocortisolism -related AEs occurred early in the trial, during the initial dose titration in Periods 1 and 2.

Lastly, the results from the supportive study C2201 are, in general, consistent with the results from the pivotal study: a total of 8/19 (42%) patients had at least one event of AI. Study C2201 used the same titration schedule as study C2301, and no serum cortisol levels were used for the definition of AI.

The likelihood that the high rate of AI may be due to fast titration is further supported by the fact that frequency of AI is already lower in the ongoing C2301 (7/60 patients) using the slower titration schedule (every 3 weeks). Moreover, the titration in the ongoing study is based on 2 UFC samples instead of 3 samples as was required in study C2301. Collection of 2 UFCs better allows for capture of the full effect of the last dose escalation since there is more time between last dose and next urine collection (see discussion above) and is more reflective of how UFCs are monitored in clinical practice. In addition, the dose titration is managed by independent endocrinologist oversight (not by individual Investigators) who take into account UFC, serum cortisol, signs and symptoms of AI and other AEs and lab biochemistry data. Such titration likely results in more uniform dose escalation approach.

Thus, additional safety data on a potentially safer, more tolerable dosing regimen may be gained by the results of this study, once it is completed (see Postmarketing Recommendations section).

In conclusion, although the occurrence of hypocortisolism-related AEs with osilodrostat treatment was substantially higher in study C2301 compared to the rate of such events associated with use of other drugs approved for the treatment of CD (Korlym 2/50 patients, Signifor and Signifor LAR - 6% and 7%, respectively), this rate is most likely overestimated due to the poor definition of AI in the protocol and can be adequately mitigated by a slower dosing regimen. In addition, adrenal insufficiency is a well-recognized adverse reaction with use of all cortisol-lowering drugs, is monitorable, and can be mitigated by appropriate labeling, monitoring and treatment with dose reduction/interruption and/or treatment with glucocorticoids. Due to the potential severity of this adverse event, the risk of hypocortisolism should be included in the WARNING and PRECAUTION section of the label to increase awareness for the practicing physician, raise the level of suspicion for diagnosis and corrective intervention (osilodrostat discontinuation and glucocorticoid supplementation, and resumption of osilodrostat at a lower dose).

It should be also noted, that the biological t1/2 of osilodrostat is longer than the elimination t1/2 of the drug for unknown reasons, and recovery of HPA axis might be prolonged in patients treated with osilodrostat after the drug is stopped. This observation is based on the following findings: 1) in study C2201, cortisol levels did not return to baseline in all patients for 2 weeks after the 10-week treatment 2) there were approximately 30% responders to placebo during 8-week withdrawal period in study C2301, 3) impaired ACTH stimulated cortisol response persisted for 1-2 weeks in patients who participated in studies for other indications (hypertension) and in healthy volunteers (Study C2108). Thus, the persistence of cortisol suppression even after the drug is discontinued also needs to be addressed in the labeling.

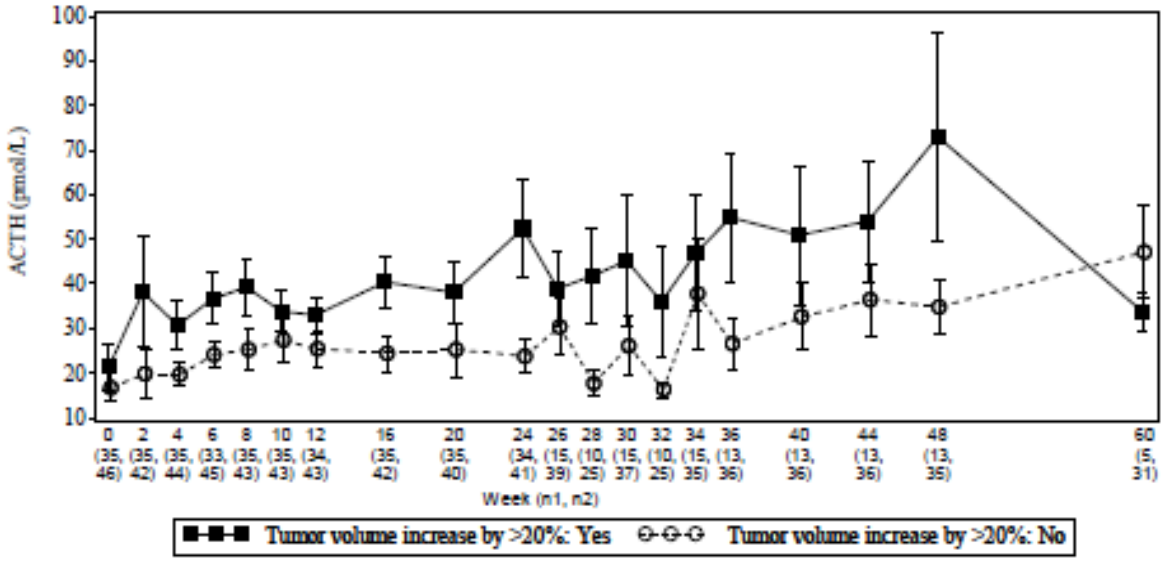
Change in pituitary tumor volume

A potential effect of osilodrostat treatment on the size of the pituitary tumor in patients with CD was evaluated by comparing pituitary MRIs obtained at various times during osilodrostat treatment to baseline measurements. All MRIs were read by one central reader. 79 patients had measurable tumor at baseline and post treatment. The majority of patients had microadenoma at baseline (n=69), and 13 patients had macroadenoma. 35/79 patients had an increase in tumor volume by > 20% from baseline as the worst assessment at any time point of the study and 44/79 patient had decrease in tumor volume from baseline as the best assessment. The Applicant stated that a cut-off value of 20% has been selected in order to exclude minor changes caused by the intrinsic variability of the imaging technique (refer to the Applicant's response to IR from 8/9/2019). Of 35 patients with increased tumor volume, 25 patients had tumor volume > 20% at the last observation.

It should be also noted, that the interpretation of the clinical significance of the increase in tumor volume/size from baseline by the prespecified 20% is complicated. Patients with microadenomas usually do not have compressive symptoms due to small tumor size, and changes in the tumor volume by a few millimeters in this tumor category are of unknown clinical significance. On the other hand, change in the size of macroadenomas even by < 20% may be of clinical significance, since these tumors are already large and tumor growth even by few millimeters may cause invasion or compression of the surrounding tissues and cause symptoms. Thus, the Applicant was asked to further analyze all patients by any increase in tumor volume (by region of interest and by increase in longest diameter). As per this analysis (submitted on 8/9/2019 as a response to the Agency's IR), there were 49 patients with any tumor increase from baseline. Of these, 8 patients had macroadenoma at baseline. The increase in tumor volume from baseline in patients with macroadenoma varied from 4.3% to 126% and in longest diameter from 0% to 32% (0-5 mm). 6/8 patients had concomitant increase in ACTH values at time of tumor enlargement. No symptoms were reported.

There was no clear relationship between dose of the drug and change in tumor volume. There was no specific pattern of timing of the tumor volume increase (ranged from Day 167 to Day 842); the first increase in tumor size was noted in some patients as early as in Period 2. There was no clear relationship between ACTH values and change in tumor volume, as the majority of patients had increase in ACTH values from baseline by the end of the study.

Figure 5. Mean (+/- SE) ACTH (pmol/L) levels by tumor category (Safety set)



Source: Applicant's table HA3-Q33; Response to the Agency's IR from 8/9/2019.

AE of pituitary tumor was reported in 11 patients. Six patients discontinued the study prematurely due to AE of pituitary tumor and 1 patient discontinued the study due to the "guardian decision" (but had pituitary surgery 10 days after study discontinuation). The Applicant reported 4 patients with SAE of pituitary tumor (Table 6, above). One additional patient had an SAE of malignant pituitary tumor. However, the size of the malignant tumor remained stable during the treatment, and thus data from this patient will not be included in further analysis and discussion. The review of patient narratives identified additional 3 patients with SAEs of pituitary tumor: tumor invasion (1) and pituitary tumor (2). Thus, a total of 7 patients ((b) (6)) had SAE associated with pituitary tumor enlargement. All but one patient with SAE of pituitary tumor discounted the study preliminary due to this AE. 5/7 patients had microadenomas at baseline (max diameter range 5 mm - 9.4 mm), and tumor size remained < 10 mm at the last assessment in all but one patient (patient (b) (6) had increase in tumor diameter from 6.2 mm at baseline to 12.9 mm). Two of 7 patients had macroadenoma at baseline with longest dimension of 12.9 mm and 21.3 mm, respectively; tumor size increased to 15.5 mm and 24.9 mm, respectively. 5/7 patients were asymptomatic, and 2 patients had tumor-related symptoms. One patient with macroadenoma (# (b) (6)) reported SAE of diplopia and 6th nerve paralysis at the time of the last tumor measurement (period 3) and one patient with microadenoma at baseline developed SAE of 6th nerve paralysis with diplopia and vomiting in the extension period and was diagnosed with invasion of pituitary tumor into the left cavernous sinus (the tumor remained < 10 mm in diameter). The drug was discontinued due to this event in both patients. Lastly, one patient (# (b) (6)) with macroadenoma at baseline (32.8 mm) developed headache, dizziness, cranial nerve paresis on Day 29; the size of tumor was 33.1 mm on that day. This patient was also discontinued from the study due to non-serious AEs of pituitary tumor.

In study C2201, of 19 patients enrolled in the study, 2 patients had SAEs of pituitary tumor enlargement (both patients had macroadenoma at baseline, size not reported). Patient # (b) (6) had increase in tumor size to 28 mm on Day 182 with concomitant increase in ACTH levels from baseline (from 43 pmol/l to 1483.2 pmol/l). Patient # (b) (6) had increase in tumor size to "visible microadenoma on MRI" on Day 386 being on a dose of 1 mg bid; ACTH level was not reported. Both patients were asymptomatic, however both were discontinued from the study due to the event and underwent gamma knife therapy/surgery.

In conclusion, I agree with Applicant that there is no distinct evidence that osilodrostat may influence tumor size one way or another to date. Overall the increase in tumor size was small and inconclusive. As stated above, the clinical significance of tumor enlargement by few millimeters in patients with small tumors is unknown. However, an interpretation of the results and causality assessment based on these results are challenging due to multiple reasons (e.g., absence of comparator, absence of stratification by tumor size in the study, decrease in microadenomas by few millimeters may be due to the reading error, natural growth of the tumors during the course of the disease). Thus, the data from study C2302 using placebo group might provide further insight regarding the change in tumor volume caused by the drug vs. change in volume due to the natural growth (refer to Postmarketing recommendations section below).
However, it remains unknown whether there is an increased risk of tumor enlargement with longer exposure to the drug. In addition, osilodrostat decreases cortisol synthesis and increases ACTH. There is known risk of corticotroph tumor progression associated with increased plasma ACTH. Thus, based on the uncertainties described above and biologically plausible link between drug-induced increase in ACTH and tumor growth, change in tumor volume should be described in section 6 of the label. Overall, description of this adverse reaction in the label will make practitioners aware not only of its existence, but also will help practitioners in making decisions regarding patient monitoring

Accumulation of adrenal hormone precursors and related AEs

Inhibitors of cortisol and aldosterone synthesis increase levels of cortisol precursors, 11-deoxycorticosterone (DOC) and 11-deoxycortisol. 11-deoxycortisol and DOC poses mineralocorticoid activity; thus, accumulation of these precursors may lead to hypokalemia, hypertension, and edema. An inhibition of cortisol and aldosterone syntheses also leads to a shift of steroidogenesis toward the androgen pathway that may result in hirsutism and acne in women. Thus, since osilodrostat blocks 11-b-hydroxylase and aldosterone synthetase, the accumulation of adrenal hormone precursors and androgens and related adverse reactions are expected based on its mechanism of action.

As expected, increase in DOC, 11-deoxycortisole, renin, and a decrease in aldosterone were observed in the study (Table 7). There was also an increase in serum estradiol, estrone, and testosterone levels. Moreover, the accumulation of testosterone was most likely drug-related as evident by the fact that levels decreased in female patients treated with placebo and increased again when osilodrostat treatment was resumed. There was a trend towards decrease in DHEAS levels at the end of the study; however, the changes were small and of unknown clinical significance.

Table 7. Summary of changes in adrenal hormone precursors values (FAS).

Parameters, mean (SD)	Baseline,	Week 12	Week 24	Week 48	
				Actual	Change from baseline, %,
DOC, pmol/l*	3879 (6976.4)	5190 (5181)	4294(3827)	4644(3979)	241.9 (420.91)
11-deoxycorticosterol, nmol/l					
male	3.4 (2.57)	20.1 (15.2)	24.5 (19.86)	23.3 (24.8)	1117.7%
female	6.3 (20.1)	33 (32.3)	33(36)	36.6 (36.9)	1520.7%
Renin, mU/l	36.9 (58.73)	79.3 (246.3)	74.6(152.6)	107 (263.44)	
Aldosterone, pmol/l	198.0 (380.14)	116.6 (255.04)	79.3 (50.66)	93.5 (103.56)	37.7 (214.03)
Estradiol, pmol/l					
male	73.2 (39.98)	117.9 (40.63)	107.6 (37.69)	121.8 (54.00)	112.6 (145.63)
female	256.7 (390.72)	296.1 (461.04)	206.9 (324.23)	331.8 (581.44)	261.8 (933.16)
DHEAS, umol/l	7.8 (5.18)	5.8 (5.70)	4.5 (3.45)	3.4 (3.25)	-50.0 (39.39)
	4.7 (3.21)	3.3 (2.67)	2.8 (2.30)	1.6 (1.63)	-63.4 (27.09)
Estrone, pmol/l					
male	187.4 (91.10)	361.8 (217.74)	346.3 (182)	303.8 (150.71)	74.3 (87.24)
female	313.1 (280.79)	441.9 (356.07)	358.1 (212.17)	396.3 (386.67)	79.2 (198.79)
Testosterone, nmol/l					
male	9.5 (5.72)	16.1 (7.96)	14.5 (5.69)	17.7 (8.04)	146.7 (149.33)
female	1.3 (1.18)	2.9 (2.30)	2.8 (2.48)	2.6 (2.39)	168.3 (252.63)

*In females (only 3 males had measurements during the study)
Source: Applicant's tables, 14.2-3.45- 14.2-3.63, CSR C2301, modified

The Applicant identified a total of 58/137 (42%) patients with at least one AE related to the accumulation of adrenal hormone precursors and/or androgens (e.g., hypertension, hypokalemia, acne, hirsutism, edema) up to the data cutoff date (Table 7). In addition, the following changes in levels of the precursors/ androgens were reported as AEs: androstenedione increased (1 patient), testosterone increase (14 patients), testosterone levels abnormal (1 patient), oxycorticosteroids increased (1 patient). Most of these AEs resolved with or without treatment; 20% of patients required dose adjustment /interruption.

Table 6. Adrenal hormone precursor accumulation-related AEs regardless of study drug relationship, by preferred term up to data cutoff date (SAS)

Adrenal hormone accumulation-related AEs/ PT	**All Patients, N=137**	
	All grades, n (%)	**Grade 3/4, n (%)**
Hypokalemia	18 (13.1)	6 (4.4)
Hypertension	17 (12.4)	15 (10.9)
Acne	12 (8.8)	0
Hirsutism	12 (8.8)	0
Edema	9 (6.6)	1 (0.7)
Weight increased	3 (2.2)	0
Blood pressure diastolic increased	2 (1.5)	1 (0.7)
Blood pressure increased	2 (1.5)	0
Blood pressure systolic increased	2 (1.5)	1 (0.7)
Blood potassium decreased	1 (0.7)	1 (0.7)
Hypertrichosis	1 (0.7)	0

Source: Applicant's table 12-13, CSR C2301, modified.

Hypertension and hypokalemia were the most common cortisol precursor-related AEs and occurred in 14 % of patients (19 patients: 18 patient had AE of hypokalemia and 1 patient- of blood potassium decreased) and 16.7% (23 patients) of patients, respectively. Elevated DOC levels were reported in 9 patients at time of the event of hypertension and/or hypokalemia event.
SAE of hypokalemia (potassium level 2.7 mmol/l) was reported in 1 patient (# (b) (6)). This patient also had non-serious AE of hypertension (BP 190/103 mmHg). This patient was discontinued from the study prematurely due to hypokalemia and AI. One more patient with non-serious AE of hypertension discontinued the study prematurely (due to AE of hypertension and SAE of AI).

All patients with AEs of hypokalemia had potassium levels in the range of 2.4-3.4 mmol/l at the time of the event. Two patients had 3 episodes of hypokalemia during the study, all other patients had one episode, each. Two patients had gastroenteritis/ vomiting/diarrhea at the time of the event, that might cause or precipitate the event of hypokalemia. All patients were asymptomatic. The majority of patients with hypokalemia AEs also had concomitant elevation in BP values. All cases resolved, but majority of them required treatment with potassium supplements and/or spironolactone. The Applicant also reported that osilodrostat exposure (Cmax, Ctrough and Cavg) was found to have statistically significant impact on the change of potassium levels from baseline during the study.

The majority of patients with hypertension had an underlying medical history of hypertension; AE of hypertension was reported as "worsening of hypertension" in 11 patients. One patient was symptomatic and reported headache and edema, and all other patients were asymptomatic. There was overall decrease in mean SBP and DBP at the end of the Core Period; however, these uncontrolled data should be interpreted with caution.

Lastly, the Applicant reported 9 patients with AE of edema; however, further review of the Applicant's data (the Applicant's response to the Agency IR from 1/8/2020) revealed a total of 26 patients who had AE of edema reported during the Core Phase of the trial (edema peripheral -21 patients, peripheral swelling -3 patients, generalized and localized edema, 1 patient each). It is unclear whether these cases were associated with elevated levels of adrenal precursors, since no other information, including precursor levels was provided.

The most common androgen-related AEs were acne and hirsutism and occurred in 8 patients each. It should be noted, that hirsutism and acne are also common features of hypercortisolism. However, the occurrence of new events of acne and hirsutism during treatment in patients with preexisting hypercortisolism might be due to accumulation of androgens. No androgen levels were reported at the time of the events in these patients, complicating the causal assessment of the events.

In study C2201, a total of 12/19 patients experienced at least one of these AEs. Hypokalemia was reported in 4/19 patients (2 patients had 2 episodes, each); the lowest potassium value was 2.9 nmol/l. The events of hypokalemia resolved in all patients with or without potassium supplements, and 1 patient required temporary drug interruption. No ECG changes or symptoms were reported in these patients. Hypertension was reported in 5/19 patients. Two patients reported hypokalemia concomitantly with hypertension. Two patients experienced hirsutism and 2 patients experienced hypertrichosis (with concomitant increase in DOC and/or testosterone values from baseline), 3 patients experienced acne, 6 -testosterone increased, 1-edema.

In conclusion, AEs related to the accumulation of cortisol precursors and androgens were frequently and consistently observed across all studies using osilodrostat in patients with CD, healthy volunteers and patients with hypertension along with increases in the levels of these substances. Some of these events can be potentially life-threatening (e.g., hypokalemia, hypertension) in patients with high risk for hypokalemia and hypertension at baseline due to hypercortisolemia. Although hirsutism and acne are not life-threatening AEs, they may be of increased concern to patients, especially females. Thus, these AEs should be listed in section 5 of the label along with the need of periodic monitoring of serum potassium and BP. Overall, listing of these AEs in the label will make practitioners aware not only of their existence, but also will help practitioners in making decisions regarding patient selection and use of concomitant medications.

QT prolongation AEs

The nonclinical findings of osilodrostat effect on QT interval prolongation and results of TQT study are discussed in Nonclinical and Clinical Pharmacology sections of this memorandum, respectively. This section will discuss QT-prolongation related AEs and overall changes in ECG parameters in patients with CD for the completeness of this review.

In study C2301, mean (SD) changes in ECG readings from baseline at week 48 were: 5.3 ms (20.67) for QTcF, 3.2 ms (7.73) for QRS, 8.6 ms (13.56) for PR interval and 1.0 bmp (10.72) for heart rate. These changes seem small and of unknown clinical significance. However, the data are not controlled, and this limits strong inferences.

During the treatment with osilodrostat, 16 patients (11.7%) had QTcF >450 msec but < 480 msec, one patient had QTcF > 480 ms but < 500 ms and one patient had QTcF >500 msec (patient # (b) (6)). 3 patients (2.2%) experienced an increase in QTcF >60 msec above baseline and 53 (38.7%) patients experienced an increase in QTcF >30 msec above baseline.

There were no adverse events of torsades or sudden death reported during the study. Five patients had non-serious AEs of QT prolongation during the study. One patient (# (b) (6)) had 2 episodes of QT prolongation; all other patients had one episode of QT prolongation each. One patient had a new QTcF of 581 msec (# (b) (6)) on Day 71 (dose 20 mg bid); patient was asymptomatic and had ongoing flue. The drug was temporary interrupted, and the event resolved; no symptoms were reported. Concomitant event of hypokalemia at time of QT-AE was a confounding factor in one patient. All patients were asymptomatic; one patient had heart rate of 117 beats per minute (BPM) at time of the event (QTcF 430 msec). All events resolved without treatment or with temporary dose decrease/drug interruption. One patient was discontinued from the study prematurely due to the event (# (b) (6)).

In study C2201, 1/19 patients (# (b) (6)) had SAE of QTcF> 480 msec (494 msec) on Day 239. The patient was asymptomatic and with heart rate in 74-80 range at time of the event. This patient also had acute gastroenteritis that might be associated with ECG abnormalities due to electrolyte disturbances. The drug was interrupted and restarted at a lower dose (10 mg), no concomitant treatment was reported.

In conclusion, given the existing signal in the preclinical studies and based on the results of TQT study and QT-related findings in patients with CD (some patients had improvement with drug interruption), I agree that the potential risk of QT prolongation should be indicated in the Warnings and Precautions Section of osilodrostat label.

Arrhythmogenic potential AE

Because the nonclinical studies have shown a proarrhythmogenic potential for osilodrostat, the Applicant evaluated cases of syncope in studies with CD since they can be cardiac related. One patient in study C2301 had a SAE of syncope (# (b) (6)). The event was most likely not drug-related; patient had ongoing influenza, dehydration and AI and had orthostatic hypotension. ECG was obtained the next day and was normal.
In Study C2201, one patient experienced two episodes of syncope. No arrythmia was reported during the event and the patient continued treatment with osilodrostat.
In conclusion, there were no convincing cases of cardiac-related syncope in patients with CD during the treatment with osilodrostat.

Other laboratory parameters

Hematology

There were no clinically meaningful changes in hematological analytes in study C2301 or C2201.

In study C2301, no patients had decrease in any hematologic parameters to grade 4, and only a few patients had decrease in these parameters to grade 3 (hemoglobin and absolute neutrophils counts - in 3 patient each, platelet - in 1 patient).
The majority of patients had a decrease in only one hematologic parameter. No patients discontinued the study prematurely due to the hematologic abnormalities.

Study C2301

- Anemia/ hemoglobin (Hgb) decreased was reported as AE in 18 patients up to data cutoff date. Two patients had SAE of anemia: one patient due to metastatic disease and one patient had iron-deficient anemia at baseline. All events resolved without dose interruption/ dose reduction. All patients were asymptomatic. The majority of the cases were also confounded by other factors such as underlying medical conditions (preexisting anemia, renal failure, hypothyroidism, congestive heart failure, hemorrhoids, etc.), concomitant medications (warfarin), etc.
- Decrease in absolute neutrophil count was reported as SAE in 2 patients. One patient (# (b) (6)) had isolated neutropenia (ANC at 0.77X 10^9/l (grade 3)) in the extension period and was diagnosed with autoimmune neutropenia (no information is provided regarding "autoimmunity"). The other patient (# (b) (6)) was diagnosed with neutropenia (ANC 1.23x10^9/l, grade 2) in Period 3 with concomitant decrease in cortisol levels. No infections were reported in both cases. The neutropenia resolved in both cases with dose reduction/temporary interruption. Both patients continued treatment on the study. No concomitant infections/ fever were reported in any of patients with decreased ANC.

Study C2201

There were no shifts to grade 3 or 4 during study C2201 Part II.
One patient had SAEs of Hgb decrease to grade 4 on Day 69 in Part I of the study. The event was considered not related to the drug; the causality assessment of the event is confounded by underling medical conditions (sideropenic anemia, folate and B12 deficiencies, renal disease). Patient continued with treatment on the study, the event resolved.

In conclusion, the decrease in Hgb and blood cell counts was small and not clinically meaningful in all studies. Moreover, the decrease in hematologic parameters values including neutrophils is known phenomenon associated with a decrease in cortisol levels and may be indicative of the improvement in hypercortisolemia[12].

Clinical Chemistry

Similar observations (i.e. small changes of unknown clinical significance) apply to chemistry analytes (electrolytes, BUN, creatinine, bilirubin, glucose, alkaline phosphatase, liver function tests, urinalysis, etc.) with the clear exception of hypokalemia (refer to AESI section above) in

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12 Masri-Iraqi H, Robenshtok E, Tzvetov G, Manistersky Y, Shimon I. Elevated white blood cell counts in Cushing's disease: association with hypercortisolism. Pituitary. 2014 Oct;17(5):436-40.

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both studies, C2301 and C2201. No patients had grade 4 changes in any chemistry values, and only few patients had grade 3 changes:

- Study C2301: hypermagnesemia -4 patients, hypomagnesemia- 1 patient, hypophosphatemia-3 patients, hyperkalemia- 3 patients.
- Study C2201, Part II: elevated creatine kinase -2 patients, hypophosphatemia- 1 patient

Changes in LFTs

In study C2301, a few patients had elevation in AST and/or ALT to < 3XULN during the study, and 5 patients had AEs of ALT/AST elevations > 3XULN. Of 5 patients with ALT/AST values > 3 X ULN, 4 patients had ALT/AST > 3XULN but < X10 ULN. None of the patients had total bilirubin values > 1.5XULN and no cases of Hy's law were reported during the study.

Two patients had SAEs associated with elevated LFTs (cholelithiasis and transaminase increased), the events were most likely not related to the study drug:

- Patient (# (b) (6)) had a SAE of liver transaminase increase: ALT of 16 XULN and AST of 8 X ULN on Day 44, bilirubin was within normal limit and ALP was X 1.1 ULN. The patient was asymptomatic; ultrasound revealed multiple gallstones. The patient was also treated with an NSAID (diclofenac) at time of the event. Osilodrostat and diclofenac were temporary interrupted, AST normalized, and ALT decreased to X 3ULN in 5 days. Patient continued with osilodrostat treatment.
- Patient # (b) (6) had suspected biliary colic and increase in ALT 3 X ULN, ALP 1.6X ULN, and AST slightly above UNL in Period 3. This patient was diagnosed with SAE of cholelithiasis and underwent surgery; the event resolved, and the patient continued with osilodrostat treatment.

In study C2201, there were no patients with increase in AST/ALT > 3X ULN, and no patients had increase in total bilirubin > 2 XULN.

In conclusion, no drug-related liver abnormalities were identified during the treatment with osilodrostat in patients with CD. The majority of patients with abnormal LFTs had multiple confounding factors including underlying medical conditions (e.g., obesity, liver metastasis, steatosis, hyperlipidemia, diabetes) or use of concomitant medications with known liver toxicity. LFT abnormalities resolved/significantly decreased without treatment by the end of the study in all patients. Lastly, elevation in LFTs may be due to hypercortisolemia itself and is frequently observed in patients with CD.

Overall safety conclusion

In conclusion, the safety profile of osilodrostat in patients with CD was well characterized in osilodrostat nonclinical and clinical programs and there is a distinct pattern of adverse events that is emerging from the osilodrostat clinical program that should constitute the basis for safety labeling. To a large extent, all safety observations are mechanistically anticipated pharmacodynamic effects, largely predictable and monitorable. They include adrenal insufficiency and associated manifestations, and AEs associated with accumulation of cortisol and androgen precursors. There was a safety signal of QT interval prolongation observed in nonclinical studies and in the clinical study at supratherapeutic doses; few cases of QT-interval prolongation were observed in patient with CD. Overall, patients with CD are at risk for ECG abnormalities due to multiple factors associated with CD itself (hypertension, diabetes,

electrolyte abnormalities, etc.); thus, QT interval prolongation should be labeled accordingly. Some potential safety signals that were observed in the preclinical studies (e.g., embryo-fetal toxicities, proarrhythmogenic potential, abnormal LFTs) were observed only at supratherapeutic doses and/or had not been observed consistently in clinical studies. Lastly, there was no evidence accumulated to date indicating that the drug causes expansion of pituitary tumor volume. In summary, the safety profile of osilodrostat is acceptable in view of the potential benefit for a disease with limited medical options, the adverse events that osilodrostat may trigger can be identified, and these adverse events can be monitored and managed by health care providers.

9. Advisory Committee Meeting

There was no Advisory Committee Meeting held for this application.

10. Pediatrics

Osilodrostat has received orphan-drug designation on September 13, 2013 for "treatment of CD". Therefore, the requirements of the Pediatric research Equity Act do not apply to this application.

11. Other Relevant Regulatory Issues

Division of Scientific Investigation

A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on 11/4/2019. Four clinical sites were investigated. Dr. Kleppinger concluded that the inspectional findings and the study data generated from three clinical sites were considered acceptable and may be used in support of this NDA. The fourth site (site 3103) was issued a Form FDA-483 citing significant inspectional observations. This site enrolled 4 subjects and 3/4 of subjects entered into the randomized, double-blind phase 3 of the study. However, two subjects enrolled in RW period (one in osilodrostat group and one in placebo group) had dose increase during Week 13-24 which made them ineligible for randomization; in addition, one of these two subjects were not excluded from the RW when his dose was increased. The third subject had dose increase in RW period but was not discontinued from the RW period. Thus, data from this site was not considered reliable and it was recommended to perform sensitivity analyses excluding the data from Site 3103 to determine the robustness of the results and the primary conclusion of the trial. Dr. Cambon conducted sensitivity analysis excluding these patients and concluded that the data from these patients did not influence the overall results of the study

Financial disclosures and compliance with Good Clinical Practice standards

Dr. El-Maouche's review indicates that the applicant has submitted FDA Form 3455 and that all investigators were certified to have no conflict of interest that could influence the outcome of the trial(s). She also confirms that all studies were conducted in accordance with the principles of Good Clinical Practice governing clinical study conduct.

Proprietary Name

A Division of Medication Error Prevention and Analysis (DMEPA) consult has reviewed the proprietary name *Isturisa* and found it to be acceptable (review in DARRTS from 4/2/2019).

Division of Pediatric and Maternal Health (DPMH) Consult

DMEP had consulted DPMH to provide an input on the proper format and content of the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of Osilodrostat labeling to follow the Pregnancy and Lactation Labeling Rule (PLLR). DPMH revised relevant sections of labeling for compliance with the PLLR and recommended to describe the lack of available human data and lack of adverse developmental effects in animal studies at clinically relevant exposures in section 8.1. DPMH also recommended to alert prescribers to the "Disease-associated Maternal and/or Embryo/Fetal Risk" in section 8.1. Refer to the DPMH review from 2/21/2020 for details.
Lastly, DPMH recommended issuing a postmarketing requirement for a single-arm pregnancy safety study (SPSS) to monitor the outcomes of women and infants exposed to osilodrostat during pregnancy. Following the discussion between DPMH and DMEP on feasibility of such study in the intended population, DPMH agreed that such study is not feasible, since osilodrostat is indicated in an orphan population with low fertility rate due to the disease itself. DPMH and DMEP agreed that if osilodrostat use during pregnancy is demonstrated through routine pharmacovigilance or published scientific literature, the applicant should be required to conduct a single-arm pregnancy safety study to monitor the outcomes of women and their infants exposed to osilodrostat during pregnancy.

I agree with all DPMH recommendations.

The Applicant agreed with the Agency's above plan and plans to conduct an enhanced pharmacovigilance with guided questionnaires and follow-up to determine effects on outcomes in women using osilodrostat during pregnancy (refer to the Applicant's response to the Agency's IR from 2/28/2020).

12. Labeling

Prescribing Information

Agreement on the final labeling language has not been reached at the time that this review was completed. Refer to the complete labeling in the approval letter. The following sections should be addressed in the label:

- INDICATIONS AND USAGE:
    - The Applicant's proposed indication is for the treatment of patients with CD. However, the indication should reflect the patient population evaluated in the osilodrostat clinical program. In addition, surgery is first-line therapy and the treatment of choice for all patients with CD; medical treatment is a second line

therapy. Lastly, pediatric patients have not been evaluated in the clinical program. Thus, the drug should be indicated for the adult population with CD in whom pituitary surgery is not an option or has not been curative reflecting.

- DOSAGE AND ADMINISTRATION:
  - To mitigate risk of hypocortisolism AEs, the dose should be slowly titrated and should be individualized. The dosage should be titrated by 1 to 2 mg per day, no more frequently than every 2 weeks based on the rate of cortisol changes, individual tolerability and improvement in signs and symptoms of Cushing's disease. If a patient tolerates osilodrostat dosage of 10 mg twice daily and continues to have elevated 24-urine free cortisol levels above upper normal limit, the dosage can be titrated further by 5 mg twice daily every 2 weeks.
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - I recommend including adverse reactions associated with accumulation of cortisol precursor synthesis and androgen precursors in the WARNINGS AND PRECAUTIONS section because they are potentially drug-related (based on mechanism of action) and some of them (hypokalemia, hypertension) are potentially serious and may be fatal in the population at risk, if not recognized and treated early.
  - (b) (4) should be deleted from the WARNINGS AND PRECAUTIONS section because of inconclusive non-clinical results (refer to Nonclinical section above).
- ADVERSE REACTIONS SECTION
  - All adverse reactions that occurred in > 10% of patients in the Core Phase of the pivotal study C2301 including those that occurred in patients who were on placebo during the RW period should be included in the label, since patients in RW were already exposed to the drug and observed AEs in patients on placebo in this period still can be drug-related.
- CLINICAL STUDIES section:
  - I agree with Dr. Cambon's recommendations that the efficacy results for study C2301 should be presented descriptively in Section 14 of the label.
    As stated above (refer to efficacy results), in clinical practice, prescribers will offer the product to patients who are naïve to osilodrostat without any insight as to whether the patient will be a responder to osilodrostat or not, thus, the efficacy estimate with use of a randomized-withdrawal phase might be overestimated in treatment-naïve patients. In addition, the magnitude of the effect observed in open-label, single arm periods of the study may not reflect the magnitude of the effect that will be seen in clinical practice in all treatment-naïve patients.
  - Labeling claims based on (b) (4)

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No safety issues rising to the level of requiring a risk evaluation and mitigation strategy was identified in the application. Safety issues will be handled through appropriate labeling (refer to the Division of Risk Management review in DARRTS from 2/11/2020).

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The DMEP review team proposed and discussed with the Applicant the following PMR:

To Complete Clinical Trial C2302, a Phase 3, multi-center, randomized, double-blind, 48-week study with an initial 12-week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease. Safety evaluations include but are not limited to the occurrence of hypocortisolism and adrenal insufficiency.

14. Recommended Comments to the Applicant

The above listed clinical PMR should be added to the Action Letter.

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/

MARINA ZEMSKOVA
03/02/2020 01:17:38 PM

LISA B YANOFF
03/02/2020 01:20:11 PM

MARY T THANH HAI
03/02/2020 03:20:17 PM