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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Diala El-Maouche, MD, MS
Original NDA 212,801
Osilodrostat, Isturisa®

CLINICAL REVIEW

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(Proposed) Trade Name	Isturisa
Applicant	Novartis
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Applicant Proposed Indication(s)/Population(s)	For treatment of Cushing's disease
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Recommended Indication(s)/Population(s) (if applicable)	Treatment of Cushing's Disease

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Glossary

AC	advisory committee
ACTH	adrenocorticotropin hormone
AE	adverse event
AESI	adverse events of special interest
BL	basal
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CD	Cushing' disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CS	Cushing's syndrome
CSR	clinical study report
CSS	Controlled Substance Staff
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DILI	drug-induced liver injury
DMC	data monitoring committee
DMEP	Division of Metabolism and Endocrinology Products
ECG	electrocardiogram
eCTD	electronic common technical document
EOP	end of phase
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

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GRMP	good review management practice
HbA1C	glycated hemoglobin A1C
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mUFC	mean urinary free cortisol
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAS	pharmacokinetic analysis set
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RAS	randomized analysis set
REMS	risk evaluation and mitigation strategy
RW	randomized withdrawal
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
UFC	urinary free cortisol
ULN	upper limit of normal

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1 Executive Summary

1.1. Product Introduction

Osilodrostat (LCI699) (proposed tradename, Isturisa) is a potent inhibitor of 11 β -hydroxylase indicated for the treatment of Cushing's disease (CD). Osilodrostat is categorized as a steroidogenesis inhibitor. It is a new molecular entity (NME) and has not been previously approved in the US or Europe.

The applicant's proposed starting dose is 2 mg orally twice daily. The applicant recommends gradual dose titration (initially by increments of 1 mg or 2 mg twice daily) based on individual response and tolerability, with the goal of achieving normal cortisol levels. The applicant further recommends initial monitoring of cortisol levels [e.g., 24-hour urinary free cortisol (UFC), late night salivary cortisol, serum/plasma cortisol] every 1-2 weeks until adequate clinical response is maintained, followed by less frequent monitoring as clinically indicated. The applicant recommends dose reduction or temporarily interruption in case of symptomatic-hypocortisolism, i.e., if cortisol levels are below the lower limit of normal (LLN), or if there is a rapid decrease in cortisol levels to the lower part of the normal range. The maintenance dose in clinical trials usually varied between 2 mg and 7 mg twice daily. The proposed maximal dose is 30 mg bid.

Osilodrostat is supplied as film-coated tablets of 1 mg, 5 mg, and 10 mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The application contains substantial evidence to support the efficacy of osilodrostat for the treatment of patients with CD for whom surgery is not an option or has not been curative. The pivotal study C2301 was a phase III, double-blind, randomized withdrawal study of osilodrostat following a 24 week, single-arm, open label dose titration and treatment period. The study enrolled 137 patients, of whom 35 patients were randomized to placebo and 36 patients were randomized to active drug in the randomized withdrawal period. The primary endpoint was met, where at the end of the 8-week randomized withdrawal period, the complete response rate in the osilodrostat group was higher than that of the placebo group (86.1% vs. 29.4% respectively, $P < 0.001$). The key secondary endpoint was also met, where by 24 weeks, 72 patients (52.6%) were complete responders. Complete response was defined as normalization of mean urinary free cortisol (mUFC) (by the end of the specified period) in patients who had no increase in osilodrostat dose after Week 12.

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The response rates in study C2301 are acceptable considering the burden of disease in the study population and small study size.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Osilodrostat (LCI699) is a steroidogenesis inhibitor, specifically an inhibitor of the enzyme 11 β -hydroxylase, indicated for the treatment of Cushing's disease. Overall the risk benefit supports approval of osilodrostat for the proposed indication.

Cushing's disease (CD) is a rare, serious, life-threatening disease that is characterized by excess circulating cortisol, caused by a pituitary tumor. CD is characterized by proximal muscle weakness, bruising, obesity, hypertension, diabetes, osteoporosis, and psychiatric symptoms. Patients with CD also have increased risk of venous thrombosis and cardiovascular events, such as myocardial infarction and stroke. First-line treatment for CD is surgical resection of the pituitary tumor. If unsuccessful or not an option, medical therapy is considered second-line. Currently, there are 2 FDA-approved drugs for CD/treatment of hyperglycemia associated with Cushing's syndrome. There are a number of off-label treatments commonly used in the treatment of CD, all of which are limited by safety.

The applicant has completed a single pivotal study, C2301, which was a double-blind randomized withdrawal study and included 137 patients with Cushing's disease. The study met the primary endpoint, where the complete response (normalization of mean urinary free cortisol, mUFC) rate in the osilodrostat group was higher than that of the placebo group (86.1% vs. 29.4% respectively, $P < 0.001$). The study also met the secondary endpoint, where by week 24, 72 patients (52.6%) were complete responders. The limitations of the study included the randomized withdrawal design of the study, where patients who received placebo were previously exposed to active drug (during the open-label, single-arm Period 1 of the study), with a washout period that was shorter than the biological half-life. Nevertheless, the response rates achieved and maintained throughout the study are significant. Another limitation of the study design was the preselection of patients who achieved complete response within 12 weeks (without further need for up-titration beyond that) for randomization. This likely resulted in exclusion of patients who are more challenging to treat. As such, the efficacy rate of 86.1% may be lower in clinical practice, where pre-selection of patients does not exist.

The most common adverse event observed with osilodrostat was adrenal insufficiency, which was observed in 51% of patients. This high rate was confounded by a variety of factors, including capturing of all the events under this term, which included a spectrum of events of cortisol-lowering (the intended effect of the drug), with a smaller number of the cases or less meeting the definition of true adrenal insufficiency (~10-15 cases). Furthermore, the dose-titration schedule appeared overly aggressive, with most patients requiring doses lower than and intermediary to those proposed by the sponsor. Last, results from unblinded ongoing phase III study using a slower titration schedule (3 weeks) resulted in lower rates of adrenal insufficiency. Other adverse events throughout the study were common and anticipated, and included

fatigue, nausea, vomiting, headache, edema, hypokalemia, and hypertension. Adverse events of special interest include acne/hirsutism, elevation of transaminases, QT prolongation, and pituitary tumor enlargement. Other rare adverse events which may of special interest included neutropenia/ bone marrow suppression. Labeling considerations would include the monitoring of CBC, ACTH, chemistry, transaminases, and standard monitoring for Cushing’s disease management as per guidelines.

To address the potential risk of adrenal insufficiency, this medical officer recommends approval of this drug, at a starting dose of 1 mg bid, to be up-titrated in 1-2 mg increments, not more often than every 2-3 weeks up to 30 mg twice a day. As a post marketing requirement, the applicant would be required to submit the results of the ongoing phase III study, C2302 following completion of data collection and analysis. I recommend the approval of this drug with the above proposed titration schedule (labelling to be finalized at a later time).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Cushing’s disease is a rare but serious condition caused by excess circulating cortisol due to an adrenocorticotropin hormone (ACTH)-secreting pituitary adenoma. It is part of the larger Cushing’s syndrome which encompasses other causes of cortisol secretion. • Complications of CD include metabolic abnormalities of obesity, hyperglycemia, and hyperlipidemia; reduced bone mineral density, proximal muscle weakness, easy bruising, facial plethora, and psychiatric symptoms (depression, irritability, psychosis, anxiety, and memory impairment); increased predisposition to infections, and increased risk of venous thrombosis and cardiovascular events, such as myocardial infarction and stroke. 	<p>Cushing’s disease is a rare disorder characterized by cortisol excess. It is associated with decreased quality of life and increased morbidity.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	<ul style="list-style-type: none"> • First-line treatment for CD is transsphenoidal surgery, with or without radiation therapy. • In patients in whom surgery is not an option or not curative, medical therapy is a second line treatment. • Currently, there are 2 FDA-approved drugs for the treatment of Cushing's syndrome (or symptoms of CS): Signifor (pasireotide), approved for treatment of CD when surgery is not an option or is not curative; and Korlym (mifepristone), which is approved for treatment of hyperglycemia secondary to hypercortisolism in patients with CS. • Off-label medical therapies to treat CS include ketoconazole, metyrapone, mitotane, cabergoline, and etomidate, which are used widely, as discussed in the Endocrine society guidelines, and are associated with a variety of adverse events. 	<p>There are 2 FDA-approved drugs for treatment of Cushing's disease and hyperglycemia of CS, and a number of off-label therapies for the Cushing's disease/Cushing's syndrome.</p>
Benefit	<ul style="list-style-type: none"> • The efficacy of osilodrostat was established in a single pivotal open-label followed by a randomized placebo-controlled withdrawal phase III trial (C2301) which evaluated the complete response rate (mUFC \leq ULN) by the end of the randomized withdrawal period, between patients randomized to osilodrostat vs. placebo. • By the end of the randomized withdrawal period, 86.1% of patients on osilodrostat vs. 29.4% of patients on placebo had mUFC \leq ULN (primary endpoint). • The proportion of patients who attained normalization of mUFC after 24 weeks of treatment (with no dose titration beyond Week 12) was 52.6% (key secondary endpoint). • The proportion of patients who attained normalization of mUFC after 12 weeks of treatment was 71.5%. 	<p>The randomized withdrawal design meant that patients who were randomized to placebo were also exposed to the drug, since the first part of the pivotal study where all patients received osilodrostat through the open-label, single-arm study. Some placebo responders therefore had a carry-over effect from the drug, and efficacy comparison between placebo and drug was therefore suboptimal. Nevertheless, the efficacy shown through the primary and secondary endpoints are acceptable and show that osilodrostat is efficacious for mUFC normalization. The</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> • The proportion of patients who attained normalization of mUFC after 48 weeks of treatment was 66.4%. • There was approximately 5% reduction in HbA1C that was consistent throughout the Core Phase of the study, and around 7-10% reduction in fasting blood glucose throughout the Core Phase. • There was a 4.1-6.8% reduction in systolic blood pressure, 3.8-6.6% reduction in diastolic blood pressure, and a progressive decline in weight and BMI throughout the Core Phase (4.6% at Week 48). 	<p>Agency considers that normalization of mUFC as an acceptable surrogate endpoint for disease control in patients with CD, as it is associated with reduction in disease-related morbidity.</p>
<p><u>Risk</u></p>	<ul style="list-style-type: none"> • The most common adverse event in the pivotal study, C2301, was adrenal insufficiency, which was reported in over half (51.1%) of patients. Adrenal insufficiency was captured via a variety of biochemical and clinical symptoms, and included patients with glucocorticoid withdrawal symptom (normal response to CD cure). There were 11 SAE of adrenal insufficiency on the other hand. The high rate of adrenal insufficiency may be in part due to an overestimation of true adrenal crises, but also a result of an overly aggressive titration dosing schedule (as most patients required intermediary doses for achieving response), and because of study design, a rapid titration timeline schedule (with an exposure of 10 days of a new dose before the mUFC collection). The majority of patients required 2-7 mg bid to establish and sustain response, which are relatively low doses given the sponsor's up-titration plan that goes to 30 mg bid. • Pituitary tumor growth was seen in a small subset of patients, without relation to drug dose or ACTH level, and a causal association is not clear. Overall, 35 patients had $\geq 20\%$ tumor volume increase however 	<p>The rate of adrenal insufficiency was high, and likely caused by a combination of a broad definition of this adverse event, an overly-aggressive dose titration, and a short (10-day) exposure of drug before assessment and decision to titrate.</p> <p>A dosing regimen that starts at 1 mg, with 1-2 mg titration increments with dose titration not occurring within less than 2-3 weeks is likely to result in a safer regimen. Although efficacy at 3 weeks was not established with this specific application, in order to mitigate the risk of adrenal insufficiency, a conservative approach is preferred when considering dose titration schedule. Labelling considerations for safety will be discussed separately.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>10 of these had a subsequent decline. Three patients (2.2%) developed diplopia but alternative causes were present in 2.</p> <ul style="list-style-type: none"> • Rise in adrenal hormone precursors (as a result of 11β-OH blockade) resulted in the following AEs: hypokalemia and hypertension (13% each), acne and hirsutism (9% each), edema and increase weight (7% and 2% respectively). • EKG changed including QT-prolongations were small and mostly non-serious SAEs. 	
<p>Risk Management</p>	<ul style="list-style-type: none"> • A post-marketing requirement (PMR) for the ongoing phase 3 study, C2302 will be in place. Completion of data collection, analysis, and reporting of the results of this study will be the only PMR for this approval. 	<p>The results from C2302 (phase III study) have to be submitted as part of a post-marketing requirement.</p>

2 Therapeutic Context

2.1. Analysis of Condition

Cushing's disease (CD) is a rare, serious, life-threatening disease that is characterized by hypercortisolemia, caused by excess secretion of adreno-corticotrophic hormone (ACTH) from the pituitary gland. CD is the most common form of endogenous Cushing's syndrome (CS) which encompasses a larger spectrum of hypercortisolemia. CD predominantly affects females in the 20-50's age range and is characterized by features that are pathognomonic for CD including facial plethora, red-purple striae, proximal muscle weakness, and unexplained bruising, as well more common characteristics like obesity, hypertension, diabetes, osteoporosis, and psychiatric symptoms (including depression, anxiety, irritability, and memory impairment). Other complications include increased infections. Patients with CD also have increased risk of venous thrombosis and cardiovascular events, such as myocardial infarction and stroke. Overall, these patients have increased morbidity, mortality (due to cardiovascular diseases) and lower quality of life as compared to age-matched controls.¹²³

2.2. Analysis of Current Treatment Options

First-line treatment for CD is surgical resection of the pituitary tumor,⁴ which may be followed by radiation therapy in patients for whom surgery is not curative. Medical therapy is more frequently used as adjunctive, mainly in patients who have failed surgery and/or radiation therapy or in those who cannot have surgery. Several therapies exist, both labelled and off-label use, as showed in Table 1.

¹ Etxabe J, Vazquez JA 1994 Morbidity and mortality in Cushing's disease: an epidemiological approach. Clin Endocrinol (Oxf) 40:479 – 484

² Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J 2001 Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab 86:117–123

³ Wei L, MacDonald TM, Walker BR 2004 Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 141:764 –770

⁴ Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100:2807-31.

Table 1-Summary of Medical Therapies for Treatment of Cushing's Syndrome

Product (s) Name	Mechanism of Action	Dosing/ Administration	Important Safety and Tolerability Issues
FDA Approved Treatments			
Pasireotide (for CD only)	Somatostatin analogue	0.3-0.9 mg twice a day, SC injection	diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, and diabetes mellitus
Pasireotide LAR (for CD only)	Somatostatin analogue	20-40 mg every 4 weeks/IM injection	Diarrhea, nausea, gallbladder abnormalities, hyperglycemia
Mifepristone (for treatment of hyperglycemia in CS)	Glucocorticoid receptor antagonist	300-1200 mg/day, oral tablets	fatigue, vomiting, nausea, arthralgia, hypertension, edema, and endometrial thickening
Off-label therapies			
Ketoconazole	Inhibits cortisol synthesis by blocking 11 β -hydroxylase and 17 α -hydroxylase	400-1600 mg/day, taken three to four times a day	Hepatic toxicity, gastrointestinal disturbance, male hypogonadism
Metyrapone	Inhibits cortisol synthesis by blocking 11 β hydroxylase	500- 6000 mg/day, taken three to four times a day	Hypertension, hypokalemia, hirsutism, acne, gastrointestinal disturbance
Mitotane	Inhibits cortisol synthesis by blocking 11 β hydroxylase, 18-hydroxylase and 3 β hydroxysteroid dehydrogenase	0.5 g daily up to maximal dose of 8 g/day	Gastrointestinal disturbance, hepatotoxicity, gynecomastia, neurologic complaints.
Etomidate	imidazole anesthetic that inhibits cortisol synthesis by blocking 11 β hydroxylase	infused intravenously at 2.5-3 mg/hour	Sedation, myoclonus, nausea, vomiting, local injection site pain

3 Regulatory Background

3.1. Regulatory Actions and Marketing History

Osilodrostat (LCI699) is a new molecular entity (NME) and is not currently marketed in US. LCI699 has a potent and clinically relevant pharmacodynamic effect of inhibiting 11 β -hydroxylase (CYP11B1), the enzyme that catalyzes the final step in the synthesis of cortisol in the adrenal cortex. LCI699 is also an inhibitor of aldosterone synthase via its blocking of 18-hydroxylase. The inhibition of aldosterone synthase was the rationale for the investigation of LCI699 for [REDACTED] (b) (4)

[REDACTED] However, because LCI699 also inhibits cortisol synthesis, the Sponsor decided to continue development of LCI699 for treatment of CD. The current clinical development program for LCI699 is focused in particular on treatment of patients with CD, since CD is the most common cause of endogenous CS. The clinical development program for LCI699 in the treatment of CD was submitted under IND 117489 in the Division of Metabolic and Endocrinologic Products (DMEP) in 2013 and orphan drug designation was granted the same year.

3.2. Summary of Presubmission/Submission Regulatory Activity

The application was submitted on March 7, 2019 which proposed the use of Osilodrostat for patients with Cushing's disease. On October 9, 2013 an End-of-Phase 2 (EOP2) meeting was held to guide the phase III clinical development program. The focus of the meeting was development of pivotal phase 3 studies to evaluate the efficacy and safety of the drug for the proposed indication. The sponsor presented the rationale for phase III, multicenter, double-blind, placebo-controlled randomized withdrawal study of LCI699 in patients with CD following a 24 week, single-arm, open-label dose titration and treatment period. FDA disagreed with the Sponsor and recommended conducting a traditional short-term, placebo-controlled trial followed by a longer-term safety extension to provide substantial evidence of efficacy and safety of the drug in the intended population. The sponsor consulted with the European and Japanese regulatory agencies and responded to FDA on November 4, 2013. The feedback from the above-mentioned entities was that there was an unequivocal response that an adequately powered placebo-controlled design would not be feasible in this study population where an initial 12 weeks of exposure to placebo is not considered safe or ethical.

FDA recommended including the following data in the NDA submission (refer to the Agency's response from January 16, 2014):

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- a. the results from Phase 3 randomized, double-blind, pivotal study with an up-front placebo-controlled design (with extension of up to 12 months for patients who respond to therapy) (in ~100 patients), and
- b. the results of the Phase 2 trial CLC1699C2201 (in 27 patients).

A pre-NDA meeting was held on August 20, 2019 during which the sponsor enquired if the inclusion of study C1201, which includes 9 Japanese patients with [REDACTED] (b) (4). The Agency recommended [REDACTED] (b) (4).

3.3. Foreign Regulatory Actions and Marketing History

LC1699 is not marketed within or outside the U.S.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The office of Scientific Investigations (OSI), conducted inspections at 5 sites: the 3 U.S. clinical sites (3101, 3113, 3103), previous for-cause⁵ domestic site that was involved with Osilodrostat (3107) and 1 foreign clinical site (1402, Canada). The findings from one site (3103) included significant inspectional observations for which the site was issued a Form FDA-483 and the data was considered not reliable. As such, it was recommended that a sensitivity analysis was performed to exclude the data.

The inspectional findings from the other sites included regulatory deficiencies which are unlikely to have a significant impact on the overall results. Inspection of the sponsor site (Novartis, Basel) revealed a number of findings for which corrective and preventive actions were provided, and the data was considered acceptable for use. A detailed report on the results of the inspections is provided by Dr. Cynthia Kleppinger dated November 7, 2019.

4.2. Product Quality

⁵ For-cause inspection is an inspection triggered by a complaint or other information sent to FDA, rather than a PDUFA application

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Not applicable.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to Dr. Daniel Minck's review for full details.

4.5. Clinical Pharmacology

Please refer to Dr. Clinical Pharmacology's review for full details and QT interval study.

4.5.1. Mechanism of Action

Osilodrostat is a novel new molecular entity which has a potent and clinically relevant pharmacodynamic effect of inhibiting 11 β -hydroxylase (CYP11B1), the enzyme that catalyzes the final step in the synthesis of cortisol in the adrenal cortex (Figure 1). Osilodrostat is also an inhibitor of aldosterone synthase via its blocking of 18-hydroxylase, which converts deoxycorticosterone to aldosterone.

4.5.2. Pharmacodynamics

The proposed dosing starts at 2 mg bid, to be titrated by increments of 1-2 mg bid based on response and tolerability. Bid dosing was based on half-life of 3-5 hours.

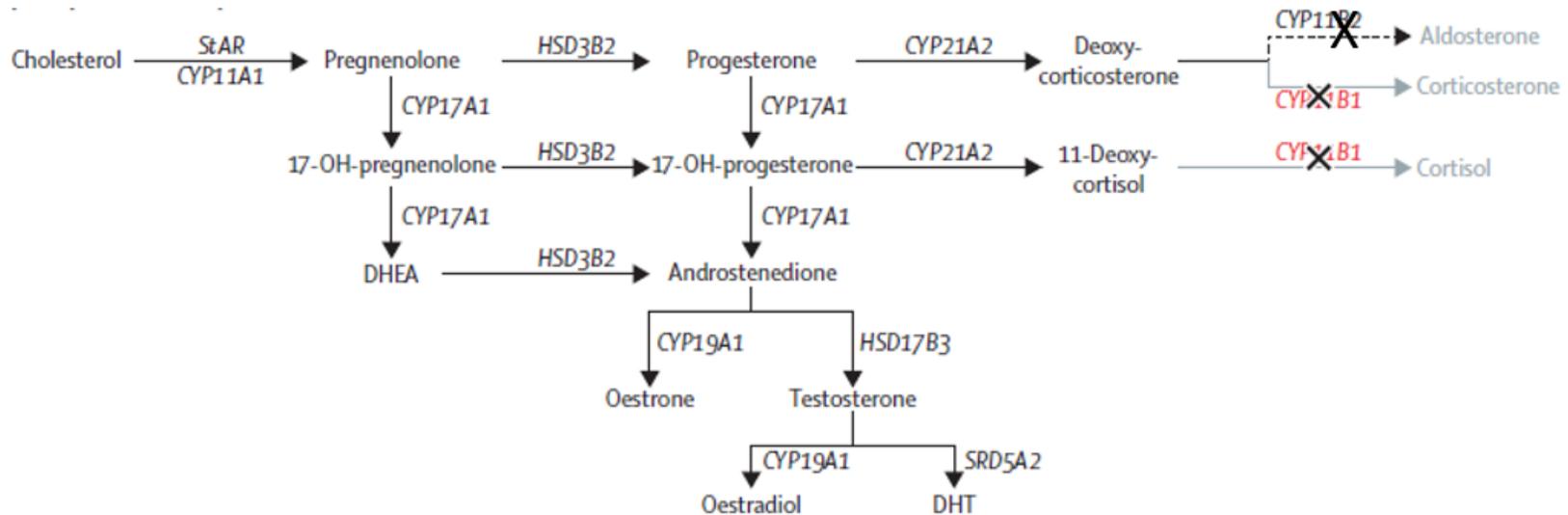
4.5.3. Pharmacokinetics

Not reviewed

4.6. Devices and Companion Diagnostic Issues

Not applicable.

Figure 1 - Adrenal steroidogenesis pathway and blockade action of osilodrostat



Source: Adapted from El-Maouche et al.

Reviewer's comment: although osilodrostat is a novel molecule which exerts its action via blocking 11 β -hydroxylase, metyrapone, which is used off-label for the treatment of Cushing's syndrome, works similarly by blocking the same enzyme.

4.7. Consumer Study Reviews

Not applicable.

5 Sources Clinical Data and Review Strategy

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5.1. Table of Clinical Studies

Table 2 - Summary of Efficacy and Safety Studies in Patients with Cushing's Disease/Syndrome

Study	Phase	Design	Study population	N of subjects, enrolled/LCI699 treated	Drug/Dose	Treatment duration
C2201 (LINC-1) (LINC-2)	2	Open-label, single arm, dose titration study of the effect of LCI699	Patients with CD	31	LCI699: 2 mg bid titrated every 2 weeks to 5 mg bid, 10 mg bid, 20 mg bid or 50 mg bid	10 weeks
C1201	2	Dose titration, multi-center study in Japanese patients with non-CD endogenous Cushing's syndrome	Patients with Cushing's syndrome	9	LCI699: 2-30mg bid dose escalation in Period 1 (12 weeks), Period 2: 36 weeks treatment.	36 weeks + extension (72 weeks)
C2301 (LINC-3)	3	8-Week, placebo-controlled, randomized withdrawal study after 24 weeks open label osilodrostat in patients with Cushing's disease	Patients with CD	137	LCI699: 2-30mg bid dose escalation in Period 1 (12 weeks), Period 2: 12 weeks treatment. Period 3: randomized placebo-controlled.	48 weeks + extension phase (24 weeks)
C2302 (LINC-4)	3	Multi-center, randomized, double-blind, 48-week study with an initial 12-week placebo-controlled period patients with Cushing's disease	Patients with CD	73	LCI699: 2-20mg bid dose escalation in Period 1 (12 weeks), Period 2: 34 weeks treatment (open-label)	48 weeks + extension phase (48 weeks)

Table 3 - Summary of Clinical Studies in Healthy Volunteers and Other Populations

Study	Phase	Design	Study population	N of subjects, enrolled/LCI699 treated	Drug/Dose	Treatment duration
A2101 (part I and II)	1	First-in-human, randomized, double-blind, placebo- and comparator-controlled (eplerenone), single and multiple dose study to assess safety, tolerability, PK and PD of LCI699	Healthy volunteers	99/63	LCI699: Part 1: 3, 10, 30, 100, 200mg Part 2: 0.5, 1, 3, 10 mg Placebo Eplerenone (Part 1)	Single dose (Part I) 14 days (Part II)
A2102	1	Randomized double-blind, placebo-controlled, parallel group study to evaluate safety, PK and PD following single and multiple doses of LCI699	Healthy Caucasian and Japanese subjects	83/63	LCI 699: 0.5, 1 and 2 mg/day qd or bid Placebo	14 days
C2101	1	Absorption, distribution, metabolism, excretion (ADME) study	Healthy male volunteers	5	LCi699 50 mg	Single dose
A2201	2	Randomized, double-blind, placebo and active controlled, parallel group, dose finding study to evaluate the efficacy and safety of LCI699	Patients with essential hypertension	524/363	LCI699:0.25,0.5,1mg qd; 0.5 mg bid Eplerenone 50 mg bid Placebo	56 - 63 days
A2206	1	Single-blind, pilot study to explore the PD, safety and tolerability of LCI699	Patients with primary hyperaldosteronism	18/14	LCI699: 0.5 mg bid x 14 days, increased to 1 mg bid x 14 days	28 days
A2215	1	Randomized, double-blind, placebo-controlled dose escalation study to evaluate the effect of LCI699 on cortisol	Patients with essential hypertension	63	LCI699: Cohort A: 0.5 mg, 1 mg qd Cohort B: 1 mg bid, 2 mg qd Placebo	42 days
A2216	2	Randomized, double blind, placebo and active controlled, parallel group, dose ranging study to explore the safety and efficacy of LCI699	Patients with resistant hypertension	155/89	LCI699: 0.25 mg bid, 1 mg qd, 0.5 mg bid titrated to 1 mg bid Eplerenone 50 mg bid Placebo	56 days
C2102	1	Open-label single sequence cross-over (effect on CYP450)	Healthy subjects	20	Oral single dose of osilodrostat 50 mg	Single dose

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C2103	1	Open-label, single dose, parallel group	Patients with hepatic impairment	33	Oral single dose of osilodrostat 30 mg	Single dose
C2104	1	Open-label, single dose, parallel group	Patients with renal impairment	15	Oral single dose of osilodrostat 30 mg	Single dose
C2105	1	Randomized, double-blind, placebo- and active- controlled, cross-over (Thorough QTC)	Healthy volunteers	86	4 single-dose treatment periods: LCI699 10mg, LCI699 150mg, placebo, moxifloxacin 400 mg.	27 days
C2108	1	Open-label, three-period, single-fixed sequence (DDI with oral contraceptive)	Healthy volunteers	24	Oral single dose of osilodrostat 10 mg	single dose
C1101	1	Open-label, single dose, two-period, cross-over (Food effect)	Healthy volunteers	20	Oral single dose of osilodrostat 30 mg	Single dose

Healthy volunteer studies are highlighted in yellow, studies in patients with hypertension and primary hyperaldosteronism are highlighted in green; PK studies are highlighted in orange.

5.2. Review Strategy

The primary source of efficacy and safety data for this review is study C2301, the pivotal phase 3 trial in patients with Cushing's disease. The supportive efficacy and safety data came from Study C2201, Phase 2 study in CD patients and 1201 Study in Japanese patients with CS (9 patients).

For additional safety analysis, the 120-day clinical safety update was reviewed to ensure that no new safety signals are present. Additionally, blinded data from the phase 3, upfront placebo-controlled, double-blinded randomized study (C2302) were reviewed, mainly also in support of safety. This review includes this medical reviewer's commentary, as well as analyses generated by this medical reviewer using the JMP Version 15.0.0 and MAED software, from the pivotal study, C2301.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study C2301 (pivotal study)

6.1.1. Study Design

Overview and Objective

The primary objective was to compare the complete response rate (defined as UHC < ULN) at the end of the 8-week period of randomization withdrawal (RW) (Week 34) between patients randomized to continue osilodrostat therapy vs. placebo.

Trial Design

This is a Phase III, multi-center, double-blind, RW study of osilodrostat versus placebo following a 24 week, single-arm, open-label dose titration and treatment period. The study has four periods combined in the Core Period (Study Period 1 to 4) and an optional Extension Period. A schematic diagram of the core period is shown in Figure 2. The study was divided into 4 periods, as described below:

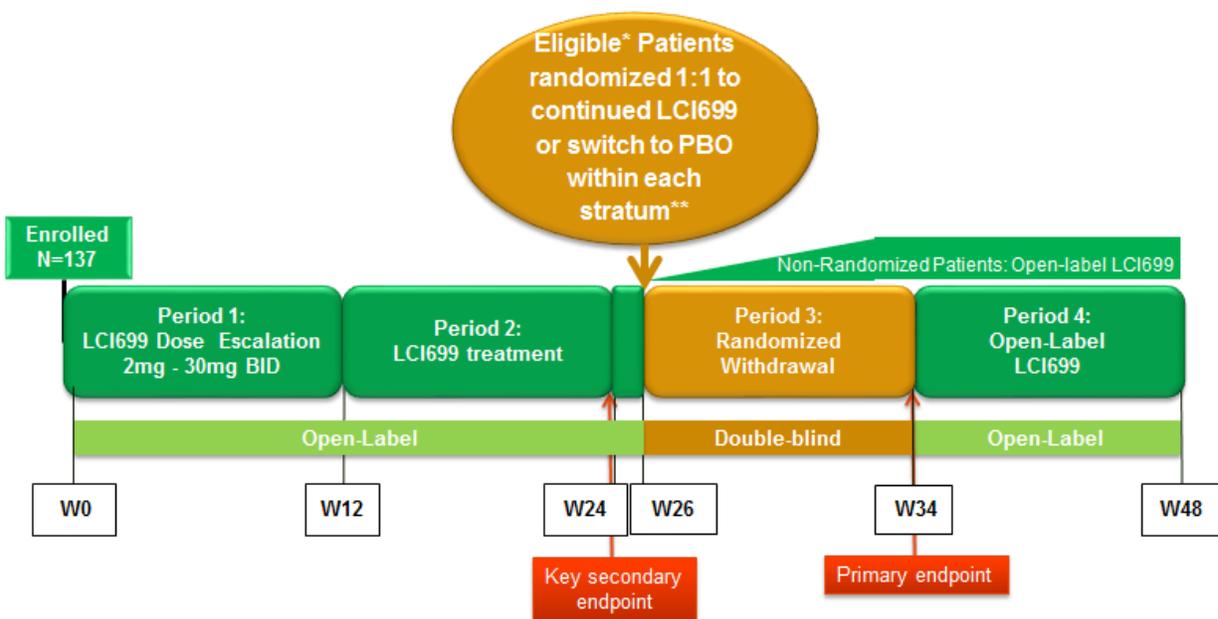
Study Period 1 (Week 1 to Week 12):

Study Period 1 consisted of a single-arm, open-label, osilodrostat dose-titration in individual patients. Dose adjustments were based on the mean of three consecutive 24-hour UFC (mUFC) values as measured by the central laboratory. Triplicate urine samples were collected every two weeks during individual dose titration with the last urine sample preferably collected the day

prior to the visit at site. The dose was increased if mUFC was above the upper limit of normal (>ULN) and was reduced if mUFC was below the lower limit of normal (LLN), or if the patient was symptomatic and mUFC was in the lower part of the normal range. The dose was maintained if mUFC was within the normal range and the patient did not have signs or symptoms of hypocortisolism or adrenal insufficiency. At Week 0 and Week 2, dose increases were not permitted.

The dosing regimen was up-titrated according to a set escalation sequence, with a starting dose of osilodrostat of 2 mg b.i.d., followed by 5 mg b.i.d., 10 mg b.i.d., 20 mg b.i.d., and 30 mg b.i.d (maximal dose) (Figure 3). The up-titration was to be continued until till the mUFC was within normal. Osilodrostat was supplied in pills of 1 mg, 5 mg, 10 mg and 20 mg film coated tablets, and to be given orally twice a day. There was no plan for dose titration or re-start once a dose has been reduced or interrupted for safety.

Figure 2- Schematic for Study Design (Core Period) for C2301



*To be eligible for randomization, the patient must have mUFC ≤ ULN at Week 24, and no further dose increase after Week 12.
**Strata are determined by the combination of two stratification factors at randomization: 1) LCI699 dose at Week 24 (≤ 5mg bid vs. > 5mg bid), and 2) history of pituitary irradiation (yes/no).

Study Period 2 (Week 13 to Week 24):

This was an open label, single-arm treatment period. During this period, patients whose mUFC became elevated during this period had their osilodrostat dose increased further, if it was tolerated, up to 30 mg bid. Such patients were followed for long-term safety and efficacy and

were not considered responders for the key secondary endpoint, hence were not randomized in Study Period 3.

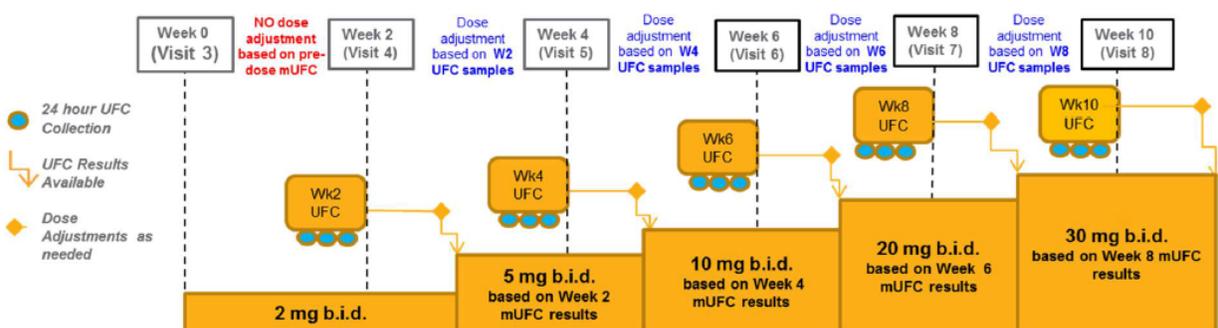
A patient was assessed as a complete responder at Week 24 (for the key secondary endpoint) and randomized in Period 3, if the following two conditions were met:

- mUFC \leq ULN based on urine samples collected at Week 24, and
- The dose of osilodrostat during study Period 2 was not increased above the level established at the end of study Period 1. Dose reduction was allowed for safety.

Dose reductions and temporary dose interruptions for reasons of safety did not preclude the possibility of complete response at Week 24.

Patients remained on open-label osilodrostat during the period between Week 24 and Week 26, in order to ensure that sufficient time was allowed for central laboratory results (Week 24 mUFC) to become available for all patients at all sites, and to standardize the time of randomization across sites.

Figure 3 - Osilodrostat dose up-titration schedule during C2301



Study visits are at Week 0 (Day1) and Weeks 2, 4, 6, 8, 10 and 12. Once mUFC results are available and a dose adjustment is required, sites should inform patients of the dose change by phone or under direct supervision by the site during an unscheduled visit prior to the next scheduled visit.

Note:

- LCI699 dose is increased if the mean of 3 urine samples (mUFC) is **above normal (> ULN)**.
- LCI699 dose is maintained if the mUFC value is in the **normal range** and the patient does **not** have signs or symptoms of hypocortisolism or adrenal insufficiency.
- LCI699 dose is reduced if the mUFC value is **< LLN OR** the patient has signs and symptoms of **hypocortisolism or adrenal insufficiency** and the mUFC value is in the **lower part of the normal range**.
- **Dose reductions and temporary dose interruptions for safety reasons are permitted at any time** during the study.

Source: Sponsor's protocol, Figure 4-2

At the end of Period 2, patients were either randomized to treatment or placebo (i.e. entered Study Period 3) if they were eligible for randomization, or received open-label osilodrostat until the end of the Core Period (Week 48) if they were not eligible for randomization.

In order to be eligible for randomization in study Period 3, patients had to have completed dose titration during study Period 1 (with no dose titration in Period 2), and had to be classified as complete responders at Week 24 of study Period 2.

Study Period 3 (Week 26 to Week 34):

This was a double-blind, placebo-controlled RW Period. Patients, investigators, and study team were all blinded to treatment assignment. Eligible patients were randomized in a double-blinded fashion at Week 26 at a 1:1 ratio either to continue treatment with osilodrostat at the same dose or to matching placebo. 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).

a. UFC monitoring during RW:

During study Period 3, mUFC was measured at scheduled visits every 2 weeks. However, patients were also allowed to have unscheduled visits at any time during the RW if they reported symptoms of hypercortisolism or hypocortisolism. The Investigator decided the dose of study drug (osilodrostat or placebo) during this period, although he/she was blinded to treatment assignment. All laboratory tests during the RW Period were sent to the central laboratory for analysis, and all treatment decisions were based on central laboratory results.

b. Dose adjustments during RW

The study drug dose (osilodrostat or placebo) remained unchanged for patients who maintained a normal mUFC and did not develop AEs related to study drug during RW. The Investigator could reduce or temporarily withhold a dose of study drug for safety reasons at any time during the RW Period. Dose reductions or interruptions for safety reasons during the RW Period did not preclude the possibility of a complete response at Week 34. Dose increases were not permitted during the RW Period. If a dose increase was required because of elevated UFCs (above the dose patients were on in Phase 2), the patient was considered as non-responder by the end of RW period.

c. Discontinuation from RW

A patient was discontinued from the RW Period and declared a nonresponder, if the mUFC increased to $>1.5 \times \text{ULN}$, and at least 2 individual urine samples showed UFC $>1.5 \times \text{ULN}$ at a single visit (scheduled or unscheduled). After discontinuation from RW treatment, or at the end of the RW Period (Week 34), whichever came first, the patient resumed open-label osilodrostat at a dose selected by the Investigator.

Study Period 4 (Week 35 to Week 48):

This was a single-arm, open-label therapy period where all patients received LCI699 treatment at the end of Week 34. The dose selection was at the discretion of the investigator. During Period 4, the dose of LCI699 could remain unchanged, increased, decreased or withheld, depending on the mUFC level, and whether or not there is an AE. Patients were allowed unscheduled visits if they report symptoms of continuing hypercortisolism, glucocorticoid withdrawal, hypocortisolism, or any adverse event (particularly during the first few weeks of open-label LCI699 treatment after randomized withdrawal).

At Week 48, patients had the option to enter an extension period or discontinue LCI699 at week 48 to conclude with an end of core study visit 4 weeks off study drug (at Week 52).

Reviewer Comments: the study design, which starts with a single-arm, open-label study followed by randomized withdrawal period, does not allow for proper comparison of safety or efficacy by default. For safety analysis, the carry-over effect of osilodrostat would be anticipated to persist throughout the randomization period, where it would be unclear if any AE occurring in the placebo group is an AE of disease recurrence, study drug carry-over, or effect of placebo. For efficacy endpoint, the sponsor only randomizes patients who did not require dose-titration beyond 12 weeks (and by default, do not include patients who are more difficult to control). This may not reflect anticipated efficacy in the clinical setting, where patients who are more difficult to control would require this drug. Although the endpoints of the study are varied and include multiple clinical and biochemical control, the study, essentially, did not have a true "placebo" comparator.

Study Endpoints

The primary endpoint was the proportion of responders at the end of RW period (Week 34), i.e. randomized patients in each arm with mUFC \leq ULN, and were neither discontinued, nor had LCI699 dose increase above the level at week 26 during the randomized withdrawal period.

The key secondary endpoint was to calculate the proportion of enrolled patients with mUFC \leq ULN at Week 24 and had no dose increase above the level established at Week 12 between Week 13 and Week 24.

Other secondary endpoints included:

- Time-to-last control of mUFC, which is defined as the time (in days) from randomization to the last mUFC collection that was \leq ULN before early discontinuation or completion of randomized withdrawal period, whichever is earlier.
- Complete response rate: proportion of enrolled patients with mUFC \leq ULN at Week 12, Week 24 and Week 48.

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- Partial response rate: proportion of enrolled patients with > 50% reduction from baseline in mUFC, but mUFC > ULN) at Week 12, Week 24, and Week 48.
- Overall response rate: proportion of enrolled patients with mUFC ≤ ULN or at least 50% reduction from baseline at Week 12, Week 24, and Week 48.
- Actual and percentage change in mUFC from baseline to each postbaseline visit during the core and extension at which UFC is collected
- Actual and percentage change in mUFC from the time of randomization (Week 26) to the end of the randomized withdrawal period (Week 34), or the last mUFC measurement prior to early discontinuation, whichever occurs earlier.

Exploratory endpoints included:

- Actual and percentage change from baseline to Week 12, Week 24 and Week 48 in: fasting glucose, HbA1c, fasting lipid profile, blood pressure, body weight, BMI and waist circumference
- Actual and percentage change from the randomization (Week 26) to the end of randomized withdrawal period (Week 34), or the last measurement available prior to early discontinuation, whichever occurs earlier (see bullet above for individual parameters).
- Change in standardized score of Cushing QoL, Beck Depression Inventory-II⁶, and EQ-5D-5L⁷, from baseline to Week 24 and Week 48.
- Change in standardized score of Cushing QoL, Beck Depression Inventory-II, and EQ-5D-5L, from the randomization (Week 26) to the end of randomized withdrawal period (Week 34), or the last measurement prior to early discontinuation, whichever occurs earlier.
- Mean change from baseline to Week 12, 24, 34, and 48 in each of the following clinical signs of Cushing's disease by photography: facial rubor, hirsutism, striae, supraclavicular fat pad, dorsal fat pad, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruises). Changes were captured by a semi-quantitative Likert-scale⁸ and assessed by shift tables.
- Absolute and percent change from baseline to Week 48 in bone mineral density as measured by DXA scan at the lumbar spine and total hip
- Time-to-escape is defined as the time (in days) from the first mUFC ≤ ULN to the first mUFC results > 1.5 x ULN with at least 2 individual UFC results > 1.5 x ULN.

⁶ Psychometric test for measurement of depression, consisting of a 4-point scale ranging from 0 to 3 based on severity of each item

⁷ QoL assessment consisting of 5-point scale (no problems, slight problems, moderate problems, severe problems and extreme problems) and covers five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

⁸ Psychometric assessment consisting of a 5- or 7-point survey scale allowing users to self-grade the assessment in question (e.g. Strongly Agree, Agree, Undecided, Disagree, Strongly Disagree, etc.).

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- Adverse events and laboratory abnormalities will be assessed using the National Cancer Institute-Common Toxicology Criteria (NCI-CTC) grading scale (version 4.0).
- AEs of special interest, as reported by the investigator, or by laboratory evaluation, ECG, Holter recording, and pituitary MRI.
- Plasma concentrations (pre-dose, 0.5 h, 1.5 h, and 3.5 h post-dose) of LCI699.

Statistical Analysis Plan

For full statistical review, please refer to the primary statistical review by Dr. Alexander Cambon.

The following analysis populations were defined:

Randomized analysis set (RAS): includes all randomized patients who received at least one dose of osilodrostat or placebo. Following the intent-to-treat principle, patients were analyzed according to the treatment they have been assigned to during the randomization. This was used for primary analysis of the primary endpoint.

Full analysis set (FAS): includes all patients who received at least one dose of osilodrostat. This was used for primary analysis of the key secondary endpoints.

Safety set: There were two safety sets defined in this study:

- a. Safety analysis set (SAS) includes all patients who received at least one dose of osilodrostat and had at least one post-baseline safety assessment.
- b. Safety Analysis Set for randomized withdrawal period (SASR) includes only randomized patients who received at least one dose of randomized treatment (osilodrostat or placebo) and had at least one valid safety assessment during the randomized withdrawal period.

Pharmacokinetic analysis set (PAS): includes all patients who received at least one dose of osilodrostat and had at least one post-dose PK assessment.

The primary endpoint tested a statistical null hypothesis as such: the complete response rate at the end of 8-week RW period (Week 34) is the same between patients randomized to placebo and patients randomized to osilodrostat. A Cochran-Mantel-Haenszel exact test was utilized using the RAS; and was stratified by the two stratification factors considered for randomization following the intent-to-treat principle. For the key secondary endpoint, the null hypothesis tested if the complete response rate at Week 24 for osilodrostat was $\leq 30\%$. The analysis utilized the Clopper-Pearson method for the 2-sided 95% exact confidence interval (CI). Descriptive and summary statistics were used for the analysis of other secondary and exploratory endpoints.

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Protocol Amendments

There were 4 protocol amendments, summarized here:

Amendment 1 (July 15, 2014):

The purpose of this protocol amendment was to address requests from the Voluntary Harmonization Procedure (VHP) review. The following amendments were therefore implemented:

- The definition of the optional extension period was revised.
- The time-to-escape definition was clarified.
- Pregnancy was identified as an absolute withdrawal criterion.
- Treatment discontinuation criteria was revised to include an increase in QTcF > 60 msec from baseline before the first dose.
- 24-hour Holter recordings were added during the extension at Weeks 72 and 96.

Amendment 2 (March 11, 2015):

The primary reason for this amendment was to add a local, country-specific intensive PK sampling for the site in China in order to investigate potential ethnic differences in LCI699 pharmacokinetics at steady-state and at doses used in the treatment of patients with Cushing's disease.

Additional major changes applicable to all sites included:

- Inclusion of recent LCI699 clinical trial results information and results of a clinical drug-drug interaction study.
- Relaxation of the protocol guidance on narrow therapeutic index/sensitive substrates of CYP1A2, CYP2C19, CYP2D6 and CYP3A4/5 as concomitant medication.
- Blinding: Corrected in the protocol, randomization is managed via an IRT system and the pharmacist, the bioanalyst and the pharmacokineticist will be blinded in the study.

Inclusion criteria:

- The minimum period of elapsed time since the last stereotactic radiosurgery was decreased from 3 years to 2 years.
- Rescreening is introduced in order to accommodate the long washout periods required for some cortisol-lowering medical therapies at the time of enrollment.

Exclusion criteria:

- QTcF exclusion limits were changed to >450 ms for males, and >460 ms for females.
- Definitions for post-menopausal status and woman not of childbearing potential were clarified.
- The criterion on optic chiasm compression is broadened to include patients at high risk from macroadenomas within 2 mm of the optic chiasm.
- Certain hormone assessments have been reduced in frequency (serum 11-deoxycortisol, serum aldosterone, late night salivary cortisol, and serum 11-deoxycorticosterone) or

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removed (urine aldosterone and urine 11-deoxycorticosterone), while other hormone assessments have been added (adrenal sex steroids: androstenedione, DHEAS, and estrone).

- Additional concomitant medications were now permitted, under certain conditions, including: spironolactone, eplerenone, cyproterone acetate or finasteride.

Amendment 3 (March 29, 2016):

This amendment addressed changes to reduce the risk of dosing errors. It included expanded description of the dose dispensation process, dose adjustments and communication of dosing instructions. This amendment also includes the addition of specific criteria for identification and management of patients with potential drug-induced liver injury (DILI).

The duration of the optional extension period was increased to collect additional long-term safety data as well as to provide continued access to the study drug for those patients benefitting from the treatment.

Amendment 4 (06-Jul-2017)

The main purpose of this amendment was to increase the duration of the optional extension period in order to collect additional long-term safety and efficacy data as well as to provide continued access to the study drug for those patients benefitting from the treatment. Based on this extension, the end of study definition has been updated. In addition, the long-term safety follow-up study modalities have been detailed.

Other protocol changes include:

-The QT-specific concomitant medication guidance for LCI699 was revised to limit the list of prohibited drugs to medications with a "Known risk to cause TdP" and "Possible risk to cause TdP", instead of all drugs known to prolong QT.

-The risks section was updated to include neutropenia, which is a known effect related to the decrease of cortisol in patients with Cushing's disease, in line with cases observed in clinical trials with LCI699.

Other changes included minor editorial changes and clarifications to the protocol and informed consent.

Medical Officer's comments-These changes/modifications are expected to have minimal impact on the integrity of the trial and interpretation of the results.

Data Quality and Integrity: Sponsor's Assurance

The study centers were visited at regular intervals. Novartis monitors were responsible for reviewing adherence to the protocol, compliance with GCP, and the completeness, accuracy, and consistency of the data. Direct access to subject medical and laboratory records was permitted to verify entries on the study-specific CRFs. Investigator staff training was provided by the Novartis Central laboratories were used to analyze samples for serum chemistry

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(including UFC) and a centralized ECG provider was used for reading of ECGs. The investigators were responsible for all data entered in the CRFs and documented their review and approval of the data by signing a form verifying the validity and completeness of the data. The investigators were responsible for appropriate retention of essential study documents. Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained. An audit of this study was included as part of the independent Global Compliance Auditing program performed by Novartis.

6.1.2. Study Results

Compliance with Good Clinical Practices

Study C2301 was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. Throughout the study, the sponsor had designated monitors who performed regular site visits to inspect the following: check the completeness of patient records, accuracy of entries on the case report form CRFs, adherence to the protocol and to Good Clinical Practice, progress of enrollment, and to ensure that study treatments were being stored, dispensed, and accounted for according to specifications.

Financial Disclosure

Financial disclosure information was collected from all clinical investigators participating in studies C2301, C2201, and C1201. Of the clinical investigators (US and non-US), all but two clinical investigators provided the financial disclosure form requested by Novartis (the remaining two investigators had left the site and attempts by Novartis to reach the investigators had failed). No clinical investigators were full or part-time employees of Novartis.

Patient Disposition

At the time of data cut-off date, 35 patients had discontinued the study (24 during the Core Period and 11 during the Extension Period). During the Core Period, 5 patients discontinued after Week 26 but prior to Week 48. One patient randomized to placebo withdrew from study during the RW Period on Day 220.

The most common reasons for discontinuation during the Core Period were AE's (10.9%, 15/137), patient consent withdrawal (2.9%, 4/137), and physician decision (2.2%, 3/137). Nearly three fourths of patients (106, 77.4%) entered the optional extension. (Table 4).

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19 patients discontinued at or prior to Week 26. Of the remaining 118 patients, 71 patients were randomized 1:1 (36 to osilodrostat, 35 to placebo) and the remaining 47 patients (not randomized) continued on open-label osilodrostat treatment (Figure 4).

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Table 4 - Patient disposition by randomized treatment group (FAS)

Disposition Reason	Randomized to osilodrostat during RW	Randomized to placebo during RW*	Non-randomized	All Patients
	N=36 n (%)	N=35 n (%)	N=66 n (%)	N=137 n (%)
Patients enrolled and treated	36 (100)	35 (100)	66 (100)	137 (100)
Discontinued at any time ‡	1 (2.8)	5 (14.3)	29 (43.9)	35 (25.5)
Primary reason for discontinuation at anytime				
Adverse event	0	2 (5.7)	18 (27.3)	20 (14.6)
Death	0	1 (2.9)	0	1 (0.7)
Physician decision	0	0	3 (4.5)	3 (2.2)
Patient withdrew consent	1 (2.8)	0	4 (6.1)	5 (3.6)
Patient/guardian decision	0	2 (5.7)	4 (6.1)	6 (4.4)
Discontinued at or prior to Week 12	0	0	7 (10.6)	7 (5.1)
Primary reason for discontinuation at or prior to Week 12				
Adverse event	0	0	4 (6.1)	4 (2.9)
Patient withdrew consent	0	0	2 (3.0)	2 (1.5)
Patient/guardian decision	0	0	1 (1.5)	1 (0.7)
Discontinued at or prior to Week 26 but after Weeks 12	0	0	12 (18.2)	12 (8.8)
Primary reason for discontinuation at or prior to Week 26 but after Week 12				
Adverse event	0	0	8 (12.1)	8 (5.8)
Physician decision	0	0	2 (3.0)	2 (1.5)
Patient withdrew consent	0	0	2 (3.0)	2 (1.5)
Discontinued prior to Week 48 but after Week 26	0	2 (5.7)	3 (4.5)	5 (3.6)
Primary reason for discontinuation prior to Week 48 but after Week 26				
Adverse event	0	2 (5.7)	1 (1.5)	3 (2.2)
Physician decision	0	0	1 (1.5)	1 (0.7)
Patient/guardian decision	0	0	1 (1.5)	1 (0.7)
Completed Week 48 (Core Phase)	36 (100)	33 (94.3)	44 (66.7)	113 (82.5)
Completed Week 48 and did not enter Extension phase §	1 (2.8)	3 (8.6)	3 (4.5)	7 (5.1)
Completed Week 48 and entered Extension phase	35 (97.2)	30 (85.7)	41 (62.1)	106 (77.4)
Ongoing in Extension phase	34 (94.4)	27 (77.1)	34 (51.5)	95 (69.3)
Discontinued study in Extension phase	1 (2.8)	3 (8.6)	7 (10.6)	11 (8.0)
Primary reason for discontinuation in the Extension phase				
Adverse event	0	0	5 (7.6)	5 (3.6)
Death	0	1 (2.9)	0	1 (0.7)
Patient withdrew consent	1 (2.8)	0	0	1 (0.7)
Patient/guardian decision	0	2 (5.7)	2 (3.0)	4 (2.9)
Discontinued at or prior to Week 72 but after Week 48	1 (2.8)	0	3 (4.5)	4 (2.9)
Discontinued prior to Week 96 but after Week 72	0	2 (5.7)	1 (1.5)	3 (2.2)
Discontinued after Week 96	0	1 (2.9)	3 (4.5)	4 (2.9)
Completed Extension phase	0	0	0	0

FAS: full analysis set; RW: randomized withdrawal.

N is the total number of patients enrolled and treated.

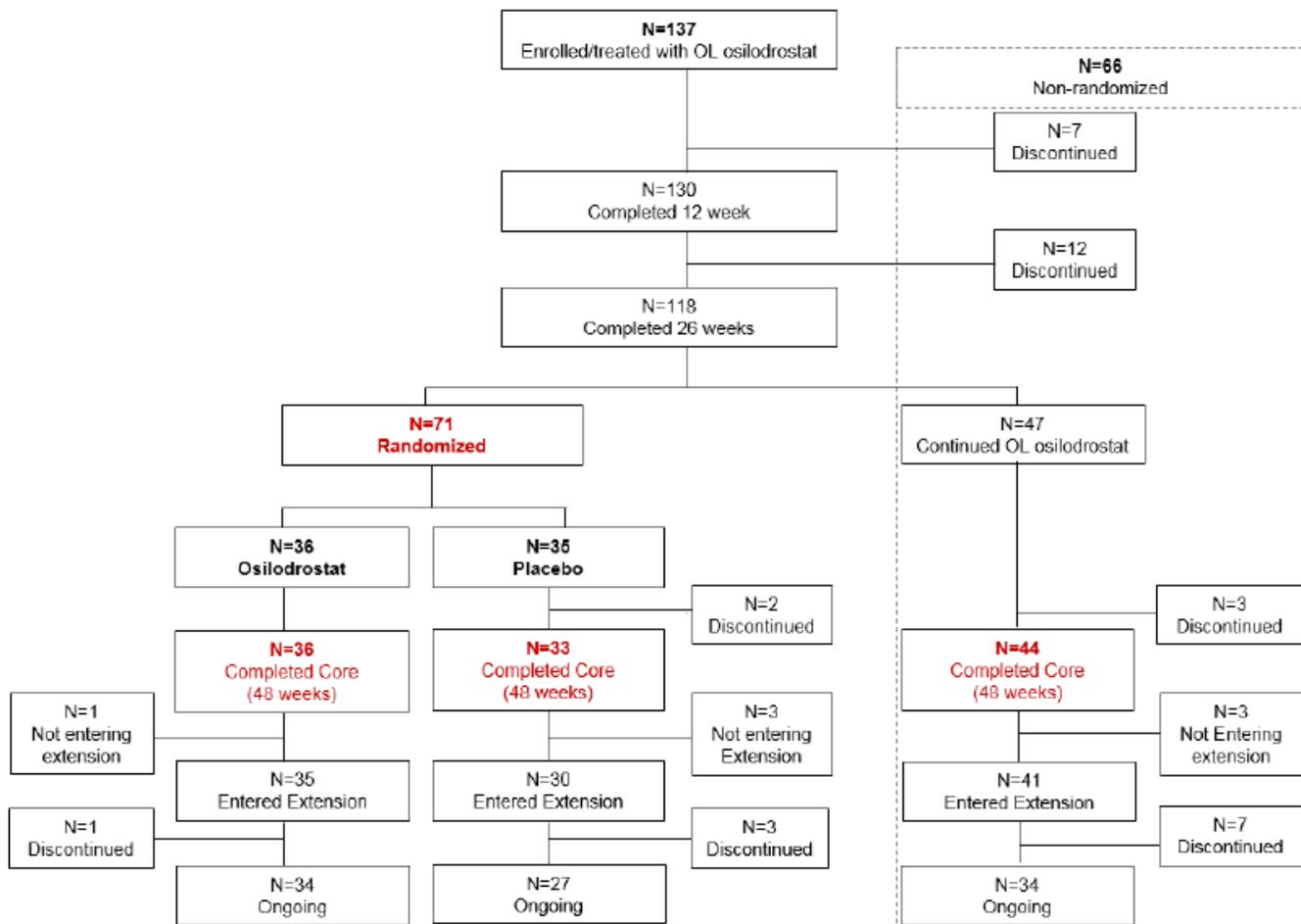
% based on N.

§ Patients who completed Week 48 and did not enter extension phase are not counted as discontinuations.

* For patients randomized to placebo during the RW Period and including all data while on either osilodrostat or placebo.

Source: Sponsor's CSR, Table 14.1-1.1

Figure 4- Patient disposition by randomized treatment group (full analysis set)



FAS: full analysis set; OL: open-label

Source: Sponsor's CSR, Table 14.1-1.1

Among patients who were not randomized, the following reasons accounted for failure to randomize:

- 19 patients had dose increased beyond Week 12 although mUFC normalization was achieved
- 20 patients did not meet the mUFC normalization criteria at Week 26
- 7 patients did not meet both of the previous criteria
- 1 patient was not randomized due to Investigator decision

Protocol Violations/Deviations

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

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Overall, 115 patients (83.9%) had protocol deviations. The most commonly reported protocol deviations (reported in >5% of patients) were related to:

- Study treatment related deviations: which included incorrect dose or missed dose (79/137, 57.7%); and treatment dispensing error occurring at Week 34 (18/137, 13.1%; 18 randomized patients received an additional two weeks of double-blind medication supply
- Prohibited medication related deviations (46/137, 33.6%)
- Two or more missing 24 hr UFC samples at least at one time point (22/137, 16.1%),
- Missing ECG assessment at Day 1 visit pre-dose (19/137, 13.9%),
- Inclusion criteria deviations (8/137, 5.8%), mainly screening assessment performed outside of the screening window
- Exclusion criteria deviations (7/137, 5.1%), included having risk factors for QTc prolongation or Torsade de Pointes

The proportion or of patients or type of deviation did not differ by patient randomization group.

Reviewer Comments: Because of the complex design of the study, protocol deviations occurred not infrequently, however, when data were analyzed (by this medical officer as well statistical support) the protocol deviations did not affect the study results.

Patient Demographic Characteristics

The study population consisted of predominantly females (77%, 106) vs. males (23%, 31) with the majority being Caucasian (65.0%) or Asian (28.5%). The median patient age was 40 years (range: 19.0-70.0); median BMI was 28.8 (range: 18.8-56.4). (Table 5).

Table 5- Patient Demographics by Treatment Group

Demographic Variable	Randomized to osilodrostat during RW N=36	Randomized to placebo during RW N=35	Non-randomized N=66	All Patients N=137
Age (years)				
n	36	35	66	137
Mean (SD)	44.3 (11.27)	42.0 (13.47)	39.0 (13.38)	41.2 (12.98)
Median	41.0	40.0	37.5	40.0
25th-75th percentile	37.5-51.5	31.0-55.0	28.0-47.0	31.0-49.0
Min-Max	20.0-69.0	19.0-68.0	19.0-70.0	19.0-70.0
Age category (years) - n (%)				
18-<65	34 (94.4)	34 (97.1)	62 (93.9)	130 (94.9)
65-≤ 75	2 (5.6)	1 (2.9)	4 (6.1)	7 (5.1)
Sex -n (%)				
Female	30 (83.3)	22 (62.9)	54 (81.8)	106 (77.4)
Male	6 (16.7)	13 (37.1)	12 (18.2)	31 (22.6)
Race - n (%)				
Caucasian	27 (75.0)	23 (65.7)	39 (59.1)	89 (65.0)
Black	0	3 (8.6)	1 (1.5)	4 (2.9)
Asian	7 (19.4)	7 (20.0)	25 (37.9)	39 (28.5)
Other	2 (5.6)	2 (5.7)	1 (1.5)	5 (3.6)
Ethnicity - n (%)				
Hispanic or Latino	5 (13.9)	2 (5.7)	5 (7.6)	12 (8.8)
Chinese	1 (2.8)	1 (2.9)	2 (3.0)	4 (2.9)
Indian	0	1 (2.9)	6 (9.1)	7 (5.1)
Japanese	2 (5.6)	2 (5.7)	5 (7.6)	9 (6.6)
Mixed Ethnicity	0	0	1 (1.5)	1 (0.7)
Other	28 (77.8)	29 (82.9)	47 (71.2)	104 (75.9)
Weight (kg)				
n	36	35	66	137
Mean (SD)	78.2 (19.02)	83.4 (24.73)	80.7 (23.06)	80.8 (22.44)
Median	73.6	75.4	74.9	74.5
25th-75th percentile	65.9-87.5	64.5-92.0	64.2-92.5	65.6-92.0
Min-Max	55.0-126.3	50.8-141.0	46.3-164.9	46.3-164.9
Height (cm)				
n	36	35	66	137
Mean (SD)	163.0 (9.01)	163.9 (10.76)	162.7 (9.04)	163.1 (9.44)
Median	160.2	163.0	162.5	161.3
25th-75th percentile	156.0-170.7	157.0-172.0	158.0-168.0	157.0-169.0
Min-Max	151.0-190.0	142.0-185.3	139.0-189.0	139.0-190.0
Body mass index (kg/m²)				
n	36	35	66	137
Mean (SD)	29.6 (7.35)	30.9 (8.37)	30.4 (7.73)	30.3 (7.76)
Median	28.5	29.0	28.8	28.8
25th-75th percentile	24.0-32.4	25.2-33.4	24.6-35.3	24.6-33.8
Min-Max	18.8-47.7	20.8-55.1	18.8-56.4	18.8-56.4

Source: Sponsor's CSR

The median time of CD diagnosis was 47.2 months (range: 2.1-286.7) and most patients (87.6%) had persistent or recurrent CD (Table 6). At baseline, the mean (SD) mUFC was 1006 nmol/24h (1589.86); which is approximately 7×ULN. The median mUFC at baseline was 476.4 nmol/24h (range: 35.6 to 9611.6); which is approximately 3.5×ULN. Most of the patients (96%) had previous treatment for CD, including surgery (87%). The majority of patients (75%) had been treated previously for CD (prior treatment included ketoconazole, metyrapone, cabergoline and pasireotide).

Table 6- Baseline Characteristics of Study Population by Treatment Group

Disease history	Osilodrostat N=36	Placebo N=35	Non-Randomized N=66	All Patients N=137
Time (months) to first osilodrostat dose since diagnosis				
N	36	35	66	137
Mean (SD)	71.4 (63.54)	88.3 (67.46)	46.5 (43.26)	63.7 (58.20)
Median	53.6	76.8	34.7	47.2
25th - 75th percentile	25.9 - 94.3	39.3 - 133.7	14.1 - 65.7	19.0 - 88.3
Min- Max	2.1 - 286.7	2.9 - 277.7	3.0 - 180.6	2.1 - 286.7
Cushing's Disease Status: n (%)				
De novo	4 (11.1)	2 (5.7)	11 (16.7)	17 (12.4)
Persistent/recurrent	32 (88.9)	33 (94.3)	55 (83.3)	120 (87.6)
Any previous surgery: n (%)				
Yes	32 (88.9)	33 (94.3)	55 (83.3)	120 (87.6)
No	4 (11.1)	2 (5.7)	11 (16.7)	17 (12.4)
Any previous treatments for Cushing's disease: n (%)				
Yes	35 (97.2)	33 (94.3)	63 (95.5)	131 (95.6)
No	1 (2.8)	2 (5.7)	3 (4.5)	6 (4.4)
Any previous pituitary irradiation: n (%)				
Yes	6 (16.7)	5 (14.3)	11 (16.7)	22 (16.1)
No	30 (83.3)	30 (85.7)	55 (83.3)	115 (83.9)
Baseline mean UFC(nmol/24h)				
n	36	35	66	137
Mean (SD)	890.0 (1275.66)	560.0 (548.84)	1305.8 (2012.21)	1006.0 (1589.86)
Median	457.0	357.9	556.9	476.4
25th - 75th percentile	268.1 - 777.1	209.7 - 652.1	347.9 - 1245.5	313.7 - 918.6
Min- Max	35.6 - 5719.5	67.9 - 2466.1	66.8 - 9611.6	35.6 - 9611.6
- Time to first osilodrostat dose since diagnosis = (first osilodrostat dose date - date of diagnosis of Cushing's disease +1)*12/365.25.				

Source: Sponsor's CSR, Table 14.1-3.1

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Medical Officer's comment: In general, the enrolled population was representative of CD (middle-age females), and demographic and medical histories were similar between the treatment groups. Patients randomized to active drug had higher UFCs compared to placebo group.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug compliance was assessed at each patient visit and captured in the Drug Accountability Form. As listed in the inclusions/exclusion criteria, concomitant medication for CD was not allowed, however, one patient randomized to placebo received a concomitant medication for CD (reported in protocol deviations). No rescue medication was listed or used in for C2301 or the supportive studies.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the proportion of the responders, i.e patients who achieved complete response rates by the end of 8-week RW Period (i.e. at Week 34) in patients randomized to osilodrostat vs. placebo (RAS population). At the time of the randomization (Week 26) all (100%) randomized patients were biochemically controlled (mUFC <ULN). At the end of the 8-week RW Period (Week 34 of study), the complete response rate in the Osilodrostat Group dropped to 86.1% (95% CI: 70.50, 95.33) but was higher than that in the placebo group (29.4%; 95% CI: 15.10, 47.48); with an estimated odds ratio of 13.71 (95% CI: 3.73, 53.44); $p < 0.001$ in favor of osilodrostat) (Table 7).

Data Quality and Integrity – Reviewers' Assessment

The data appear to be adequate without concerns for quality or integrity.

Efficacy Results – Secondary and other relevant endpoints

For the key secondary endpoint, a responder was defined by meeting the following criteria:

- mUFC \leq ULN at Week 24
- No osilodrostat dose increase between Weeks 12 and 24

If a patient discontinued prior to Week 24 for any reason, they were considered as non-responder. At Week 24, 72 patients (52.6%) met the criteria for the key secondary endpoint (95% CI: 43.9, 61.1). The responder rate was evaluated in FAS population.

Other Secondary Endpoints:

1- Proportion of mUFC responders over the various study periods:

The overall response rate to osilodrostat at Week 8 was 85.4%, with 68.6% of patients (94/137) being complete responders and 16.8% (23/137) being partial responders.

At the end of Period 1 (Week 12) the overall response rate was 85.4% (117/137), with 71.5% of patients (98/137) being complete responders and 13.9% (19/137) being partial responders. At the end of the RW Period, the overall response rate was 94.4% (34/36) in the Osilodrostat Group (with 33 patients being complete responders and one being a partial responders) and 68.6% (24/35) in the Placebo Group (with 17 patients being complete responders and 7 being partial responders).

Table 7- Assessment of Primary Response (Complete Response) by end of randomization

	Responder/ N (%)	95% CI*	CMH exact test	
			Odds ratio (95% CI)	2-sided p-value
All Randomized Patients				
Osilodrostat	31/36 (86.1)	(70.50, 95.33)	Osilodrostat vs. Placebo	
Placebo	10/34 (29.4)	(15.10, 47.48)	13.71 (3.73, 53.44)	<.001
Osilodrostat dose at Week 24 ≤ 5 mg bid and with history of pituitary irradiation				
Osilodrostat	5/5 (100.0)	(47.82, 100.00)	Osilodrostat vs. Placebo	
Placebo	1/5 (20.0)	(0.51, 71.64)	NE (1.49, NE)	
Osilodrostat dose at Week 24 ≤ 5 mg bid and without history of pituitary irradiation				
Osilodrostat	17/21 (81.0)	(58.09, 94.55)	Osilodrostat vs. Placebo	
Placebo	7/21 (33.3)	(14.59, 56.97)	8.50 (1.74, 46.22)	
Osilodrostat dose at Week 24 >5mg bid and with history of pituitary irradiation				
Osilodrostat	0			
Placebo	0			
Osilodrostat dose at Week 24 >5 mg bid and without history of pituitary irradiation				
Osilodrostat	9/10 (90.0)	(55.50, 99.75)	Osilodrostat vs. Placebo	
Placebo	2/8 (25.0)	(3.19, 65.09)	27.00 (1.45, 1373.96)	

CI: confidence interval; CMH: Cochran-Mantel-Haenszel; RAS: randomized analysis set.

A primary efficacy responder is defined as a randomized patient who has mUFC ≤ ULN at Week 34 and who was neither discontinued (study or RW treatment) nor had osilodrostat dose increase above the level at Week 26 during the RW Period of the study.

Patients who discontinued during the RW Period were counted as non-responders for the primary efficacy.

*2-sided 95% CIs are based on the exact (Clopper-Pearson) method.

Source: Sponsor's CSR, Table 14.2-1.1

By the end of the Core Period (Week 48) 76% of patients (95% CI: 67.87, 82.80) were responders (with 91/137 (66.4%) being complete responders and 13/137 (9.5%) being partial responders).

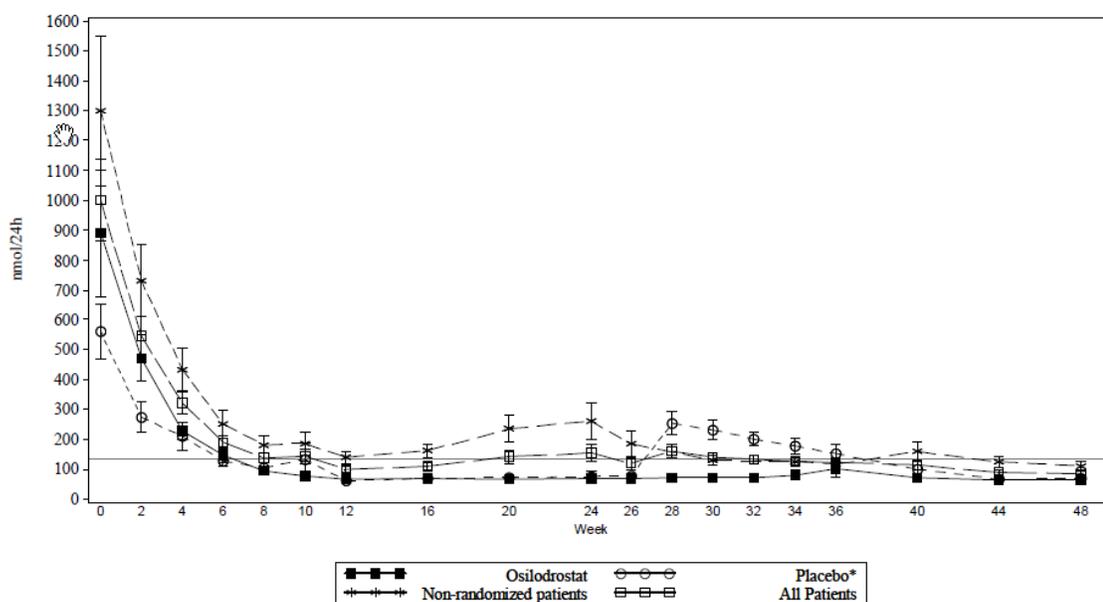
At the last assessment 88% of patients (95% CI: 81.73, 93.18) were still responders (with 98/137 (71.5%) being complete responders and 23/137 (16.8%) being partial responders).

2- Change in mUFC from baseline during the study

For most patients, the mean mUFC levels decreased from high values and stabilized to normal levels around Week 6 of osilodrostat treatment (Figure 5).

After Week 6, normal mUFC levels were generally observed throughout the study in most patients (except in non-randomized patients at Weeks 20 -24 and patients randomized to placebo at Weeks 28 -34). The proportion of patients with mUFC ≤ ULN up to Week 48 is shown in Figure 6; whereas individual patient mUFC values at baseline and Week 24 are shown in Figure 7.

Figure 5- Mean (SE) mUFC at time points up to Week 48 by randomized treatment group



FAS: full analysis set; mUFC: mean urinary free cortisol; SE: standard error.

This analysis includes scheduled visits only. Standard error is shown.

RW Period starts at Week 26 and ends up to Week 34.

The reference line is the upper limit of normal range of 138 nmol/24 hr.

* For patients randomized to placebo during the RW Period and including all data while on either osilodrostat or placebo.

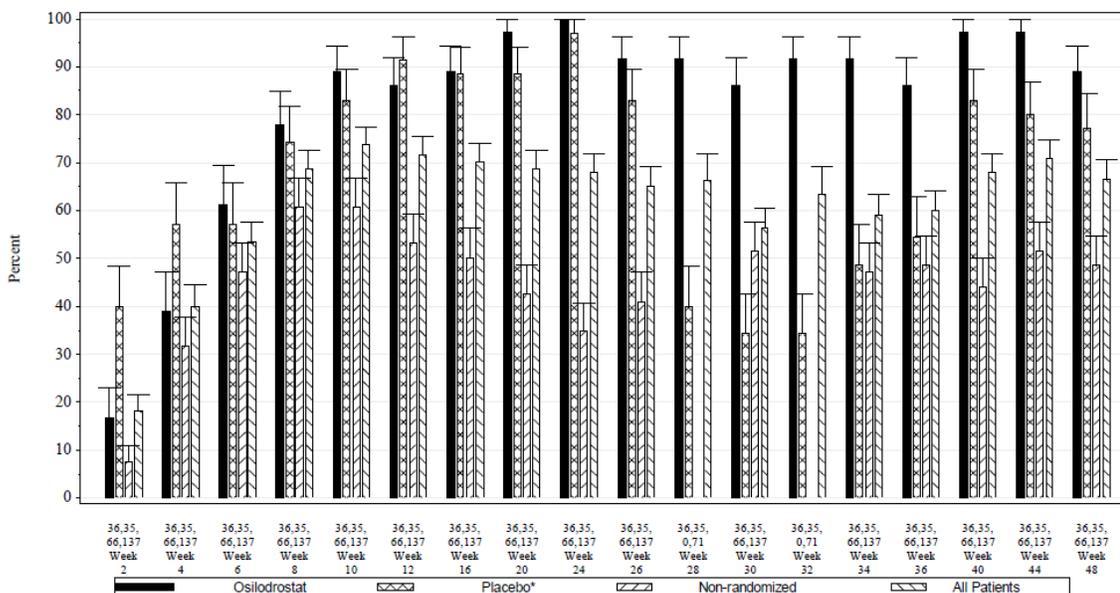
Source: Sponsor's CSR, Figure 14.2-1.2

In the All Patients group, the median (range) mUFC and corresponding median (range) percentage change from baseline was (mUFC ULN=138 nmol/24hr):

- 476.4 (35.6 to 9611.6) nmol/24h at baseline
- 62.5 (5.3 to 1006.2) nmol/24h at Week 12 (end of Period 1); -84.1% (-99.8 to 23.0)
- 75.5 (5.6 to 2511.6) nmol/24h at Week 24 (end of Period 2); -82.3% (-99.4 to 339.5)
- 77.3 (5.7 to 2145.8) nmol/24h at Week 26 (start of RW Period); -83.1% (-99.5 to 95.5)
- 63.3 (8.2 to 514.6) nmol/24h at Week 48 (end of Core Period); -87.9% (-99.6 to 105.7)
- 79.0 (5.3 to 5422.4) nmol/24h at the last available assessment; -82.1% (-99.9 to 39.5)

At Week 2 there was approximately a 42% reduction in the adjusted mean mUFC value from baseline. After the dose-titration period (Week 12), there was approximately an 85% reduction, which was maintained until the end of the Core Period (89%).

Figure 6- Proportion of patients with normal mUFC up to Week 48 by randomized treatment



FAS: full analysis set; mUFC: mean urinary free cortisol; ULN: upper limit of normal.

The numbers xx, xx at the bottom of the bars are the denominators for the percentages in each dose regimen.

This analysis includes scheduled visits only. +1 standard error is displayed on each bar.

* For patients randomized to placebo during the RW Period and including all data while on either osilodrostat or placebo.

Source: Sponsor's CSR, Figure 14.2-1.3

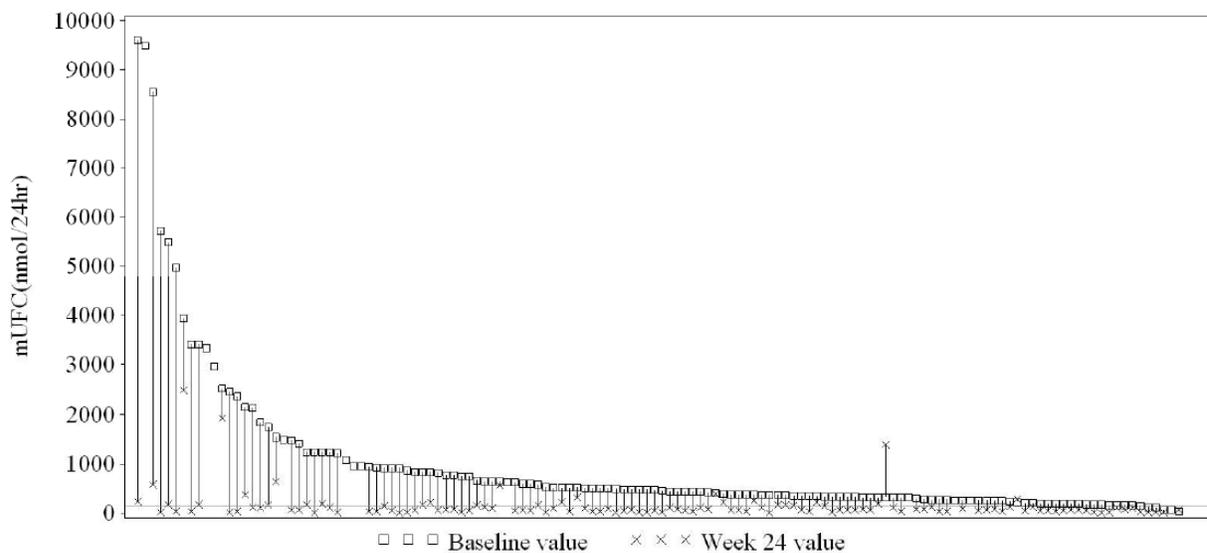
3- Change in mUFC from randomization during the RW Period

At randomization, mean (SD) mUFC levels were similar in the Osilodrostat Group (70.9 nmol/24h (43.53)) and Placebo Group (79.1 nmol/24h (57.9)), as set by randomization criteria where all patients randomized had normal mUFC (Table 9)Table 9.

At the end of the RW Period, the median (range) mUFC levels were lower in patients who were randomized to osilodrostat (50.01 nmol/24h (11.9 to 610.8)) as compared to patients randomized to placebo Group (139.7 nmol/24h (29.8 to 849.5)). The corresponds median (range) percent change from randomization was -13.9% (-70.1 to 1019.9) in the Osilodrostat Group and 174.6% (-58.1 to 2588.8) in the Placebo Group.

The overall change in mUFC in the 2 randomized groups was opposite in direction: patients on osilodrostat had a 10% reduction from the mean mUFC at randomization baseline during the RW period; whereas patients on placebo had up to a 200% increase in the mean mUFC from randomization baseline.

Figure 7 - Individual mUFC values at baseline and Week 24



FAS: full analysis set; mUFC: mean urinary free cortisol.
The reference line is the upper limit of normal range of 138 nmol/24 hr.
Sorting is by baseline mUFC value.

Source: Sponsor's CSR, Figure 14.2-1.5

4-Time to first controlled mUFC response

The median time to first controlled mUFC response was 41 days (95% CI: 30.0, 42.0). Almost all patients (132/137; 96.4%) had mUFC \leq ULN at least once at some stage while on study (Figure 8). By Day 56, patients receiving osilodrostat had 75% probability of achieving normal mUFC whereas by Day 84, the probability of achieving response was 93%.

5-Time to loss of control of mUFC during the RW Period

The median time to loss of control of mUFC in the Placebo Group was 28 days (Table 8). In patients who were randomized to osilodrostat, 2/36 patients lost mUFC control during the RW Period (1 of the 2 patients had a dose interruption due to AE). In the Placebo Group, 20/34 patients lost mUFC control.

Table 8 -Time to loss of control of mUFC during RW Period by treatment group (FAS)

	Osilodrostat N=36	Placebo N=34
n/N (%)	2/36 (5.6)	20/34 (58.8)
Percentiles (95% CI)		
25th	NE (NE, NE)	15.0 (13.0, 18.0)
50th	NE (NE, NE)	28.0 (15.0, NE)
75th	NE (NE, NE)	NE (48.0, NE)
% Event probability estimates (95% CI)		
2 weeks after randomization	2.8 (0.4, 18.1)	24.2 (12.9, 42.7)
4 weeks after randomization	2.8 (0.4, 18.1)	51.5 (35.9, 69.2)
6 weeks after randomization	5.6 (1.4, 20.4)	54.5 (38.8, 71.8)
8 weeks after randomization	5.6 (1.4, 20.4)	61.1 (45.0, 77.5)

CI: confidence interval; mUFC: mean urinary free cortisol; NE: not estimable; RAS: randomized analysis set.

% Event probability estimate is the estimated probability that a patient will have an event prior to the specified time point. % Event probability estimates are obtained from the Kaplan-Meier survival estimates for each

treatment groups; Greenwood formula is used for CIs of KM estimates.

n: Total number of events included in the analysis.

N: Total number of patients included in the analysis.

Source: Sponsor's CSR, Table 14.2-3.1

Dose/Dose Response

The dose and dose-response for osilodrostat was determined by studies A2101, A2102, C2201, and is discussed under Section 7.1.4

There was no clear relation between dose and dose-response in C2301. Although dosing adjustment allowed for a maximum of 30 mg bid of osilodrostat, most patients achieved normalization of mUFC (and stabilization of response) at dose range of 2-7 mg bid. There was no relation between baseline mUFC or duration of disease at baseline and osilodrostat dose required to achieve response.

Table 9 - Summary of actual and % mUFC change during RW period (RAS)

Statistics	Osilodrostat N=36			Placebo N=34		
	Actual	Change from randomization Actual	Change from randomization Percent	Actual	Change from randomization Actual	Change from randomization Percent
Randomization	n	35		33		
	Mean (SD)	70.9 (43.53)		79.1 (57.90)		
	Median	57.6		57.0		
	Min-Max	5.7-226.5		8.9-245.0		
Week 28	n	35	35	32	32	32
	Mean (SD)	72.7 (52.62)	1.8 (38.16)	13.5 (63.35)	249.4 (211.34)	174.9 (203.47)
	Median	53.5	-2.4	-3.5	192.8	114.6
	Min-Max	14.7-247.1	-68.0-98.8	-78.2-181.1	27.3-908.8	-8.1-790.7
	95% CI		(-11.3, 14.9)	(-8.3, 35.3)		(101.6, 248.3)
Week 30	n	35	35	29	29	29
	Mean (SD)	73.0 (63.47)	2.1 (56.25)	11.9 (92.17)	195.8 (117.62)	124.7 (113.39)
	Median	50.2	-8.2	-16.6	176.0	119.6
	Min-Max	11.8-313.1	-79.8-258.6	-69.3-474.2	45.0-599.9	-6.1-567.1
	95% CI		(-17.2, 21.5)	(-19.8, 43.5)		(81.6, 167.9)
Week 32	n	34	34	34	24	24
	Mean (SD)	68.3 (51.51)	2.0 (49.86)	16.0 (91.84)	191.4 (117.47)	125.2 (108.34)
	Median	52.7	-6.2	-9.8	163.6	98.9
	Min-Max	7.9-230.7	-93.7-176.2	-88.2-323.1	29.2-439.4	-22.0-428.9
	95% CI		(-15.4, 19.4)	(-16.0, 48.1)		(79.4, 170.9)
Week 34	n	34	34	34	23	23
	Mean (SD)	80.8 (102.43)	14.5 (100.38)	32.7 (181.99)	191.3 (172.68)	124.3 (178.90)
	Median	50.1	-6.0	-13.9	139.7	62.3
	Min-Max	11.9-610.8	-69.4-556.2	-70.1-1019.9	29.8-849.5	-98.1-809.0
	95% CI		(-20.5, 49.6)	(-30.8, 96.2)		(46.9, 201.7)

CI: confidence interval; RAS: randomized analysis set; RW: randomized withdrawal; SD: standard deviation.

Patients having two or more 24h UFC assessments at a visit are included.

One patient on osilodrostat (Patient C2301- (b) (6)) and one patient on placebo (Patient C2301- (b) (6)) were randomized at Week 24 but had missing data at Week 26 and were not included in the analysis.

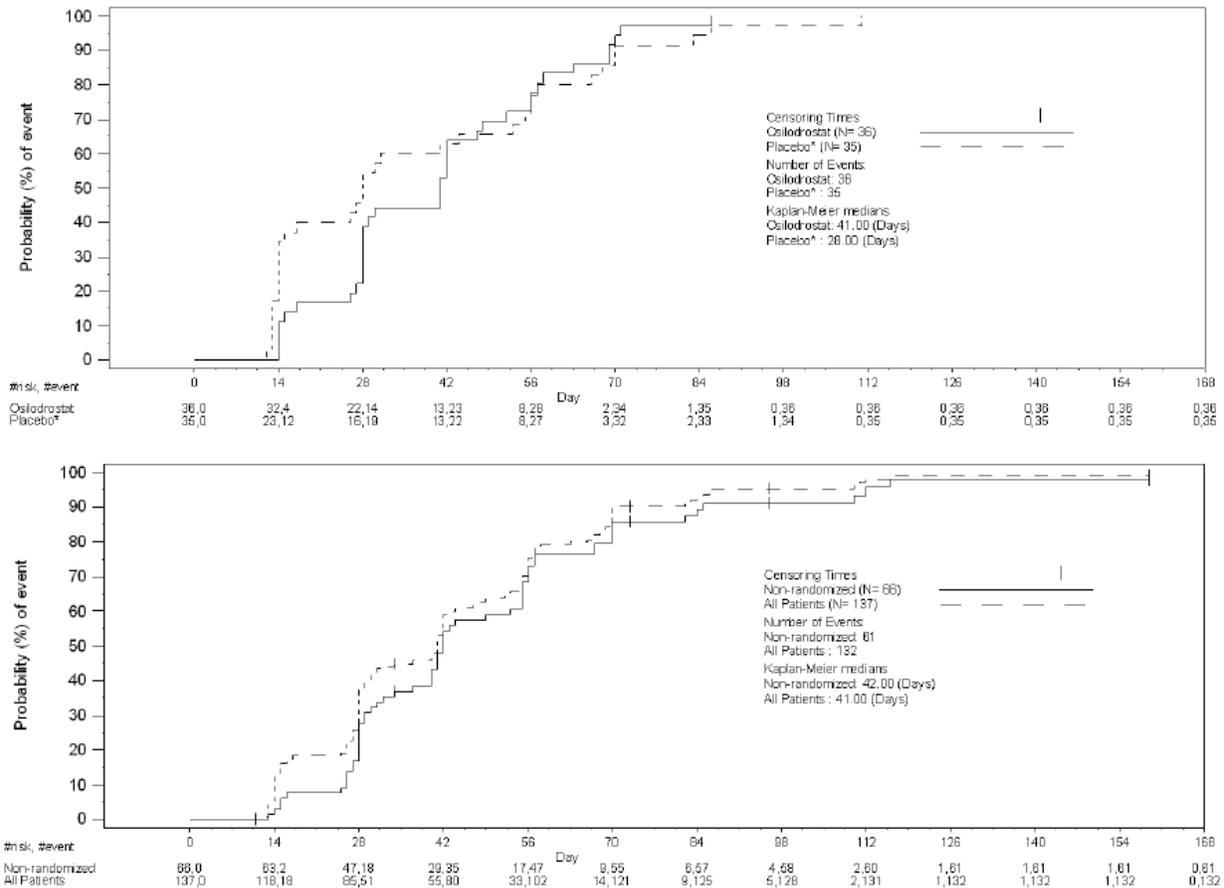
2-sided 95% CI shown are on the mean change and mean percentage change from randomization.

Source: CSR, Table 14.2-3.4

Durability of Response

The elimination half-life ($t_{1/2}$) of osilodrostat is 3-5 hours which underlies the rationale of bid dosing. PK studies have shown that osilodrostat does not accumulate in plasma following twice-daily multiple dosing up to 3 mg bid and there is no change in kinetics on repeated dosing. It is therefore anticipated that osilodrostat should be eliminated ~ 20 hours ($5 t_{1/2}$) after the last dose. It is noted however, that the effect of osilodrostat remains well after 20 hours, as observed in patients randomized to placebo in Period 3, of whom one-third remained responders by the end of 8 weeks of randomization. Studies with healthy volunteers have also showed similar findings. It is unclear why the biological effect of osilodrostat outlasts the elimination half-life, and one possibility could be related to downregulation of receptors, which may take a longer time (up to 12 weeks) to recover.

Figure 8 - Kaplan-Meier plot of time to first normal mUFC by treatment group (FAS)



FAS: full analysis set; mUFC: mean urinary free cortisol; ULN: upper limit of normal.

* For patients randomized to placebo during the randomized withdrawal period and including all data while on either osilodrostat or placebo.

Source: Sponsor's CSR, Figure 14.2-1.4

Persistence of Effect

In C2301 study, up-titration of osilodrostat occurred every 2 weeks, with 97% of patients achieving first response (normalization of mUFC) within the first 12 weeks, although almost all patients required dose lowering after reaching the first normal mUFC for safety reasons, mainly adrenal insufficiency. Although the proportion of total responders was highest by Week 12 (71.5%) as compared to Week 24 (67.9%) and Week 48 (66.4%); the proportion of responders thereafter remained consistent until the end of the study, with the proportion of complete responders being 71.5% at the time of the last available assessment (beyond Week 120).

Reviewer's comments: The decline in the proportion of complete responders seen during the Core Phase of the study followed by persistent response suggests an overly- aggressive titration schedule, which lead to interruption of treatment (due to safety, mainly adrenal insufficiency), followed by a "catch-up" dose-response was attempted. This led to dose fluctuations in the majority of patients, and possibly rendered dose stabilization harder. In contrast, the proportion of complete responders at Weeks 48 and end of study suggest persistence of effect once a safe, stable dose is reached.

Additional Analyses Conducted on the Individual Trial

Exploratory Endpoints:

1. Serum and salivary cortisol levels

A. Serum cortisol levels

A reduction in serum cortisol level during the Core Phase was seen in all 137 patients as depicted in Figure 9. The greatest reduction was in the first 12 weeks (dose-titration period). This decline in levels was maintained in Period 2, after which in Period 3 (RW Period), an increase in cortisol levels was seen in patients randomized to placebo as compared to patients who remained on osilodrostat. In patients who were on placebo, the mean cortisol levels declined upon resuming osilodrostat in Period 4. By the end of the Core Phase (Week 48), the mean serum cortisol levels in all patients was within the normal range, with a 45% reduction in cortisol levels from baseline as such: At baseline, the mean (SD) serum cortisol was 630.2 (248.87) nmol/L or 22.8 mcg/dL (9) mcg/dL; at 12 weeks, 313.4 (157.46) nmol/L or 11.4 (5.7) mcg/dL; at 24 weeks it was 323.3 (146.79) nmol/L or 11.8 (5.3) mcg/dL; and by Week 48 it was 304.2 (134.43) nmol/L or 11 (4.8) mcg/dL.

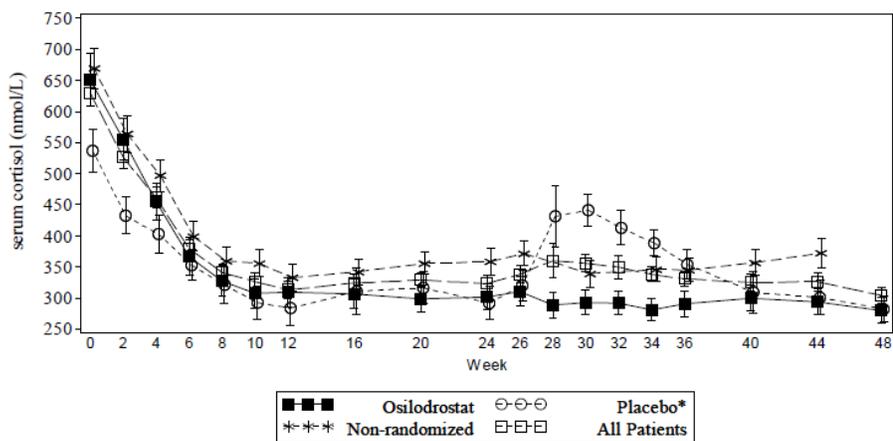
B. Morning salivary cortisol levels

Similar to serum cortisol levels, there was a reduction in mean morning salivary cortisol levels during the dose-titration period (Period 1), which was sustained during Period 2 where the mean salivary cortisol levels remained within normal range for all patients (Figure 10). As anticipated, patients who were randomized to placebo in Period 3 had a

rise in morning salivary cortisol levels followed by a decline once they resumed osilodrostat.

Overall, there was a 53% decline in mean morning salivary cortisol levels by end of Core Phase as compared to baseline in all patients, with a mean (SD) morning salivary cortisol of 12.6 (11.6) nmol/L or 0.5 (0.4) mcg/dL at baseline, and 4.4 (3.2) nmol/L 0.2 (0.1) mcg/dL at Week 48.

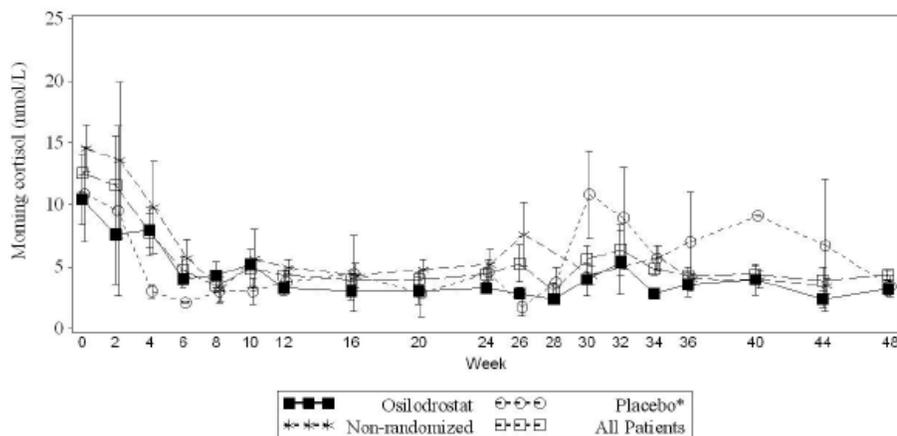
Figure 9- Mean (SE) serum cortisol during Core Phase by treatment group (FAS)



- This analysis includes scheduled visits only.
 - RW period starts at Week 26 and ends up to Week 34.
 * For patients randomized to placebo during the randomized withdrawal period and including all data while on either osilodrostat or placebo.

Source: Sponsor's CSR, Figure 14.2-1.7

Figure 10 - Mean (SE) morning salivary cortisol levels during Core Phase by treatment group (FAS)



FAS: full analysis set; SE: standard error.

Includes scheduled visits only. Randomized withdrawal (RW) Period starts at Week 26 and ends up to Week 34.

* For patients randomized to placebo during the RW Period and including all data while in either osilodrostat or placebo.

Source: Sponsor's CSR, Figure 14.2-1.7

C. Late-night salivary cortisol levels

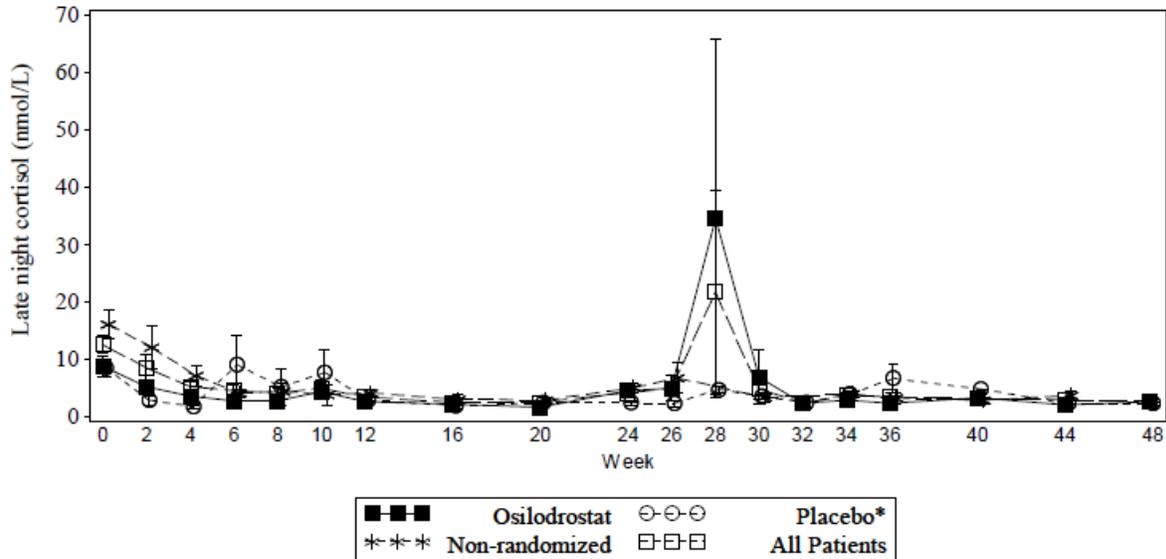
Mean late-night salivary cortisol levels throughout the Core phase are shown in Figure 11. The trend in the levels are similar to that of morning salivary and serum cortisol levels; however, at Week 28 the number of patients included was small (7) leading to a large inter-patient variability.

Overall, there was a 48% decline in mean late-night salivary cortisol levels by end of Core Phase as compared to baseline in all patients, with a mean (SD) late-night salivary cortisol of 12.5 (13.9) nmol/L or 0.5 (0.5) mcg/dL at baseline, and 2.7 (1.6) or 0.2 (0.06) mcg/dL at Week 48.

2. Correlation between late night/morning salivary cortisol and mUFC

There was a moderate positive correlation between both, the late-night salivary cortisol as well morning salivary cortisol with mUFC. The coefficient of determination ranging from 0.21 to 0.73 for late-night salivary cortisol and 0.22 to 0.77 for morning salivary cortisol, for all patients during the Core Phase.

Figure 11 - Mean (SE) late-night salivary cortisol during Core Phase by treatment group (FAS)



- This analysis includes scheduled visits only.
- RW period starts at Week 26 and ends up to Week 34.
- * For patients randomized to placebo during the randomized withdrawal period and including all data while on either osilodrostat or placebo.

Source: Sponsor's CSR, Figure 14.2-1.9

3. Time to Escape

Escape was defined as the first loss of control of UFC after at least one occurrence of UFC normalization, for which the following criteria had to met:

- prior normalization of UFC had occurred ($mUFC \leq ULN$)
- both $mUFC$ and at least 2 individual values contributing to that $mUFC$ had to be $>1.5 \times ULN$
- loss of control of UFC was not related to dose interruption or dose reduction for safety
- happened after Study Period 1

Nearly half (47.4%; 46/97 patients) had "escape" (including 36 who were non-randomized). Patients randomized to placebo were not included in the analysis (Table 10). Many of the patients who had an escape event regained $mUFC$ control with or without osilodrostat dose increase. Kaplan-Meier event probability estimates that the probability of escape at 1.5 years was 49% (Figure 12).

Table 10 - Time-to-escape under osilodrostat treatment (FAS)

Statistics	All Patients N=137
n/N (%)	46/97 (47.4)
Maximum follow-up	1079
Median follow-up	253
Median time to censoring	515
Percentiles (95% CI)	
25th	128.0 (106.0, 162.0)
50th	560.0 (212.0-NE)
75th	NE
% Event probability estimates (95% CI)	
180 days	36.9 (27.8, 47.8)
365 days	44.1 (34.4, 55.1)
545 days	48.8 (38.6, 60.1)
725 days	53.1 (42.2, 64.9)
905 days	59.0 (46.8, 71.7)

CI: confidence interval. FAS: full analysis set; NE: not estimable.

Patients randomized to placebo are not included in the analysis.

% Event probability estimate is the estimated probability that a patient will have an event prior to the specified time point.

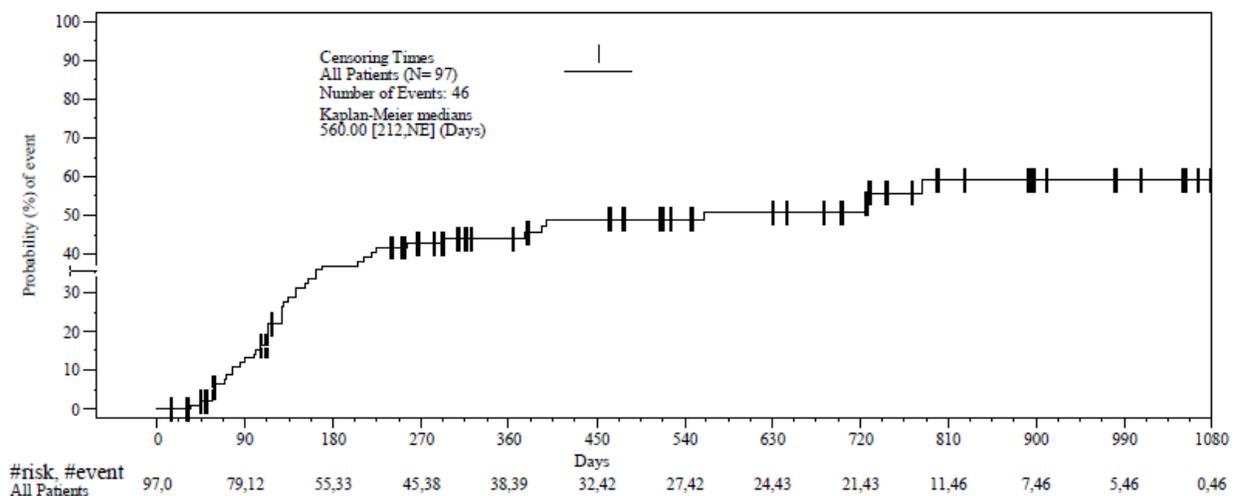
% Event probability estimates are obtained from the Kaplan-Meier survival estimates for each treatment groups; Greenwood formula is used for CIs of KM estimates.

n: Total number of events included in the analysis.

N: Total number of patients included in the analysis.

Source: Sponsor's CSR, Table 14.2-3.14

Figure 12 - Time-to-escape under osilodrostat treatment (FAS)



- Escape is defined as the first loss of control of UFC that meets all of the following criteria:
- prior normalization of UFC has occurred (mUFC ≤ ULN)
- both the mUFC and at least 2 individual values contributing to that mUFC have to be >1.5 x ULN
- the loss of control of UFC is not related to a dose interruption or dose reduction due to safety reasons
- Happens beyond 12-week dose titration period (Study Period 1).
- Patients randomized to placebo are not included in the analysis.

Source: Sponsor's CSR, Figure 14.2-1.6

4. Cardiovascular and metabolic parameters

An improvement in cardiovascular and metabolic parameters including fasting blood glucose, HbA1C, LDL-cholesterol, BMI, systolic and diastolic blood pressure was seen following treatment with osilodrostat. The baseline level and mean % change from baseline in these parameters are shown in Table 11. Improvement in HDL-cholesterol and triglycerides however were not observed. The changes were present by the end of dose-titration (Period 1), further improved by 24 weeks, and generally sustained by end of Core phase.

The adjusted mean changes from baseline to Week 48 (end of Core Period) ranged from:

- -1.69 mg/dL to -38.46 mg/dL for fasting plasma glucose
- 0.71% to -0.60% for HbA1c
- 0.37 nmol/L to -0.75 nmol/L for cholesterol
- -0.09 mmol/L to -0.42 mmol/L for HDL cholesterol
- 0.36 mmol/L to -0.45 mmol/L LDL cholesterol
- 0.83 mmol/L to -0.18 mmol/L for triglycerides
- -0.98 mm Hg to -6.56 mm Hg for DBP
- -2.79 mm Hg to -10.87 mm Hg for SBP
- 0.50 Kg to -4.09 Kg for weight
- 0.18 kg/m² to -1.50 kg/m² for BMI
- -0.02 cm to -5.46 cm for waist circumference

These changes were maintained during the RW Period, however, by the end of the RW Period, improvements in SBP and DBP were more evident in the Osilodrostat Group compared to Placebo Group.

Table 11 - Mean (SD) % change from baseline in cardiovascular and metabolic parameters during Core Phase (FAS)

Parameter	All Patients N=137			
	Baseline Mean (SD)	Week 12 Mean (SD)	Week 24 Mean (SD)	Week 48 Mean (SD)
Fasting glucose (mg/dL)	n=129 99.2 (29.83)	n=117 -7.0 (18.69)	n=112 -10.0 (15.74)	n=101 -7.1 (16.60)
HbA1C (%)	n=137 6.0 (0.96)	n=124 -5.0 (8.12)	n=121 -4.6 (8.80)	n=110 -5.4 (9.57)
Cholesterol (mmol/L)	n=136 5.3 (1.16)	n=124 -8.9 (16.46)	n=123 -9.0 (17.13)	n=108 -8.8 (15.72)
LDL cholesterol (mmol/L)	n=135 3.0 (0.95)	n=121 -5.0 (27.86)	n=122 -3.5 (30.69)	n=107 -5.4 (26.12)
HDL cholesterol (mmol/L)	n=136 1.6 (0.45)	n=124 -19.9 (16.56)	n=123 -14.3 (15.05)	n=108 -14.4 (15.77)
Triglycerides (mmol/L)	n=136 1.5 (1.31)	n=124 15.2 (54.08)	n=123 -1.8 (35.07)	n=108 5.4 (102.02)
SBP (mm Hg)	n=137 132.2 (15.14)	n=130 -4.8 (12.55)	n=124 -4.1 (11.85)	n=111 -6.8 (11.40)
DBP (mm Hg)	n=137 85.3 (10.56)	n=130 -4.7 (12.99)	n=124 -3.8 (13.41)	n=111 -6.6 (12.72)
Weight (kg)	n=137 80.8 (22.44)	n=130 -0.9 (4.11)	n=124 -3.0 (5.24)	n=112 -4.6 (6.72)
BMI (kg/m ²)	n=137 30.3 (7.77)	n=130 -0.9 (4.10)	n=124 -3.0 (5.24)	n=112 -4.6 (6.73)
Waist circumference (cm)	n=133 103.4 (19.34)	n=125 -0.9 (6.54)	n=116 -2.6 (6.97)	n=109 -4.2 (7.63)

BMI: body-mass index; DBP: diastolic blood pressure; HbA1c: glycated hemoglobin; FAS: full analysis set; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; SD: standard deviation.

Source: Sponsor's CSR, Table 14.2-3.7

5. Physical Features of Cushing's Disease

Of the 97 patients with an assessment at the end of the Core period (Week 48), the majority (86%; 83/97) had improvement in at least one physical feature in CD.

Improvement in facial rubor, dorsal fat pad, central obesity, and supraclavicular fat pad were slightly more common (around 50%) as compared to improvement in ecchymosis, proximal muscle wasting, striae and hirsutism (female patients) (around one third for each

of latter 4 features of CD). Changes were seen by the end of Period 1 in some patients and were generally progressive towards the end of Core period.

6. Bone Mineral Density

An increase in BMD by the end of Core phase as compared to baseline was seen in all patients; with greater increase at the lumbar spine of 3% (6.45) as compared to the total hip BMD of 0.4% (5.48) for total hip. The change was more pronounced in the males as compared to females (Table 12).

7. Patient reported outcomes during the Core Period:

A. Cushing QoL

Improvement in Cushing QoL total score (which consists of Physical subscale and Psychological subscale) from baseline was observed for all 137 patients. The changes were observed after treatment initiation and reached the distribution-based minimal important difference value (MID; corresponding to a minimum 10.1-point change from baseline) at Weeks 26, 30, 32, 34 and 48.

B. EQ-5D-5L utility index

Similarly, improvement for EQ-5D-5L utility index were observed in the All Patients group at all post-baseline visits. A score difference of 0.037-0.069 for the EQ-5D-5L utility score was used as MID. These changes reached the lower-bound MID value at Week 4, 24, 26, 30, 34 and 48.

C. BDI

Improvement in BD-II total score from baseline was seen in the All Patients group at all post-baseline assessments. These changes reached the MID values (17.5% reduction in scores from baseline) at Weeks 24, 26, 28, 30 and 48.

Reviewer's comments: Overall, changes appear to offer improvement in measures of patient-related outcomes, however, none of the reported measures have been validated in Cushing's disease. There appears to a reduction of 5% in HbA1C as well as LDL at 48 weeks, however, it is likely that with continued therapy beyond 48 weeks which was studied here, would result in continued weight loss and reversal of adverse effects of glucocorticoid excess. The changes seen in BMD are consistent with real changes seen with reversal of glucocorticoid excess, as the lumbar spine is first site to change with beneficial or adverse actions, and is primarily affected in conditions of glucocorticoid excess. Further improvements in fracture rates, and overall morbidity and mortality from the above measured outcomes is not known.

Table 12 - Summary of change in BMD at Week 48 by gender

Gender	BMD parameter (g/cm ²)	Time point	Statistics	All Patients	
				Actual	Change from BL
			Actual	Change from BL	Percent
Male			N=31		
L1-L4 lumbar spine			n	25	
Baseline			Mean (SD)	0.9 (0.19)	
			Median	0.9	
			Min-Max	0.6-1.4	
Week 48			n	21	21
			Mean (SD)	1.0 (0.16)	0 (0.07)
			Median	0.9	0
			Min-Max	0.7-1.3	-0.1-0.2
			95% CI		(-0.01,0.06)
					(-0.15,8.02)
Male			N=31		
Total hip			n	25	
Baseline			Mean (SD)	0.9 (0.15)	
			Median	0.8	
			Min-Max	0.6-1.2	
Week 48			n	21	21
			Mean (SD)	0.9 (0.14)	0 (0.04)
			Median	0.9	0
			Min-Max	0.6-1.1	-0.1-0.1
			95% CI		(-0.01,0.03)
					(-0.52,3.99)
Female			N=106		
L1-L4 lumbar spine			n	88	
Baseline			Mean (SD)	1.0 (0.18)	
			Median	1.0	
			Min-Max	0.6-1.3	
Week 48			n	60	60
			Mean (SD)	1.0 (0.19)	0 (0.05)
			Median	1.0	0
			Min-Max	0.6-1.4	-0.1-0.1
			95% CI		(0.01,0.04)
					(1.32,4.08)
Female			N=106		
Total hip			n	88	
Baseline			Mean (SD)	0.9 (0.16)	
			Median	0.9	
			Min-Max	0.4-1.2	
Week 48			n	59	59
			Mean (SD)	0.9 (0.16)	0 (0.06)
			Median	0.8	0
			Min-Max	0.4-1.2	-0.4-0.1
			95% CI		(-0.02,0.01)
					(-1.58,1.34)

BL: baseline; BMX: bone mineral density; CI: confidence interval; FAS: full analysis set; SD: standard deviation.

2-sided 95% CI shown are on the mean change and mean percentage change from baseline.

Source: Adapted from sponsor's CSR, Table 14.2-3.13
CDER Clinical Review Template 2015 Edition
Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

6.2. Study C2201 (supportive study)

6.2.1. Study Design

Overview and Objective

Study C2201 was a phase II, proof-of-concept study that aimed to assess the safety and efficacy of osilodrostat in patients with CD.

Trial Design

Study C2201 was comprised of 2 parts:

Part I was a 10-week exploratory proof-of-concept study with sequential dose-escalation study of osilodrostat over a 10-week period in 12 patients with Cushing's disease.

Part II was a 22-week treatment, after which patients could continue to receive treatment through a 48-week extension (Extension 1); and subsequently through Extension 2 (until data cut-off date).

Study Endpoints

The primary endpoint was the proportion of patients with mUFC \leq ULN or represented a $\geq 50\%$ decrease from baseline at Week 10. Secondary endpoint (Part II only): Assessment of the effects of 22 weeks treatment of osilodrostat monotherapy on 24-hour UFC with proportion of patients with complete and partial response

6.2.2. Study Results

Efficacy Results – Primary Endpoint

For Part I: 9/9 patients had mUFC \leq ULN achieving 100% response rate.

For Part II: By end of Week 10 (end of dose titration period) 84.2% (16/19) of patients were complete responders and 5.3% (1/19) had a partial response.

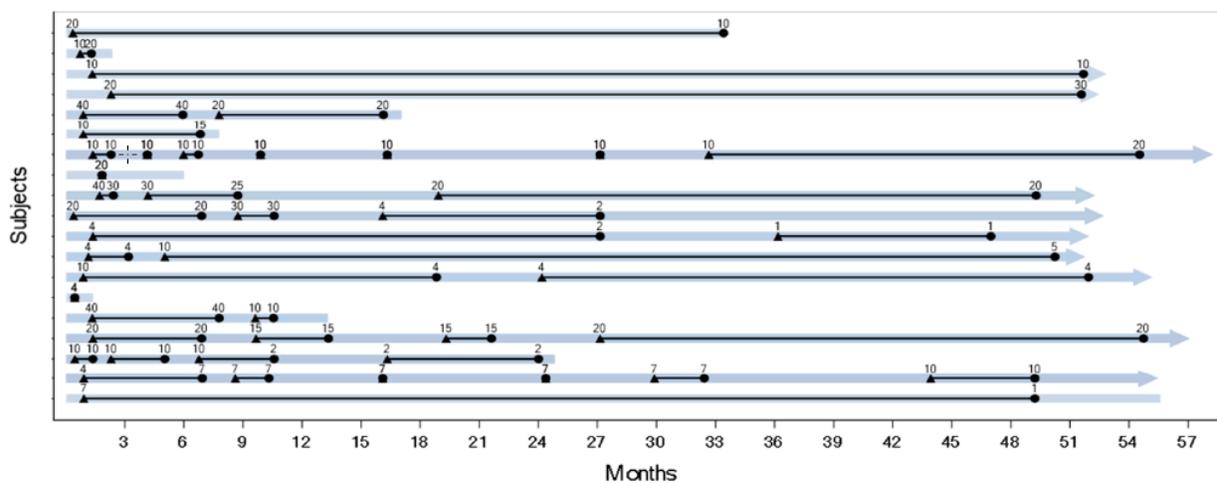
Efficacy Results – Secondary and other relevant endpoints

At month 22, 58.8% of patients (10/17) patients were complete responders and 11.8% (2/17) were partial responders.

Dose/Dose Response

The total daily dose required for UFC normalization in C2201 Part II was ≤ 20 mg/day in the majority (75%) of the patients, with half of patients requiring 10-20 mg/day.

Figure 13- Individual patient mUFC response and total daily dose (mg/day) during C2201 Part II (FAS)



Complete response is defined as mUFC \leq upper limit of normal
 The numbers in the graph indicate the dose at the start and end of the complete response
 Source: Sponsor's SCE Appendix 1- Figure 4.1-1.1

Additional study (C1201)

Study C1201 was a Phase II, single arm, open-label, dose titration study to assess safety and tolerability of osilodrostat in Japanese patients with endogenous Cushing's syndrome (except Cushing's disease). The treatment regimen consisted of osilodrostat 2 mg bid starting dose, with titration up 5 mg bid, 10 mg bid, 20 mg bid to a maximum of 30 mg bid. Dose increases were based on weekly serum cortisol levels during the initial 4 weeks of treatment, and thereafter every 2 weeks as needed.

The primary endpoint was % change from baseline to Week 12 in the mUFC. There were multiple secondary endpoints, which evaluated the absolute and % change in mUFC and serum cortisol at Weeks 12, 24, and 48 from baseline; as well as proportion of patients with partial and complete response rates at Weeks 12, 24, and 48; and evaluation of various biochemical and clinical criteria throughout the study.

Primary endpoint: the mean percent change from baseline at Week 12 ranged from -52.6% to -99.0%. The median reduction in mUFC from baseline at Week-12 was 94.5%. At Week 12, 6/9 (66.7%) achieved complete response and 1/9 (11.1%) achieved partial response.

Patients enrolled in C2301 and C2201 had similar demographic characteristics. Study C1201 on the other had minor differences as compared to the other 2 studies in that patients were

slightly older with median age of 46 years, and the BMI was lower than in studies C2301 and C2201

Reviewer's comments: the rationale of using serum cortisol in C1201 was that patients with CS typically have cortisol levels that persistently elevated (and generally higher) as compared of CD, without change with diurnal circadian rhythm.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The efficacy evaluation for this submission is primarily based on the pivotal study, C2301, summarized in Section 6. The supportive phase II study C2201 is briefly discussed above. In studies C2301 and C2201 (Part I and II), the complete response rate ranged from 84-72% (Week 10-12), and declined to 66- 59 % (week 48-month 22). The titration regimen, mUFC monitoring, and criteria for interruption of treatment of osilodrostat were similar for both studies, and as such, the results of both studies are consistent.

7.1.2. Secondary and Other Endpoints

Secondary endpoints from pivotal study C2301 are supportive and discussed in Section 6.

7.1.3. Subpopulations

There was no difference in efficacy, as measured using the primary endpoint, when data was stratified by sex, age, race, and other baseline characteristics including baseline mUFC level, duration of disease, or prior radiation history.

7.1.4. Dose and Dose-Response

The dosing regimen used by the pivotal study as well as studies C2201 and C1201 was consistent, and ranged from a starting dose of 2 mg bid, to a maximal dose of 30 mg bid. The titration schedule was based on mUFC results in both studies (C2301, C2201) as well as the safety and tolerability of osilodrostat.

For PK analysis, both PD endpoints, mUFC and serum cortisol, were evaluated. An exposure-response relationship between the decrease in cortisol level (urine and serum) from

baseline and osilodrostat exposure levels (C_{max}, C_{trough} and C_{avg}) was found based on various modeling analyses methods. However, a clear conclusion of the exposure-efficacy relationship could not be made.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Persistence of effect of osilodrostat was shown both in the pivotal study as well as the supportive study, C2201. In Study C2301, the overall median duration of exposure was 74.7 weeks (range 0.9 – 165 weeks). The median duration of exposure to osilodrostat in study C2201 (Part II) was substantially longer than in C2301: 226 weeks (range 2 - 253 weeks). In both studies, persistence of effect was seen once a stable, safe dose was reached: In study C2301, 71.5% were complete responders by Week 12; 66.4% of patients were complete responders by Week 48 and 71.5% of patients were complete responders at the last available assessment (beyond Week 120). For study C2201 (Part II); at month 22, 58.8% of patients (10/17) patients were complete responders whereas at month 52, 56.3% of patients (9/16) were complete responders.

For both C2301 and C2201, the highest rate of complete response was seen by the end of the titration period (Week 12 for C2301 and Week 10 for C2201), with the onset of action similar, likely because of the similar titration schemes. In study C2201, the mean time to response (partial of complete) was 34.3 days (SD 14 days); whereas in C2301, the median time to first normal mUFC was 41 days (95% CI: 30, 42).

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Multiple therapies (labelled and off-label) currently exist on the market for the treatment of Cushing's disease, and the optimal use of these therapies is limited by safety. As most patients with CD require multiple therapies, it is unknown how or if osilodrostat could be combined with other therapies (with different mechanism of action). The pivotal study relied on UFC as a primary measure of efficacy, although serum and salivary cortisol was also evaluated. The utilization of cortisol levels (other than mUFC) would likely be used in patients in whom mUFC cannot be collected. Fluctuations in serum cortisol levels, especially in patients with Cushing's disease, whose levels may not be nearly as elevated as in patients with Cushing's disease, may falsely guide up titration or down titration of osilodrostat. Furthermore, studies in metyrapone have shown that 11-DOC cross-reacts with reagent antibodies in cortisol immunoassay,⁹ leading

⁹ Monaghan PJ, Owen LJ, Trainer PJ, Brabant G, Keevil BG, Darby D. Comparison of serum cortisol measurement by immunoassay and liquid chromatography-tandem mass spectrometry in patients receiving the 11beta-hydroxylase

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to falsely elevated cortisol levels. This may lead to unnecessary increase in osilodrostat dose, which would then pose a safety risk. On the other hand, it may also provide false reassurance in patients in whom there is suspicion for adrenal insufficiency. It would therefore be warranted to warn clinicians of this cross-reactivity, and that cortisol levels may, in fact, be slightly falsely higher.

7.2.2. Other Relevant Benefits

inhibitor metyrapone. *Annals of clinical biochemistry* 2011;48:441-6.

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Not applicable.

7.3. Integrated Assessment of Effectiveness

The applicant has completed a double-blind randomized withdrawal (pivotal) study which included 137 patients with Cushing's disease. The primary endpoint was the complete response rate at the end of the 8 weeks period of randomized withdrawal (Week 34) between patients randomized to continue osilodrostat therapy vs. placebo by comparing the proportion of randomized patients in each arm with: mUFC \leq ULN at the end of 8 weeks of randomized withdrawal (Week 34), and were neither discontinued nor had osilodrostat dose increase above the level at week 26 during the randomized withdrawal period. The study met the primary endpoint, where the complete response rate in the osilodrostat group was higher than that of the placebo group (86.1% vs. 29.4% respectively, $P < 0.001$). The key secondary endpoint was to assess the complete response rate at the end of individual dose-titration and treatment with LCI699 in the initial single-arm, open label period (Week 24) by assessing the proportion of enrolled patients with mUFC \leq ULN at Week 24 and had no dose increase above the level established at Week 12. The study also met the secondary endpoint, where by week 24, 72 patients (52.6%) were complete responders. Although the design of the study did not allow for proper comparison to placebo, as all patients entered the study as an open-label, single-arm treatment group, nevertheless the complete response rates achieved in Period 1 and maintained throughout the study are significant.

The effect of osilodrostat seemed to persist beyond the elimination half-life of 4 hours, as was evident in patients who entered the RW period and were randomized to placebo, where nearly one-third (29%) retained response and had normal mUFC. This was also seen by median time to loss of control (in placebo group, RW) which was 28 days. Normalization of mUFC is an acceptable surrogate endpoint for disease in patients with Cushing's disease, and is associated with reduction in disease-related morbidity. Assessment of other secondary endpoints as well as exploratory endpoints (including reduction in HbA1C, blood pressure, weight, and BMI) showed favorable changes, consistent with what was observed with mUFC reduction and normalization. In addition to complete response rate, the applicant also evaluated partial response with $>50\%$ mUFC reduction from baseline at various timepoints. Although reduction in mUFC without normalization does not on its own bear clinical significance as any elevation in cortisol levels is associated with signs and symptoms of Cushing's with no relation between hormone levels and burden of disease, the treatment of Cushing's disease often exists of combination therapy of more than one agent to treat Cushing's disease. Although C2301 excluded and prohibited the use of other therapies for Cushing's disease, in clinical practice it is likely to be combined with other therapies, especially when one agent is insufficient to achieve eucortisolemia/ normal mUFC or combination therapy is needed to minimize adverse events of one drug which cannot be maximally titrated.

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In a large, retrospective multi-center study of metyrapone in patients with CS¹⁰, the patients who achieved control (as measured by serum cortisol or UFC) with metyrapone monotherapy ranged from 43-76%. Although this cannot be controlled head to head with osilodrostat, the efficacy rates in C2301 are similar or better to what was observed with metyrapone, given the same mechanism of action. In conclusion, osilodrostat has shown to be an effective drug for the treatment of Cushing's disease. It's use in Cushing's syndrome or in combination with other drugs for Cushing's disease however is unknown.

¹⁰ Daniel E, Aylwin S, Mustafa O, et al. Effectiveness of Metyrapone in Treating Cushing's Syndrome: A Retrospective Multicenter Study in 195 Patients. J Clin Endocrinol Metab 2015;100:4146-54.

8 Review of Safety

8.1. Safety Review Approach

The safety data in support of the proposed indication is primarily derived from pivotal study C2301 and extension study and included all subjects who were enrolled and received at least one dose of the study drug (safety set). The supportive data is obtained from a total of 3 studies: 2 studies in CS patients: C1201 and C1201, and one study in healthy volunteers: C2108 (only data regarding cortisol suppression). Additionally, blinded data from ongoing phase III study (C2302) was used to analyze adverse events of special interest, including hypocortisolemia adverse events.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The median exposure to osilodrostat across the 4 studies included in the safety analysis ranged from 80 days to 226 weeks (Table 13).

In Study C2301, the median duration of exposure to osilodrostat was 74.7 weeks (range: 0.9 to 165.3 weeks). The longest duration of exposure to osilodrostat was for 38 months (1 patient), whereas 6 patients received osilodrostat for ≥ 3 years. In the majority of patients (>65%), the exposure exceeded 1 year.

In Study C2201 (part 2), the median duration of exposure to osilodrostat was 226 weeks (~52 months; range: 2 to 253 weeks). The longest duration of exposure was ≥ 58 months (1 patient)

In study C1201, the median duration of exposure to osilodrostat was 12 weeks. The longest duration of exposure to osilodrostat was for 68 weeks.

In Study C2108, the majority of patients (83.3%) received the planned 24 doses of osilodrostat, over a duration of 12 days, with no longer duration of exposure beyond that.

Table 13 - Duration of exposure to osilodrostat up to data cut-off in the pivotal and 2 supportive studies

	Study C2301 N=137	Study C2201 Part 2 N=19	Study C1201 N=9
Duration of exposure (weeks)			
Mean (SD)	80.3 (44.02)	158.0 (97.71)	24.6 (24.86)
Median	74.7	226.0	12.0
Q1-Q3	48.1-117.0	54.0 - 240.0	-
Min-Max	0.9-165.3	2.0 - 253.3	1.3-68.0

SD: standard deviation.

Source: Sponsor's SCS- Table 1.4

8.2.2. Relevant characteristics of the safety population:

Demographic and baseline characteristics of the safety population are summarized in Table 5 and discussed under Section 6.2.

8.2.3. Adequacy of the safety database:

The safety population was adequate for the proposed indication.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall data integrity and submission quality were adequate to perform an effective safety review.

8.3.2. Categorization of Adverse Events

Safety assessments consisted of monitoring and recording of all treatment-emergent AEs

- On-treatment AE was defined if:
 - AE occurred following the date of the first administration of study treatment through the date of the last administration of study treatment + 28 days (C2201) or 30 days (C2301, C1201, C2108).
 - AE that started before the first dose but worsened during the treatment.
- AEs were coded using Medical Dictionary for Drug Regulatory Activities (MedDRA), with following versions used in the respective studies as such: Study C2301, Study C2201 Part 2 and Study C2108 used MedDRA version 20.1, and Study C1201 used version 21.0.

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- C2108 was not conducted on the intended patient population exposed to osilodrostat and as such, no AESI data was reported.
- Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If CTCAE grading was not present for a specific adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, was utilized. CTCAE Grade 5 (death) was not used however information about deaths was collected through eCRF.

8.3.3. Routine Clinical Tests

Safety monitoring consisted of physical examination, vital signs, laboratory evaluations, radiological assessments, cardiac assessments, in addition to collection of the adverse events. The schedule of assessment for C2301 is shown in Appendix 1 (Table 32; Table 33; Table 34; Table 35). Biochemical parameters collected throughout the study are shown in Table 14.

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Table 14 - Clinical laboratory collection

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry - full	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Glucose, Calcium, Chloride, Creatinine, Creatine kinase, GGT, Lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, sodium, Total Bilirubin (and Direct Bilirubin, Indirect Bilirubin if total Bilirubin is above 1.5 times the upper limit of normal), Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Chemistry - partial	Sodium, potassium, chloride, bicarbonate, Blood Urea Nitrogen (BUN) or Urea, creatinine, glucose, calcium, magnesium
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity,)
Coagulation	Prothrombin time (PT), Activated partial thromboplastin time (APTT)
Thyroid Panel	Serum TSH, free T4
Additional tests	Pregnancy test: serum (central laboratory testing) and urine dipstick (local laboratory testing) Serum testosterone and estradiol Plasma ACTH, serum cortisol, serum 11-deoxycortisol Serum aldosterone Renin Salivary cortisol (morning and late night) Serum 11-Deoxycorticosterone Fasting serum insulin and plasma glucose HbA1C LH, FSH Serum Androstenedione, DHEAS, Estrone Serum cortisol and salivary cortisol (Extensive PK subset)

Source: Sponsor's CSR, Table 7.7

8.4. Safety Results

Deaths

One death occurred in Study C2301 (pivotal study) whereas no deaths were reported in Studies C2201 or C1201 to date of completion of this review.

The death case reported in C2301 is that of a 55-year old Caucasian female (patient C2301-^{(b) (6)}) who committed suicide on Day 551 after starting Osilodrostat (during the Extension Period). The patient had pre-existing psychiatric history including depression, anxiety, and panic disorder. The patient was treated with a maximal dose of 5 mg bid of Osilodrostat in Period 1 (titrated down to 2 and then 1 mg bid) and had a normal mUFC while on Osilodrostat (since Period 1). She was randomized to placebo in Period 2, and restarted on Osilodrostat (maximal dose of 2 mg bid). During that time her psychiatric medications were being adjusted according to her depressive and anxiety symptoms. At the time of suicide, she was on Osilodrostat 1 mg bid and her most recent mUFC from Day 508 was normal at 72.5 mol/day.

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Medical Officer's comment:

This Medical Officer agrees with the Sponsor's conclusion. The reported death does not appear to be drug-related given the extensive psychiatric history of this patient and the timing of event (suicide) on Day 551.

8.4.2. Serious Adverse Events

Pivotal Study C2301:

Over on third (36.5%; 50/137) of patients had at least one SAE, of which 15% (21/137) had an SAE suspected to be related to study drug. The most common SAEs, reported in >2% of patients, regardless of relation to drug, were adrenal insufficiency (which included the preferred terms adrenal insufficiency, adrenal insufficiency acute, cortisol deficiency) occurred in 13 of 137 patients (9.5%), pituitary tumor (5/137; 3.6%), and gastroenteritis (3/137; 2.2%). SAEs by system organ class and preferred term by study period are shown in Table 15. SAEs occurred throughout the study and did not occur at a higher rate with higher doses. A proportionate number of patients (~ 25%) experienced an SAE in the 3 different time periods (Period 1, 2, and 3)

During Period 3 (RW), SAEs were observed in few patients 2 patients on osilodrostat and 1 patient in placebo group), all of which were suspected to be related to study drug by the Investigator. The SAEs were cholelithiasis and neutropenia in osilodrostat group and increased blood corticotrophin in placebo group.

Most SAEs suspected to be drug-related were managed by dose adjustment or interruption, or concomitant medication.

Table 15 - Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT) by Study Period (Core Period)

System Organ Class Preferred Term	Period 1 (N=137)	Period 1 (N=130)	Period 3, randomized patients (N=70)	Period 3, non-randomized patients (N=47)	Period 4 (N=116)	Entire Core Study (N=137)
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)- 6 events			1 (0.9)	10 (8)
Adrenal Insufficiency	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)
Adrenal insufficiency 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 (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)

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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)- 2events				2 (1.5)
Cholecystitis						1 (0.7)^
Immune system disorders	1 (0.7)					1 (0.7)
Anaphylactic shock	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)

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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					1 (0.9)	1 (0.7)
Migraine	1 (0.7)					1 (0.7)
Syncope	1 (0.7)					1 (0.7)
6 th 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)

*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. Source: The Applicant's response to Agency's information request on 7/9/2019

Study 2201 (supportive study in patients with CD)

The rate of SAEs C2201 was similar to that of study C2301.

In Part 1, one patient experienced an SAE (decreased hemoglobin, tachycardia, palpitations and chest pain). In Part 2, around one-third (32%; 6/19) experienced an SAE as shown in Table 16. In contrast to C2301, the dose of osilodrostat was not reduced or interrupted for the majority of SAEs for C2201. There was no relation between dose of osilodrostat and rate of SAE.

Table 16 - Serious Adverse Events Regardless of Study Drug Relationship by Preferred Term and Severity in at Least 2 Patients in C2201

Preferred Term	C2201 Part 2 N=19	
	All grades n (%)	Grade 3/4 n (%)
Number of patients with at least one event	6 (31.6)	5 (26.3)
Adrenal insufficiency	1 (5.3)	0
Pituitary tumour	0	0
Gastroenteritis	1 (5.3)	1 (5.3)
Adrenocortical insufficiency acute	0	0
Pituitary tumour benign	1 (5.3)	0
Abdominal pain	0	0
Anxiety	0	0
Cholelithiasis	0	0
Glucocorticoid deficiency	0	0
Influenza	0	0
Pneumonia	0	0
VI th nerve paralysis	0	0
Pituitary-dependent Cushing's syndrome	2 (10.5)	2 (10.5)

Numbers (n) represent counts of patients.

Preferred terms are sorted in descending frequency, as reported in the all grades column for C2301.

A patient with multiple severity grades for an AE is only counted under the maximum grade.

For C2301, any events experienced by patients randomized to placebo while on placebo are not included in this analysis.

MedDRA version 20.1, CTCAE version 4.0 (C2201) and 4.03 (C2301).

C2201 Study data cut-off date: 14-Nov-2017; 2301 Study data cut-off date: 21-Feb-2018

Study C1201 (supportive study in Japanese patients with CS)

In study C1201, 4/9 patients experienced SAEs as such: adrenal insufficiency (2 patients), pneumonia and psychiatric symptoms (both in 1 patient), in addition to one patient who discontinued due to grade 3 myocardial infarction.

Study C2108 (supportive study in healthy volunteers)

In study C2108, 19/24 patients experienced SAEs, all of which were related to abnormal ACTH-stimulation testing following study drug exposure. Specifically, serum cortisol levels < 300 nmol/L (11 mcg/dL) after 30 days of extended hydrocortisone taper or abnormal ACTH stimulation testing after 2 weeks of hydrocortisone taper, were deemed to be "incomplete adrenal recovery" per protocol. Of the 19 patients, 18 were asymptomatic and one was

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symptomatic (asthenia, tiredness, common cold). At the time of data cut-off, 14 patients had complete recovery of the adrenal system (cortisol \geq 300 nmol/L), 4 patients were lost to follow-up, and 1 had ongoing SAE of abnormal ACTH stimulation testing.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study C2301

In study C2301, 18/137 patients (13.1%) had at least one AE which led to discontinuation of osilodrostat, mostly commonly adrenal insufficiency and pituitary tumors (Table 17). Of the 18 patients, 13 had events suspected to be drug-related.

During the RW period, 2 of 35 (5.7%) patients in the placebo group discontinued study drug due to AEs of increased blood corticotrophin and hyponatremia. No patient discontinued study drug in the osilodrostat group.

Study C2201

The rate of discontinuation of osilodrostat due to AEs was similar to that of C2301 (Table 18). In Part 1, there were no discontinuations due to AEs. In Part 2, 3 of 19 patients (15.8%) discontinued study drug because of an AE. In 2 of the 3 patients who discontinued treatment, AEs were suspected to be drug-related.

Study C1201

One third (3/9) of patients discontinued study drug due to the following AEs: grade 3 myocardial infarction, grade 3 hypokalemia and grade 1 abdominal distension.

Study C2108

Four of 24 subjects (16.7%) had AEs leading to discontinuation of osilodrostat. The AEs were as follows: grade 2 palpitations, grade 1 throat tightness, grade 2 asthenia and grade 2 exhaustion, and positive pregnancy test (one patient).

Table 17 - Adverse Events leading to drug discontinuation regardless of drug relationship by preferred term in Study C2301

Preferred Term	C2301 Osilodrostat N=137	
	All grades n (%)	Grade 3/4 n (%)
Number of patients with at least one event	18 (13.1)	11 (8.0)
Adrenal insufficiency	4 (2.9)	2 (1.5)
Pituitary tumour	4 (2.9)	3 (2.2)
Pituitary tumour benign	2 (1.5)	2 (1.5)
Asthenia	1 (0.7)	0
Blood corticotrophin increased	0	0
Blood pressure diastolic increased	1 (0.7)	1 (0.7)
Blood pressure systolic increased	1 (0.7)	1 (0.7)
Diarrhoea	0	0
Electrocardiogram QT prolonged	1 (0.7)	0
Fatigue	1 (0.7)	0
Headache	1 (0.7)	1 (0.7)
Hypokalaemia	1 (0.7)	1 (0.7)
Malaise	0	0
Malignant pituitary tumour	1 (0.7)	1 (0.7)
Muscular weakness	0	0
Nausea	0	0
Neoplasm progression	0	0
Pain in extremity	1 (0.7)	1 (0.7)
Papule	0	0
Paresis cranial nerve	1 (0.7)	1 (0.7)
Rash	1 (0.7)	0
Tumour invasion	1 (0.7)	0
Vlth nerve paralysis	1 (0.7)	0
Visual impairment	1 (0.7)	1 (0.7)

Numbers (n) represent counts of patients.

Preferred terms are sorted in descending frequency, as reported in the all grades column for C2301.

A patient with multiple severity grades for an AE is only counted under the maximum grade.

For C2301, any events experienced by patient randomized to placebo while on placebo are not included in this analysis.

MedDRA version 20.1, CTCAE version 4.0 (C2201) and 4.03 (C2301).

Source: Applicant's Summary of Clinical Safety Appendix 1- Table 1.3-2.7

Table 18 - Adverse Events leading to drug discontinuation regardless of drug relationship by preferred term in Study C2201

Preferred Term	C2201 Part 2 N=19	
	All grades n (%)	Grade 3/4 n (%)
Number of patients with at least one event	3 (15.8)	1 (5.3)
Adrenal insufficiency	0	0
Pituitary tumour	0	0
Pituitary tumour benign	1 (5.3)	0
Asthenia	0	0
Blood corticotrophin increased	1 (5.3)	0
Blood pressure diastolic increased	0	0
Blood pressure systolic increased	0	0
Diarrhoea	1 (5.3)	0
Electrocardiogram QT prolonged	0	0
Fatigue	0	0
Headache	0	0
Hypokalaemia	0	0
Malaise	1 (5.3)	0
Malignant pituitary tumour	0	0
Muscular weakness	1 (5.3)	0
Nausea	1 (5.3)	0
Neoplasm progression	1 (5.3)	0
Pain in extremity	0	0
Papule	1 (5.3)	1 (5.3)
Paresis cranial nerve	0	0
Rash	0	0
Tumour invasion	0	0
Vlth nerve paralysis	0	0
Visual impairment	0	0

Numbers (n) represent counts of patients.

Preferred terms are sorted in descending frequency, as reported in the all grades column for C2301.

A patient with multiple severity grades for an AE is only counted under the maximum grade.

For C2301, any events experienced by patient randomized to placebo while on placebo are not included in this analysis.

MedDRA version 20.1, CTCAE version 4.0 (C2201) and 4.03 (C2301).

Source: Applicant's Summary of Clinical Safety Appendix 1- Table 1.3-2.7

8.4.4. Significant Adverse Events

Hyponatremia:

(after discontinuation of osilodrostat, because of removal of mineralocorticoid effect, in vulnerable/ patients with borderline low Na).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events (TEAE) are adverse events that occurred anytime for the duration of the study, irrespective of relation to study drug. The sponsor's analysis of adverse events excluded patients on placebo during the randomized withdrawal period, due to likely carry-over effect of osilodrostat and instead a separate summary of AEs occurring the RW for patients on osilodrostat vs. placebo was provided.

All patients experienced at least one AE at any point throughout the study and 97.8% had AEs the first 26 weeks. Over half (57%) of the AEs were of grade 3 or 4 in severity. The proportion of patients with AEs by SOC is shown in Table 19.

The following preferred terms (PTs) were used to capture adrenal insufficiency and included a variety of reported events as such:

1. "glucocorticoid deficiency" which includes the following reported events: hypocortisolism, hypocorticism, symptoms of hypocortisolism, relative hypocortisolism, suspicion of hypocortisolism, asymptomatic/symptomatic hypocortisolism, relative hypocortisolism, and subjective symptoms of hypocortisolism.
2. "adrenal insufficiency" includes which includes: relative adrenal insufficiency, adrenocortical insufficiency, hypoadrenalism, suspected hypoadrenalism, mild adrenal insufficiency, and adrenal deficiency.

Table 19 - Adverse events regardless of study drug relationship by primary system organ class and treatment group (SAS)

Primary system organ class	Randomized to osilodrostat during RW N=36		Randomized to placebo during RW* N=35		Non-randomized N=66		All Patients N=137	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients with at least one event	36 (100)	18 (50.0)	35 (100)	22 (62.9)	66 (100)	38 (57.6)	137 (100)	78 (56.9)
Blood and lymphatic system disorders	5 (13.9)	1 (2.8)	4 (11.4)	1 (2.9)	8 (12.1)	3 (4.5)	17 (12.4)	5 (3.6)
Cardiac disorders	4 (11.1)	0	4 (11.4)	0	14 (21.2)	0	22 (16.1)	0
Ear and labyrinth disorders	5 (13.9)	0	0	0	6 (9.1)	0	11 (8.0)	0
Endocrine disorders	17 (47.2)	2 (5.6)	16 (45.7)	3 (8.6)	36 (54.5)	10 (15.2)	69 (50.4)	15 (10.9)
Eye disorders	5 (13.9)	0	5 (14.3)	0	12 (18.2)	2 (3.0)	22 (16.1)	2 (1.5)
Gastrointestinal disorders	23 (63.9)	3 (8.3)	23 (65.7)	2 (5.7)	48 (72.7)	5 (7.6)	94 (68.6)	10 (7.3)
General disorders and administration site conditions	23 (63.9)	2 (5.6)	22 (62.9)	2 (5.7)	44 (66.7)	2 (3.0)	89 (65.0)	6 (4.4)
Hepatobiliary disorders	2 (5.6)	1 (2.8)	2 (5.7)	1 (2.9)	1 (1.5)	0	5 (3.6)	2 (1.5)
Immune system disorders	2 (5.6)	1 (2.8)	1 (2.9)	0	0	0	3 (2.2)	1 (0.7)
Infections and infestations	25 (69.4)	3 (8.3)	23 (65.7)	3 (8.6)	44 (66.7)	2 (3.0)	92 (67.2)	8 (5.8)
Injury, poisoning and procedural complications	13 (36.1)	2 (5.6)	8 (22.9)	3 (8.6)	19 (28.8)	2 (3.0)	40 (29.2)	7 (5.1)
Investigations	25 (69.4)	4 (11.1)	15 (42.9)	3 (8.6)	35 (53.0)	9 (13.6)	75 (54.7)	16 (11.7)
Metabolism and nutrition disorders	10 (27.8)	2 (5.6)	13 (37.1)	4 (11.4)	32 (48.5)	8 (12.1)	55 (40.1)	14 (10.2)
Musculoskeletal and connective tissue disorders	20 (55.6)	2 (5.6)	21 (60.0)	2 (5.7)	34 (51.5)	3 (4.5)	75 (54.7)	7 (5.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (5.6)	0	1 (2.9)	1 (2.9)	18 (27.3)	8 (12.1)	21 (15.3)	9 (6.6)
Nervous system disorders	17 (47.2)	2 (5.6)	15 (42.9)	2 (5.7)	41 (62.1)	5 (7.6)	73 (53.3)	9 (6.6)
Pregnancy, puerperium and perinatal conditions	1 (2.8)	1 (2.8)	0	0	0	0	1 (0.7)	1 (0.7)
Psychiatric disorders	11 (30.6)	2 (5.6)	5 (14.3)	2 (5.7)	23 (34.8)	1 (1.5)	39 (28.5)	5 (3.6)
Renal and urinary disorders	4 (11.1)	0	5 (14.3)	1 (2.9)	3 (4.5)	0	12 (8.8)	1 (0.7)
Reproductive system and breast disorders	3 (8.3)	0	5 (14.3)	1 (2.9)	15 (22.7)	1 (1.5)	23 (16.8)	2 (1.5)
Respiratory, thoracic and mediastinal disorders	10 (27.8)	0	9 (25.7)	2 (5.7)	29 (43.9)	3 (4.5)	48 (35.0)	5 (3.6)
Skin and subcutaneous tissue disorders	21 (58.3)	1 (2.8)	16 (45.7)	0	36 (54.5)	1 (1.5)	73 (53.3)	2 (1.5)
Surgical and medical procedures	1 (2.8)	0	0	0	1 (1.5)	0	2 (1.5)	0
Vascular disorders	12 (33.3)	1 (2.8)	7 (20.0)	3 (8.6)	18 (27.3)	12 (18.2)	37 (27.0)	16 (11.7)

SAS: safety analysis set; RW: randomized withdrawal.

Numbers (n) represent counts of patients.

A patient with multiple severity grades for a SOC is only counted under the maximum grade. Data is sorted alphabetically by SOC.

MedDRA version 20.1, CTCAE version 4.03.

* For patients receiving placebo during the RW Period and excluding data while on placebo.

Source: Sponsor's CSR, Table 14.3.1-1.4

The most commonly reported (in >20% of patients) AEs regardless of study drug relationship were nausea (41.6%), headache (33.6%), fatigue (28.5%), adrenal insufficiency, (27.7%), nasopharyngitis (22.6%), vomiting (21.9%), and glucocorticoid deficiency (21.2 %) (Table 20). Combining the 2 PTs used for capturing adrenal insufficiency (adrenal insufficiency, 27.7% and glucocorticoid deficiency, 21.2%), shows an overall rate of 47.4% of patients who experienced one of more overlapping symptoms of the adrenal deficiency spectrum. Adrenal insufficiency, as a treatment-specific AE is further discussed in section

Adverse events reported in >5% of patients are shown in Table 21 and include hypertension (11%); whereas grade 3.4 adverse events in <5% of patients include vomiting, pituitary tumor and headache (2.9% each).

Most patients (93.4%) had AEs suspected to be study drug related. Overall, most commonly reported (in >15% of patients) AEs suspected to be study drug related were adrenal insufficiency and nausea (27%, each), fatigue (21.2%), glucocorticoid deficiency (20.4%), and increased blood corticotrophin (ACTH) (15.3%).

Adverse events during the RW Period by treatment group (placebo vs. osilodrostat)
The rate of AEs between the placebo and osilodrostat was similar during the RW period: 72.2% in the osilodrostat and 65.7% in the Placebo Group (Table 22). By PT, AEs were reported in no more than 4 patients in the osilodrostat treatment group and in no more than 3 patients in the placebo treatment group.

Nausea, arthralgia, headache, asthenia and constipation were reported only in the Osilodrostat Group, whereas diarrhea and gastroesophageal reflux disease AEs were reported only in the Placebo Group. During the RW Period one glucocorticoid deficiency AE was reported in 1 patient in the Osilodrostat Group.

Table 20 - Adverse events in > 10% of all patients, by preferred term and treatment group (SAS)

Preferred term	Randomized to osilodrostat during RW	Randomized to placebo during RW*	Non-randomized	All Patients
	N=36 n (%)	N=35 n (%)	N=66 n (%)	N=137 n (%)
Total	36 (100)	35 (100)	66 (100)	137 (100)
Nausea	15 (41.7)	9 (25.7)	33 (50.0)	57 (41.6)
Headache	10 (27.8)	7 (20.0)	29 (43.9)	46 (33.6)
Fatigue	8 (22.2)	10 (28.6)	21 (31.8)	39 (28.5)
Adrenal insufficiency	8 (22.2)	9 (25.7)	21 (31.8)	38 (27.7)
Nasopharyngitis	7 (19.4)	11 (31.4)	13 (19.7)	31 (22.6)
Vomiting	5 (13.9)	5 (14.3)	20 (30.3)	30 (21.9)
Glucocorticoid deficiency	10 (27.8)	9 (25.7)	10 (15.2)	29 (21.2)
Arthralgia	7 (19.4)	9 (25.7)	11 (16.7)	27 (19.7)
Back pain	8 (22.2)	13 (37.1)	6 (9.1)	27 (19.7)
Diarrhoea	4 (11.1)	8 (22.9)	13 (19.7)	25 (18.2)
Influenza	5 (13.9)	8 (22.9)	11 (16.7)	24 (17.5)
Asthenia	10 (27.8)	3 (8.6)	10 (15.2)	23 (16.8)
Blood corticotrophin increased	7 (19.4)	4 (11.4)	12 (18.2)	23 (16.8)
Oedema peripheral	7 (19.4)	5 (14.3)	9 (13.6)	21 (15.3)
Pyrexia	4 (11.1)	4 (11.4)	12 (18.2)	20 (14.6)
Urinary tract infection	6 (16.7)	5 (14.3)	9 (13.6)	20 (14.6)
Decreased appetite	3 (8.3)	5 (14.3)	11 (16.7)	19 (13.9)
Dizziness	2 (5.6)	3 (8.6)	14 (21.2)	19 (13.9)
Hormone level abnormal	6 (16.7)	2 (5.7)	11 (16.7)	19 (13.9)
Myalgia	2 (5.6)	6 (17.1)	11 (16.7)	19 (13.9)
Hypokalaemia	3 (8.3)	3 (8.6)	12 (18.2)	18 (13.1)
Rash	7 (19.4)	2 (5.7)	9 (13.6)	18 (13.1)
Cough	4 (11.1)	5 (14.3)	8 (12.1)	17 (12.4)
Hypertension	2 (5.6)	3 (8.6)	12 (18.2)	17 (12.4)
Blood testosterone increased	2 (5.6)	1 (2.9)	12 (18.2)	15 (10.9)
Dyspepsia	2 (5.6)	4 (11.4)	8 (12.1)	14 (10.2)

RW: randomized withdrawal; SAS: safety analysis set.

Preferred terms are sorted in descending frequency, as reported in the All Patients column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events is counted only once in the total row.

* For patients receiving placebo during the RW Period and excluding data while on placebo.

Source: Sponsor's CSR, Table 14.3.1-1.10

Table 21 - Adverse events suspected be drug-related, in > 5% of all patients, by preferred term and treatment group (SAS)

Preferred term	Randomized to osilodrostat during RW	Randomized to placebo during RW*	Non-randomized	All Patients
	N=36 n (%)	N=35 n (%)	N=66 n (%)	N=137 n (%)
Total	34 (94.4)	32 (91.4)	62 (93.9)	128 (93.4)
Adrenal insufficiency	8 (22.2)	9 (25.7)	20 (30.3)	37 (27.0)
Nausea	9 (25.0)	6 (17.1)	22 (33.3)	37 (27.0)
Fatigue	7 (19.4)	8 (22.9)	14 (21.2)	29 (21.2)
Glucocorticoid deficiency	10 (27.8)	9 (25.7)	9 (13.6)	28 (20.4)
Blood corticotrophin increased	6 (16.7)	4 (11.4)	11 (16.7)	21 (15.3)
Asthenia	9 (25.0)	2 (5.7)	8 (12.1)	19 (13.9)
Hormone level abnormal	6 (16.7)	2 (5.7)	10 (15.2)	18 (13.1)
Headache	4 (11.1)	1 (2.9)	11 (16.7)	16 (11.7)
Arthralgia	4 (11.1)	5 (14.3)	6 (9.1)	15 (10.9)
Blood testosterone increased	1 (2.8)	1 (2.9)	12 (18.2)	14 (10.2)
Decreased appetite	2 (5.6)	4 (11.4)	7 (10.6)	13 (9.5)
Hypokalaemia	3 (8.3)	1 (2.9)	8 (12.1)	12 (8.8)
Acne	1 (2.8)	1 (2.9)	9 (13.6)	11 (8.0)
Hirsutism	3 (8.3)	3 (8.6)	5 (7.6)	11 (8.0)
Vomiting	0	2 (5.7)	9 (13.6)	11 (8.0)
Hypertension	1 (2.8)	3 (8.6)	6 (9.1)	10 (7.3)
Hypotension	5 (13.9)	2 (5.7)	3 (4.5)	10 (7.3)
Oedema peripheral	2 (5.6)	3 (8.6)	5 (7.6)	10 (7.3)
Oedema	1 (2.8)	3 (8.6)	5 (7.6)	9 (6.6)
Cortisol free urine decreased	6 (16.7)	1 (2.9)	1 (1.5)	8 (5.8)
Dizziness	0	3 (8.6)	5 (7.6)	8 (5.8)
Myalgia	1 (2.8)	2 (5.7)	5 (7.6)	8 (5.8)
Diarrhoea	0	3 (8.6)	4 (6.1)	7 (5.1)
Malaise	1 (2.8)	2 (5.7)	4 (6.1)	7 (5.1)

RW: randomized withdrawal; SAS: safety analysis set.

Preferred terms are sorted in descending frequency, as reported in the All Patients column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events is counted only once in the total row.

* For patients receiving placebo during the RW Period and excluding data while on placebo.

Source: Sponsor's CSR, Table 14.3.1-1.12

Table 22 - Adverse events in > 5% of patients, by preferred term and randomized treatment group during RW period only (SAS)

Preferred term	RW Period	
	Osilodrostat N=36 n (%)	Placebo N=35 n (%)
Total	26 (72.2)	23 (65.7)
Nausea	4 (11.1)	0
Anaemia	3 (8.3)	3 (8.6)
Arthralgia	3 (8.3)	0
Headache	3 (8.3)	0
Asthenia	2 (5.6)	0
Blood corticotrophin increased	2 (5.6)	1 (2.9)
Constipation	2 (5.6)	0
Cortisol free urine decreased	2 (5.6)	1 (2.9)
Depression	2 (5.6)	1 (2.9)
Dizziness	2 (5.6)	1 (2.9)
Fatigue	2 (5.6)	3 (8.6)
Hirsutism	2 (5.6)	1 (2.9)
Nasopharyngitis	2 (5.6)	1 (2.9)
Cough	1 (2.8)	2 (5.7)
Insomnia	1 (2.8)	2 (5.7)
Urinary tract infection	1 (2.8)	2 (5.7)
Diarrhoea	0	2 (5.7)
Gastroesophageal reflux disease	0	2 (5.7)

RW: randomized withdrawal; SAS: safety analysis set.

Preferred terms are sorted in descending frequency, as reported in the Osilodrostat column.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple adverse events is counted only once in the total row.

Source: Sponsor's CSR, Table 14.3.1-1.9

Reviewer's comment: because of the open-label nature of the first 26 weeks of the study, most, if not all of the TEAEs were considered/suspected to be drug-related. Although Table 22 summarizes TEAEs during the RW only, comparing placebo vs. osilodrostat, as mentioned earlier in this review, the biological half-life of osilodrostat is longer than the elimination half-life of 4 hours, and as the sponsor stated, the confounding carry-over effect of osilodrostat could not be eliminated. Some AE/SAEs occurring during the RW period in patients with placebo were due to recurrence of disease and stopping of osilodrostat, and specifically, withdrawal of the mineralocorticoid effect of osilodrostat (such as hyponatremia), and are discussed under the previous section (significant adverse effects).

8.4.6. Laboratory Findings

Newly occurring or worsening biochemical findings were minor and included reduced hemoglobin in 3 patients (grade 3), in addition to neutropenia in 3 patients. Biochemical laboratory findings that occurred newly or worsened during C2301 are shown in Appendix 1, Table 36 and discussed further below.

1. Neutropenia:

SAE of neutropenia was reported in 3 patients and resolved upon discontinuation of osilodrostat (all in C2301). No other cases of neutropenia occurred in the supportive studies.

Reviewer's comments: Metyrapone, a different molecule that works by the same mechanism as osilodrostat (blocking 11 β -hydroxylase), lists bone marrow suppression under its 'Warnings & Precautions' label. In clinical practice, neutropenia seen with metyrapone is relatively rare, and reduction in other cell lines is not commonly seen. The mechanism of possible bone marrow suppression is unclear. In C2301, neutropenia and reduction in hemoglobin were both observed, however occurred in different patients. Although the number of neutropenia and/or hemoglobin reduction is low, and causality with osilodrostat cannot be ascertained or excluded, periodic monitoring of CBC would be warranted.

2. Hypokalemia:

Grade 3 hypokalemia was reported in 8 patients whereas grade 4 hypokalemia was reported in 1 patient. Hypokalemia was managed by interruption or dose adjustment with or without concomitant medication.

Reviewer's comments: hypokalemia is an expected AE with osilodrostat, which by blocking 11 β -hydroxylase, increases the level of 11-deoxycortisol (11-DOC), a potent mineralocorticoid. It is notable however, that very high cortisol levels can also cause hypokalemia, by binding the mineralocorticoid receptor, and this is seen more often in non-CD Cushing's syndrome, where cortisol levels are much higher. Because of osilodrostat's mechanism of action and temporal relation between hypokalemia and initiation of osilodrostat, hypokalemia would be considered treatment-related adverse event. There does not seem to be a relation however between dose or severity of disease, to the timing or severity of hypokalemia.

3. Increase uric acid:

Grade 4 increased urate was reported in 13 patients, and the highest increase in uric acid was 1.5x ULN in one patient with tuberculosis AE, who was treated with drugs known to induce hyperuricemia. None of the hyperuricemia events was considered an SAE, and most patients were on a concomitant medication known to induce hyperuricemia. There was no treatment interruption or dose change with any of these grade 4 events.

Reviewer's comments: there is no clear mechanism of elevated uric acid with the use of osilodrostat, and upon review of the cases, it does not appear that increased uric acid is a treatment-emergent-adverse event.

4. Increased transaminases

Around 19% of patients had AST elevation (any grade) and 29% had ASLT elevation (any grade (Table 36). Five patients had an increase in ALT/AST >3× ULN; however, they all had normal total bilirubin levels throughout the study (Table 23). Further investigations for these patients revealed the following causes: cholelithiasis and concomitant use of diclofenac, liver steatosis with obesity or diabetes, and in one patient, a diagnosis of liver metastases from a pituitary carcinoma.

Most elevations in liver enzyme reversed spontaneously or following dose adjustment and No patients discontinued the study drug due to liver enzyme elevations. Most liver enzyme elevations occurred during the dose-titration period of the study (Period 1) (Table 24).

Reviewer's comments: there seems to be a temporal and a dose-relationship between liver enzyme elevation and initiation/titration of osilodrostat. Although no criteria met Hy's law, warning about liver enzyme elevation should be present when osilodrostat is being used, so that monitoring of liver enzymes occurs, especially in patients with baseline abnormal liver enzymes.

5. Rise in ACTH

In response to steroidogenesis blockade, a rise in ACTH was seen over time in all patients. In the All Patients group, mean (SD) plasma ACTH was 18.4 (35.52) pmol/L at baseline, 31.2 (42.05) pmol/L at Week 12, 35.3 (46.82) pmol/L at Week 24 and 50 (69.73) pmol/L at Week 48. At Week 48, the mean (SD) percentage change from baseline in plasma ACTH levels was 339.8% (514.85). ACTH levels changes over time during the Core phase are shown in . At the last available assessment, the mean (SD) percentage change in plasma ACTH levels from baseline was 472.5% (919.77).

Table 23 - Number of patients with elevation of liver enzymes during the study by randomized treatment group

Test	Randomized to osilodrostat during RW N=36 n (%)	Randomized to placebo during RWS N=35 n (%)	Non-randomized N=66 n (%)	All Patients N=137 n (%)
ALT or AST >ULN but ≤ 3.0×ULN	11 (30.6)	10 (28.6)	26 (39.4)	47 (34.3)
ALT >3.0×ULN	0	2 (5.7)	2 (3.0)	4 (2.9)
AST >3.0×ULN	0	1 (2.9)	2 (3.0)	3 (2.2)
ALT or AST >3.0×ULN	0	2 (5.7)	3 (4.5)	5 (3.6)
ALT or AST >5.0×ULN	0	1 (2.9)	2 (3.0)	3 (2.2)
ALT or AST >10.0×ULN	0	1 (2.9)	0	1 (0.7)
ALT or AST >20.0×ULN	0	0	0	0
ULN <TBIL <2.0×ULN	3 (8.3)	3 (8.6)	1 (1.5)	7 (5.1)
TBIL ≥ 2.0×ULN	0	0	0	0
ALT or AST >3.0×ULN and TBIL ≥ 1.5×ULN*	0	0	0	0
ALT or AST >3.0×ULN and TBIL ≥ 2.0×ULN and ALP < 2.0×ULN*	0	0	0	0

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAS: safety analysis set; TBIL: total bilirubin; ULN: upper limit of normal.

Categories are based on worst post-baseline value for any specific parameter (patients with baseline abnormalities were not excluded). Categories with multiple parameters are based on worst post-baseline value for each parameter. Worst post-baseline value refers to maximum post-baseline value except for ALP for which it refers to the minimum post-baseline value.

n=number of patients who satisfied the criteria. Percentage is based on N.

Patients with both ALT>3×ULN and ULN<AST≤ 3×ULN at the same or different time points will be counted once in the ALT or AST > 3xULN category.

Patients with both AST > 3×ULN and ULN<ALT≤ 3×ULN at the same or different time points will be counted once in the ALT or AST >3×ULN category.

§ For patients receiving placebo during the RW Period and excluding data while on placebo.

Unscheduled visits are considered for this analysis.

*Criteria are based on the concurrent values, i.e., ALT/AST, TBIL, and ALP are measured at the same time.

Source: Sponsor's CSR, Table 14.3-3.38

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Table 24 - Number of patients with elevation of liver enzymes during the study by study period (First 26 weeks and RW Period)

Test	First 26 Weeks	RW Period	
	All Patients N=137 n (%)	Osilodrostat N=36 n (%)	Placebo N=35 n (%)
ALT or AST >ULN but ≤ 3.0×ULN	35 (25.5)	5 (13.9)	0
ALT >3.0×ULN	3 (2.2)	0	0
AST >3.0×ULN	2 (1.5)	0	0
ALT or AST >3.0×ULN	4 (2.9)	0	0
ALT or AST >5.0×ULN	2 (1.5)	0	0
ALT or AST >10.0×ULN	1 (0.7)	0	0
ALT or AST >20.0×ULN	0	0	0
ULN <TBIL <2.0×ULN	4 (2.9)	2 (5.6)	0
TBIL ≥ 2.0×ULN	0	0	0
ALT or AST >3.0×ULN and TBIL ≥ 1.5×ULN*	0	0	0
ALT or AST >3.0×ULN and TBIL ≥ 2.0×ULN and ALP <2.0×ULN*	0	0	0

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; RW: randomized withdrawal; SAS: safety analysis set; TBIL: total bilirubin; ULN: upper limit of normal.

Categories are based on worst post-baseline value for any specific parameter. Categories with multiple parameters are based on worst post-baseline value for each parameter. Worst post-baseline value refers to maximum post-baseline value except for ALP for which it refers to the minimum post-baseline value.

n=number of patients who satisfied the criteria. Percentage is based on N.

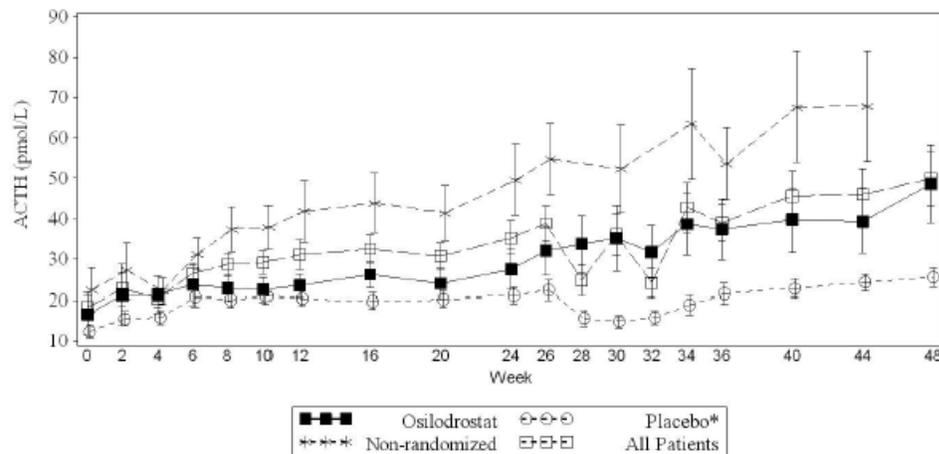
*Criteria are based on the concurrent values, i.e., ALT/AST, TBIL, and ALP are measured at the same time.

Patients with both ALT>3×ULN and ULN<AST≤ 3×ULN at the same or different time points will be counted once in the ALT or AST > 3×ULN category.

Patients with both AST > 3×ULN and ULN<ALT≤ 3×ULN at the same or different time points will be counted once in the ALT or AST > 3×ULN category.

Source: Sponsor's CSR, Table 14.3-3.37

Figure 14 - Mean (SE) ACTH at various time points during Core phase by treatment group (FAS)



FAS: full analysis set; SE: standard error.

Includes scheduled visits only. Randomized withdrawal (RW) Period starts at Week 26 and ends up to Week 34.

* For patients randomized to placebo during the RW Period and including all data while in either osilodrostat or placebo.

Source: Sponsor's CSR, Table 13.2-1.1

8.4.7. Vital Signs

Hypertension of any grade occurred in 17 of 137 patients (12%) of patients in C2301; of which 15 had grade ≥ 3 hypertension. For the majority of these (10 patients), hypertension was suspected to be drug-related and in the majority of patients (13), this AE led to additional therapy and/or study drug interruption or dose modification.

Reviewer's comments: by blocking 11β -hydroxylase which leads to upstream accumulation of 11-DOC, osilodrostat is anticipated to cause hypertension, mainly due to the mineralocorticoid activity of 11-DOC. However, the clinical spectrum of Cushing's disease also includes hypertension among other features of metabolic abnormalities, and patients with CD are often on anti-hypertensive treatment. Study C2301 excluded patients with uncontrolled hypertension, therefore worsening hypertension during treatment with osilodrostat, given the known mechanism, is considered a treatment-emergent adverse event and should be included in adverse event section of labeling.

8.4.8. Electrocardiograms (ECGs)

Data for EKG changes during the Core Phase are shown in Table 37. The mean (SD) change from baseline at Week 48 was 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 bpm (10.72) for heart rate. One patient discontinued the study drug due to ECG

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QT prolonged AE. No conclusions about ECG changes could be made for patients on placebo vs. patients on osilodrostat for Period 3 (RW), as there was insufficient ECG interval data (most patients switched to osilodrostat). The number of patients with notable ECG changes from randomization during the RW Period by randomized treatment is shown in Table 25, and from baseline by randomized treatment group is shown in Table 26.

During the overall study period, over one-third of patients (38.7%| 53/137) had at least one occasion of had a >30 ms increase from baseline in QTcF interval. A much smaller number (2.2 %; 3/137) had a >60 ms increase from baseline in QTcF interval, and none of these patients experienced accompanying clinical symptoms. There were no findings of of QTcF interval prolongation exceeding 480 ms in any patient.

8.4.9. QT

Please refer to Electrocardiograms (ECGs) section above.

Table 25 - Number (%) of patients with notable ECG changes from randomization during the RW Period by randomized treatment

	RW Period					
	Osilodrostat N=36			Placebo N=35		
	Total	n	%	Total	n	%
QTcF (ms)						
Increase from baseline >30 ms	36	1	(2.8)	34	3	(8.8)
Increase from baseline >60 ms	36	0		34	1	(2.9)
New >450 to ≤ 480 ms	36	2	(5.6)	34	3	(8.8)
New > 480 to ≤ 500 ms	36	0		34	0	
New >500 ms	36	0		34	0	
Heart rate (bpm)						
Increase from baseline >25% and to a value >100 bpm	36	0		34	0	
Decrease from baseline >25% and to a value <50 bpm	36	1	(2.8)	34	1	(2.9)
PR (ms)						
New PR >200 ms	36	1	(2.8)	34	0	
QRS (ms)						
New QRS >110 ms	36	0		34	2	(5.9)

ECG: electrocardiogram; RW: randomized withdrawal; SAS: safety analysis set.
Total is the number of patients with both randomization and post randomization evaluations.
n is the number of patients meeting the criteria at least once.
Randomization is defined as the last ECG measurements taken before 1st dose of randomized treatment.
Change from randomization: post randomization – randomization.
Only data while on RW treatment is included.
Unscheduled visits are included.

Source: Sponsor's CSR, Table 14.3-5.4

Table 26 - Number (%) of patients with notable ECG changes from baseline by randomized treatment group (SAS)

Parameter	First 26 Weeks						During study up to cutoff date								
	All Patients			Randomized to osilodrostat during RW			Randomized to placebo during RW*			Non-randomized			All Patients		
	N=137			N=36			N=35			N=66			N=137		
	Total	n	%	Total	n	%	Total	n	%	Total	n	%	Total	n	%
QTcF (ms)															
Increase from baseline >30 ms	137	39	(28.5)	36	18	(50.0)	35	10	(28.6)	66	25	(37.9)	137	53	(38.7)
Increase from baseline >60 ms	137	2	(1.5)	36	1	(2.8)	35	1	(2.9)	66	1	(1.5)	137	3	(2.2)
New >450 to ≤ 480 ms	137	14	(10.2)	36	7	(19.4)	35	4	(11.4)	66	5	(7.6)	137	16	(11.7)
New >480 to ≤ 500 ms	137	1	(0.7)	36	1	(2.8)	35	0		66	0		137	1	(0.7)
New >500 ms	137	1	(0.7)	36	0		35	0		66	1	(1.5)	137	1	(0.7)
Heart rate (bpm)															
Increase from baseline >25% and to a value >100 bpm	137	15	(10.9)	36	6	(16.7)	35	3	(8.6)	66	8	(12.1)	137	17	(12.4)
Decrease from baseline >25% and to a value <50 bpm	137	2	(1.5)	36	1	(2.8)	35	1	(2.9)	66	4	(6.1)	137	6	(4.4)
PR (ms)															
Increase from baseline >25% and to a value >200 bpm	137	3	(2.2)	36	1	(2.8)	35	2	(5.7)	66	1	(1.5)	137	4	(2.9)
New pulse rate >200 ms	137	12	(8.8)	36	5	(13.9)	35	4	(11.4)	66	6	(9.1)	137	15	(10.9)
QRS (ms)															
Increase from baseline >25% and to a value >110 ms	137	4	(2.9)	36	2	(5.6)	35	4	(11.4)	66	1	(1.5)	137	7	(5.1)
New QRS >110 ms	137	16	(11.7)	36	4	(11.1)	35	9	(25.7)	66	12	(18.2)	137	25	(18.2)

ECG: electrocardiogram; RW: randomized withdrawal; SAS: safety analysis set.

Total is the number of patients with both baseline and post baseline evaluations.

n is the number of patients meeting the criteria at least once.

Baseline is defined as the last ECG measurements taken at pre-dose on Day 1/study defined time window.

Change from baseline: post baseline – baseline.

Unscheduled visits are included.

* For patients receiving placebo during the RW Period and excluding data while on placebo.

Source: Sponsor's CSR, Table 14.3-5.4

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

Submission-specific safety issues, or adverse-events of special interest (AESI) are adverse events anticipated to occur during treatment with osilodrostat as a consequence of its mechanism of action or identified during the nonclinical and clinical program. They included 5 categories as collected by the sponsor: Hypocortisolism, adrenal hormone precursor accumulation, QT-prolongation, pituitary tumor enlargement, and arrhythmogenic potential. These AESI are summarized in Table 27, regardless of study drug relationship, although almost all were suspected to be drug-related. The occurrence of AESI was low during the randomization period and this is shown in Table 28.

Table 27 - Adverse events of special interest, regardless of study drug relationship by randomized treatment group (SAS)

AESI Groups	Randomized to osilodrostat during RW		Randomized to placebo during RW*		Non-randomized		All Patients	
	N=36		N=35		N=66		N=137	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hypocortisolism related AEs	21 (58.3)	2 (5.6)	17 (48.6)	3 (8.6)	32 (48.5)	9 (13.6)	70 (51.1)	14 (10.2)
Adrenal hormone precursor accumulation-related AEs	10 (27.8)	1 (2.8)	14 (40.0)	7 (20.0)	34 (51.5)	14 (21.2)	58 (42.3)	22 (16.1)
QT-prolongation-related AEs	1 (2.8)	0	1 (2.9)	0	3 (4.5)	1 (1.5)	5 (3.6)	1 (0.7)
Pituitary tumor enlargement-related AEs [1]	0	0	1 (2.9)	0	2 (3.0)	0	3 (2.2)	0
Arrhythmogenic potential AEs	0	0	0	0	1 (1.5)	1 (1.5)	1 (0.7)	1 (0.7)

AE: adverse event; RW: randomized withdrawal; SAS: safety analysis set.

A patient with multiple occurrences of an AE under one treatment is counted only once for that treatment.

* For patients receiving placebo during the RW Period and excluding data while on placebo.

[1] Includes only patients with diplopia, cranial nerve palsy, extraocular muscle paresis, pituitary infarction, and visual field defect

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Source: Sponsor's CSR, Table 14.3-1.31

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Table 28 - Adverse events of special interest, regardless of study drug relationship by treatment period and treatment group (SAS)

AE of Special Interest	First 26 Weeks All Patients N=137		RW Period			
	All Grades n (%)	Grade 3/4 n (%)	Osilodrostat N=36		Placebo N=35	
			All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
-Any AE of Special Interest						
-Total	84 (61.3)	24 (17.5)	5 (13.9)	0	2 (5.7)	0
Adrenal Hormone Precursor Accumulation-related AEs						
-Total	48 (35.0)	17 (12.4)	2 (5.6)	0	1 (2.9)	0
Hypokalaemia	14 (10.2)	4 (2.9)	0	0	0	0
Hypertension	13 (9.5)	12 (8.8)	0	0	0	0
Acne	12 (8.8)	0	0	0	0	0
Oedema	9 (6.6)	1 (0.7)	0	0	0	0
Hirsutism	7 (5.1)	0	2 (5.6)	0	1 (2.9)	0
Blood pressure diastolic increased	2 (1.5)	1 (0.7)	0	0	0	0
Blood pressure increased	2 (1.5)	0	0	0	0	0
Blood pressure systolic increased	2 (1.5)	1 (0.7)	0	0	0	0
Weight increased	2 (1.5)	0	0	0	0	0
Blood potassium decreased	1 (0.7)	1 (0.7)	0	0	0	0
Hypertrichosis	1 (0.7)	0	0	0	0	0
Arrhythmogenic potential AEs						
-Total	1 (0.7)	1 (0.7)	0	0	0	0
Syncope	1 (0.7)	1 (0.7)	0	0	0	0
Hypocortisolism related AEs						
-Total	54 (39.4)	10 (7.3)	3 (8.3)	0	1 (2.9)	0
Adrenal insufficiency	31 (22.6)	4 (2.9)	0	0	0	0
Glucocorticoid deficiency	22 (16.1)	5 (3.6)	1 (2.8)	0	0	0
Cortisol free urine decreased	2 (1.5)	0	2 (5.6)	0	1 (2.9)	0
Steroid withdrawal syndrome	2 (1.5)	0	0	0	0	0
Adrenocortical insufficiency acute	1 (0.7)	1 (0.7)	0	0	0	0
QT-prolongation-related AEs						
-Total	3 (2.2)	1 (0.7)	0	0	0	0
Electrocardiogram QT prolonged	3 (2.2)	1 (0.7)	0	0	0	0

- Preferred terms within a category are presented by descending frequency in 'All grades' column as reported in the 'All patients'.

- A patient with multiple occurrences of an AE under one treatment is counted only once for that treatment.

Source: Sponsor's CSR, Table 14.3-1.30

8.5.1. Hypocortisolism-related adverse events

Hypocortisolism-related AEs encompassed 6 preferred terms (Table 29), with the most common AE being adrenal insufficiency (27.7%) and glucocorticoid deficiency (21.2%). As mentioned in Section, the PT “glucocorticoid deficiency” and “adrenal insufficiency” further included several reported events which in many aspects are overlapping.

The median duration of exposure to osilodrostat in patients who experienced a hypocortisolism-related AE (N=70) was 93.9 weeks (range: 0.9 - 165.3 weeks) as compared to 57.9 weeks, (range: 1.0 - 159.3 weeks) in those without an event (N=67).

Most of the hypocortisolism-related AEs occurred during the dose titration phase (Period 1) where 60% (42/70) of patients with hypocortisolism-related AEs reported AEs in the first 12 weeks of the study. Hypocortisolism-related AEs were managed with dose reduction (39/70) or interruption (30/70) and then restarting at either the same or lower dose when the AE was deemed resolved by the investigator. Most of the events were mild (grade 1 or 2), and glucocorticoid supplementation was only used in some patients. Grade 3 AEs were infrequent and were reported for adrenal insufficiency (4.4%), glucocorticoid deficiency (3.6%) and acute adrenocortical insufficiency (2.2%). There were no grade 4 (deaths) AEs within this category of AESI. Most of the patients experienced one episode and a few patients had more than two. Only 4 patients (2.9%) discontinued the study drug because of adrenal insufficiency.

There was no relation between hypocortisolism-related AEs and higher osilodrostat dose (Figure 16). Similarly, there was no correlation between cortisol levels and severity of the AEs. The Kaplan Meier (K-M) estimated probability of experiencing an event by Week 48 was 43.7% (95% CI: 35.7, 52.2). The median dose at the time of first hypocortisolism-related event was 10 mg/day (range: 2 - 60 mg/day) (Figure 16).

Table 29 - Hypocortisolism-related AEs regardless of study drug relationship by treatment group (SAS)

Hypocortisolism related AEs Preferred term	Randomized to osilodrostat during RW N=36		Randomized to placebo during RW* N=35		Non-randomized N=66		All Patients N=137	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Adrenal insufficiency	8 (22.2)	0	9 (25.7)	2 (5.7)	21 (31.8)	4 (6.1)	38 (27.7)	6 (4.4)
Glucocorticoid deficiency	10 (27.8)	1 (2.8)	9 (25.7)	1 (2.9)	10 (15.2)	3 (4.5)	29 (21.2)	5 (3.6)
Cortisol free urine decreased	7 (19.4)	0	1 (2.9)	0	1 (1.5)	0	9 (6.6)	0
Adrenocortical insufficiency acute	1 (2.8)	1 (2.8)	0	0	2 (3.0)	2 (3.0)	3 (2.2)	3 (2.2)
Cortisol decreased	1 (2.8)	0	0	0	1 (1.5)	0	2 (1.5)	0
Steroid withdrawal syndrome	0	0	0	0	2 (3.0)	0	2 (1.5)	0

AE: adverse event.

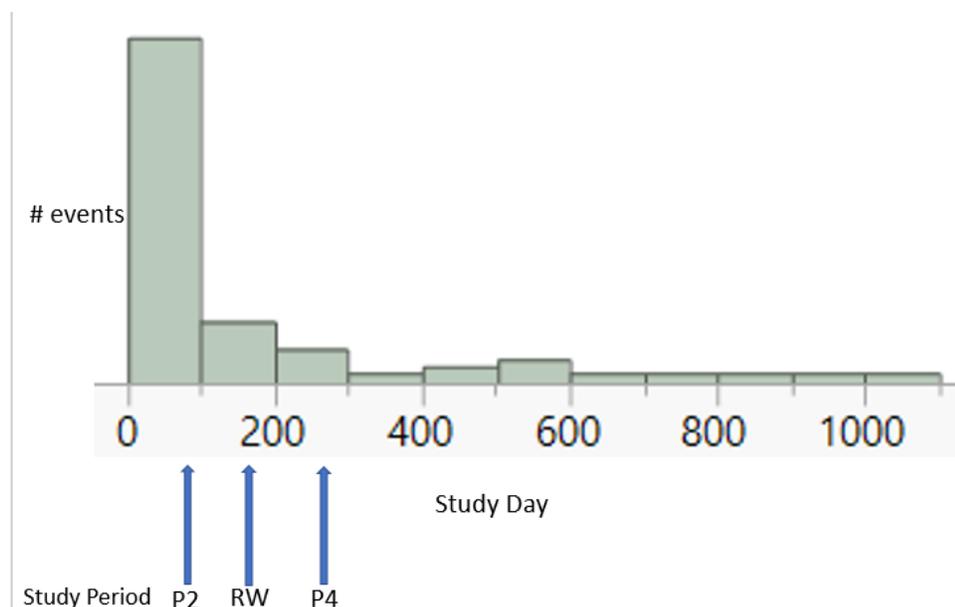
Preferred terms within a category are presented by descending frequency in All grades column as reported in the All Patients.

A patient with multiple occurrences of an AE under one treatment is counted only once for that treatment.

* For patients receiving placebo during the RW Period and excluding data while on placebo.

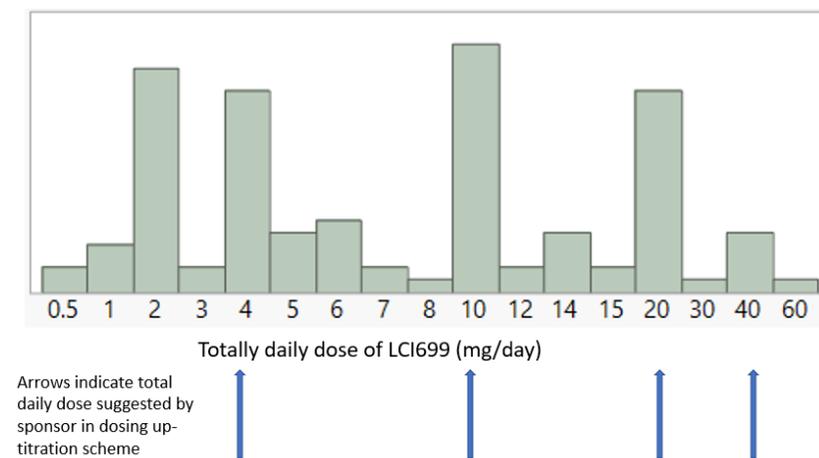
Source: Sponsor's CSR, Table 14.3.1-1.31

Figure 15 - Timeline of first hypocortisolism-related AE over Core Phase (C2301)



JMP analysis of ADAE dataset, AETERM = (PT for hypocortisolism-induced related AE) and AE day

Figure 16 - Total daily osilodrostat dose for all hypocortisolism-related AE (C2301)



JMP analysis of ADAE dataset, AETERM = (PT for hypocortisolism-induced related AE) and study drug dose

Reviewer's comment:

- 1. Definition of hypocortisolism: the definition of hypocortisolism as set by the sponsor included a variety of terms, all of which represent a spectrum of the (desired) outcome response: lower cortisol levels. It is known when patients with CS or CD experience rapid cortisol lowering (via surgery or medical therapy), they often experience symptoms of glucocorticoid (glucocorticoid withdrawal syndrome) that are consistent with treatment response, without truly going into adrenal insufficiency or adrenal crisis. Only 11/137 experienced hypocortisolism as SAE, with clinical symptoms and biochemical levels suggestive of acute, or true adrenal insufficiency or crises. As such, the rate of true acute adrenal insufficiency or crisis in C2301 is likely much lower than the reported 50%, perhaps closer to 8% (11/137) or slightly higher; whereas the reported 50% likely includes, for the most, proportion of patients who experienced either glucocorticoid withdrawal syndrome or relative adrenal insufficiency*
- 2. Rate of hypocortisolism: over half (60%) of patients reported AEs during the dose-titration and required a subsequent osilodrostat dose reduction or interruption. As a number of off-label treatments exist for CD and CS and are used commonly (adrenal steroidogenesis inhibitors or adrenolytic), it is not uncommon in clinical practice to up titrate gradually and "overshoot" before scaling back down on the dose and achieving response with an optimal dose. That said however, the rate of hypocortisolism-related AEs in C2301 is still considered high, and dose-interruption or reduction occurred in over half of the patients: at least 1 in 2 of patients at any timepoint was up-titrated to a dose higher than necessary, and achieved a response at a dose intermediate to that recommended by the sponsor. This suggests an overly-aggressive dosing regimen:*

starting from 4 mg daily to 10 mg (2.5 x the dose), and then doubling dose to 20 mg followed by 30 mg and 60 mg, which is further discussed in the next point.

- 3. Titration schedule: Although there was a clear up-titration schedule for osilodrostat for Period 1, there was no clear restarting dose guide for osilodrostat and that was left to the discretion of the investigator. This, in turn, lead to a variety of osilodrostat dose that are intermediate between the sponsor's recommended dosing (4 mg, 10mg, 20mg, 40mg, and 60 mg daily) and many patients responded and remained on those intermediate doses. As seen by in C2301, most patients required a total of 2-7 mg bid daily to achieve and maintain response, it would be more appropriate that osilodrostat be increased by 1-2 mg increments at a time, rather than the regimen used in C2301.*
- 4. Mechanism of action: because osilodrostat results in elevation of 11-DOC which has a mineralocorticoid activity, true adrenal crises (which requires the absence of both glucocorticoid and mineralocorticoid hormones) would in theory be less expected, but at the same time, also possible at lower doses of osilodrostat, where mineralocorticoid induction of 11DOC is insufficient. This further supports the lack of correlation between dose and the occurrence of adrenal insufficiency.*
- 5. Dosing schedule: up-titration of mUFC was based on the average of 3 consecutive mUFCs which were sent to a central lab, and collected every 2 weeks. The challenge and burden of 3 UFC collections, sending to a central lab, awaiting results, and the limited number of days between time adjustment and the next series of 24-hour urine collection, the turn-around time between starting a new dose and obtaining the new set of UFCs was 10 days. This was discussed in a mid-cycle meeting with the sponsor on August 28, 2019 and detailed in the sponsor's mid-cycle communication listed here [\cdsesub1\evsprod\nda212801\0031\m1\us\fda-response-mid-cycle-comm-20190828.pdf](#). Therefore, in reality the dose titration was 10 days as opposed to 10 weeks. Based on blinded data from C2304, where the dose titration scheme is the same as C2301, however, the titration schedule is every 3 weeks as opposed to every 2 weeks, the rate of adrenal insufficiency is much lower 15%. Of note however, the mUFC in C2304 is based in 2 UFC collections (as opposed to 3), and the definition of adrenal insufficiency was tightened to include clinical and biochemical manifestations. It is unknown if the lower rate is related to the more spacious titration, or better capturing of the term adrenal insufficiency, however, a titration schedule of 2-3 weeks appears to provide lower rate of adrenal insufficiency and overall improved safety.*

8.5.2. Pituitary tumor enlargement

Of 137 enrolled, 13 patients had macroadenoma whereas 69 patients had microadenoma, (defined as maximum tumor diameter \geq 10 mm for macroadenoma and $<$ 10 mm for microadenoma) Among the 69 patients with microadenoma, 32 had tumors with the longest

diameter <6 mm. The proportion of patients who achieved the threshold of change in tumor volume/dimension is shown in Table 30.

Out of 35 pts who had an increase of $\geq 20\%$ from baseline, 10 patients had subsequent decrease in tumor volume which did not exceed 20% increase from baseline at the last MRI. Twenty-five patients had tumor volume >20% higher compared to the BL volume by region of interest. There was no correlation between tumor volume increase and time course or dose of osilodrostat treatment. There was also no correlation between ACTH levels and tumor volume. (Figure 17).

Table 30 - Number (%) of patients achieving thresholds of change in tumor dimension or volume during the study (SAS)

Parameter	All Patients N=137	
	n/N'	%
$\geq 20\%$ increase in tumor volume by ROI (mm ³) or 2mm increase in longest diameter	36/79	45.57
$\geq 20\%$ decrease in tumor volume by ROI (mm ³) or 2mm decrease in longest diameter	48/79	60.76
$\geq 20\%$ increase in tumor volume by 3 maximum dimensions (mm ³) or 2mm increase in longest diameter	35/79	44.30
$\geq 20\%$ decrease in tumor volume by 3 maximum dimensions (mm ³) or 2mm decrease in longest diameter	44/79	55.70

ROI: region of interest.

N' is the number of patients with both baseline and post baseline evaluations.

n is the number of patients meeting the criteria at least once.

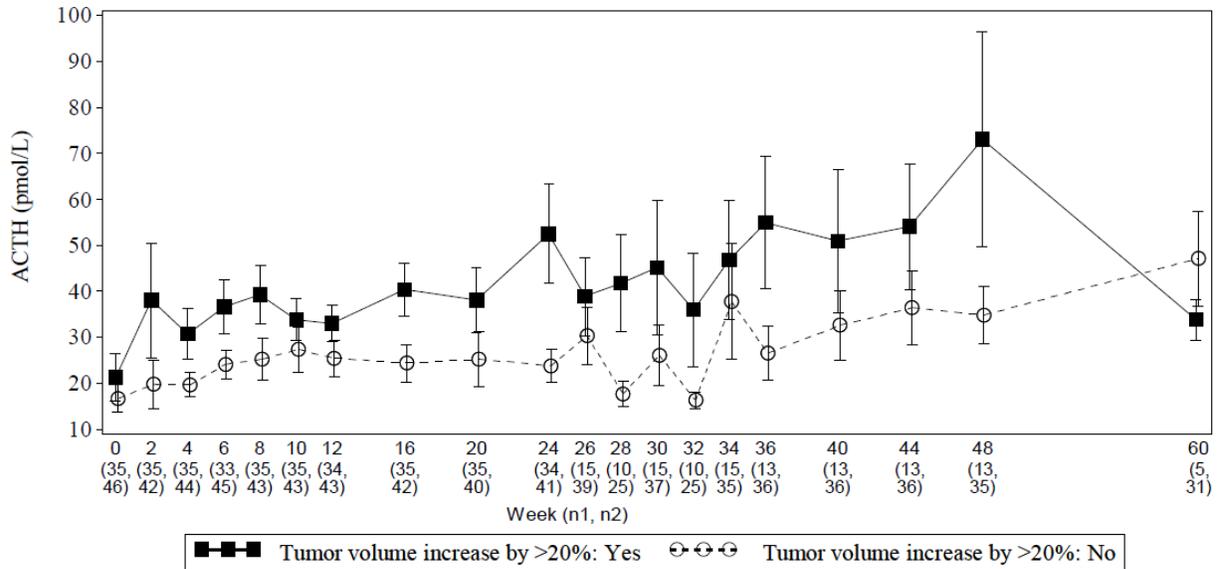
Baseline is defined as the last available value prior to the first study treatment.

Change from baseline: post baseline – baseline.

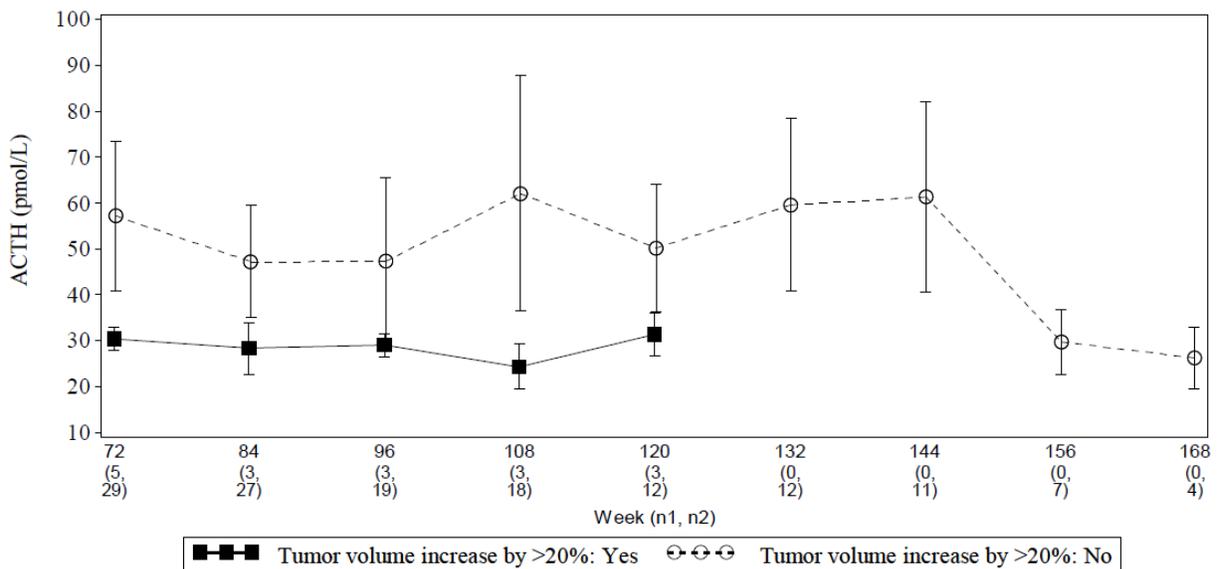
The method used to summarize the longest diameter is based on the method of tumor assessment that yielded the longest diameter at baseline. If all methods that were collected yielded the same baseline measurement, the one with the largest post-baseline diameter was used.

Source: Sponsor's CSR, Table 14.2-6.3

Figure 17 - Mean (SE) ACTH levels by pituitary tumor category (increase > 20% vs. no)



Patients are included up to the time point of the first increase in tumor volume >20% is detected.
 Only patients with a tumor assessment at baseline are included.
 n1, n2 represents the number of patients in the Yes and No category at each timepoint.



Patients are included up to the time point of the first increase in tumor volume >20% is detected.
 Only patients with a tumor assessment at baseline are included.
 n1, n2 represents the number of patients in the Yes and No category at each timepoint.

Source: Sponsor's response to IR: <\\cdsesub1\evsprod\nda212801\0020\m1\us\fda-response-clinical-app1.pdf>

Reviewer's comment: because of its mechanism, osilodrostat, like other steroidogenesis-inhibitors, is anticipated to cause ACTH elevation. Mifepristone, a glucocorticoid receptor blocker, is another treatment approved for symptoms of CS, which by mechanism also causes ACTH elevation, would be anticipated to cause greater elevations in ACTH, because of its direct glucocorticoid blockade. However, the largest prospective, long-term study of mifepristone found that patients with significant increases in ACTH levels without evidence of tumor growth.¹¹ Unlike what was seen with mifepristone, where ACTH rise was dose-dependent, the rise in ACTH levels in C2301 was not dose-dependent. However, because pituitary enlargement was seen in C2301 (both as adverse event and serious adverse events), this adverse event should be included in labelling for patients and physicians, and recommendation for routine ACTH monitoring, in addition to pituitary tumor monitoring (per society guidelines), would also be recommended.

Additionally, an "escape effect" is sometimes observed with some steroidogenesis inhibitors where a sufficient rise in ACTH would eventually overcome the drug blockade and higher drug doses are needed to overcome this and re-establish efficacy, there was no clear evidence of such a phenomenon in C2301.

8.5.3. Adrenal hormone precursor

Not reviewed.

8.5.4. Arrhythmogenic and QT-prolongation AEs

Not reviewed.

8.6. Safety Analyses by Demographic Subgroups

Not reviewed.

8.7. Specific Safety Studies/Clinical Trials

¹¹ Fleseriu M, Findling JW, Koch CA, Schlaffer SM, Buchfelder M, Gross C. Changes in plasma ACTH levels and corticotroph tumor size in patients with Cushing's disease during long-term treatment with the glucocorticoid receptor antagonist mifepristone. J Clin Endocrinol Metab 2014;99:3718-27

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Not reviewed.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not reviewed.

8.8.2. Human Reproduction and Pregnancy

Not reviewed.

8.8.3. Pediatrics and Assessment of Effects on Growth

Osilodrostat was not studied in pediatric patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no specific reports regarding overdose of osilodrostat. Doses up to 100 mg bid have been studied in healthy volunteers (QT study).

There is no known or expected abuse potential for osilodrostat. No signs of dependency have been observed in clinical trials.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

Because osilodrostat has not been studied in combination with other treatments for CD, it is anticipated that the safety profile would change when and if used with other labelled or off-label treatments for CD. Combination therapy is common in CD,¹² and in C2301, partial response was one of the endpoints evaluated and met, in clinical practice osilodrostat may be combined or added if one drug is not sufficient in achieving normalization of cortisol. Other osilodrostat-specific adverse events, such as elevation in adrenal androgen precursors would be expected to worsen acne and hirsutism; and in the case of metyrapone, combination therapy with ketoconazole is used for both, improved efficacy, as well androgen blockade, in order to

¹² Kamenicky P, Droumaguet C, Salenave S, et al. Mitotane, metyrapone, and ketoconazole combination therapy as an alternative to rescue adrenalectomy for severe ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 2011;96:2796-804

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minimize these symptoms. Added safety issues from using a similar approach with osilodrostat may emerge, if a combination therapy is to be used.

8.10. Additional Safety Issues From Other Disciplines

No safety concerns were raised by other disciplines.

8.11. Integrated Assessment of Safety

Using the safety dataset (coming from studies C2301, C2201, and C1201), the sponsor has evaluated the rate of adverse reactions that were reasonably thought to be associated to drug exposure, namely "Adverse drug reactions" (ADRs).

Below is the sponsor's description of the term and additional criteria of the detailed methodology for ADR is presented in Appendix 1, Table 38.

"Adverse drug reactions (ADRs) were defined by the sponsor as events for which there was sufficient evidence to ascertain a causal relationship with osilodrostat. The adverse drug reactions (ADRs) were obtained from C2301 and the supportive clinical studies C2201 and C1201. No pooling of safety data was performed.

Adverse drug reaction candidates were identified in Study C2301 from all AEs, all ADRs (suspected to be related to osilodrostat by the Investigator reported in 2 or more patients ($\geq 1.5\%$)), active drug/placebo AE imbalance during the randomized withdrawal phase, AEs leading to discontinuation, and AEs according to the Novartis designated medical event (DME) list.

Additionally, potential ADR candidates were identified using all available safety data for osilodrostat, including AEs, ECG and laboratory findings in other ongoing osilodrostat studies (Study C2201, Study C1201, Study C2302), and additional SAEs in the safety database from studies in healthy volunteers or hypertensive patients, important product risks, and class effects.

ADRs were confirmed when the potential candidates showed evidence of a causal relationship following evaluation based on Bradford-Hill criteria and medical judgement, and/or were already established as a known risk for osilodrostat or class effect."

The highest ADR occurring in over half of patients (51.1%) exposed to osilodrostat was adrenal insufficiency (- Number and % of patients with adverse reactions in C2301 Table 31).

Table 31 - Number and % of patients with adverse reactions in C2301

Adverse drug reactions	All Grades N=137 %	Frequency category
Endocrine disorders		
Adrenal insufficiency ¹	51.1	Very common
Hypokalaemia ²	13.9	Very common
Decreased appetite	13.9	Very common
Nervous system disorders		
Dizziness ³	14.6	Very common
Headache ⁴	34.3	Very common
Syncope ⁵	1.5	Common
Cardiac disorders		
Tachycardia ⁶	7.3	Common
Vascular disorders		
Hypotension ⁷	13.9	Very common
Gastrointestinal disorders		
Vomiting	21.9	Very common
Nausea	41.6	Very common
Diarrhea	18.2	Very common
Abdominal pain ⁸	16.8	Very common
Skin and subcutaneous tissue disorders		
Rash ⁹	16.1	Very common
Hirsutism* ¹⁰	9.5	Common
Acne*	8.8	Common
General disorders and administration site conditions		
Fatigue ¹¹	43.8	Very common
Oedema ¹²	21.2	Very common
Malaise	6.6	Common
Investigations		
Blood testosterone increased*	10.9	Very common
Blood corticotrophin increased	16.8	Very common
Electrocardiogram QT prolonged	3.6	Common
Transaminases increased ¹³	4.4	Common

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1. Adrenal insufficiency includes glucocorticoid deficiency, adrenocortical insufficiency acute, steroid withdrawal syndrome, cortisol free urine decreased, cortisol decreased.
2. Hypokalemia includes blood potassium decreased.
3. Dizziness includes dizziness postural.
4. Headache includes head discomfort.
5. Syncope includes pre-syncope
6. Tachycardia includes sinus tachycardia, heart rate increased
7. Hypotension includes orthostatic hypotension, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased.
8. Abdominal pain includes abdominal pain upper, abdominal discomfort.
9. Rash includes rash erythematous, rash generalized, rash maculopapular, and rash papular.
10. Hirsutism includes hypertrichosis.
11. Fatigue includes lethargy, asthenia.
12. Oedema includes oedema peripheral, generalised oedema, localised oedema
13. Transaminases increased include alanine aminotransferase increased, aspartate aminotransferase increased

Source: Sponsor's CSC, Table 2.17

Reviewer's comments: A large, retrospective multi-center study of metyrapone in patients with CS showed an adverse event rate of 25%, mostly gastro-intestinal and dizziness, occurring within 2 weeks of initiation. As the mechanism of action is similar to that of osilodrostat, the adverse events in the study were similar to those reported in osilodrostat.¹³

As evident by the adverse drug reaction tabulation, adrenal insufficiency, which is both, an adverse event of, and an extreme measure of the efficacy of osilodrostat, was very prevalent (51%). This was followed by fatigue, nausea, headache, and vomiting, all of which could also be a part of glucocorticoid withdrawal syndrome. Other adverse events included hypokalemia and hypertension, as well as symptoms of androgen excess (such as acne and hirsutism).

1. Adrenal insufficiency: which encompassed a variety of terms, included 11 serious adverse events requiring hospitalization or additional therapy, with the remainder of cases likely a combination of glucocorticoid withdrawal syndrome and relative adrenal insufficiency. As discussed in 8.5.1, the majority of AI events occurred in the dose-titration phase, and required dose interruption or dose reduction. As the maintenance dose in C2301 ranged from 2-7 mg twice a day, it was evident that the titration scheme set by C2301 was overly aggressive in titration, from 2 mg bid to 5 mg bid to 10 mg bid, 20 mg bid, and 30 mg bid, which in many instances constituted increasing the dose by more than 100%. Additionally, blinded data from C2302 which employs the same up-titration dosing scheme but a schedule of 3-week period between subsequent mUFC collections (as opposed to 2-week period in C2301) has shown a much lower rate of adrenal insufficiency (15%). To optimize the safety of osilodrostat in relation to adrenal insufficiency, it would be optimal to employ both: a less aggressive schedule (starting at 1 mg bid and increasing

¹³ Daniel E, Aylwin S, Mustafa O, et al. Effectiveness of Metyrapone in Treating Cushing's Syndrome: A Retrospective Multicenter Study in 195 Patients. *J Clin Endocrinol Metab* 2015;100:4146-54

by 1-2 mg increments) as well as a slower schedule (checking cortisol levels every 2-3 weeks) for potential up-titration.

2. Hypokalemia and hypertension: occurred in 13% of patients, and are a result of the excess mineralocorticoid activity induced by 11-DOC (as a result of 11 β -hydroxylase blockade). These would also go under "adverse events" section.
3. Pituitary tumor: as a result of steroidogenesis blockade, elevation in ACTH is not unexpected with osilodrostat. Overall, 35 patients had \geq 20% tumor volume increase however 10 of these had a subsequent decline. Three patients (2.2%) developed diplopia but alternative causes were present in 2. There was no relation between ACTH rise and osilodrostat dose, and no correlation between ACTH level and (potential) tumor growth. Overall, the median pituitary volume was stable throughout the study.
4. Rise in adrenal hormone precursors (as a result of 11 β -OH blockade) resulted in the following AEs: hypokalemia and hypertension (13% each), acne and hirsutism (9% each), edema and increase weight (7% and 2% respectively).
5. There were no relevant EKG changes from baseline, QT-interval, or other EKG intervals.

9 Advisory Committee Meeting and Other External Consultations

None.

10 Labeling Recommendations

Labeling recommendations will be reviewed separately.

11 Risk Evaluation and Mitigation Strategies (REMS)

This medical reviewer agrees with the DRISK assessment that the primary safety issues identified in this application can be adequately addressed with appropriate labeling and there is no need for a REMS for this application.

12 Post-marketing Requirements and Commitments

A post-marketing requirement to assess the risk of adrenal insufficiency and the optimal dose titration and dosing interval would accompany the approval of osilodrostat. Currently the sponsor has completed a placebo-controlled, double-blinded, randomized trial of osilodrostat

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in patients with CD (Study C2302; LINC-4). The PMR would include the completion of data collection, analysis, and submission of the results of LINC-4.

13 Appendices

13.1. References

13.2. Financial Disclosure

Not reviewed.

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): _____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information

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minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

13.3. Additional Tables

Table 32 - Schedule of Assessment for Period 1 and Period 2 (C2301)

	Category	Protocol Section	Screening	Baseline	Dose escalation period							EOT titration	Treatment period		
					1	2	3	4	5	6	7		8	9	10
Visit Number			1	2								775			
Day			-35 to -8	-7 to -1	1	15	29	43	57	71	85		113	141	169
week			-5 to -2	-1	0	2	4	6	8	10	12		16	20	24
Obtain Informed consent	D	7.1.1.	x												
IWRS/IRT	S		x	x	x	x	x	x	x	x	x		x	x	x
Patient history															
Demography	D	7.1.1.3.	x												
Inclusion/Exclusion criteria	D	5.2 & 5.3.	x	x											
Relevant medical history/Current medical conditions	D	7.1.1.3.	x												
Cushing's Disease history/prior therapy	D	7.1.1.3.	x												
Prior/concomitant medication	D	7.1.1.3.			As required										
Physical examination	S	7.2.2.1.	x	x		x	x	x	x	x	x		x	x	x
Body height	D	7.2.2.3.	x												
Body weight	D	7.2.2.3.	x	x		x	x	x	x	x	x		x	x	x
Waist circumference	D	7.2.2.3.	x	x		x	x	x	x	x	x		x	x	x
Vital signs															
Body temperature	D	7.2.2.2.	x	x		x	x	x	x	x	x		x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.	x	x		x	x	x	x	x	x		x	x	x
Laboratory assessments															
Hematology	D	7.2.2.4.1.	x	x			x		x		x		x	x	x
Chemistry - full	D	7.2.2.4.2.	x	x			x		x		x		x	x	x
Chemistry - partial	D	7.2.2.4.2.				x		x		x					
Thyroid Panel	D	7.2.2.4.5.		x							x				x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.		x		x					x				x

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Visit Number	Category	Protocol Section	Screening	Baseline	Dose escalation period							EOT titration	Treatment period			
			1	2	3	4	5	6	7	8	9	775	10	11	12	
Day			-35 to -8	-7 to -1	1	15	29	43	57	71	85		113	141	169	
week			-5 to -2	-1	0	2	4	6	8	10	12		16	20	24	
Coagulation	D	7.2.2.4.4.		x							x					
Urinalysis	D	7.2.2.4.3.	x	x		x	x	x	x	x	x		x	x	x	
Pregnancy test (serum)	D	7.2.2.4.8.	x	x												
Pregnancy test (urine)	D	7.2.2.4.8.				x	x	x	x	x	x		x	x	x	
Efficacy Assessment																
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.	x	x		x	x	x	x	x	x		x	x	x	
Serum testosterone and estradiol	D	7.2.2.4.6.		x		x					x				x	
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.		x		x					x				x	
Plasma ACTH, serum cortisol	D	7.2.2.4.6.		x		x	x	x	x	x	x		x	x	x	
Serum 11-deoxycortisol	D	7.2.2.4.6.		x		x					x				x	
Serum aldosterone	D	7.2.2.4.6.		x		x					x				x	
Renin	D	7.2.2.4.6.		x		x					x				x	
Salivary Cortisol (morning and late night)	D	7.2.2.4.6.		x							x				x	
Serum 11-Deoxycorticosterone	D	7.2.2.4.6.		x		x					x				x	
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.		x							x				x	
HbA1C	D	7.2.2.4.7.	x	x							x				x	
Safety																
Adverse Events	D	8.1.	As required													
12 Lead safety ECG assessment	D	7.2.2.6.2.	x	x	x	x	x	x	x	x	x	x		x	x	x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1.		x		x					x					x
Biomarkers (urine metabolomics)	D	7.2.4.1.		x							x					x
Optional pharmacogenetic sampling	D	7.2.4.2.		x												

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Visit Number	Category	Protocol Section	Screening	Baseline	Dose escalation period							EOT titration	Treatment period		
			1	2	3	4	5	6	7	8	9	775	10	11	12
Day			-35 to -8	-7 to -1	1	15	29	43	57	71	85		113	141	169
week			-5 to -2	-1	0	2	4	6	8	10	12		16	20	24
Pituitary MRI (or CT)	D	7.2.2.5.		x											x
Photography	D	7.2.1.2.		x							x				x
DXA scan	D	7.2.1.3.		x											
Patient Reported Outcomes															
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.		x			x		x		x				x
Study Drug administration	D	6.1.1.			continuous b.i.d. dosing										
PK sampling	D	7.2.3.			x	x	x	x	x	x	x		x	x	x
Serum cortisol, salivary cortisol, plasma ACTH (China subset)	D	7.2.2.4.6.		x	x	x	x	x	x	x	x		x	x	x
Serum cortisol (Extensive PK subset)	D	7.2.2.4.6.			x	x	x	x	x	x	x		x	x	x
Salivary cortisol (Extensive PK subset)	D	7.2.2.4.6.			x	x	x	x	x	x	x		x	x	x
End of treatment titration form	D											x			

Source: Sponsor's CSR, Table 7-1

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Table 33 - Schedule of Assessment for Period 3 (RW) and Period 4 (open-label) for randomized patients (C2301)

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
			13	14	15	16	17		18	19	20		
Visit Number			13	14	15	16	17	776	18	19	20	777	779
Day			183	197	211	225	239		253	281	309	337	30 days from last dose
week			26	28	30	32	34		36	40	44	48	
IWRS/IRT	S		x	x	x	x	x		x	x	x	x	x
Prior/concomitant medication	D	7.1.1.3.	As required										
IWRS/IRT Randomization	S		x										
Physical examination	S	7.2.2.1.	x	x	x	x	x		x	x	x	x	x
Body weight	D	7.2.2.3.	x	x	x	x	x		x	x	x	x	x
Waist circumference	D	7.2.2.3.	x	x	x	x	x		x	x	x	x	x
Vital signs													
Body temperature	D	7.2.2.2.	x	x	x	x	x		x	x	x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.	x	x	x	x	x		x	x	x	x	x
Laboratory assessments													
Hematology	D	7.2.2.4.1.	x	x	x	x	x		x	x	x	x	x
Chemistry - full	D	7.2.2.4.2.	x		x		x		x	x	x	x	x
Chemistry - partial	D	7.2.2.4.2.		x		x							
Thyroid Panel	D	7.2.2.4.5.					x					x	x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.					x					x	x
Coagulation	D	7.2.2.4.4.										x	x
Urinalysis	D	7.2.2.4.3.	x	x	x	x	x		x	x	x	x	x
Pregnancy test (urine)	D	7.2.2.4.8.	x	x	x	x	x		x	x	x	x	x
Efficacy Assessment													
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.	x	x	x	x	x		x	x	x	x	x

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	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
			13	14	15	16	17		18	19	20		
Visit Number			13	14	15	16	17	776	18	19	20	777	779
Day			183	197	211	225	239		253	281	309	337	30 days from last dose
week			26	28	30	32	34		36	40	44	48	
Serum testosterone and estradiol	D	7.2.2.4.6.					x					x	x
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.					x					x	x
Plasma ACTH, serum cortisol	D	7.2.2.4.6.	x	x	x	x	x		x	x	x	x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.					x					x	x
Serum aldosterone	D	7.2.2.4.6.					x					x	x
Renin	D	7.2.2.4.6.					x					x	x
Salivary Cortisol (morning and late night)	D	7.2.2.4.6.					x					x	x
Serum 11-Deoxycorticosterone	D	7.2.2.4.6.					x					x	x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.	x	x	x	x	x					x	x
HbA1C	D	7.2.2.4.7.	x	x	x	x	x					x	x
Safety													
Adverse Events	D	8.1.	As required										
12 Lead safety ECG assessment	D	7.2.2.6.2.	x	x	x	x	x		x	x	x		x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1.										x	
Biomarkers (urine metabolomics)	D	7.2.4.1.		x									
Imaging													
Pituitary MRI (or CT)	D	7.2.2.5.										x	
Photography	D	7.2.1.2.					x					x	
DXA scan	D	7.2.1.3.										x	
Patient Reported Outcomes													
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.	x	x	x	x	x					x	
Study Drug administration	D	6.1.1.	continuous b.i.d. dosing										

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	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
			13	14	15	16	17		18	19	20		
Visit Number			13	14	15	16	17	776	18	19	20	777	779
Day			183	197	211	225	239		253	281	309	337	30 days from last dose
week			26	28	30	32	34		36	40	44	48	
PK sampling	D	7.2.3.	x	x	x	x	x		x	x	x	x	
Serum cortisol, salivary cortisol, plasma ACTH (China subset)	D	7.2.2.4.6.	x	x	x	x	x		x	x	x	x	
Serum cortisol (Extensive PK subset)	D	7.2.2.4.6.	x	x	x	x	x		x	x	x	x	
Salivary cortisol (Extensive PK subset)	D	7.2.2.4.6.	x	x	x	x	x		x	x	x	x	
End of randomized withdrawal period form	D							x					
End of treatment core form	D											x	
End of study form	D												x

Source: Sponsor's CSR, Table 7-2

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Table 34 - Schedule of Assessment for Period 3 (RW) and Period 4 (open-label) for non-randomized patients (C2301)

	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
			13	14	15	16	17		18	19	20		
Visit Number			13	14	15	16	17	776	18	19	20	777	779
Day			183	197	211	225	239		253	281	309	337	30 days from last dose
week			26	28	30	32	34		36	40	44	48	
IWRS/IRT	S		x		x		x		x	x	x	x	x
Prior/concomitant medication	D	7.1.1.3.	As required										
IWRS/IRT Randomization	D		x										
Physical examination	S	7.2.2.1.	x		x		x		x	x	x	x	x
Body weight	D	7.2.2.3.	x		x		x		x	x	x	x	x
Waist circumference	D	7.2.2.3.	x		x		x		x	x	x	x	x
Vital signs													
Body temperature	D	7.2.2.2.	x		x		x		x	x	x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.	x		x		x		x	x	x	x	x
Laboratory assessments													
Hematology	D	7.2.2.4.1.	x		x		x		x	x	x	x	x
Chemistry - full	D	7.2.2.4.2.	x		x		x		x	x	x	x	x
Thyroid Panel	D	7.2.2.4.5.					x					x	x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.					x					x	x
Coagulation	D	7.2.2.4.4.										x	x
Urinalysis	D	7.2.2.4.3.	x		x		x		x	x	x	x	x
Pregnancy test (urine)	D	7.2.2.4.8.	x		x		x		x	x	x	x	x
Efficacy Assessment													
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.	x		x		x		x	x	x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6.					x					x	x

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	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
			13	14	15	16	17		18	19	20		
Visit Number			13	14	15	16	17	776	18	19	20	777	779
Day			183	197	211	225	239		253	281	309	337	30 days from last dose
week			26	28	30	32	34		36	40	44	48	
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.					x					x	x
Plasma ACTH, serum cortisol	D	7.2.2.4.6.	x		x		x		x	x	x	x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.					x					x	x
Serum aldosterone	D	7.2.2.4.6.					x					x	x
Renin	D	7.2.2.4.6.					x					x	x
Salivary Cortisol (morning and late night)	D	7.2.2.4.6.					x					x	x
Serum 11-Deoxycorticosterone	D	7.2.2.4.6.					x					x	x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.					x					x	x
HbA1C	D	7.2.2.4.7.					x					x	x
Safety													
Adverse Events	D	8.1.	As required										
12 Lead safety ECG assessment	D	7.2.2.6.2.	x		x		x		x	x	x		x
12-Lead 24-hour Holter ECG recording	D	7.2.2.6.1.										x	
Imaging													
Pituitary MRI (or CT)	D	7.2.2.5.										x	
Photography	D	7.2.1.2.					x					x	
DXA scan	D	7.2.1.3.										x	
Patient Reported Outcomes													
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.	x		x		x					x	
Study Drug administration	D	6.1.1.	continuous b.i.d. dosing										
PK sampling	D	7.2.3.	x		x		x		x	x	x	x	

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	Category	Protocol Section	Randomized Withdrawal period					EOT randomized withdrawal period	Open Label period			EOT core	Study completion
			13	14	15	16	17		18	19	20		
Visit Number			13	14	15	16	17	776	18	19	20	777	779
Day			183	197	211	225	239		253	281	309	337	30 days from last dose
week			26	28	30	32	34		36	40	44	48	
Serum cortisol, salivary cortisol, plasma ACTH (China subset)	D	7.2.2.4.6.	x		x		x		x	x	x	x	
Serum cortisol (Extensive PK subset)	D	7.2.2.4.6.	x		x		x		x	x	x	x	
Salivary cortisol (Extensive PK subset)	D	7.2.2.4.6.	x		x		x		x	x	x	x	
End of randomized withdrawal period form	D							x					
End of treatment core form	D											x	
End of study form	D												x

Source: Sponsor's CSR, Table 7-3

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Table 35 - Schedule of Assessment for Optional Extension Period (Year 1)

Visit Number	Category	Protocol Section	Extension								
			21	22	23	24	25	26	27	28	29
Day			337	365	393	421	449	477	505	589	673
week			48	52	56	60	64	68	72	84	96
Obtain Informed consent	S		x								
IWRS/IRT	S		x	x	x	x	x	x	x	x	x
Prior/concomitant medication	D	7.1.1.3.	As required								
Physical examination	S	7.2.2.1.		x	x	x	x	x	x	x	x
Body weight	D	7.2.2.3.		x	x	x	x	x	x	x	x
Waist circumference	D	7.2.2.3.		x	x	x	x	x	x	x	x
Vital signs											
Body temperature	D	7.2.2.2.		x	x	x	x	x	x	x	x
Blood pressure/Pulse rate	D	7.2.2.2.		x	x	x	x	x	x	x	x
Laboratory assessments											
Hematology	D	7.2.2.4.1.		x	x	x	x	x	x	x	x
Chemistry - full	D	7.2.2.4.2.		x	x	x	x	x	x	x	x
Thyroid Panel	D	7.2.2.4.5.				x			x		x
Luteinizing Hormone (LH) and Follicle stimulating hormone (FSH)	D	7.2.2.4.6.				x			x		x
Coagulation	D	7.2.2.4.4.				x			x	x	x
Urinalysis	D	7.2.2.4.3.				x			x	x	x
Pregnancy test (urine)	D	7.2.2.4.8.		x	x	x	x	x	x	x	x
Efficacy Assessment											
24-hour Urinary Free Cortisol and creatinine	D	7.2.1.1.				x			x	x	x
Serum testosterone and estradiol	D	7.2.2.4.6.				x			x	x	x
Plasma ACTH, serum cortisol	D	7.2.2.4.6.				x			x	x	x
Serum 11-deoxycortisol	D	7.2.2.4.6.				x			x	x	x

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Visit Number	Category	Protocol Section	Extension								
			21	22	23	24	25	26	27	28	29
Day			337	365	393	421	449	477	505	589	673
week			48	52	56	60	64	68	72	84	96
Serum Androstenedione, DHEAS, Estrone	D	7.2.2.4.6.				x			x	x	x
Serum aldosterone	D	7.2.2.4.6.				x			x	x	x
Renin	D	7.2.2.4.6.				x			x	x	x
Salivary Cortisol (morning and late night)	D	7.2.2.4.6.				x			x	x	x
Serum 11-Deoxycorticosterone	D	7.2.2.4.6.				x			x	x	x
Fasting serum Insulin and plasma glucose	D	7.2.2.4.7.				x			x	x	x
HbA1C	D	7.2.2.4.7.				x			x	x	x
Safety											
Adverse Events	D	8.1.	As required								
12 Lead safety ECG assessment	D	7.2.2.6.2.	x			x			x	x	x
24-hour Holter ECG recording	D	7.2.2.6.1.							x		
Imaging											
Pituitary MRI (or CT)	D	7.2.2.5.							x		
Photography	D	7.2.1.2.							x		
DXA scan	D	7.2.1.3.									
Patient Reported Outcomes											
HRQoL EQ-5D-5L, CushingQoL, Beck Depression Inventory	D	7.2.6.							x		x
Study Drug administration	D	6.1.1.	continuous b.i.d. dosing								

Source: Sponsor's CSR, Table 7-4

Table 36 - Newly occurring or worsening biochemical abnormalities by randomized group (SAS)

Laboratory test	Worsening from BL to	Randomized to osilodrostat during RW N=36			Randomized to placebo during RW* N=35			Non-Randomized N=66			All Patients N=137		
		Total	n	%	Total	n	%	Total	n	%	Total	n	%
Activated PTT (secs)	Grade 1	28	4	14.3	29	10	34.5	60	13	21.7	117	27	23.1
	Grade 2	34	3	8.8	33	2	6.1	62	2	3.2	129	7	5.4
	Grade 3	34	0	0	33	1	3.0	64	0	0	131	1	0.8
	Grade 4	34	0	0	33	0	0	64	0	0	131	0	0
ALT increase (U/L)	Grade 1	33	7	21.2	29	4	13.8	64	22	34.4	126	33	26.2
	Grade 2	36	0	0	34	1	2.9	66	0	0	136	1	0.7
	Grade 3	36	0	0	34	1	2.9	66	2	3.0	136	3	2.2
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Albumin decrease (g/L)	Grade 1	35	0	0	34	0	0	66	0	0	135	0	0
	Grade 2	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 3	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
ALP increase (U/L)	Grade 1	36	7	19.4	34	6	17.6	64	6	9.4	134	19	14.2
	Grade 2	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 3	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Amylase increase (U/L)	Grade 1	36	2	5.6	35	4	11.4	64	2	3.1	135	8	5.9
	Grade 2	36	0	0	35	0	0	66	0	0	137	0	0
	Grade 3	36	0	0	35	0	0	66	0	0	137	0	0
	Grade 4	36	0	0	35	0	0	66	0	0	137	0	0

Source: Sponsor's CSR, Table 12-15

Laboratory test	Worsening from BL to	Randomized to osilodrostat during RW N=36			Randomized to placebo during RW* N=35			Non-Randomized N=66			All Patients N=137		
		Total	n	%	Total	n	%	Total	n	%	Total	n	%
AST increase (U/L)	Grade 1	36	6	16.7	32	4	12.5	65	12	18.5	133	22	16.5
	Grade 2	36	0	0	34	0	0	66	2	3.0	136	2	1.5
	Grade 3	36	0	0	34	1	2.9	66	0	0	136	1	0.7
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hyperbilirubinemia (µmol/L)	Grade 1	34	1	2.9	33	3	9.1	66	1	1.5	133	5	3.8
	Grade 2	36	2	5.6	34	0	0	66	0	0	136	2	1.5
	Grade 3	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hypercholesterolemia (mmol/L)	Grade 1	18	8	44.4	18	11	61.1	38	15	39.5	74	34	45.9
	Grade 2	34	2	5.9	33	2	6.1	62	4	6.5	129	8	6.2
	Grade 3	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
CK increase (U/L)	Grade 1	32	5	15.6	32	10	31.3	64	10	15.6	128	25	19.5
	Grade 2	36	2	5.6	33	1	3.0	66	2	3.0	135	5	3.7
	Grade 3	36	0	0	33	0	0	66	1	1.5	135	1	0.7
	Grade 4	36	1	2.8	33	0	0	66	0	0	135	1	0.7
Creatinine increase (µmol/L)	Grade 1	35	5	14.3	34	4	11.8	66	8	12.1	135	17	12.6
	Grade 2	36	1	2.8	34	0	0	66	1	1.5	136	2	1.5
	Grade 3	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
GGT increase (U/L)	Grade 1	31	8	25.8	30	2	6.7	50	9	18.0	111	19	17.1
	Grade 2	33	1	3.0	33	0	0	64	4	6.3	130	5	3.8
	Grade 3	36	1	2.8	34	1	2.9	65	1	1.5	135	3	2.2
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hyperglycemia (mg/dL)	Grade 1	24	7	29.2	27	5	18.5	42	4	9.5	93	16	17.2
	Grade 2	31	1	3.2	33	1	3.0	58	2	3.4	122	4	3.3
	Grade 3	34	1	2.9	33	0	0	62	0	0	129	1	0.8
	Grade 4	34	0	0	33	0	0	62	0	0	129	0	0
Hypoglycemia (mg/dL)	Grade 1	33	2	6.1	32	4	12.5	60	6	10.0	125	12	9.6
	Grade 2	34	0	0	33	0	0	62	1	1.6	129	1	0.8
	Grade 3	34	0	0	33	0	0	62	0	0	129	0	0
	Grade 4	34	0	0	33	0	0	62	0	0	129	0	0
Hypermagnesemia (mmol/L)	Grade 1	31	3	9.7	33	5	15.2	59	6	10.2	123	14	11.4
	Grade 2	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 3	36	1	2.8	34	1	2.9	66	2	3.0	136	4	2.9
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hypomagnesemia (mmol/L)	Grade 1	36	0	0	34	0	0	66	1	1.5	136	1	0.7
	Grade 2	36	0	0	34	0	0	66	1	1.5	136	1	0.7

Source: Sponsor's CSR, Table 12-15

Laboratory test	Worsening from BL to	Randomized to osilodrostat during RW N=36			Randomized to placebo during RW* N=35			Non-Randomized N=66			All Patients N=137		
		Total	n	%	Total	n	%	Total	n	%	Total	n	%
	Grade 3	36	0	0	34	0	0	66	1	1.5	136	1	0.7
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hypophosphatemia (mmol/L)	Grade 1	33	0	0	33	0	0	62	0	0	128	0	0
	Grade 2	33	3	9.1	33	2	6.1	62	3	4.8	128	8	6.3
	Grade 3	36	1	2.8	34	1	2.9	66	2	3.0	136	4	2.9
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hyperkalemia (mmol/L)	Grade 1	36	3	8.3	34	3	8.8	66	4	6.1	136	10	7.4
	Grade 2	36	0	0	34	1	2.9	66	2	3.0	136	3	2.2
	Grade 3	36	3	8.3	34	0	0	66	0	0	136	3	2.2
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hypokalemia (mmol/L)	Grade 1	34	0	0	33	0	0	64	0	0	131	0	0
	Grade 2	34	5	14.7	33	4	12.1	64	14	21.9	131	23	17.6
	Grade 3	36	1	2.8	34	3	8.8	65	4	6.2	135	8	5.9
	Grade 4	36	0	0	34	0	0	66	1	1.5	136	1	0.7
Hypematremia (mmol/L)	Grade 1	36	3	8.3	33	1	3.0	64	5	7.8	133	9	6.8
	Grade 2	36	0	0	33	0	0	65	0	0	134	0	0
	Grade 3	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Hyponatremia (mmol/L)	Grade 1	36	3	8.3	33	4	12.1	66	9	13.6	135	16	11.9
	Grade 2	36	0	0	33	0	0	66	0	0	135	0	0
	Grade 3	36	0	0	33	0	0	66	0	0	135	0	0
	Grade 4	36	0	0	34	0	0	66	0	0	136	0	0
Triglycerides increase (mmol/L)	Grade 1	26	7	26.9	24	11	45.8	52	22	42.3	102	40	39.2
	Grade 2	35	3	8.6	34	2	5.9	64	3	4.7	133	8	6.0
	Grade 3	36	2	5.6	34	0	0	65	2	3.1	135	4	3.0
	Grade 4	36	0	0	34	0	0	65	0	0	135	0	0
Urate increase (µmol/L)	Grade 1	35	2	5.7	32	0	0	65	13	20.0	132	15	11.4
	Grade 2	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 3	36	0	0	34	0	0	66	0	0	136	0	0
	Grade 4	36	2	5.6	34	4	11.8	66	7	10.6	136	13	9.6

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase;
CK: creatine kinase; CTC: common terminology criteria; GGT: gamma glutamyl transferase;
PTT: partial thromboplastin time; RW: randomized withdrawal; SAS: safety analysis set.
Total=number of patients evaluable post-baseline, who had less than grade x at baseline.
n=number of patients who had less than grade x at baseline, and worsened to grade x post-baseline.
Missing baseline values were excluded.
Patients are counted only for the worst grade observed post-baseline.
Each % is based on the corresponding Total.
N is the # patients in the safety analysis set.
* For patients receiving placebo during the RW Period and excluding data while on placebo.

Source: Sponsor's CSR, Table 12-15

Table 37 - ECG changes from baseline at Week 48 by randomized treatment group by local assessment (SAS)

Parameter Visit Statistics	Randomized to osilodrostat during RW N=36		Randomized to placebo during RW* N=35		Non-randomized N=66		All Patients N=137	
	Actual	Change from baseline	Actual	Change from baseline	Actual	Change from baseline	Actual	Change from baseline
QTcF (ms)								
Baseline								
n	36		35		66		137	
Mean (SD)	402.8 (18.24)		404.2 (17.88)		402.1 (19.89)		402.8 (18.85)	
Median	401.8		402.3		402.5		402.3	
Q1-Q3	391.3 -413.8		395.0 -415.3		388.0 -415.0		390.7 -414.3	
Min-Max	366.0 -442.7		372.3 -445.3		355.0 -451.7		355.0 -451.7	
Week 48								
n	29	29	27	27	35	35	91	91
Mean (SD)	409.2 (21.78)	6.5 (17.69)	409.0 (18.43)	3.1 (23.72)	406.3 (20.82)	6.1 (20.92)	408.0 (20.28)	5.3 (20.67)
Median	407.0	3.0	405.0	2.0	411.0	8.0	406.0	4.7
Q1-Q3	396.0 -422.0	-6.3 -16.0	396.0 -419.0	-11.0 -18.0	391.0 -423.0	-7.7 -22.0	395.0 -422.0	-9.3 -20.3
Min-Max	356.0 -452.0	-24.7 -47.0	385.0 -453.0	-36.7 -78.0	350.0 -438.0	-45.0 -43.3	350.0 -453.0	-45.0 -78.0
QRS (ms)								
Baseline								
n	36		35		66		137	
Mean (SD)	92.8 (9.39)		93.4 (10.85)		89.2 (9.23)		91.2 (9.84)	
Median	92.7		91.3		87.8		90.3	
Q1-Q3	87.8 -96.0		87.0 -98.0		82.0 -96.0		83.7 -96.7	
Min-Max	78.7 -123.0		76.7 -129.7		73.0 -112.0		73.0 -129.7	
Week 48								

Source: Sponsor's CSR, Table 14.3-5.1

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Parameter Visit Statistics	Randomized to osilodrostat during RW N=36		Randomized to placebo during RW* N=35		Non-randomized N=66		All Patients N=137	
	Actual	Change from baseline	Actual	Change from baseline	Actual	Change from baseline	Actual	Change from baseline
n	29	29	27	27	35	35	91	91
Mean (SD)	97.2 (11.76)	4.5 (6.46)	95.6 (13.45)	3.3 (9.74)	93.1 (10.07)	2.1 (6.98)	95.2 (11.69)	3.2 (7.73)
Median	95.0	3.7	94.0	1.7	91.0	3.0	94.0	3.0
Q1-Q3	89.0 -101.0	0.3 -6.7	88.0 -103.0	-1.7 -5.7	86.0 -98.0	-1.3 -5.7	88.0 -101.0	-0.7 -6.0
Min-Max	78.0 -136.0	-7.7 -24.0	76.0 -136.0	-11.7 -40.0	78.0 -125.0	-19.3 -21.0	76.0 -136.0	-19.3 -40.0
PR (ms)								
Baseline								
n	36		35		66		137	
Mean (SD)	154.5 (22.26)		151.8 (18.47)		150.7 (22.04)		152.0 (21.15)	
Median	153.3		150.0		146.7		149.7	
Q1-Q3	140.7 -167.3		137.7 -165.3		135.3 -163.3		137.7 -165.3	
Min-Max	111.7 -215.3		115.0 -196.7		107.3 -210.7		107.3 -215.3	
Week 48								
n	29	29	27	27	35	35	91	91
Mean (SD)	161.7 (26.45)	8.2 (12.47)	165.9 (21.40)	11.6 (14.10)	156.1 (19.24)	6.5 (13.95)	160.8 (22.51)	8.6 (13.56)
Median	163.0	7.3	163.0	10.0	157.0	6.7	158.0	8.0
Q1-Q3	144.0 -176.0	0.0 -16.3	151.0 -182.0	3.3 -22.7	140.0 -168.0	-2.0 -12.7	143.0 -178.0	-1.0 -16.3
Min-Max	112.0 -220.0	-17.0 -35.0	130.0 -203.0	-23.0 -37.7	119.0 -191.0	-19.7 -48.0	112.0 -220.0	-23.0 -48.0
HR (bpm)								
Baseline								
n	36		35		66		137	
Mean (SD)	67.9 (11.31)		70.1 (13.67)		73.3 (13.94)		71.1 (13.34)	
Median	66.0		69.0		71.5		69.0	
Q1-Q3	61.7 -74.0		60.7 -81.0		62.3 -83.0		62.0 -80.0	

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Parameter Visit Statistics	Randomized to osilodrostat during RW N=36		Randomized to placebo during RW* N=35		Non-randomized N=66		All Patients N=137	
	Actual	Change from baseline	Actual	Change from baseline	Actual	Change from baseline	Actual	Change from baseline
Min-Max	46.0 -95.0		42.7 -105.7		52.0 -127.0		42.7 -127.0	
Week 48								
n	29	29	27	27	35	35	91	91
Mean (SD)	69.4 (11.62)	1.4 (8.72)	71.3 (14.19)	1.4 (11.58)	72.1 (11.33)	0.4 (11.77)	71.0 (12.25)	1.0 (10.72)
Median	66.0	3.0	70.0	2.0	71.0	1.7	70.0	2.0
Q1-Q3	63.0 -76.0	-2.0 -5.7	62.0 -84.0	-5.7 -9.3	64.0 -81.0	-7.0 -8.7	63.0 -81.0	-5.7 -7.7
Min-Max	47.0 -97.0	-19.0 -20.3	44.0 -94.0	-21.7 -25.0	51.0 -99.0	-36.0 -20.0	44.0 -99.0	-36.0 -25.0

ECG: electrocardiogram; SAS: safety analysis set; SD: standard deviation.

The table displays results of local ECG reading.

Baseline is defined as the last ECG measurements taken at pre-dose on Day 1/study defined time window.

Change from baseline: worst post baseline from a given visit – baseline.

For each ECG parameter, only patients with both baseline value and at least one post baseline at a given visit were included.

* For patients receiving placebo during the RW Period and excluding data while on placebo.

Table 38 - Adverse drug reaction-selection methodology

Adverse drug reaction – selection methodology

Candidates for ADRs were reviewed in a step-wise fashion as follows:

1. AEs reported as suspected in 2 or more patients ($\geq 1.5\%$). All terms were medically reviewed. Thirty-five terms were identified as ADRs: adrenal insufficiency/adrenocortical insufficiency acute/glucocorticoid deficiency/steroid withdrawal syndrome/cortisol free urine decreased/cortisol decreased, hypokalemia, decreased appetite, headache, dizziness, tachycardia/heart rate increased, hypotension/orthostatic hypotension/ blood pressure diastolic decreased, nausea, vomiting, diarrhea, abdominal pain, abdominal pain upper, acne, hirsutism, rash, fatigue/ lethargy/asthenia, malaise, edema /edema peripheral / generalized edema, electrocardiogram QT prolonged, blood testosterone increased, blood corticotrophin increased, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased.

The following 40 terms were removed due to the following alternative plausible explanations:

13 events: More likely reflecting complications of underlying chronic hypercortisolism/recognized complications of CS: Urine cortisol/creatinine ratio increased, hyperuricemia, gamma-glutamyltransferase increased, back pain, arthralgia, myalgia, muscular weakness, muscle spasms, pain in extremity, menstruation irregular, amenorrhea, pituitary tumor benign/pituitary tumor ([Lee et al 2006](#), [Li et al 2013](#), [Pivonello et al 2016](#)).

5 events: Cumulative data from CS program (and experience in hypertension and in healthy volunteer studies) does not support causality: hypertension/blood pressure systolic increased/blood pressure diastolic increased (observations consistently show a decrease in BP), weight increased (C2301 data shows consistent decrease in weight and BMI), hyponatremia (observations consistently showed no overall change in serum sodium).

17 events: Events confounded by other plausible etiology either from ongoing medical conditions, comorbid illness, concomitant medication, implausible time to onset, and/or negative dechallenge: tinnitus, sleep disorder/somnolence, pyrexia, pruritus generalized/pruritus, joint swelling, hypoaesthesia, hyperhidrosis, dysphonia, dyspepsia, dry skin, constipation, blood creatine phosphokinase increased, blood alkaline phosphatase increased, anemia, alopecia.

3 events: Not considered an adverse finding/adverse event: weight decreased (while C2301 data shows consistent decrease in weight and BMI, this is a desired outcome in CS patients), renin increased and hormone level abnormal (reflecting 11-deoxycortisol increased and 11-deoxycorticosterone increased) (in the context of aldosterone blockade this laboratory finding is not considered clinically relevant).

2 events: Term too vague to be considered medically meaningful/assessable: pain, gastrointestinal disorder.

2. All remaining suspected AEs reported at a lower frequency. Important considerations were whether the events were identified risks for osilodrostat and previously identified as ADRs and reflected in the current reference safety information of the Investigators' Brochure (IB). This review identified no additional terms as ADRs.
3. AEs reported with an osilodrostat/placebo imbalance (difference of ≥ 2 patients [5.6%]) during the randomized withdrawal phase only. All terms were medically reviewed, no additional ADRs were identified in this step. An imbalance was seen only in five terms, four of which (nausea, headache, arthralgia, and asthenia) are described above. The fifth event was constipation which was confounded by comorbid ongoing conditions of obesity, diabetes, hypothyroidism, depression/mood changes, mobility issues/musculoskeletal pain, ongoing constipation at baseline, occurred following hospitalization for adrenal thrombosis, or had a prolonged time to onset.
4. AEs leading to discontinuation. All terms were medically reviewed, no additional ADRs were identified in this step.
5. AEs according to the Novartis designated DME list. All terms were medically reviewed, no additional ADRs were identified in this step.
6. Review of abnormal laboratory, ECG, and imaging findings did not identify any further safety findings
7. Previously identified as ADRs and reflected in the current reference safety information of the IB. One additional ADRs was identified: Syncope/Presyncope. This reported event did not fall into the above categories
8. Review of known risks for osilodrostat or for other cortisol synthesis inhibitors. All terms were medically reviewed, no additional ADRs were identified in this step.
9. Remaining reported AEs, but which may be notable due to seriousness, severity or high frequency. No additional ADRs were identified in this step.

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