14 November 2019
EMA/653461/2019 **Corr.[2]**
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Isturisa

International non-proprietary name: osilodrostat

Procedure No. EMEA/H/C/004821/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACTH	adrenocorticotropic hormone
AE	adverse event
AESI	adverse event of special interest
BDI	Beck Depression Inventory
bid	bis in diem/twice a day
BMD	bone mineral density
BMI	body-mass index
CD	Cushing's disease
CI	confidence interval
Cmax	the maximum (peak) plasma concentration after single dose administration
CMH	Cochran-Mantel-Haenszel
CR	complete responder
CS	Cushing's syndrome
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interactions
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EAS	ectopic adrenocorticotropic hormone syndrome
ECG	electrocardiogram
EU	European Union
GC	Gas Chromatography
HbA1c	glycosylated hemoglobin
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
MS	Mass Spectrometry
mUFC	mean urinary free cortisol
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia

PK	pharmacokinetics
PR	partial responder
QoL	quality of life
QTPP	Quality target product profile
RW	randomized withdrawal
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
TGA	Thermo-Gravimetric Analysis
Tmax	time of maximum observed concentration
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
VAS	visual analog scale
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 9 November 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Isturisa, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 April 2017.

Isturisa was designated as an orphan medicinal product EU/3/14/1345 in the following condition:

Treatment of Cushing's syndrome.

The applicant applied for the following indication:

Treatment of endogenous Cushing's syndrome in adults.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Isturisa as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Isturisa

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0011/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0011/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance osilodrostat to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European

Union.

Scientific Advice/Protocol Assistance

The applicant received Scientific Advice from the CHMP on the development for the indication on 24 October 2013 () and Protocol Assistance from the CHMP on 26 April 2018. The Scientific Advice and Protocol Assistance pertained to the following *quality, non-clinical, and clinical* aspects:

Protocol assistance

- The applicant received Protocol assistance from the CHMP on the development of Osilodrostat for the treatment of Cushing's disease from the CHMP on 24 October 2013 and for the treatment of Cushing's syndrome on 26 April 2018. The initial advice in 2013 concerned pre-clinical and clinical questions while in 2018, the applicant asked questions related to the quality development.

Clinical development

- Clinical questions concerned the acceptability of the pivotal LCI699C2301 study that was a double-blind, placebo-controlled, randomized withdrawal study following a 24-week, single-arm, open-label dose titration and treatment period, to demonstrate the efficacy and safety of LCI699.
- The specific design aspects discussed were patient population, inclusion of patients with a history of pituitary irradiation, duration of the withdrawal and the overall study duration, dose titration scheme, adequacy of the primary and secondary endpoints, stratification factors, adequacy of the efficacy analysis and sample size. A question was also asked about the adequacy of the one pivotal study together with supportive data to support a MAA.
- In addition, questions were asked about the clinical pharmacology program and cardiac safety monitoring in the phase II and pivotal studies.

Preclinical development

- Preclinical question concerned the adequacy of nonclinical safety program to support registration of LCI699 in Cushing's disease in adult patients.

Quality Development

- Quality questions concerned the selection of starting materials and manufacturing process.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Bart Van der Schueren

The application was received by the EMA on	9 November 2018
The procedure started on	29 November 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2019

The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	19 February 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 March 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 March 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 May 2019
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at one investigator site in the Netherlands between 21.01.2019 to 25.01.2019, two investigator sites in South Korea between 11.02.2019 to 15.02.2019 and 18.02.2019 to 22.02.2019, respectively, and one sponsor site in Switzerland between 11.03.2019 to15.03.2019. The outcome of the inspection carried out was issued on	06 May 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	1 July 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	02 October 2019
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	17 October 2019
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	21 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	30 October 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a	14 November 2019

marketing authorisation to Isturisa on	
The CHMP adopted a report on similarity of Isturisa with Signifor and Ketaconazole HRA on (Appendix 1)	14 November 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The therapeutic indication for Isturisa as requested by the applicant was:

"Isturisa is indicated for the treatment of endogenous Cushing's syndrome in adults."

2.1.2. Epidemiology

Endogenous Cushing's syndrome (CS) denotes a group of rare diseases with an estimated overall prevalence of 0.7 to 2.4 per million population per year. The disease affects most commonly adults aged 20 to 50 and has a marked female preponderance. The chronic hypercortisolaemic state is associated with multiple comorbidities that increase the risk of cardiovascular disease and mortality. Compared to patients with controlled disease, patients with incompletely controlled disease are seriously ill and have at least a fivefold increased mortality, mainly due to metabolic and cardiovascular complications.

2.1.3. Aetiology and pathogenesis

CS is divided into adrenocorticotropic hormone (ACTH)-dependent CS and ACTH-independent CS. ACTH-dependent CS accounts for about 80% of all cases and is caused by an ACTH-secreting pituitary corticotroph adenoma (Cushing's disease (CD)) or by ectopic ACTH secretion by a non-pituitary tumour. The ectopic ACTH syndrome (EAS) causes approximately 10% of all cases of CS. EAS is predominantly caused by neuroendocrine tumours. ACTH-independent CS accounts for 20% of all causes of CS and is most frequently caused by a unilateral cortisol-secreting adrenal adenoma and less frequently by bilateral macro- or micronodular adrenal hyperplasia and a cortisol-producing adrenal carcinoma.

2.1.4. Clinical presentation

Clinical manifestations of chronic hypercortisolism include metabolic syndrome, insulin resistance, visceral obesity, glucose intolerance, hypertension, dyslipidaemia, and hypercoagulable state. Other clinical signs and symptoms of CS include: supraclavicular and dorsal fat pads; proximal muscle weakness; osteoporosis with increased risk of fractures; skin changes (wide purple striae, hirsutism, acne); impaired immune function with increased risk of infection; neuropsychiatric disorders (depression, mood changes, and cognitive impairment), hypogonadism, and menstrual disorders in women.

The diagnosis of CS is challenging, and patients often remain undiagnosed for many years before receiving appropriate diagnosis and therapy.

2.1.5. Management

Surgical resection of underlying tumour

The first-line treatment of nearly all forms of CS is surgical resection of the underlying tumour (exceptions include CS due to metastatic adrenal carcinoma or EAS with an unknown source of ACTH secretion or EAS associated with a metastatic malignant tumour). In a number of patients, medical intervention is initiated to bridge the time until surgery is scheduled or to improve their clinical conditions before surgery. Post-surgical remission rates of 60 to 90% have been reported in CD and up to 80% in EAS (Newell-Price et al 2006, Kelly 2007, Wagner-Bartak et al 2017). However, long-term follow-up of CD patients in remission shows a recurrence rate of up to 60% at 10 years (Newell-Price et al 2006).

Radiotherapy

Radiotherapy is a possible alternative for CD patients in whom surgery is not indicated or has not been successful; however, the treatment is associated with significant side effects and reoccurrence of disease (Kelly 2007, Biller et al 2008, Pivonello et al 2015). Radiotherapy may take many years to be effective and medical therapy is required until radiotherapy becomes effective.

Bilateral adrenalectomy

Bilateral adrenalectomy is associated with life-threatening primary adrenal insufficiency, life-long replacement therapy with mineral- and glucocorticoid therapy, possible hypercortisolism due to excess ACTH stimulation of residual adrenal tissue, and the development of an aggressive corticotroph tumor, Nelson syndrome (Azad et al 2015).

Medical therapy

To date, there is no single, established standard of care medical therapy for endogenous CS worldwide. Medical therapy is indicated in patients with hypercortisolism of adrenal origin (i.e., patients with adrenal hyperplasia, adenomas, and carcinomas) who are not surgical candidates or for whom surgery is not available or which is unlikely to cure the CS/hypercortisolism) and for patients not cured after surgery or have recurred after initial control by surgery. The goal is clinical normalization using cortisol levels as a proxy endpoint (except for mifepristone). This can be achieved either with a "block and replace" strategy in which circulating cortisol is reduced to minimally detectable levels and glucocorticoid replacement is added (avoiding supraphysiological doses) or with a "normalization" strategy aimed to achieve eucortisolism. If there is evidence of significant cyclicity, block and replace may be preferable, but it carries additional risk if higher doses and multiple medications are needed. Currently available medical therapies for CS are classified based on the site of drug action and include pituitary-directed drugs, adrenal steroidogenesis inhibitors and glucocorticoid receptor antagonists (Tritos and Biller 2018).

Pituitary-directed drugs

Pasireotide (Signifor, Novartis) approved via centralized procedure for the "treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed." since Apr-2012. In the pivotal study of the intramuscular formulation, 41% of patients were controlled at the primary endpoint (Lacroix 2018). Advantages include the once monthly frequency of administration (for the recently approved intramuscular formulation) and the causal nature of therapy (reduction of excess pituitary ACTH secretion). Disadvantages include a risk of hyperglycemia resulting from the inhibition of insulin secretion. Due to its mode of action, pasireotide cannot be used in patients with ACTH-independent causes of Cushing's syndrome.

Adrenal steroidogenesis inhibitors

Steroidogenesis inhibitors are recommended under the following conditions:

- As second-line treatment after transsphenoidal surgery in patients with CD, either with or without RT/radiosurgery;
- As primary treatment of EAS in patients with occult or metastatic EAS together with targeted therapies to treat the underlying tumor;
- As adjunctive treatment to reduce cortisol levels in adrenocortical carcinoma.

Ketoconazole (Ketoconazole HRA, HRA Pharma) is approved via centralized procedure for "the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years" since Nov-2014, after its removal from the market for the treatment of fungal infections due to the high risk of hepatotoxicity. A control rate of 49% at last available assessment has been reported in a retrospective patient record review (Castinetti 2014; no prospective trial data are currently available). **Ketoconazole** can be used in all types of Cushing's syndrome however it has the potential for severe and sometimes fatal hepatotoxicity, its high drug-drug-interaction potential (because of its relatively unspecific inhibitory effects, a broad range of enzymes both within the steroidogenesis pathway and elsewhere are inhibited, resulting e.g. in near complete testosterone suppression), and the limited titration range (starting dose is one 200mg tablet tid; maximum dose is two 200mg tablets tid). **Metyrapone** (Metopirone, HRA Pharma) inhibits adrenocorticosteroid synthesis and is approved via national or mutual recognition procedure in 15 member states for "the management of patients with endogenous Cushing's syndrome" (first EU approval UK 1973). The response to metyrapone is rapid, and the desired cortisol levels can be achieved after two weeks of treatment (Verhelst et al 1991). Control rates ranging from 64% to 94% have been reported with long-term use (>6 months) in a retrospective study (Daniel et al 2015), however the choice of biochemical monitoring tests and frequency of monitoring varied. **Metyrapone** has a lower impact on testosterone levels compared to ketoconazole (Fleseriu et al 2016). Gastrointestinal side effects are common but may be reduced by taking the capsules with milk or after a meal. The product is large (8x19 mm) and due to the short half-life three to four times daily administration is required.

Mitotane (Lysodren, HRA Pharma) is approved via centralized procedure for the "symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (ACC)" since Apr-2004. It has a strong adrenolytic effect in the symptomatic treatment of advanced adrenal corticocarcinoma but a very slow onset of action and accumulation in storage sites in fat (reported terminal plasma half-lives range from 18 to 159 days) and the need for serum level monitoring. Mitotane has serious neurological, gastrointestinal and hepatic side effects and causes hypercholesterolemia, which significantly limits its benefit risk in non-malignant Cushing's syndromes.

Cabergoline is a dopamine agonist that has been used off-label in the treatment of Cushing's disease, based on an observed reduction in UFC levels in patients who have tumours with high expression of D2 receptors (De Bruin 2008).

Etomidate is a sedative which is sometimes used as a parenteral (intravenous) hypocortisolaemic agent before or during adrenalectomy in patients with severe life-threatening hypercortisolaemia where rapid control of cortisol levels is required and oral therapy is problematic. However, a highly co-ordinated multidisciplinary approach is necessary for the management of unwell hypercortisolaemic patients, as these patients have complex problems beyond the daily ward scope of medical and nursing staff. The clinical setting of an intensive

care or high dependency unit is therefore recommended for close patient and biochemical testing monitoring, particularly for serum cortisol and potassium levels and the documentation of the level of sedation.

Glucocorticoid receptor antagonists

Use of these class of products with their action on the glucocorticoid receptor has been described in patients with Cushing's syndrome, but are not authorised for this use in the EU and have limited or no availability in the EU.

Following the unmet medical need in CS, attempts have been made to combine different medical treatments in order to improve the biochemical control rate and, potentially, improving the safety profile by using lower doses. The number of such studies is quite limited and they included a low number of patients.

2.1.6. About the product

Osilodrostat (also known as LCI699) is a potent inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyses the last step in the biosynthesis of cortisol in the adrenal gland. Due to the mechanism of action (i.e., inhibition of cortisol synthesis), osilodrostat is expected to be effective in all types of endogenous Cushing's Syndrome (CS). The product has been developed as a film-coated tablet in three strengths (1 mg, 5 mg and 10 mg) that allows for convenient, finely graded dose titration.

Aspects on development

This application is based on the efficacy, safety, tolerability and pharmacokinetics (PK) from the Phase III pivotal Study C2301 and two supportive Phase II studies (Studies C2201 (Part I and II) and CLCI699C1201 (referred to as Study C1201)). These studies all included subjects with Cushing's syndrome and are assessed in the clinical sections of this report.

Osilodrostat was initially investigated for the treatment of hypertension, and primary hyperaldosteronism in four Phase II studies (Study CLCI699A2201, Study CLCI699A2206, Study CLCI699A2215, Study CLCI699A2216]. Further development in these indications was discontinued in 2010 because of the suppression of ACTH-stimulated cortisol response observed in these studies. The four studies included over 500 patients treated with osilodrostat at low doses (0.25 to 2 mg/day) for durations of 4 to 8 weeks. Some data on pharmacokinetics, pharmacodynamics and safety data are provided from some of these studies.

The clinical development program for osilodrostat was planned based on its mechanisms of action and on applicable scientific guidelines on the diagnosis of the disease (Arnaldi et al 2003, Pivonello et al 2008), regulatory guidelines (in particular, the FDA 2012 Guidance on Enrichment Strategies and the ICH 2000 E10 on Choice of Control Groups). There are no relevant CHMP guidance in the indication.

The application concerns an orphan condition, thus the number of subjects included in the clinical development program is limited, with 137 subjects included in the pivotal study. Only 7 subjects above the aged 65 to 75 years were included in the pivotal study.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the notion that other treatment alternatives are available and therefore patients are today not lacking treatment options and thus there is not an absolute unmet need.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 1 mg, 5 mg and 10 mg of osilodrostat as active substance.

Other ingredients are: cellulose microcrystalline, mannitol, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, hypromellose, titanium dioxide (E171), macrogol, talc, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172).

The product is available in Alu/Alu blisters.

2.2.2. Active Substance

General information

The chemical name of osilodrostat phosphate is (5*R*)-5-(4-Cyano-2-fluorophenyl)-6,7-dihydro-5*H* pyrrolo[1,2-*c*]imidazolium dihydrogen phosphate corresponding to the molecular formula $C_{13}H_{11}FN_3(H_2PO_4)$. It has a molar mass of 325.24 g/mol and the following structure:

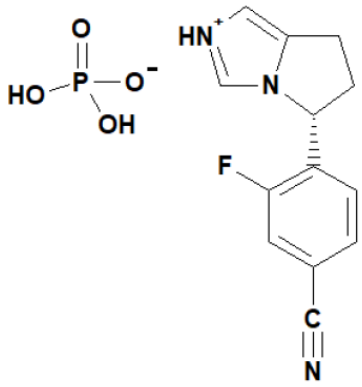


Figure 1: active substance structure

The chemical structure of osilodrostat phosphate was elucidated by a combination of elemental analysis, UV, MS, IR and NMR. The solid state properties of the active substance were measured by XRPD, X-ray crystallography, DSC and TGA.

The active substance is a white to practically white powder with high solubility in water and aqueous buffers. It is less soluble in organic solvents. The pH value of 1 % solution in water is 4.45, pK_a = 6.9.The active substance is not hygroscopic. Osilodrostat phosphate consists of agglomerates/aggregates with a consistent primary particle size.

Osilodrostat exhibits stereoisomerism due to the presence of one chiral centre. The manufacturing process consistently produces a single isomer (*R*-enantiomer). Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for osilodrostat. Osilodrostat phosphate is crystalline, anhydrous and non-hygroscopic. A single polymorphic form is obtained by the manufacturing process.

Manufacture, characterisation and process controls

Osilodrostat is synthesised by a convergent synthesis in three main stages from well-defined starting materials with acceptable specifications.

A number of steps are true chemical transformations wherein covalent bonds are formed and/or broken. The remaining steps include the formation and neutralisation of salts, in order to achieve purifications by chiral resolution, the preparation of an intermediate for the next reaction step and eventually the introduction of the phosphate counter ion into the active substance.

The selection of the GMP starting materials is justified by the Applicant by the consideration of the general principles of the ICH Q11 guideline. The syntheses of the starting materials are presented, along with the names and addresses of their manufacturers and corresponding specifications and Certificates of Analysis. Taking into account the information provided, the general principles of ICH Q11, as well as the conclusions of a previously obtained scientific advice, the proposed starting materials were deemed to be acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. A detailed discussion on the origin and characterisation of potential and actual impurities is presented for the starting materials and every intermediate along the manufacturing process. The structures and molecular formulas of all impurities are given, along with a toxicological assessment, observations on the origin and fate of each impurity, level detected at an appropriate stage and the corresponding control strategy.

Potential genotoxicity was assessed applying computational (Q)SAR methodologies following the recommendations of the ICH M7 guideline. The *in silico* analyses were performed using expert rule based (Derek Nexus, Lhasa Ltd) and statistical-based (Case Ultra, MCASE, Inc. and Sarah Nexus, Lhasa Ltd) systems. Impurities showing a structural alert for mutagenicity using the (Q)SAR methodologies were usually tested in a bacterial reverse mutation assay (AMES test). In case no AMES was performed, the alerting impurity was considered to be mutagenic. Spiking studies, carry-over studies and assessments of the purge safety factors have been carried out for potentially mutagenic impurities in order to justify their control strategy. Control by the ICH M7 control Option 4 is proposed to control such impurities occurring at earlier stages of the manufacturing process.

Potentially genotoxic impurities are controlled in appropriate intermediates of the manufacturing process. The final levels in the active substance have been established to be <30 % of the TTC limit in three validation batches. This control is acceptable according to Option 3 of ICH M7. The later-stage potential genotoxic impurities are routinely tested in the final active substance.

During the procedure, a major objection was raised related to the potential formation of *N*-nitrosamine impurities in the synthesis. In response, the applicant provided analytical data to demonstrate that levels of possible nitrosamine impurities are controlled to an acceptable level and introduced routine testing for the specified nitrosamine impurities in active substance specification using a combined direct injection GC MS/MS method.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The chemistry of the synthesis of Osilodrostat phosphate has remained basically unchanged since early pre-clinical development of the compound, with only minor process variations as a result

of optimization of process parameters. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in in polyethylene bags, which are in turn placed into triple laminated foil bags which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, particle size (air-jet sieving), identity (HPLC, IR (ATR), XRPD), related substances / impurities (HPLC, GC MS/MS), enantiomer (HPLC), residual solvents (GC), water (KF), assay (HPLC, potentiometric titration) and microbial quality (Ph Eur).

The acceptance criteria for specified impurities have been justified based on general ICH thresholds where applicable and qualified in non-clinical and clinical studies. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (commercial scale and development batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three pilot scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH and 30°C / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on one batch. The active substance is not photosensitive.

Results of forced degradation studies at stress conditions were also provided. Mass balance of >98% was achieved under all stress conditions, confirming the method is suitable and stability indicating. The active substance was found to be stable in solid state, but sensitive to degradation under acidic, alkaline and oxidative (H_2O_2) stress conditions and hydrolytic stress conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage conditions.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as film-coated tablets containing 1 mg, 5 mg and 10 mg of osilodrostat as active substance. The product is available in Alu/Alu blisters.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The finished product has been developed by a combination of a traditional development approach, based on common knowledge and prior experience, and a more systematic enhanced approach involving quality by design elements. However, no formal design space or regulatory flexibility is claimed.

Osilodrostat is a BCS class I compound, characterized by its high solubility, high permeability and extensive absorption. Design of Experiments (DoE) study on the formulation composition was performed to investigate the influence of excipients on the tablet properties. The applicant has applied QbD principles in the development of the finished product and their manufacturing process.

The formulation development is described in detail. The finished product was initially formulated as 0.25 mg, 0.5 mg, 1 mg, 5 mg and 50 mg hard-gelatin capsules to supply early Phase 1 and Phase 2 clinical trials. In 2014 the capsules were replaced by 1 mg, 5 mg, 10 mg and 20 mg immediate release film-coated tablets which were used in late Phase 1, Phase 2 and the pivotal Phase 3 clinical trials for the targeted indication. Only 1 mg, 5 mg and 10 mg film-coated tablets will be marketed. Comparative dissolution profiles between hard-gelatin capsules and commercial tablets support the BCS-based biowaiver. All (historic) changes made to the formulation during development are described in detail in the dossier.

Osilodrostat 1 mg, 5 mg and 10 mg film-coated tablets are manufactured by processes commonly used in the production of oral solid dosage forms. The selection and development of the manufacturing methods is justified and documented in detail.

The dissolution method development is described. Dissolution Apparatus I (Basket) was selected during method development. Overall there is no significant impact of the dissolution medium pH on the dissolution rate as expected with this compound based on its high solubility, and rapid dissolution is observed across the physiological pH range. The phosphate buffer of pH 6.8 has been selected for the routine test as during formulation and method development in some experiments a slightly slower dissolution and thus higher discriminatory power was observed in pH 6.8 phosphate buffer compared to other media. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is aluminium-aluminium blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process for 1 mg film-coated tablets consists of twelve main steps including several (pre)-blending and screening steps, compression, film-coating and packaging. The process for 1 mg tablets is considered a non-standard manufacturing process due to the low active substance content (<2% of the composition).
The manufacturing process for 5 mg and 10 mg film-coated tablets consists of fourteen main steps including blending and screening steps, roller compaction, final blending, compression, film-coating and packaging. The process for 5 mg and 10 mg tablets is considered a standard manufacturing process.

Critical steps have been identified in both manufacturing processes. The control strategies for these critical steps (proven acceptable ranges, IPCs) are based on the process development studies performed. No critical intermediates are defined in the manufacturing processes.

The robustness of the manufacturing processes have been assessed at production scale using 3 consecutive batches of each strength. The 1 mg tablet is a low-dose formulation and full-scale results have been provided. All nine batches consistently meet the quality control specifications. Additional validation studies with three consecutive batches of each strength manufactured at the target settings for commercial production will be performed.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; appearance, mean mass, identity (UV, HPLC), water, dissolution (HPLC), uniformity of dosage units (Ph Eur), assay (HPLC), degradation products (HPLC), microbiological purity (Ph Eur).

The finished product is released on the market through traditional final product release testing. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Batch analysis results are provided for representative clinical, registration stability and confirmatory production scale batches of 1 mg, 5 mg and 10 mg Film-coated tablets (three batches of each strength for clinical, registration and production scale) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 30 months under long term conditions (25°C / 60% RH and 30°C/75%RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Isturisa are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The batches were tested for appearance (shape, colour, imprint, thickness, diameter), assay and degradation products, dissolution, water content, microbial enumeration testing. Three additional parameters are monitored which are not included in the specifications: enantiomer by HPLC, disintegration time and crushing strength. No significant trends or changes are observed for any of the parameters tested.

Additional stress studies have been performed such as a freeze/thaw cycle study with one registration batch per strength, and an open dish study with two registration batches per dosage strength. The stability samples were stored for four complete freeze/thaw cycles (i.e. -20°C/ambient RH for 6 days, followed by 1 day at 25°C/60%RH) and analysed after 28 days. No significant change is observed in chemical and physical stability after 28 days of storage. The results for open dish study demonstrate that the finished product is stable for up to 3 months after removal from the original Alu-Alu blisters at 25°C/60% RH and 30°C/75%RH however no in-use shelf-life is claimed in the SmPC.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All dosage strengths show acceptable chemical and physical stability in the photostability study. The results obtained for the unpacked samples exposed to light met the specifications for all the quality parameters tested. The results were comparable to the ones determined on dark control samples (samples protected from light). However, a slight decrease in disintegration time and crushing strength was observed in the unpacked samples when compared to the control samples for all the dosage strengths. This did not have any impact on the samples since the appearance, assay, degradation products, water content and dissolution met the analytical specifications.

Based on available stability data from registration stability and supportive stability, the proposed shelf-life of 36 months and "do not store above 25°C, store in the original container in order to protect from moisture" as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamics

One of the submitted in vitro studies (study RD2007-51927) has investigated the pharmacodynamics of the indication applied for, i.e. inhibition of CYP11B1. The results show that osilodrostat inhibit CYP11B1 activity in V79-4 cell homogenates from CYP11B1 transfected cells. The Applicant has constructed a cell line stable transfected with human CYP11B1, and with adrenodoxin and adronodoxin reductase (cell line #618 as described in LaSala et al) to maximize the enzyme activity. The IC50 value for osilodrostat of 2.5 nM (RD-2007-51927) and 3.2 nM (RD-2014-00299) is several hundred times lower than clinically relevant concentrations (Cmax at therapeutic doses 233 ng/mL = 1 µM). IC50 for recombinant rat CYP11B1 is 410 nM showing that osilodrostat is considerably more potent at the human CYP11B1 compared with the rat (Menard et al 2014).

In ACTH stimulated monkeys no inhibition of cortisol concentrations was noted, as opposite to what have been found in humans. The Applicant argued that this discrepancy could be due to different osilodrostat pre-treatment schedules (daily for 6 and 13 days in humans versus one single administration in monkeys) and/or the time prolonged to the ACTH stimulation (2 h versus 3 hours). Using a different experimental design including higher doses (up to 10000 ug/kg), Weldon et al showed that osilodrostat inhibited ACTH stimulated cortisol synthesis in monkeys with an EC50 of 1500 nM being approximately 300-fold higher than EC50 for aldosterone synthesis.

Secondary pharmacodynamics

Osilodrostat was first developed as a CYP11B2 inhibitor and therefore several studies have been conducted to test the ability to inhibit aldosterone synthesis. In this application this is considered a secondary PD effect rather than a primary PD effect. The IC50 value for aldosterone inhibition (CYP11B2 activity) is in the same range (1.8 nM) as for cortisol inhibition (CYP11B1 activity) in vitro (3.2 nM). Plasma aldosterone concentration (PAC) decreases in rats in a dose dependent manner with ED50 of 0.6 mg/kg (exposure=127 nM) and 1.1 mg/kg for inhibiting Ang-II stimulated and ACTH stimulated responses, respectively. The estimated ED50 for ACTH stimulated aldosterone PAC in monkeys was 13 ug/kg. Even though these doses are clinically relevant this is in line with the fact that osilodrostat first was developed as a CYP11B2 inhibitor with a poor PD effect in humans.

Moreover, the inhibitory effect on aromatase was investigated in vitro (RD-2007-51924). An IC50 of 1.7 uM was found whereas when the "certified LCI699-AZA" osilodrostat was used (RD-2014-365) the IC50 value was >16 uM. The later IC50 concentration is above the clinically relevant Cmax of approximately 1 µM. The reason for discrepancy between RD-2007-51924 and RD-2014-365 result is that in the "certified LCI699-AZA" osilodrostat drug formulation the (+) enantiomer LCI698 is present at lower levels (<0.05% compared to approximately 3 %). LCI698 was shown to be a potent aromatase inhibitor (IC50=9 nM). PK/TK studies indicate that no chiral conversion from osilodrostat to LCI698 occurs in rat and dogs, and also no chiral conversion has been observed in humans. So conclusively LCI698 induced aromatase inhibition may not be of clinical relevance and the concern raised in the SA 2013 (EMEA/H/SA/2614/1/2013/III) has been addressed. Nevertheless, it may be possible that local conversions can take place, resulting in aromatase inhibition in some organs.

Pharmacodynamics of Metabolites

In addition to osilodrostat (LCI699), three metabolites have been studied in vitro (LXB168/M34.5, LFD085/M24.9 and LWP114/M16.5) to assess their inhibitory effect on cortisone synthase, aldosterone synthase and aromatase. One of the metabolites, LFD085 (M24.9) inhibits all three CYP enzymes investigated. The IC50 values for cortisone and aldosterone activity were higher than osilodrostat whereas for aromatase inhibition the metabolite is more potent than osilodrostat itself. Since <10 % of the M24.9 metabolite is formed in humans, it most likely will not exert any inhibition of clinical importance. However, the metabolites have only been measured after a single dose of osilodrostat and the exposure after repeated dosing is not known (see clinical pharmacokinetic section for more discussion). An in vitro binding study including a panel of 73 G-coupled receptors, transporters, ion channels, nuclear receptors and enzymes did not identify off-target activity for M34.5 and M24.9 when tested at concentrations up to 30 µM.

Safety pharmacology

The screening for off-targets shows that osilodrostat has low affinity for several receptors with safety concerns regarding particularly CNS, and cardiovascular effects. The only receptor that osilodrostat show a >50 % affinity to, is H1 histamin receptor. The relevance of this binding is not known, and it could not be discerned if osilodrostat binding lead to agonistic or antagonistic effects.

In the telemetry studies conducted in dogs no effects on QT interval were observed, whereas in one rabbit study (in vitro) and in four studies conducted in monkeys, QT prolongation was found. In the isolated rabbit hearts also Tp-e prolongation and increase contractile forces were noted at 0.4 and 43 µM, respectively. According to the (0616814) study, osilodrostat inhibits hERG channel activity in stably transfected HEK293 cells with IC50 = 54 µM (which is approximately 50 times higher than Cmax concentrations in patients). The telemetry single dose studies in monkeys all demonstrated a clear signal for QT prolongation (13-29 % increase) at doses ≥30 mg/kg. When osilodrostat was administered for 2 weeks (study 1270612), 10 mg/kg/day resulted in QTs prolongation (11 % increases). QTc interval prolongation has also been observed in patients (Study C2301 – see clinical section). The proposed SmPC contains information and warnings concerning this risk in section 4.4, 4.8, and 4.9. From a non-clinical point of view, no further action is considered necessary.

No effects on CNS (observational study) or respiratory function (tidal volume, respiration rate, minute volume) were noted after single oral gavage dose of osilodrostat in the rat. In the repeat dose toxicity studies CNS effects (aggression, hypersensitive to touch and increased motor activity) were observed in the mouse, rat and dog (see toxicology section).

2.3.2. Pharmacokinetics

According to the Applicant the LC-MS/MS bioanalysis used in the GLP toxicity studies of osilodrostat have been validated. According to Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2) aspects of method validation not performed according to GLP should be clearly identified and their potential impact on the validation status of the method indicated. Accordingly, the applicant presented an overview of validation activities for all bioassays employed and all methods are of high-quality standards.

Absorption

According to the Applicant a rapid absorption with a high bioavailability (>100 %) was seen in the rat after administration of 14C-osilodrostat (study 0600206A), which indicates a minimal first-pass activity on osilodrostat. However, in study RD2006-50315 the bioavailability of osilodrostat in rats was dose dependent and between 13 – 63 %, suggesting that osilodrostat indeed is subject to first-passage metabolism. In rat and dog, no accumulation of osilodrostat in the plasma was observed. Plasma half-lives in rat and dogs were short (1-2 h) and similar to what was reported in humans (T1/2 of 4 h). Low plasma protein binding was seen in all species investigated (27-37 %). None of the absorption studies were performed in female rats and hence gender comparison in PK could not be assessed, but no gender differences were noted in the TK analysis.

Distribution

Oral intake of osilodrostat was widely and rapidly distributed to tissues. Cmax was higher in all tissues investigated than blood when radioactivity was studied. The highest tissue to blood ratios were found in the uveal tract, skin (pigmented), eye, glandular stomach, small intestine, liver and adrenal cortex. Affinity to melanin was confirmed since 11-fold higher radioactivity in skin was noted in pigmented rats than in albino rats. Retention to melanin appears to be reversible.

No placental transfer studies have been performed.

Metabolism and excretion

Several metabolites are formed in vitro and in vivo. The metabolic pathways include particularly oxidative metabolism and glucuronidation. The main metabolite found in plasma after single dose administration of 14C-osilodrostat in human and rat is M34.5 (about 60 % of total radioactivity in both rats and humans). Two

other metabolites M16.5 and M24.9 are formed just below 10 % after a single oral dose administration in rats and humans. M16.5 is of no toxicological concern, as per the ICH M3(R2) Q&A document, since M16.5 is a non-acyl glucuronide metabolite.

Notably, since no pharmacokinetic data of the metabolites were provided after repeated osilodrostat dosing the exposure margins between human and rats could not be determined. See2.3.5 for more discussion on estimated M34.5 exposure in toxicity studies.

In addition to M34.5, M16.5 and M24.9, all other metabolites are all formed to a much lesser extent. Thus, it is believed than none of them will have any clinical significance.

Urinary excretion of the metabolites is the main elimination pathway of osilodrostat in all species investigated.

2.3.3. Toxicology

The toxicological profile of osilodrostat has been evaluated in agreement with recommendations in ICH M3. The performed studies included single-dose toxicity in mice, repeat-dose toxicity studies for up to 13 weeks in mice, 26 weeks in rats and 39 weeks in dogs, in vitro and in vivo genotoxicity, embryo-foetal development toxicity in rats and rabbits, in vitro phototoxicity and investigative gene expression/profiling studies of rat liver. In addition, toxicological qualification of potential impurities has been addressed.

The observed osilodrostat related toxicity in the tested animals may be of uncertain clinical relevance for humans since the main target for osilodrostat in animals (rats and monkeys) is aldosterone synthase and secondarily (and to a much lesser content) 11β-hydroxylase which is the opposite in humans. Since no inhibition on PCC (plasma corticosterone concentration) in rats and monkeys not infused with ACTH is seen, toxicity associated with cortisol inhibition cannot be studied. However, the adverse effects of hypocortisolism are clinically well known (e.g. nausea, vomiting, fatigue, abdominal pain, dizziness). Consequently, warnings in SmPC 4.4 and 4.9 states that patients should be alerted to these hypocortisolism related events and are advised to carry a patient card with package leaflet indicating that they may be at risk of hypocortisolism and that appropriate actions should be taken if emergency care is needed. These species differences are therefore not critical for the overall safety assessment.

The rat was found to produce the metabolite M34.5 which was identified as a major circulating metabolite in human (even if not pharmacologically active). No TK assessments of M34.5 have been performed in any of the pivotal safety studies (including carcinogenicity and reproductive toxicity studies) conducted in the rat. Instead the applicant assumed that sufficient exposure was achieved by comparing the predicted exposure levels in human volunteers administered a single 50 mg of osilodrostat with exposure data in rat and mouse of the ADME (non-GLP) studies scaled to doses used in toxicity studies. See 3.2.5 for more discussion on estimated M34.5 exposure in toxicity studies.

Single-dose toxicity

An oral single-dose tolerability study was performed in mice. Osilodrostat was well tolerated up to 125 mg/kg. At 150 mg/kg, two animals died within 30 min post-dose and one animal 4-hours post-dose with clinical signs of quivering, abnormal gait and abnormal stance preceding death. The remaining animals appeared normal throughout the study with no significant bodyweight changes or pathology findings. The lethal dose for osilodrostat was set to 150 mg/kg.

Repeated-dose toxicity

In repeated-dose toxicity studies osilodrostat was tested in mice for up to 13 weeks at 10 to 200 mg/kg/day, in rats for up to 26 weeks at 0.2 to 50 mg/kg/day and in dogs for up to 39 weeks at 0.1 to 10 mg/kg/day. The major toxic effects of osilodrostat were found in adrenal glands and of CNS-related nature in mice, rats and dogs and in female reproductive organs and liver in mice and rats.

The effects of CNS origin observed were mainly aggression, hypersensitivity to touch and increased motor activity. These effects appeared more frequent and severe in mice and dogs and were observed at doses of ≥10 mg/kg in mice and at ≥30 mg/kg in dogs. The severity of these effects was dose dependent. The Cmax drug exposure with regards to the CNS finding at the NOAEL in the dog (1 mg/kg/day) is less than 2-fold the free Cmax exposure in humans at the efficacious dose of 30 mg twice daily. Consequently, the exposure margin should be stated in SmPC 5.3 (see SmPC comment)

In a 13-week mice study, animals were dosed up to 200 mg/kg, i.e. above the lethal dose as concluded in the single toxicity study, with following death of 3 males and 3 females and termination of the remaining animals of this dose group due to severe clinical signs of CNS origin such as hypersensitivity to touch, increased locomotor after the initial dose. The choice of doses was based on a previous 2-weeks non-GLP repeated-dose toxicity study in mice where the animals were dosed up to 200 mg/mg without any test article related mortality or moribundity

Osilodrostat-related effects on the adrenal gland were reported in mice, rats and dogs. In mice, findings were mostly organ weight changes but did show hypertrophy in the zona fasciculata in the adrenal cortex at 100 mg/kg/day in a single study (non-GLP 2-weeks repeated dose study). In rats, additional vacuolation in the same adrenal layer and in the zona glomerulosa were observed at doses of ≥50 mg/kg/day with reversibility in the 13-weeks study and in a 2-weeks study, respectively. In dogs, morphological changes, mainly hypertrophy and vacuolation, were mainly observed in zona glomerulosa at ≥1 mg/kg/day in the 39-weeks study. Atrophy recovered post-treatment but vacuolation of the zona glomerulosa of the adrenal gland persisted. No evidence of adrenal dysfunction was noted in the repeat-dose toxicity studies following oral administration of osilodrostat.

Osilodrostat-related effects of female reproductive organs were observed in both mice and rats but not in dogs. Effects in mice were limited to organ weight changes of ovaries and uterus but in addition to this, follicular degeneration in ovaries and atrophy in uterus at ≥5 mg/kg/day, and mucification of vagina at 50 mg/kg/day were observed in the 13-weeks rat study. Except for uterine weights, all these effects showed reversibility after the recovery period. Osilodrostat-related effects on male reproductive organs consisted of reduced prostate weight observed in rats after 26 weeks of treatment that persisted after the recovery period.

Hepatic changes such as hepatocellular hypertrophy and cytosolic vacuolation were seen in rats at doses ≥ 0.5 mg/kg for 13 weeks and in mice at doses ≥ 10 mg/kg for 13 weeks. Minimal (~ 2-fold) elevations of liver enzymes were noted in mice and dogs. In rats, hepatocellular hypertrophy was reversed but vacuolation persisted after 8-weeks of recovery period. Increased cytoplasmic glycogen or plasma glucose and mitosis in the liver were observed in mice after 2 doses of 200 mg/kg and in rats after continuous intravenous infusion for 2-weeks at 50 mg/kg/day. Hypertrophy appears consistent with the adaptive physiological response noted with the induction of microsomal enzymes.

Total or partial reversibility of toxicological changes was observed in all studies with recovery with the exception of rats dosed at 50 mg/kg in a 4 week and a 13-week study were liver changes (vacuolation) persisted.

Toxicokinetics

The NOAELs observed in the 26- and 39-week repeated-dose toxicity studies in the rat and the dog were 2.0 and 10 mg/kg/day, respectively, based on the frequency and severity of findings in the liver and female reproductive

organs (rat) and in the adrenal gland (rat and dog). The margins to clinical exposure are approximately 4 and 14-16 based on Cmax and AUC0-24, respectively.

Genotoxicity

The genotoxicity of osilodrostat has been studied with respect to gene mutations in bacteria and chromosomal aberrations *in vitro* and *in vivo*. Additionally, test of primary DNA damage *in vivo* has been conducted.

Osilodrostat did not induce mutations when adequately tested in five histidine-requiring strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA102) at concentrations up to 5000 µg/plate in the absence and in the presence of a rat liver metabolic activation system (S9). Osilodrostat induced structural chromosome aberrations when adequately tested in cultured human peripheral blood lymphocytes in both the absence and presence of a rat liver metabolic activation system (S9). Osilodrostat did not show any evidence of chromosomal aberrations *in vivo* in the rat bone marrow micronucleus test when adequately tested up to a single oral dose of 300 mg/kg. Osilodrostat did not induce any DNA damage when adequately tested in the Comet assay in hepatocytes or leukocytes of rats dosed twice orally up to 150 mg/kg. When considering the negative outcome of two *in vivo* studies the weight of evidence suggests that osilodrostat does not constitute a genotoxic risk following oral use in humans.

Carcinogenicity

Long-term carcinogenicity studies have been performed in mice and rats with dosing at 1, 3 and 30 mg/kg/day for up to 103/104 weeks and 104 weeks, respectively. The survival in mice was low in all dose groups; being lowest in the high-dose males (24%), and in control females (29%). Dosing started in 70 mice / sex and dose group, and there were therefore still a reasonable number of animals for assessment at final sacrifice. The survival in rats was higher ranging from 68% in control males to 86% in the low dose females.

Osilodrostat related neoplastic changes (adenoma and/or carcinoma) were observed in liver in male mice and rats at 10 mg/kg and in female rats at 30 mg/kg, and in thyroid gland in male rats at 10 mg/kg (see table).

Study ID/Species	Tissue	Neoplastic findings	Dose (mg/kg/day)							
			Males				Females			
			0	3	10	30	0	3	10	30
1270062/Mouse	Liver	Hepatocellular adenoma	13	15	**29**	**27**	2	1	1	2
		Hepatocellular carcinoma	3	8	7	**18**	0	0	1	0
	Thyroid gland	Follicular cell adenoma	1	1	1	2	0	1	1	2
		Follicular cell carcinoma	0	0	0	0	0	0	0	0
1270061/Rat	Liver	Hepatocellular adenoma	0	1	**7**	**5**	3	0	0	**16**
		Hepatocellular carcinoma	0	0	0	0	0	1	0	**6**
	Thyroid gland	Follicular cell adenoma	4	2	**9**	**16**	0	1	2	2
		Follicular cell carcinoma	0	0	3	2	0	1	0	0

Bold numbers indicate osilodrostat related findings

Non-neoplastic changes were observed in liver (hypertrophy), thyroid gland (follicular hyperplasia and hypertrophy) in mice and rats and in pituitary (hyperplasia) in male mice, changes that was also observed in the repeated dose toxicity studies.

The applicant suggests that the neoplastic changes in the liver and thyroid (adenoma/carcinoma) of both mice and rats are related to constitutive androstane receptor (CAR) activation in liver causing increased elimination of thyroid hormones that subsequently lead to increased secretion of thyroid stimulating hormone (TSH) and increased follicular cell proliferation, a phenomena considered to be rodent-specific and of no human relevance. The hypertrophy observed in liver of mice and rat indicates a response to induction of xenobiotic enzymes. The expression gene analysis data from rat livers show that osilodrostat induces metabolic enzymes, including

CYB2B1/CYP2B2 and UDP- glucuronosyltransferase (UDP- GT) known to be targets of CAR activators, and that the gene expression profile is similar to that of phenobarbital known to produce liver (and thyroid) tumours in rodents but not in humans. The proposed secondary effect due to the hepatic enzyme induction that leads to increased secretion of TSH is considered not likely to be relevant for humans due to species-specific differences in thyroid hormone metabolism. However, the lack of TSH and thyroid hormone data is a shortcoming and there was an obvious gender effect regarding the osilodrostat-mediated liver tumours, the male rats and in particular the male mice being more prone than the females.

Reproductive and developmental toxicity

The reproductive and developmental program included studies on fertility and embryonic development in rats, embryo-foetal development in rats and rabbits, and pre- and postnatal and juvenile development in rats. In the fertility and early embryonic study, female reproductive toxicity consisted of abnormal oestrous cycles, predominantly prolonged and profound decreases in mating and fertility at 50 mg/kg. No effects on male fertility or performance were seen, although transient low levels of testosterone were observed in occasional males in the juvenile study.

In the developmental toxicity studies osilodrostat induced also early and late resorptions, decreased viable foetuses and caused foetal malformations and variations in rabbits and rats at ≥10 mg/kg and 50 mg/kg, respectively. In rabbits, there was an indication of dose-related increase of early resorptions and post implantation loss at ≥3 mg/kg/day. In rats, embryo toxicity was observed by various types of skeletal variations such as incomplete ossification of the supraoccipital, incomplete or bipartite ossification of sternebra and misshapen or fused sternebra. In rabbits, embryo toxicity consisted of skeletal variations such as bipartite ossification of sternebra or fused sternebra, and visceral malformation (anorchia) in one single foetus.

In the peri-post natal study in rats, profound adverse effects on parturition index, mean duration of gestation (prolonged about 32 days), reduced live birth index, and some animals with dystocia were seen at the 20 mg/kg dose. This necessitated early termination of this group, and therefore osilodrostat-related effects on postnatal survival or development of pups in the 20 mg/kg/day group could not be evaluated. In the lower dose groups, in the F1 post weaning mating, there was a reduction in the mean number of implantations in the 5 mg/kg/day group.

Local tolerance

Local tolerance following oral administration was not explicitly investigated in the repeated-dose toxicity studies. However, no signs of changes in the gastrointestinal tract, that may be associated to local irritation due to osilodrostat, were reported in any of these studies.

Osilodrostat did not cause skin irritation or corrosion in a GLP-compliant study in the rabbit. Osilodrostat was classified as a skin sensitizer, Category 1A in a GLP-compliant Local Lymph Node Assay in the mouse.

Other toxicity studies

Osilodrostat spiked with the degradation products 540-07, 061-14 and 185-14 at 3.21%, 3.50 % and 3.1 %, respectively, did not induce mutations when adequately tested in five histidine-requiring strains of Salmonella typhimurium (TA98, TA100, TA1535, TA97a and TA102) at concentrations up to 5000 µg/plate in the absence and in the presence of a rat liver metabolic activation system (S9).

The 4-week repeated dose toxicity profile for osilodrostat was similar between batches with or without the degradation products 540-07, 061-14 and 185-14 at 3.21%, 3.50 % and 3.1 %, respectively, indicating no additional safety risk. In addition, there were no statistically significant increases in micronucleus observed in any of the treatment groups compared to the controls.

2.3.4. Ecotoxicity/environmental risk assessment

The Fpen was refined based on published literature data on prevalence resulting in a $PEC_{SURFACEWATER}$ of 0.00237 µg/L. This is below the trigger value for requiring a Phase II assessment, and a Phase II assessment was not provided. The provided log D at pH 4, 7 and 9 are -1.4 and 1.1 and 1.5, respectively, indicating that osilodrostat is not a PBT substance. The use of osilodrostat in the proposed indication is not considered to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

Scientific Advice has been requested from CHMP on June 2013 with question regarding preclinical aspects. The recommendations given by CHMPS were that the general package of nonclinical data was sufficient for MAA evaluation and that the Applicant may need to further study the potential of osilodrostat to convert to the LCI1698 enantiomer. The advice given by CHMP has been followed.

Osilodrostat has not been investigated for any other CYP enzymes than aldosterone synthases (CYP112B) and aromatase (CYP19A1). It is generally known that CYP inhibitors are promiscuous and it is possible that osilodrostat tends to inhibit particularly other steroid producing CYPs such as CYP17A1 and CYP21A2. The correlated enzyme activities i.e. hormone concentration of Progesterone and 17-OH Progesterone have not been monitored in the animal studies. But the Applicant provides an in vitro study performed in an adrenocortical tumour cell line showing that osilodrostat induces modest inhibitory effect on progesterone and 17-OH progesterone, as well as to testosterone (Creemers et al). However, in the clinical studies conducted in CD patients, testosterone appears to increase, particularly in females. Since in vitro conditions do not mimic in vivo situations, particularly for hormone signalling where regulatory feedback signals between endocrine effects cannot be assessed in vitro. The contradictory in vitro and vivo findings regarding testosterone can be due to a compensatory increase of ACTH in vivo. In men, testosterone is produced mainly from the testis whereas in women adrenal contribute to approximately 50 % of the testosterone production. Such compensatory stimulation of ACTH may be more sensitive in women.

Osilodrostat and/or its metabolites crossed the blood brain barrier in rats and distributed in brain and spinal cord with a tissue-to-blood ratio ranged between 0.73 – 2.4 suggesting a potential for significant exposure in the brain. It is not possible to ensure that enough exposure to the major human circulating metabolite was achieved under the condition of the in vivo safety pharmacology studies. 2nd pharmacology data for the metabolite M34.5 including CNS receptor binding assays did not reveal potential for off target effects.

M34.5 was detected in vitro in rat, mouse, and monkey hepatocytes but neither in the human nor dog hepatocytes. The reason why the M34.5 was found in vivo, but not detected in the in human hepatocytes may be that M34.5 is formed at a slow rate since in experiments in hepatocyte co-cultures, M34.5 was observed following HPLC-radiometric detection in samples derived from the day 6 and day 7, but not in day 2 or earlier time points. The peak area associated with the M34.5 metabolite constituted ~1.4% and ~1.6% of the total chromatographic radioactivity derived from Day 6 or Day 7 samples, respectively.

The Applicant has presented PK plasma concentration-time profile of the main metabolite M34.5, only after single dose administration of osilodrostat in rats (and humans). Hence, the extent of exposure to M34.5 metabolite after repeat-dosing is unknown, and it cannot be experimentally verified if this metabolite has been adequately qualified regarding embryofoetal development (EFD) and carcinogenicity studies which are recommended (ICH M3(R2) guideline). Nevertheless as evidence of adequate exposure to this metabolite in the animals in the pivotal repeat dose toxicity studies is lacking, and since PK parameters for M34.5 have not been

measured following repeated dosing of osilodrostat in the clinic at the intended therapeutic dose, it is impossible to experimentaly establish safety margins with regards to the CNS (and QTc) findings as compared to the exposure achieved at steady state in the clinic. Distribution studies showed that osilodrostat (and/or metabolites) distribute in the brain but whether the major metabolite accumulates following repeat administration of osilodrostat remains unknown. Based on assumptions of linear kinetics of M34.5 both in human and in rats an estimated exposure margins of 0.9 (based on NOAEL of 2mg/kg/day) after repeated dosing was calculated. As the human exposure of M34.5 after repeat dosing of osilodrostat is only estimated in an uncertain simulation model, the addition of an uncertainty factor of 10 was used, resulting in exposure margin of 1.3 in the high osilodrostat dose (30 mg/kg/day) used in the chronic rat toxicity study (2-year rat carcinogenicity). Thus, based on these extrapolations M34.5 has likely been toxicologically qualified. It is already established that osilodrostat has a potential for embryo-fetal toxicity which has resulted to strict warnings in relation to use in pregnancy in the SmPC, it is of less importance if this is due to osilodrostat itself or if M34.5 contributes. As the human exposure of M34.5 after repeat dosing of osilodrostat is only estimated in an uncertain simulation model, the addition of an uncertainty factor of 10 was used, resulting in exposure margin of 1.3 in the high osilodrostat dose (30 mg/kg/day) used in the 2-year rat cancer study. Thus, based on these extrapolations M34.5 has likely been toxicologically qualified. An in vitro binding study including a panel of 73 G-coupled receptors, transporters, ion channels, nuclear receptors and enzymes did not identify off-target activity for the major human metabolite M34.5 when tested at concentrations up to 30 µM.

The changes in the zona fasciculata and zona glomerulosa of the adrenal cortex noted in the repeat-dose toxicity studies are likely considered adaptive responses due to the inhibition of 11β-hydroxylase and aldosterone synthase, respectively. It remains unclear why in both species (rat and dog) females appeared more sensitive than males though there was only minor gender effect on osilodrostat exposure. An explanation could be related to the decreased levels of corticosterone in female rats but not in male rats given osilodrostat for 13 weeks despite at baseline the level of such a hormone was higher in females than in males. Nevertheless, as measurement of corticosterone was not systematically investigated but was done in one toxicology study only, whether a correlation exist between this biomarker and the incidence of the microscopic adrenal findings cannot be established.

Osilodrostat-related effects on female reproductive organs were observed in repeated dose toxicity studies in mice and rats. Osilodrostat produced also embryo toxicity and teratogenicity in rats and rabbits. The NOAEL in foetal rats was 5 mg/kg/day which corresponds to approximately a 10-fold clinical AUC exposure and the NOAEL in foetal rabbits was 3 mg/kg/day that correspond to 0.6-fold the clinical AUC exposure. The applicant has not adequately addressed the low exposure margin in rabbit in section 5.3 of the SmPC (see SmPC comments).

No mortality was noted in female rats in any of the pivotal repeat dose toxicity studies conducted with osilodrostat (alone) at doses up to 50 mg/kg/day including in the EFD study 0770784. However, in the EFD study 1170415, four pregnant dams died following administration of 50 mg/kg osilodrostat containing the (-)-S-LCI698 at 0.07% or <0.006%, despite such an impurity alone at dose up to 0.03 mg/kg did not cause maternal toxicity.

In the pre-and postnatal development study (PPND) in the rat, dystocia and delays in the start of parturition were observed at 20 mg/kg. Pup malformation were noted at 5 mg/kg but was not considered treatment-related.

2.3.6. Conclusion on non-clinical aspects

So conclusively it has been shown that osilodrostat inhibits human CYP11B1 in vitro and PCC in ACTH infused rats and monkeys, i.e. in animals mimic Cushing syndrome (high PCC) whereas in no species the baseline PCC is inhibited. Any toxicity associated with low cortisol/corticosterone levels could therefore not be assessed in the toxicity studies, but this is not considered critical for the overall assessment since adverse effects of hypocortisolism are clinically well known. The pharmacokinetics of a main osilodrostat metabolite, M34.5, has not been analysed after repeat dosing, and it is therefore not experimentally determined if the animals have been adequately exposed in the toxicity studies. However, based on extrapolation of PK data and osilodrostat dosing in the toxicity studies, M34.5 is considered adequately addressed from the non-clinical perspective.

Osilodrostat related toxicity was confined to heart (as QT prolongation & TdP) CNS, liver, adrenal glands and female reproductive organs. In reproductive and developmental studies osilodrostat displayed embryo/foetal toxicity and teratogenicity.

Osilodrostat is not considered as mutagenic or clastogenic in vivo. Overall, impurities have been qualified and/or are below limits, in conformity with the guidance on impurities ICH Q3A and ICH M7 for mutagenic impurities.

Osilodrostat is not considered a PBT substance. The use of osilodrostat in the proposed indication is not considered to pose a risk to the environment.

From a non-clinical view osilodrostat was considered approvable by CHMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A GCP compliance evaluation / clinical data verification was undertaken as part of the assessment of the MAA. The conclusion of the inspection was that the data of the inspected studywas considered acceptable for being used and evaluated in the process of the MAA. Identified deviations with regards to PD and AE reporting were not considered to affect the interpretation of the study.

- ***Tabular overview of clinical studies***

Table 1 Overview of studies included in the clinical pharmacology package of osilodrostat

Description	Phase	Subject	n	Dose (mg)	Reference
SAD / MAD	I	HV - M	37 62	0.5-200 0.5-10 bid	A2101, 2008
Food effect / Japanese	I	HV - M/F	20	30	C1101, 2016
Japanese	I	HV - M	83	- 0.25, 0.5, 1, 2 single - 0.25, 0.5, 1 bid for 2w	A2102, 2010
Mass balance	I	HV - M	5	50 (3.7 MBq)	C2101, 2013
Renal impairment	I	RI - M/F	15	30	C2104, 2016

Description	Phase	Subject	n	Dose (mg)	Reference
Hepatic impairment	I	HI - M/F	32	30	C2103, 2017
QT	I	HV - M/F	86	10, 150	C2105, 2015
DDI - caffeine, omeprazole, dextromethorphan, midazolam	I	HV	20	50	C2102, 2014
DDI - oral contraceptive	I	HV	24	30	C2108, 2018
PD	II	Pats	9	2-30 bid	C1201, 2018
PoC	II	Pats	31	2-50 bid	C2201, 2017
Efficacy	III	Pats	137	2-30 bid	C2301, 2018

Table 2 Overview of modelling and simulation reports with osilodrostat

Description	Reference
PBPK - osilodrostat as CYP perpetrator	R1800128, 2018
Pop PK - in HV and pats	LC1699 PopPK, 2018

Table 3 Overview of key studies with osilodrostat in the target indication

Study Number of patients Sponsor/Status	Study design and patient population	Selected study endpoints	Dose
Study C2301 Enrolled: N=137 Treated: N=137 Novartis / Interim data cut-off of 21-Feb-2018	Phase III, multi-center, double-blind, randomized withdrawal study of osilodrostat following a 24-week, single-arm, open-label dose titration and treatment period to evaluate the efficacy and safety of osilodrostat for the treatment of patients with CD Adult male and female patients with CD	**Primary:** Proportion of randomized patients in each arm with: mUFC ≤ ULN at the end of 8 weeks of randomized withdrawal (Week 34), and were neither discontinued, nor had osilodrostat dose increased above the level at Week 26 during the randomized withdrawal period **Key secondary:** Proportion of enrolled patients with mUFC ≤ ULN at Week 24 and had no dose increase above the level established between Week 12 and Week 24.	Multiple dose: 2 mg bid starting dose, with titration up to a maximum of 30 mg bid[1]
Study C2201 Part I Enrolled: N=12 Treated: N=12 Novartis / Completed	Phase II, proof-of concept, open label, forced titration, multicenter study to assess the safety/ tolerability and efficacy of 10-weeks treatment of osilodrostat in patients with CD / Male and female adult patients with CD	**Primary (Part I of the study):** Proportion of patients with mUFC ≤ ULN Week 10 or represented a ≥50% decrease from baseline **Key secondary:** None	Multiple dose: 2 mg bid starting dose, with titration up to 50 mg bid[1,2]
Study C2201 Part II Core	Phase II, proof-of concept, open label, forced titration, multicenter	**Secondary:** Assessment of the effects of 22 weeks treatment of osilodrostat	Multiple dose:

Study Number of patients Sponsor/Status	Study design and patient population	Selected study endpoints	Dose
Study C2201 Part II extension Enrolled: N=19[3] Treated: N=19 Novartis / Ongoing Extension data cut-off date of 14-Nov-2017	study to assess the safety/ tolerability and efficacy of 10-weeks treatment of osilodrostat followed by a 12-week treatment period in patients with CD Male and female adult patients with CD	monotherapy on 24-hour UFC with proportion of patients with complete and partial response	2 mg bid starting dose, with titration up to a maximum of 30 mg bid[1,2]
Study C1201 Enrolled: N=9 Treated: N=9 Novartis / Interim data cut-off of 07-Jun-2018	Phase II, open-label, dose titration, multi-center study to assess the safety/tolerability and efficacy of osilodrostat in patients with other types of endogenous Cushing's syndrome except CD Male and female adult patients with CS	**Primary:** Percent change in mUFC from baseline to Week 12 based on individual patient-level data **Key secondary:** None	Multiple dose: 2 mg bid starting dose, with titration up to a maximum of 30 mg bid[4]

[1] The up-titration regimen until mUFC ≤ ULN
[2] With Study C2201 Part II Core following Amendment 4, the highest dosing regimen was 50 mg osilodrostat bid. With Protocol Amendment 5 the highest dosing regimen was changed to 30 mg osilodrostat bid for those patients who did not have normalization of UFC at 20 mg bid.
[3] In the Part II Core of the study, a total of 19 patients were enrolled and treated in study Part II Core: 4 from Part 1 of the study and 15 patients who were newly enrolled.
[4] The up-titration regimen until morning serum cortisol or mUFC ≤ ULN.
bid=twice-daily dosing; CD=Cushing's disease; CS=Cushing's syndrome; mUFC=mean urine free cortisol; ULN=upper limit of normal

2.4.2. Pharmacokinetics

Bioanalysis

Plasma concentrations of osilodrostat were determined, after protein precipitation, using a HPLC-MS/MS method. The calibration range was 1-1000 ng/ml using 50 µL Na-EDTA plasma. $^{13}C\ ^{2}H_4{}^{15}N$-osilodrostat was used as internal standard. The assay was pre- and within study validated. The assay was further developed and cross-validated in the calibration range 0.5-50 ng/ml.

The assay was further developed and validated in the concentration range 0.1-100 ng/ml osilodrostat, using K2-EDTA plasma and a sample volume of 100 µL.

A chiral LC-MS/MS method was used for explorative determination of S-osilodrostat in plasma. The assay consisted of protein precipitation followed by evaporation and analysis of reconstituted extracts. The calibration

range was 0.5-500 ng/ml using 100 µL sample volumes. The method was qualified with a mean bias of ±30% and a precision of ≤30%.

Osilodrostat in the urine was determined after dilution and followed by analysis of the reconstituted samples by LC-MS/MS. The calibration range was 1-1000 ng/ml using a sample volume of 20 µL.

LC-MS/MS methods for determination of caffeine and paraxanthine, dextromethorphan and dextrophan, omeprazole and 5-hydroxyomeprazole and midazolam, OH-midazolam, ethinyl-estradiol and levonorgestrel were also developed and validated for intended purposes.

Absorption

Osilodrostat demonstrated a high permeability in Caco-2 cells and a high solubility and is characterized as a BCS-1 compound. Active Pgp- and MRP-transport seem to be only marginally involved.

An absolute bioavailability study has not been performed.

Osilodrostat was rapidly absorbed with a t_{max} of approximately 1-2h, consistent at all doses studied. Majority of dose administered was eliminated in urine (91%), suggesting that osilodrostat oral absorption is nearly complete, as expected for BCS Class I compounds.

Concentration dependent PK, with a more than dose-proportional increase in exposure, was seen following single oral doses of 0.5-200 mg. A fairly dose proportional increase in exposure was seen after 0.5-3 mg od.

Steady state was reached at day 2 following repeated dosing and the accumulation was 0.9-1.3 after od dosing. An accumulation ratio of 1.3 was determined based on PopPK analysis following 2-30 mg bid.

A small decrease in exposure of osilodrostat was seen when co-administered with food (high fat meal), with a C_{max} of 0.8-fold and an AUC of 0.9-fold compared to when dosed alone.

A relative bioavailability comparison between the early capsule and the investigational tablet used in phase 3 (equal to the to-be-marketed formulation) showed comparable exposure but with a lightly higher C_{max} after the capsule.

Distribution

The median apparent volume of distribution was approximately 100 L. Based on PopPK analysis, the apparent volume of distribution was estimated to be 107 L for the central compartment (Vc/F) and to 326 L for the peripheral compartment (Vp/F).

The f_u (unbound fraction) for osilodrostat was 0.63 and independent of plasma concentration in the studied concentration range 0.02-100 µg/ml (0.09-440 µM). The C_B/C_p ratio was determined to 0.85 and consistent with the blood-to-plasma ratio for total radioactivity 0.88 after an oral dose of [14C]osilodrostat.

The f_u for M34.5 was determined to 0.64.

Metabolism

No inter-conversion from administered R-osilodrostat (active) to S-osilodrostat was seen.

Thirteen metabolites were characterized in the urine. Three large metabolites M16.5, M22 and M24.9 were identified with 17, 13 and 11% of the dose, respectively. M22 was identified as M34.5-glucuronide.

Osilodrostat represents *ca* 20% of the total radioactivity in plasma following a single oral dose of [14C]osilodrostat 50 mg (3.7 MBq). Three large metabolites were identified M34.5, M16.5 and M24.9 with about 51, 9 and 7% of total exposure of radioactivity, respectively.

The current data indicate a longer $t_{1/2}$ of both M34.5 and M24.9 compared to osilodrostat, thus accumulation is expected at bid dosing. (M34.5 and M16.5 showed weak/no inhibitory activity *in vitro* but M24.9 was active with an IC50 of less than 12-fold as potent as osilodrostat (*cf* Non-clinical assessment).

The formation of the largest metabolite in the urine M16.5 (direct N-glucuronide) was catalysed by UGT1A4, 2B7 and 2B10.

Twenty-four percent of the dose excreted in the urine as M24.9 (OH-osilodrostat) and its secondary metabolites M15 and M19.9 (11, 7 and 6% of the dose, respectively) was formed *via* CYP3A4, 2B6 and 2D6 mediated metabolism.

Less than 1% of the dose was excreted as M34.5 (di-oxygenated osilodrostat) in the urine but 13% of the dose was identified as M22 (M34.5-glucuronide). The formation of M34.5 was concluded to be non-CYP-mediated as the metabolite was not identified *in vitro.* Thus 14% of the dose was eliminated *via* non-CYP-mediated metabolism that way.

Six metabolites in the urine were identified as oxidative metabolites (M18B, M23.1, M16.4B, M6, M16 and M10), altogether 20% of the dose, but not identified *in vitro* and were concluded to be formed *via* non-CYP-metabolism.

Elimination

The elimination $t_{1/2}$ was calculated to about 4h.

Ninety-one percent of a [14C]osilodrostat dose was excreted in the urine and <2% in faeces. *Ca* 5% of the dose was excreted as parent compound in the urine.

Time-dependency

Based on population PK results, mean accumulation ratio (based on AUC) between single dose and steady state was approximately 1.3 and similar for all doses within therapeutic dose range 2-30 mg bid.

PK in the target population

The between-subject variability at steady-state AUC and steady-state C_{max} were approximately 33 CV% and 22 CV%, respectively, over the range of 2–30 mg.

The systemic exposure of osilodrostat was about 1.3-fold higher in Caucasian subjects compared to Japanese at steady state.

Special populations

Renal impairment

Comparable systemic exposure of osilodrostat was seen in subjects with severe RI, ESRD and normal renal function following a single dose of osilodrostat 30 mg.

Hepatic impairment

Total systemic exposure increased with decreasing liver function with an AUC of *ca* 1.4- and 2.7-fold in moderate and severe HI compared to in healthy subjects. C_{max} was *ca* 0.8-fold for mild, moderate and severe HI compared to subjects with normal liver function.

Co-variates

Based on PopPK, no dose adjustment is required based on gender, age and weight factor. But an effect of the race has been identified. The drug has mainly been studied in the Caucasian and Asian populations.

Interactions

The PK interaction potential of osilodrostat has been evaluated in a number of *in vitro* studies and in two *in vivo* DDI studies. The interaction potential with the main metabolite M34.5 was also investigated *in vitro.*

In vitro

Osilodrostat is a substrate of

- CYP3A4, 2B6 and 2D6
- UGT1A4, 2B7 and 2B10

Signals were shown for clinically relevant

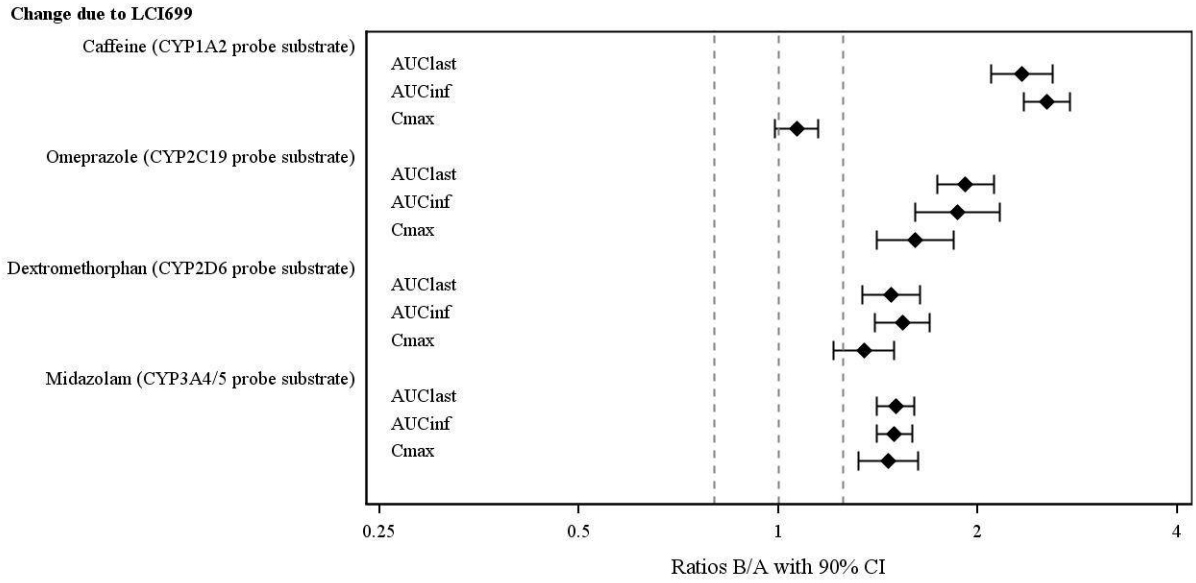
- inhibition of CYP1A2, 2B6, 2C19 (TDI), 2D6, 2E1 and 3A4, UGT1A1 (M34.5)
- induction of CYP1A2, 2B6 (osilodrostat, M34.5) and 3A4 (osilodrostat, M34.5)
- inhibition of OATP1B1 (osilodrostat, M34.5, TDI? M34.5), OATP1B3 (TDI? M34.5), OAT3 (M34.5, TDI?), OCT1, OCT2, MATE1

In vivo

Victim

No *in vivo* on the effect of other medicinal products on the PK of osilodrostat have been presented.

Perpetrator



- Osilodrostat is a mild CYP2D6 inhibitor
- Osilodrostat was a mild CYP3A4 inhibitor after single dose *in vivo*, however, osilodrostat also has an *in vitro* signal for induction (both osilodrostat and M34.5) which is not explored in a single dose study.
- Osilodrostat did not show any clinically relevant effect on a combined oral contraceptive (CYP3A4/UGT substrate) *in vivo* following osilodrostat 30 mg bid for 7 days. It can be concluded that osilodrostat is not a potent PXR-inducer (not a sensitive substrate) but if a weak PXR-inducer is unknown.
- It cannot be concluded that osilodrostat is characterized as moderate CYP1A2 inhibitor (about a 2.5-fold increase in exposure of a CYP1A2 substrate when co-administered) as the signal of induction *in vitro* cannot be evaluated after a single dose *in vivo.*

- Osilodrostat is a mild CYP2C19 inhibitor following a single dose of osilodrostat, however, if an *in vivo* TDI potential exist for CYP2C19, has not been evaluated as just a single dose was given
- *In vivo* inhibition/induction of CYP2B6 cannot be ruled out
- *In vivo* inhibition of CYP2E1 cannot be ruled out
- *In vivo* inhibition of UGT1A1 by M34.5 cannot be ruled out
- It cannot be ruled out that osilodrostat is a OCT1, OCT2, OATP1B1, MATE1 and OAT3 inhibitor *in vivo*

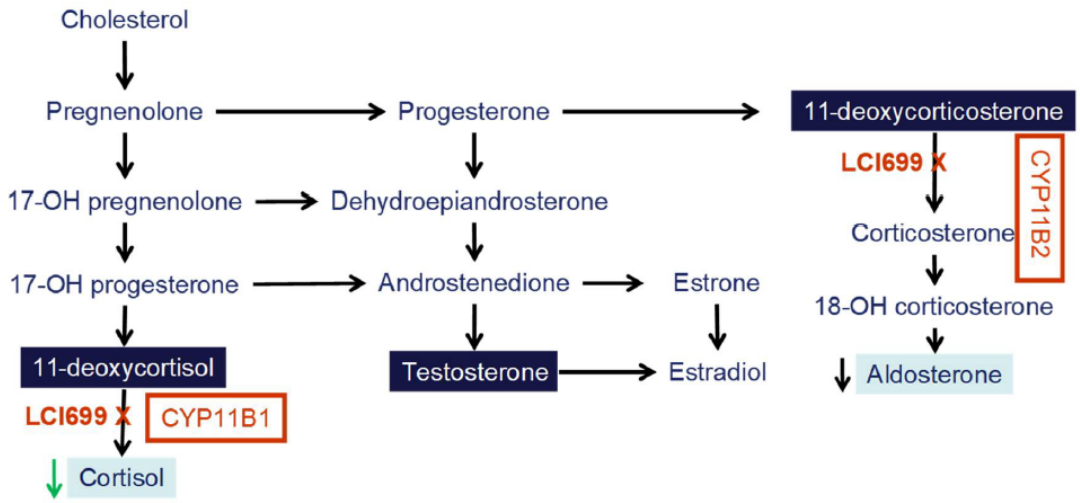
2.4.3. Pharmacodynamics

The PD of osilodrostat was investigated in healthy volunteers (studies A2101 and A2102, the latter compared the PD in Japanese and Caucasian subjects) and in patients with Cushing's disease (study C2201). In addition, a thorough QT study (C2105) was conducted.

Mechanism of action

Osilodrostat (LC1699) is a potent, oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyses the last step in the biosynthesis of cortisol in the adrenal gland, thereby inhibiting cortisol synthesis.

Figure 2 Site of action of osilodrostat (LCI699) in the aldosterone and cortisol synthesis pathways



Cortisol synthase (11β-Hydroxylase, CYP11B1) and aldosterone synthase (11β-Hydroxylase, CYP11B2) are intracellular enzymes located specifically within mitochondria. An *in vitro* cell-based enzyme assay was used to select potential inhibitors. CYP11B2 has high nucleotide sequence and amino acid homology with CYP11B1 i.e. the enzyme that is responsible for cortisol generation in humans. Using these screening assays, osilodrostat was identified as a potent inhibitor of CYP-11B1 and CYP11B2.

Primary pharmacology

Osilodrostat was shown to cause dose-dependent inhibition of CYP11B1 in vitro. In the following, data from two studies in healthy subjects is summarised.

Study A2101 – in healthy subjects

This was a first-in-human, double-blind, placebo- and comparator-controlled (eplerenone), interwoven single- and multiple-ascending dose study. Part I consisted of five single-ascending dose (SAD) cohorts, while Part II

consisted of four multiple-ascending dose (MAD) cohorts. Oral doses up to 200 mg were administered as a single dose, and daily doses up to 10 mg were administered orally for up to 14 days.

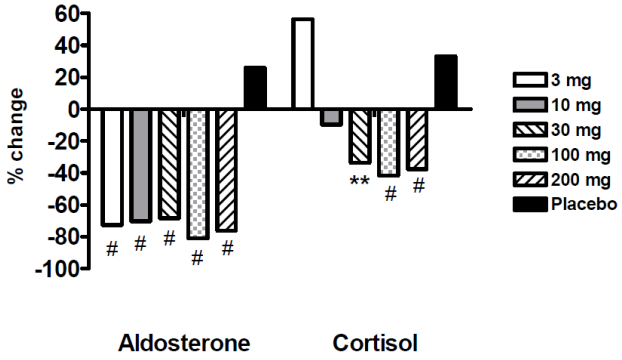
Pharmacodynamic results

Part I: Single ascending dose

Cortisol (plasma and urine)

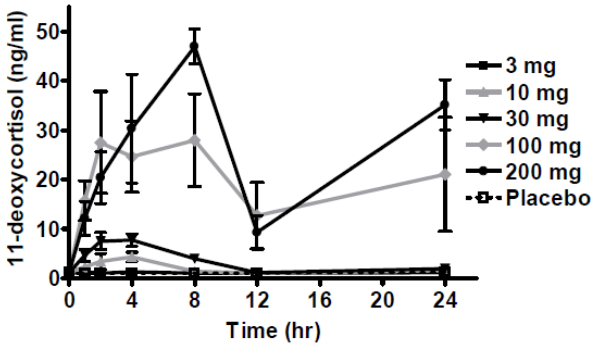
Following single doses of ≤100 mg LCI699, no significant changes in plasma cortisol were observed 12 or 24 hr post-dose. A single dose of 200 mg LCI699 did result in a 19% decrease in plasma cortisol 24 hr post-dose (p=0.029 compared to placebo). A significant reduction in 24 h urine cortisol (34-42%) was observed following single LCI699 doses of ≥30mg, compared to a 33% increase for placebo treatment (≤0.001; Figure 6).

Figure 3 Change in 24 hour urine aldosterone and cortisol following single dose of LCI699



The diurnal rhythm of cortisol was also maintained for all doses. While a clear dose-dependent inhibition of plasma cortisol was not observed following a single dose of LCI699, plasma levels of the cortisol precursor 11-deoxycortisol did show an increase at ≥100 mg (p<0.001 compared to placebo) suggesting a compensatory rise due to inhibition of 11-β hydroxylase (CYP11B1). The increases in 11-deoxycortisol were statistically significant starting 1 hr post-dose for LCI699 doses of ≥100 mg, and were sustained through 24h post-dose (Figure 7).

Figure 4 Plasma 11-deoxycortisol levels following single dose of LCI699

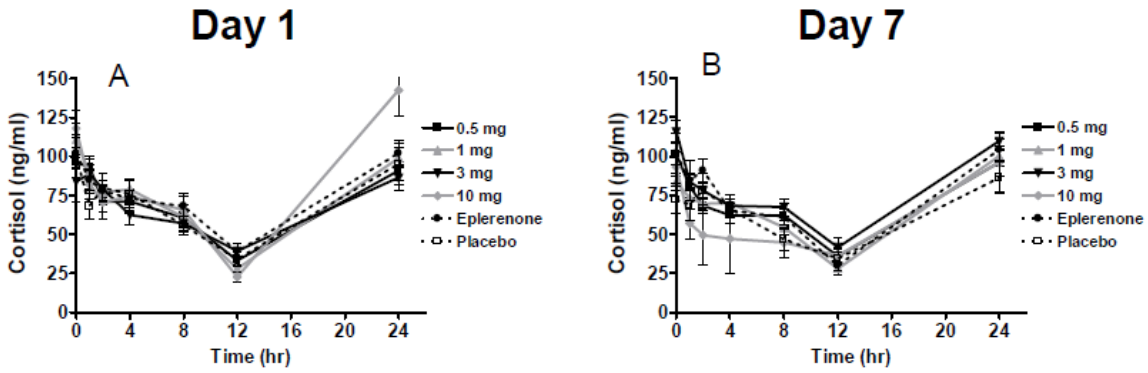


Part II: Multiple ascending dose

Cortisol (plasma and urine)

LCI699 did not inhibit morning, basal cortisol at doses of 0.5 – 3 mg yet repeated doses of 10 mg LCI699 did cause a marked decrease in the diurnal cortisol pattern (Figure 8).

Figure 5 Plasma cortisol on Days 1 and 7



No significant decrease in plasma (AUC_{0-24h}) or 24 h urine was observed on Day 1 or 7 for any dose. LCI699 did not inhibit ACTH-stimulated cortisol after 13 doses of 0.5 mg LCI699, however, following 13 doses of 1 mg LCI699, a 22% decrease in cortisol production upon ACTH-stimulation was noted. A categorical analysis was performed on these data to show the number and percentage of subjects that mounted a sufficient plasma cortisol response (≥ 500 mmol/l or ≥ 550 mmol/l). Note that at 1 mg, 25% of the subjects did reach a cortisol level of ≥ 550 mmol/l after ACTH stimulation, but all did achieve ≥ 500 mmol/l. In addition, a build-up of cortisol precursor (11-deoxycortisol) was observed at doses ≥3 mg LCI699, though only 10 mg showed statistical significance ($p<0.001$).

No compensatory increase in trough or peak ACTH levels were observed at doses ≤ 3 mg. Following 6 doses of 10 mg LCI699, trough ACTH levels had increased almost 200% ($p<0.001$), confirming the inhibitory effect of this dose of LCI699 on the transformation of 11-deoxycortisol to cortisol.

Study A2102 – in Japanese and Caucasian healthy subjects

This was a randomized, placebo-controlled, parallel-group, single and multiple-dose study that compared the safety and pharmacokinetic properties of osilodrostat between Caucasian and Japanese subjects and explored pharmacodynamics in these two groups. A total of 83 subjects were randomized and received treatment (n=40 Caucasian subjects, n=43 Japanese subjects). Four parallel groups (0.5, 1.0, 2.0 mg/day and placebo) were used in this study.

Pharmacodynamic results

Cushing's disease-related PD results are summarized below:

Cortisol: Single or multiple doses of LCI699 did not significantly impact the basal levels or the diurnal rhythm of plasma cortisol in Caucasians or Japanese populations. In addition, there was no effect on the 24-hour urinary cortisol concentration following single or multiple doses of LCI669 in either race.

Plasma 11-deoxycortisol: Treatment with osilodrostat 1 mg b.i.d. dose for 14 days was associated with a greater increase in cortisol precursor, 11-deoxycortisol, in Japanese compared to Caucasian subjects.

Plasma ACTH: The post-treatment increase in plasma ACTH levels was higher in Japanese (~5-fold) compared to that in Caucasian (~2-fold) population upon multiple dosing with 1 mg b.i.d. osilodrostat.

ACTH-stimulated cortisol increase: The frequency of ACTH stimulation test failure in Caucasians was 0%, 11%, 11% and 22% for PBO, 0.25 mg twice daily, 0.5 mg twice daily and 1 mg twice daily groups, respectively. Similarly, the frequency of ACTH stimulation test failure in Japanese was 0%, 11%, 22% and 70% for PBO, 0.25 mg twice daily, 0.5 mg twice daily and 1 mg twice daily groups, respectively. Analysis of individual subject C_{max}

(or AUC) on Day 14 vs. failure of ACTH-induced cortisol test on Day 13 indicated that there was no clear exposure-dependency in subjects that passed or failed the test. However, the 1 mg b.i.d. dose in Japanese subjects who failed the ACTH test had a trend for higher exposure.

Secondary pharmacology

Study A2101 – in healthy subjects

For study description, see above.

Pharmacodynamic results

Part I: Single ascending dose

Aldosterone (plasma and urine)

A single dose of LCI699 (3-200 mg) resulted in a 60-77% reduction of plasma aldosterone levels by 12h post-dose, compared to a 30% decrease for placebo treatment (p=0.019 to 0.004). Reductions in plasma aldosterone were still observed 24 h post-dose (15-56% reduction compared to a 15% increase with placebo; p=0.002 to <0.001) for all doses. Decreases in time-normalized urine aldosterone (68-81%) were also observed following a single dose of LCI699, compared to a 25% increase for placebo patients (p,0.001; Figure 6). No apparent dose response was observed in plasma or urine aldosterone levels; however, the 3 mg dose did appear to result in a less inhibition of plasma aldosterone at 24 h post-dose compared to the higher LCI699 doses.

Plasma renin activity (PRA)

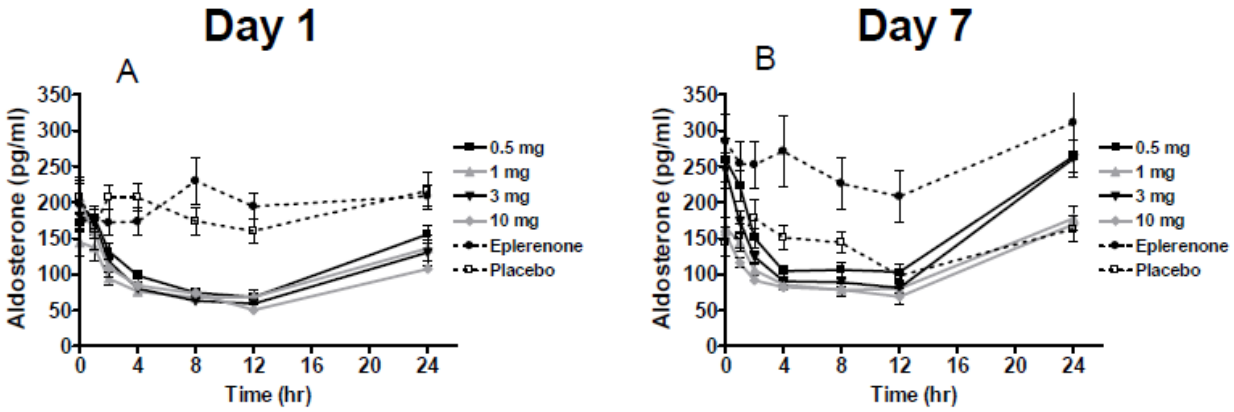
Following a single dose of LCI699, PRA increased with the 2 lowest doses (3 and 10 mg) having a >100% increase 24 h post-dose (p=0.004 and 0.042 compared to placebo), whereas doses >10 mg showed an increase similar to placebo (51-64% for LCI699 and 51% for placebo).

Part II: Multiple ascending dose

Aldosterone (plasma and urine)

Similar to the results for the single-dose part of the study, LCI699 (0.5-10 mg) treatment resulted in a 60-77% reduction of plasma aldosterone levels 12h after the first dose (Day 1), while only a 30% decrease was observed in placebo treated subjects (Figure 9). Administration of LCI699 also resulted in a significant, dose dependent decrease in 24 hr urine aldosterone (40-74%) compared to Day-1 (p<0.001). However, by Day 7, pre-dose plasma aldosterone levels had increased in the 0.5 and 3 mg treated subjects, and the normal daytime decrease was noticeably enhanced in placebo subjects (Figure 9). These 2 effects resulted in essentially no difference in $AUC_{0\text{-}24h}$ of plasma aldosterone for subjects treated with 0.5 – 3 mg LCI699 compared to placebo on Day 7.

Figure 6 Plasma aldosterone on Days 1 and 7



Due to the 4 hr half-life of the drug, $AUC_{0\text{-}12h}$ for plasma aldosterone was also calculated for Days 1 and 7. These results suggest that LCI699 consistently reduces aldosterone over the first 12 hours post-dose, but leads due to the 4 hr half-life an increase in aldosterone production over the second 12 hours, and hence 24 hour reductions in aldosterone are not observed.

Plasma renin activity (PRA)

An increase in PRA levels was observed after a single dose of ≥ 1 mg LCI699 (53-95%), however only the 1 mg dose was significantly different than placebo (p=0.04). Following repeated dosing with LCI699, trough PRA levels continued to increase. By Day 7 a dose-dependent trend was evident and levels had significantly increased compared to placebo (90, 158 and 287% for 0.5, 1 and 3 mg LCI699 compared to -23% for placebo p=0.006 to <0.001). The levels achieved by these LCI699 doses were higher than those observed with 100 mg eplerenone (56%; p=0.046 vs placebo).

Electrolyte changes

As expected for an aldosterone synthase inhibitor, changes in plasma and urine electrolytes (sodium and potassium) were observed.

Urinary potassium excretion was increased with LCI699 by approximately 40% after 7 daily doses, whereas this increase was not noted in the eplerenone group. In the multiple dose part of this study, 7 subjects (all on LCI699) recorded a plasma potassium above upper limit of normal (ULN) after the switch to the higher potassium diet. All increases in potassium were either isolated (single incident), or transient (decreased upon retest), and no changes in ECG were observed.

On Day 1 of treatment LCI699 increased sodium excretion to a similar extent as eplerenone (~60-110%) at LCI699 dose of ≤ 3mg. After 7 daily doses the increase in sodium excretion was more modest (~13-40%) and dose dependent. For placebo and eplerenone, the changes were ~19 and 26%, respectively on Day 7. Six subjects (all on LCI699) recorded plasma sodium levels at or below 135 mmol/l (hyponatremia) during the multiple dose part of the study.

Aldosterone synthase precursor

Inhibition of aldosterone should lead to a build-up of the aldosterone synthase precursor 11-DOC. No notable increase in unstimulated 11-DOC levels were observed for LCI699 dose ≤1 mg. In contrast, the 3 mg dose showed a marked increase in both trough and peak levels of 11-DOC, that increased with further exposure. Upon stimulation of the aldosterone pathway with ACTH, all 3 doses (0.5, 1 and 3 mg) showed augmented 11-DOC

levels, suggesting significant inhibition of aldosterone synthase, and accumulation of its precursor. These increases were dose-dependent (with the 3 mg treated subjects reaching ~1200 pg/ml) and increased with prolonged exposure. These results suggest no accumulation of 11-DOC at LCI699 doses ≤1 mg, but a time dependent accumulation of this precursor at 3 mg.

Study C2201 (Part I) - in patients with Cushing's disease

This (Part I) is a Phase II, open-label, single arm, sequential dose-escalation, multicenter study of osilodrostat in patients with Cushing's disease.

In addition to data on ACTH, cortisol, 11-deoxycortisol, renin, aldosterone and 11-deoxycorticosterone, serum samples were used to determine insulin, testosterone, oestradiol, IGF-1, TSH, free T4, LH, and FSH. Whole blood samples were used to determine HbA1c.

Pharmacodynamic results

Table 12 summarizes the results of the paired t-test performed on the plasma and serum PD variables.

Table 4 Summary of results from the paired t-test comparing Week 10 to baseline for all plasma and serum PD variables (PD analysis set)

Variable		N	Geometric means at		Ratio of geometric means	95% CI	P value
			Baseline	Day 70			
HPA-axis							
Cortisol (nmol/L)		12	687.5	280.5	0.41	0.28, 0.60	<0.001
11-deoxycortisol (ng/dL)		12	84.2	1097.6	13.0	7.01, 24.3	<0.001
Aldosterone (pmol/L)		12	116.1	38.2	0.30	0.11, 0.87	0.030
11-deoxycorticosterone (pmol/L)		12	105.7	4468.5	42.3	22.8, 78.5	<0.001
ACTH (pmol/L)		12	15.66	38.24	2.44	1.27, 4.68	0.012
Renin (ng/L)		12	13.17	7.86	0.60	0.26, 1.35	0.19
Metabolic markers							
HbA1c (%)		12	6.04	5.76	0.95	0.91, 1.00	0.056
Insulin (pmol/L)		12	117.7	123.4	0.97	0.78, 1.20	0.74
IGF-1		12	24.71	20.94	0.85	0.71, 1.02	0.072
Free thyroxine (pmol/L)		12	13.75	12.43	0.90	0.84, 0.97	0.011
TSH (mU/L)		12	0.745	0.998	1.34	0.94, 1.90	0.096
Sex hormones							
Total testosterone		12	1.389	3.396	2.45	1.43, 4.18	0.004
	Male	4	2.873	8.835	3.08	0.70, 13.29	0.094
	Female	8	0.965	2.105	2.18	1.08, 4.39	0.034
LH (U/L)		12	2.15	1.13	0.53	0.15, 1.81	0.28
	Male	4	0.75	0.10	0.13	0.01, 2.98	0.13
	Female	8	3.63	3.82	1.05	0.27, 4.12	0.93
E2 (pmol/L)		12	143.2	130.5	0.93	0.34, 2.59	0.89
	Male	4	68.8	136.8	1.99	1.03, 3.85	0.045
	Female	8	206.6	127.5	0.62	0.14, 2.69	0.46
FSH (U/L)		12	4.20	2.38	0.57	0.27, 1.17	0.11
	Male	4	2.04	0.46	0.23	0.03, 1.57	0.092
	Female	8	6.04	5.42	0.90	0.45, 1.80	0.73

Effect on QT

In both human and animal studies, osilodrostat showed concentration/dose-dependent QT prolongation and a potential to cause cardiac rhythm abnormalities, including torsades de pointes.

The mechanism by which osilodrostat may cause QT-prolongation is not fully understood.

However, hypokalaemia seen in CS is often associated with hypomagnesaemia and increases the risk of malignant ventricular arrhythmias. Worsening of hypokalaemia has been reported with adrenal-directed drugs that can increase cortisol precursors with mineralocorticoid activity. In addition, myocardial fibrosis caused by an enhanced responsiveness to angiotensin II and activation of the mineralocorticoid receptor in direct response to cortisol excess could exacerbate the effects of hypokalaemia on QT interval prolongation seen in patients with CS.

Preclinical studies have identified a potential for QT prolongation and arrhythmia with osilodrostat and in healthy volunteers, there was a positive correlation between osilodrostat concentration and ΔΔQTcF (study C2105 described below).

Study C2105 – thorough QT/QTc study

Study C2105 was a single center, Phase I, randomized, placebo and active (moxifloxacin 400 mg)-controlled, double blind, thorough QT/QTc study to assess the effect of single doses of osilodrostat (10 mg and 150 mg) on cardiac repolarization in 86 healthy male and female subjects.

There was no relevant QT effect on osilodrostat 10 mg. The estimated maximum mean ΔΔQTcF was 1.73 ms (90% CI: 0.15, 3.31 ms) at 3 hour post-dose, and the upper bound of 90%CI of ΔΔQTcF was less than 10 ms at all time-points. However, the inter-individual variability is considerable (Figure 10).

A maximum mean ΔΔQTcF of 25.4 ms (90%CI: 23.53, 27.22) was observed at 1 hour post-dose, at the observed T_{max} on a single dose of osilodrostat 150 mg (5-fold higher than the maximum clinical dose of 30 mg). The regression analysis of concentration-response relationship based on the linear mixed effect model including Baseline QTcF as covariate indicated a positive correlation between the concentration and placebo-corrected changes of QTcF from Baseline values as shown in Figure 6. Based on the exposure-response relationship, predicted mean ΔΔQTcF was generated at the expected median of maximum plasma concentration ($C_{max,ss}$) at 30 mg b.i.d. as reported in the population PK analysis. Based on the population PK predicted median of $C_{max,ss}$ (232.26 ng/mL) following 30 mg b.i.d. dose, the mean ΔΔQTcF for 30 mg b.i.d. dose (the maximum recommended dose in clinical practice) is estimated to be 5.27 ms (90%CI: 4.12, 6.42), and the mean ΔΔQTcF for 20 mg b.i.d. dose is 3.53 ms (90%CI: 2.38, 4.69).

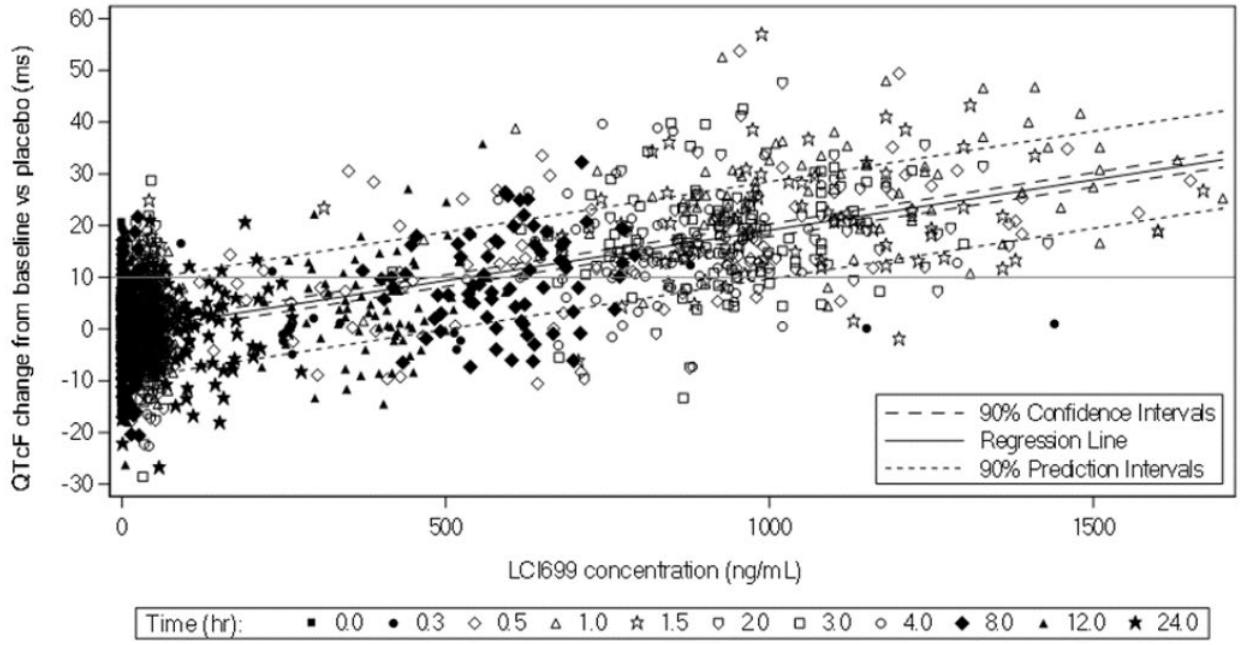
Following administration of moxifloxacin 400 mg, QTcF exceeded the Baseline value from 0.25 hours post dose up to 24 hours post dose. The maximum ΔΔQTcF was observed at 4 hours post dose, and was 12.86 ms (90% CI: 11.14, 14.58).

No subject experienced QTcF values >500 ms, or increases from baseline of >60 ms. The maximum effect at 150 mg was observed at T_{max} (1 hour post-dose). No dose-related effects were observed for the cardiac intervals (QRS, PR, or HR), or on blood pressure on osilodrostat 10 mg or 150 mg.

Single dose administration of osilodrostat 10 mg and 150 mg was associated with over proportional increase in drug exposure. The geometric mean C_{max} (%CV) of 57.9 ng/mL (25.2%) and 1190 ng/mL (18.5%), respectively, were observed at 1 hour post-dose. Elimination of osilodrostat was monophasic. The overall exposure levels for osilodrostat 10 mg and 150 mg were 359 ng·h/mL (28.2%) and 12200 ng·h/mL (19.4%), respectively, measured by geometric mean AUC_{inf} (%CV).

A negative correlation of osilodrostat concentration on serum cortisol level was present, with a predicted mean placebo adjusted cortisol change from Baseline of −40.22 nmol/L (90%CI: −55.66, −24.78) at the observed mean C_{max} of 1210.66 ng/mL after a 150 mg dose of osilodrostat (p-value of <0.0001 for a slope of −0.04).

Figure 7 Placebo corrected QTcF change from period-specific time-averaged Baseline versus osilodrostat plasma concentration including inter-individual variability (Study C2105) (ECG analysis set)



Note: - The model is QTcF change from baseline compared to placebo = intercept + alpha* baseline QTcF + beta* concentration + subject, where subject is a random effect.
- Baseline QTcF is taken as the median baseline for the display.
- Mean and 90% CI regression lines are included.
- 90% Prediction Intervals (PI) are included.

Relationship between plasma concentration and effects

Based on original PK-PD modelling and simulation, 4 - 5 mg b.i.d. was expected to achieve a plasma concentration above the in vitro IC50 for CYP11B1 (2.5 nM) for a full 24-hour period. There was a broad range (up to 25-fold in osilodrostat dose) of inter-patient sensitivity to osilodrostat to achieve normalization of mUFC. Thus, individual dose titration was required. A starting dose of 2 mg b.i.d. and a maximum dose at 30 mg b.i.d. were chosen based on safety considerations.

Dose titration was based on individual response and tolerability; therefore, no traditional exposure-response analyses were used to provide justifications to the recommended dosing regimen. The brief descriptive exposure-response analyses are summarized below.

Exposure-efficacy

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 the fitted E_{max} and linear mixed effects modelling analyses. However, as the dose titration scheme implemented in the study was affected by the cortisol level, it is difficult to draw a clear conclusion regarding the predictability of cortisol levels by osilodrostat exposure.

Exposure-safety analysis for QTcF interval

In the thorough QT Study C2105 (further assessed in 2.2.4. Study 2105), there was a positive correlation between osilodrostat concentration and ΔΔQTcF. The wider dose range and higher dose studied in this trial (i.e.

supratherapeutic dose of 150 mg) resulted in the detection of the positive correlation. In Study C2105, QTcF tended to decrease after a 10 mg dose but the maximum mean ΔΔQTcF revealed a small QTcF increase of 1.73 ms (90% CI: 0.15, 3.31) at 3 hours post-dose. At a supratherapeutic dose of 150 mg, this study identified a maximum mean ΔΔQTcF of 25.38 ms (90% CI: 23.53, 27.22) at 1 hour post-dose.

The relationship observed in Study C2301 should be interpreted with caution due to limited amount of information collected in the study (no pre-dose QT and no time-matched placebo control). No relationship was detected between osilodrostat concentration (dose range from 1 to 30 mg) and change of QTcF interval from baseline in Study C2301; the estimated slope for concentration in the linear mixed model was -0.02 (90% CI: -0.08, 0.03) for QTcF change from baseline. At the highest tested incident dose of 30 mg (median C_{max} 167 ng/mL), the model estimated a mean QTcF change from baseline of -2.13 ms (90% CI: -10.51; 6.24).

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology program conducted was in line with the program proposed and accepted by the CHMP in the scientific advice. In line with the advice, the Applicant explored exposure-response relationships for a better understanding of exposure-efficacy/exposure-safety for optimization of future dosing paradigms.

Pharmacokinetics

One LC-MS/MS assay, with further development and validations/cross-validations, has been used for determination of osilodrostat in plasma.

In the combined SAD/MAD study osilodrostat was given up to 200 mg as single doses. The MAD was original designed with ascending doses between 10-100 mg od, however, potent PD effects were seen thus repeated dosing for two weeks of 0.5, 2 and 3 mg od were evaluated.

Osilodrostat was rapidly absorbed with a t_{max} of *ca* 1-2 h and steady state was reached by Day 2 following repeated dosing. The accumulation ratio of 1.3 with 2-30 mg bid. Osilodrostat can be taken without or with food as only a nonclinical relevant decrease in exposure was seen when osilodrostat was co-administered with a high fat meal.

Osilodrostat is characterized as a BCS-1 compound *ie* a compound with high solubility and high permeability. However, a more than dose proportional increase in systemic exposure with increasing dose was seen and a dose-dependent relative bioavailability was identified in the PopPK analysis. The reason to the increasing bioavailability with dose is unknown and should be it should be mentioned in the SmPC 5.2 that exposure increased more than dose-proportionally over the therapeutic range. Nevertheless, as the proposed dosing regimen is dose titration based on response and tolerability with steps of 2 mg should not warrant extra caution.

A relative bioavailability comparison between the early capsule and the investigational tablet used in phase 3 trials (equal to the to-be-marketed formulation) was performed based on descriptive statistics. A rapid/very rapid dissolution was demonstrated for both formulations with cumulative percent after 15 or 30 min exceeding 85% for the different strengths. A difference in mannitol between the two formulations exists, which may influence the bioavailability. But considering that osilodrostat is a BCS-1 compound and that the low total amount of mannitol is low both formulations, a significant difference in bioavailability is not expected. Thus, the results in the early studies following dose administration with the capsule can be used in the total evaluation of osilodrostat.

Following a single oral dose of [14C]osilodrostat, *ca* 20% of the of the total radioactivity in plasma was identified as parent compound. The mean $t_{1/2}$ of radioactivity was 24h and the $t_{1/2}$ of osilodrostat has been determined to

ca 4h. Three large metabolites have been identified M34.5, M16.5 and M24.9 representing *ca* 57, 9 and 7% of total plasma radioactivity, respectively. Considering the much longer $t_{1/2}$ of radioactivity compared to osilodrostat implies that the metabolites have longer $t_{1/2}$ than parent compound. The reported $t_{1/2}$ of 22h for M34.5 agrees with the reported $t_{1/2}$ of 24h for total plasma radioactivity, this can be expected as M34.5 represents ca 60% of total plasma radioactivity. The single dose data are very uncertain as only one single data is available in the elimination phase. The proposed dose regimen is twice daily thus accumulation of M34.5 and M24.9 are expected. Simulated/ predicted exposure of M34.5, M24.9 and M16.5 at steady state following repeated dosing with osilodrostat 30 mg bid have been provided, based on a 1-compartment extravascular model fitted to the single dose data after osilodrostat 50 mg. The accumulation ratio was predicted to *ca* 10-, 4- and 2-fold for M34.5, M24.9 and M16.5, respectively, compared to 1.3-fold for osilodrostat. The single dose data are very uncertain as only few samples were collected in the elimination phase. The $t_{1/2}$ seems, however, overpredicted leading to an overprediction in accumulation. Furthermore, the 30 mg dose is the maximum recommended dose while the expected maintenance dose is 2-7 mg. Thereby, 30 mg depicts an absolute worst case.

The elimination $t_{1/2}$ of osilodrostat was calculated to about 4h and most of an oral dose, 91%, was eliminated in the urine with *ca* 5% as parent compound. The elimination pathways are not fully presented thus the potential clinical consequences of concomitant medications cannot be foreseen. Polypharmacy is expected in patients diagnosed with Cushing syndrome. However, as dose titration, based on response and tolerability, is recommended at initiation of treatment and this will cover stable patients (impaired organ function, on co-medications *etc*). But the clinical consequences are unclear for changes during treatment e.g. addition/discontinuation of other medications. The SmPC 4.5 should be updated to include that patients should be closely monitored if co-treatment with strong CYP inhibitors or strong enzyme inducers are added or stopped, during ongoing treatment due to potential increase or decrease in systemic exposure of osilodrostat, respectively.

Clinical consequences of potential genetic polymorphism have not been discussed in the current dossier. However, given the multiple enzymes involved in the metabolic pathways and that the dosing regimen is dose titration based on response and tolerability, no clinical consequences are expected due to genetic polymorphism.

A PopPK model was developed using a data-driven approach. The methodology described by the Applicant was overall state of the art but several methodological and reporting issues were identified that need to be addressed before the results and conclusions from modelling are fully endorsed.

The clinical consequences of osilodrostat when co-administered with other products and the risk of changing their PK and effect have not been completely investigated. PBPK modelling and simulation have been used to predict potential *in vivo* interactions with osilodrostat. This approach is appreciated; however, the platform cannot be considered qualified according to the EMA PBPK guideline. It has to be clearly stated in the SmPC, the uncertainties of potential effects of osilodrostat *in vivo* on other medicinal products when co-administered.

CYP3A4 mediated metabolism is very common and polypharmacy is common in the targeted patient population. Potential clinical consequences following co-treatment with osilodrostat and sensitive CYP3A4 substrates should be able to predict. A small increase (1.5-fold) was seen in systemic exposure of midazolam (sensitive CYP3A4 substrate) when dosed together with osilodrostat compared to when dosed alone. However, the single dose DDI study is not predictable for the potential induction signal on CYP3A4 (PXR coupled enzymes). Osilodrostat did not show any clinically relevant effect on a combined oral contraceptive (estradiol/levonorgestrel CYP3A4/UGT substrate) following osilodrostat 30 mg bid for 7 days. Thus, it can be concluded that osilodrostat is not a potent PXR-inducer (not a sensitive substrate) but if a weak PXR-inducer is unknown.

The SmPC needs to be updated, especially with respects to potential drug-drug-interactions (SmPC 4.5) but also information on basic PK should be added in SmPC 5.2.

Pharmacodynamics

Osilodrostat blocks both the synthesis of cortisol and aldosterone and was originally developed to treat patients with hyperaldosteronism but showed a larger effect on the HPA-axis and was further developed for the treatment of endogenous hypercortisolism. Due to the mechanism of action, a build-up of precursor may be expected. The mechanism of action for osilodrostat has been adequately described.

In healthy subjects (study A2101), single doses of osilodrostat ≥30mg resulted in a reduction in urine cortisol, notably the urine cortisol increased in the placebo-treated group. The diurnal rhythm of cortisol was not affected. An increase in the precursor 11-deoxycortisol was increased. In the MAD part of study A2101, repeated doses of 10 mg osilodrostat resulted in a decrease in the diurnal cortisol pattern. At the 1 mg dose, there was an attenuated response to ACTH stimulation. This was observed in spite of the fact that osilodrostat was given once daily. A build-up of 11-deoxycortisol was observed as well as an increase in ACTH at a dose of 10 mg.

In study A2102, the doses were lower than in study A2101. There appeared to be a stronger effect of osilodrostat in Japanese subjects than in Caucasian subjects, otherwise the results were in line with the data obtained in study A2101. This is in line with the higher exposure observed in Japanese subjects.

Effects on aldosterone and the renin-angiotensin system as well as effects on the HPG-axis are considered as secondary pharmacology effects.

In the single dose part of study A2101, plasma aldosterone levels were decreased in both actively and placebo-treated groups, but to a larger extent in subjects treated with osilodrostat. There was no apparent dose response. In the MAD part of the study, osilodrostat was given once daily. With this regimen, aldosterone was decreased over the 12-hour post-dose period and then subsequently rose up and above the baseline level at Day 7. A significant increase in PRA levels was observed. There was a modest increase in sodium excretion. A build-up of precursors, both 11-DOC and 11-deoxycortisol, was observed at doses exceeding 3 mg. ACTH was also increased at doses above 3 mg.

Study C2201 (Part I) was the PoC study in patients with CD, the efficacy data from this study is further discussed in the efficacy part of this report. In this study, the effect of osilodrostat on the HPA-axis, thyroid hormones and sex hormones was evaluated. There was a marked decrease in aldosterone and renin. Due to the blocked cortisol synthesis, a build-up of precursors is expected and was indeed observed.

The exposure-efficacy and safety analyses based on data from study C2301 is of limited valued since the exposure is conditioned on the cortisol response, and the exposure can thereby not be considered independent to the responses. Due to this limitation, the exposure-response analyses of cortisol response and ACTH are not assessed.

Overall, ACTH levels were increased and although mean levels show modest increases below the threshold of clinical concern, individual patients may have ACTH values that are above the ULN. The SmPC has now been updated to inform the prescriber of the potential risk of increased ACTH levels. The data further indicate an increase in testosterone in both males and females whereas there was a decrease in oestrogen in females and an increase in oestrogen in males. In male patients the increase in testosterone rather represent a normalisation of testosterone levels, whereas in female patients the increase in testosterone resulted in a mean level above ULN and associated events such as hirsutism and acne. These ADRs are listed in the SmPC and did not lead to discontinuations during the study. An additional statement is proposed in SmPC section 4.8 to highlight the role

of precursor accumulation and testosterone increases in these events. The increased testosterone levels seem to be furthermore reversible in the female patients that entered a placebo period.

Effects on DHEAS, FSH and LH are noted but toward normalisation due to cortisol level normalisation.

As cortisol levels increase during a normal pregnancy, disruption of the cortisol synthesis is expected to have important impact on the mother and foetus. The actions to be taken in order to avoid exposure in pregnancy is further discussed in the safety and RMP sections of this report.–

The information regarding the exposure-QTc relation should be based on the TQT study (C2105). There was limited amount of QTc information collected in study C2301 and it is not considered reliable for exposure-response modelling.

The thorough QT-study was adequately conducted. The data show that osilodrostat has a clinically significant effect on QT-prolongation. Although limiting the maximum dose to 30 mg would reduce the risk of QT-prolongation in susceptible individuals, this would not eliminate the risk taking the variety of exposure into account. The predicted exposure (Cmax) given doses from 2 to 30 mg, range (min, max) from 1.6 to 495 ng/mL.

The risk of QT-prolongation is reflected in the SmPC. See also the safety section of this report.

The potential impact of PD interactions between medication known to prolong the QT interval and osilodrostat is added in the SmPC section 4.5.

2.4.5. Conclusions on clinical pharmacology

Overall the PK of osilodrostat have been described but data are missing following repeated dosing on major metabolites. The data on osilodrostat as a potential perpetrator with respect to drug-drug-interactions are very limited.

The mechanism of action and the primary pharmacology for osilodrostat have been adequately described and the primary pharmacology data are further supported by the clinical data. The secondary pharmacology and its implications for safety is adequately reflected in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

No formal dose response study was conducted. Modelling of PK exposure estimated that a dose of 4 to 5 mg bid is expected to achieve a plasma concentration above the in vitro IC50 for CYP11B1 inhibition (2.5 nM) for a full 24 hours for efficacy consideration. However, in Study C2201, a starting dose of 2 mg bid followed by individual dose titration was chosen based on mUFC response, tolerability and safety considerations, i.e., to reduce the risks associated with potential hypocortisolism-related AEs. This starting dose was also supported by the observations in the initial studies with normo-cortisolaemic subjects, where a notable reduction of ACTH-stimulated cortisol secretion was seen already at 2 mg/day (given as either 2 mg qd or 1 mg bid).

The rationale for bid dosing of osilodrostat is based on its half-life of 3 to 5 hours. The 10-week analysis of Study C2201 showed that the dose of osilodrostat required for normalization of mUFC ranged from 2 mg bid to 50 mg bid after individual dose titration, with nearly all patients (11/12) achieving mUFC normalization at >2 mg bid. Trough concentrations at mUFC normalization also varied widely, ranging from 0.336 to 204 ng/mL. This

indicated that there was a broad range (up to 25-fold in osilodrostat dose) of inter-patient sensitivity to osilodrostat with respect to normalization of mUFC, and there was no apparent relation between the therapeutic dose or exposure (trough concentrations) needed for UFC normalization and the baseline mUFC. Thus, individual dose titration was required due to high inter-patient variability in effective dose and the potential for resulting AEs in sensitive patients (potential risk of hypocortisolism or acute adrenal insufficiency). Based on the available data, an individual dose titration starting at 2 mg bid was an appropriate method to assess the efficacy and safety of osilodrostat. The original titration plan was to escalate to a maximum of 50 mg bid in Study C2201. An exploratory post-hoc analysis of QTcF in relation to osilodrostat dose from an earlier Phase-I study (Study A2101) found substantial QTcF changes (some patients with QTcF prolongation >30ms) at single doses of 100 and 200 mg. As a precaution, the maxim dose was lowered from 50 mg bid dose to 30 mg bid.

In Study C2301, the osilodrostat dosing regimen was up-titrated following a 2 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid escalation sequence with the maximum dose of osilodrostat being 30 mg bid. The individual dose titration was required for the same reasons of high inter-patient variability seen in Study C2201. Dose increases were determined by the mean UFC based on three 24-hour UFC values collected every two weeks during the dose-titration period. The uptitration scheme was also governed by the desire to apply a limited number of uniform dose escalation steps in the confirmatory clinical trial setting while still allowing all patients the possibility to reach the 30 mg maximum dose if needed as well as the goal to achieve UFC control in all patients by week 12 while still allowing uptitration to be based on central laboratory UFC values.

Main study

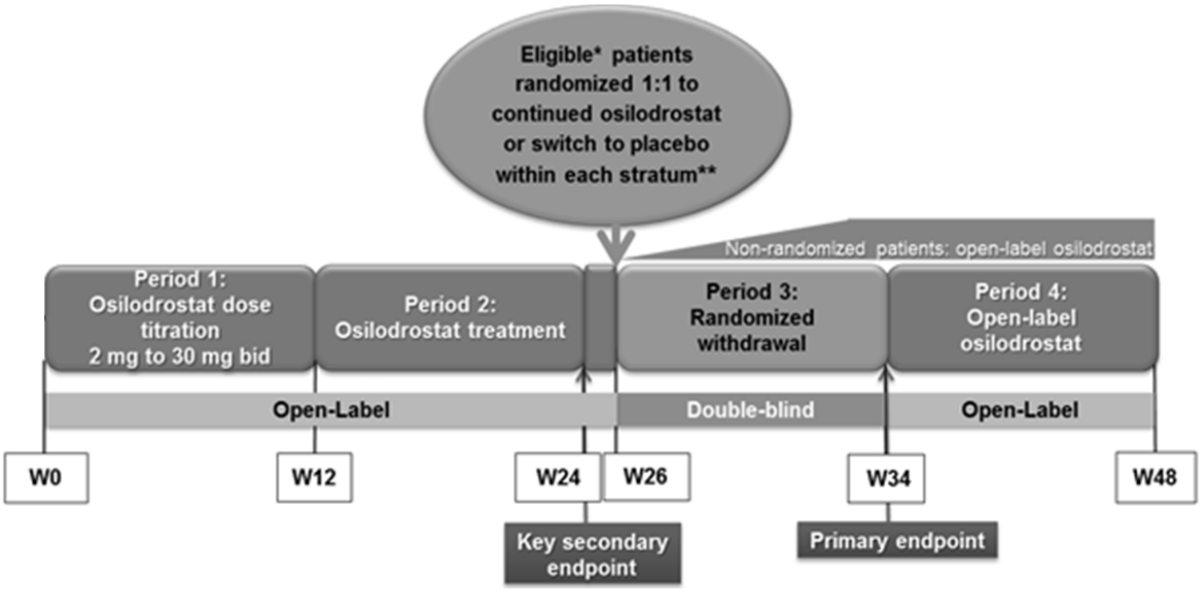
C2301 – A Phase III, multi-center, double-blind, randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease

Methods

Study C2301 is a Phase III, multi-centre, double-blind, RW study of osilodrostat following a 24-week, single-arm, open-label dose titration and treatment period to evaluate the efficacy and safety of osilodrostat for the treatment of patients with CD.

The study schematic is displayed in Figure 11.

Figure 8 Schematic of core study design



Descriptions of the study periods:

Period 1 (Week 1 to Week 12) (dose-titration period): Patients were assessed for mUFC during the first two weeks of the dose-titration period and the dose of osilodrostat was adjusted accordingly. The dose was increased if mUFC was above the >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.

Period 2 (Week 13 to Week 24) (dose-titration and treatment period): During this period, the efficacy and safety of osilodrostat were assessed at the therapeutic dose as determined for attaining mUFC ≤ULN during the dose-titration period in Period 1. Patients with mUFC>ULN had their osilodrostat dose increased as tolerated and the maximum dose of 30 mg bid had not yet been reached. These patients were followed for long-term efficacy and were not considered responders for the key secondary endpoint, hence were not randomized in Study Period 3.

Period 3 (Week 26 to Week 34) (RW period): Patients were eligible for randomisation (either to continue with osilodrostat or to switch to placebo) if they had completed the dose titration during study Period 1, and were classified as complete responders at Week 24 with no dose increase between Week 13 and Week 24. Randomisation was implemented at the Week 26 visit. Patients not eligible for randomisation received open-label osilodrostat until the end of the Core Period (Week 48), unless there was a reason to discontinue from the study prematurely.

Period 4 (Week 34 to Week 48): At the end of Week 34, all patients received open-label osilodrostat treatment at a dose selected at the discretion of the Investigator. Dosing could also be adjusted based on the mUFC levels during this treatment period.

Open extension period: Patients who continued to receive clinical benefit, as assessed by the study Investigator and who wished to enter the extension period, had to be re-consented at Week 48. Patients who entered the extension period did so without interruption of study drug or scheduled assessments. The optional extension period will end after all patients have completed Week 72 or discontinued prior to Week 72.

Study Participants

Key inclusion criteria

Male or female patients 18 to 75 years old with confirmed persistent or recurrent CD as evidenced by mUFC >1.5×ULN at screening, morning plasma ACTH above the LLN and confirmed pituitary source of excess ACTH were included.

Patients with de novo CD were included only if they were not considered candidates for surgery (e.g. poor surgical candidates, surgically unapproachable tumours, patients who refuse to have surgical treatment, or surgical treatment was not available). Patients with a history of pituitary irradiation were included, provided that at least 2 years (for stereotactic radiosurgery) or 3 years (for conventional radiation) had elapsed from the time of last radiation treatment to the time of enrolment into this study. Patients were permitted to washout current drug therapy to meet these entry criteria if they had known diagnosis of CD. Rescreening was used as needed to ensure washout was complete.

Key exclusion criteria

Patients with compression of the optic chiasm due to a macroadenoma or patients at high risk of compression of the optic chiasm were excluded.

Patients who had a known inherited syndrome as the cause for hormone over secretion and patients with CS due to ectopic ACTH secretion or ACTH-independent (adrenal) CS were excluded.

Patients with risk factors for QTc prolongation or Torsade de Pointes were excluded.

In addition, hypertensive patients with uncontrolled blood pressure, diabetic patients with poorly controlled diabetes and patients who were not euthyroid were to be excluded.

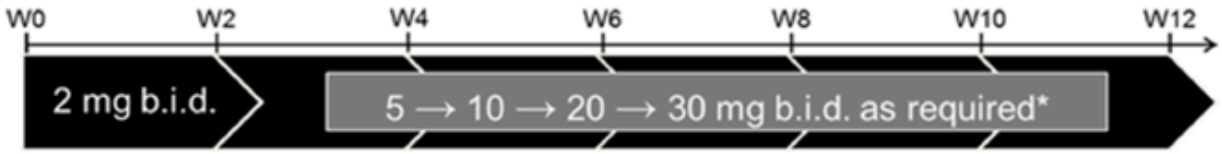
Patients with a history of significant CV disease, moderate to severe renal impairment or significant liver disease were also excluded.

Treatments

Study Period 1, 2 and 4, as well as the Extension Period were single treatment group designs using open-label osilodrostat.

The osilodrostat dosing regimen was up-titrated following a 2 mg bid, 5 mg bid, 10 mg bid, 20 mg bid, and 30 mg bid escalation sequence. If hypocortisolism occurs at 2 mg bid, the dose can be lowered to 1 mg bid or lower, e.g., 1 mg once daily or 1mg every other day, if needed. The up-titration continued until the mUFC ≤ ULN.

Figure 9 Schematic of study Period 1



* If needed, the dose was down-titrated to 1 mg bid.

Once the patient's mUFC was controlled (mUFC ≤ ULN) during the dose titration period, intermediate doses (i.e., 3 mg bid, 7 mg bid and 15 mg bid) could be given.

The maximum dose of osilodrostat in this study was 30 mg bid.

In study Period 3, 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 receive matching placebo.

Dose adjustments during RW

The dose of study drug (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 temporally withhold a dose of study drug for safety reasons at any time during the study, including 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.

Discontinuation from RW

During study Period 3, a patient was discontinued from the RW Period and declared a non-responder, if the mUFC increased to >1.5×ULN, and at least 2 individual urine samples showed UFC >1.5×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.

Patients who discontinued from the study during the RW Period were no longer in the study, and consequently they were not permitted to receive open-label osilodrostat and could not move to study Period 4.

Objectives

Primary objective

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

Key secondary objective

To assess the complete response rate at the end of individual dose-titration and treatment with osilodrostat in the initial single-arm, open label period (Week 24).

Outcomes/endpoints

Table 5 Description of efficacy assessments and endpoints - Study C2301

Efficacy assessments and endpoints	Study C2301
Primary efficacy assessments	
24-hour UFC	Mean of three 24-hour UFC (mUFC) values; triplicate urine samples[1]
Assay for UFC (ULN)	LC-MS/MS[1]
UFC normal ranges	ULN=138 nmol/24hr; LLN=11 nmol/24hr[1]
Other assessments	
Photography	Baseline, treatment/extension periods, EOT in extension[2]
DXA scan of lumbar spine and total hip	Baseline, EOT for core/extension periods
Cushing QoL Beck Depression Inventory-II EQ-5D-5L	Completed prior to any clinical assessments or diagnostic testing
Serum cortisol	Dose-escalation period, randomized withdrawal period and open-label periods

Efficacy assessments and endpoints	Study C2301
	for randomized and non-randomized patients
Endpoints: Responders	**Responders** • Primary efficacy variable: based on the mean of three 24-hour (mUFC) collections, mUFC ≤ ULN at Week 34 (end of the 8-week RW period) and neither discontinued nor had osilodrostat dose increase above the level Week 26 during the randomized withdrawal period • Key secondary efficacy variable: based on mUFC ≤ ULN at Week 24 and had no dose up-titration between Week 12 and Week 24. **Partial responder:** Patient had mUFC ≤ ULN reduced by ≥ 50% from baseline

[1] Also apply to the key secondary endpoint
[2] Two photographs, one frontal and one lateral from the shoulders up will be taken to assess facial plethora (rubor), supraclavicular and dorsal fat pads. Two photographs, frontal and dorsal of the trunk with patient in standing position will be taken to assess hirsutism (females only), striae, proximal muscle wasting (atrophy), central (abdominal) obesity, and ecchymoses (bruising)
EOT=End of treatment; LC-MS/MS=liquid chromatography - tandem mass spectrometry assay; LLN-Lower limit of normal; mUFC=Mean urinary-free cortisol; QoL=Quality of life; ULN=Upper limit of normal; RW=Randomized withdrawal

Randomisation and blinding

The study 2301 had a randomised withdrawal design.

In order to be eligible for randomisation, patients must have completed dose titration during the first 12 weeks, continued on LCI699 treatment with no further dose increase during Weeks 13-24, and have normal UFC (mUFC ≤ ULN) from urine samples collected at Week 24. Randomisation was implemented at the Week 26 visit. Patients that were not eligible for randomisation were followed on open-label LCI699 until the end of the core treatment (Week 48), unless there was a reason to discontinue from the study prematurely.

Eligible patients were randomised in a double-blinded fashion at Week 26 at a 1:1 ratio either to continue treatment with LCI699 at the same dose or to matching placebo. Patients were stratified at randomisation according to: LCI699 dose at Week 24 (≤ 5mg bid. vs. > 5 mg bid.), and history of pituitary irradiation (yes/no).

Patients, Investigator, and persons performing the assessments (with the exception of drug supply management personnel) remained blinded to the identity of the treatment from the time of randomization (Week 26) until database lock.

The Applicant's Drug Supply Management department members were not blinded to the identity of the treatment in order to prepare the study drug supplies. Unblinding was only permitted in the case of patient emergencies

Statistical methods

Analysis populations: The following analysis populations were defined

Randomised analysis set (RAS): comprised all randomised patients who had received at least one dose of randomised drug (osilodrostat or placebo). Following the intent-to-treat principle, patients were analysed according to the treatment and stratum they have been assigned to during the randomisation.

Full analysis set (FAS): comprises all enrolled patients who received at least one dose of osilodrostat.

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

a. Safety analysis set (SAS) comprises all enrolled patients who received at least one dose of osilodrostat and had at least one valid post-baseline safety assessment.

b. Safety Analysis Set for randomized withdrawal period (SASR) comprises 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.

Per-Protocol set: There were two per-protocol sets defined in this study.

a. Per-Protocol Set for RAS (PPRAS) consists of a subset of the patients in the RAS who had no selected clinical study report (CSR)-reportable protocol deviation.

b. Per-Protocol Set for FAS of a subset of the patients in the FAS who had no selected CSR-reportable protocol deviation.

Pharmacokinetic analysis set (PAS): consists of all enrolled patients who receive at least one dose of osilodrostat and have at least one evaluable post-dosing pharmacokinetics assessment.

Analysis of the primary endpoint: The primary efficacy variable was the proportion of randomized patients in each treatment arm that are complete responders at the end of the 8 weeks of the randomized withdrawal period (Week 34). A Cochran–Mantel–Haenszel exact test stratified by the two stratification factors at randomization was performed using the Randomized Analysis Set (RAS) following the intent-to-treat principle. The test was performed at a 2-sided alpha of 0.05. Patients who discontinued during the randomized withdrawal period will be counted as non-responders for the primary endpoint. Patients with mean UFC > 1.5 x ULN (with at least 2 of the 3 individual UFC levels > 1.5 x ULN) during the randomized withdrawal period were to be discontinued from randomized withdrawal and changed to open-label treatment with LCI699. The applicant was asked to provide more information on patients that fulfilled these criteria, and clarified that two patients (one was withdrawn and one was not) randomised to osilodrostat and 21 patients (10 were withdrawn (including patient 200500013 who withdrew from the study) and 11 were not) randomised to placebo met the criteria.

Key secondary endpoint: The key secondary efficacy variable was the proportion of complete responders at the end of 24 weeks of dose-titration and treatment with LCI699 in the initial single-arm, open label part of the trial, using the Full analysis set (FAS). The analysis of the key secondary objective was based on the 2-sided 95% exact confidence interval (Clopper-Pearson method), which was compared with the limit 30%, in order to be able to state that the complete response rate is considered at least 30% after 24 weeks of treatment with LCI699. This endpoint was tested sequentially after the primary endpoint, in order to preserve of the overall 2-sided type 1 error at 5%.

Subgroups: Predefined subgroups for this study were the two stratification factors for randomization: history of pituitary irradiation, and LCI699 dose at Week24:

- History of pituitary irradiation: Yes and No
- LCI699 dose at Week24: ≤ 5mg b.i.d. and > 5mg b.i.d.

Missing data: The mean of the results from the 3 samples was used to obtain the corresponding mUFC level for a given assessment. If a patient had two or more missing UFC values for a particular visit, the mUFC assessment for that patient at that visit was considered missing. Otherwise, the mean of UFC collections was considered as the mUFC level for that visit.

Randomized patients who discontinued during the RW Period or had a missing mUFC assessment at end of the RW Period (Week 34) were counted as non-responders for the primary endpoint.

Supportive and sensitivity analyses: An un-stratified Fisher's exact test of the primary endpoint using RAS was performed as a supportive analysis to the primary analysis. In addition, both stratified CMH exact test and un-stratified Fisher's exact test of the primary endpoint were performed using PPRAS. The key secondary endpoint was also analysed using PPFAS.

Interim analyses: The current study report is based on interim data, with long term safety follow up still ongoing. The study had no interim analysis for purpose of adaptation of the study.

Results

Participant flow

This study was conducted in 66 centers across 19 countries. A total of 202 patients were screened for the study, of which 137 were enrolled and 65 patients were screening failures. Nineteen patients discontinued at or prior to Week 26. Of the remaining 118 patients, 71 patients were randomized (36 to osilodrostat and 35 to placebo) and 47 patients who were not randomized continued on open-label osilodrostat treatment (Figure 13, Table 14).

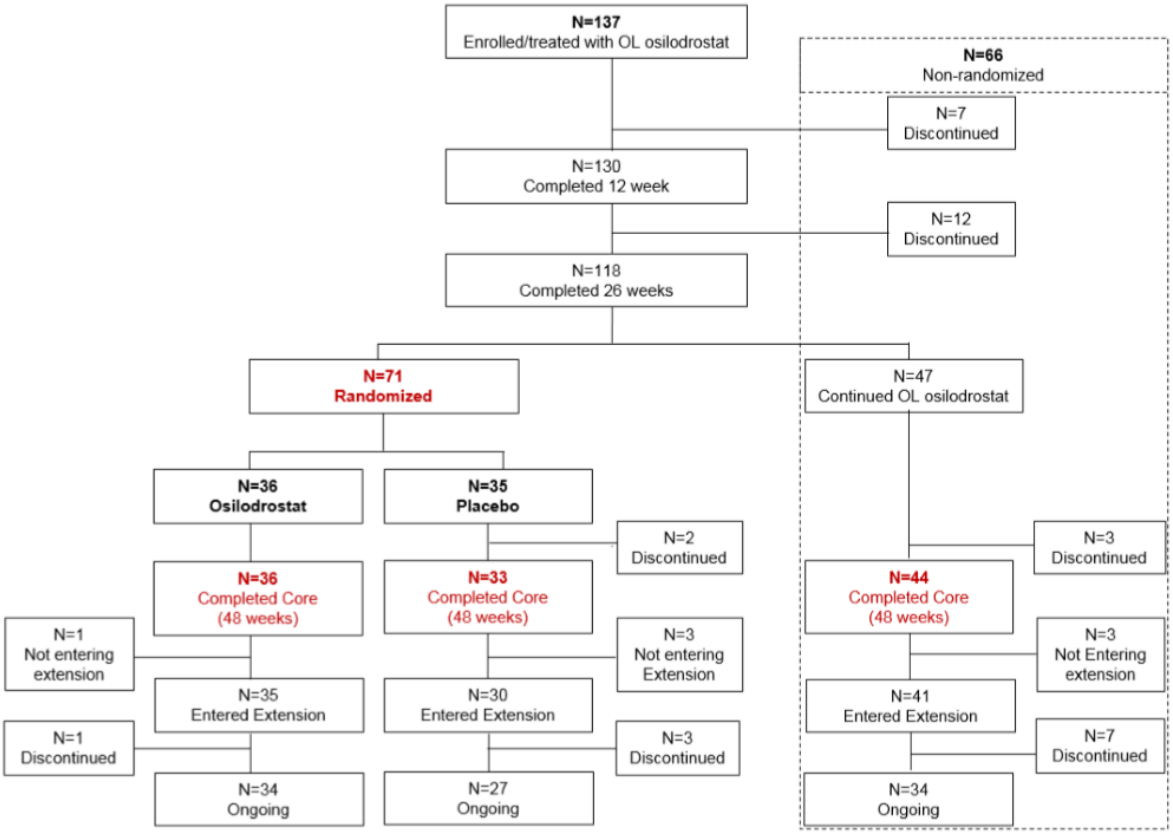
Patients were not randomized for the following reasons:

- 19 patients had their dose increased beyond the established one at Week 12 (i.e., the end of the dose titration period) although they met the mUFC normalization criteria,
- 20 patients did not meet the mUFC normalization criteria at Week 26,
- 7 patients did not meet both of the previous criteria and
- 1 patient was not randomized due to Investigator decision.

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. Of note, only one patient, who was 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 (10.9%, 15/137), followed by patient withdrew consent (2.9%, 4/137), and physician's decision (2.2%, 3/137) (Table 14). A total of 106 patients (77.4%) entered the optional extension, of which 95 (69.3%) patients were still on treatment at the time of the data cut off date.

Figure 10 Patient disposition by randomized treatment group (FAS)



FAS: full analysis set; OL: open-label

Table 6 Patient disposition by randomized treatment group (FAS)

Disposition Reason	Randomized to osilodrostat during RW N=36 n (%)	Randomized to placebo during RW* N=35 n (%)	Non-randomized N=66 n (%)	All Patients 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.
The description of treatment groups is provided in Section 9.7.2.
Source: Table 14.1-1.1

Baseline data

The demographic and baseline disease characteristics were representative of a patient population with CD. The disease history and other baseline characteristics were generally well balanced in the patients who were later randomized to osilodrostat or placebo treatment groups during the RW Period (Table 15).

Table 7 Demographics summary by randomized treatment group (FAS) - Study C2301

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/m^2)				
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

FAS: full analysis set; RW: randomized withdrawal; SD: standard deviation.

Disease history characteristics

The median time to the first osilodrostat dose since initial CD diagnosis was 47.2 months (range: 2.1-286.7) and most patients (87.6%) had persistent/recurrent CD.

Overall, 95.6% had received treatment for CD prior to study entry, and 87.6% of patients had previously undergone surgery. Forty-five patients (32.85%) had at least two previous neurosurgeries and 9 patients (6.57%) had at least three previous neurosurgeries. A large proportion of patients (74.5%) had been treated with other medication for CD prior to study entry (such as ketoconazole, metyrapone, cabergoline and pasireotide.

The mean (standard deviation (SD)) mUFC at baseline was 1006.0 nmol/24h (1589.86); this corresponds to approximately 7×ULN. The median mUFC at baseline was 476.4 nmol/24h (range: 35.6 to 9611.6); this corresponds to approximately 3.5×ULN.

Relevant medical history and current medical conditions

All patients (N=137) reported at least one relevant medical history/current medical condition. Overall, the most common conditions were: hypertension (93/137, 67.9%), obesity (41/137, 29.9%), osteoporosis (38/137, 27.7%), diabetes mellitus (30/137, 21.9%), depression (27/137, 19.7%) and hypothyroidism (25/137, 18.2%).

Relevant medical histories and current medical conditions were similar in the patients who were later randomized to osilodrostat or placebo treatment groups during the RW Period.

Numbers analysed

Table 8 Analysis patient sets by stratum and randomized treatment group (all randomized patients)

Analysis Set	Randomized to osilodrostat during RW N=36 n (%)	Randomized to placebo during RW N=35 n (%)	All Randomized Patients N=71 n (%)	Non-Randomized Patients N=66 n (%)	All Patients N=137 n (%)
Randomized analysis set (RAS)	36 (100.0)	34 (97.1) [1]	70 (98.6)		
osilodrostat dose at Week 24 ≤ 5 mg bid and with history of pituitary irradiation	5 (13.9)	5 (14.3)	10 (14.1)		
osilodrostat dose at Week 24 ≤ 5 mg bid and without history of pituitary irradiation	21 (58.3)	21 (60.0)	42 (59.2)		
osilodrostat dose at Week 24 >5 mg bid and with history of pituitary irradiation	0	0	0		
osilodrostat dose at Week 24 >5 mg bid and without history of pituitary irradiation	10 (27.8)	8 (22.9)	18 (25.4)		
Full analysis set (FAS)	36 (100.0)	35 (100.0)	71 (100.0)	66 (100.0)	137 (100.0)
Safety analysis set	36 (100.0)	35 (100.0)	71 (100.0)	66 (100.0)	137 (100.0)
Safety analysis set for RW Period	36 (100.0)	34 (97.1)	70 (98.6)		
Per-protocol set for RAS	35 (97.2)	33 (94.3)	68 (95.8)		
Per-protocol set for FAS	36 (100.0)	35 (100.0)	71 (100.0)	64 (97.0)	135 (98.5)
Pharmacokinetic analysis set	36 (100.0)	35 (100.0)	71 (100.0)	66 (100.0)	137 (100.0)

RW: randomized withdrawal.
[1] Patient C2301-200500013, who was randomized to placebo, never received treatment and withdrew from study during the RW Period on Day 220.
The definition of each analysis set is provided in Section 9.7.2.
Randomized strata are based on assignment from interactive voice response.

Outcomes and estimation

Primary efficacy results – Week 34 complete response rate - Study C2301

The primary efficacy endpoint was met. The null hypothesis that the complete response rates at the end of 8-week RW Period (i.e. at Week 34) were the same between the two randomized groups was rejected.

Osilodrostat was superior to placebo at Week 34, the end of the RW period, in maintaining biochemical control (mUFC to ≤ ULN) in patients with CD showing statistical significance (Cochran-Mantel-Haenszel [CMH] exact test 2-sided p<0.001) (Table 17). The complete response rate in the osilodrostat arm was higher at 86.1% (95% CI: 70.5, 95.3) than that in the placebo arm at 29.4% (95% CI: 15.1, 47.5) (odds ratio of osilodrostat vs. placebo = 13.7; 95% CI: 3.7, 53.4). Ten patients in the placebo arm (29.4%) did not lose mUFC control at the

end of the RW Period. In 9/10 patients, mUFC increased at the end of Week 34 close to the ULN. This finding was expected considering the individual response in mUFC. This is also consistent with the observation in Study C2201 where mean mUFC returned to baseline after 2 weeks following discontinuation of osilodrostat, although some patients maintained UFC<ULN for a longer period of time.

Table 9 Proportion of primary efficacy responder at Week 34 (end of randomized withdrawal) by randomized treatment and strata – Study C2301 (RAS)

			CMH exact test	
	Responder N (%)	95% CI[1]	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

[1] 2-sided 95% CIs are based on the exact (Clopper-Pearson) method.
A primary efficacy responder is defined as a randomized patient who has mUFC ≤ ULN at Week 34 and who was neither discontinued (study or randomized withdrawal treatment) nor had osilodrostat dose increase above the level at Week 26 during the randomized withdrawal period of the study. Patients who discontinued during the randomized withdrawal period were counted as non-responders for primary efficacy.
CI: confidence interval; CMH: Cochran-Mantel-Haenszel; RAS: randomized analysis set.

Supportive analysis for the primary endpoint

The robustness of the primary analysis was confirmed by the predefined supportive analyses, one based on the Randomized analysis set (RAS) and one based on the Per-protocol RAS (PPRAS), further supporting the efficacy of osilodrostat in controlling the notably high mUFC values in patients with CD.

Key secondary results – Week 24 complete response rate - Study C2301

The study also met its key secondary objective. At Week 24, 72 patients (52.6%) were responders in the FAS (95% 2-sided CI: 43.9, 61.1). The lower bound of the 95% CI was above the pre-specified threshold for significant clinical benefit (i.e., ≥ 30%). However, the number of controlled patients at Week 24 was 93/137 (67.9%). Hence an additional 21 patients had normal mUFC at Week 24 but they were not considered eligible for randomization.

Secondary efficacy results – Study C2301

Proportion of mUFC responders over time

The proportion of patients with mUFC ≤ ULN responding to treatment with osilodrostat remained consistent over time for 'All patients', patients without prior surgery and patients in the non-randomized arm (Table 18).

Table 10 Proportion of mUFC responders over time

	Week 12	Week 24	Week 48
All patients	**% (n/N) (95% CI)**	**% (n/N) (95% CI)**	**% (n/N) (95% CI)**
Overall responders	85.4 (117/137) (78.36, 90.85)	82.5 (113/137) (75.06, 88.44)	75.9 (104/137) (67.87, 82.80)
- Complete responders	71.5 (98/137)	67.9 (93/137)	66.4 (91/137)

	Week 12	Week 24	Week 48
All patients	**% (n/N) (95% CI)**	**% (n/N) (95% CI)**	**% (n/N) (95% CI)**
	(63.20, 78.91)	(59.37, 75.60)	(57.86, 74.26)
- Partial responders	13.9 (19/137) (8.56, 20.81)	14.6 (20/137) (9.15, 21.64)	9.5 (13/137) (5.15, 15.68)
Patients with no prior surgery	**% (n/N)**	**% (n/N)**	**% (n/N)**
Overall responders	100 (17/17)	88.2 (15/17)	76.5 (13/17)
- Complete responders	70.5 (12/17)	76.5 (13/17)	70.5 (12/17)
- Partial responders	29.4 (5/17)	11.8 (2/17)	5.9 (1/17)
Non-randomised patients	**% (n/N) (95% CI)**	**% (n/N) (95% CI)**	**% (n/N) (95% CI)**
Overall responders	N/A	65.2 (43/66) (52.42, 76.47)	59.1 (39/66) (46.29, 71.05)
- Complete responders	N/A	34.8 (23/66) (23.53, 47.58)	48.5 (32/66) (35.99, 61.12)
- Partial responders	N/A	30.3 (20/66) (19.59, 42.85)	10.6 (7/66) (4.37, 20.64)

Up to the time of the last available assessment, response rates were consistent with those for 'All patients' at Week 12. An overall response rate of 88.3% (95% CI: 81.73, 93.18) with 71.5% (98/137) (95% CI: 63.20, 78.91) being complete responders and 16.8% (23/137) being partial responders (95% CI: 10.95, 24.12).

The durability of response rate was evident with 64 patients (66.0%) in the FAS who had initial normalization of mUFC were still considered to be responders after at least 6 months (95%: 55.7, 75.3).

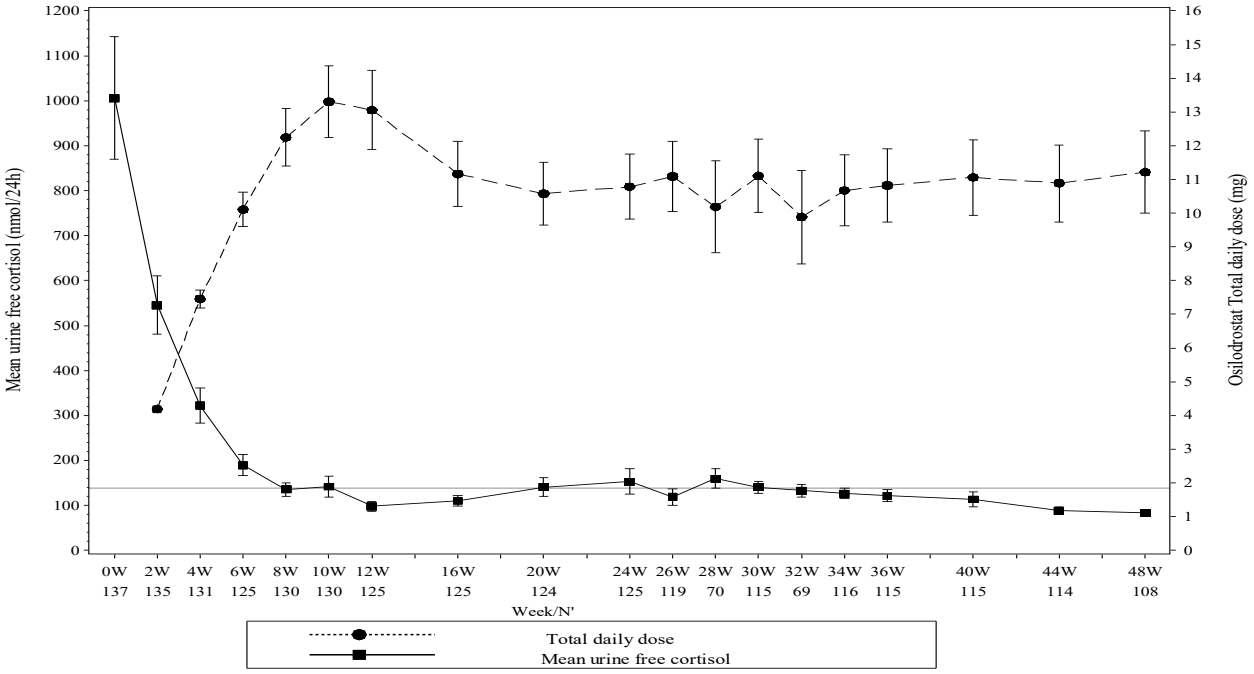
Change in mUFC from baseline during the study

In Study C2301, mUFC levels (≤ ULN) were maintained without any consistent dose increase as evidenced by the total daily dose of osilodrostat with the range of doses consistent between 10 mg/day to 12 mg/day (Figure 14).

During treatment with osilodrostat, the mean mUFC levels decreased from high baseline values stabilizing to a normal level (mUFC ≤ UFC) around Week 6 in most patients at an average total daily dose of 8.6 mg/day (Figure 14). After Week 6, normal mUFC (≤ ULN) levels were observed in most patients with the exception of non-randomized patients at Week 20 to Week 24 and patients randomized to placebo at Week 28 to Week 34 (Figure 14). Normalized mUFC (≤ ULN) levels were maintained at Week 24 at an average total daily dose of 10.7 mg/day and at Week 48 at 11.0 mg/day.

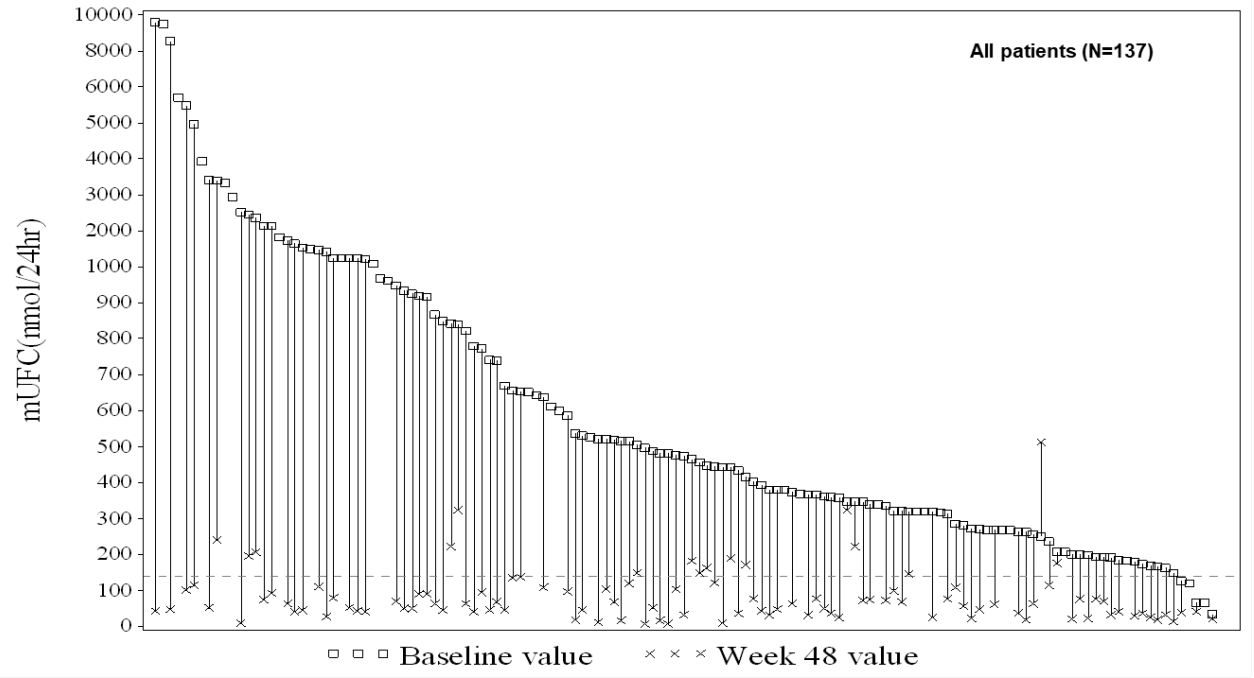
Individual patient mUFC values at baseline and Week 48 in Study C2301 are graphically depicted in Figure 15.

Figure 11 Mean (+/-SE) mUFC (nmol/24h) and osilodrostat total daily dose (mg) (+/-SE) during the core period for all patients – Study C2301 (FAS)



The horizontal line at 138 nmol/24h is the ULN for the mUFC.
This analysis includes scheduled visits only. ± standard error is displayed.
N' is the number of patients with as mUFC assessment at that visit.

Figure 12 Individual patient mUFC values at baseline and Week 48 – Study C2301 (FAS)



Sorting is by baseline mUFC value.
The horizontal reference line is the upper limit of normal range = 138 nmol/24hr.

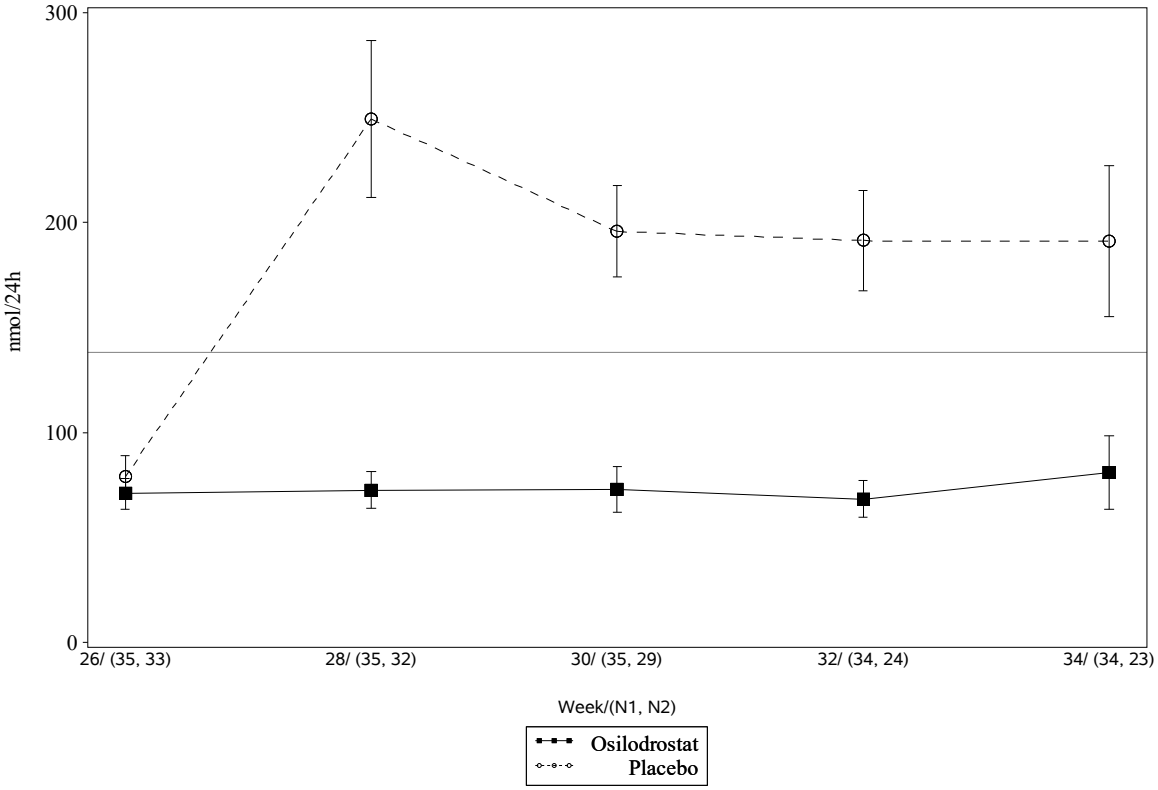
A repeated measures analysis of mUFC shows a consistent biochemical effect of osilodrostat during the study. At Week 2, there was approximately a 42% reduction in the adjusted mean mUFC value from baseline. After the dose-titration period (Week 12), there was approximately an 85% reduction that was maintained until the end of the Core Period (89%).

Change in mUFC from randomization during the RW Period

At randomization (Week 26), mean (SD) mUFC levels were similar in the osilodrostat arm (70.9 nmol/24h, SD=43.53) and placebo arm (79.1 nmol/24h (57.90). Once patients stopped treatment with osilodrostat at Week 26 and were randomized to receive placebo, mUFC levels increased rapidly (Figure 16). Only data while the patients were on RW medication are included. At the end the RW period and when patients resumed treatment with osilodrostat, mUFC levels decreased quickly.

At the end of the 8-week RW Period (Week 34), the median mUFC levels were lower in the osilodrostat arm (50.1 nmol/24h; range: 11.9 to 610.8) compared with the placebo arm (139.7 nmol/24h; range: 29.8 to 849.5). This corresponded to a median percent change from randomization of -13.9% (-70.1 to 1019.9) in the osilodrostat arm and 174.6% (-58.1 to 2588.8) in the placebo arm.

Figure 13 Mean (+/-SE) mUFC (nmol/24h) during the randomized withdrawal period – Study C2301 (RAS)



The horizontal line at 138 nmol/24h is the ULN for the mUFC.
This analysis includes scheduled visits during the randomized withdrawal period only.
± standard error is displayed.
(N1, N2) presents the number of patients on osilodrostat
and placebo respectively with a mUFC assessment at that visit. Only data while on randomized withdrawal treatment are included.

The repeated measures analysis of change in mUFC shows a consistent biochemical effect of osilodrostat over placebo during the RW Period. In the osilodrostat arm there was approximately a 10% reduction from the mean mUFC at randomization baseline during the RW period. However, in the placebo arm, there was up to a 200% increase in the mean mUFC from randomization during the same period.

Time to first-controlled mUFC response

During the course of the study, 132 patients of 137 (96.4%) achieved biochemical control (mUFC ≤ ULN) at least once while on study treatment. The median time from the start of treatment with osilodrostat to the first-controlled mUFC response was 41 days (95% CI: 30.0, 42.0) for all patients with similar first-control in patients in the osilodrostat arm (41.0 days, 95% CI: 28.0, 47.0) and in the non-randomized arm (42.0 days, 95% CI: 37.0, 55.0).

Time to loss of control during the randomized withdrawal period

During the RW period, two (5.6%) patients of 36 in the osilodrostat arm had a loss of mUFC control (of the two patients, one patient required a dose interruption due to AEs) compared with 20 patients (58.8%) of 34 in the placebo arm. The median time to loss of control of mUFC was not estimable (NE) in the osilodrostat arm and was 28 days in the placebo arm.

There was a 94% lower risk of losing mUFC control in the osilodrostat group compared with the placebo group (HR=0.06; 95% CI: 0.01, 0.28) during the RW period.

Protocol-defined 'time to escape'

In Study C2301, the protocol definition of 'escape' is as follows: Escape is defined as the first loss of control of UFC after at least one instance of UFC normalization that meets all of the following criteria: prior normalization of UFC had occurred (mUFC≤ ULN); both the mUFC and at least two individual values contributing to that mUFC had to be >1.5×ULN; and the loss of control of UFC had not been related to a dose interruption or dose reduction due to safety reasons; happens beyond 12-week dose titration period (Study Period 1).

When considering 'escape' according to the protocol, it is in contrast with the following:

- The mean mUFC overtime in the 'All patient' group remains <ULN for most of the time during the study without a need for dose increase as seen in Figure 14.
- The proportion of complete responders remains high over time up to 48 weeks, too, as seen in Table 18. The durability of response rate was evident with 64 patients (66.0%) in the FAS were still considered to be responders after at least 6 months (95%: 55.7, 75.3) from the initial normalization of mUFC.
- Many of the patients who had an escape event regained mUFC control with or without a osilodrostat dose increase.

With a rather conservative protocol definition of 'escape,' the median (KM method) time to 'escape' was 560 days (95% CI: 212.0-NE); a median follow-up of 253 days was observed in patients treated with osilodrostat.

Other efficacy results

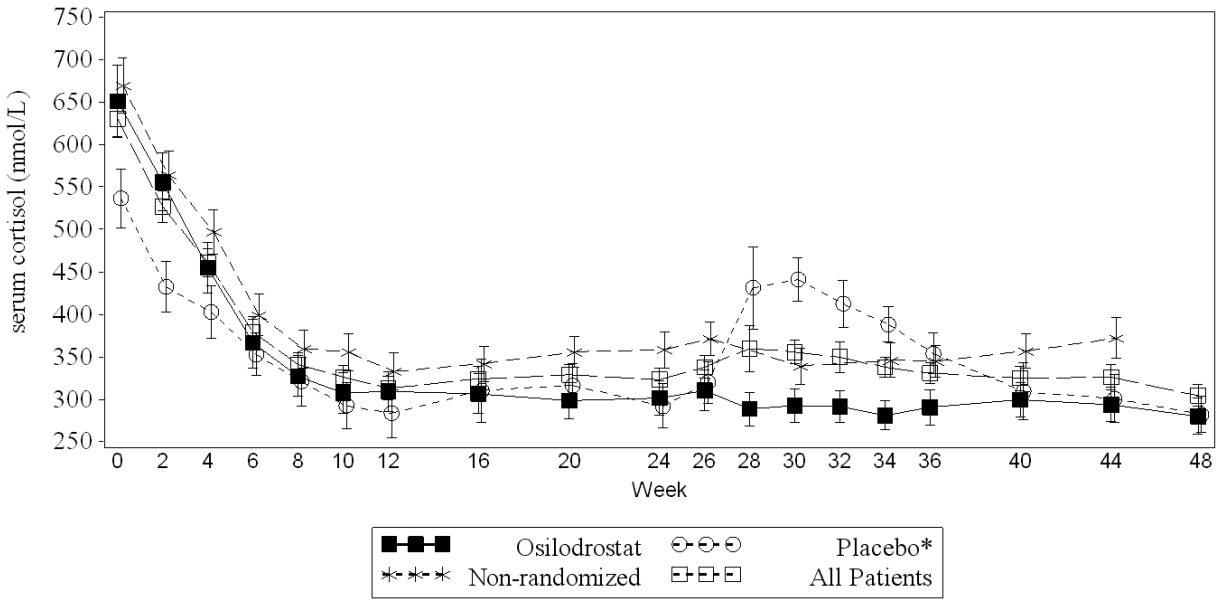
As per the protocol and SAP, no imputation for missing data was specified and hence change from baseline was calculated based on observed case data.

Serum cortisol levels

Individual dose-titration over 12 weeks achieved control of serum cortisol levels. Compared to baseline, patients had a sustained reduction in mean serum cortisol levels during the dose-titration period of the study (up to Week 12) (Figure 17). During study Period 2 (Week 13 to Week 24) the decrease in mean serum cortisol levels was maintained with mean cortisol levels being within the normal range in the 'All patients' grouping. During the RW Period, as was expected, an increase in mean cortisol levels was observed in patients taking placebo when compared with those taking osilodrostat. In these patients, the mean cortisol levels decreased upon resuming osilodrostat. At the end of the Core Period (Week 48), the mean serum cortisol levels were within the normal range in the 'All patients' grouping.

For 'All patients' (N=134), mean (SD) serum cortisol levels were high (630.2 (248.87) nmol/L) at baseline decreasing to 313.4 (157.46) nmol/L at Week 12, 323.3 (146.79) nmol/L at Week 24, and 304.2 (134.43) nmol/L at Week 48. At Week 48, the mean (SD) percentage change from baseline in serum cortisol levels was -44.9% (29.31).

Figure 14 Mean (SE) serum cortisol at time points up to Week 48 by treatment group – Study C2301 (FAS)



* For patients randomized to placebo during the Randomized withdrawal (RW) Period and including all data while in either osilodrostat or placebo.
Includes scheduled visits only. RW Period starts at Week 26 and ends up to Week 34.
FAS: full analysis set; SE: standard error.

Cardiovascular-related metabolic parameters

Treatment with osilodrostat led to an overall improvement in key cardiovascular-related metabolic parameters associated with hypercortisolism at Week 48 (Table 19). The repeated measures analysis of change from baseline in cardiovascular- and metabolic-related parameters associated with endogenous hypercortisolism shows a consistent and cumulative improvement throughout the study with osilodrostat in all parameters.

Table 11 Mean (SD) percentage change from baseline in cardiovascular-related metabolic parameters associated with Cushing's disease at selected visits during the Core Period -Study C2301 (FAS)

			All Patients N=137	
Parameter	**Baseline**	**Week 12**	**Week 24**	**Week 48**

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

Physical features of hypercortisolism

As early as Week 12, 70.3% of patients had improvement in at least one physical feature associated with hypercortisolism (facial rubor, dorsal fat pad, central (abdominal) obesity, supraclavicular fat pad, whereas approximately one third had a favourable shift from baseline for ecchymosis (bruising), proximal muscle wasting (atrophy), striae and hirsutism (in female patients only).

At the end of the Core period (Week 48), 83/97 patients (85.6%) with an assessment had improvement in at least one physical feature in CD.

Bone mineral density

Both male and female patients in Study C2301 had decreased bone mineral density (BMD) when compared with that found in a gender- and age-matched population without endogenous hypercortisolism. During the study, treatment with osilodrostat led to an increase from baseline in BMD in the lumbar spine (L1-L4) and total hip at Week 48. A mean (SD) percentage change from baseline of 3.0% (6.45) was reported for L1-L4 of the lumbar spine and of 0.4% (5.48) for total hip BMD at Week 48 and the improvement was more pronounced in male patients compared with female patients.

Patient reported outcomes during the Core period

Cushing QoL

Increases from baseline for Cushing QoL total score (indicative of improvement) were observed in the All Patients group (N=137) at all post-baseline visits. These changes and the adjusted mean change from baseline

occurred early after initiation of treatment 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.

Furthermore, improvement was observed for 'All patients' (N=137) for the Cushing's QoL subscales of 'physical problems' and for 'psychosocial issues'. These changes including the adjusted mean change from baseline reached the distribution-based MID value (10.1 point change from baseline) for the 'physical problems' subscale at Weeks 12, 24, 26, 28, 30, 32, 34 and 48 and for the 'psychosocial issues' subscale at Weeks 30, 32, 34, and 48.

EQ-5D utility index

Changes from baseline, indicative of improvement for EQ-5D utility index, were observed for 'All patients' (N=137) at all post-baseline visits. These changes reached the lower-bound MID value (score difference of 0.037-0.069) at Weeks 4, 24, 26, 30, 34, and 48. The adjusted mean change from baseline on the utility index score reached the MID value (score increase of 0.037-0.069) at Week 4, 16, 24, 26, 30, 34 and 48.

BDI

Changes from baseline on BDI-II total score indicative of improvement were observed in the 'All patients' group (N=137) at all post-baseline assessments. These changes reached the MID values (17.5% reduction in scores from baseline) at Weeks 24, 26, 28, 30, 32, 34, and 48.

The adjusted mean change from baseline on the BDI-II total score shows a decrease from mean change of -2.31 (95% CI: -3.61, -1.00) at Week 4 to -5.52 (95% CI: -7.10, -3.93) at Week 48 in the Osilodrostat Group. These changes are indicative of improvement at each visit.

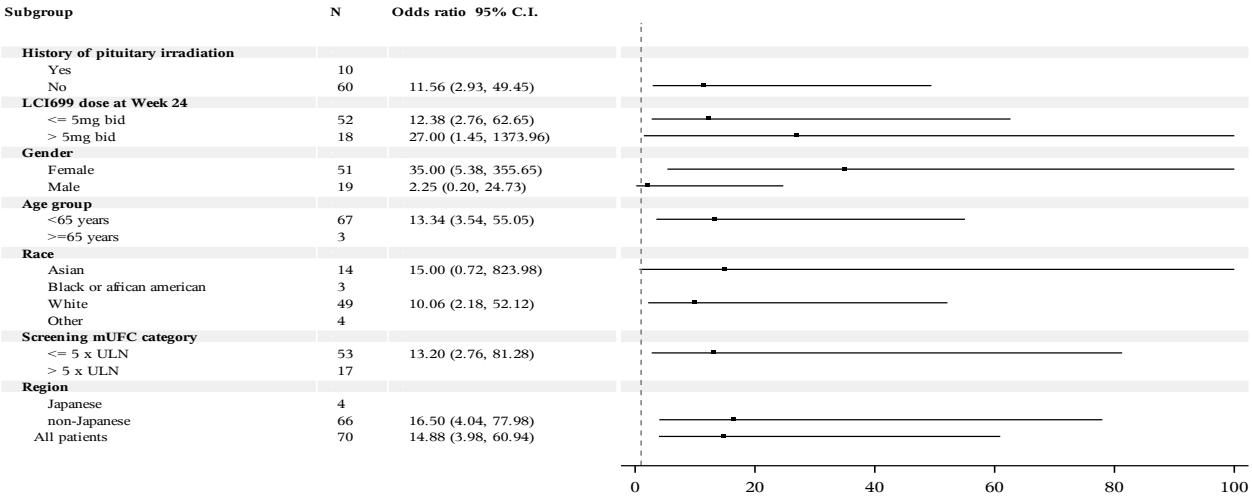
Ancillary analyses

Subgroup analyses

Subgroup analysis of the primary endpoint at Week 34 (Figure 18) with odds ratio and associated 95% CI demonstrate consistency with the overall population. Subgroup analyses of the response rate at Week 24 demonstrate consistency with that reported for the overall population in clinically meaningful mUFC response rates across all subgroups at Week 24 of the study (Figure 19).

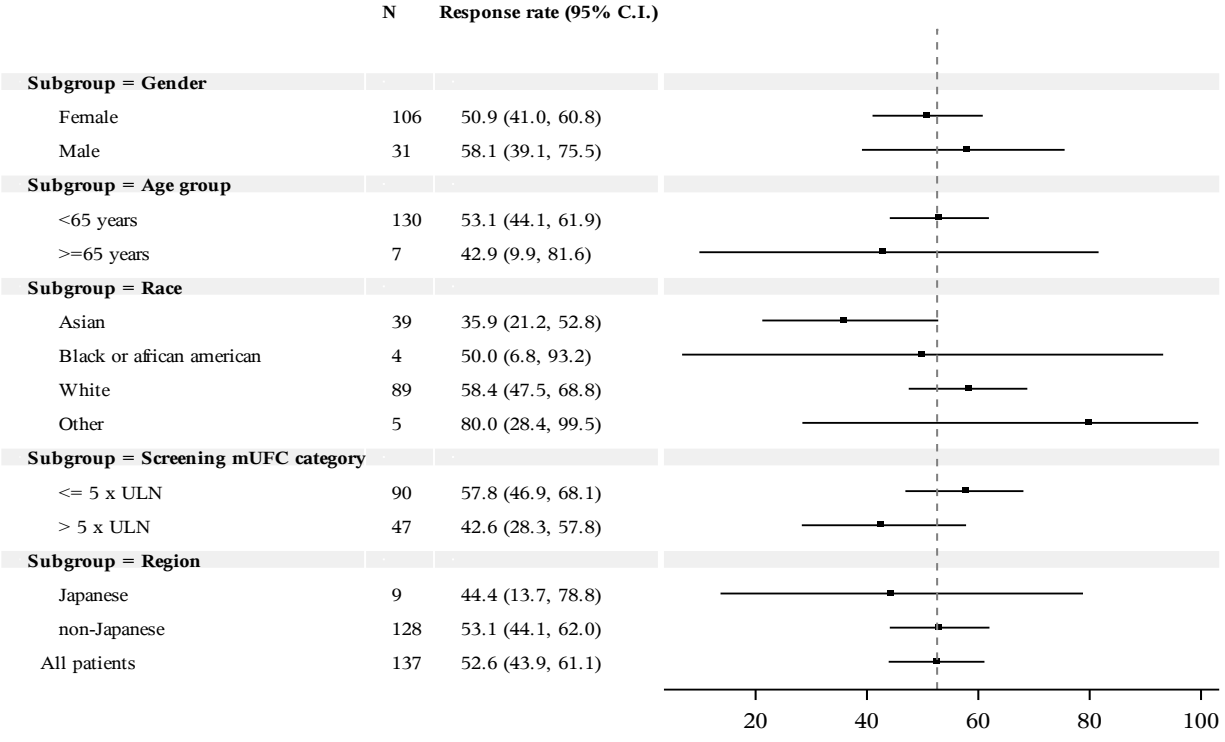
The analysis in some subgroups are based on limited numbers of patients; therefore, no definitive conclusions should be drawn for these subgroups.

Figure 15 Forest plot of odds ratio (95% CI) at the end of the randomized withdrawal period (Week 34) by subgroups and randomized treatment – Study C2301 (FAS)



The vertical reference line is at 1 on the x-axis.
Responder at the end of the randomized withdrawal period (Week 34) was defined as a randomized patient who has mUFC ≤ ULN at Week 34 and who was neither discontinued nor had an osilodrostat dose increase above the level at Week 26 during the randomized withdrawal period of the study. Patients who discontinued during the randomized withdrawal period were counted as non-responders for primary efficacy.
Odds ratio (95% confidence interval) was based on Fisher exact method. Some odds ratios have an upper limit of the confidence interval greater than 100. However in order to improve the layout, the upper limit is capped at 100.

Figure 16 Forest plot of proportion of responder at Week 24 by subgroups – Study C2301 (FAS)



Responder at Week 24 is defined as a patient in FAS who has mUFC ≤ ULN at Week 24 and the dose of osilodrostat during Study Period 2 (Weeks 13-24) was not increased above the level established at the end of Study Period 1 (Week 12). Patients who had missing mUFC assessment at Week 24 were counted as non-responders for the key secondary endpoint.

N is the number of patients in the FAS. The vertical reference line on the x-axis is at 52.6 - the response rate for 'All patients'. 2-sided 95% Confidence Intervals are based on the exact (Clopper-Pearson) method.

Subgroup analyses in Japanese and non-Japanese patients

Reductions of mUFC levels were similar when examined in a subgroup of Japanese patients compared with non-Japanese patients. High baseline levels of mUFC were reduced in both groups by Week 2 and were stabilized to mUFC (≤ ULN) prior to Week 6 in the Japanese patients and by Week 8 in the non-Japanese patients.

Post-hoc subgroup analyses by treatment group, race and region

Overall, mUFC response rates tended to be lower and average daily doses tended to be higher in the non-randomized treatment group. These results were expected since these patients were not mUFC responders at Week 24 or had a dose increase between Weeks 13 and 24.

Table 12 mUFC endpoints and average dose by treatment group, race and region (study C2301)

	Non-randomized	All Patients
Caucasian	**N=39**	**N=89**
Overall mUFC response at week 48: n/N` (%)	22/39 (56.4)	69/89 (77.5)
Asian	**N=25**	**N=39**
Overall mUFC response at week 48: n/N` (%)	16/25 (64.0)	29/39 (74.4)
Caucasian	**N=39**	**N=89**
Mean daily dose in mg/day (SD)	14.4 (10.22)	11.6 (9.45)
Asian	**N=25**	**N=39**
Mean daily dose in mg/day (SD)	6.9 (5.12)	5.6 (4.72)

Note - all Asian patients were treated at sites in Asia and the results by region and by race are therefore the same for Asian patients and patients at Asian sites; the number of "Black" and "Other" patients was small (n=4 and n=5, respectively) and those subgroup results should be interpreted with caution.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of efficacy for trial C2301

Title: A Phase III, multi-center, double-blind, randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing's disease	
Study identifier	CLCI699C2301 EudraCT no. 2013-004766-34
Design	This is a multi-center, double-blind, randomised withdrawal study of osilodrostat following a 24 week, single-arm, open-label dose titration and treatment period. 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. Randomization was stratified by osilodrostat dose at Week 24 (≤ 5mg bid vs. >5mg bid); and history of pituitary irradiation (yes/no).

	Duration of dose titration: Duration of treatment phase: Duration of RW phase: Duration of open label phase:		12 weeks 12 weeks 8 weeks 14 weeks
Hypothesis	Superiority		
Treatments groups	Osilodrostat		8 weeks, N=36
	Placebo		8 weeks, N=34
Endpoints and definitions	Primary endpoint	Complete responders at week 34	Proportion of randomised patients with mUFC ≤ ULN at the end of 8 weeks of randomised withdrawal in each treatment arm.
	Key secondary endpoint	Complete responders at week 24	Proportion of enrolled patients with mUFC ≤ ULN at Week 24, without dose increase after Week 12.
	Secondary efficacy variable	Time to last control of mUFC during the RW period	Time (in days) from randomisation to the last normal UFC assessment (mUFC ≤ ULN)
	Secondary efficacy variable	Proportion of overall mUFC responders over time (Week 48)	Proportions of overall responders (enrolled patients with mUFC ≤ ULN or with at least 50% reduction from baseline)
	Secondary efficacy variable	Time to escape	Loss of control of UFC after prior UFC normalization in patients who had completed the dose titration period (Period 1)
Database lock	First database lock: 10-May-2018, Report date: 06-Sep-2018 (content final)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomised analysis set (RAS); all randomised patients who received at least one dose of randomised drug (osilodrostat or placebo). Randomised withdrawal period week 26 to 34.		
Descriptive statistics and estimate variability	Treatment group	Osilodrostat	Placebo
	Number of subjects	36	34
	Complete responders at week 34 (n (%))	31 (86.1)	10 (29.4)
	95% CI	(70.50, 95.33)	(15.10, 47.48)
	Time to last control of mUFC during the RW period (days) (50^{th} percentile)	NE	28.0

	(95% CI)	(NE, NE)	(15.0, NE)
	Number of subjects	137	N/A
	Complete responders at week 24 (n (%))	72 (52.6)	N/A
	95% CI	(43.9, 61.1)	N/A
	Proportion of overall mUFC responders over time (Week 48) (n (%))	104 (75.9)	N/A
	95% CI	(67.87, 82.80)	N/A
	Time to escape (days) (50th percentile)	560.0	N/A
	95% CI	(212.0-NE)	N/A

Effect estimate per comparison	Primary endpoint: Complete responders at week 34	Comparison groups	Osilodrostat vs Placebo
		Odds ratio	13.71
		95% CI	(3.73, 53.44)
		P-value	<0.001
	Secondary efficacy variable: Time to last control of mUFC during the RW period (days) (50th percentile)	Comparison groups	Osilodrostat vs Placebo
		Hazard ratio	0.06
		95% CI	(0.01, 0.28)
		P-value	NE
Notes	Comparison between groups were only made for the RW period.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

No dedicated studies in special populations were conducted. Only seven subjects aged 65 to 74 years were included in study C2301. Three subjects aged 75 to 84 years were included in the non-randomised trials, one of these subjects participated in the supportive study C1201.

Supportive studies

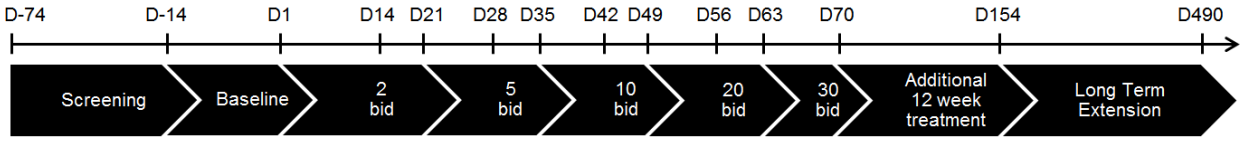
Study C2201

Study C2201 Part I was a 10-week exploratory proof-of-concept study with the last patient assessed on 06-Mar-2012 (interim CSR: 07-Dec-2012). This sequential dose-escalation study assessed the short-term safety/tolerability and the efficacy of osilodrostat after a 10-week treatment period in patients with CD (Figure 20). 12 patients were enrolled and treated with up-titrated doses of osilodrostat. All 12 patients completed the study.

Study C2201 Part II Core was a 22-week treatment period after which the long-term efficacy and safety of osilodrostat were further investigated in an optional 48-week extension (Extension 1) (Figure 20). The extension phase was continued as Extension 2 to provide continued access to osilodrostat for patients who completed Extension 1. Efficacy results from the extended long-term phase of Part II Core are presented in this report. The study remains ongoing.

A total of 19 patients were enrolled (4 patients from Part I in the Follow-up cohort and 15 newly enrolled patients in the Expansion cohort) between January and July of 2013. After Week 22, 16 patients entered the extension phase. Of the 16 patients that entered the extension phase, 10 are still ongoing as of the data cut-off date (14-Nov-2017).

Figure 17 Study design – Study C2201 (following Protocol Amendment 4)



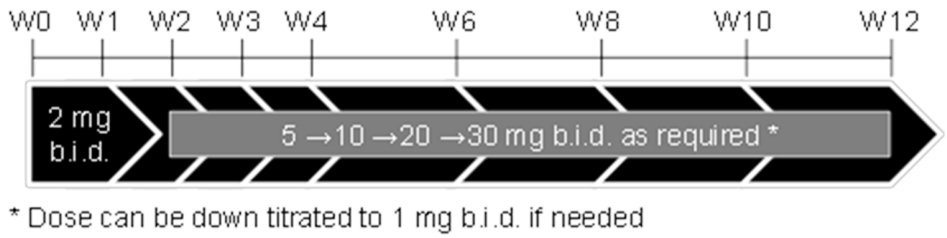
Study C1201

Study C1201 is an ongoing Phase II, single-arm, open-label, dose-titration study to assess the safety/tolerability and efficacy of osilodrostat in 9 Japanese patients with endogenous CS except CD (hereafter referred to non-CD CS).

The study consists of two distinct study periods plus an optional extension period. The study schematic is displayed in Figure 21.

Study period I (12-week duration): the dose titration period achieved an individual stable therapeutic dose and assessed the efficacy and safety.

Figure 18 Study design – Study C1201



Study period II (36-week duration): assessed the sustainability of efficacy and the long-term safety for the patients who tolerated and who agreed to continue study treatment to derive further clinical benefit.

Optional extension period: ends after all patients have completed Week 72 or discontinued prior to Week 72.

As of the data cut-off date (07-Jun-2018), all nine patients were treated with up-titrated doses of osilodrostat with seven (77.8%) of patients completing Period 1 (Week 12) of the study; two patients discontinued prior to Week 12. Four patients of the seven entered Period 2 of the study and, as of the data cut-off of 07-Jun-2018, two patients completed Period 2 (Week 48); one patient of the two entered the ongoing extension.

Endpoints in study C2201 and C1201

Table 14 Description of efficacy assessments and endpoints - Study C2201, and Study C1201

Efficacy assessments and endpoints	Study C2201[1]	Study C1201
Primary efficacy assessments		
24-hour UFC	Mean value of three 24-hour urine samples	Mean value of three 24-hour urine samples
Assay for UFC (ULN)	LC-MS/MS	LC-MS/MS
UFC normal ranges	ULN=138 nmol/24hr; LLN=11 nmol/24hr	ULN=138 nmol/24hr; LLN=11 nmol/24hr
Other assessments		
Cushing QoL Beck Depression Inventory-II EQ-5D-5L	NA	Completed prior to any clinical assessments
Serum cortisol	Baseline, dose-escalation period, 12-week treatment period, EOT, and 28-days post last dose; long-term extension, EOT and 28-days post last dose then every 3 months and every 6 months thereafter	Collected at Baseline, during dose-titration, Study Period II, optional extension, EOT, and 30-days from last dose
Endpoints: Responders	**Responders** • Based on the mean of three 24-hour urinary free cortisol (mUFC) collections, patient has mUFC is UFC ≤ ULN (complete responder) at Weeks 10, 22, and in the extension **Controlled UFC responder:** patient has mean UFC ≤ 1.0 x ULN	• **Complete responder**: patients had mUFC ≤ ULN at Week 12, Week 24 and Week 48
	• **Partial responder:** mUFC >1.0 X ULN with at least a 50% reduction from baseline (partial responders) at Weeks 10, 22, and in the extension	• **Partial responder:** patients had ≥ 50% reduction from baseline in mUFC, but mUFC > ULN

[1] Study C2201 includes the Part I core-phase of the study and the Part II the long-term extension of the study.
EOT=End of treatment; LC-MS/MS=liquid chromatography - tandem mass spectrometry assay; LLN-Lower limit of normal; mUFC=Mean urinary-free cortisol; QoL=Quality of life; ULN=Upper limit of normal; RW=Randomized withdrawal

Demographic and baseline characteristics

Study C2201 Part II Core, enrolled patients had persistent or recurrent hypercortisolism, including patients with de novo CD, after primary pituitary surgery and/or irradiation as well as patients with de novo CD who are not surgical candidates for medical reasons, or who refused to undergo surgery. At screening, patients had to have a mUFC > 1.5 x ULN (Table 23). More females than males were enrolled with a median age of 36 years. The majority of patients were Caucasian.

In Study C1201, patients with non-CD CS were enrolled. All patients enrolled were Japanese and demographic characteristics were similar with those reported for C2201 Part II in that more females than males were enrolled. Patients in Study C1201 were slightly older with the median age of 46 years (Table 23). The BMI in patients was higher in Study C2201 Part II Core compared to Study C1201.

Table 15 Summary of demographics and baseline characteristics

	Study C2201 Part 2 (Safety set)	Study C1201 (FAS)
	All Patients	All Patients
Demographic Variable	**N=19**	**N=9**
Age (years)		
Mean (SD)	36.8 (8.35)	51.0 (18.17)
Median	36.0	46.0
Min-Max	25 - 52	20 - 75
Age category (years) -n (%)		
18-<65	19 (100)	6 (66.7)
65-≤ 75	--	3 (33.3)
Sex -n (%)		
Female	14 (73.7)	7 (77.8)
Male	5 (26.3)	2 (22.2)
Race -n (%)		
Caucasian	15 (78.9)	--
Asian	3 (15.8)	9 (100)
Other	--	--
Black	1 (5.3)	--
Weight (kg)		
Mean (SD)	85.1 (23.96)	64.53 (19.704)
Median	75.8	59.30
Min-Max	61.9 - 139.0	47.0 - 106.5
Height (cm)		
Mean (SD)	166.0 (13.336)	158.6 (7.986)
Median	163.40	156.00
Min-Max	147.32 - 192.00	145.0 - 170.0
Body mass index (kg/m^2)		
Mean (SD)	30.7 (6.959)	25.4 (5.9994)
Median	28.9	23.876
Min-Max	23.06 – 47.54	19.31 - 38.19

BMI: body mass index; FAS: full analysis set; SD: standard deviation.

Disease history and baseline characteristics

Study C2201 Part 2

In Part 2 of the Core study (with a cut-off of 23-Dec-2013), the median time to first osilodrostat dose since initial CD diagnosis in the Expansion cohort was 63.4 months (range: 12.2 to 155.2) and 82.5 months (range: 57.6 to 100.3) in the Follow-up cohort and all patients had persistent/recurrent CD. Overall the vast majority of patients had received prior treatment for CD prior to study entry, with 86.7% of patients in the Expansion cohort having had previously undergone pituitary surgery and all had received prior radiation treatment whereas all four patients in the Follow-up cohort had received prior treatment for CD prior to study entry and had previous pituitary surgery. The baseline median mUFC was 386.903 nmol/24h in the Expansion cohort and 454.933 nmol/24h in the Follow-up cohort.

As of the 14-Nov-2017 cut-off date, in the Safety set, the median time to first osilodrostat dose since initial CD diagnosis was 70.2 months (range: 12.2-155.2) and all patients had persistent/recurrent CD. Overall the vast majority of patients had received prior treatment for CD prior to study entry, with 89.5% of patients having had previously undergone pituitary surgery. The baseline mean (SD) mUFC was 1370.65 (2733.5).

Study 1201

Disease characteristics at baseline are described below:

- Five patients had adrenal adenoma and four had no prior surgery; one patient of the five had received prior medication.
- Three patients had ectopic corticotropin syndrome and only one had prior surgery; all had received prior medication.
- One patient had ACTH-independent macronodular adrenal hyperplasia with prior medication and no surgery.

The five patients with prior medication were previously treated with metyrapone.

Efficacy results

Study C2201 Part 1

At the time of the completed Part I of the 10-week core study, a notable decrease in UFC was seen after 28 days of dosing (when most subjects had completed dosing with 5 mg bid) and continued to decline to Day 70 when treatment stopped. The total daily dose required for UFC normalization was ≤20 mg/day in 75% of the patients, with at least 50% of the patients requiring 10-20 mg/day.

Although mUFC levels increased again upon stopping osilodrostat at the end of the 10-week study, once treatment was resumed for patients who continued in Part II of the study, reduction in mUFC (≤ ULN) levels were achieved. While mean fold ULN declined to <1 (ULN) by Day 56, the mean time to response (UFC normalization or 50% reduction) was 34.3 days (SD = 14.1 days).

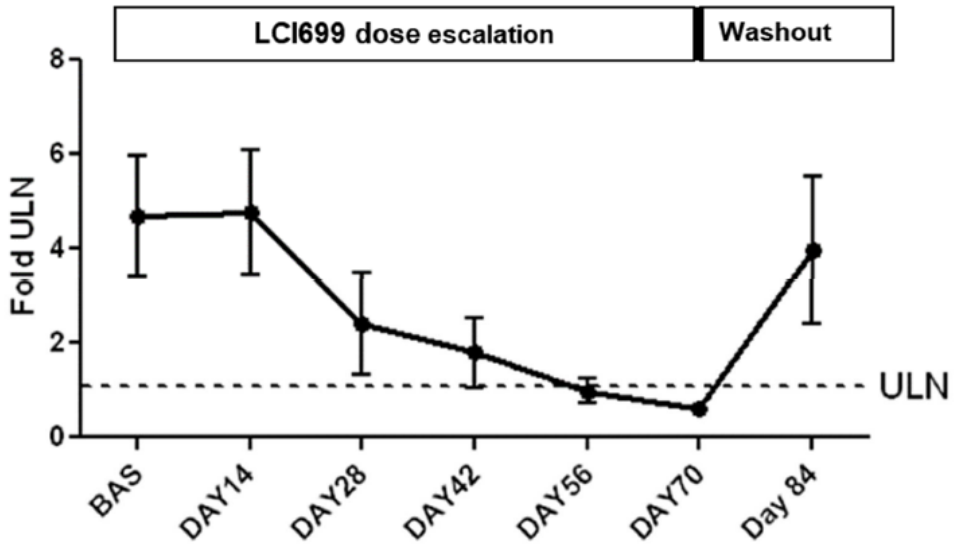
Furthermore, nine patients of the 12 had three UFC measurements at both baseline and Week 10 (Day 70) and were therefore included in the primary analysis set.

- All nine patients were considered to be responders achieving either a mUFC ≤ ULN or ≥ 50% decrease in mUFC at Day 70, so the response rate was 100% (95% CI: 66%, 100%).

- All 9 patients met both responder criteria: the mean UFC level was ≤ ULN as defined by local laboratories (from the three 24-hour urine samples collected at Week 10) and represented a ≥ 50% decrease from baseline.

The paired t-test comparing geometric means at Week 10 to baseline gave a ratio of 0.103, indicating an average of 90% reduction in UFC over the 10-week dosing period.

Figure 19 Arithmetic mean and SE plots for fold ULN of UFC – Study C2201 (PD analysis set)



Study C2201 Part 2

Changes in mUFC and responder status by UFC levels

In Study C2201 Part II, mUFC levels (≤ ULN) were maintained without any consistent dose increase as evidenced by the total daily dose of osilodrostat with the range of doses consistent between 10 mg/day to 12 mg/day and some patients had dose decreases. Reduction of mUFC≤ ULN with osilodrostat is evident by mUFC responses over time:

- Part II Core (Week 10), the end of the dose titration period: An overall response rate of 89.5% (95% CI: 66.86, 98.70) was achieved with 84.2% of patients (16/19) being complete responders and 5.3% (1/19) being partial responders.
- Part II (Week 22), the core phase: An overall response rate of 78.9% (95% CI: 54.43, 93.95) was achieved with 78.9% of patients (15/19) being complete responders; there were no partial responders. The response rate was maintained at Month 22 as evidenced by an overall response rate of 70.6% (95% CI: 44.0, 89.7) was achieved and 58.8% of patients (10/17) patients were complete responders and 11.8% (2/17) were partial responders. Response to osilodrostat was maintained through Month 46 with 58.8% (10/17) patients as complete responders.
- Part II (Week 22), the core phase: At the time of the last available assessment, an overall response rate of 63.2% (95% CI: 38.36, 83.71) was achieved with 47.4% of patients (9/19) being complete responders and 15.8% (3/19) being partial responders.

The median mUFC level at baseline was 2.9xULN (404.97 nmol/24hr) and mUFC ≤ ULN is evident with osilodrostat at various time points throughout the study. mUFC levels during the study are as follows: 43.96

nmol/24hr (95% CI for percentage change from baseline: -92.69, - 78.25) at the end of Week 10; 59.78 nmol/24hr (95% CI for percentage change from baseline: -88.86, -71.71) at the end of Week 22; and 86.90 nmol/24hr (95% CI for percentage change from baseline: -81.92, -52.33) at the time of the last available assessment.

Escape analysis

No escape event was reported during the 22-week period in Part 2 of the Core study. In both the Expansion and Follow-up cohorts, all patients attained UFC normalization and no patient lost UFC control (i.e. UFC >ULN) on at least 2 consecutive visits at the highest tolerated dose after previously attaining UFC normalization.

Other assessments

Cardiovascular-related metabolic parameters

Decreases were observed in cholesterol and triglycerides whereas a small increase was observed in LDL cholesterol. Although a reduction in both SBP and DBP was observed at Week 70, this was not maintained at Month 58. A persistent decrease in BMI and FPG was observed up to Month 58.

Study C1201

Primary efficacy results

In Study C1201, seven patients completed the study of the nine enrolled in Period 1 and all seven had reductions in mUFC with osilodrostat at Week 12. At Week-12, the median change in mUFC was: -98.97% (3/5 patients with prior metyrapone experience) vs -86.65% (4 patients without prior metyrapone experience), however due to small sample size the results should be interpreted with caution. Two patients discontinued prior to Week 12. The mean percent change from baseline at Week 12 ranged from -52.6% to -99.0%.

Reduction in mUFC (≤ ULN) were evident based on the median percent change in mUFC from baseline as follows: Week 4, -83.3%; Week 8, -94.4%; and Week-12, -94.5%. The median decrease in mUFC from baseline at Week 12 was -94.47% (95% CI: 95% CI: -103.49%, -72.55%).

At Week-24 (n=3), a 91.6% decrease from baseline in the mUFC levels was observed and the median mUFC was 63.90 nmol/24 hr. At Week 48 (n=2), a 95.0% decrease from baseline in the mUFC levels was observed and the median mUFC was 511.30 nmol/24hr. The median decrease in mUFC from baseline at Week 48 (Day 337) was -95.0% (95% CI: -146.6, -43.5%). As the number of patients continuing the study after Week-12 was low (≤ 3), the results at Week-24 and Week-48 should be interpreted with caution.

Secondary efficacy results

- Response rates

An overall response rate (i.e. mUFC <ULN or mUFC >ULN but with at least 50% reduction from baseline) of 77.8% (7/9) was achieved in patients at Week 12 with 66.7% of patients (6/9) being complete responders and 11.1% (1/9) being a partial responder; two patients discontinued the study prior to Week 12 and were counted as a non-responders. At Week 24, of the three patients still on study treatment, two patients were complete responders (66.7%) and one patient (33.3%) was a partial responder. At Week 48, with only two patients still on treatment, one patient was a complete responder and one patient was a partial responder.

- Percentage change from baseline in Week-12 morning serum cortisol

At baseline (N=9), the median morning serum cortisol level was 535.0 nmol/L (range: 309 to 1330). At Week 12 (Day 85; n=7), and the median morning serum cortisol level was 235.0 nmol/L (range: 94 to 381 nmol/L) and

the median percentage change of -56.07% (from baseline) was observed (range: -78.0% to -3.5%). Among the four patients who entered study Period II, three patients had assessments at Week 24. At Week 24 (Day 169; n=3), the median morning serum cortisol level was 257.0 nmol/L (range: 174 to 403 nmol/L) and the median percentage change of -68.96% (from baseline) was observed with the range of -69.7 to -43.7%.

- Cardiovascular-related metabolic parameters

Improvements were observed in key cardiovascular-related metabolic parameters despite the limitations of a small number of patients and a short exposure to study drug. As the number of patients continuing the study after Week-12 was low (≤ 3), results should be interpreted with caution.

- Patient-reported Outcomes

Patient-reported outcome assessments based on Cushing QoL and BDI-II showed little to no improvement with scores at Week 12 that were similar to those reported at baseline. As the number of patients continuing the study after Week-12 was low (≤ 3), results should be interpreted with caution.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study program consists of one pivotal study, C2301, and two supportive studies, C2201 and C1201, and is considered adequate to support the proposed indication. The number of subjects with non-CD CS is however low. The design of the pivotal study is adequate and is in line with the CHMP scientific advice provided in 2013.

No formal dose-response study was conducted. The starting dose was selected based on data from the initial studies in normo-cortisolaemic patients where a reduction in cortisol secretion was observed at a dose of 2 mg/day. Although the modelling of PK exposure indicated that higher doses would be needed, other data showed a broad range inter-patient sensitivity to osilodrostat. Thus, the selection of a lower starting dose is justified. BID dosing was based on the half-life of osilodrostat. The maximum dose was reduced from the originally selected dose of 50 mg BID to 30 mg BID due to the observed risk of QT-prolongation. The uptitration scheme was partly designed to meet methodological restraints, where uptitration intervals were limited by the availability of central laboratory UFC values as the sample turnaround time was close to two weeks.

The pivotal study (C2301) had a randomised withdrawal design. The study design included four treatment periods and the primary endpoint was evaluated in the third; randomised withdrawal period into which only complete responders on stable therapy were randomised. Generally, a randomised withdrawal design introduces an increased risk that subjects infer their own treatment assignment from disease symptoms and AEs. However, the primary effect measure (mUFC) is not likely to be affected by patient´s expectations in any clinically meaningful magnitude.

The pivotal study provides information on the titration of osilodrostat as well as long-term efficacy data up to week 48. The inclusion and exclusion criteria are considered adequate. The study allowed for patients with a history of pituitary irradiation, but at least 2 years (for stereotactic radiosurgery) or 3 years (for conventional radiation) should have elapsed from the time of last radiation treatment to the time of enrolment into this study. In previous CHMP advice, the CHMP agreed that irradiated subjects did not need to be excluded due to the usually slow onset of action. Notably, patients with risk factors for QT-prolongation were excluded from participation. Dose titration could continue throughout the study in case the patient showed insufficient response, however, only patients who had stabilised by week 12 were eligible for the RW period. Patients with UFC > 1.5 x ULN could discontinue treatment in the RW period and resume open-label osilodrostat.

The objectives, outcomes and endpoints are adequate. Validity and clinical relevance of the outcomes was already confirmed in former CHMP advice, both for the primary and secondary endpoints of number of responders (mUFC ≤ ULN) at 34 weeks and 24 weeks respectively.

Also, the sample size calculation, randomisation procedures as well as blinding procedures were adequate. Taking into account the expected proportion of patients eligible for randomisation week 26 (at least 50%), a total of 132 patients were planned to be enrolled to have at least 33 patients per treatment arm in the randomised withdrawal period. Based on the number needed a power calculation was performed also for the key secondary endpoint. As mentioned before in CHMP advice, the potential radiation effect over an eight weeks period is considered of limited impact. Stratification according to previous pasireotide treatment was suggested in the same advice, but this was not followed. However, of the 22 patients with previous pasireotide treatment who were randomised, 13 were included in the osilodrostat treated group and 9 were treated with placebo. Additionally, 21 patients with previous pasireotide treatment were not randomised. Subgroup analyses did not indicate a different response in patients previously on pasireotide compared to the overall population.

The primary effect analysis was performed on the Randomised Analysis Set. This set included patients that had mUFC <ULN at week 24, which restricts the patient population studied and enriches it with patients responding to treatment. Some patients with high baseline UFC were excluded from the randomised part of the study; although they experienced a clinically meaningful drop in UFC they did not fulfil the formal criteria. This means that effect estimates may not be applicable to the group that would be prescribed the drug in clinical practice. Also, there were 19 patients that withdrew before randomisation, 12 of these due to AES. Another concern in randomised withdrawal studies is withdrawal effects, which may lead to overestimated effect estimates. This may be the case here, due to increased ACTH and therefore, it could be argued that the key secondary endpoint is more appropriate than the primary endpoint in showing effect of osilodrostat.

During the randomised study period only two patients discontinued the study. These patients were randomised to placebo and the reasons for discontinuation were classified as adverse events. These patients were counted as non-responders in the analysis, which may overestimate the treatment effect somewhat. However, none of these patients had initiated placebo treatment at discontinuation and the potential bias is not considered to be substantial in context of the observed treatment effect.

The key secondary endpoint uses the Full Analysis Set, and this analysis uses data from the single arm open label periods initiating the study i.e. period 1; dose titration and period 2; efficacy and safety assessment at the therapeutic dose determined during the dose titration period. Such an analysis may be subject to bias due to regression to the mean and due to expectation of effect. A large placebo/expectation effect is not considered likely in this endpoint, but regression to the mean may be an issue since an inclusion criterion was to have mUFC >1.5×ULN, and since patients may be more motivated to enter the study when symptoms are severe. The observed effect may therefore be overestimated but is considered unlikely to be primarily driven by the methodological issues.

The sensitivity analyses and subgroup analyses planned and performed were sparse and what regards the sensitivity analyses considered not to be very challenging. Given convincing outcomes and overall few study discontinuations no new analyses will be requested. The submitted version of the SAP (dated 06-Jul-2018) was dated after database lock (10-May-2018), but a detailed document history was provided, so this raises no concern about pre-specification of the analyses.

In conclusion the statistical methodology in study 2301 were adequate but special care has to be taken in the interpretation of the efficacy results so that the effect estimates are interpreted in context of the randomised withdrawal study design.

Concerning the conduct of the study, there were four amendments out of which three occurred after the inclusion of the first patient. The applicant was asked to discuss how a rescue procedure, introduced in amendment 3, may have affected the interpretation of the results. The applicant explained that patients with UFC > 1.5 x ULN could discontinue treatment in the RW period and resume open-label osilodrostat, and that this procedure was introduced in the original protocol. Other amendments are not considered to affect the interpretation of the study results.

It is agreed that the protocol deviations as reported in the CSR had no impact on the interpretation of the study, but the relatively high number of dosing and dispensing errors raise some concerns on the conduct of the study. Furthermore, serious concerns did arise from a GCP inspection about protocol deviations with respect to dose adjustments based on mUFC values and other changes to the IMP-regimen or temporarily complete interruption of IMP-dosing. The Applicant has provided information on the actions taken in relation to the deficiencies in GCP compliance. The deviations with regards to PD reporting were not considered to affect the outcome and interpretation of the study data.

Efficacy data and additional analyses

A total of 202 patients were screened for the pivotal study C2301, of which 65 patients were screening failures. The number of enrolled patients was 137 which is close to what had been planned (i.e. 132). Overall, 25% of subjects discontinued at any time of the study, the most common reason for discontinuation was AEs. However, 4 additional patients met discontinuation criteria but continued in the study, the discontinuation rate would then have increased to 28.5%. Five (5) percent of subjects withdrew at or before week 12. There was one death reported. All enrolled patients further received at least one dose of osilodrostat and were hence included in the Full Analysis Set.

The study enrolled a population representative for the condition. Of note, the mean age was rather low (41 years), ranging from 19 to 70 years. A number of patients had a baseline mUFC below 1.5 ULN. Inclusion was based on screening values and the Applicant has provided data supporting that the lower mUFC values at baseline can be explained by the known variability of the mUFC values in CD.

Of the total number of patients enrolled 71/137 (51.8%) were randomised in Period 3, which is according to what had been expected at the planning stage (at least 50%). The primary analysis set for the analyses of the randomised withdrawal period was the RAS in which one patient randomised to placebo was excluded due to failing the criterion of having received at least one dose of randomised treatment.

The primary endpoint was met as the proportion of patients who completed the randomised withdrawal period and maintained mUFC ≤ ULN was significantly higher in the osilodrostat treated group (86.1% vs 29.4%; OR 13.71 [3.73, 53.44]). The high placebo response was explained by a too short placebo exposure period in some cases to lose biochemical control after prolonged steroidogenesis inhibition. The outcome was supported by the sensitivity analyses. These data support the efficacy of osilodrostat, but the outcome does not provide a clinically meaningful measure of the effect size considering that only patients responding and on stable treatment were randomised.

There was a rather rapid increase in mUFC two weeks after withdrawal in the placebo treated group, and the risk of losing control was substantially lower in the osilodrostat treated group. The median time to loss of control was 28 days. In total 10 patients in the placebo treated group discontinued/received rescue therapy (open-label osilodrostat), whereas one patient in the osilodrostat treated group discontinued. Since a large proportion of patients in the placebo treated group discontinued placebo treatment already at week 26, the absolute difference in mUFC is difficult to interpret but the data supports the efficacy of osilodrostat.

The study also met its key secondary objective. The key secondary endpoint was responder rate at week 24, applying a strict definition of responders (i.e. with mUFC<ULN and without dose increase after week 12). Patients with missing data at week 24 were considered non-responders. With this definition, a response rate of 52.6% (72/137) was observed; the 95% CI was (43.9, 61.1) and hence, the lower bound of the 95% CI was above the pre-specified threshold (i.e. ≥ 30%). If patients who had continued the titration in period 2 were included, the response rate increased to 67.9%. When applying this strict definition, the response rate is higher than observed for pasireotide (26.3 % in the 900 µg b.i.d. group at 6 Months; EPAR for Signifor). Comparisons with other cortisol synthesis blockers, e.g. ketoconazole, are difficult due to the nature of the data but responder rates appear to be comparable (EPAR for Ketoconazole HRA).

Subgroup analyses were in general consistent with the overall outcome for the primary and key secondary endpoints. With regards to the primary endpoint, the point estimate was above 0 for all groups, and CIs were very large due to the low numbers. With regards to the key secondary endpoint, the subgroup of Asian subjects showed a lower response rate. There was however no apparent difference in the outcome for Japanese or non-Japanese subjects. Only seven subjects aged 65 to 75 years were included in study C2301. The mUFC response rates tended to be lower and average daily doses tended to be higher in the non-randomized treatment group: this is programmed by study design as these patients were not mUFC responders at Week 24 or had a dose increase between Weeks 13 and 24.

The proportion of responders was largely maintained from week 12 and up to week 48 with a slight decrease from 71.5% complete responders at week 12 compared to 66.4% complete responders at week 48. There was a trend towards a decrease in the proportion of partial responders in favour of complete responders over time. The number of patients without prior surgery was low (17) but there was no difference in the responder rate in this group compared to the overall population. When looking at individual data, all but one patient showed a decrease in mUFC.

Non-randomised patients continued open-label osilodrostat treatment throughout the course of the study. The overall response rate in this group was somewhat lower than in the total population at week 24 (65.2% vs 82.5%) and at week 48 (59.1% vs 75.9%). Thus, also in this population, potentially more difficult to treat, a clinically relevant proportion achieved normalisation of mUFC.

In the exploratory PoC study C2201, all nine patients who had three UFC measurements both at baseline and week 10 were responders. During the washout period, UFC increased after stopping osilodrostat. The responder rates observed in the second part of study C2201, up to week 22, were in the same range (78.9%) as observed in the pivotal study.

The data indicate that the effect is maintained over time in patients responding to treatment, with 64 patients showing maintained response 6 months after the initial normalisation of mUFC. In study C2301, "escape" was evaluated in patients who had achieved control of UFC. When applying the protocol definition of escape, the median (KM method) time to "escape" was 560 days.

The supportive study C2201 was divided in two parts, of which the second part was a long-term extension to evaluate the efficacy and safety of osilodrostat. Ten of the patients enrolled in Part II of the study are still ongoing and have thus been treated for more than 4 years. Data is available for 17 patients up to 46 months, at which time point 58.8% were still complete responders.

In line with the data on mUFC, normalisation of plasma cortisol levels was observed after week 10 except for the placebo treated group during the RW period.

Hypercortisolism causes negative effects on both CV and metabolic risk factors as well as characteristic changes to the patient's habitus. In study C2301, reductions were observed for all CV parameters included in the evaluation except for triglycerides. SBP and DBP decreased by 6.8 and 6.6%, respectively. Body weight decreased by 4.6%. An increase in BMD was observed, most prominent in the lumbar spine where a 3% increase in BMD was observed. There was a favourable shift with regards to features of CD as assessed from two photographs taken and reviewed locally by the Investigator. Improvements in QoL scores were also observed.

In study C2201, some improvements were observed in CV related metabolic parameters such as cholesterol, triglycerides, FPG and BMI. There was an initial decrease in SBP and DBP which was not maintained at month 58.

The second supportive study, C1201, was conducted in Japan and enrolled a small population of patients with CS other than CD. The uptitration schedule was similar to that applied in the pivotal study. Notably, only seven of the nine patients completed the 12 week uptitration period and only four patients entered the second period of the study. Only one patient entered the optional extension period. The data from this study, supporting the use of osilodrostat in patients with non-CD CS, is of importance as proof-of-concept.

In study C1201, osilodrostat treatment resulted in a mean percent change in mUFC from baseline to week 12 ranging from 52% to 99%. At week 24 the median mUFC in the median mUFC was well below ULN (63.9 nmol/24 hr) but only three patients remained in the study. At week 48, the two remaining patients showed a 95% decrease from baseline in mUFC levels, but the median mUFC was above ULN. The response rate in the first part of the study was comparable to that observed in the studies in patients with CD. Importantly, the two patients still on treatment at week 48 were still responding to treatment. Data on morning cortisol levels show a normalisation compared to baseline. There were some improvements in CV related metabolic parameters whereas no improvements were observed in the PROs.

Thus, most patients in study C1201 showed a persistent response, whereas one patient with adrenal adenoma appears to have lost control at week 16. Further data on this patient has been provided and the apparent loss of control is related to discontinuation of treatment with osilodrostat.

The limited data is considered sufficient to support the proposed target population of CS taking the mechanism of action for osilodrostat into account.

Most patients had achieved ≤ ULN at week 16. The median time to response was 41 days, both in the total study population and in the non-randomised group. There was however a slight shift to the right in the curve for non-randomised patients, indicating longer time to response in this group compared to the total study population. Single patients reached controlled mUFC after about 4 months of treatment.

The highest osilodrostat dose was observed at week 10, after which the mean dose decreased and stabilised at a mean dose of 10-11 mg daily. Dose decrease was presumably due to low mUFC values. In the study, dose increments were made in steps of 5 mg, in the SmPC a more precautious uptitration is proposed with increments of 1 to 2 mg instead of 5 mg as in the study. As explained by the Applicant, the uptitration scheme applied in the study was partly due to methodological restraints. As more frequent cortisol monitoring is feasible in clinical practice, smaller but more frequent dose increases than applied in the study can be made to achieve control while minimising the risk of hypocortisolism. Recommendation on how to uptitrate the dose, and how to monitor the patients, have been included in the SmPC.

In the study, patients who were on medical treatment were eligible for inclusion after washout periods, which were adapted for the different medicinal products used and 74.5% of patients had been treated with other medication for CD prior to study entry. Switching from other products is likely and recommendations have been

added in the SmPC to highlight that a washout period is needed if patients are switched from e.g. pasireotide or ketoconazole.

2.5.3. Conclusions on clinical efficacy

The data from the pivotal study show that osilodrostat is efficient in lowering the mUFC in patients with CD and that the effect is maintained up to at least 48 weeks without indications of "escape". The response rate of about 70% is considered clinically relevant. Secondary endpoints on CV related metabolic parameters, physical features of hypercortisolism and BMD indicate further beneficial effects of treatment. Limited long-term data indicate that the effect of osilodrostat can be maintained over time.

The small study in non-CD CS provide support for the adequacy of extrapolating efficacy data from patients with CD to patients with non-CD CS, taking the knowledge on the mechanism of action into account. Thus, the overall data support the use of osilodrostat in the proposed target population.

2.6. Clinical safety

Safety data presented are based primarily on the results from the pivotal study C2301 conducted in patients with Cushing disease (CD) due to ACTH producing pituitary adenoma and is supported by an additional study in CD (Study C2201). To support the proposed indication of endogenous Cushing Syndrome caused by diseases other than ACTH producing pituitary adenoma, data from the Japanese Study (C1201) has been submitted (see section 2.5.).

Study C2108, performed in 24 healthy female receiving cortisol supplementation (30 mg for 12 days) conducted to study pharmacokinetics of use of oral contraceptive together with osilodrostat, was also submitted.

The substance was initially developed for the treatment of hypertension and hyperaldosteronism. The clinical studies in these indications used lower doses (0.25 mg/day to 2 mg/per day) of osilodrostat used for shorter durations (4-8 weeks). Even though these studies are not included in the safety data set for use of osilodrostat in intended population, the Applicant has in short summarised and submitted safety data and experience from these studies (A2201, A2206, A2215 and A2216). In this AR, data from these studies have been referred to when applicable. The studies are described in more detail in section "Common adverse events in other indications".

Patient exposure

Overall exposure

Three studies (C2301, C2201 and C1201) were performed in subjects covering the intended population. Cut-off dates for study C2301 was 21-Feb-2018 (ongoing), 14-Nov-207 for study C2201 part II (ongoing), 06-Mar-2012 for study C2201 Part 1 and 07-Jun-2018 for study C1201(ongoing). Median exposures in the pivotal study (C2301) were 74.7 weeks and overall, across studies the median lengths ranged from 80 days to 226 weeks (Table 24).

In total, 134 subjects have been treated with osilodrostat in more than 6 months and 107 subjects have been treated more than 12 months (study 2301 and 2201 part II). At time of cut-off, 11 subjects had been treated for 48 months or more (all in study C2201 part II). Thus, long-term experience is limited however further long-term safety date is pending from all three studies performed in the intended population.

For study C2301 a safety update was submitted with a data cut-off date as of 15-Oct-2018. In this up-date the median (range) exposure to treatment was 104.1 weeks (range 0.9 to 199.0) weeks with some patients being treated for more than 192 weeks. One hundred and ten patients were exposed to osilodrostat for at least 156 weeks. The additional median exposure compared to the primary cut-off date was approximately 30 weeks.

The safety database is not representative for the full target population of endogenous CS as for the non-CD form of CS, only 9 patients were included (5 with adrenal adenoma, 3 with ectopic corticotropin syndrome and 1 with ACTH-independent macronodular adrenal hyperplasia (AIMAH)) which were all of Japanese origin, and of which only 4 patients continued after week 12 and only 2 completed the study period II at week 48.

It is recognized that the number of non-CD CS patients is very limited and that the safety profile can be different in these patients but mainly due to AE related to the disease, its extent and complications.

However, the study data in the non-CD CS patients, although very limited, in combination with an acceptable mechanistic reasoning and a high unmet medical need currently results in a positive benefit-risk analysis. To ensure this the safety data "*Use in non-Cushing disease Cushing syndrome subjects including long-term effects*" has been characterised as a population with missing information in the RMP.

In addition, the Applicant should take any opportunity to gather extra information in the post-approval setting, once marketing authorisation is granted: this holds for both CD and non-CD CS patients and is outlined in the pharmacovigilance plan evaluation**.**

Moreover, the CD population primarily consisted of second-line patients with persistent/recurrent disease after pituitary surgery. In total, only 17 subjects were "*de novo treated patients*" without any history of pituitary surgery (all in study C2301). Thus, safety data in the "*de novo"* patients is limited. A subgroup analyses comparing the subjects without previous pituitary surgery ("de novo") and subjects with prior surgery did not raise any new safety concern for the "de novo" subjects. It is therefore considered acceptable to extrapolate safety information from the "prior surgery" to the subjects with "no prior surgery".

Among all subjects six subjects (all in study C2301) had not received any previous treatments for Cushing's disease.

In addition to data in subjects with Cushing syndrome, 520 subjects with hypertension have been exposed to osilodrostat in low dose 0.25 mg/day to 2 mg/per day) in the four Phase II hypertension short-term (4-8 weeks) studies (A2201, A2206, A2215 and A2216). These studies are described in section "Common adverse events in other indications".

Overall, the number of subjects treated in the intended population, endogenous Cushing´s syndrome in adults, is low (n=165). However, considering the status of orphan drug and the fact that information regarding safety is available from the population with hypertension the size of the safety database, at present, seems sufficient.

Table 16 Duration of exposure to osilodrostat up to data cut-off – Study C2301, Study C2201 Part 2 and Study C1201

	Study C2301	**Study C2201 Part 2**	**Study C1201**
	N=137	**N=19**	**N=9**
Duration of exposure (weeks)			
Mean (SD)	80.3 (44.02)	158.0 (97.71)	24.6 (24.86)

	Study C2301	Study C2201 Part 2	Study C1201
	N=137	N=19	N=9
Median (weeks)	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

Dosing

In line with the recommendation in the SmPC, the pivotal study (C2301) and the two supportive studies (C2201 and C1201) used an up-titration schema based on individual efficacy and tolerability.

The mean average-maintained dose after up-titration ranged between 10 to 12 mg/day in study C2301 and C2201 but was lower in the Japanese subjects (3.5 mg/day). The usual maintenance dose (presented in the SmPC section 4.2) was calculated as Q1-Q3 was 4-14 mg/day in the pivotal study (Table 25).

Although a wide range of **doses** of osilodrostat has been administered in the clinical studies (up to 100 mg/day in 1 patient) and the maximum dose is 30 mg bid, the doses used in the pivotal study were generally quite **low.** According to the SmPC the highest recommended dose is 30 mg twice daily (=60 mg). This recommendation is in line with the highest dose used in the clinical trials. In total a few subject (n=5) was treated with doses of 60 mg osilodrostat at any time of the study. The first start date for this dose varied between Day 63-261. The subjects seemed stayed on this dose a sufficient time (11- 867 days) to consider that the treatment probably have been acceptable tolerated. No new safety concern was raised when safety for subjects on high doses of osilodrostat (> 20 mg b.i.d; n=25) was compared to subjects on lower doses (<20 mg b.i.d; n=137), respectively.

Table 17 Summary of dose level - Study C2301, Study C2201 Part 2 and Study C1201

	Study C2301 Osilodrostat	Study C2201 Part 2	Study C1201*
	N=137	N=19	N=9
Highest Dose (mg/day)			
Mean (SD)	18.4 (14.00)	23.9 (15.40)	5.7 (2.74)
Median	14.0	20.0	5.0
Q1-Q3	10.0 - 20.0	10.0 - 40.0	4.0 - 6.0
Min – Max	4.0 - 60.0	4.0 - 60.0	2 - 10
Average Dose (mg/day)			
Mean (SD)	10.0 (8.51)	12.1 (7.28)	3.541 (2.1937)
Median	7.1	11.3	2.571
Q1-Q3	3.8 - 14.0	5.3 - 16.0	2.197 - 3.778
Min – Max	1.1 - 53.9	4.0 - 27.9	1.33 - 7.54
Dose with longest duration (mg/day)			

Mean (SD)	10.6 (11.20)	13.0 (13.35)	4.1 (3.48)
Median	6.0	10.0	2.0
Q1-Q3	3.0 - 14.0	4.0 - 20.0	2.0 - 4.0
Min – Max	0.5 - 60.0	1.0 - 60.0	1 - 10

*Data reported without taking dose interruptions into account.

Dose modifications/interruptions

While guidance for dose decrease/interruption and consequent re-initiation has been included in section 4.2 and 4.4 of the proposed SmPC, and guidance regarding the fact that treatment can be resumed at a lower dose has also been added in section 4.2**.**

Adverse events

An overview of adverse events and deaths in Study C2301 and Study C2201 Part 2 is presented in Table 26. For C2301, events experienced by patient randomized to placebo while on placebo are not included in the analysis.

Table 18 Overview of adverse events and deaths – Study C2301 and Study C2201 Part 2 (Safety set)

	C2301 Osilodrostat N=137		**C2201 Part 2 N=19**	
Category	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
All deaths*	1 (0.7)	1 (0.7)	0	0
Adverse events	137 (100)	78 (56.9)	19 (100)	12 (63.2)
Suspected to be drug-related	128 (93.4)	43 (31.4)	18 (94.7)	8 (42.1)
SAEs	50 (36.5)	39 (28.5)	6 (31.6)	5 (26.3)
Suspected to be drug-related	21 (15.3)	16 (11.7)	3 (15.8)	1 (5.3)
AEs leading to discontinuation	18 (13.1)	11 (8.0)	3 (15.8)	1 (5.3)
Suspected to be drug-related	13 (9.5)	7 (5.1)	2 (10.5)	1 (5.3)
AEs requiring dose interruption and/or change	106 (77.4)	39 (28.5)	15 (78.9)	4 (21.1)
Suspected to be drug-related	96 (70.1)	26 (19.0)	13 (68.4)	3 (15.8)
AEs requiring additional therapy	130 (94.9)	55 (40.1)	17 (89.5)	7 (36.8)
Suspected to be drug-related	86 (62.8)	26 (19.0)	14 (73.7)	3 (15.8)
AEs of special interest	98 (71.5)	32 (23.4)	14 (73.7)	5 (26.3)

Category	C2301 Osilodrostat N=137 All grades n (%)	C2301 Osilodrostat N=137 Grade 3/4 n (%)	C2201 Part 2 N=19 All grades n (%)	C2201 Part 2 N=19 Grade 3/4 n (%)
Suspected to be drug-related	92 (67.2)	25 (18.2)	11 (57.9)	3 (15.8)

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories. * All deaths occurring up to 28 days after end of study treatment.

Common adverse events

Adverse events by system organ class

All subjects (100%) included in the studies experienced at least one AE. In the pivotal study (C2301) and the supportive study C2201 (part 2) AEs were most commonly reported within the SOCs *Gastrointestinal disorders* (67% and 68% respectively), *Infections and infestations* (67% and 74%, respectively) and *General disorders and administration site conditions* (65% and 79%, respectively). The reported SOC pattern in study C1201 and C2201 (part 1) were in line with the most common SOCs reported in the safety set of subjects with CS (study C2301 and C2201 part 2) (Table 27).

Table 19 Adverse events regardless of study drug relationship by system organ class and grade (severity) – Study C2301 and Study C2201 Part 2 (Safety set)

Primary system organ class	C2301 Osilodrostat N=137 All grades n (%)	C2301 Osilodrostat N=137 Grade 3/4 n (%)	C2201 Part 2 N=19 All grades n (%)	C2201 Part 2 N=19 Grade 3/4 n (%)
Number of patients with at least one event	**137 (100)**	**78 (56.9)**	**19 (100)**	**12 (63.2)**
Gastrointestinal disorders	94 (68.6)	10 (7.3)	13 (68.4)	2 (10.5)
Infections and infestations	92 (67.2)	8 (5.8)	14 (73.7)	1 (5.3)
General disorders and administration site conditions	89 (65.0)	6 (4.4)	15 (78.9)	1 (5.3)
Investigations	75 (54.7)	16 (11.7)	17 (89.5)	3 (15.8)
Musculoskeletal and connective tissue disorders	75 (54.7)	7 (5.1)	13 (68.4)	1 (5.3)
Nervous system disorders	73 (53.3)	9 (6.6)	12 (63.2)	1 (5.3)
Skin and subcutaneous tissue disorders	73 (53.3)	2 (1.5)	12 (63.2)	1 (5.3)
Endocrine disorders	69 (50.4)	15 (10.9)	9 (47.4)	4 (21.1)
Metabolism and nutrition disorders	55 (40.1)	14 (10.2)	9 (47.4)	0
Respiratory, thoracic and mediastinal disorders	48 (35.0)	5 (3.6)	5 (26.3)	0

	C2301 Osilodrostat N=137		C2201 Part 2 N=19	
Primary system organ class	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Injury, poisoning and procedural complications	40 (29.2)	7 (5.1)	8 (42.1)	0
Psychiatric disorders	39 (28.5)	5 (3.6)	6 (31.6)	1 (5.3)
Vascular disorders	37 (27.0)	16 (11.7)	5 (26.3)	4 (21.1)
Reproductive system and breast disorders	23 (16.8)	2 (1.5)	6 (31.6)	0
Cardiac disorders	22 (16.1)	0	5 (26.3)	1 (5.3)
Blood and lymphatic system disorders	17 (12.4)	5 (3.6)	6 (31.6)	1 (5.3)
Eye disorders	22 (16.1)	2 (1.5)	1 (5.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (15.3)	9 (6.6)	2 (10.5)	1 (5.3)
Renal and urinary disorders	12 (8.8)	1 (0.7)	4 (21.1)	0
Ear and labyrinth disorders	11 (8.0)	0	4 (21.1)	0
Hepatobiliary disorders	5 (3.6)	2 (1.5)	2 (10.5)	0
Immune system disorders	3 (2.2)	1 (0.7)	0	0
Surgical and medical procedures	2 (1.5)	0	0	0
Pregnancy, puerperium and perinatal conditions	1 (0.7)	1 (0.7)	0	0

A patient with multiple severity grades for a SOC 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.

Adverse events by system organ class regardless of study drug relationship (study C2301) were similar in the updated safety data set (cut-off 15 Oct 2019) as to those reported in the primary analysis with regard to the nature, severity and frequency of event.

AEs over time

The AE profile over time- derived from each of the three observation periods in the Core phase (week 1-12, week 12-26 and >26 weeks). There was no trend of increasing AEs over time as treatment with osilodrostat proceeded (Table 28). However, it has to be noted that the observation periods have varied duration in the different studies (12 weeks, 14 weeks, and up to approximately 3 years, respectively).

Table 20 Adverse events over time in study C2301

	Time on therapy					
	0-12 weeks		**12-26 weeks**		**> 26 weeks**	
	(N=137)		**(N=130)**		**(N=118)**	
	All grades	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**

System organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	131 (95.6)	43 (31.4)	107 (82.3)	27 (20.8)	108 (91.5)	44 (37.3)

Common adverse events by preferred term

The overall most common AE was *nausea* experienced in 41%-58% among all studies*. Headache* and *fatigue* was also frequently reported both in study 2301 (34% and 28%) and part 2 of study C2201 (42% and 26%). *Adrenal insufficiency* was reported in 28-32% of the subjects (Table 29). In study C2201 (part 2), high blood corticotrophin levels were reported in 8/19 (42%) of the patients. As discussed by the Applicant the frequencies of individual AEs differ, sometimes a lot, between the two studies included in the safety set (study C2301 and C201 part 2). However, it is agreed that this could most probably be explained by the different duration of exposure between the two studies and the low number of subjects in study 2201.

The AE profile in the placebo group during the randomised withdrawal phase in study 2301 demonstrates a slightly higher incidence of AEs for subjects in the osilodrostat group (72%) compared to the placebo group (66%). The most conspicuous differences between the two groups are a higher frequency of subjects reporting *naus*ea in the osilodrostat treatment group (n=4/36) compared to the placebo group (n=0). An imbalance was also noted for *arthralgia* and *headache* with 3 cases reported in the osilodrostat group compared to none in the placebo group. *Nausea* and *headache* is listed in the proposed SmPC which is endorsed. However, *arthralgia* is by the Applicant considered reflecting a complication of the underlying chronic hypocortisolism. This is accepted.

Table 21 Adverse events regardless of study drug relationship by preferred term and grade (severity) in at least 15% patients in any study– Study C2301 and Study C2201 Part 2

	Study C2301 Osilodrostat N=137		**Study C2201 Part 2 N=19**	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	**137 (100)**	**78 (56.9)**	**19 (100)**	**12 (63.2)**
Nausea	57 (41.6)	3 (2.2)	9 (47.4)	0
Headache	46 (33.6)	4 (2.9)	8 (42.1)	1 (5.3)
Fatigue	39 (28.5)	3 (2.2)	5 (26.3)	0
Adrenal insufficiency	38 (27.7)	6 (4.4)	6 (31.6)	1 (5.3)
Nasopharyngitis	31 (22.6)	1 (0.7)	5 (26.3)	0
Vomiting	30 (21.9)	4 (2.9)	3 (15.8)	0
Glucocorticoid deficiency	29 (21.2)	5 (3.6)	1 (5.3)	0
Arthralgia	27 (19.7)	3 (2.2)	5 (26.3)	0
Back pain	27 (19.7)	0	2 (10.5)	0
Diarrhoea	25 (18.2)	1 (0.7)	6 (31.6)	0
Influenza	24 (17.5)	0	3 (15.8)	0
Blood corticotrophin increased	23 (16.8)	1 (0.7)	8 (42.1)	0

	Study C2301 Osilodrostat N=137		Study C2201 Part 2 N=19	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Asthenia	23 (16.8)	1 (0.7)	6 (31.6)	0
Oedema peripheral	21 (15.3)	0	4 (21.1)	0
Urinary tract infection	20 (14.6)	1 (0.7)	5 (26.3)	0
Hormone level abnormal	19 (13.9)	0	7 (36.8)	0
Dizziness	19 (13.9)	0	4 (21.1)	0
Hypertension	17 (12.4)	15 (10.9)	4 (21.1)	4 (21.1)
Blood testosterone increased	15 (10.9)	0	6 (31.6)	0
Abdominal pain	13 (9.5)	3 (2.2)	5 (26.3)	0
Anaemia	13 (9.5)	2 (1.5)	3 (15.8)	1 (5.3)
Acne	12 (8.8)	0	3 (15.8)	0
Upper respiratory tract infection	12 (8.8)	0	3 (15.8)	0
Depression	10 (7.3)	2 (1.5)	3 (15.8)	1 (5.3)
Malaise	9 (6.6)	0	4 (21.1)	0
Toothache	5 (3.6)	0	3 (15.8)	0
Blood creatine phosphokinase increased	4 (2.9)	1 (0.7)	3 (15.8)	1 (5.3)
Lipase increased	4 (2.9)	2 (1.5)	3 (15.8)	1 (5.3)
Vertigo	4 (2.9)	0	3 (15.8)	0
Weight increased	3 (2.2)	0	3 (15.8)	0
Hypertrichosis	1 (0.7)	0	3 (15.8)	0
Pituitary-dependent Cushing's syndrome	1 (0.7)	1 (0.7)	3 (15.8)	3 (15.8)

A patient with multiple severity grades for an AE is only counted under the maximum grade. For C2301, any event experienced by patients randomized to placebo while on placebo are not included in this analysis.

AEs reported in the safety update (study C2301) with cut-off 15 Oct 2018 were similar to those reported in the primary analysis with regard to the nature, severity and frequency of events.

Common AEs with osilodrostat in other indications (i.e. hypertension)

Osilodrostat was previously studied in patients with hypertension. The clinical studies in this indication used low doses (0.25 mg/day to 2 mg/per day) for shorter durations (4 to 8 weeks). Overall, besides in general lower frequencies of reported AEs, no new safety finding have been identified regarding the AE profile when comparing treatment with low-dose osilodrostat in subjects with hypertension with higher doses in the subjects with endogenous Cushing syndrome (Table 30).

Table 22 Summary of AEs regardless of study drug relationship by system organ class across studies A2201, A2216 and C2301

	A2201	A2216	C2301
	0-8 weeks	0-8 weeks	0-12 weeks
	N=363	N=89	N=137
Primary system organ class	n (%)	n (%)	n (%)
Any primary system organ class	**96 (26.4)**	**38 (42.7)**	**131 (95.6)**
Blood and lymphatic system disorders	0	0	3 (2.2)
Cardiac disorders	6 (1.7)	0	10 (7.3)
Congenital, familial and genetic disorders	1 (0.3)	0	0
Ear and labyrinth disorders	2 (0.6)	0	4 (2.9)
Endocrine disorders	0	1 (1.1)	43 (31.4)
Eye disorders	5 (1.4)	1 (1.1)	10 (7.3)
Gastrointestinal disorders	20 (5.5)	10 (11.2)	65 (47.4)
General disorders and administration site conditions	11 (3.0)	5 (5.6)	66 (48.2)
Hepatobiliary disorders	2 (0.6)	0	2 (1.5)
Immune system disorders	1 (0.3)	1 (1.1)	1 (0.7)
Infections and infestations	28 (7.7)	2 (2.2)	46 (33.6)
Injury, poisoning and procedural complications	6 (1.7)	3 (3.4)	12 (8.8)
Investigations	0	11 (12.4)	42 (30.7)
Metabolism and nutrition disorders	3 (0.8)	4 (4.5)	32 (23.4)
Musculoskeletal and connective tissue disorders	11 (3.0)	8 (9.0)	40 (29.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	3 (2.2)
Nervous system disorders	20 (5.5)	6 (6.7)	39 (28.5)
Psychiatric disorders	1 (0.3)	3 (3.4)	13 (9.5)
Renal and urinary disorders	0	1 (1.1)	6 (4.4)
Reproductive system and breast disorders	1 (0.3)	0	8 (5.8)
Respiratory, thoracic and mediastinal disorders	10 (2.8)	4 (4.5)	18 (13.1)
Skin and subcutaneous tissue disorders	10 (2.8)	4 (4.5)	51 (37.2)
Vascular disorders	2 (0.6)	2 (2.2)	17 (12.4)

SOCs are sorted in alphabetical order.

A2201

Study A2201 was a multi-center, randomized, double-blind, placebo and active controlled, parallel group, dose finding (0.25 mg QD, 0.5 mg QD, 1.0 mg QD and 0.5 mg BID) study to evaluate the efficacy and safety of osilodrostat compared to placebo after 8 weeks treatment in patients with stage 1-2 hypertension (N=524 including 77 in the placebo group and 84 in active substance group [eplerenone]). Most frequent AEs (>1%)

among patients receiving osilodrostat were nasopharyngitis, dizziness, headache, influenza, upper respiratory tract infection and fatigue.

A2206

A pilot, single-blind, forced-titration study to assess the hemodynamic and hormonal effects, safety and tolerability of osilodrostat after 4 weeks of treatment in patients with primary hyperaldosteronism (N=18). All patients received 0.5 mg b.i.d for 2 weeks, followed by 1 mg b.i.d for 2 weeks. Most frequent AEs among patients receiving osilodrostat were hypertension, diarrhoea, headache, rhinitis and myodesopia (all 1 patient each).

A2215

A Phase II, randomized, double-blind, placebo controlled, multi-center study to evaluate the effects of osilodrostat (0.5-2.0 mg once daily) on cortisol after 6 weeks of treatment in patients with hypertension (N=63 including 13 subjects on placebo). Most frequent AEs among patients receiving osilodrostat (>2%) were: headache, ACTH stimulation test abnormal, dizziness, diarrhoea, dyspepsia, hyponatremia, nausea, sinusitis, arthritis, back pain, blood creatine phosphokinase increased, chest discomfort, fatigue, nasopharyngitis, vomiting.

A2216

A Phase II, randomized, double-blind, placebo controlled, multi-center study to evaluate the effects of osilodrostat (0.25mg BID, 1.0 mg QD, and 0.5mg BID titrated to 1.0mg BID after 4 weeks of treatment) on cortisol after 6 weeks of treatment in patients with hypertension (N=155 including 33 subjects in the placebo group and 33 in the active control group [eplerenone]). Most frequent AEs >2% were: hyponatremia (including blood sodium decreased), blood cortisol decreased, diarrhea, muscle spasms, nausea, upper abdominal pain, increased blood creatinine, increased blood glucose, dizziness, dyspepsia, fatigue, headache, hyperhidrosis, and peripheral edema.

Adverse events suspected to be drug related

Overall, 93-95% of the subjects in study C2301 and Study C2201 Part 2 (CS) experienced AE that was judged as related to study drug by the investigators. Of these, 30-40% was a grade 3 or 4 AE. The most common PTs judged as related to study drug was *adrenal insufficiency* and *nausea* (37/137 [27%] and 6/16 [32%] in study C2301 and C2291 respectively) and *fatigue* (29/137 [21%] and 4/19 [21%]).

Adverse events leading to dose interruption or adjustment

Overall, the vast majority of subjects (78%) in the pivotal study (C2301) experienced at least one AE that lead to a dose interruption or adjustment. Most commonly (>6% of patients) reported AEs requiring dose adjustment of interruption regardless of study drug relationship were *adrenal insufficiency* (25%), *glucocorticoid deficiency* (18%), *nausea* (15%), *fatigue* (12%) and *asthenia* (9.5%).

Adverse events of special interest

The AESI considered by the Applicant for osilodrostat are:

- hypocortisolism-related AEs
- adrenal hormone precursor accumulation-related AEs
- pituitary tumor enlargement-related AEs
- QT-prolongation-related AEs

- arrhythmogenic potential AEs

See Table 31 and Table 32.

Table 23 Study C2301 -Adverse events of special interest, regardless of study drug relationship by group name, severity and randomized treatment group up to data cut-off date

	Randomized to osilodrostat during RW		Randomized to placebo during RW*		Non-randomized		All Patients	
	N=36		N=35		N=66		N=137	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
AESI Groups	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AESI	**25 (69.4)**	**3 (8.3)**	**23 (65.7)**	**9 (25.7)**	**50 (75.8)**	**20 (30.3)**	**98 (71.5)**	**32 (23.4)**
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	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)

Table 24 Study C2201 Part 2 - Adverse events of special interest regardless of study drug relationship by category and maximum CTC grade - up to cut off data (14-Nov-2017)

	All patients N=19	
Safety topic	**All grades n (%)**	**Grade 3/4 n (%)**
Any AESI	**14 (73.7)**	**5 (26.3)**
Adrenal Hormone Precursor Accumulation-related AEs	12 (63.2)	4 (21.1)
Hypocortisolism related AEs	8 (42.1)	1 (5.3)
Arrhythmogenic potential AEs	1 (5.3)	0
QT-prolongation-related AEs	1 (5.3)	0

Hypocortisolism-related AEs

Symptoms (e.g. nausea, fatigue and dizziness) and clinical manifestations (e.g. hypotension, hypoglycaemia, hyponatraemia and hyperkalaemia) related to decreased cortisol is expected based on the mechanism of action of osilodrostat. If untreated, hypocortisolism could lead to fatal outcomes (like Addison crisis). However, if early detected this condition is manageable.

The following PTs were used to identify hypocortisolism related Adverse events; Addison's disease, Adrenal insufficiency, Adrenal suppression, Adrenocortical insufficiency acute, Cortisol decreased, Cortisol deficiency, Cortisol free urine decreased, Glucocorticoid deficiency, Glucocorticoids decreased, Primary adrenal insufficiency, Secondary adrenocortical insufficiency and Steroid withdrawal syndrome. The initially identified hypocortisolism related Adverse events were not checked for related laboratory values (i.e. cortisol levels).

Study C2301

- *Adverse events related to hypocortisolism irrespective of laboratory values*

In an up-dated analyse the Applicant concludes that 71/137 patients (52%) reported 167 AEs related to hypocortisolism in study C2301 (see search criteria above). The most reported PT was *adrenal insufficiency,* reported in 28% (n=38) (Table 33).

One third (56/167; 33%) of the hypocortisolism related adverse events occurred within the titration period i.e. first 12 weeks (84 days). The remaining events (67%) occurred after the first 12 weeks (Table 34). However, in individual cases up-titration occurred even after the first 12 weeks and overall 40% (67/167) of the reported adverse events related to hypocortisolism occurred during any period of up-titration and 57% (96/167) of the reported events occurred during periods with stable doses of osilodrostat. Among the in total 96 events reported during maintenance periods 15% were reported with confounding factors.

Most of the patient with hypocortisolism-related AEs had just one episode.

Among the 70 patients initially identified with a hypocortisolism-related event (in study C2301), 39 had dose reductions. Most patients (25/39) had 1 dose reduction. Dose interruptions occurred in 30 of the 70 patients, in most cases, one instance of dose interruption (23). Four patients (2.9%) with adrenal insufficiency AEs discontinued the study drug.

- *Adverse event related to hypocortisolism vs laboratory values*

In study C2301 laboratory values were identified in 64 of the 67 events reported during any period of titration. Among these only 27% (17/64) were reported cortisol values below the normal lower level. Thus in 73% of the cases (47/64) the events seem to have been reported with values within the normal range (or above normal). Based on this finding the Applicant presented a deeper analyse of the hypocortisolism related AEs (during titration) in relation to mUFC levels. Thus, it could be concluded that there is an incoherence between the PT reported and the factual mUCF levels. Based on this observation the Applicant assume that the frequency of true hypocortisolism in C2301 study may have been be over-estimated because of misclassification of the AEs. The assumption is based on the following:

The symptoms suggestive of adrenal insufficiency (sometimes just fatigue or malaise) with normal or even high mUFC were reported as hypocortisolism or adrenal insufficiency (sometimes specified as "suspected", "relative", "mild", "acute", "symptomatic") and coded into obligatory PTs of "glucocorticoid deficiency" or "adrenal insufficiency". The most appropriate term for these events associated with mUFC > ULN or in the upper part of the normal range would be "glucocorticoid withdrawal syndrome", as the reported symptoms were probably caused by a fast decrease in cortisol levels from the pre-treatment baseline.

According to the Applicant, investigators may not have considered this term in some cases because "glucocorticoid withdrawal syndrome" is not a usual term used in clinical endocrinology practice.

However, it is of importance to also consider that the incoherence between the AEs and factual laboratory values might to some extent reflect the experience of a reduction in cortisol from high to normal levels. Therefore, when subjective symptoms of hypocortisolism appear, it is of importance to confirm these events by laboratory values. This is reflected in the SmPC.

No values of cortisol levels in connections to the events during the maintenance periods have been presented by the Applicant. However, it could be assumed that even events, reported during the maintenance period, to some extent not either are associated with true hypocortisolism due to misclassifications by the investigators.

Study C2201

In study C2201 (part II) 8 out of 19 subjects (42%) reported an event of hypocortisolism. As for study C2301 the most reported PT was *adrenal insufficiency,* reported in 32% (n=6/19). Four of the six patients experienced one event each, and the other two patients experienced two events each. The adrenal insufficiency event in one patient was reported as an SAE. All events were suspected to be related to study drug by the Investigator.

Summary of adverse events related to hypocortisolism

There is an incoherence between adverse events related to hypocortisolism and laboratory values. The reason for this is probably a misclassification of the AEs by the investigators but also the fact that the subjects sometimes experience subjective symptoms when the cortisol levels decreases from high to normal levels. However, it could be concluded that the frequency of "true" hypocortisolism events seems lower than initially reported. This is reassuring. However, it is a weakness with the study that the factual frequency of hypocortisolism not is possible to estimate in the data presented. This depends on different factors; ambiguity regarding the description of AEs (GCP finding) and uncertainty in laboratory values due to different measuring methods. Furthermore, the recommended dosing in the proposed SmPC differs from that used in the studies. Thus, further analyses of the study data is not considered to change the B/R balance or result in major SmPC changes.

Hypocortisolism is characterised as an important identified risk in the RMP. In addition, the Applicant has proposed a targeted follow-up questionnaire (including laboratory values) to follow events of hypocortisolism in routine pharmacovigilance. Events related to hypocortisolism will also be studied as a topic related to long-term safety**.**

The overall risk for hypocortisolism is currently reflected in the SmPC section 4.4 and 4.8. In section 4.8 *Adrenal insufficiency* (including clinically similar PTs) is labelled as very common. *Hypotension* could be a symptom related to hypocortisolism and this ADR is reflected in SmPC section 4.8. In order to avoid overtreatment and non-recognition of hypocortisolism, a recommendation for the use of **specific laboratory methods** for cortisol monitoring without significant cross-reactivity with cortisol precursors is given in the SmPC to avoid cortisol overestimation.

It is agreed with the Applicant that the new data presented do not warrant any extended up-date of the PI and proposed pharmacovigilance and RMM activities are considering sufficient.

Table 25 Hypocortisolism-related AEs regardless of study drug relationship, by preferred term, and treatment group up to data cut-off (study C2301).

	Randomized to osilodrostat during RW		**Randomized to placebo during RW ***		**Non-randomized**		**All Patients**	
	N=36		**N=35**		**N=66**		**N=137**	
Hypocortisolism related AEs	**All Grades**	**Grade 3/4**	**All Grades**	**Grade ¾**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**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

	Randomized to osilodrostat during RW		Randomized to placebo during RW *		Non-randomized		All Patients	
	N=36		N=35		N=66		N=137	
Hypocortisolism related AEs	**All Grades**	**Grade 3/4**	**All Grades**	**Grade ¾**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
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

Table 26 Hypocortisolism-related adverse events in study C2301

Time to event onset	Number of events
0-28 days	14
29-56 days	23
57-84 days	19
85-112 days	14
113-140 days	6
141-168 days	5
> 6 months – 1 year	32
>1 to 2 years	33
>2 to 3 years	16
>3 to 4 years	4
>4 to 5 years	1

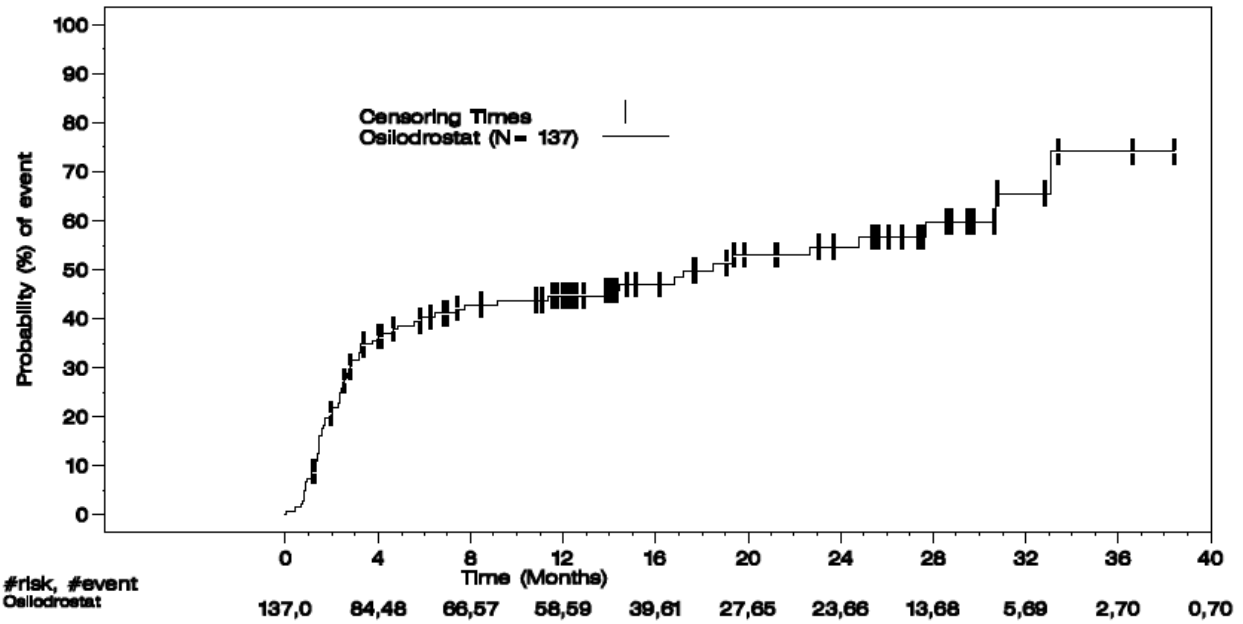


Figure 20 Time to first occurrence of hypocortisolism related adverse events (C2301)

Adrenal hormone precursor accumulation-related AEs

Adrenal hormone precursor accumulation is a result of the mechanism of action of most cortisol inhibitors resulting in potential increase in circulating levels of cortisol and aldosterone precursors (11- deoxycortisol, 11-deoxycorticosterone), and sexual steroids.

In total, adrenal hormone precursor accumulation-related AEs was reported in 58/137 (42%) in study C2301 and 12/19 (63%) in study C2201 part 2. The most common reported PTs were *hypokalaemia* (13% [2301] and 10% [2201]), *hypertension* (12% [2301] and 21% [2201]) and *acne* (9% [2301] and 16% [2201]). Most of the cases with *hypertension* reported severe/grade 3 events (Table 35).

See also section "Laboratory findings" regarding measurements of sexual hormones.

The Applicant has proposed to label most of the common adverse reactions related to adrenal hormone precursor accumulation in SmPC section 4.8 (i.e. *hypokalaemia, acne, hirsuti*sm and *oedema*).

However, "*hypertension"* is not proposed in the ADR table. In response to the D120 LoQ the Applicant informs that in total there were 23 patients who experienced hypertension (including PTs of Hypertension, Renovascular hypertension, Blood pressure increased, Blood pressure systolic increased, Blood pressure diastolic increased; 3 patients reported more than 1 event PT) in study C2301 and a further 5 patients in C2201. No patients in C1201 reported an AE of hypertension. Thus, in total 28 subjects reported hypertension. A review of the cases concluded that all were confounded by underlying Cushing's disease and associated comorbidities (including hypertension) and that there was no evidence of dose response or consistent temporal relationship, and the sporadic findings of hypertension were not consistent with the overall higher rates of hypotension and the effects on blood pressure seen in both the Cushing's and hypertension programs. Overall, it was concluded that there was no robust evidence that the onset of worsening or new onset hypertension was associated with increases in 11-DOC that warranted any up-date of the SmPC.

Increase in testosterone as part of adrenal hormone precursor accumulation-related AEs is now reflected in the section "Description of selected adverse reactions" in SmPC section 4.8.

Table 27. Adrenal hormone precursor accumulation-related AEs regardless of study drug relationship, by preferred term, and treatment group up to data cut-off- Study C2301

	Randomized to osilodrostat during RW		Randomized to placebo during RW*		Non-randomized		All Patients	
Adrenal hormone	**N=36**		**N=35**		**N=66**		**N=137**	
precursor Accumulation-related AEs	**All Grades**	**Grade 3/4**	**All Grades**	**Grade ¾**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hypokalaemia	3 (8.3)	0	3 (8.6)	2 (5.7)	12 (18.2)	4 (6.1)	18 (13.1)	6 (4.4)
Hypertension	2 (5.6)	1 (2.8)	3 (8.6)	3 (8.6)	12 (18.2)	11 (16.7)	17 (12.4)	15 (10.9)
Acne	1 (2.8)	0	2 (5.7)	0	9 (13.6)	0	12 (8.8)	0
Hirsutism	4 (11.1)	0	3 (8.6)	0	5 (7.6)	0	12 (8.8)	0
Oedema	1 (2.8)	0	3 (8.6)	1 (2.9)	5 (7.6)	0	9 (6.6)	1 (0.7)
Weight increased	1 (2.8)	0	1 (2.9)	0	1 (1.5)	0	3 (2.2)	0
Blood pressure diastolic increased	0	0	0	0	2 (3.0)	1 (1.5)	2 (1.5)	1 (0.7)
Blood pressure increased	0	0	1 (2.9)	0	1 (1.5)	0	2 (1.5)	0
Blood pressure systolic increased	0	0	0	0	2 (3.0)	1 (1.5)	2 (1.5)	1 (0.7)
Hyperkalaemia	0	0	0	0	2 (3.0)	0	2 (1.5)	0
Blood potassium decreased	0	0	1 (2.9)	1 (2.9)	0	0	1 (0.7)	1 (0.7)
Hypertrichosis	0	0	0	0	1 (1.5)	0	1 (0.7)	0

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

Pituitary tumour enlargement-related AEs

Tumour volume increase is a potential risk due to a lowering of blood cortisol and a negative feed-back leading to a potential increased ACTH production but may also be part of the natural history of the disease. Pituitary tumour enlargement could compress the surrounding tissues and cause vision problems.

The size of the pituitary tumour was measured in study C2301. At baseline the median (min-max) tumour volume was 78.2 (4.6-6405.8) mm^3, after 24 weeks the median size had decreased to 71.1 (5.0-1556.2) mm^3 and after 48 weeks to 70.7 (5.6-919.3) mm^3.

Overall, an enlargement of the pituitary tumour ≥ 20% (by region of interest) from baseline was noticed in 45% (36/79) of the subjects with both a baseline and post baseline value. Tumour volume decrease (≥20%) from baseline was observed in 61% (48/79) of these patients.

In addition, a search was performed with the pre-defined search criteria for the AESI category of pituitary tumour enlargement AEs including the following preferred terms:

- Cavernous sinus syndrome
- Diplopia
- Extraocular muscle paresis
- Pituitary enlargement
- Pituitary infarction
- Visual field defect

The search identified three cases of diplopia. An additional search was conducted to include also non-serious events of pituitary tumour and pituitary tumour benign in C2301 to 15Oct2018. In total, 16 patients (including the 7 serious reports tabulated above) reported these events. In all cases, the event reflected growth of the underlying pituitary adenoma as evidenced by the reported term and/or tumour volume by ROI on MRI.

Although, a decrease in mean tumour volume was reported in study C2301 an individual enlargement of the pituitary tumour ≥ 20% (in tumour volume by 3 maximum dimensions (mm^3) or 2mm increase in longest diameter from baseline) was noticed in 44% of the subjects and a decrease in 56% of the subjects. It is agreed with the Applicant that overall, there was no evidence of tumour enlargement in association with use of osilodrostat. However, due to the mechanism of action (with increased ACTH production due to a negative feed-back of low cortisol levels) an increase in tumour volume could not be excluded in individual cases. Regular MRI monitoring of the adenoma to detect growth of the pituitary tumour should (always) be performed in clinical practice. Therefore, it is not considered relevant to up-date the SmPC with a warning regarding this.

The pivotal Phase III study CLCI699C2301 was amended (Amendment 5) on 29-Jun-2018 to implement a number of changes to the protocol. One of these was to add two features to the central Pituitary MRI/CT assessments (corticotroph tumour re-occurrence and corticotroph tumour invasiveness.

Corticotroph tumour re-occurrence: Among the 46 subjects without measurable pituitary tumour at baseline one subject with a re-occurrence of the *corticotroph tumour* was identified. This case had previously undergone pituitary surgery twice (latest in 2007). The re-occurrence was not associated with any AE in this case.

New corticotroph tumour invasiveness: Among the 46 subjects with non-invasive pituitary tumours at baseline a "new" *corticotroph tumour invasiveness* was reached by 6 subjects. In all the six cases a tumour volume increase was documented. Further, adverse events related to tumour volume increase were reported during the study in five of the six cases and all these five cases either discontinued study drug or was withdrawn from the study, which is considered relevant.

in the individual cases it is difficult to assess if an enlargement of the pituitary tumour is only due to the disease (CD) or might have been enhanced by osilodrostat treatment. However, in subjects reaching tumour invasiveness when not showing tumour invasiveness before start of treatment it would be unfortunate, should osilodrostat treatment enhance tumour growth. Therefore, it would be of value to inform the prescriber that treatment with osilodrostat should be discontinued in case of a tumour enlargement reaching the degree of invasiveness in subjects without invasiveness before treatment. This information is now included in SmPC section 4.4 and the PL**.**

Arrhythmogenic potential AEs

Preclinical studies have shown a proarrhythmic potential for osilodrostat. The following PTs was included in the MedDRA search for AESI Arrhythmogenic potential AEs: *Cardiac arrest, Cardiac death, Cardiac fibrillation, Cardio-respiratory arrest, Loss of consciousness, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia and Ventricular tachycardia*. QT-prolongation is separately characterized as Adverse Event of Special Interest. See section below.

According to the Applicant the search of events related to arrythmia described above identified one patient had a SAE of grade 3 syncope in study C2301 and one patient experienced two grade 2 events of syncope in study C2201. Neither of these events were reported in association with arrhythmia.

However, in study C2301 additional events considered related to Arrhythmogenic potential are noted to have been reported (Table 14.3.1-1.4; CLCI699C2301 Primary CSR). In this table a total of 22 (16%) events in the SOC Cardiac disorders was reported including 7 cases reported "tachycardia", 3 cases reported "palpitations", 2 cases reported "Bundle branch block right" and one each of the following PTs: "atrial fibrillation", "AV-block 1", "bradycardia2, "Bundle branch block left", "sinus bradycardia", "sinus tachycardia" and "Ventricular extrasystoles". Reassuring, none of these events were reported as grade 3 or 4 and the most common PT of these, "tachycardia", is included in the ADR table in SmPC section 4.8. However, they are AEs potential related to arrhythmia that also preferable should have been reflected in this section. At present since osilodrostat are known to a have a proarrhythmogenic potential and the that risk for QT-prolongations have strict SmPC wordings in section 4.4 it is not considered that any additional analyses of ECGs should provide any further information that should influence B/R or major SmPC writings. The risk is considered acceptable taken care of in the SmPC.

QT-prolongation AEs

In both human and animal studies, osilodrostat showed concentration/dose dependent QT prolongation and a potential to cause cardiac rhythm abnormalities, including Torsades de pointes. Due to substantial QTcF changes observed in a post-hoc analysis of a Phase I study, the maximum dose was decreased from 50 mg bid to 30 bid as a precaution.

The mechanism by which osilodrostat may cause QT-prolongation is not well understood: it does not seem to be through hERG or other cardiac ion channels, but a hypothetical mechanism is through an effect on intracellular calcium transients, energy and/or mitochondrial function.

Hypokalaemia seen in CS is often associated with hypomagnesaemia and increases the risk of malignant ventricular arrhythmias. Worsening of hypokalaemia has been reported with adrenal directed drugs that can increase cortisol precursors with mineralocorticoid activity. In addition, myocardial fibrosis caused by an enhanced responsiveness to angiotensin II and activation of the mineralocorticoid receptor in direct response to cortisol excess could exacerbate the effects of hypokalaemia on QT interval prolongation seen in patients with CS.

In all three studies (C2301, C2201 and C1201) subjects with risk factors for QTc prolongation or Torsade de Pointes including deranged electrolyte values (potassium, sodium or magnesium) were exclusion criteria as well as patients who had a history of CV diseases.

In the dossier submitted there were differences between the SCS, the CSRs and the RMP, and issues lacking, in the number of events/ECG measurements and the information on dose-dependency. During the procedure, more information was requested from the applicant, and based partially on that as well as on CHMP's analysis a compilation with the most up-to-date numbers seemed to be as summarised in Table 28 (below):

Table 28 ECG prolonged clinically relevant effects

	C2301	C2201	C1201	TOTAL
ECG QTcF				
>30 to < 60 ms vs baseline	**52**	5	3	**60**
>60 ms vs baseline	3	3	2	8
New >450 - ≤480 ms	**17**	3	4	**24**
New >480 - ≤ 500 ms	1	1	1	3
New >500 ms	1	0	0	1
ECG QT-prolonged AEs	5	2	0	7
Discontinuations	1	0	0	1
Dose adjustment/interruption	3	1	0	4
Ongoing	1	0	0	1
SAE	0	1	0	1
Grade 3/4	2	0	0	2

Based on local reading data

The amount of subjects with measured clinically significant QT-prolongations in study C2301, C2201 and C1201 is considered low. Considering a small population where the majority of individuals with risk factors have been excluded it is not expected to identify (m)any patients with serious events of arrhythmia including *Torsade de pointes* during the relatively short treatment period. In study C2301 the mean (SD) change from baseline at Week 48 was 5.3 ms (20.67) for QTcF. In total three subjects had QTcF values >480 to 500 ms (one in each study, based on central reading). No new QTcF of > 500 ms confirmed by central reading was observed in any of the studies, while one based on local reading was reported in C2301.

In total, there were 7 subjects QT-prolonged AEs reported in the three studies, five (non-serious) in the pivotal study (C2301) and 2 (of which 1 serious) in study C2201. Considering a small population where the majority of individuals with risk factors have been excluded it is not expected to identify (m)any patients with serious events of arrhythmia including *Torsade de pointes* during the relatively short treatment period.

The Applicant has confirmed that not all ECG measurements of clinical relevance (QTcF >480 ms, >500 ms and increase versus baseline >60 ms) were reported as ECG QT prolonged AE in the 3 studies i.e. the following were not reported: 5 patients, and a first finding in a 6th patient for whom a second finding was reported as an AE), without explaining why. While this is considered to be in contradiction to the protocol, no further action is possible at this stage.

The risk for arrhythmia including QT-prolongations potentially leading to Torsade de pointes can occur at any treatment duration.

The requested analysis, of the cases was not able to identify unknown risk factors/contributing factors nor a specific pattern regarding time-to-onset, duration, dosing phase or dose, so no further SmPC updates were considered relevant. Addition of a warning regarding the concomitant use of QT-prolonging medicinal products is included in the SmPC, section 4.5, and section 4.4 has been adequately up-dated regarding risk patients.

Only 1 patient discontinued the study drug in C2301 due to ECG QT QT prolonged AEs and none in the other studies. None of the 8 patients with a > 60 ms increase versus baseline (local reading) was discontinued from the studies. For study C2201, this was not a discontinuation criterion; for C1201 and C2301, it depended on cardiologist review.

Nine of the events did not require any action towards osilodrostat, while for 4 events, osilodrostat was temporarily interrupted and re-initiated at the same dose (in 1 patient) or at reduced dose (in 3 patients) after which no new QT event was reported; 1 event required permanent discontinuation.

The risk for QT-prolongations is reflected in SmPC section 4.4 with recommendations for ECG monitoring before and one week after initiation of osilodrostat and when clinically indicated thereafter, and electrolyte monitoring before and periodically during treatment, as well as in section 4.8. It was judged not possible to predict a time period where monitoring of electrolytes or ECGs should be specifically focused, and conversely intense monitoring throughout the lifetime of each patient is likely to result in undue burden. In case the QTc interval exceeds 480 ms prior or during treatment, cardiology consultation is recommended to consider whether to initiate or to continue osilodrostat, or (temporarily) reduce or interrupt its dose.

The uncertainty regarding patients at risk for QT-prolongation and CV diseases remains as these were not included in the studies. It was asked to propose strengthened RMM for this population including a contraindication and updated warning in the SmPC. Taking into account the inherent risk of QT prolongation in CS, the quite large safety margin measured in the TQT study, the limited number of AEs and clinically significant ECG findings in the phase III studies, as well as the fact that it would be inappropriate to formally exclude all of these patients from osilodrostat treatment as there are only limited treatment options and the fact that it is hypothesised that the improvement of hypercortisolism with osilodrostat will reduce the inherent risk of QT prolongation, it is agreed with the Applicant not to add a contra-indication. However, these high-risk patients have been excluded from clinical studies, so some of the above stated elements are still theoretical and therefore, a warning in section 4.4 was added regarding the fact that the B/R should be carefully weighed in high-risk patients.

The risk is characterized as an important identified risk in the RMP with routine PhV activities including a targeted follow-up check list and routine RMM. More results regarding cardiac safety after long-term use of osilodrostat will be available by the ongoing extension of the studies (C2301, C2201 and C1201).

In addition, the risk for QT-prolongation in a real-world population after long-term use and in the population with CV diseases and risk for QT-prolongations will be followed within the topic "Long-term safety" characterised as missing information in the RMP which will be followed up in the Category 3 PASS studies.

Serious adverse events and deaths

Death

Within all studies, one death (suicide) was reported (study C2301). The patient, a 55-year-old female, committed suicide during the Extension Period on Day 551. The patient's active medical conditions included depression, grade 2, since 2010. It is agreed with the Applicant that most probably the fatal case was due to a medical history of depression. However, a worsening of symptoms related to depression while on treatment could not be excluded.

In total, events of depression were reported in 10 cases (7.3%) of the subjects in study C2301 and 3 subjects (16%) in study C2201. In total, one event of depression was reported as serious.

In the safety up-date (cut-off date 15 Oct 2018) no additional deaths occurred until the database lock for the safety update but one additional death was reported after the database lock (Fatal viral gastroenteritis and cardiopulmonary failure; assessed as not related to study drug by the investigator).

Other serious adverse events

In the studies performed in subjects with Cushing disease (C2301 and C2201 part II) approximately one third of the subjects experienced a SAE, 36% (50/137) in study C2301 and 32% (6/19) in study C2201 part II.

In study C2301, the most common SAEs were *adrenal insufficiency or adrenocortical insufficiency acute* (11/50 cases; 22%) and pituitary *tumour or pituitary tumour benign* (7/50 cases; 14%) respectively (Table 37), see also section "Pituitary tumour enlargement-related AEs" above.

Table 29 SAEs regardless of study drug relationship by preferred term and severity in at least 2 patients in any study – Study C2301 and Study C2201 Part 2 (Safety set)

	C2301 Osilodrostat N=137	**C2201 Part 2 N=19**
Preferred Term	**n (%)**	**n (%)**
Number of patients with at least one event	50 (36.5)	6 (31.6)
Adrenal insufficiency	8 (5.8)	1 (5.3)
Pituitary tumour	5 (3.6)	0
Gastroenteritis	3 (2.2)	1 (5.3)
Adrenocortical insufficiency acute	3 (2.2)	0
Pituitary tumour benign	2 (1.5)	1 (5.3)
Abdominal pain	2 (1.5)	0
Anxiety	2 (1.5)	0
Cholelithiasis	2 (1.5)	0
Glucocorticoid deficiency	2 (1.5)	0
Influenza	2 (1.5)	0
Pneumonia	2 (1.5)	0
VIth nerve paralysis	2 (1.5)	0
Pituitary-dependent Cushing's syndrome	1 (0.7)	2 (10.5)

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

In the safety up-date, with cut-off 15 Oct 2018, there are 2 additional patients with the first occurrence of a SAE after the primary CSR cut-off date, 7 other patients also reported a SAE but had already reported another one in the primary analysis period. Thus, the number of patients that reported a SAE has increased from 50 to 52, and the number of those in whom they were considered drug-related has increased from 21 to 22.

The nature and frequency of SAEs in the safety up-date with cut-off 15 Oct 2018, was similar to those reported in the primary CSR.

Laboratory findings

The Applicant informs that laboratory analysis included evaluations of shift tables, worst post-baseline grade, Grade 3 or 4 lab abnormalities as well as laboratory abnormalities that were considered clinically relevant (reported as AEs).

The analyse below focus on study C2301 since a low number of subjects were included in study C2201 and C1201.

Haematology

At the time of the data cut-off date, no patients had newly occurring grade 4 haematology abnormalities or worsening haematology abnormalities to grade 4. Newly occurring or worsening to grade 3 haematology abnormalities were infrequent and were reported for haemoglobin decrease and absolute neutrophils decrease (in 3 patients, each) and leucocyte increase and platelets decrease (in 1 patient, each).

Haemoglobin decreases

Anaemia/haemoglobin decreased is a known effect of related to the intended normalisation of chronic cortisol excess, has been documented with other therapies (including surgical treatment), and is not considered a direct toxic effect of the drug.

In total, a decrease in haemoglobin (CTC grade 1-3) was reported in 38% of the patients in the pivotal study (C2301). including three cases of newly occurring or worsening to grade 3 The mean Hb value slightly decreased over time (137±18.03 g/L at baseline compared to 132.2±16.68 g/L after 12 weeks, 129.5±17.39g/L after 26 weeks and 133.0±16.94 g/L after 44 weeks).

In parallel, anaemia/iron deficiency anaemia/haemoglobin decreased was reported as an AE in 18/137 (13%) patients in C2301 as of 15-Oct-2018, in 5/19 (26%) patients in C2201 (as of 14-Nov-2017), and one patient in C1201. Across the 4 hypertension studies, there was a single case of non-serious 'mild anaemia' reported. Most of the relevant cases reported with anaemia had confounding factors of which several were present already at baseline,

Since it is acknowledged that normalisation of chronic cortisol excess in subjects with CS is associated with a decrease haemoglobin, that the mean Hb value in study C2301 had a modest decreased over time and that a substantial amount of the cases with anaemia were confounded and in study C2301 it is acknowledged that no up-date of the SmPC is warranted.

Neutrophil decrease

Treatment with osilodrostat can potentially be associated with neutropenia which is considered to be an indirect effect of cortisol reduction, regardless of the treatment. In study C2301, a grade 3 absolute neutrophils decrease was noted in 3 subjects (including one SAE). In addition, grade 1-2 decreased was noted in 15/137 subjects (11%). In the cases observed, neutropenia rapidly was reversed with interruption of osilodrostat, and reversed when osilodrostat was continued, typically with decreasing doses. According to information in the SCS, osilodrostat was dos adjusted, interrupt or discontinued due to AEs of the PT neutrophil decrease. It is, in clinical practice, of importance to consider that a decrease of neutrophils is a "natural" reaction to treatment reducing cortisol levels and that a decrease in neutrophils *per see* not should lead to a reduced dose or interruption of osilodrostat unless there is a risk for an associated AE or SAE.

However, due to the limited number of subjects with severe (grade 3) or serious cases it is considered acceptable to conclude that the findings regarding neutrophil decrease did not warrant any changes to the proposed SmPC**.**

Basophile increase

The Applicant describes that relatively high mean changes were observed for basophils with a highest mean change from baseline of 130%. An explanation given by the Applicant is that this phenomenon may be due to an "immune rebound" often seen after disease remission in Cushing Syndrome.

Clinical chemistry

Overall, biochemistry laboratory values including the pattern of newly occurring or worsening abnormalities in study C2201 part 2 were in line with the results in study C2301 and did not warrant any further safety issues.

In study C2301 newly occurring or worsening biochemistry abnormalities to grade 3 or 4 were reported for:

Hypokalaemia

Hypokalaemia is a comorbidity of Cushing Disease but also considered as adrenal hormone precursor accumulation potentially related AEs and included in the ADR table in SmPC section 4.8 as very common.

In total low potassium values were reported in 32/137(23%) of which 9 reported newly occurring or worsening abnormalities grade 3 (8 subjects) or 4 (one subject).

Hyperkalaemia

Hyperkalaemia could be a direct effect of osilodrostat due to accumulation of mineralocorticoid precursors and is included as a symptom of hypocortisolism. This is reflected in the SmPC section 4.4.

Hyperkalaemia was reported in total in 16/137(12%) of the subjects of which 3 reported newly occurring or worsening abnormalities grade 3. In total, three AEs (all non-serious) of hyperkalaemia were reported in Study C2301 and one in Study C2201. Three of the four patients were taking concomitant spironolactone, with additional antihypertensive agents throughout the study, the fourth patient had a first episode after more than 2 years of osilodrostat. The cases were all resolved without any action taken with osilodrostat. Thus, even if a potential causal relationship could be present with osilodrostat and hyperkalaemia this safety concern seems sufficiently addressed in SmPC section 4.4.

Based on data presented it is considered that no changes to the SmPC are warranted.

Triglycerides increase

Hyperlipidaemia is a known co-morbidity for Cushing Disease. Triglycerides increase was reported in total 52/137 (38%) of the subjects of which 4 reported newly occurring or worsening abnormalities grade 3.

Hypermagnesemia

Overall, laboratory values (grade 1-3) reported in total in 18/137 (13%) of the subjects. Grade 3 hypermagnesemia laboratory elevations (>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L) was noted in four subjects. The values were resolved at the next evaluation with no dose adjustments and none of the elevations were temporarily associated with hypokalaemia or AEs of neuromuscular or conduction system abnormalities.

Hypomagnesemia

Hypomagnesemia was reported in total in 2/137 subjects (1.4%) of which one reported newly occurring or worsening abnormalities grade 3.

Hyperphosphatemia

Hyperphosphatemia was reported in total in 12/137 (8.7%) of the subjects of which four were reported newly occurring or worsening abnormalities grade 3. Only one of these four subjects presented repeated grade 3 values without any increase at baseline. The remaining subjects had occasional grade 3 values or an increased level at baseline. No AE was reported in association with the increased values.

Activated partial prothrombin time

Prolonged *activated partial prothrombin time was re*ported in total in 35/137 (25%) of which one reported a newly occurring or worsening abnormalities grade 3 (without any AE).

Creatine kinase (CK) increase

In study C2301, increased CPK was reported in total in 32/137 (23%) of subjects of which one reported newly occurring or worsening abnormalities grade 3 (a single value) and one grade 4 (increased also at baseline). In total, seven cases with (non-serious) AEs of "increased CPK" was reported in study C2301 and C2201. The Applicant states that no clear evidence of a causal relationship between osilodrostat (4/7 subjects with AEs had confounding factors) and increase in CPK and therefore no changes to the SmPC are warranted. Based on the character of the cases with confounding factors present in 4/7 cases and that all events but one was resolved spontaneously even if no action to study treatment was taken, wording regarding "CPK increase" was accepted for the SmPC for osilodrostat as proposed.

Hyperglycaemia and HbA1c

Impaired glucose intolerance is a known co-morbidity for Cushing Disease and at baseline 22% (30/137) of the subjects in study C2301, presented with a medical history related to increased FBG. In total 26 subjects (19%) of the 137 included subjects reported a newly or worsening increase in FBG compared to baseline and of these 22 were confounded by disease with a medical history of for example diabetes mellitus, hyperglycaemia or diabetes insipidus. The four remaining cases (classified as mild in severity) had a BMI >25 <30 kg/m^2.increased fasting glucose was reported in 21/137 (23%) of subjects of which one was reported as newly occurring or worsening abnormalities grade 3.

It is noted that a shift to a worsening in HbA1c (divided by HbA1c groups) from baseline to last post-baseline value during the first 26 weeks was reported in 9/137 subjects (6.5%). An HbA1c improvement on the other hand was reported in 36/137 (26%) of the subjects.

In conclusion, the elevation of FBG were in most cases presented in subjects with a medical history of diseases related to increased FBG and the initially proposed wording of the SmPC was accepted.

Uric acid

In study C2301 increase in uric acid from baseline was noted in 20% (n=28) of the subjects of which 13/137 (9.5%) reported newly occurring or worsening abnormalities grade 4. The increase included 5 related AEs. No AEs of gout was reported. Confounding factors was present in 12 of the 13 subjects with a grade 4 uric acid increase. The Applicant claim that that there was no dose relationship between use of osilodrostat and the increase of uric acid and that the cases appeared without any pattern after initiation of osilodrostat. It is not possible to determine if the increase in uric acid in is related to the underlying disease or a consequence related

to initiation of treatment with osilodrostat. However, since most of the cases with potential clinically significant increases had confounding factors the proposed SmPC wording was acceptable.

Liver Chemistry

In the pivotal study the overall number of patients with elevations of liver chemistry tests (i.e. ALT or AST > ULN but <= 3.0xULN) during the up to data cut-off was 47/137 (34%). Most liver abnormal parameters occurred during the dose-titration period. The number of patients with ALT or AST > ULN but <= 3.0xULN during the first 26 weeks was 35/137 (25.5%) and in 5/137 (13%) during the RW phase (all five in the osilodrostat treatment group). Five subjects had an increase in AST and/or ALT above 3xULN. All these cases were confounded by disease or concomitant medication.

Overall, it is agreed with the Applicant that based on the data provided no clinically relevant relationship was observed between osilodrostat exposure and liver function test parameters.

The PT "Transaminases increased" is labelled in SmPC section 4.8 which is endorsed.

Special laboratory evaluations

Hormones of the H-P-A (Hypothalamic-pituitary-adrenal) axis (i.e. ACTH, Aldosterone, 11-deoxycortisol and 11-deoxycorticosterone, renin, sex hormones and DHEA) were monitored in Studies C2301 and C2201.

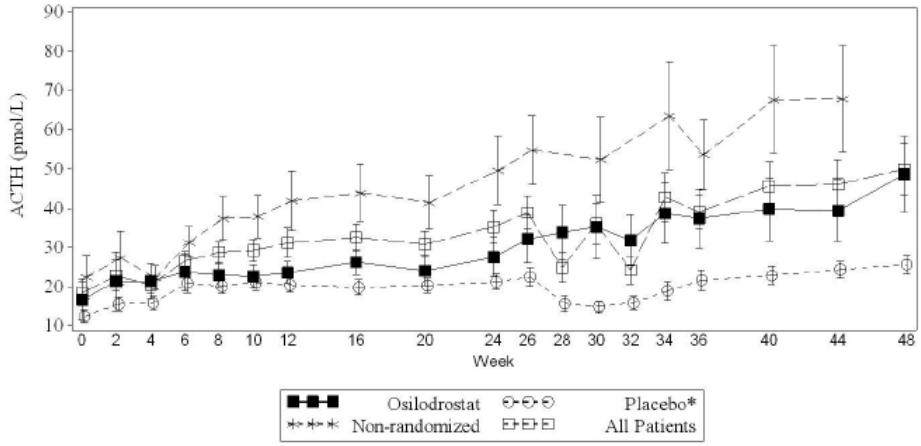
- **ACTH**

As expected, based on the mechanism of action of osilodrostat, an increase in ACTH was noted in all studies. In study C2301, 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 50.0 (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). At the last available assessment, the mean (SD) percentage change from baseline in plasma ACTH levels was 472.5% (919.77) (Figure 24).

The Applicant argues that 'most of the patients' have 'at most' a mild ACTH increase above ULN, based on mean (SD) values in updated study C2301 of 56.7 pmol/L (153.3). Updated study C2201 Part II has ranges from 11 to 637 pmol/L. Although mean levels might show modest increases below the threshold of clinical concern, there is clinical concern for the individual patients that have ACTH values that are above the ULN. The applicant has updated the SmPC informing the prescriber of the risk to reach high ACTH levels in SmPC section 4.8 accordingly.

Long-term safety including hormones of the HPA-axis including ACTH increase is characterised as missing information in the RMP which will be followed up in the PASS studies.

Figure 21 Mean (SE) ACTH at time points up to Week 48 by treatment group



- **Aldosterone, 11-deoxycortisol and 11-deoxycorticosterone**

Aldosterone

Compared to baseline, a decrease in aldosterone was observed over time. In the All Patients group, mean (SD) plasma aldosterone was 198.0 (380.14) pmol/L at baseline. At Week 48, the mean (SD) percentage change from baseline in plasma aldosterone levels was 37.7% (214.03; n=31).

11-deoxycorticosterone

An increase in 11-hydroxicorticosterone is expected due to the known aldosterone synthase (CYP11B2) inhibition reported for osilodrostat. Thus, compared to baseline an increase in mean plasma 11-deoxycortisol and 11-deoxycorticosterone levels was observed over time

Female patients had higher levels of 11-deoxycortisosterone levels at baseline and during the study compared with male patients. In female patients, 11- deoxycortisosterone levels peaked at W12, after which they slightly decreased and stabilized thereafter.

- **Renin**

In the development program of osilodrostat for treatment of hypertension an increased plasma renin activity, ranging from 0.4 to 1.2 µg/L*h, was observed.

Compared to baseline, an increase in mean plasma renin levels was observed over time in all patients (study C2301). In study C2201, mean values were fluctuating throughout the study but the mean change was ~155% at end of study.

- **Sex hormones**

Estradiol and estrone

In study C2301, an increase in mean serum estradiol and estrone levels was observed over time in both male and female patients compared to baseline.

In study C2201, estradiol values in females fluctuated between 112.7 to 993 pmol/L from a baseline value of 232.13 pmol/L. Compared to baseline, there was little change in estradiol values in males.

Testosterone

During the dose-titration period in study C2301, an increase from baseline in mean testosterone levels was observed in both male and female patients in the all patients group.

Testosterone levels decreased in female patients randomized to placebo and the effect was reversed when osilodrostat treatment resumed (study C2301).

In study C2201, testosterone values in males increased from a baseline value 7.44 nmol/L to maximum of ~15 nmol/L. The values remained stable for the remainder of treatment. There was little change in testosterone levels in females.

Follicle stimulation hormone (FSH) and Luteinisation hormone (LH)

In study C2301, the mean (SD) percentage change from baseline in plasma follicle stimulating (FSH) hormone levels was 26.5% (103.28) at week 48 and the mean (SD) percentage change from baseline in plasma luteinizing hormone (LH) levels was 34.1% (118.89).

Menstrual disorders

A total of 27 patients/subjects had menstrual AEs clustered under the "reproductive system and breast disorders" in studies C2301 (16/137), C2201 (4/19) and C2108 (7/24). When looking at patients or subjects with menstrual disorders (amenorrhea/hypomenorrhea, irregular menstruation, or menorrhagia/vaginal haemorrhage), after excluding the cases with clear confounders (ongoing conditions of menstrual disorders, presence of fibroids or endometrial polyp), the testosterone, androstenedione or oestradiol profile in each patient did not provide evidence for an influence of sex hormone accumulation as the reason for the event.

Adrenal hormone precursor accumulation-related AEs including sexual steroids is discussed in the section regarding "Adverse Events of Special Interest".

In summary, the Applicant refers to multiple (cofounding) factors as reasons for the change in sexual hormones, such as normalisation of cortisol levels (immediate effect of therapy), hypercortisolism and effect on HPG axis, gonadotrophic hormones producing pituitary cells that are damaged (or on the other hand are again recovering) after surgery or radiotherapy. In male patients rather a normalisation of testosterone levels can be seen, in female patients an increase with a mean level above ULN. However, ADRs are listed in the SmPC and did not lead to discontinuations during the study. An additional statement is proposed in SmPC section 4.8 to highlight the role of precursor accumulation and testosterone increases in these events. These increased testosterone levels seem to be furthermore reversible in the female patients that entered a placebo period. Effects on DHEAS, FSH and LH are noted but toward normalisation due to cortisol level normalisation.

To note is that effect of osilodrostat on sexual hormones is a potential safety issue when used in children and adolescent. However, at present osilodrostat should not be used in the paediatric population. This is reflected in the SmPC.

Long-term safety including clinical consequences of increased sexual hormones is characterised as missing information in the RMP which will be followed up in the PASS studies.

Vital signs, physical findings, and other observations related to safety

Blood-pressure

At baseline mean SBP was 132±15.1 mmHg and mean DBP 85.3±10.6 mmHg in the pivotal study (C2301). After 48 weeks treatment mean SBP had decreased by 4.8±12.3 mmHg and DBP 6.3±11.0 mmHg. A shift from

normal baseline levels to the worst post-baseline level "high only" in SBP was reported in 2/137 (1.4%) and a "low only" worst post-baseline value was reported in 9/137 (6.5%). Shifts from normal baseline DBP levels to the worst "high only" post-baseline was also reported in 3/137 (2.2%) subjects and a "low only" post-baseline DBP value in 8/137 (5.8%) subjects.

As discussed above *hypotensio*n could, in individual patients, be a symptom of hypocortisolism or arrhythmia and is further discussed in respectively heading in the section "Adverse events of special interest".

Body weight

In the pivotal study, weight was decreased during the study. At base-line median (min-max) weight was 75 (51-141) kg, at week 26 the median weight had decreased to 71 (44-147) kg and at week the median weight was 69 (44-148) kg.

Of the 137 patients with body weight data at baseline, 6/137 patients (4.3%) had a higher weight value, 44/137 (32%) had a lower weight value, one had a higher and lower value, and 86 remained in the same weight category post-baseline. Overall, the AE of oedema did not correlate with significant body weight change: one of the patients had a weight increase of 10% (grade 2) at the time of oedema, and 2 patients had an increase of 5% in body weight.

In study C2201 Part 2, there was, a slight reduction in mean body weight (~5%) from baseline, over the long-term exposure to osilodrostat.

Of the total 11 patients with at least one AE of weight decreased (9 in study C2301 and 2 in study C2201), only one patient also had preceding or concomitant AEs of at least Grade 2 decreased appetite and/or nausea.

Electrocardiogram

For clinically significant ECG results during the studies see the topic QT-prolongations AEs in section "*Adverse events of special interest*".

Safety in special populations

Race

The limited data in C1201 suggested that Japanese patients (or non-CD versus CD CS) could be at higher risk for hepatic AEs/abnormal lab values and hypocortisolism-related events. Additional analyses were requested based on study C2301 (98 non-Asian patients, 30 Asian [excluding Japanese] and 9 Japanese patients). The assessment whether Japanese patients are at higher risk of certain AEs than non-Asian patients was hindered by the fact that only a low number of Japanese patients (9) were included in C2301. For Asian patients, the Applicant concluded that the overall safety was largely comparable versus non-Japanese Asian patients.

However, for the assessment of non-Japanese Asian patients versus non-Asian patients:

● 5 events occurred with a significantly higher frequency in non-Japanese Asians than in non-Asian patients (adrenal insufficiency, diplopia, pituitary tumour benign, pruritus generalized and skin hyperpigmentation);

● there was a significantly higher number of SAEs in non-Japanese Asians;

● 9 (30%) non-Japanese Asians discontinued; while the number of discontinuations in non-Asian patients is not specifically mentioned, as the total number of discontinuations (Asians and non-Japanese Asians) was 25.5%, and 3 Japanese patients discontinued (33.3%), it can be deducted that the discontinuations in non-Asians was 21.4% so the number of discontinuations for non-Japanese Asian patients is higher than for non-Asian patients.

Therefore, it is of importance that a reduction of initial dose in Asian patients should be recommended: 1 mg twice daily instead of 2 mg twice daily, taking into account also the higher relative bioavailability, exposure (AUCss) and Cmax,ss in Asian patients than in non-Asian patients, as well as the fact that the mean and median average dose used in C1201 was lower than the proposed initial dose. This was requested and is now reflected in the SmPC.

Age

Overall, in all studies the number of subjects above 65 years were limited (n=10) which is now reflected in the SmPC. At baseline the oldest subjects on osilodrostat was 69 years in study 2301 and 75 years in study 1201, respectively.

Although, there seems to be no evidence that elderly patients have a different safety profile for osilodrostat than the <65 years old population, this is based on only very limited data in CS patients: 9 patients ≥65 years - ≤74 years old, and only 1 patient ≥75 years old. Some additional data are provided by the hypertension program in 130 patients ≥75 years old, although the use is different than in CS patients because at low doses and short duration.

Moreover, CS is less well characterized in elderly (Qiao et al. 2018) and elderly are likely more prone to osilodrostat-associated AEs like adrenal insufficiency, hypertension, electrolyte disturbances, cardiovascular AEs and there is a decrease in hepatic/renal/cardiac function, or possibly an increase in underlying disease with advancing age, which could have an impact on the safety profile. On the contrary, the normalisation of cortisol levels with osilodrostat might lead to an improvement of comorbidities like hypertension and CV disease. Therefore, as there are still many uncertainties about the safety profile of osilodrostat in elderly, it is added in SmPC section 4.2 that caution is recommended.

Gender

More females (N=106) were enrolled in Study C2301 than males (N=31).

Adverse events belonging to the SOC reproductive system and breast disorders were observed more frequently among females (21/106; 19.8%) compared to males (2/31; 6.5%), primarily driven by menstrual AE.

By PT, acne and hirsutism were observed only among female patients (12/106; 11.3% each). None of the AEs were grade 3 or higher; none of these AEs led to discontinuation of study drug.

The most obvious gender difference is regarding testosterone level increases in females, reversible at treatment interruption, and associated with mild to moderate cases of hirsutism and acne in some of these patients. This is now adequately reflected in SmPC section 4.8.

Renal impairment

Use in subjects with renal impairment was studied in 9 subjects in study 2104 (phase 1 PK). All subjects in the study received only a single osilodrostat dose of 30 mg. In study 2301 and 2201 subjects with moderate to severe renal impairment was excluded. Thus, safety in subjects with renal impairment treated for the intended indication could not be considered sufficiently covered by the presented data. However, since there is an individual dose up-titration based on monitoring including tolerability there is no suspicious regarding safety in these populations.

Hepatic impairment

Dose recommendations and adjustments for subjects with moderate and severe hepatic impairment is reflected in SmPC section 4.2.

See section 2.4.2. for assessment of pharmacokinetics in subjects with hepatic impairment.

In the clinical studies patients with liver disease or with serum alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) >3×ULN, or serum total bilirubin >1.5×ULN in study C2301 and >2 ULN in study C2201, were excluded.

Safety of use of osilodrostat in subjects with hepatic impairment has not fully been studied in the pivotal trials due to the exclusion criteria. It is reflected in the SmPC section 4.2 that experience of use in subjects with hepatic impairment is limited**.**

Immunological events

Antibody formation is not relevant for the substance.

Safety related to drug-drug interactions and other interactions

Oral contraceptives

No clinically significant drug-drug interaction was observed when oral contraceptives (containing EES and LVG) was co-administered with osilodrostat (40 mg during 12 days) in 24 healthy female subjects receiving cortisol replacement therapy (study C2108), suggesting that OC can be co-administered with osilodrostat and provide adequate contraception. This is reflected in SmPC section 4.5

CYP enzymes

Osilodrostat is a moderate inhibitor of CYP1A2, a weak to moderate inhibitor of CYP2C19, and a weak inhibitor of CYP2D6 and CYP3A4/5 at a single dose of 50 mg. Co-administration of osilodrostat was studied (Study C2102) and resulted in:

- a 2.54-fold increase in exposure of caffeine (a CYP1A2 substrate); there was no change in the rate of absorption of caffeine
- a 1.86-fold increase in exposure of omeprazole (a CYP2C19 substrate)
- a 1.54-fold increase in exposure (AUCinf) of dextromethorphan (a CYP2D6 substrate)
- a 1.50-fold increase in exposure of midazolam (a CYP3A4/5 substrate)

In SmPC section 4.5 interactions with osilodrostat and CYP1A2 and CYP2C19 substrates is reflected.

Discontinuation due to AES

Discontinuations of study drug due to AEs were reported in 18/137 (13%) in study C2301 and 3/19 (16%) in study C2201 (part 2). As for adverse events leading to dose interruption or adjustment, the most common PT reported was *adrenal insufficiency* (n=4 in study C2301). Besides this PT and *Pituitary tumour/Pituitary tumour benign*, no PT was reported in more than one subject.

The Applicant confirmed that 3 additional discontinuations because of AEs were grouped in the "Patient withdrawals" instead of in the "Discontinuations for AEs" reasons. Additionally, in the safety up-date, with cut-off 15 Oct 2018, the number of patients with discontinuations due to AEs has increased from 18 to 24 patients, so in total there were 27.

Use in pregnancy

General toxicology and reproductive toxicology studies in rats/mice have identified reproductive organs (ovaries, uterus, vagina and prostate) as target organs of toxicity for osilodrostat. There are no adequate and well-controlled studies in pregnant or breast-feeding women. Based on these findings in animals and the mechanism of action of osilodrostat, it can cause foetal harm when administered to a pregnant woman. For this reason, females that participated in the clinical trials were to refrain from getting pregnant for the duration of the study.

In study C2301, one unconfirmed pregnancy (positive pregnancy test could later not be confirmed by ultrasound scan and the serum human chorionic gonadotropin values subsequently reverted to normal) and one elective abortion for social reasons (no abnormalities were reported in the foetus) following maternal exposure were reported.

Non-clinical data demonstrates reproductive toxicity of osilodrostat. Therefore, osilodrostat should not be used during pregnancy and in women of childbearing potential not using contraception. This is reflected in the SmPC section 4.4 and 4.6. The argument by the Applicant that there in fact is a high risk for foetal (and maternal) morbidity and mortality for subjects with Cushing's disease by the nature of the disease is supported. Therefore, for this specific population it is agreed that a contraindication for pregnancy seems unnecessary.

The risk "Reproductive toxicity/Embryofoetal development" is characterized as an important potential risk in the RMP with routine PV and RMM, which is endorsed.

Post marketing experience

No post-marketing data are available.

2.6.1. Discussion on clinical safety

Overall, the number of subjects treated in the intended population, endogenous Cushing´s syndrome in adults, is low (n=165). In the pivotal study (C2301) and the proof-of concept study (C2201) part II, 134 subjects have been treated more than 6 months and 107 subjects have been treated more than 12 months. In the safety update submitted for study C2301 (cut-off date 15-Oct-2018), 110 patients were exposed to osilodrostat for at least 156 weeks. The additional median exposure compared to the primary cut-off date was approximately 30 weeks.

Additional safety results are pending and will be available from extension of all three studies performed in the intended population.

The safety database is not considered representative for the full target population of endogenous CS as for the non-CD form of CS, only 9 patients were included which were all of Japanese origin, and of which only 4 patients continued after week 12 and only 2 completed the study period II at week 48. The safety profile can be different in these patients but mainly due to AEs related to the disease, its extent and complications. The study data in the non-CD CS patients, although very limited, in combination with an acceptable mechanistic reasoning and a high unmet medical need currently results in a positive benefit-risk analysis. To ensure this the safety data "*Use in non-Cushing disease Cushing syndrome subjects including long-term effects*" has been characterised as a population with missing information in the RMP which will be followed up in the PASS studies.

Common adverse events

Subjects with CS have several co-morbidities which makes the assessment of a potential relationship between osilodrostat and the event difficult. In addition, the number of subjects is low and a comparison to placebo is only possible during the 8 weeks withdrawal phase in study C2301. However, during this phase the 36 subjects randomised to placebo all had been treated with osilodrostat before randomisation.

All subjects (100%) included in the studies experienced at least one AE. In the studies performed in subjects with Cushing's disease (C2301 and C2201 part II) AEs were most commonly reported within the SOCs "*Gastrointestinal disorders", "Infections and infestations"* and "*General disorders and administration site conditions"*. The overall most common PTs reported were *nausea, fatigue* and *headache*. To note is that both *nausea* and *headache* was reported with higher frequencies in subjects on osilodrostat compared to placebo during the RW period (C2301), indicating a direct unfavourable effect of osilodrostat (and not background disease). The most common AEs are considered adequately reflected in the SmPC. Overall, 93-95% of the subjects in study C2301 and Study C2201 Part II (CS) experienced AE that was judged as related to study drug by the investigators.

Overall, besides in general lower frequencies of reported AEs, no new safety findings have been identified regarding the AE profile when comparing treatment with low-dose osilodrostat in subjects with hypertension (study A2201, A2206 and A2216) with treatment with osilodrostat in higher doses in the subjects with endogenous Cushing syndrome.

Serious adverse events were reported in subjects in approximately one third (30% to 45%) of the subjects across the studies covering the intended population. The most commonly reported PTs were adrenal insufficiency/ adrenocortical insufficiency acute and pituitary tumour/pituitary tumour benign. Overall, one death (suicide) occurred.

AEs leading to study drug discontinuation were observed in approximately 15% patients/subjects across studies. The most common PT reported were adrenal insufficiency and pituitary tumour/pituitary tumour benign reported by 4, 4 and 2 subjects respectively (study C2301).

The considered major safety concerns related to use with osilodrostat in the actual doses are included in the topics of categorised as adverse events of special interest. The selected AESIs are considered adequate and discussed in the following:

Adverse events of special interest

- *Hypocortisolism-related AEs*

Approximately half of the population reported hypocortisolism related AEs (regardless laboratory values) in study C2301 (52%) and C2201 part 2 (42%). Among the 167 events reported in study C2301 the Applicant concludes that 67 events (40%) occurred during any up-titration (defined as occurred within 14 days after dose increase) and 96 events (57%) occurred during "maintenance" periods when the subjects used stable doses.

However, when relating the AEs during periods of titration, to laboratory values it was noted that 27% of the events, reported had correspondingly mUFC values below LLN. In the remaining cases the values were normal or even above ULN. Thus, there is an incoherence between adverse events related to hypocortisolism and laboratory values. The reason for this is probably a misclassification of the AEs by the investigators but also the fact that the subjects sometimes experience subjective symptoms when the cortisol levels decreases from high to normal levels. However, it could be concluded that the frequency of "true" hypocortisolism events seems lower than initially estimated. This is reassuring. However, it is a weakness with the study that the factual

frequency of hypocortisolism is not possible to estimate in the data presented. This depends on different factors; ambiguity regarding the description of AEs (GCP finding) and uncertainty in laboratory values due to different measuring methods. Furthermore, the recommended dosing in the proposed SmPC differs from that used in the studies. Thus, further analyses of the study data was not considered to change the B/R balance or result in major SmPC changes.

The proposed pharmacovigilance and RMM activities are considering sufficient; hypocortisolism is characterised as an important identified risk in the RMP. In addition, the Applicant has committed to a targeted follow-up questionnaire (including laboratory values) to follow events of hypocortisolism in routine pharmacovigilance. Events related to hypocortisolism will also be studied as a topic related to long-term safety**.**

The risk for hypocortisolism is reflected in the SmPC (mainly in section 4.4).

- *QT-prolongation*

Potential for arrhythmia including QT prolongation is a known safety issues with osilodrostat and a dose-dependent risk for QT-prolongations has been demonstrated both in pre-clinical data and healthy subjects (TQT study C2105). The mechanism by which osilodrostat may cause QT-prolongation is not well understood. In line with the scientific advice provided by the CHMP in 2013, ECG was monitored in study C2301.

A QTcF change of 5.3 ms was observed in C2301 from baseline at Week 48 and was also predicted based on concentration-dependent QT model from the TQT study and the population PK predicted Cmax following 30 mg dose. In the pivotal study (C2301) five patients out of 137 (3.6%) had electrocardiogram QT prolonged non-serious AEs (none had a SAE) and overall, the number of subjects with clinically significant QT-prolongations in study C2301 is considered low and no new QTcF of > 500 ms was observed (confirmed by central reading). Only 1 patient discontinued the study drug due to ECG QT prolonged AEs; for 4 events osilodrostat was temporarily interrupted and re-initiated at the same or at reduced dose after which no new QT event was reported while for 9 of the events no action towards osilodrostat was required.

However, subjects with risk for QT-prolongations and subjects with several CV diseases were excluded in the studies.

Recommendations for monitoring of ECG and electrolytes to manage the risk are described in SmPC section 4.4.

The requested analysis did not permit to identify a time period in which it would be appropriate to have a more focused monitoring, no new risk factors/contributing factors could be identified either. In case the ECG interval exceeds 480 ms prior or during treatment, cardiology consultation is recommended (as stated in the SmPC).

While it was agreed with the Applicant not to add a formal CI in patients with CV diseases or risk factors for QT prolongation, further warning about the fact that the B/R should be carefully weighed in these high-risk patients that were excluded from the studies was added. In addition, CV safety/QT prolongation in patients with CS, including those with CV diseases or risk factors for QT prolongation is in place as missing information in the RMP for osilodrostat which will be followed-up in the PASS studies.

Adrenal hormone precursor accumulation-related AEs

Adrenal hormone precursor accumulation is a result of the mechanism of action of most cortisol inhibitors resulting in potential increase in circulating levels of cortisol and aldosterone precursors (11- deoxycortisol, 11-deoxycorticosterone), and sexual steroids.

Overall, based on results from the pivotal study a risk for adrenal hormone precursor accumulation-related AEs could be considered since 42% of the subjects reported any of these events. Severe cases (grade 3) were

reported mainly for *hypertension* (15/17 cases) and *hypokalaemia* (6/18 cases). However, the overall seriousness of these events is considered relatively low and manageable.

Hormones of the HPA-axis and clinical consequences of increased sexual hormones will also be studied as a topic related to long-term safety.

- *Pituitary tumour enlargement-related AEs*

In total, six subjects reported "pituitary tumour" and "pituitary tumour benign" initially as AEs (including 7 SAEs) and they were all related to events reflecting growth of the underlying pituitary adenoma. In addition, three cases of diplopia were reported.

In MRI data from study 2301 an enlargement of the pituitary tumour was observed in 44% of the subjects and a tumour volume decrease was observed in 56% of the patients (measured as ≥ 20% increase/decrease in tumour volume by 3 maximum dimensions (mm^3) or 2mm increase in longest diameter). Reassuringly, additional data submitted after implementation of Amendment 5 identified only one subject with a re-occurrence, among the 46 subjects without measurable pituitary tumour at baseline. However, a new invasiveness of pituitary tumour growth was reached by 6 subjects among the 46 subjects with non-invasive pituitary tumours at baseline. Five of the six cases had adverse events related to tumour volume increase and either discontinued study drug or was withdrawn from the study, which is considered relevant. It is agreed with the Applicant that overall there was no evidence of tumour enlargement in association with use of osilodrostat. However, due to the mechanism of action (with increased ACTH production due to a negative feed-back of low cortisol levels) an increase in tumour volume could not be excluded in individual cases. Therefore, in the individual cases it is difficult to assess if an enlargement of the pituitary tumour is only due to the disease (CD) or might have been enhanced by osilodrostat treatment. However, with the data presented regarding subjects reaching tumour invasiveness when not showing tumour invasiveness before start of treatment, a stage/degree of tumour growth could be identified where continued osilodrostat treatment might not be advisable, should osilodrostat treatment enhance tumour growth. Therefore, it was considered of value to inform the prescriber that treatment with osilodrostat should be discontinued in case of a tumour enlargement reaching the degree of invasiveness in subjects without invasiveness before treatment. This information is now included in SmPC section 4.4 and the PL.

Laboratory findings

Anaemia/decreased haemoglobin is a known effect related to the intended normalisation of chronic cortisol excess.

Anaemia/iron deficiency anaemia/haemoglobin decreased was reported as an AE in 13% patients in C2301 as of 15-Oct-2018, in 5/19 (26%) patients in C2201 (as of 14-Nov-2017), and one patient in C1201. However, the mean Hb value in study C2301 had only a modest decreased over time and a substantial amount of the cases with anaemia were confounded and in study C2301.

Hormones of the HPA-axis (including ACTH increase) and clinical consequences of increased sexual hormones will also be studied as a topic related to long-term safety.

Safety in special populations

- There seem to be some differences in the safety profile of non-Japanese Asian patients versus non-Asian patients based on data from C2301. Asian patients also had differences in some PK parameters and the mean and median average dose used in C1201 was lower than the proposed initial dose. Therefore, a reduction of initial dose in Asian patients is recommended which is now reflected in the SmPC.

- The most obvious gender difference is regarding testosterone level increases in females, reversible at treatment interruption. This is now reflected in SmPC section 4.8.
- Overall, the number of subjects above 65 years are limited in the studied population (n=10). As there still are many uncertainties about the safety profile of osilodrostat in elderly, it has been added in SmPC section 4.2 that caution is recommended.
- Safety of use of osilodrostat in subjects with renal impairment has not fully been studied in the pivotal trials due to the exclusion criteria. However, since there is an individual dose up-titration based on monitoring including tolerability there is no specific concern regarding safety in these populations.
- Patients with moderate and severe hepatic impairment were excluded from the three pivotal studies. However, dose recommendations, based from results of PK study C2103, have been established for subjects with moderate and severe hepatic impairment, and general safety is not considered a problem in this population. In study C2301, liver parameters (AST/ALT) were increased in 25% of the subjects during the titration phase. However, the increases were in general small (< 3xULN) without any clinically significance for the included subjects (with normal and mild hepatic impairment). However, specifically hepatic safety effects of osilodrostat in subjects with moderate and severe hepatic impairment have not been studied (due to exclusion criteria). Thus, it is now reflected in the SmPC section 4.2 that experience of use of osilodrostat in subjects with hepatic impairment is limited**.**

Use during pregnancy

General toxicology and reproductive toxicology studies in rats/mice have identified reproductive organs (ovaries, uterus, vagina and prostate) as target organs of toxicity for osilodrostat. Thus, as reflected in the SmPC (section 4.6) osilodrostat should not be use in pregnant women.

2.6.2. Conclusions on clinical safety

The population with Cushing disease has several co-morbidities and it is a challenge to distinguish these symptoms from adverse events related to treatment. Adverse events were reported in all subjects and most commonly reported were PTs related to GI events. The most common reported events were *nausea, fatigue* and *headache*.

Significant safety issues identified were the known risks for osilodrostat namely *hypocortisolism related AEs* which were reported in high frequencies (51% in the pivotal study) especially during the titration phase (however these events did not always correspond low cortisol levels), *QT-prolongations* and *adverse events related to adrenal precursor accumulation*. Subjects with risk factors for QT-prolongations including several cardiovascular diseases were excluded in the clinical trials.

The two major safety concerns (*hypocortisolism* and *QT prolongations*) can be serious and potentially life-threatening, if not adequately treated, require specific monitoring and in some cases temporary dose reduction or interruption, or discontinuation of osilodrostat. They will be further followed up in a real-life post-marketing setting in the form of PASS studies, including also a specific follow-up of hormones of the HPA-axis (including ACTH increase) and clinical consequences of increased sexual hormones. Use in non-CD CS subjects is limited and will also be further evaluated and followed in the PASS studies.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Hypocortisolism QT prolongation
Important potential risks	Reproductive toxicity/Embryofetal development
Missing information	Breast-feeding women
	Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones) Use in non-Cushing Disease Cushing Syndrome patients including long-term effects

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
Study CLCI699C2X01B **Study title:** An open-label, multi-center, roll-over study to assess long term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat (LCI699) study and are judged by the investigator to benefit from continued treatment with osilodrostat. **Status:** ongoing	To evaluate the long-term safety data with osilodrostat treatment (i.e., AEs and SAEs); To evaluate the clinical benefit as assessed by the Investigator; To evaluate the long-term safety of osilodrostat treatment, as assessed by physical examination, laboratory data, vital signs, ECG and pituitary MRI.	Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones)	Final report submission	Q4 2024
Registry **Study title:** Multi-country, observational study to collect clinical information	The aim is to further document the long-term safety of osilodrostat administered in routine clinical practice in patients	Long-term safety (including hypocortisolism, CV safety and QT-prolongation,	Final protocol	Within 4 months after market approval

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
on patients with endogenous Cushing's syndrome treated with osilodrostat and to document the long-term safety. **Status:** planned	with CS treated with osilodrostat. The primary objective is to collect and assess safety data with a particular focus on hypocortisolism, CV safety, QT prolongation and hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones. The long term safety of non-CD CS patients will also be assessed	hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones) Use in non-Cushing Disease Cushing Syndrome patients including long-term effects	Final report submission	Q4 2027

For the category 3 Registry study (*Multi-country, observational study to collect clinical information on patients with endogenous Cushing's syndrome treated with osilodrostat and to document the long-term safety*), the applicant is expected to submit a full PASS protocol for review by PRAC within 4 months post approval.

The main considerations to be addressed at the time of full PASS protocol submission are as follows:

- **Study design:**

- Taking into account the advantages of using patient registries to perform observational studies to evaluate the long-term safety of medicinal products used to treat rare diseases, the applicant is encouraged to make efforts to perform this study in ERCUSYN registry study.

- The design of the study proposed by the applicant is purely descriptive. In order to evaluate the possible association between exposure and outcomes, the applicant is encouraged to select a control group. The possible selection bias should be discussed among the limitations of this study. In addition, the measures to avoid or minimize it should be provided.

- The applicant should discuss the period of 3 years as follow-up period. In addition, they should clarify if the period of recruitment will finish when the proposed number of patients (50 patients) is reached and if the period of follow-up will be different depending on the time of entry into the cohort.

- The applicant should explain if all the patients who discontinue osilodrostat prematurely (follow-up < 3 years) will be excluded. The information of the patients who discontinue the treatment with osilodrostat could be relevant for the evaluation of the safety. It would be important to analyse if there are differences between the patients who discontinued prematurely the osilodrostat and the patients that do not stop the treatment.

- **Research questions and objectives:**

- The two major safety concerns (hypocortisolism and QT prolongations) may be covered with the design of this study but is not clear if other safety endpoints included among the objectives of the study such as the clinical consequences of increased ACTH or the cardiac safety will be reached with such small sample size. The applicant should justify this in order to update the research questions and objectives or to discuss it as limitations of the study. Note that according to the Part III.3, this registry will also address the missing information "Use in non-Cushing Disease Cushing syndrome patients including long-term effects" but it is not reflected in the objective of the studies and should be clarified. In addition, the applicant should explain if a

minimum number of patients with non-CD are expected among these 50 patients (only 9 patients were included in the development clinical programme).

- The endpoint primary for primary objective is the incidence of osilodrostat related adverse events and serious adverse events during the 3-year observation period. The applicant should clarify if the estimation will be cumulative incidence or incidence rate. Also, if a comparator group is finally used, measures to compare the incidence should be used.

- **Study size:**

- Apart from the power of the sample size to observe the events of hypocortisolism and QT prolongation, if the study is performed in the ERCUSYN database, an approximation of how many of the patients included in the registry are susceptible to be treated with medical therapy, and how many are estimated to be treated with osilodrostat should be provided.

- Nonetheless, the applicant should discuss the limitations derived from the small the sample size.

- This observational study will allow the inclusion of patients excluded from the clinical development such as patients with risk factors for QT prolongation and CV diseases. It is unlikely that a representative number of patients with these risk factors are included in a sample size of 50 patients. This should be discussed by the MAH and if necessary, it should be included in the limitations of the study.

Risk minimisation measures

Safety concern	**Risk minimization measures**
Important identified risks	
Hypocortisolism	**Routine risk minimization measures**: SmPC Section 4.4, Section 4.8, and Section 4.9. Package leaflet Section 2 (What you need to know before you take Isturisa). **Additional risk minimization measures**: None.
QT prolongation	**Routine risk minimization measures**: SmPC Section 4.4, Section 4.8, and Section 4.9. Package leaflet Section 2. **Additional risk minimization measures**: None.
Important potential risks	
Reproductive toxicity/Embryofetal development	**Routine risk minimization measures**: SmPC Section 4.6 and

Safety concern	Risk minimization measures
	Section 5.3. Package leaflet Section 2. **Additional risk minimization measures**: None.
Missing information	
Breast-feeding women	**Routine risk minimization measures**: SmPC Section 4.6. Package leaflet Section 2.
	Additional risk minimization measures: None.
Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones)	**Routine risk minimization measures**: None. **Additional risk minimization measures**: None.
Use in non-Cushing Disease Cushing Syndrome patients including long-term effects	**Routine risk minimization measures**: None **Additional risk minimization measures**: None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The new EURD list entry will use the European birth date (EBD) to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of osilodrostat with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers osilodrostat to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Isturisa (osilodrostat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Isturisa was:

"Isturisa is indicated for the treatment of endogenous Cushing's syndrome in adults."

Cushing's syndrome (CS) is divided into adrenocorticotropic hormone (ACTH)-dependent CS and ACTH-independent CS. ACTH-dependent CS accounts for about 80% of all cases and is caused by an ACTH-secreting pituitary corticotroph adenoma (Cushing's disease (CD)) or by ectopic ACTH secretion by a non-pituitary tumour. The ectopic ACTH syndrome (EAS) causes approximately 10% of all cases of CS. ACTH-independent CS accounts for 20% of all causes of CS and is most frequently caused by a unilateral cortisol-secreting adrenal adenoma and less frequently by bilateral macro- or micronodular adrenal hyperplasia and a cortisol-producing adrenal carcinoma.

The aim of the therapy is not to cure the disease but to control the hypercortisolism, thereby limiting the consequences of the disease.

3.1.2. Available therapies and unmet medical need

The first-line treatment of nearly all forms of CS is surgical resection of the underlying tumour. Post-surgical remission rates of 60 to 90% have been reported in CD and up to 80% in EAS. However, long-term follow-up of CD patients in remission shows a recurrence rate of up to 60% at 10 years.

Radiotherapy is a possible alternative for CD patients; however, the treatment is associated with significant side effects and reoccurrence of disease.

For ACTH-dependent CS patients not controlled by removal of the ACTH-secreting tumour and when medical therapy did not result in biochemical control, bilateral adrenalectomy is the remaining non-medical treatment option.

Medical therapy

To date, there is no single, established standard of care medical therapy for endogenous CS worldwide. Medical therapy is indicated in patients with hypercortisolism of adrenal origin (i.e., patients with adrenal hyperplasia, adenomas, and carcinomas) who are not surgical candidates or for whom surgery is not available or which is unlikely to cure the CS/hypercortisolism) and for patients not cured after surgery or have recurred after initial control by surgery. The goal is clinical normalization using cortisol levels as a proxy endpoint (except for mifepristone). This can be achieved either with a "block and replace" strategy in which circulating cortisol is reduced to minimally detectable levels and glucocorticoid replacement is added (avoiding supraphysiological doses) or with a "normalization" strategy aimed to achieve eucortisolism. If there is evidence of significant cyclicity, block and replace may be preferable, but it carries additional risk if higher doses and multiple medications are needed. Currently available medical therapies for CS are classified based on the site of drug action and include pituitary-directed drugs, adrenal steroidogenesis inhibitors and glucocorticoid receptor antagonists (Tritos and Biller 2018).

Pituitary-directed drugs

Pasireotide (Signifor) was approved in 2012 via centralized procedure for the "treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed." In the pivotal study of the intramuscular formulation, 41% of patients were controlled at the primary endpoint (Lacroix 2018). Advantages include the once monthly frequency of administration (for the recently approved intramuscular formulation) and the causal nature of therapy (reduction of excess pituitary ACTH secretion). Disadvantages include a risk of hyperglycaemia resulting from the inhibition of insulin secretion. Due to its mode of action, pasireotide cannot be used in patients with ACTH-independent causes of Cushing's syndrome.

Adrenal steroidogenesis inhibitors

Steroidogenesis inhibitors are recommended under the following conditions:

- As second-line treatment after transsphenoidal surgery in patients with CD, either with or without RT/radiosurgery;
- As primary treatment of EAS in patients with occult or metastatic EAS together with targeted therapies to treat the underlying tumour;
- As adjunctive treatment to reduce cortisol levels in adrenocortical carcinoma.

Ketoconazole (Ketoconazole HRA) was approved in 2014 via centralized procedure for "the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years" (Ketoconazole was previously approved for the treatment of fungal infections but removed from the market due to the high risk of hepatotoxicity). A control rate of 49% at last available assessment has been reported in a retrospective patient record review (Castinetti 2014; no prospective trial data are currently available). Ketoconazole can be used in all types of Cushing's syndrome however it has the potential for severe and sometimes fatal hepatotoxicity, its high drug-drug-interaction potential (because of its relatively unspecific inhibitory effects, a broad range of enzymes both within the steroidogenesis pathway and elsewhere are inhibited, resulting e.g. in near complete testosterone suppression), and the limited titration range (starting dose is one 200mg tablet tid; maximum dose is two 200mg tablets tid).

Metyrapone (Metopirone) inhibits adrenocorticosteroid synthesis and is approved via national or mutual recognition procedure in 15 member states for "the management of patients with endogenous Cushing's syndrome" (first EU approval UK 1973). The response to metyrapone is rapid, and the desired cortisol levels can be achieved after two weeks of treatment (Verhelst et al 1991). Control rates ranging from 64% to 94% have been reported with long-term use (>6 months) in a retrospective study (Daniel et al 2015), however the choice of biochemical monitoring tests and frequency of monitoring varied. Metyrapone has a lower impact on testosterone levels compared to ketoconazole (Fleseriu et al 2016). Gastrointestinal side effects are common but may be reduced by taking the capsules with milk or after a meal. The product is large (8x19 mm) and due to the short half-life three to four times daily administration is required.

Mitotane (Lysodren) was approved via centralized procedurein 2004 for the "symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma (ACC)" since Apr-2004. Advantages include the strong adrenolytic effect in the symptomatic treatment of advanced adrenal corticocarcinoma; disadvantages include the very slow onset of action and accumulation in storage sites in fat (reported terminal plasma half-lives range from 18 to 159 days) and the need for serum level monitoring. Mitotane has serious neurological, gastrointestinal and hepatic side effects and causes hypercholesterolemia, which significantly limits its benefit risk in non-malignant Cushing's syndromes.

Cabergoline is a dopamine agonist that has been used off-label in the treatment of Cushing's disease, based on an observed reduction in UFC levels in patients who have tumours with high expression of D2 receptors (De Bruin 2008).

Etomidate is a sedative which is sometimes used as a parenteral (intravenous) hypocortisolaemic agent before or during adrenalectomy in patients with severe life-threatening hypercortisolaemia where rapid control of cortisol levels is required and oral therapy is problematic. However, a highly co-ordinated multidisciplinary approach is necessary for the management of unwell hypercortisolaemic patients, as these patients have complex problems beyond the daily ward scope of medical and nursing staff. The clinical setting of an intensive care or high dependency unit is therefore recommended for close patient and biochemical testing monitoring, particularly for serum cortisol and potassium levels and the documentation of the level of sedation.

Glucocorticoid receptor antagonists

Inhibition Use of these class of products with their action on the glucocorticoid receptor has been described in patients with Cushing's syndrome, but are not authorised for this use in the EU and have limited or no availability in the EU.

Following the unmet medical need in CS, attempts have been made to combine different medical treatments in order to improve the biochemical control rate and, potentially, improving the safety profile by using lower doses. The number of such studies is quite limited and they included a low number of patients.

3.1.3. Main clinical studies

Study **C2301** is the main study supporting this application. This was a Phase III, multi-center, double-blind, randomised withdrawal (RW) study of osilodrostat following a 24-week, single-arm, open-label dose titration and treatment period to evaluate the efficacy and safety of osilodrostat for the treatment of patients with CD. The study included 137 patients with CD. Patients were eligible for randomisation to the RW part of the study (either to continue with osilodrostat or to switch to placebo) if they had completed the dose titration during study Period 1, and were classified as complete responders at Week 24 with no dose increase between Week 13 and Week 24. Randomisation was implemented at the Week 26 visit. Patients not eligible for randomisation received open-label osilodrostat until the end of the Core Period (Week 48), unless there was a reason to discontinue from the study prematurely. Of the total study population, 72 patients were participating in the RW part of the study.

The primary objective was to compare the complete response rate at the end of the 8-week period of randomization withdrawal (RW) (Week 34). The key secondary objective was to assess the complete response rate at the end of individual dose-titration and treatment with osilodrostat in the initial single-arm, open label period (Week 24).

Further data to support the indication sought is provided by study **C1201**, which is an ongoing Phase II, single-arm, open-label, dose-titration study to assess the safety/tolerability and efficacy of osilodrostat in 9 Japanese patients with endogenous CS except CD (hereafter referred to non-CD CS).

Some supportive data is also achieved from Study **C2201** in which part I was a 10-week exploratory proof-of-concept study and part II was a 22-week treatment period after which the long-term efficacy and safety of osilodrostat were further investigated in an optional 48-week extension (Extension 1). The extension phase was continued as Extension 2 to provide continued access to osilodrostat for patients who completed Extension 1. The study remains ongoing.

3.2. Favourable effects

The primary endpoint was met as the proportion of patients who completed the *randomised withdrawal* period and maintained mUFC ≤ ULN was significantly higher in the osilodrostat treated group (86.1% vs 29.4%; OR 13.71 [3.73, 53.44]). The outcome was supported by the sensitivity analyses.

There was a rather rapid increase in mUFC two weeks after withdrawal in the placebo treated group, and the median time to loss of control was 28 days. Since a large proportion of patients in the placebo treated group discontinued placebo treatment already at week 26, the absolute difference in mUFC is difficult to interpret.

The study also met its key secondary endpoint, which was the responder rate at week 24. The definition of responders was subjects with mUFC<ULN and without dose increase after week 12. A response rate of 52.6% (72/137) was observed at week 24 and the 95% 2-sided CI was (43.9, 61.1) hence, the lower bound of the 95% CI was above the pre-specified threshold (i.e. ≥ 30%). If patients who had continued the titration in period 2 were included, the response rate increased to 67.9%.

Subgroup analyses were in general consistent with the overall outcome for the primary and key secondary endpoints.

The proportion of responders was largely maintained from week 12 and up to week 48 with a slight decrease from 71.5% complete responders at week 12 compared to 66.4% complete responders at week 48. The number of patients without prior surgery was low (17) but there was no difference in the responder rate in this group compared to the overall population. Non-randomised patients continued open-label osilodrostat treatment throughout the course of the study. The overall response rate in this group was somewhat lower than in the total population at week 24 (65.2% vs 82.5%) and at week 48 (59.1% vs 75.9%). When looking at individual data, all but one patient showed a decrease in mUFC.

The responder rates observed in the second part of the supporting study C2201, up to week 22, were in the same range (78.9%) as observed in the pivotal study.

The data indicate that the effect is maintained over time in patients responding to treatment, with 64 patients showing maintained response 6 months after the initial normalisation of mUFC. The supportive study C2201 provides data for 17 patients who have been treated up to 46 months, at which time point 58.8% were still complete responders. In study C2301, "escape" was evaluated in patients who had achieved control of UFC. When applying the protocol definition of escape, the median (KM method) time to "escape" was 560 days.

In line with the data on mUFC, normalisation of plasma cortisol levels was observed after week 10 except for the placebo treated group during the RW period.

Hypercortisolism causes negative effects on both CV and metabolic risk factors as well as characteristic changes to the patient's habitus. In study C2301, reductions were observed for all CV parameters included in the evaluation except for triglycerides. SBP and DBP decreased by 6.8 and 6.6%, respectively. Body weight decreased by 4.6%. An increase in BMD was observed, most prominent in the lumbar spine where a 3% increase in BMD was observed. There was a favourable shift with regards to features of CD as assessed from two photographs taken and reviewed locally by the Investigator. Improvements in QoL scores were also observed.

In study C1201, which included patients with non-CD Cushing's syndrome, osilodrostat treatment resulted in a mean percent change in mUFC from baseline to week 12 ranging from 52 to 99%. At week 24 the median mUFC in the median mUFC was well below ULN (63.9 nmol/24 hr) but only three patients remained in the study. At week 48, the two remaining patients showed a 95% decrease from baseline in mUFC levels, but the median mUFC was above ULN. The response rate in the first part of the study was comparable to that observed in the

studies in patients with CD. The two patients still on treatment at week 48 were still responding to treatment. Data on morning cortisol levels show a normalisation compared to baseline. There were some improvements in CV related metabolic parameters whereas no improvements were observed in the QoL scores.

In study C2301, most patients had achieved ≤ ULN at week 16. The median time to response was 41 days, both in the total study population and in the non-randomised group. Single patients reached controlled mUFC after about 4 months of treatment. The highest osilodrostat dose was observed at week 10, after which the mean dose decreased and stabilised at a mean dose of 10-11 mg daily. In the study, dose increments were made in steps of 5 mg twice daily, but in the SmPC a more precautious uptitration is proposed with increments of 1 to 2 mg twice daily, since uptitration can be made more frequently in clinical practice. A more cautious uptitration is important to avoid hypocortisolism.

3.3. Uncertainties and limitations about favourable effects

Only seven subjects aged 65 to 74 years were included in study C2301 and only 3 subjects aged 75 to 85 years were included in the development program, thus, the experience in elderly patients is limited but this is reflected in the SmPC.

The study data in patients with non-CD CS of different aetiologies is very limited. The combination of an acceptable mechanistic reasoning and a high unmet medical need however results in a positive benefit-risk analysis for this population.

Patients who were on medical treatment were eligible for inclusion in study C2301 after washout periods, which were adapted for the different medicinal products used. Since switching from other products, e.g. pasireotide or ketoconazole, may occur if osilodrostat is approved, section 4.5 of the SmPC was amended to highlight the need for a washout period.

3.4. Unfavourable effects

Non-clinical findings

- CNS findings

Although not observed in the rat in single dose safety pharmacology study, unexpected adverse CNS clinical signs, without microscopic correlates, were observed in all the animal species used in the pivotal repeat-dose toxicity studies (mouse, rat, dog) at osilodrostat exposure multiple <2. However, no concern to that regard did arise in the subsequent clinical studies.

- QT prolongation (non-clinical part)

A single dose of osilodrostat caused QT prolongation and also torsade de pointe at high exposure multiples in cynomolgus monkey. QTc was also noted in the dog following repeated dosing but not after a single oral dose of osilodrostat (max 8mg/kg).

Clinical findings

- Exposure

The overall number of subjects treated in the intended population, endogenous Cushing´s syndrome in adults, is low (n=165). In the pivotal study (C2301) and the proof-of concept study (C2201) part II, 134 subjects have been treated more than 6 months, 107 subjects have been treated more than 12 months and 11 subjects had

been treated for 48 months or more (all in study C2201 part II). However, further long-term safety data is pending from all three studies performed in the intended population.

For study C2301 a safety update was submitted with a data cut-off date as of 15-Oct-2018. In this up-date the median (range) exposure to treatment was 104.1 weeks (range 0.9 to 199.0) weeks. One hundred and ten patients were exposed to osilodrostat for at least 156 weeks. The additional median exposure compared to the primary cut-off date was approximately 30 weeks.

Only nine patients for the non-CD form of CS were included, all of Japanese origin, and of which only 4 patients continued after week 12 and only 2 completed the study period II at week 48.

Thus, it is recognized that the number of non-CD CS patients is very limited and that the safety profile can be different in these patients but mainly due to AE related to the disease, its extent and complications.

- Common AEs

All subjects (100%) included in the studies experienced at least one AE. The most commonly reported SOCs were "*Gastrointestinal disorders", "Infections and infestations"* and "*General disorders and administration site conditions"*, reported in 68%, 67% and 65% respectively in the pivotal study (C2301). In this study, the overall most common PTs reported were *nausea (42%), fatigue* (34%) and *headache (28%)*. The majority (> 97%) of these events were grades as mild in severity (grade 1 or 2). Dose interruptions or adjustments to manage these events was reported in 35% (20/57), 43% (17/39) and 5/46 (11%) of the subjects with *nausea*, *fatigue* and *headache*, respectively. Overall in study C2301 and C22012, discontinuations of study drug were reported for one subject each of the respectively PT. To note is that both *nausea* and *headache* was reported with higher frequencies in subjects on osilodrostat compared to placebo during the RW period (C2301), indicating a direct unfavourable effect of osilodrostat (and not background disease). The most common AEs are considered adequately reflected in the SmPC.

Serious adverse events were reported in approximately one third of the subjects across the studies. The most commonly reported PTs were *adrenal insufficiency/ adrenocortical insufficiency acute* (6%/2% respectively in study C2301) and *pituitary tumour/pituitary tumour benign* (4%/1.5% respectively in study C2301).

The up-dated safety data for study C2301 with a data cut-off date as of 15-Oct-2018 did non reveal any new safety concerns not reflected previous.

Based on the mechanism of action of osilodrostat several safety issues are known for the substance, these include:

- Hypocortisolism-related AEs

All patients treated for endogenous CS are at risk of hypocortisolism; hypocortisolism events have also been observed in patients with CS/CD treated with surgery and are listed for other CS/CD medicinal products (CAP: ketoconazole, pasireotide), although at a frequency of 'common' compared to 'very common' for osilodrostat.

Up-dated data submitted by the Applicant indicated that approximately half of the population reported hypocortisolism-related AEs (regardless laboratory values) study C2301 (71/137: 52%) and C2201 part 2 (8/19; 42%). In study C2301 the 71 subjects reported in total 167 events. Of these 67 events (67/167; 40%) occurred during any period of up-titration (defined as occurred within 14 days after dose increase) and 96 events (57%) occurred during "maintenance" periods when the subjects used stable doses.

Most of the patient with hypocortisolism-related AEs had just one episode. In total, four patients discontinued the study drug due to the *adrenal insufficiency* AE.

Based on initial data submitted for study C2301, a total of 13 patients experienced a SAE of hypocortisolism: 9 SAEs of adrenal insufficiency were reported in 8 patients, 5 of the SAEs were of grade 3. Two other patients had 3 SAEs of glucocorticoid deficiency. All episodes of adrenal insufficiency SAE were managed with temporary reduction or interruption of the study drug, and with or without administration of glucocorticoids in some patients; in 2 patients the event led to study discontinuation.

However, in an additional analyse it was noted by the Applicant that there was an incoherence between adverse events related to hypocortisolism and laboratory values. Correspondingly mUFC values below LLN were noted only in 27% (of the hypocortisolism related events during periods of titrations). In the remaining cases the values were normal or even above ULN. The reason for this is, according to the Applicant, probably a misclassification of the AEs by the investigators. However, it should also be taken into account that subjects sometimes experience subjective symptoms when the cortisol levels decrease from high to normal levels. Overall, it can be concluded that the frequency of "true" hypocortisolism events seems lower than initially estimated.

Some risk factors for hypocortisolism are known, thus monitoring of cortisol levels with potentially dose decrease or interruption is important for prevention.

- Arrhythmia and QT prolongations

Preclinical safety studies have demonstrated that osilodrostat exert cardiovascular concerns, i.e. QT prolongation both in vitro and in vivo. In addition, in the thorough QT-study (C2105) data showed that osilodrostat had a clinically significant effect on QT-prolongation in healthy volunteers. A positive correlation between osilodrostat concentration and ΔΔQTcF was noted.

A QTcF change of 5.3 ms was observed in C2301 from baseline at Week 48 and five patients out of 137 (3.6%) had electrocardiogram QT prolonged non-serious AEs, none had SAEs, and no new QTcF of > 500 ms was observed (confirmed by central reading). Only 1 patient discontinued the study drug due to ECG QT prolonged AEs; for 4 events osilodrostat was temporarily interrupted and re-initiated at the same or at reduced dose after which no new QT event was reported while for 9 of the events no action towards osilodrostat was required.

There are some known risk factors, however in the three clinical studies included in the safety data set (C2301, C2201 and C1201) individuals with risk factors for relevant CV diseases and QT–prolongations were excluded. Thus, as expected a low number of subjects with QT-prolonged AEs was reported.

QT prolongation is usually asymptomatic, so ECG and electrolytes monitoring is important with a cardiology consultation in case the QTc interval exceeds 480 ms prior or during treatment, to consider whether to initiate or to continue osilodrostat, or (temporarily) reduce or interrupt its dose.

- Pituitary tumour enlargement

In MRI data from study 2301 an enlargement of the pituitary tumour was observed in 44% of the subjects and a tumour volume decrease was observed in 56% of the patients (measured as ≥ 20% increase/decrease in tumour volume by 3 maximum dimensions (mm^3) or 2mm increase in longest diameter). Additional data (submitted after implementation of Amendment 5 [July 2019]) identified one subject with corticotroph tumour re-occurrence among the 46 subjects without measurable pituitary tumour at baseline. A new invasiveness of corticotroph tumour was reached by 6 subjects among the 46 subjects with non-invasive pituitary tumours at baseline. Five of the six cases had adverse events related to tumour volume increase and either discontinued study drug or was withdrawn from the study.

- Adrenal hormone precursor accumulation AEs

Adrenal hormone precursor accumulation-related AEs were reported in 42% (n=58) of the subjects in study C2301 and 63% (n=12) in study C2201 (part 2). Most reported PTs in the pivotal study (C2301) were *hypokalaemia* (13%; n=18), *hypertension* (12%; n=17), *acne* and *hirsutism* (both reported in 9% [n=12] each). Severe cases (grade 3/4) was mainly reported for *hypertension* (15/17 cases; all cases were considered confounded) and *hypokalaemia* (6/18 cases).

- ACTH increase

Most of the patients had a mild ACTH increase above ULN, based on mean (SD) values in updated study C2301 of 56.7 pmol/L (153.3). Updated study C2201 Part II had ranges from 11 to 637 pmol/L.

Use during pregnancy

General toxicology and reproductive toxicology studies in rats/mice have identified reproductive organs (ovaries, uterus, vagina and prostate) as target organs of toxicity for osilodrostat. The SmPC (section 4.4 and 4.6) states that osilodrostat should not be use in pregnant women. A contraindication for pregnancy is considered unnecessary since there in fact is a high risk for foetal (and maternal) morbidity and mortality for subjects with (untreated) Cushing's disease by the nature of the disease.

3.5. Uncertainties and limitations about unfavourable effects

Multiple factors related to the clinical data can be the source of uncertainties about the safety of osilodrostat in CS patients in general:

An overall limitation with the safety dataset is that the number of subjects treated in the intended population, endogenous Cushing´s syndrome, is low (n=165). However, considering the status of orphan drug and the fact that information regarding safety is available from the population with hypertension (treated with lower doses and shorter durations) the overall exposure is considered sufficient. The proposed indication includes all subjects with Cushing´s syndrome, safety in the population with CS due to other reasons than pituitary ACTH-producing tumours was however only studied in nine (Japanese) subjects (study C1201). This population has now been included in the RMP as missing information and as a topic for long-term safety post-marketing follow-up.

Another limitation with the safety data set is that a comparison to placebo is only possible during the 8 week withdrawal phase in study C2301. But during this phase the 36 subjects randomised to placebo all had been treated with (and proved to tolerate) osilodrostat before randomisation. Thus, due to lack of placebo-data in combination with a population with several comorbidities (AEs overlap with symptoms of the underlying disease or comorbidities) it is often difficult to consider a certain causal relationship to the treatment.

Not all data are currently available as the main studies are still ongoing. However, the Applicant has submitted an up-dated safety report for study C2301 with a data cut-off date as of 15-Oct-2018. The result of this report did not reveal any new safety concerns not reflected previously. However, lack of sufficient long-term safety data is still a limitation. Uncertainties are identified regarding long-term safety mainly concerns hypocortisolism, CV safety and QT-prolongations, use in non-CD CS subjects, hormones of the HPA-axis including ACTH increase and secondary PD effects (e.g. on sexual hormones):

Hypocortisolism: The risk for hypocortisolism is a non-negligible daily risk for the subjects. The incidence of factual hypocortisolism related events with cortisol levels below LLN in the pivotal study (C2301) is an uncertainty. The reason for the difficulties to estimate the incidence of hypocortisolism-related events with related laboratory values in the data presented, in study C230, is that there was an ambiguity regarding the description of AEs for the investigators but also since there appeared to be an uncertainty in laboratory values due to different measuring methods.

Further, the frequency of these events including serious cases (like Addison crisis) in a real-life setting is uncertain.

Considering these uncertainties and the risk for serious cases of hypocortisolism, the most important is at present to adequately describe the risk and give adequate dosing and monitoring recommendations in the product information. It is considered that SmPC sections 4.2 and 4.4 now sufficiently reflect this. Moreover, as the long-term frequency of serious cases related to events of hypocortisolism is still uncertain and will be followed in the long-term safety PASS.

QT-prolongation including arrhythmia and Torsade de pointes: The mechanism by which osilodrostat may cause QT prolongation is not well understood which adds a factor of uncertainty.

In clinical practice there are uncertainties for this risk regarding the individuals with known risk factors for QT-prolongations since this population was excluded in the clinical trials and the incidences and severity/seriousness after long-term use of osilodrostat in all patients in a real-world setting could be higher. Some results regarding cardiac safety after long-term use of osilodrostat will be available by the ongoing extension of the studies (C2301, C2201 and C1201). However, in these studies there was a close monitoring through scheduled visits and high-risk patients were excluded. Therefore, the risk for QT-prolongation is included in the RMP as an important identified risk and will be followed in a real-life long-term study.

The requested analysis did not permit to identify a time period in which it would be appropriate to have a more focused monitoring, and no new risk factors/contributing factors could be identified either. In case the ECG interval exceeds 480 ms prior or during treatment, cardiology consultation is recommended.

While it was agreed with the Applicant not to add a formal contraindication in patients with CV diseases or risk factors for QT prolongation, further warning about the fact that the B/R should be carefully weighed in these high-risk patients that were excluded from the studies was added in the SmPC.

Pituitary tumour enlargement: Overall there is no evidence of tumour enlargement in association with use of osilodrostat but still, due to the mechanism of action (with increased ACTH production due to a loss of feed-back with low cortisol levels), an increase in tumour volume could not be excluded in individual cases. Therefore, in the individual cases it is difficult to assess if an enlargement of the pituitary tumour is only due to the disease (CD) or might have been enhanced by osilodrostat treatment. With the data presented regarding subjects reaching tumour invasiveness when not showing tumour invasiveness before start of treatment, a stage/degree of tumour growth could be identified where continued osilodrostat treatment would not be advisable, should osilodrostat treatment enhance tumour growth. Therefore, it was considered of value to inform the prescriber

that treatment with osilodrostat should be discontinued in case of a tumour enlargement reaching the degree of invasiveness in subjects without invasiveness before treatment. This information is now included in SmPC section 4.4 and the PL.

There are also uncertainties regarding long-term safety in relation to hormones of the HPA-axis including clinical consequences of increased sexual hormones. Therefore, this topic will be studied through long-term post authorisation safety study (PASS).

Although mean levels might show modest ACTH-increases below the threshold of clinical concern, there is concern for the individual patients that have ACTH values that are above the ULN and which might reach the ACTH threshold for clinical concern reported for Nelson's syndrome. The SmPC (section 4.8) therefore includes information for the prescriber of the risk to reach high ACTH levels. In addition, long-term safety, including hormones of the HPA-axis, including ACTH increase, is characterised as missing information in the RMP and will be followed in the planned PASS.

3.6. Effects Table

Table 30 Effects Table for osilodrostat in the treatment of Cushing's syndrome (data cut-off: 06-Sep-2018).

Effect	Short Description	Unit	Osilodrostat	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Complete responders at w 34	mUFC to ≤ ULN at w 34 (end of RW)	n/N, (%)	31/36 (86.1)	10/34 (29.4)	Odds ratio (95% CI) 13.71 (3.73, 53.44) P <0.001	Pivotal study (C2301)
Responders at w 24	mUFC ≤ ULN at Week 24 No dose increase after w 12	n/N, (%)	72/137 (52.6)	N/A	(95% 2-sided CI: 43.9, 61.1) The lower bound of the 95% CI above the pre-specified threshold (≥ 30%).	Pivotal study (C2301)
Overall response at w 24	mUFC ≤ ULN at Week 24	n/N, (%)	113/137 (82.5)	N/A	(95% CI: 75.06, 88.44)	Pivotal study (C2301)
Overall response at w 48	mUFC ≤ ULN at Week 48	n/N, (%)	104/137 (75.9)	N/A	(95% CI: 67.87, 82.80)	Pivotal study (C2301)
Unfavourable Effects						
Gastro intestinal (GI) adverse events (nausea)	Frequency of subjects reported events within the SOC GI events (nausea)	%	67% (42%)		During the RW period 11% on osilodrostat and 0% in placebo reported nausea	Pivotal study (C2301)

Effect	Short Description	Unit	Osilodrostat	Placebo	Uncertainties/ Strength of evidence	References
Hypocortisolism-related AEs (irrespectively of corresponding laboratory values)	Frequency of subjects reported Hypocortisolism-related AEs	% (n/n)	52% (71/137)		Dose-reductions or dose interruption occurred in 89% of subjects with reporting events on *adrenal insufficiency* and 86% of subjects with *glucocorticoid deficiency*	Pivotal study (C2301)
Hypocortisolism AEs (with low cortisol levels)	Frequency of hypocortisolism event during titration with related low cortisol levels	% n/n	27% (17/64)		This indicate that only one third of the reported events were in fact associated with low cortisol levels. The incidence of true hypocortisolism is therefore considered lower than 52% in study C2301	Pivotal study (C2301)
QT-prolongation related AEs	Frequency of subjects reported QT-prolongation related AEs	%	3.6%		Strong preclinical and phase 1 data from healthy volunteers (C2105)	Pivotal study (C2301)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

Irrespective of the aetiology in Cushing's syndrome, controlling the hypercortisolism is an important treatment target due to the increased risk of co-morbidities such as CV disease, diabetes and osteoporosis.

Osilodrostat was shown to effectively lower mUFC in all but one patient in the pivotal study and all but one patient in the supportive study in non-CD CS also responded to treatment. Responder rates in the CD population was high and clinically relevant with 52.6% of patients being complete responders at week 24. This may be compared with data for pasireotide in a comparable study population where 26.3 % in the 900 µg b.i.d. group were responders at 6 months. The data from the randomised withdrawal phase of the study further support that the effect observed can be contributed to osilodrostat. The reduction in cortisol levels was shown to positively affect the consequences of high cortisol levels such as metabolic parameters associated with an increased CV risk as well as the Cushingoid habitus of the patients. Treatment with osilodrostat was also associated with a meaningful improvement of QoL scores. Furthermore, although limited, the long-term data indicate that the effect is maintained up to 46 months. This is of importance since loss of efficacy ("escape") is frequently observed with currently available medical therapies.

The mechanism of action has been adequately characterised in the development program. Since osilodrostat blocks the synthesis of cortisol it is expected to be efficient in all forms of endogenous Cushing's syndrome. This is supported by the data from the study in patients with non-CD CS, albeit the limitations of a very small sample size. Limitations of data with non-CD CS are reflected in the SmPC.

Importance of unfavourable effects

Based on available data, and apart from hypocortisolism, the overall tolerability of osilodrostat appears satisfactory.

Study data in **non-Cushing Disease Cushing Syndrome** patients is still very limited but in combination with an acceptable mechanistic reasoning and a high unmet medical need currently results in a positive benefit-risk analysis. Safety in this population with be further studied in the PASS.

The risk for "objective" events of **hypocortisolism** based on laboratory values and the frequency of these events including serious cases (like Addison crisis) in a real-life setting is uncertain. Hypocortisolism could lead to fatal outcome untreated. However, with the now included recommendations in the SmPC section 4.2 and 4.4 regarding this risk and dosing, titration and monitoring of cortisol levels during treatment with osilodrostat, the risk seems manageable. In addition, the risk is will be further investigated in the PASS.

Osilodrostat has been shown to cause **QT-prolongation,** although the overall incidence of clinically significant QT-prolongations in the clinical studies was low and only 1 patient discontinued the study drug due to ECG QT prolonged AEs while for 4 events osilodrostat was temporarily interrupted but re-initiated at the same or at reduced dose after which no new QT event was reported.

QT-prolongation *per see* is not automatically considered as serious condition. However, the condition could, if not detected, lead to fatal events such as *Torsades de pointes*. Associated symptoms such as syncope might precede (serious) events but most probably not, and prevention and clinical follow-up with ECG and electrolyte monitoring is therefore crucial. Cardiology consultation in case the QTc interval exceeds 480 ms is recommended to consider whether osilodrostat can be initiated or continued or should be (temporarily) reduced or dose interrupted.

An additional analysis provided during the procedure upon request by CHMP did not permit to identify a time period in which it would be appropriate to have a more focused monitoring, and no new risk factors/contributing factors could be identified either. Further evaluation of this risk is necessary, since these events are rare and can occur at any time during osilodrostat treatment, and high-risk patients were excluded from the clinical studies. Therefore, CV safety/QT prolongation in patients with CS, including those with CV diseases or risk factors for QT prolongation is included as missing information in the RMP and will be followed up in the PASS . For high-risk patients, a warning was added in the SmPC about the fact that the B/R should be carefully balanced.

There are still some uncertainties of importance regarding the **secondary pharmacology** effects of osilodrostat, e.g. effects on other hormones such as sex hormones. These effects together with the fact that osilodrostat has been shown to be teratogenic in non-clinical studies, has implications for the risk if osilodrostat is used in pregnancy. The SmPC wording has been updated to mitigate the risk of negative effects on the foetus (SmPC section 4.6) and the risk increased levels of testosterone (SmPC 4.8). In addition, hormones of the HPA-axis including c*linical consequences of increased sexual hormones* will be followed up in the PASS. Overall, ACTH levels were increased and although mean levels show modest increases below the threshold of clinical concern, individual patients may have ACTH values that are above the ULN. the SmPC section 4.8 now reflects the risk for increased ACTH levels. In addition, hormones of the HPA-axis including ACTH increase will be followed up in the PASS.

3.7.2. Balance of benefits and risks

The reduction in mUFC shown with osilodrostat treatment in Cushing's syndrome is considered highly clinically relevant and is considered to outweigh the two major risks, hypocortisolism and QT-prolongation. The risk of hypocortisolism is considered manageable through careful titration, monitoring of cortisol levels and with osilodrostat dose decrease or interruption if necessary. The risk of QT-prolongation is considered to be manageable through ECG and electrolyte monitoring, and cardiology consultation if QTc > 480 ms.

Overall, osilodrostat appears to be well tolerated. However, long-term safety will be followed up in two PASS, including follow-up on hypocortisolism, CV safety and QT prolongation, use in non-CD CS patients, hormones of the HPA-axis including ACTH increase and clinical consequences of increased sexual hormones.

3.7.3. Additional considerations on the benefit-risk balance

The agreed, indication for osilodrostat is "treatment of endogenous Cushing's syndrome in adults", but it is noted that the vast majority of the included patients had Cushing´s disease (i.e. caused by an ACTH-secreting pituitary corticotroph adenoma). Since osilodrostat blocks the synthesis of cortisol it is expected to be efficient in all forms of endogenous Cushing's syndrome and extrapolation of efficacy to patients with non-CD CS is uncontroversial. However, the safety data in these patients, in particular those with ectopic ACTH-production is very limited. Further post marketing data will be collected through the PASS to follow these patients and to confirm effects of efficacy and safety.

3.8. Conclusions

The overall B/R of Isturisa is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Isturisa is not similar to Signifor and Ketaconazole HRA within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Isturisa is favourable in the following indication:

Treatment of endogenous Cushing's syndrome in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6

months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that osilodrostat is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0011/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.