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APPLICATION NUMBER:

212801Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	212801
Link to EDR	\\CDSESUB1\evsprod\NDA212801\0000
Submission Date	March 7, 2019
Submission Type	Standard Review
Brand Name	ISTURISA [®]
Generic Name	Osilodrostat
Dosage Form and Strength	Film-coated oral tablets; 1 mg, 5 mg, and 10 mg
Route of Administration	Oral
Proposed Indication	Treatment of Cushing's disease
Applicant	Novartis
Associated IND	117489
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1. EXECUTIVE SUMMARY

The applicant submitted this original New Drug Application (NDA) for the treatment of patients with Cushing's disease.

Osilodrostat is an inhibitor of 11 beta-hydroxylase and it is shown to inhibit cortisol synthesis. Osilodrostat is a new molecular entity and it has been developed as an investigational drug for Cushing's disease.

Osilodrostat was evaluated in a total of 12 clinical trials; 9 Phase 1 trials, 2 Phase 2 trials and 1 Phase 3 trial. Pivotal clinical pharmacology information of osilodrostat was characterized for its labeling including pharmacokinetics (PK) using to-be-marketed formulation.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the Clinical Pharmacology information of NDA 212801, and concludes that the clinical pharmacology information of osilodrostat is adequate for labeling as follows:

Review Issue	Comments and Recommendations
Pivotal or supportive evidence of effectiveness	Data supporting effectiveness is based on the results of a single pivotal Phase 3 trials (Study C2301) with supplemental clinical information including Phase 2 trials in Cushing's disease patients.
General dosing instructions	The proposed initial dose is 2 mg orally twice daily. The dose should be titrated (initially by increments of 1 mg or 2 mg twice daily) based on individual response and tolerability with the goal of achieving normal cortisol levels.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The recommended initial dose for Cushing's disease patients with moderately impaired hepatic function (Child-Pugh B) is 1 mg twice daily. For patients with severe hepatic impairment (Child-Pugh C), the recommended starting dose is 1 mg once daily in the evening.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal study and there is no proposed change.

1.2 Post-Marketing Requirements (PMR) and Commitments

PMR: Conduct a drug-drug interaction clinical trial to determine a quantitative estimate of the change in PK and PD of osilodrostat following co-administration of a strong CYP3A inhibitor

(such as ketoconazole at 400 mg QD) in patients with Cushing’s disease and stabilized osilodrostat dosing. Design and conduct the trial in accordance with the FDA Guidance for Industry; “*Clinical Drug Interaction Studies - Study Design, Data Analysis, and Clinical Implications*”.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Regulatory Background

Osilodrostat was

(b) (4)

Through Mid-Cycle Communication (MCC) of this NDA dated 8/28/2019, the Agency provided the following clinical concerns to the applicant (see further details in DARRTS memo dated 10/16/2019);

“We have concerns about the high rate of adrenal insufficiency (AI) observed in the study. The high rate of adrenal insufficiency might be related to poorly defined AI in the protocol, as it seems that some patients who had adverse events of “adrenal insufficiency” had nonspecific symptoms related to rapid decrease in cortisol levels that can be managed without decreasing the dose. However, we also believe that up-titration of drug was too aggressive during the study: the majority of patients had their dose increased to the next dose level even though there was a decrease in urinary free cortisol (UFC) levels from baseline. Rapid dose escalation occurring every 2 weeks (from 4 to 10 to 20 mg), when the steady state of the drug may not yet have been reached, seems likely to be causing the high rate of AI observed in study. Cortisol suppression persisted during the study after the dose was decreased or the drug was stopped, and the biological t1/2 of cortisol suppression might be longer than drug elimination t1/2. In addition, important components of the titration schedule, e.g., down or up titration after occurrences of ‘adrenal insufficiency’, were not clearly pre-defined in the protocol. This led to a wide range of dose adjustments by investigators with no discernable pattern during the study. We believe a more cautious titration schedule may be more appropriate for your drug. However, there are no clinical data to clearly define the optimal dosing strategy, both at the time of dose initiation and uptitration as well as down-titration in the case of AI. You will need to propose a dosing strategy for our consideration that improves the safety profile of the drug so that the overall benefit risk profile is favorable. You may rely on a rationale based on typical dosing strategies in patients with Cushing’s Disease in clinical practice or a Clinical Pharmacology modeling rationale if appropriate data are available.”

The Agency clarified during the telecommunication for MCC that the applicant may provide any clinical pharmacology data to demonstrate the duration of cortisol suppression after the drug is discontinued. The applicant indicated that because patients have different responses and large variability in cortisol levels, PK/PD modeling may not be helpful as the drug has a short half-life (4 hours) and none of the metabolites are pharmacologically active. The applicant followed up with the question if there were any clinical pharmacology data to link PK and PD for the persistent pharmacodynamic response after the discontinuation of osilodrostat in some patients, and concluded that PK can not explain observed PD as follows;

- The elimination half-life of osilodrostat is short (~ 4 hours), so osilodrostat should reach its new steady state quickly after dose changes or eliminate quickly after dose interruption.
- There are no long-lived metabolites of osilodrostat that contribute to the inhibition of its target, CYP11B1.
- Cortisol levels adjust rapidly to non-osilodrostat related factors such as stress and diurnal patterns (elimination half-life of cortisol is ~ 1 hour).

The applicant (b) (4)
 (b) (4) To support the indication, 1, 5 and 10 mg of drug products are being introduced (Table 1).

Table 1 Components of drug products (Source: Table 1-2, eCTD 2.3.P)

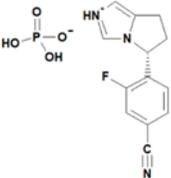
Ingredients	Amount per 1 mg film-coated tablet (mg)	Amount per 5 mg film-coated tablet (mg)	Amount per 10 mg film-coated tablet (mg)	Function	Reference to standards
Tablet core					
Osilodrostat phosphate (corresponding to Osilodrostat free base)	1.4 (b) (4) (1.000)	7 (b) (4) (5.000)	14.3 (b) (4) (10.000)	Active ingredient	Novartis monograph
(b) (4) Microcrystalline cellulose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Ph. Eur., USP/NF
Mannitol					Ph. Eur., USP/NF
Magnesium stearate					Ph. Eur., USP/NF
(b) (4) Colloidal silicon dioxide					Ph. Eur., USP/NF
Croscarmellose sodium					Ph. Eur., USP/NF
Weight of tablet core:					
Film-coat ¹					
Hypromellose/ (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Ph. Eur., USP/NF
Titanium dioxide (b) (4)					Ph. Eur., USP/NF
Iron oxide, yellow (b) (4) Ferric oxide (yellow)					Regulation (EU) 231/2012 ^a , USP/NF
Iron oxide, red (b) (4) Ferric oxide (red)					Regulation (EU) 231/2012 ^a , USP/NF
Iron oxide, black (b) (4) Ferrosoferric oxide					Regulation (EU) 231/2012 ^a , USP/NF
(b) (4) Polyethylene glycol (PEG) 4000					Ph. Eur., USP/NF
Talc					Ph. Eur., USP/NF
(b) (4)					Ph. Eur., USP/NF
Total coating weight:					
Total weight of film-coated tablet:	95.00	118.00	234.00		(b) (4)

² E: Official European Union numbering system
 (b) (4)

^a Regulation (EU) 231/2012: Commission regulation (EU) laying down specifications for food additives

2.2 Clinical Pharmacokinetics

Table 2. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information Pharmacologic Activity
Established pharmacologic class (EPC)	Cortisol synthase inhibitor
Mechanism of action	Inhibition of 11 beta-hydroxylase (CYP11B1 and CYP11B2 enzyme), which is known to be mainly distributed in mitochondria of adrenal gland. <ul style="list-style-type: none"> • IC₅₀ was 0.7 nM against CYP11B2 in a Chinese hamster lung cell line. • IC₅₀ was 17 nM for the inhibition of aldosterone product in a human adrenocortical carcinoma cell line. See further details in non-clinical review
Active moieties	 <p>(Molecular weight; 325.24 g/mol)</p> <p>The major metabolite in plasma was M34.5 contributing 51% to the plasma radioactivity and it is not pharmacologically active.</p>
QT prolongation	There was significant QTc prolongation effect of osilodrostat following 150 mg, a supra-therapeutic dose; $\Delta\Delta\text{QTcF} = 25.4$ ms (90% CI: 23.8, 27.0) in the TQT study (Study C2105). No relevant QT effect was observed following 10 mg ($\Delta\Delta\text{QTcF} = 1.73$ ms (90% CI: 0.15, 3.31), Study C2105). The estimated $\Delta\Delta\text{QTcF}$ for 30 mg, maximum recommended therapeutic dose, was 4.3 ms (90% CI: 3.7, 4.9) using the concentration-QT analysis, and the QT-IRT team concluded that osilodrostat is not associated with significant QTc prolongation at the proposed therapeutic dose. (b) (4) See further details in the review by QT-IRT team.
General Information	
Bioanalysis	Validation of the bioanalytical method (LC-MS/MS) was acceptable overall. See summary of validation report in Appendix.
Healthy subjects versus patients	PK is comparable between patients and healthy subjects. However, PD appears to be different between two population due to different feedback sensitivity in the HPA-axis.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	The predicted maximum total plasma concentration at steady state ($C_{\text{max,ss}}$) at 30 mg is 232 ng/mL (1.02 μM) following 30 mg bid in Phase 3 based on population PK analysis. The geometric mean (Geo-CV%) pre-dose C_{trough} concentrations of osilodrostat on Day 9, Day 11, Day 13, and Day 15 were 90.3 ng/mL (37.8%), 79.8 ng/mL (62.0%), 69.1 ng/mL (63.1%), and 54.5 ng/mL (47.9%) respectively, following <u>30 mg bid</u> in female healthy volunteers (N=19, Study C2108). There was no significant accumulation nor diurnal PK difference (morning versus evening) (Study A2102).
Range of effective dose(s) or exposure	The daily dose required to reach UFC response was 1.35 ± 13.9 mg bid with 75% of patients normalizing on ≤ 20 mg/day (Study C2201, Part 1, N=12). The C_{trough} ranged from 0.336 ng/mL (2 mg bid) to 204 ng/mL (50 mg bid).
Maximally Tolerated Dose or Exposure	Single doses up to 200 mg was tolerated (Study A2101). 30 mg bid for 15 days was well tolerated (Study C2108).

Dose proportionality	PK was more than proportional to dose (slope (b) in a power model: $PK=a \cdot Dose^b$); <ul style="list-style-type: none"> slope = 1.292 (90% CI: 1.240, 1.344) and 1.084 (90% CI: 1.042, 1.127) for AUC_{inf} and C_{max}, respectively, following dosing range from 0.5 mg to 200 mg (Study A2101, SAD/MAD)
Accumulation	No significant accumulation with accumulation index of 0.85 to 1.32 following 0.5 mg to 200 mg (Study A2101).
Time to achieve steady-state	Steady-state was reached in two days (Study A2101)
Bridge between to-be marketed and clinical trial formulations	No need for formulation bridging as to-be-marketed formulation was used in the pivotal Phase 3 trial.
Absorption	
Bioavailability	Absolute bioavailability is not known. The applicant considered osilodrostat (b) (4) based on 90.6% recovery of the drug in urine (Study C2101 for ADME) and rapid dissolution ($Q > \frac{(b)}{(4)}\%$ in 15 min).
T_{max}	Approximately 1 hour (Study A2101)
Food effect (Fed/fasted) Geometric least square mean and 90% CI	Following 30 mg final market image, exposure was reduced with a high fat meal: <ul style="list-style-type: none"> AUC_{inf}: 11% reduced (GMR = 0.888; 90% CI: 0.857, 0.921) C_{max}: 21% reduced (GMR=0.786, 90% CI: 0.739, 0.835) T_{max}: 25% increased (GMR=1.25, 90% CI: -2.00, 3.50)
Distribution	
Volume of distribution	Median apparent volume of distribution was 101 L (population PK)
Plasma protein binding	36.4%
Drug as substrate of transporters	Not a sensitive substrate of P-gp or MRP as a high intrinsic permeability with low efflux ratio and modest impact of inhibitors in Caco-2 system.
Elimination	
Mass balance results	Following 50 mg, the overall recovery of radioactivity was $\geq 86.5\%$. The majority of radioactivity dose was eliminated in the urine (mean: 90.6%) with a minor amount eliminated in the feces (mean: 1.58%). The dose eliminated in the urine as unchanged was minor (mean: 5.19%). Median terminal half-life was 3.98 hours. The most abundant circulating metabolite in plasma was M34.5 contributing 51% to the plasma radioactivity (AUC_{48h}) (Study C2101)
Clearance	16.4 L/h (95% CI: 14.9, 18.1) (population PK)
Half-life	Terminal half-life was approximately 4 hours following single doses and ranged from 3 to 5 hours following multiple doses., apparent, or multiple phases.
Metabolic pathway(s)	The relative contributions of the CYP enzymes to osilodrostat clearance were estimated to be ~11.7% by CYP3A4, ~6.25% by CYP2B6, and ~8.07% by CYP2D6 (total CYP contribution 26%). Multiple UDP-glucuronosyltransferase (UGT) enzymes (UGT1A4, UGT2B7, and UGT2B10) were shown to contribute to osilodrostat glucuronidation (total UGT contribution 19%). Other non-CYP, non-UGT mediated metabolism (such as other oxidative metabolism by unknown enzymes, ribose conjugation etc.) was shown to contribute to ~50% of total clearance. Primary metabolite (M34.5, see Figure 2) was not pharmacologically active.
Primary excretion pathways (% dose)	The majority of radioactivity dose was eliminated in the urine (mean: 90.6%).
Intrinsic Factors and Specific Populations	
Body weight	Body weight was a predictor of osilodrostat dose to ED_{50} in the population PK analysis. However, the impact of body weight on the exposure was considered negligible and did not warrant dose adjustment.

Race	<p>Following 1 mg bid on Day 14 in the morning (Mean±SD, N=10 HV):</p> <ul style="list-style-type: none"> • AUC_{tau}: 21.13±5.78 (Caucasian), 31.42±9.22 (Japanese) ng/mL*hr • C_{max}: 4.70±0.80 (Caucasian), 5.89±1.74 (Japanese) ng/mL <p>Adjustment by weight did not reduce the effect of race (Study A2102). The population PK analysis indicates that exposure in the Asian subjects (mostly Japanese) was approximately 30% higher than that of Caucasian.</p>
Age	No significant impact on PK parameters in the population PK analysis (age range; 19-72 years).
Renal impairment	<p>No significant changes for severe or ESRD (ratio of AUC_{inf} or C_{max}, respectively):</p> <ul style="list-style-type: none"> • Severe/normal; 0.964 (0.751, 1.24) and 0.899 (0.732, 1.10) • ESRD/normal; 0.992 (0.731, 1.34) and 0.824 (0.641, 1.06)
Hepatic impairment	<p>Increase in AUC for moderate and severe without significant changes in C_{max}:</p> <ul style="list-style-type: none"> • mild/normal; 0.860 (0.569, 1.30) and 0.912 (0.645, 1.29) • moderate/normal; 1.44 (0.950, 2.18) and 0.846 (0.598, 1.20) • severe/normal; 2.66 (1.73, 4.09) and 0.798 (0.557, 1.14) <p>Mean (CV%) of half-life was 5.31 (21%), 4.67(25%), 9.33 (50.9%) and 19.5 (29.6%) for normal, mild, moderate and sever group, respectively.</p>
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	<p>In vitro osilodrostat showed inhibitory potency for CYP1A2, CYP2C19, CYP2D6 and CYP2E1. Relatively weak inhibitory potency was seen for CYP3A4/5 (with midazolam, 1'-hydroxylation) and CYP2C9. Osilodrostat showed apparent time-dependent inhibition of CYP2C19 ($K_I = 52.3 \pm 29.3 \mu\text{M}$ and $k_{inact} = 0.0260 \pm 0.00695 \text{ min}^{-1}$) in pooled HLM. The impact of osilodrostat 50 mg on the CYP probe substrates exposure was evaluated (Study C2102). Osilodrostat is a moderate inhibitor of CYP1A2 (2.5-fold increase in caffeine exposure), a weak to moderate inhibitor of CYP2C19 (1.9-fold increase in omeprazole exposure), and a weak inhibitor of CYP2D6 and CYP3A4/5 (1.5-fold increase in dextromethorphan and midazolam exposure).</p> <p>Induction potential for CYP1A2, CYP2B6 and CYP3A4 was shown in vitro studies as corresponding mRNA levels were dose dependently increased by osilodrostat.</p>
Inhibition/induction of transporter systems	Osilodrostat may increase the systemic exposure of co-medications with clearance mediated by OCT2, MATE1 and MATE2K according to in vitro estimation. However, it was concluded that the potential risk was not considered of significant clinical concern based on the estimated C _{max} and IC ₅₀ values.

2.2.1 What are osilodrostat clearance pathways?

Osilodrostat clearance pathways were assessed from the standard mass balance study (Study C2101). Osilodrostat 50 mg containing 100 microCi of ^{14}C was administered to healthy male volunteers (N=5).

Mean total recovery of radioactivity with $92.2\pm 4.46\%$ of dose was acceptable. Recovery of radioactivity was mainly in the urine (90.6% of dose) and minor in the feces (1.58% of dose) (Figure 1).

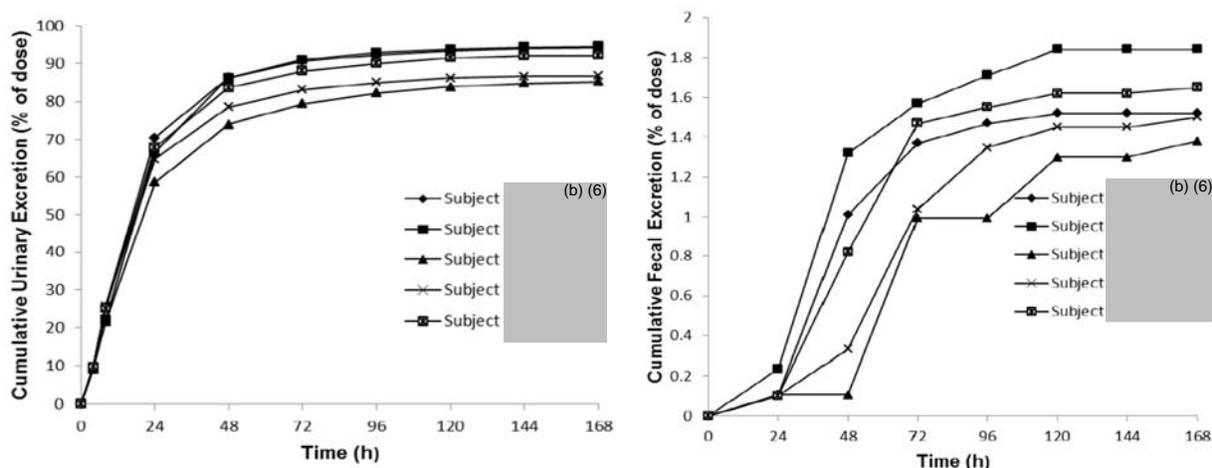


Figure 1 Cumulative urinary (left) and fecal (right) excretion of radioactivity following 50 mg osilodrostat (Source; Figure 11-14, CSR)

Metabolism was extensive as urinary elimination of osilodrostat was minor (5.19% of dose). Multiple metabolites were characterized (Figure 2). The following metabolites were identified in the mass balance study (see further details in Appendix 3.1);

- M24.9, hydroxylation of the pyrrolidine- ring system (10.8% of dose),
- M23.1, N-methylation (4.35% of dose),
- M34.5, most abundant metabolite in plasma, imidazole ring (0.81% of dose), additional metabolism (M6, M10, M16 and M16.4B) (10.5% of dose) and its glucuronide conjugate M22 (12.6% of dose)
- M16.5, direct glucuronidation (17.3% of dose)
- M20.8, ribose conjugate (2.28% of dose)

In plasma, osilodrostat was approximately 68% of circulating radioactivity after 2 hours of dosing but it gradually decreased to less than 24% after 12 hours (Figure 3).

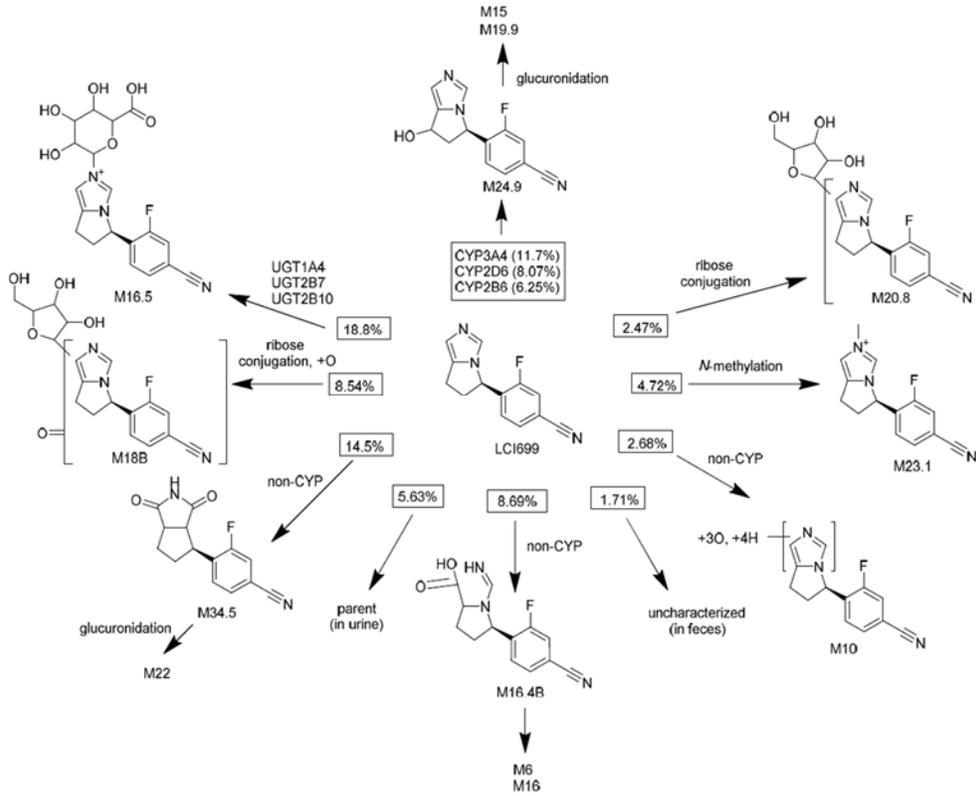


Figure 2 Biotransformation scheme for osilodrostat in humans (Source; Figure 3-1, eCTD 2.7.2)

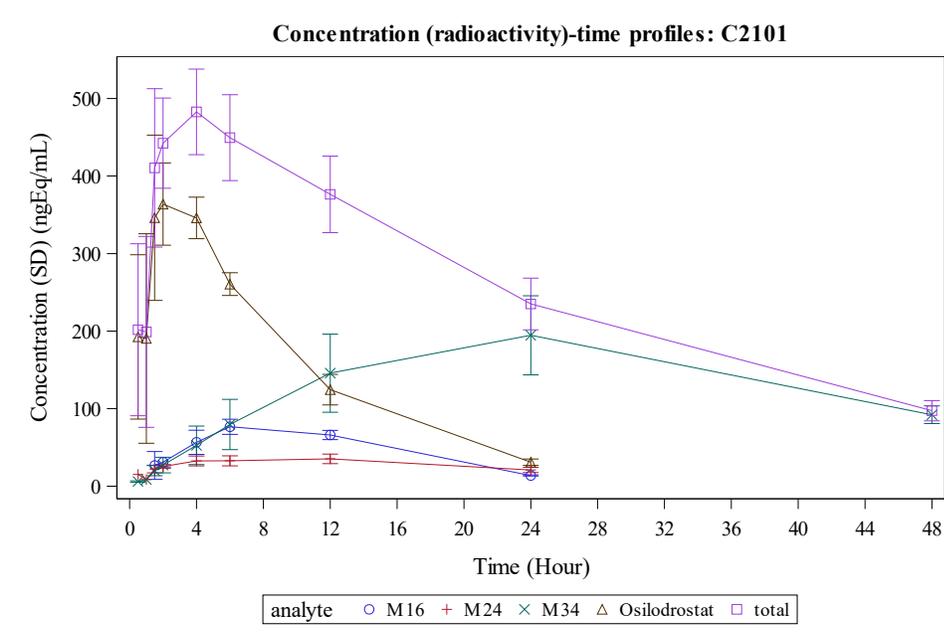


Figure 3 Concentration as radioactivity – time profiles (Study C2101, Mass balance study, M34 was the major metabolite)

2.2.2 What is clinical relevance of non-linear PK of osilodrostat?

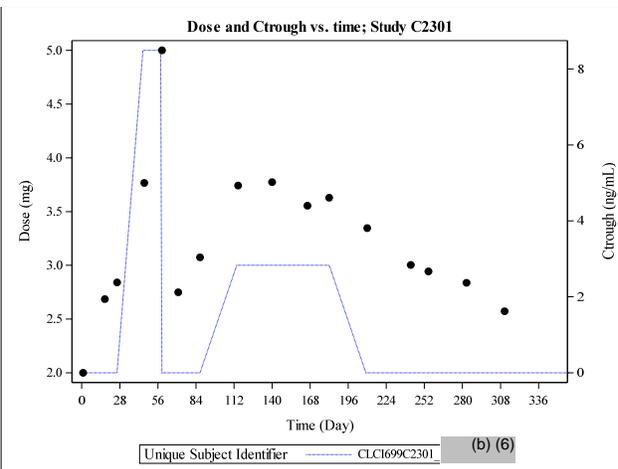
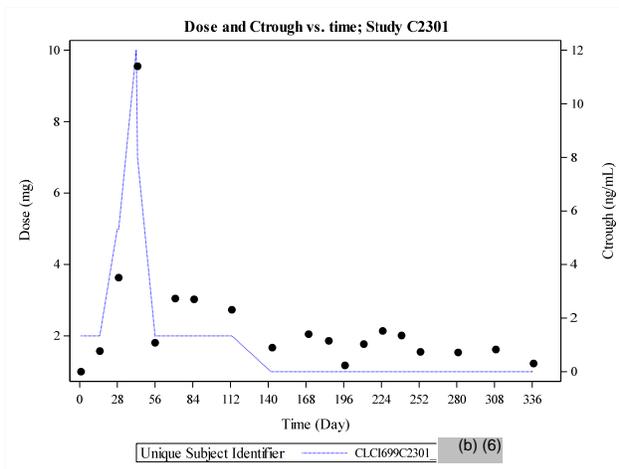
Osilodrostat showed that PK increase was more than proportional to dose increase (dose related non-linearity). In addition, it seems that there is a time-dependent non-linearity due to potential auto-induction in metabolism.

Uncertainty of non-linear PK seems to be manageable within the proposed dosing regimen and labeling as follows;

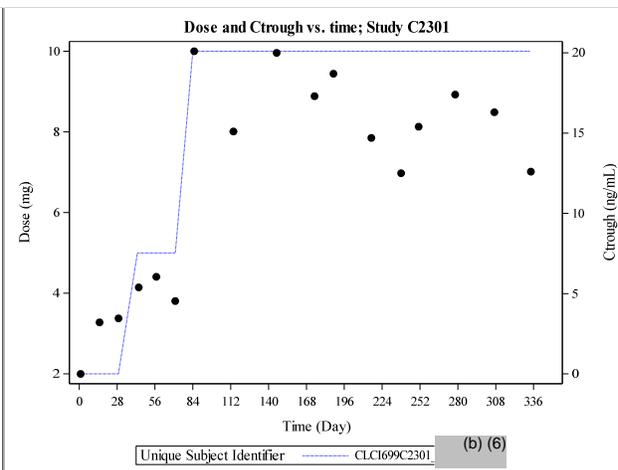
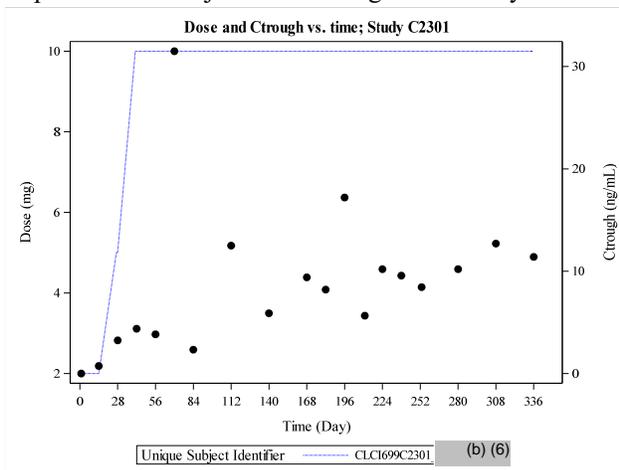
- There was no significant difference between AUC_{inf} following single dose and AUC_{tau} following multiple doses. It indicates that potential of a time-dependent PK is not significant.
- There is no apparent accumulation following multiple doses as the terminal half-life is approximately 4 hours and significantly less than the dosing interval (12 hours).
- Although there was non-linearity in PK following single doses, the degree of non-linearity was comparable following multiple doses (Figure 9, Study A2101 and A2102, Appendix).
- There was apparent trend that C_{trough} concentrations were decreased following 30 mg bid over 15 days in DDI study (Figure 11, Study C2108, Appendix). However, it was not clear if it was due to changes in clearance or variability in C_{trough} as there was no significant accumulation. Further, there was no significant impact of osilodrostat 30 mg bid for 15 days on exposure of levonorgestrel, which is metabolized by multiple enzymes (e.g., sulfation, glucuronidation, CYP3A4 and reduction) and ethinyl estradiol, which is also metabolized by multiple enzymes (e.g., SULT1E1, UGT1A1, CYP3A4 and CYP2C9).
- There were no apparent changes in C_{trough} at apparent steady-state in Phase 2 and 3 trials (Figure 4 and additional figures in Appendix; Figure 12 and 13).
- Dose was individualized with adjustment to clinical responses; until normalization of mUFC or intolerable as protocol-specified (Figure 5, and additional figures in Appendix). It indicates that exposure-response is confounded as dose is adjusted to clinical responses without exposure consideration.
- There was no dose adjustment in Phase 3 trial due to concomitant medications including strong metabolic perpetrators.

However, we recommend conducting a drug-drug interaction clinical trial to estimate the effect of strong CYP3A4 inhibitors on osilodrostat exposure change as 1) there is significant uncertainty in the drug interaction according to the assessment in PBPK modeling and 2) there is potential for off-label co-administration of ketoconazole, a strong CYP3A4 inhibitors with osilodrostat in patients with Cushing's disease. See further details of the proposed PMR (see section 1.2 of review) and PBPK review (see Appendix).

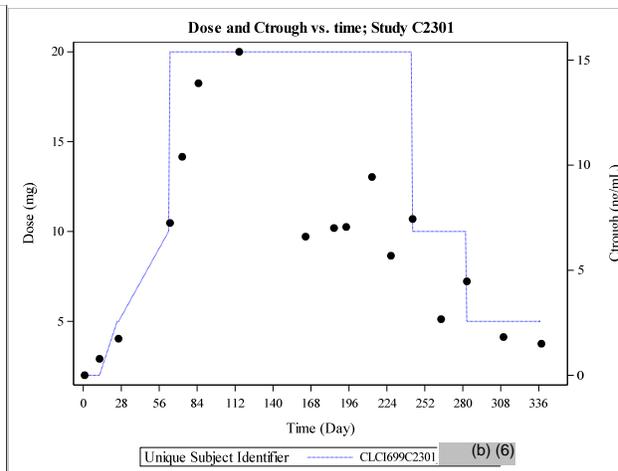
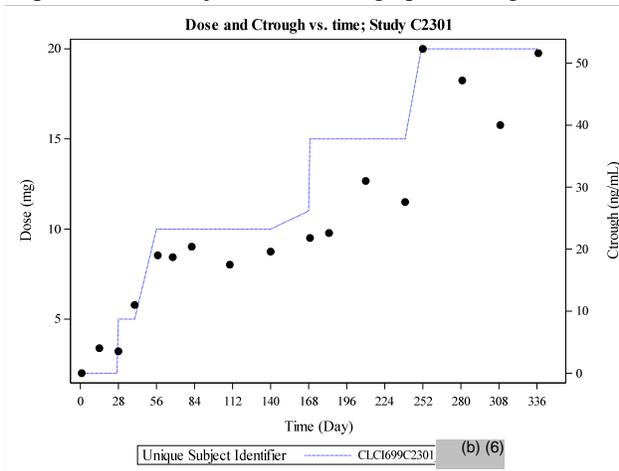
Representative subjects with dosing less than 10 mg bid



Representative subjects with 10 mg bid at steady-state



Representative subjects with dosing up to 20 mg bid



Representative subjects with 30 mg bid at steady-state

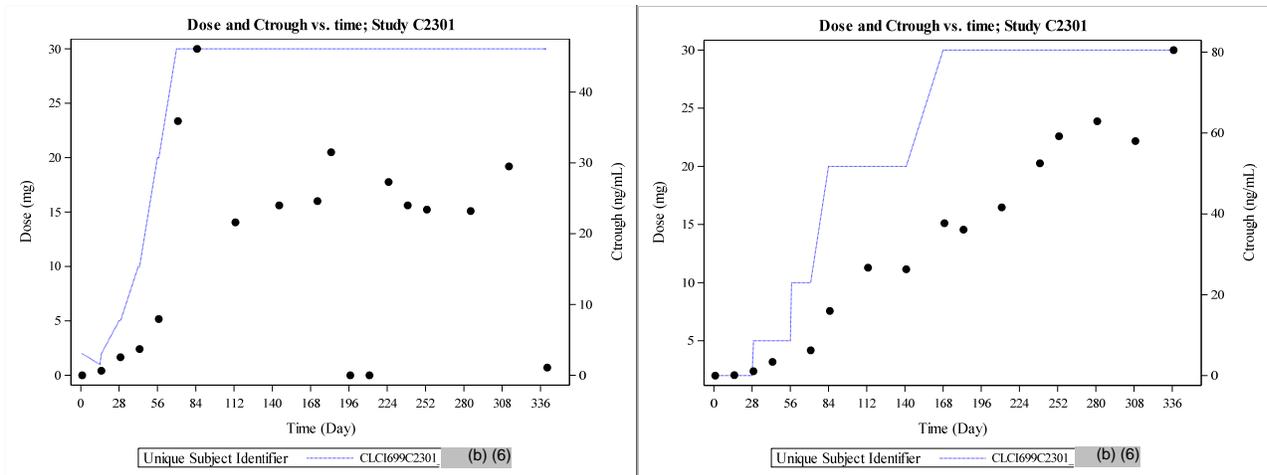


Figure 4 Dose adjustment (broken line) and C_{trough} (black filled circle) changes over the treatment period (Study C2301, Phase 3 PK sub-groups)

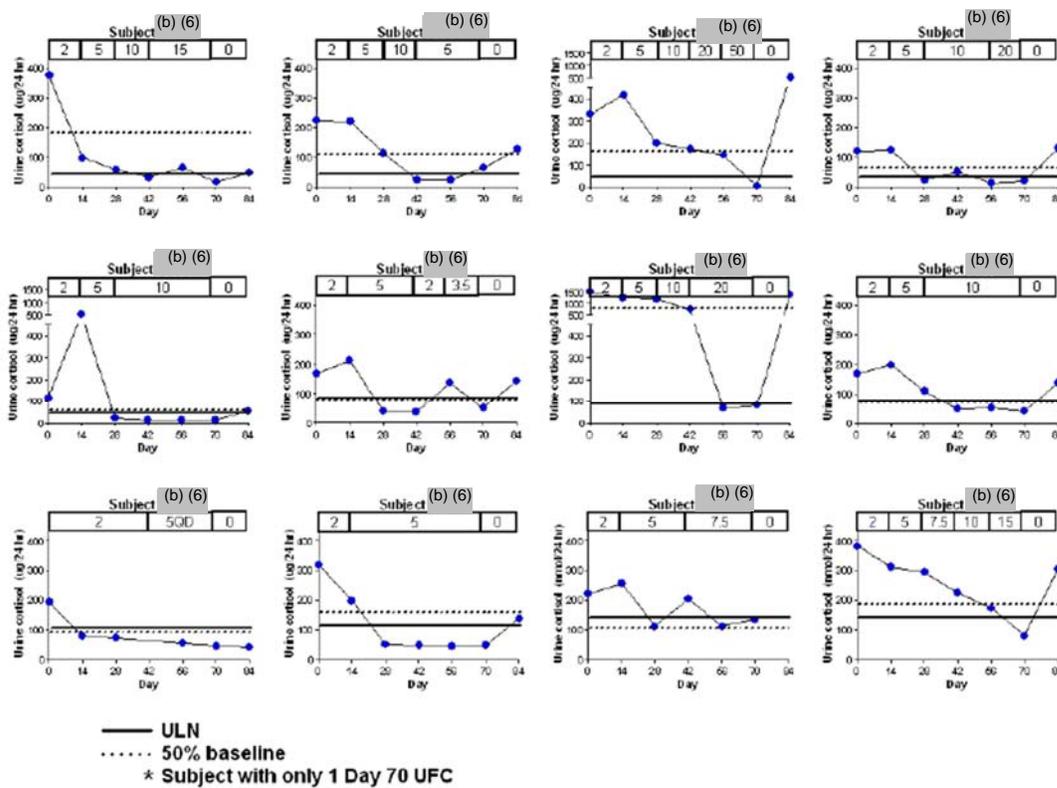


Figure 5 Individual dose-response (mUFC) relationship (Source; Figure 2-1, CSR, Study C2201)

2.2.3 What was the dose selection procedures?

The bid dosing was selected based on the PK characteristics including a short half-life (3-5 hours). A dose of 4-5 mg bid was estimated to achieve above the *in vitro* IC₅₀ for CYP11B1 (2.5 nM) according to the modeling of PK exposure. The starting dose of 2 mg bid was chosen for the proof-of-concept (PoC) trial (Study C2201, Part I, study design in Appendix) in the consideration of reduction the risks associated with hypocortisolism-related adverse events.

In the PoC trial, dose was titrated from 2 mg, to 5 mg, 10 mg, 20 mg or 30 mg in every two weeks following clinical responses. The results of individual dose titration in PoC trial indicate that the dosing range was from 2 mg bid to 50 mg bid, and majority of patients achieved the primary efficacy endpoint, UFC normalization. The range of C_{trough} of osilodrostat ranged from 0.336 ng/mL to 204 ng/mL corresponding to the wide dosing range (Figure 5). Based on the results of the TQT study, the maximum dose was amended to 30 mg in PoC trial due to the potential risk of QTc prolongation.

The study design to evaluate efficacy and safety of osilodrostat (Study 2301, schematic study design summary in Appendix) was based on results of the PoC trial. Starting dose was selected as 2 mg, dose was adjusted to 5 mg bid, 10 mg bid, 20 mg bid, or 30 mg bid in every two weeks based on mean UFC (mUFC) of three 24-hour UFC values collected every two weeks during the dose-titration period. Dose was reduced for safety reasons at any time during the study. Throughout the Core Period of the study the median average total daily dose ranged from 4.0 mg/day to 10.0 mg/day (Figure 6).

In first-in-human SAD/MAD study (Study A2101), there was no dose proportional inhibition in 24-hour urinary cortisol over the 0.5-3 mg dose range. Osilodrostat showed mild inhibition of plasma cortisol without increase in ACTH following 3 mg, and inhibition of cortisol and aldosterone with an increase in ACTH following 10 mg daily dosing. Results indicate that PD changes may not be directly explained by PK in healthy volunteers. Based on the result, the applicant concluded that 10 mg might (b) (4)

. In patients with Cushing's syndrome, a higher dose may be needed than that of healthy subjects to suppress cortisol synthesis as patients have increased ACTH and thus cortisol secretion. In the PoC trial, the daily dose required to reach UFC response was estimated as 1.35 mg bid with high variability (i.e., ±13.9 mg). Between-subject variability in response is expected to be significantly high as responses are confounded by individual status of hypothalamic-pituitary-adrenal axis and its feedback sensitivity.

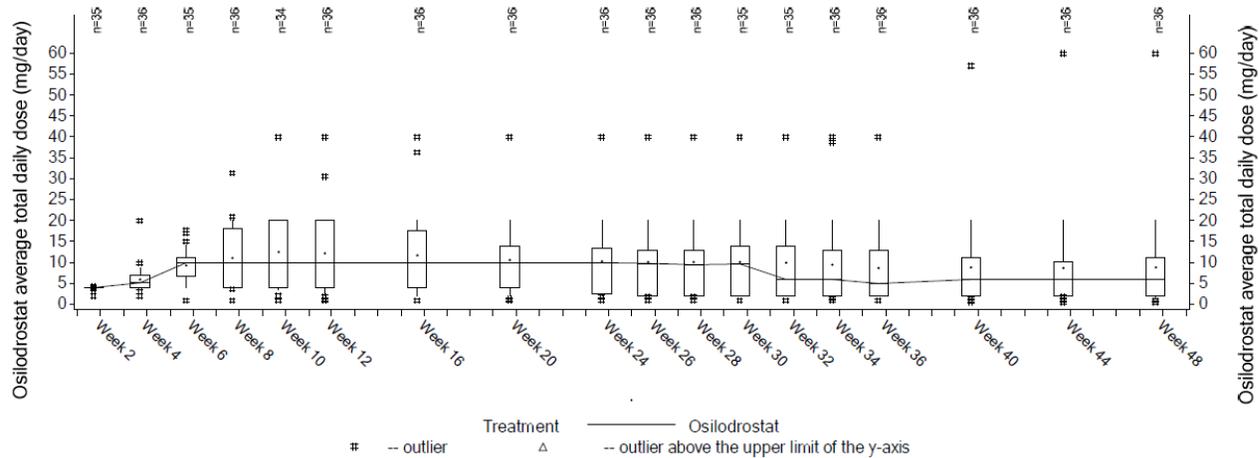


Figure 6 Box plot of osilodrostat average total daily dose (mg/day) by visit during the core (Source; Figure 14.3-1.1, CSR, C2301, see study design in Appendix.)

2.2.4 Was drug interaction potential evaluated?

Yes, the applicant addressed drug interaction potential and provide reasonable information for labeling as follows:

Evaluation of drug interaction potential with osilodrostat 50 mg

Multiple metabolic enzymes were known to responsible osilodrostat clearance and osilodrostat was shown to affect multiple metabolic enzymes (Table 2). The applicant evaluated metabolic perpetrator potential of osilodrostat using a study design with cocktail probe substrate (Study C2102). Change of PK for the following known in vivo probe substrate was assessed with and without osilodrostat 50 mg; caffeine 100 mg, omeprazole 20 mg, dextromethorphan 30 mg and midazolam 2 mg for probe substrate of CYP1A2, CYP2C19, CYP2D6 and CYP3A4/5, respectively.

Results showed inhibition of CYP1A2, CYP2C19, CYP2D6 and CYP3A4/5 with 2.5-, 1.9-, 1.5- and 1.5-fold increase in caffeine, omeprazole, dextromethorphan and midazolam exposure, respectively (Figure 7).

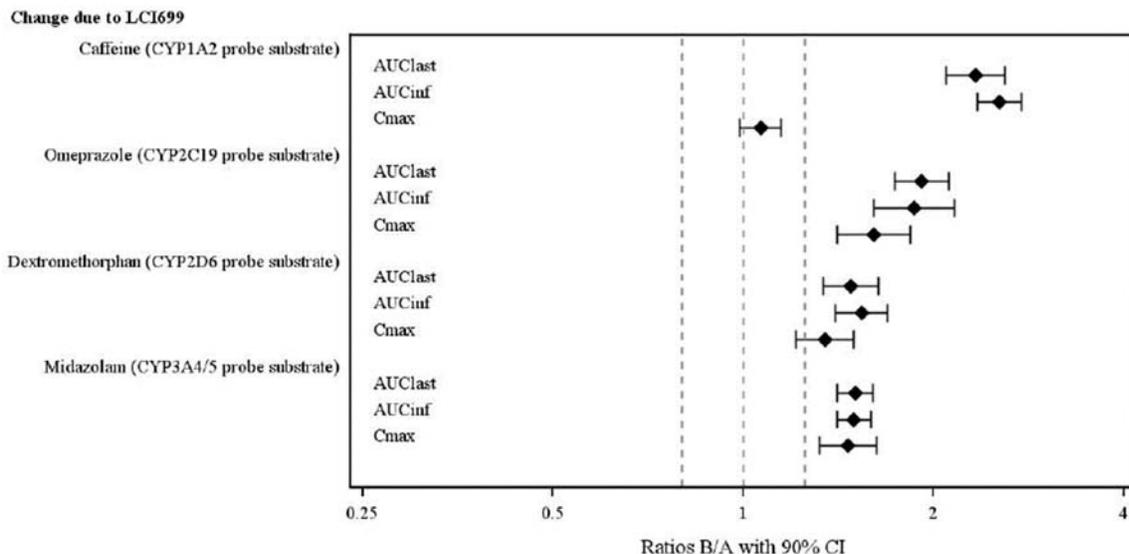


Figure 7 Summary of the effect of osilodrostat on CYP probe substrates (Source; Figure 3-2, eCTD 2.7.2)

Effect of osilodrostat 30 mg bid on exposure of oral contraceptives

The impact of osilodrostat 30 mg bid for 15 days on exposure of oral contraceptive (OC) containing 30 mcg estradiol and 150 mcg levonorgestrel was evaluated using an open-label, three-period drug-drug interaction study in healthy female subjects (Study C2108). Subjects received cortisol replacement at the end of investigational treatments (period 3) to avoid potential safety events relate to cortisol lowering effect of osilodrostat (schematic summary of study design in Appendix).

There was no significant impact of osilodrostat on the PK of OC (Table 3).

Table 3 Statistical analysis of primary PK parameters for ethinylestradiol (upper) or levonorgestrel (lower) with and without osilodrostat 30 mg bid for 15 days (Source; Table 2-9 and 2-10, eCTD 2.7.2)

Ethinylestradiol

PK parameter (unit)	Treatment	n ¹	Adjusted geo-mean	Comparison(s)	Treatment comparison		
					GMR ²	90% CI	
					Lower	Upper	
AUClast (pg*h/mL)	OC alone	24	537				
	OC + osilodrostat	19	556	OC + osilodrostat / OC alone	1.03	0.962	1.11
Cmax (pg/mL)	OC alone	24	59.8				
	OC + osilodrostat	19	52.8	OC + osilodrostat / OC	0.882	0.830	0.938

Levonorgestrel

PK parameter (unit)	Treatment	n ¹	Adjusted geo-mean	Comparison(s)	Treatment comparison		
					GMR ²	__90% CI__ Lower Upper	
AUC _{last} (pg*h/mL)	OC alone	24	42300				
	OC+osilodrostat	19	43000	OC+osilodrostat/ OC alone	1.02	0.916	1.13
C _{max} (pg/mL)	OC alone	24	3800				
	OC+osilodrostat	19	3270	OC+osilodrostat/ OC alone	0.860	0.737	1.00

Evaluation of drug interaction potential with osilodrostat 30 mg

The applicant evaluated drug interaction potential of osilodrostat 30 mg from results of 50 mg (Study C2102) using physiologically-based PK (PBPK) modeling and simulation.

The followings are conclusions by the PBPK review team. See details in review by Dr. Jianghong Fan in the Appendix.

- The osilodrostat PBPK model is adequate to predict the osilodrostat PK following a single dose administration over a dose range of 0.5-200 mg, and following multiple dose administration of 0.5, 1, 3 and 30 mg osilodrostat.
- The osilodrostat PBPK model is adequate to predict the PK of metabolite LXB168 following a single dose administration of 50 mg osilodrostat.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on caffeine (a CYP1A2 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The predicted caffeine AUC ratio is between 1.00-1.91 in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on midazolam (a CYP3A4 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The predicted midazolam AUC ratio is between 0.52-1.28 in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on omeprazole (a CYP2C19 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The predicted omeprazole AUC ratio is between 1.06-2.28 following a single dose administration of omeprazole (20 mg) and between 0.86-1.52 following multiple dose administration of omeprazole (20 mg, qd) in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on dextromethorphan (a CYP2D6 substrate) PK following multiple dose administration of

osilodrostat in healthy subjects. The predicted dextromethorphan AUC ratio is 1.23 in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.

- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on warfarin (a CYP2C9 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The warfarin exposure would not be expected to be significantly affected by concomitant osilodrostat (30 mg, bid).
- The PBPK models are not adequate to predict the effect of osilodrostat on bupropion PK because bupropion active metabolites were not included in the model, but they contribute significantly to the efficacy of bupropion in human.
- The DDI potential of osilodrostat as a victim of CYP modulators cannot be excluded. Therefore, a study is recommended as part of PMR (see Section 1.2 of review).

2.2.4 Was there any clinically significant covariates for osilodrostat pharmacokinetics?

No, there was no significant covariates that warrant dose adjustment based on intrinsic factors.

Population PK analysis was conducted with PK data (N=8936 observations, Figure 11, Table 4 and 5) from a total of 8 clinical trials including both healthy and patients (N=414 subjects, Table 4) using a two-compartment model with dose-dependent relative bioavailability, mixed zero- and first-order absorption with lag time, and first order elimination (Figure 10, Appendix).

Clinically relevant covariates were evaluate using typical covariate models. The goodness-of-fit was assessed by conventional plots and metrics (Figure 12, Appendix). The predictive performance of the final model was assessed by applying a posterior prediction-corrected visual predictive check (Figure 13, Appendix).

The population PK analysis concluded as follows (see parameter estimates, Table 7, Appendix):

- age (yr) at baseline; no significant impact on PK parameters (i.e., CL/F, Vd/F, Ka, Tlag and relative bioavailability)
- body weight (kg) at baseline; a predictor for ED₅₀, but does not warrant dose adjustment as no impact on AUC_{ss} nor C_{trough}
- gender; no significant impact
- race; 30% higher exposure (AUC_{ss} nor C_{max,ss}) in Asian (~66% contributed by Japanese) compared to that of non-Asian with 20% higher relative bioavailability, not a level of dose adaptation due to the individual dose titration
- population (healthy subject vs. Cushing's patient); similar PK between two populations
- overall variability (CV%) was approximately 33%, 22% and 55% respectively on AUC_{ss}, C_{max,ss} and C_{min,ss}. Variability did not change under the influence of the covariates (dose, race and

weight). Additionally, the intra-subject variability (residual error) was estimated to be 38% (derived from the variance of the residual error)

Conventional exposure-response analyses were not attempted as dose titration was based on individual responses and tolerability.

APPEARS THIS WAY ON ORIGINAL

3. Labeling Comments

(b) (4) Patients With Renal Impairment

No dose adjustment is required for patients with renal impairment. Urinary free cortisol levels should be interpreted **(b) (4)** in patients with moderate to severe renal impairment, due to reduced **(b) (4)** [Clinical Overview – Section 3.1.2.2]

(b) (4) Patients With Hepatic Impairment

No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh A). For patients with moderate hepatic impairment (Child-Pugh B), the recommended starting dose is 1 mg twice daily. For patients with severe hepatic impairment (Child-Pugh C), the recommended starting dose is 1 mg once daily **in the evening**. More frequent monitoring of adrenal function may be required during dose titration in all patients with hepatic impairment **(b) (4)** [Clinical Overview – Section 3.2.1.1]

Comment: the applicant did not provide rationale for the proposed evening dosing. Therefore, we recommend removing the proposed dosing condition.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on TRADENAME

(b) (4)

7.2 Effect of TRADENAME on Other Drugs

(b) (4)

Comment: proposed labeling seems acceptable.

8.4 Pediatric Use

The safety and efficacy of TRADENAME in pediatric patients (b) (4) have not been established. [Summary of Clinical Pharmacology – Section 3.2.7].

8.5 Geriatric Use

(b) (4) in patients older than 65 years, (b) (4) is required. [Summary of Clinical Pharmacology – Section 3.2.5].

8.6 Renal Impairment

No dosage adjustment of TRADENAME in patients with impaired renal function is required (b) (4). In patients with moderate to severe renal impairment, UFC levels should be interpreted with caution due to reduced UFC excretion. [Summary of Clinical Pharmacology – Section 2.2.4]. [Summary of Clinical Pharmacology – Section 3.2.5].

8.7 Hepatic Impairment

Dose adjustment is not required in patients with mild hepatic impairment (Child-Pugh A), but is required for patients with moderately impaired hepatic function (Child-Pugh B) and for patients with severe hepatic impairment (Child-Pugh C) [see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]. More frequent monitoring of adrenal function may be required during dose titration in all patients with hepatic impairment. [Summary of Clinical Pharmacology – Section 2.2.6], [Summary of Clinical Pharmacology – Section 3.2.9].

Comment: proposed labeling seems acceptable.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Osilodrostat is a cortisol synthesis inhibitor. It (b) (4) inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. [Clinical Overview – Section 1.1.2]

12.2 Pharmacodynamics

Cardiac Electrophysiology

A thorough QT study in 86 male and female healthy volunteers showed a maximum mean placebo-corrected QTcF interval increase of 1.73 ms [90% confidence interval (CI): 0.15, 3.31] at a 10 mg dose, and 25.38 ms (90% CI: 23.53, 27.22) at a (b) (4) 150 mg dose [see Warnings and Precautions (5.2)]. [Summary of Clinical Pharmacology – Section 3.4.2], [Summary of Clinical Pharmacology – Section 2.2.8].

The predicted mean placebo-corrected QTcF change from baseline at the highest recommended dose in clinical practice (30 mg twice daily) was estimated as 5. (b) (4) ms (90% CI: (b) (4)), based on an interpolation of the data from the thorough QT Study and population PK analysis [see Warnings and Precautions (5.2)]. [Summary of Clinical Pharmacology – Section 1.2.2.2].

Comment: we recommend taking out (b) (4) and provide clinical pharmacodynamic information related to mechanism of actions (e.g., cortisol, ACTH).

12.3 Pharmacokinetics

Absorption

Osilodrostat is (b) (4) absorbed with a time of maximum observed concentration (T_{max}) of approximately 1 hour. (b) (4)

Comment: we recommend taking out promotional language

Effect of Food

In a healthy volunteer study ($N = 20$), subjects administered with a single, 30 mg oral dose of TRADENAME film-coated tablets with a high-fat meal resulted in reduction of AUC by 11% and C_{max} by 21%, respectively. The median T_{max} was delayed from 1 to 2.5 hours. These changes are not considered to be clinically significant, therefore TRADENAME can be administered with or without food. [Summary of Clinical Pharmacology – Section 3.1.2]

Distribution

The median apparent volume of distribution of osilodrostat is approximately 100 L. Protein binding is low (36.4%). The osilodrostat blood-to-plasma concentration ratio is 0.85. [Summary of Clinical Pharmacology – Section 3.1.5]

Elimination

The elimination half-life of osilodrostat is approximately 4 hours.

In an absorption, distribution, metabolism, and excretion (b) (4) study, the majority of the radioactivity dose of osilodrostat is eliminated in the urine (mean: 90.6% of administered dose) with only a minor amount eliminated in the feces (1.58% of dose). The low percentage of the dose eliminated in the urine as unchanged osilodrostat (5.2%) indicates that metabolism is the major clearance pathway in humans. [Summary of Clinical Pharmacology – Section 1.2.1.2]

Metabolism

Multiple CYP enzymes and UDP-glucuronosyltransferases contribute to osilodrostat metabolism and no single enzyme contributes greater than 25% to the total clearance. The metabolites are not expected to contribute to the pharmacological effect of osilodrostat. [Summary of Clinical Pharmacology – Section 3.1.6]

(b) (4)
Exposure (AUC_{inf} and C_{max}) slightly increases over dose-proportionally within the therapeutic dose range of (b) (4) mg to 30 mg. [Summary of Clinical Pharmacology – Section 3.1.3]

Comment: for format consistency, PK linearity can be located under absorption section unless specific mechanism can be linked to other section.

Specific Populations

Age and gender have no significant impact on osilodrostat exposure in adults. [Summary of Clinical Pharmacology – Section 3.2]

Race/Ethnicity

The relative bioavailability in Asian patients is ~20% higher, along with higher T_{max} and C_{max} , compared to other ethnicities. [Summary of Clinical Pharmacology – Section 3.2.4]

Patients with Hepatic Impairment

There was a trend of increasing AUC_{inf} to osilodrostat in moderate and severe hepatic impaired subjects (geo-mean ratios are 1.44 and 2.66, respectively) as compared to normal subjects. Exposures (C_{max} and AUC) of osilodrostat in the mild hepatic impairment group were similar to those in the normal group. (b) (4)

(b) (4)

Comment: see comment for section 2.3

Patients with Renal Impairment

Osilodrostat exposure was similar in the three renal function groups [normal, severe, and end stage renal disease (ESRD) groups] and thus a study was not conducted in mild and moderate renal impairment groups. The results showed that the PK of osilodrostat was not influenced by varying degrees of renal impairment to any clinically significant extent. (b) (4)

(b) (4)

Comment: proposed labeling is acceptable

4. APPENDIX

4.1 Contributions of clearance pathways from the ADME study

Metabolite/LCI699	Proposed reaction	Proposed enzyme/pathway involved	Amount excreted (mean % of dose)	Amount excreted (normalized to 100%) ^a
<u>Urine</u>				
Non-CYP mediated:				
M10	oxidation, +3O, +4H	likely non-CYP; not seen in HLM or by individual rhCYPs	2.47	2.68
M6	secondary to <u>M16.4B</u>	non-CYP	3.37	3.66
M16	secondary to <u>M16.4B</u>	non-CYP	1.77	1.92
M16.4B	metabolism on imidazole ring (opening)	likely non-CYP; not seen in HLM or by individual rhCYPs	2.87	3.11
M16.5	direct <i>N</i> -glucuronide	UGT1A4, UGT2B7, UGT2B10	17.3	18.8
M18B	ribose conjugate +O	non-CYP ^b	7.87	8.54
M20.8	ribose conjugate	non-CYP	2.28	2.47
M23.1	<i>N</i> -methylation	non-CYP	4.35	4.72
M22	glucuronide of M34.5	non-CYP	12.6	13.7
M34.5 (LXB168)	di-oxygenated LCI699	non-CYP; not seen in HLM or by individual rhCYPs	0.81	0.879
LCI699	n.a.	n.a.	5.19	5.63
CYP mediated:				
M15	secondary to <u>M24.9</u>	The primary reaction was CYP-mediated	7.23	7.84
M19.9	Possibly secondary to M24.9; glucuronic acid conjugate of mono-hydroxy LCI699	Likely the primary reaction was CYP-mediated	5.97	6.48
M24.9	hydroxylation of the pyrrolidine- ring system	CYP3A4 (45%), CYP2D6 (31%), CYP2B6 (24%)	10.8	11.7
<u>Feces</u>	Uncharacterized	Assumed non-CYP	1.58	1.71
<u>Other</u>	Uncharacterized	Non-assigned radioactivity	5.74	6.23
TOTAL %			92.2	100
TOTAL % UGT			UGT1A4, UGT2B7, UGT2B10	18.8
TOTAL % CYP			CYP3A4 (45%), CYP2B6 (24%), CYP2D6 (31%)	26.0 = 11.7 CYP3A4 8.07 CYP2D6 6.25 CYP2B6
n.a., not applicable				
^a based upon a mean dose recovery of 92.2%				
^b based upon LC-MS/MS data, the position of the additional oxygen is not at the same position as M24.9, therefore is unlikely to have been derived by a CYP-mediated reaction				
Source data: [DMPK R1600650 -Table 6-1]				

4.2 Dose proportionality of PK

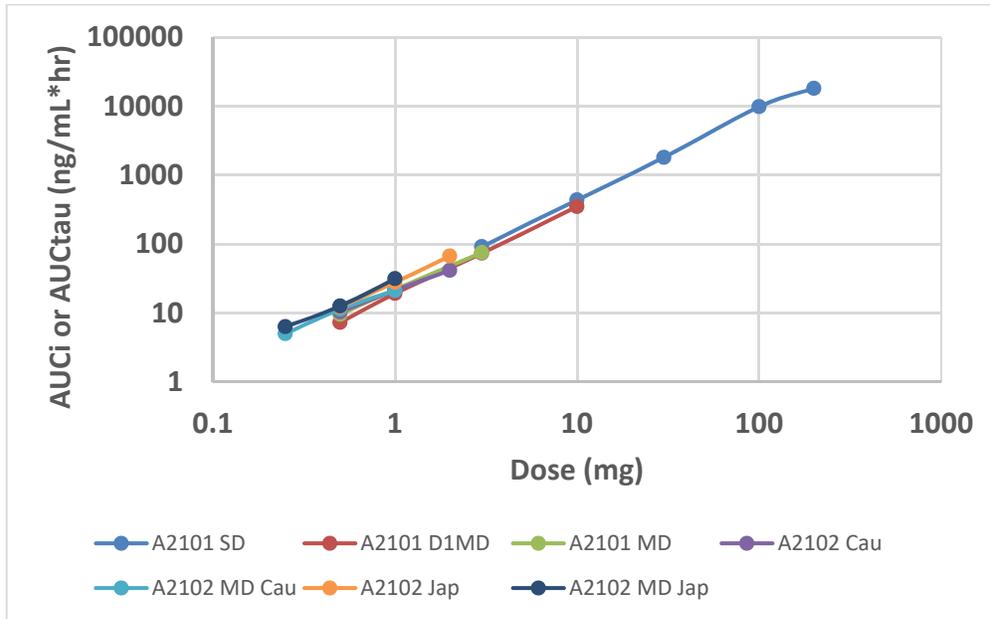


Figure 8 AUC versus dose; following single doses (AUCinf) or multiple doses from two studies (Study A2101 for SAD/MAD and A2102 for Caucasian/Japanese)

4.3 Study C2108 (DDI with oral contraceptives)

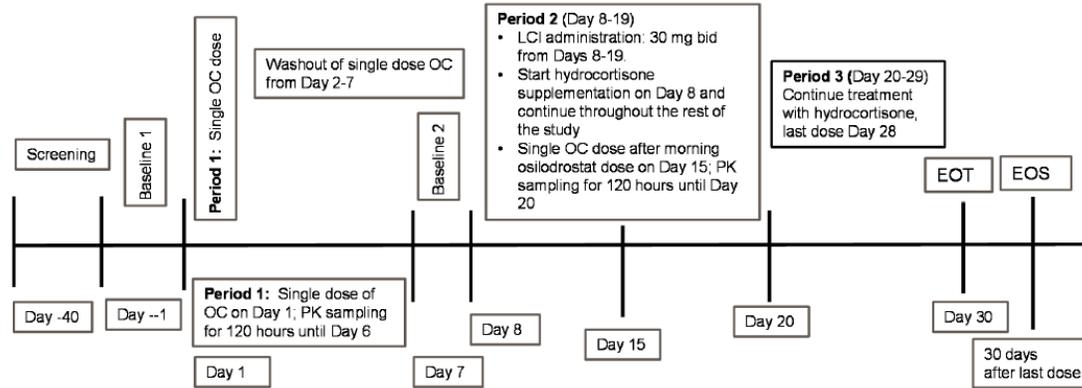


Figure 9 Study design (Study C2108)

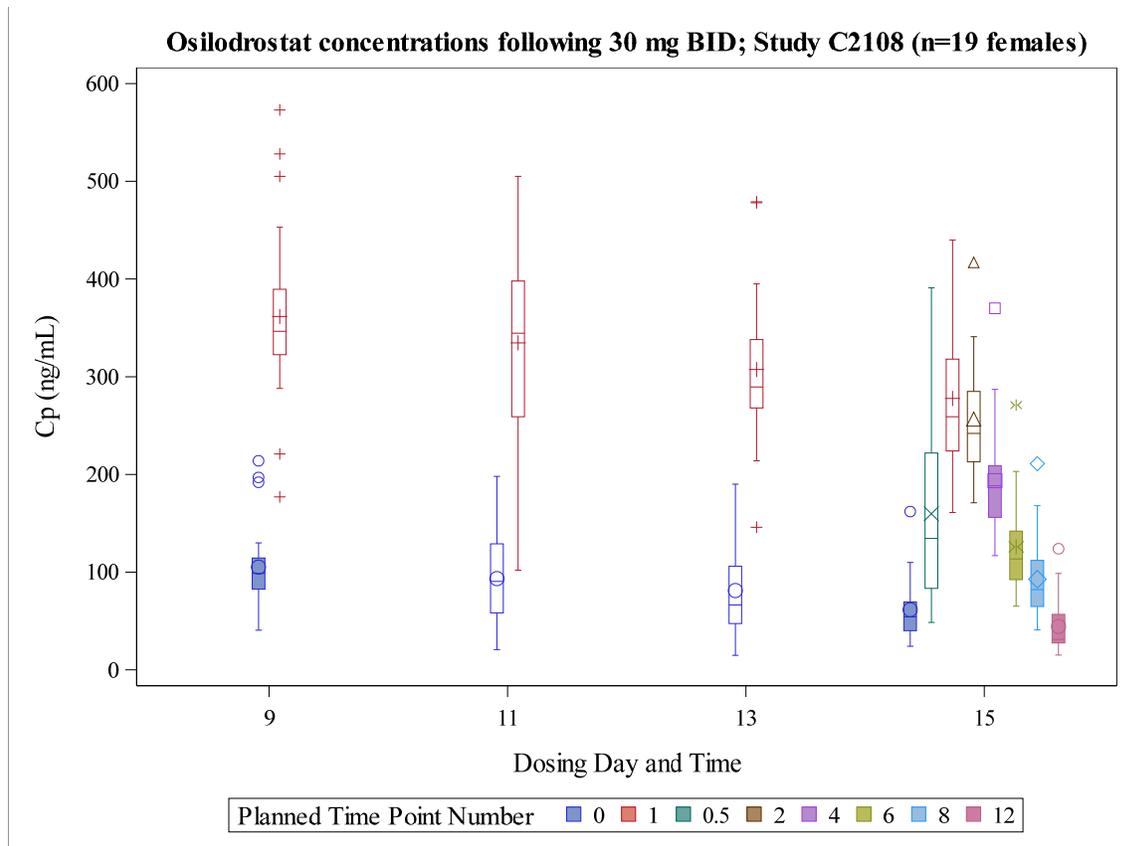
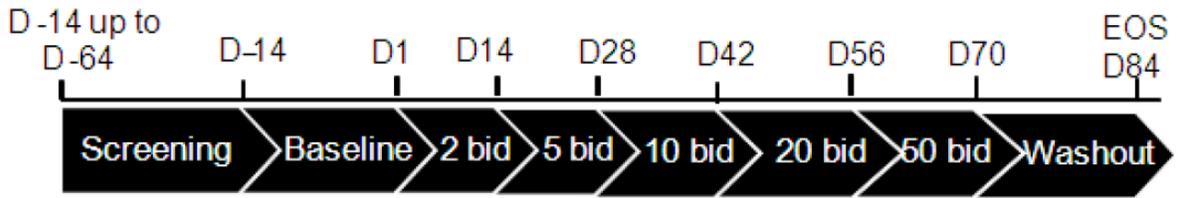


Figure 10 Osilodrostat concentrations on Day 9, 11, 13 and 15 following 30 mg bid in healthy female volunteers (Study C2108)

4.4 Study C2201 (Proof-of-Concept; study design)



N=12 subjects

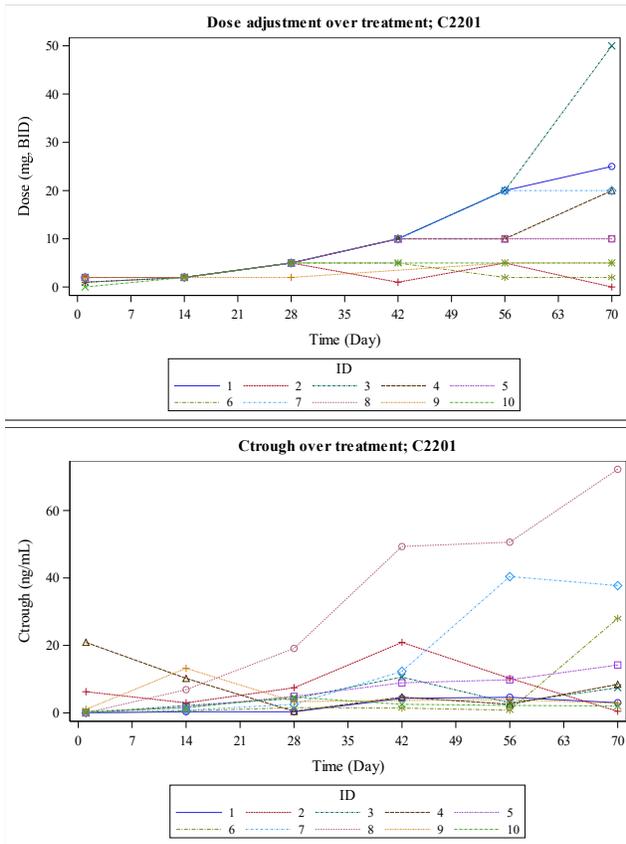


Figure 11 Dose adjustment (left) and C_{trough} changes over the treatment period (Study C2201, Part 1)

4.5 Study C2301 (pivotal Phase 3 study, study design)

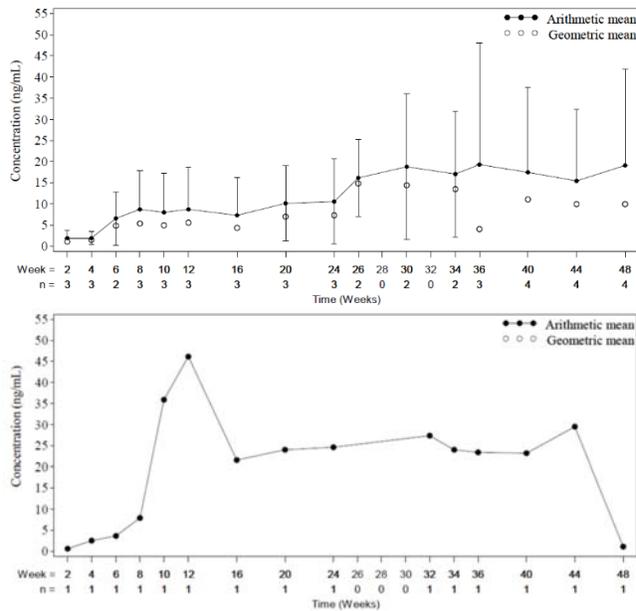
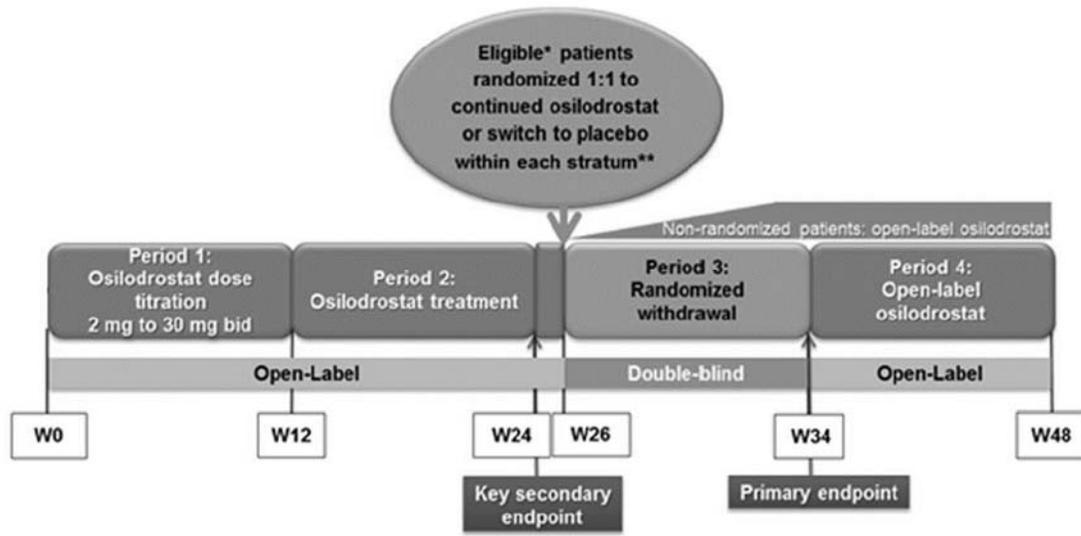


Figure 12 Mean (SD) C_{trough} versus time by week 24 dose up to week 48; 30 mg/day (left) and 60 mg/day (right) at week 24

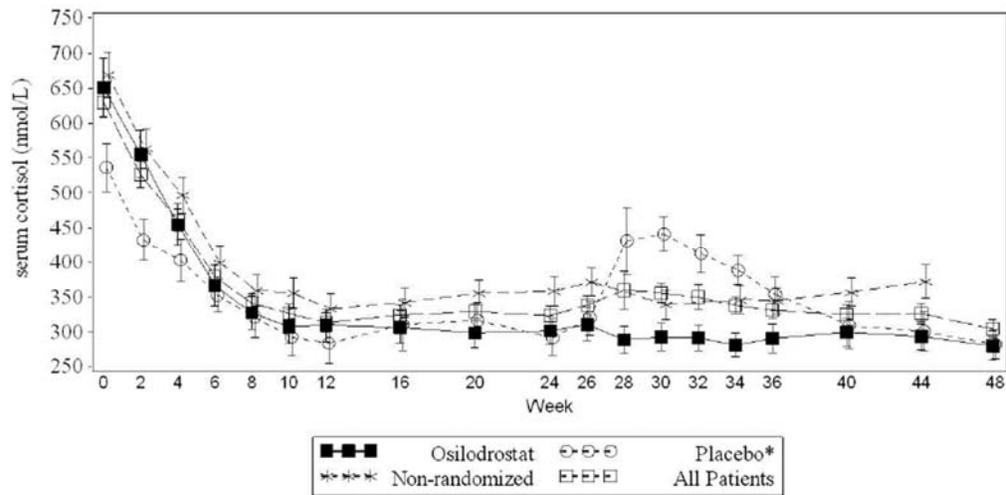
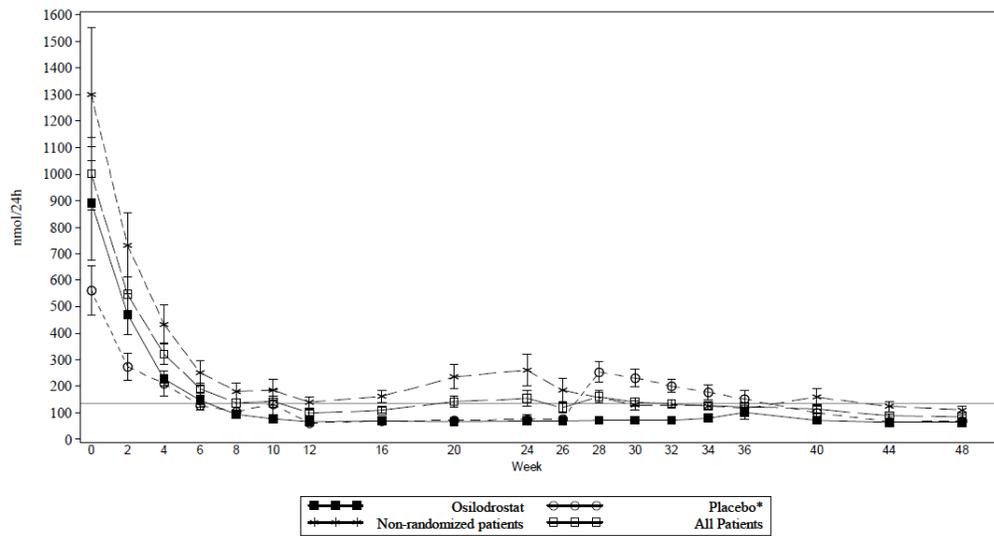


Figure 13 Mean (SE) mUFC (upper) and serum cortisol (lower) over the treatment period (to Week 48) (Source; Figure 11-1 and 11-6, CSR, C2301)

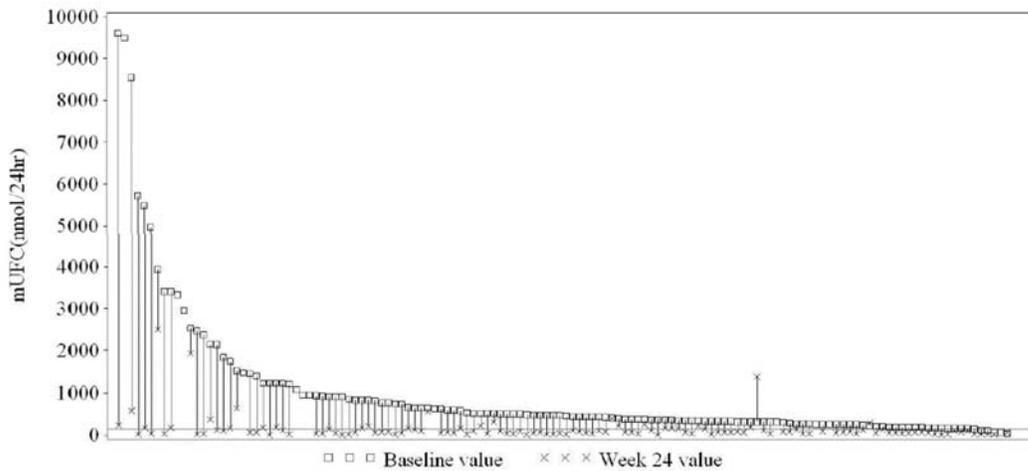


Figure 14 Individual patient mUFC values at baseline and Week 24 (Source; Figure 11-3, CSR, C2301)

4.1 Summary of bioanalytical method validation

Method: The method is suitable for the determination of LCI699 (over the range of 0.10 (LLOQ) to 100 ng/mL) in human plasma when using 50 µL plasma (DMPK-R1701082)

Validation item	Acceptance criteria	Parameters / Results
Specificity	LCI699: Interference $\leq 20\%$ of the mean of the LLOQ C standard peak signals.	Fulfilled
	[¹³ C, D ₄ , ¹⁵ N]-LCI699: Interference $\leq 5\%$ of the mean internal standard peak signal.	Fulfilled
Matrix effect	The quantitative measure of matrix effect can be termed as Matrix Factor (MF) and defined as a ratio of LCI699 peak response in the presence of matrix ions to LCI699 peak response in the absence of matrix ions. The variability in matrix effects, as measured by the global CV calculated from the mean MF, should be less than 15%.	Fulfilled
Recovery	Range of recovery for LCI699	86.82% - 94.51%
	Recovery for [¹³ C, D ₄ , ¹⁵ N]-LCI699	86.73%
	CV% on all extraction recoveries for LCI699 < 30%	Fulfilled
Carryover	LCI699: Interference $\leq 20\%$ of the mean of the LLOQ C standard peak areas.	Fulfilled
	[¹³ C, D ₄ , ¹⁵ N]-LCI699: Interference $\leq 5\%$ of the reference value for the internal standard.	Fulfilled
Calibration	Deviation of $\pm 15\%$ ($\pm 20\%$ at the LLOQ) for all C standards from nominal value. For each accepted analytical run, r^2 had to be higher than 0.98, no more than 25% of calibration standards should be discarded from each series of calibration standards and the final calibration line must contain at least 6 concentration levels including the LLOQ and the ULOQ.	Fulfilled
Intra-run accuracy and precision	Mean bias within $\pm 15\%$ ($\pm 20\%$ at LLOQ) of the nominal values	Fulfilled
	Precision of $\leq 15\%$ ($\leq 20\%$ at LLOQ)	Fulfilled
Inter-run accuracy and precision	Mean bias within $\pm 15\%$ ($\pm 20\%$ at LLOQ) of the nominal values	Fulfilled
	Precision of $\leq 15\%$ ($\leq 20\%$ at LLOQ)	Fulfilled

Validation item	Acceptance criteria	Parameters / Results
Dilution	Bias within $\pm 15\%$ from the theoretical concentration for samples (5 times the ULOQ) diluted (10-fold 500 ng/mL)	Fulfilled
Stability of LCI699	Precision $\leq 15\%$	Fulfilled
	Stock solutions*:	
	Mean bias $\pm 10\%$ and mean precision $\leq 10\%$	Fulfilled
	Storage temperature	Room temperature
	Number of hours	16.5
	Storage temperature	$-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$
	Number of days	92
	Working solutions:	
	Mean bias $\pm 10\%$ and mean precision $\leq 15\%$	Fulfilled
	Storage temperature	$+5^{\circ}\text{C} \pm 5^{\circ}\text{C}$
	Number of days	21
	Post-preparative stability in extracts:	
	Mean bias $\pm 15\%$ ($\pm 20\%$ at LLOQ)	Fulfilled
	Mean precision $\leq 15\%$ ($\leq 20\%$ at LLOQ)	Fulfilled
	Storage temperature	Approximately $+10^{\circ}\text{C}$
	Number of hours	105
	Freeze-thaw stability of spiked human plasma**:	
	Precision $\leq 15\%$	Fulfilled
	Mean bias $\pm 15\%$	Fulfilled
	Cycles	5
Storage temperature	$-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ or $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$	
Short-term stability in spiked human plasma:		
Mean bias $\pm 15\%$	Fulfilled	
Mean precision $\leq 15\%$	Fulfilled	
Storage temperature	Room temperature	
Number of hours	23	
Long-term stability in spiked human plasma**:		
Mean bias $\pm 15\%$	Fulfilled	
Mean precision $\leq 15\%$	Fulfilled	
Storage temperature	$-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$	
Number days	35, 90	
Storage temperature	$-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$	
Number days	35, 90, 935	
Incurring samples	Cross-validation between two sites***	Fulfilled

*Source: Novartis Method Validation Report [DMPK R0600661i](#)

**Source: Novartis Method Validation Report [DMPK R0600661g](#)

***Cross-validation between validated methods [DMPK R0600661g](#) (b) (4) and [DMPK R1701082](#) (b) (4)

4.2 Synopsis, and supplemental figures and tables of population PK analysis

Synopsis

Report title: Population pharmacokinetics of oral Osilodrostat/LCI699 in healthy volunteers and patients with Cushing's disease

Objectives:

- To modify the historical population PK model based on Phase 1 and 2 data, to accurately describe differences in the PK disposition between healthy volunteers, Cushing's disease patients, Caucasian and Japanese populations, low (1 mg) and high (30 mg) doses.
 - To update the model based on new data from the Phase 3 study (C2301).
-

Data:

Plasma osilodrostat concentration-time, dose, demographic and covariate data from seven Phase 1/2 studies in adult healthy volunteer and Cushing's disease patients were initially analyzed. Phase 3 data (Study C2301) were merged with the dataset once they became available.

Data was pooled from a total of eight studies:

- A2101: a first-in-human, two-center, randomized, double-blind, placebo- and comparator controlled, interwoven single- and multiple-ascending dose study to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of osilodrostat in healthy male subjects
- A2102: a randomized, double-blind, placebo-controlled, parallel-group study to compare safety/tolerability, PK, and to explore PD between Caucasian and Japanese healthy male subjects following single and multiple doses of osilodrostat
- C1101: a Phase I, randomized, open-label, single-dose, two-period, crossover study in healthy Japanese subjects to evaluate the effect of food on the bioavailability of osilodrostat tablet (Only data under fasted conditions were included for this population analysis)
- C2103: a Phase 1, open-label, multi-center, single-dose, parallel-group study to evaluate the PK and safety of osilodrostat in subjects with varying degrees of impaired hepatic function compared to subjects with normal hepatic function (Only subjects in the normal hepatic function arm were included for this population analysis)
- C2104: a Phase 1, open-label, multi-center, single-dose, parallel-group study to evaluate the PK and safety of osilodrostat in subjects with varying degrees of impaired renal function compared to subjects with normal renal function (Only subjects in the normal renal function arm were used for this population analysis)
- C2105: a randomized, double-blind, placebo- and active-controlled, four-way crossover study to investigate the electrocardiogram (ECG) effects of therapeutic and supratherapeutic doses of osilodrostat in healthy volunteers
- C2201: a proof-of-concept, open-label, forced-titration, multi-center study to assess the safety/tolerability and efficacy of 10-weeks treatment of osilodrostat followed by a 12-week treatment period in patients with Cushing's disease
- C2301: a Phase 3, multi-center, double-blind, randomized withdrawal study of osilodrostat following a 24-week, single-arm, open-label dose titration and treatment period to confirm the long-term efficacy and safety of osilodrostat for the treatment of patients with Cushing's disease

The initial analysis dataset from the first seven studies contained 5,687 quantifiable osilodrostat concentrations from 277 subjects with osilodrostat dose levels ranging from 0.25 to 200 mg. Study C2301 contributed a further 3,249 quantifiable concentrations from 137 subjects, with doses ranging from 1 to 30 mg. The analysis datasets were split into 90% and 10% for the purpose of modeling and validation, respectively.

Methods and Results:

The population PK model was developed using a non-linear mixed-effect modeling approach; the NONMEM VII software with the Monte Carlo Importance Sampling Expectation Maximization (EM) Assisted by Mode a Posteriori (IMPMP) estimation method with “Mu Referencing” was used.

The initial analysis, based on data from Phase 1/2 studies, applied a stepwise approach to develop separate structural models in the non-Japanese and Japanese population prior to combining the populations. A two-compartment model with dose-dependent E_{max} model on the relative bioavailability, sequential zero- and first-order absorption, and Michaelis-Menten elimination from the central compartment was found to adequately describe the PK of osilodrostat following oral administration. Additionally, the structural model incorporated separate parameters for oral absorption, covariate effect on bioavailability, as well as change in bioavailability with multiple dosing in the Japanese population.

Following development of the base model, covariates of interest were examined for their influence on the parameters of the model. The full model with backward deletion approach was utilized for covariate selection. Lean body weight (LBW) was found to be a significant predictor of osilodrostat dose that was estimated to achieve half-maximal of the relative bioavailability (ED_{50}). Upon the availability of data from the Phase 3 study, the predictive performance of the interim model on Study C2301 was assessed and further model refinement was performed to accurately describe osilodrostat concentrations in both healthy volunteers and Cushing’s disease patients. Osilodrostat doses ranging from 0.25 to 200 mg were initially entered into the PK model and Michaelis-Menten elimination was required to describe the nonlinear behavior for supratherapeutic doses (> 30 mg). With the addition of the Phase 3 data (1 to 30 mg), the overall contribution of these supra-therapeutic doses was relatively small (10.5% of overall data). Modeling of doses above the upper clinical dose range would have little practical utility at the expense of prolonged computation time. Therefore, doses above 30 mg were excluded from subsequent model development and the structural model was simplified to include a simple linear elimination process.

The performance of the final PK model was evaluated using a prediction-corrected visual predictive check (pcPVC) method based on the validation dataset that was not involved in the model development. Precision of the parameter estimates of the final model was also evaluated using Markov Chain Monte Carlo (MCMC) Bayesian analysis.

Conclusions:

- The PK of osilodrostat in both healthy volunteers and Cushing’s disease patients following oral administration were adequately described by a two-compartment model with dose-dependent (0.25 to 20 mg) E_{max} relationship on the relative bioavailability, parallel zero- and first-order absorption after absorption lag time for the first-order process only, and first-order linear elimination within the therapeutic dose range (1 mg to 30 mg).
- The relative bioavailability for 30 mg dose was higher than predicted based on the E_{max} model, and therefore, was estimated as an independent parameter.
- Asian population was associated with slower rate and longer duration of absorption, as well as a 20% higher relative bioavailability, than non-Asian subjects, leading to higher T_{max} and C_{max} .
- Body weight was a predictor of osilodrostat dose that was estimated to achieve half-maximal of the relative bioavailability. For the range of weights in the present analysis population (46.3-165 kg), ED_{50} ranged from 78% lower to 23-fold higher than the typical estimates for a 70-kg individual. At the 0.25 mg dose level, this would translate to 38% increase or 57% decrease in the relative bioavailability for a 46.3-kg or 165-kg individual, respectively. At the 20 mg dose level, this would translate to 14% increase or 38% decrease in the relative bioavailability for a 46.3-kg or 165-kg individual, respectively.
- Age, gender, Cushing’s disease, and formulation had no significant impact on osilodrostat PK.

Reviewer’s Comments: The goodness-of-fit plots and the visual predictive check indicate that the applicant’s population PK model is generally adequate in characterizing the PK profile of osilodrostat in subjects with Cushing’s disease. The inter-individual variability for CL/F and Vc/F are modest, while shrinkages for Vc/F and Ka are relatively high. Overall, the developed model was acceptable to support applicant’s proposed labeling statements about intrinsic factors as follows;

The structural model was based on a typical two-compartment model; ALAG (absorption lag time), Ka (first-order absorption rate constant), Q/F (linear inter-compartmental disposition) between V_c/F (central) and V_p/F (peripheral) compartment, and Michaelis-Menten elimination from the central compartment parameterized with V_{max} (maximal rate) and K_m (osilodrostat concentration achieving 50% of the maximal rate) (Figure 7). Relative bioavailability (F) of osilodrostat was modeled as a dose-dependent phenomenon parameterized with BIO (maximal change in bioavailability) and ED₅₀ (dose at which change in bioavailability was half-maximal).

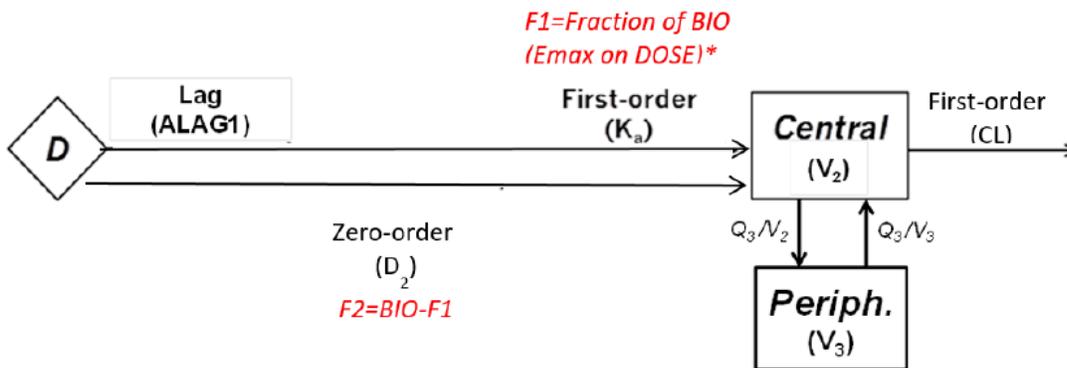


Figure 15 Final structural PK model for osilodrostat (Source: Figure 5-5)

Table 4 Number of Subjects and Osilodrostat Concentrations Included in the Population PK Analysis by Study (Source; Table 5-1, Population PK report)

	Study								Overall
	C1101	A2101	A2102	A2103	C2104	C2015	C2201	C2301	
Number of Subjects (%)	20 (5)	68 (16)	63 (15)	10 (2)	6 (1)	84 (20)	26 (6)	137 (33)	414
Number of Osilodrostat Concentrations (%)	241 (3)	1434 (16)	2056 (23)	102 (1)	64 (1)	1465 (16)	325 (4)	3249 (36)	8936

Table 5 Summary of clinical studies used in the population analysis (Source; Table 3-1)

Study	Analysis Population	Formulation	Dose	Total planned number of subjects	PK sampling in plasma
A2101	Healthy male subjects	0.25, 0.5, 1, 5, and 50 mg capsule	SAD: 3 – 200 mg MAD: 0.5 – 10 mg q.d.	112 subjects 1:1 in favor of osilodrostat	Part 1: trough (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hr post-dose Part 2: Days 1 and 14: trough (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hr post-dose Days 3, 4 and 6: trough Day 14: trough (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hr post-dose
A2102	Caucasian and Japanese healthy males	0.25 and 0.5 mg capsule	Day 1: 0.5 to 2 mg single dose Day 2-14: 0.25 to 1 mg b.i.d.	64 subjects 1:1	Predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hr post-dose. Group I: Day 1 only Groups II and III: Day 1 and 14, Additional predose on Day 7 and 13.
C1101	Healthy Japanese subjects	10 and 20 mg tablets	30 mg single dose	20 subjects in Williams design 1:1	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 36 hr postdose, Day 1 and 5
C2103	Healthy subjects	10 mg tablet	30 mg single dose	18 subjects with normal liver function	Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96 hr following dose administration
C2104	Healthy subjects	10 mg tablets	30 mg single dose	6 to 12 healthy volunteers	0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hr postdose.
C2105	Healthy volunteers	5 and 50 mg capsule	10 and 150 mg single dose	86 subjects, Williams design, 4 arms	At each sequence: trough (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hr post-dose
C2201	Patients with Cushing's disease	0.25, 0.5, 1, 5, and 50 mg capsule	Part 1: 2, 5, 10, 20 and 30 mg b.i.d. Part 2: 1 – 30 mg b.i.d.	Part 1: 12 subjects Part 2: 16 subjects	Core phase: Weeks 2, 4, 6, 8, and 10 weeks: trough Week 2 after dose change: trough, and 1, 1.5, 2, 4, 6 hr post-dose Expansion phase: Weeks 14, 18, and 22: trough
C2301	Patients with Cushing's disease	1, 5, 10 or 20 mg film-coated tablets	2, 5, 10, 20 or 30 mg b.i.d	132 patients 1:1	Extensive design Period 1 (~20 patients): trough, 0.25 – 0.75 hr, 1 – 2 hr, and 3 – 4 hr post-dose Period 2 to 4: trough and peak Sparse design Period 1 and 2: trough and peak (1 – 2 hr post-dose) Period 3 to 4: trough

b.i.d.=twice-daily; MAD=multiple-ascending dose; mg=milligram; q.d.=once-daily; SAD=single-ascending dose.

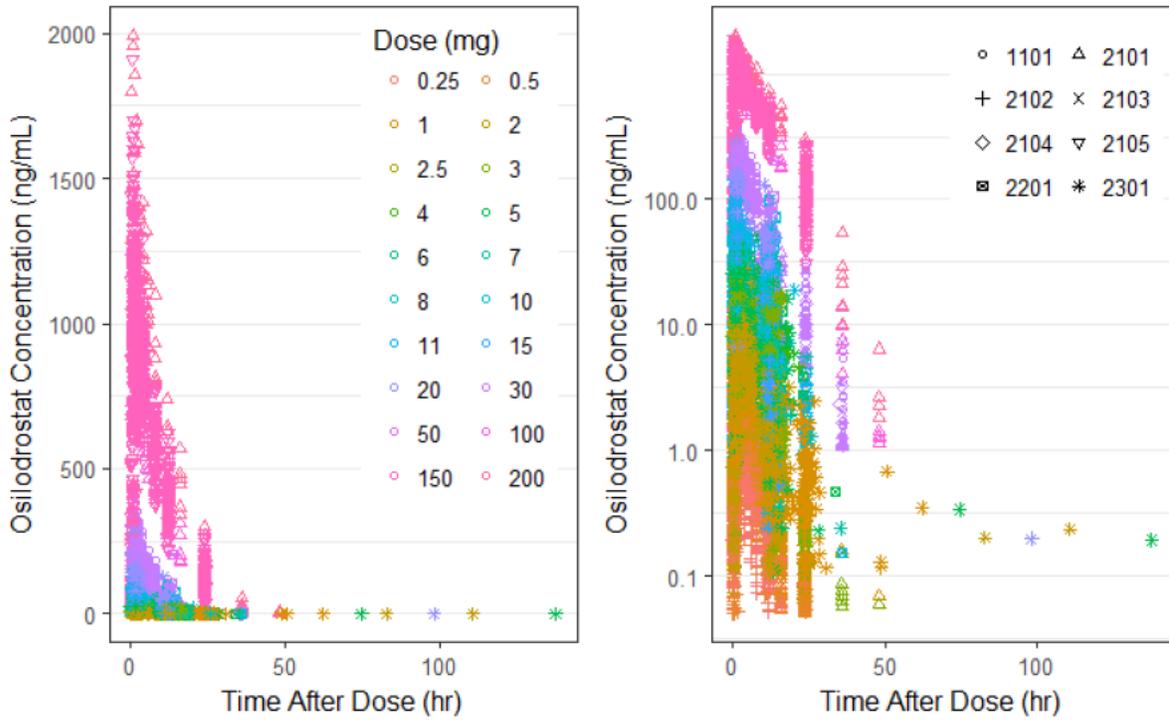


Figure 16 Observed Osilodrostat Plasma Concentrations versus Time after Previous Dose, All Data (Left: Linear Y Scale, Right: Logarithmic Y Scale) (Source: figure 5-2)

Table 6 Parameter Estimates of the Final Population PK Model (Run 072) (Source: Table 5-7)

$$ED_{50} = 1.73 \times (WT/70)^{3.66}$$

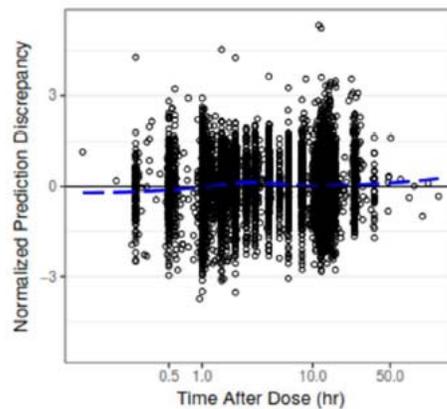
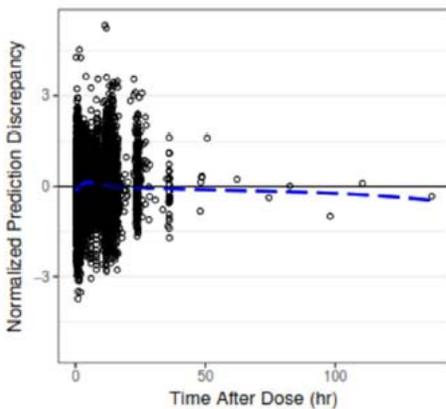
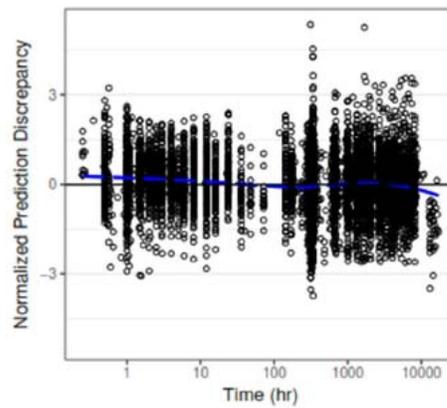
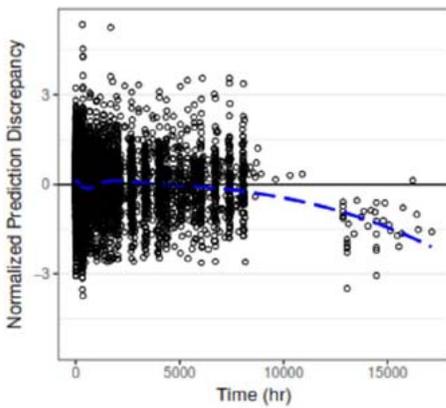
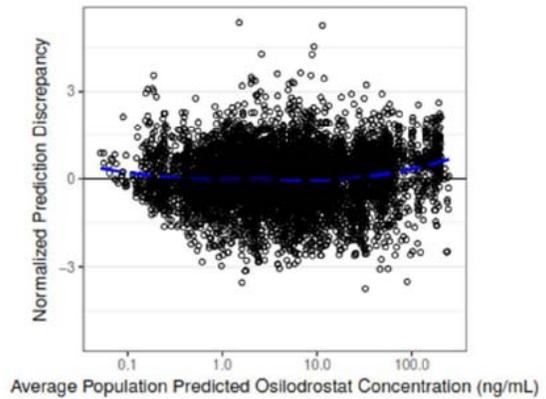
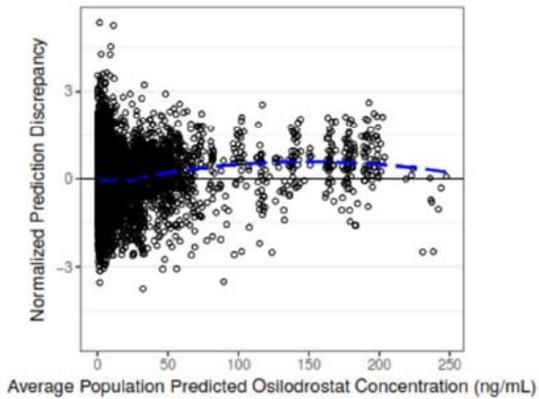
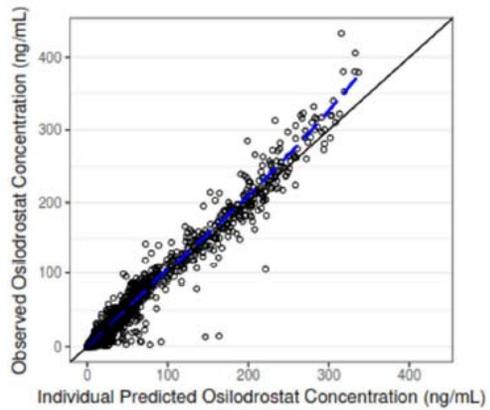
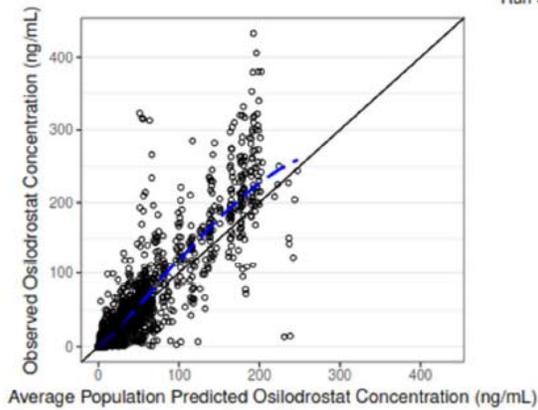
Osilodrostat < 30 mg: BIOA = (DOSE^{0.352} × 1.20^{ASIAN}) / (1.73^{0.352} + DOSE^{0.352}) (ASIAN=1 Asian and =0 for non-Asian)

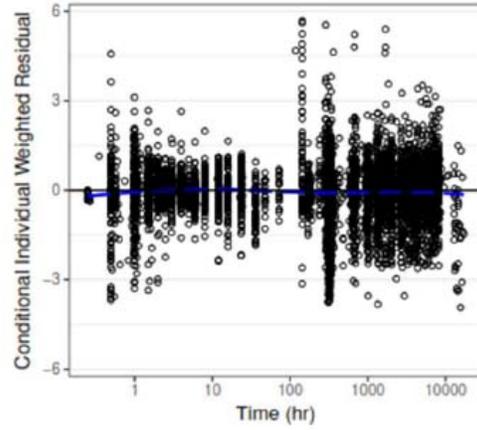
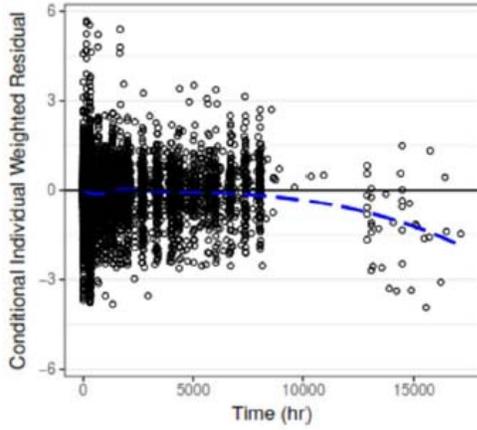
Osilodrostat 30 mg: BIOA=0.769

Parameter ^a [Units]	NONMEM Estimates			MCMC BAYES Estimates ^b			
	Point Estimate	%RSE	95% CI	Median	95% CI		
V _d /F [L]	107	4.66	97.6-117	98.3	89.3-114		
CL/F [L/hr]	16.4	4.94	14.9-18.1	14.6	13.0-17.2		
Q/F [L/hr]	2.73	10.2	2.24-3.34	2.79	2.08-3.48		
V _p /F [L]	326	19.7	222-479	580	321-1110		
K _a [hr ⁻¹]	7.58	11.1	6.10-9.43	10.3	7.85-15.6		
D ₂ [hr]	0.673	19.6	0.458-0.988	0.616	0.196-0.967		
ED ₅₀ [mg]	1.73	17.5	1.23-2.44	2.87	1.20-5.40		
γ	0.352	9.52	0.292-0.424	0.313	0.262-0.383		
F ₁	0.951	0.964	0.929-0.966	0.927	0.873-0.974		
ALAG [hr]	0.476	1.23	0.465-0.488	0.491	0.475-0.516		
K _a ^{ASIAN}	5.10	19.6	3.47-7.49	6.66	4.69-9.97		
D ₂ ^{ASIAN}	3.36	40.5	1.52-7.44	2.26	1.00-3.93		
BIOA~ASIAN	1.20	6.75	1.05-1.36	1.17	1.11-1.23		
BIOA, 30mg	0.769	5.61	0.685-0.854	0.723	0.619-0.844		
ED ₅₀ ~WT	3.66	10.2	2.93-4.39	3.89	3.03-4.74		
Inter-individual variability		Shrinkage% CV%^c or R					
ω ² _{V_d/F}	0.0297	45.5	0.00324-0.0562	53.2	17.2	0.0414	0.0252-0.0592
corr(η _{V_d/F} , η _{CL})	0.0422	39.6	0.00947-0.0749	-	0.666	0.0542	0.0361-0.0822
ω ² _{CL/F}	0.135	17.8	0.0880-0.182	26.6	36.7	0.160	0.127-0.213
corr(η _{V_d/F} , η _{Q/F})	0.117	27.9	0.0529-0.181	-	0.556	0.166	0.0927-0.253
corr(η _{CL/F} , η _{Q/F})	0.0971	47.3	0.00714-0.187	-	0.217	0.142	0.0566-0.249
ω ² _{Q/F}	1.49	17.0	0.994-1.99	46.6	185	1.61	1.12-2.28
corr(η _{V_d/F} , η _{V_p/F})	-0.104	48.0	-0.202- -0.0062	-	-0.355	-0.188	-0.322- -0.0808
corr(η _{CL/F} , η _{V_p/F})	-0.338	20.9	-0.476- -0.200	-	-0.541	-0.548	-0.765- -0.359
corr(η _{Q/F} , η _{V_p/F})	0.463	51.6	-0.00544-0.931	-	0.223	-0.234	-0.891-0.467
ω ² _{V_p/F}	2.89	13.8	2.11-3.67	50.7	412	4.36	2.90-6.15
corr(η _{V_d/F} , η _{ka})	-0.0956	47.2	-0.184- -0.0072	-	-0.498	-0.0888	-0.167- -0.0212
corr(η _{CL/F} , η _{ka})	-0.0466	120	-0.156-0.0630	-	-0.114	0.0115	-0.103-0.114
corr(η _{Q/F} , η _{ka})	-0.478	38.3	-0.837- -0.119	-	-0.352	-0.439	-0.859- -0.063
Inter-individual variability		Shrinkage% CV%^c or R					
corr(η _{V_p/F} , η _{ka})	-0.0214	1160	-0.509-0.467	-	-0.0113	-0.311	-1.00-0.219
ω ² _{ka}	1.24	17.1	0.824-1.66	34.6	157	1.44	1.04-2.02
corr(η _{V_d/F} , η _{D2})	0.0241	125	-0.0351-0.0833	-	0.171	-0.0184	-0.0988-0.0501
corr(η _{CL/F} , η _{D2})	0.0715	103	-0.0728-0.216	-	0.238	0.0290	-0.0906-0.166
corr(η _{Q/F} , η _{D2})	0.328	93.9	-0.276-0.932	-	0.328	-0.0499	-0.465-0.356

$\text{corr}(\eta_{VDF}, \eta_{D2})$	0.265	117	-0.343-0.873	-	0.190	0.386	-0.383-1.16
$\text{corr}(\eta_{Ka}, \eta_{D2})$	-0.400	44.5	-0.749- -0.0511	-	-0.439	-0.386	-0.749- -0.092
ω^2_{D2}	0.671	42.3	0.114-1.23	69.4	97.8	0.786	0.471-1.36
$\text{corr}(\eta_{VDF}, \eta_{ED50})$	-0.139	49.3	-0.273- -0.00474	-	-0.769	-0.214	-0.328- -0.116
$\text{corr}(\eta_{CLF}, \eta_{ED50})$	-0.117	66.0	-0.268-0.0343	-	-0.304	-0.215	-0.372- -0.0991
$\text{corr}(\eta_{Q/F}, \eta_{ED50})$	-0.494	35.6	-0.839- -0.149	-	-0.386	-0.953	-1.52- -0.463
$\text{corr}(\eta_{VDF}, \eta_{ED50})$	0.967	27.8	0.440-1.49	-	0.542	1.61	0.865-2.55
$\text{corr}(\eta_{Ka}, \eta_{ED50})$	0.328	56.7	-0.0366-0.693	-	0.281	0.233	-0.177-0.722
$\text{corr}(\eta_{D2}, \eta_{ED50})$	0.118	138	-0.201-0.437	-	0.137	0.398	-0.0343-0.875
ω^2_{ED50}	1.10	27.2	0.514-1.69	54.6	142	1.60	1.04-2.46
$\text{corr}(\eta_{VDF}, \eta_V)$	0.0118	162	-0.0256-0.0492	-	0.121	0.00303	-0.0323-0.0361
$\text{corr}(\eta_{CLF}, \eta_V)$	0.0193	175	-0.0469-0.0855	-	0.0931	0.0196	-0.0356-0.0728
$\text{corr}(\eta_{Q/F}, \eta_V)$	0.092	116	-0.118-0.302	-	0.134	0.128	-0.0410-0.345
$\text{corr}(\eta_{VDF}, \eta_V)$	-0.0928	169	-0.401-0.215	-	-0.0968	-0.328	-0.659-0.0191
$\text{corr}(\eta_{Ka}, \eta_V)$	-0.150	62.6	-0.334-0.0340	-	-0.239	-0.0767	-0.310-0.119
$\text{corr}(\eta_{D2}, \eta_V)$	0.157	84.7	-0.104-0.418	-	0.340	0.123	-0.0370-0.315
$\text{corr}(\eta_{ED50}, \eta_V)$	-0.0886	94.0	-0.252-0.0747	-	-0.150	-0.137	-0.364-0.0841
ω^2_V	0.318	28.9	0.138-0.498	63.4	61.2	0.339	0.227-0.487
$\text{corr}(\eta_{VDF}, \eta_{F1})$	0.115	62.2	-0.0251-0.255	-	0.502	0.134	0.0250-0.224
$\text{corr}(\eta_{CLF}, \eta_{F1})$	-0.00319	3450	-0.219-0.212	-	-0.00653	0.00884	-0.157-0.158
$\text{corr}(\eta_{Q/F}, \eta_{F1})$	1.09	19.4	0.674-1.51	-	0.671	1.04	0.549-1.62
$\text{corr}(\eta_{VDF}, \eta_{F1})$	0.152	281	-0.685-0.989	-	0.0672	0.224	-0.657-1.76
$\text{corr}(\eta_{Ka}, \eta_{F1})$	-0.565	36.6	-0.971- -0.159	-	-0.381	-0.559	-1.15- -0.008
$\text{corr}(\eta_{D2}, \eta_{F1})$	0.272	123	-0.383-0.927	-	0.250	-0.00885	-0.492-0.441
$\text{corr}(\eta_{ED50}, \eta_{F1})$	-0.744	35.8	-1.27- -0.223	-	-0.533	-0.818	-1.42- -0.00526
$\text{corr}(\eta_V, \eta_{F1})$	-0.0149	872	-0.270-0.240	-	-0.0199	-0.0949	-0.356-0.190
ω^2_{F1}	1.77	23.1	0.968-2.57	56.0	221	2.04	1.32-3.41
$\text{corr}(\eta_{VDF}, \eta_{ALAG})$	0.00348	118	-0.00456-0.0115	-	0.263	0.0117	0.00323-0.0239
$\text{corr}(\eta_{CLF}, \eta_{ALAG})$	0.00563	90.8	-0.00439-0.0156	-	0.199	0.0199	0.00759-0.0392
$\text{corr}(\eta_{Q/F}, \eta_{ALAG})$	0.0449	41.2	0.00864-0.0812	-	0.479	0.0811	0.0303-0.153
$\text{corr}(\eta_{VDF}, \eta_{ALAG})$	-0.0105	264	-0.0648-0.0438	-	-0.0804	-0.174	-0.332- -0.0523
$\text{corr}(\eta_{Ka}, \eta_{ALAG})$	-0.0272	58.1	-0.0582-0.00377	-	-0.318	-0.0287	-0.0915-0.0235
$\text{corr}(\eta_{D2}, \eta_{ALAG})$	0.00747	201	-0.0219-0.0369	-	0.119	-0.0172	-0.0871-0.0442
$\text{corr}(\eta_{ED50}, \eta_{ALAG})$	-0.00977	202	-0.0484-0.0288	-	-0.121	-0.0824	-0.169- -0.0187
$\text{corr}(\eta_V, \eta_{ALAG})$	0.0129	72.4	-0.00541-0.0312	-	0.298	0.0358	0.00694-0.0721
$\text{corr}(\eta_{F1}, \eta_{ALAG})$	0.00302	917	-0.0513-0.0573	-	0.0296	-0.0539	-0.166-0.00901
ω^2_{ALAG}	0.00590	33.7	0.002-0.0098	67.9	7.68%	0.0252	0.0120-0.0460
Residual variability					CV%		
$\sigma^2_{prop, Phase 1/2}$	0.0589	6.11	0.0518-0.0660	15.8	24.3	0.0587	0.0558-0.0619
$\sigma^2_{prop, Phase 3}$	0.141	5.91	0.125-0.157	8.64	37.5	0.139	0.131-0.147

Run = 072





Run = 072

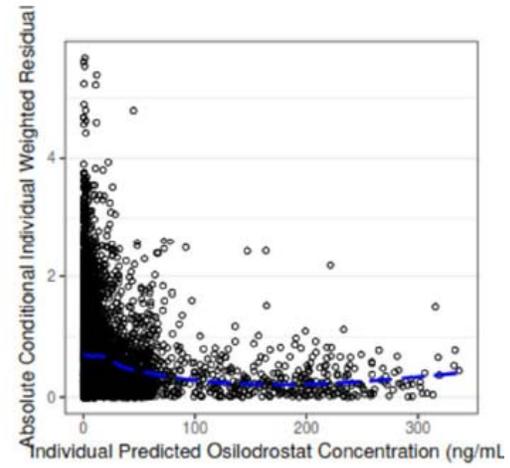
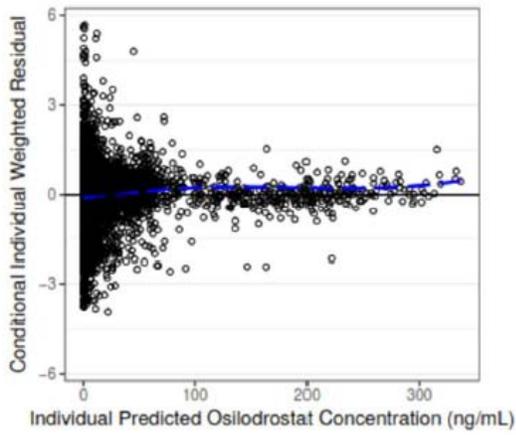


Figure 17 Goodness-of-fit plots for the final population PK model

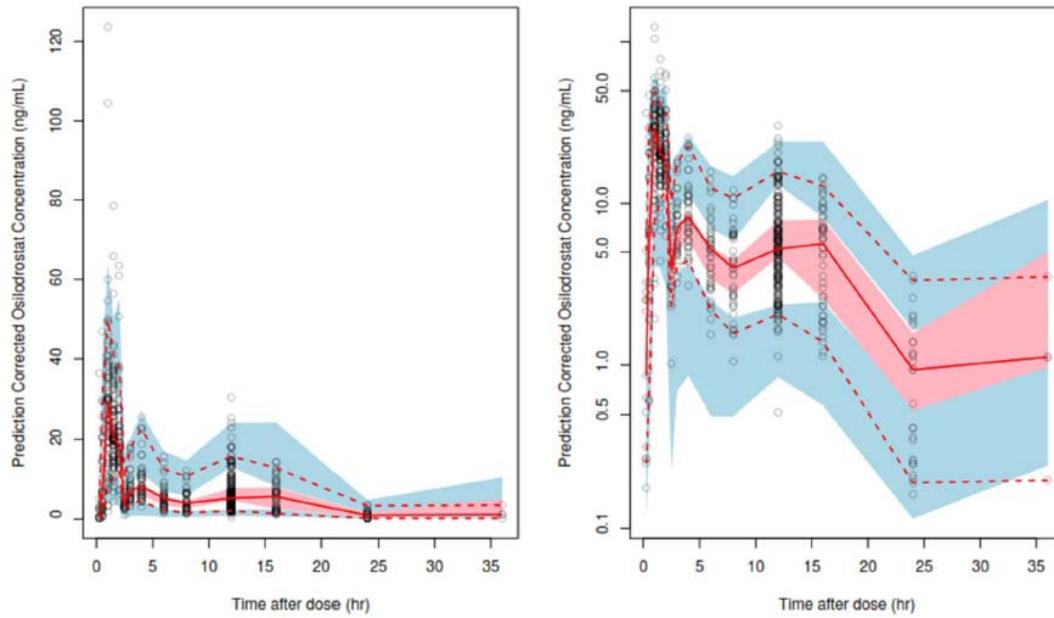


Figure 18 Prediction-Corrected Visual Predictive Check for the Final Population PK Model (Run 072), All Data (Left: Linear Y Scale, Right: Logarithmic Y Scale) (Source; Figure 5-7)

4.3 PBPK review

Physiologically based Pharmacokinetic Modeling Review Division of Pharmacometrics, Office of Clinical Pharmacology

NDA Number	212801
Generic Name	Osilodrostat
Trade Name (proposed)	Isturisa
Submission Type	505(b)(1)
Applicant	Novartis Pharmaceuticals
Dosage Form and Strengths	Oral tablet, 1 mg, 5 mg, 10 mg
Proposed Indication	for the treatment of Cushing's disease (CD)
Dose Regimen	<ul style="list-style-type: none">• <u>Starting dose</u>: 2 mg BID Titrated by increments of 1 or 2 mg BID based on response and tolerability• <u>Maximum recommended dose</u>: 30 mg BID• With or without food
Primary PBPK Reviewer	Jianghong Fan, Ph.D.
Secondary PBPK Reviewer	Xinyuan Zhang, Ph.D.

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK reports to support the intended uses.

- DMPK R1701026_PBPK of osilodrostat (LCI699) drug interaction after single or multiple doses with cytochrome P450 probe substrates;
- DMPK R1800128_Updated PBPK model for osilodrostat (LCI699) to include metabolite LXB168 kinetics and drug interaction potential;
- DMPK R1800128-01_Updated physiologically-based pharmacokinetic (PBPK) model for osilodrostat (LCI699) to include metabolite LXB168 kinetics and drug interaction potential.

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to FDA's information requests (IRs) submitted on September 20, and concluded the following:

- The osilodrostat PBPK model is adequate to predict the osilodrostat PK following a single dose administration over a dose range of 0.5-200 mg, and following multiple dose administration of 0.5, 1, 3 and 30 mg osilodrostat.
- The osilodrostat PBPK model is adequate to predict the PK of metabolite LXB168 following a single dose administration of 50 mg osilodrostat.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on caffeine (a CYP1A2 substrate) PK following multiple dose administration of osilodrostat in healthy

subjects. The predicted caffeine AUC ratio is between 1.00-1.91 in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.

- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on midazolam (a CYP3A4 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The predicted midazolam AUC ratio is between 0.52-1.28 in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on omeprazole (a CYP2C19 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The predicted omeprazole AUC ratio is between 1.06-2.28 following a single dose administration of omeprazole (20 mg) and between 0.86-1.52 following multiple dose administration of omeprazole (20 mg, qd) in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on dextromethorphan (a CYP2D6 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The predicted dextromethorphan AUC ratio is 1.23 in the presence and absence of osilodrostat (30 mg, bid) at steady state in healthy subjects. The effect is dose dependent and is lower at lower dose levels.
- The osilodrostat PBPK model is adequate to predict the effect of osilodrostat on warfarin (a CYP2C9 substrate) PK following multiple dose administration of osilodrostat in healthy subjects. The warfarin exposure would not be expected to be significantly affected by concomitant osilodrostat (30 mg, bid).
- The PBPK models are not adequate to predict the effect of osilodrostat on bupropion PK because bupropion active metabolites were not included in the model, but they contribute significantly to the efficacy of bupropion in human.
- The DDI potential of osilodrostat as a victim of CYP modulators cannot be excluded.

Applicant's PBPK Modeling Effort

PBPK software

Simcyp V17 (Simcyp Ltd, UK) was used to develop the PBPK models and predict the effects of osilodrostat on the PK of midazolam, caffeine, omeprazole, dextromethorphan, bupropion and warfarin.

Model development

Osilodrostat

The first order absorption model was used. The fraction absorbed (f_a) was estimated to be 1.0 since mass balance study have demonstrated nearly complete oral absorption of osilodrostat following oral administration. The absorption rate constant (k_a) was estimated to be 2.8/h based on the fitting of the clinical PK data after a single oral dose of osilodrostat (30 or 50 mg). The $f_{u,gut}$ (unbound fraction in enterocytes) was set to be 1.0. The $P_{eff,man}$ (permeability in man) and Q_{gut} (nominal flow

in gut) were predicted to be 6.88×10^{-4} cm/s and 16.8 L/h, respectively, based on the permeability data in Caco-2 cells.

The minimal PBPK model was used with a predicted volume of distribution (V_{ss}) of 1.277 L/kg. The fraction unbound in plasma (f_{up}) and blood-to-plasma ratio was 0.636 and 0.85, respectively.

Osilodrostat hepatic intrinsic clearance was back calculated based on clinically observed plasma clearance (~16.6 L/h) after a 30 mg single oral dose using retrograde model. The contribution of oxidative metabolism to the osilodrostat overall clearance was estimated to be 26% based on the total amount of oxidative metabolite in both urine and feces samples in mass balance study. In vitro metabolism studies involving recombinant enzymes indicated that CYP3A4, CYP2D6, and CYP2B6 were responsible for the oxidative metabolism of osilodrostat. The relative contributions of the individual CYP enzymes to total clearance of osilodrostat was estimated to be 11.7% for CYP3A4, 8.07% for CYP2D6 and 6.25% for CYP2B6 based on the enzyme reaction phenotyping study results. The intrinsic clearances mediated by CYP3A4, CYP2D6 and CYP2B6 are 0.0466, 0.0246 and 0.0322 mL/h/mg protein, respectively. The enzyme used in the model for the metabolite LXB168 formation was arbitrarily selected as “user UGT1”, as the enzyme responsible for the formation of LXB168 could not be determined through the investigation. The contribution of “user UGT1” to the overall osilodrostat clearance was set as 35% to better account for recovery of LXB168 PK. The additional clearance was assigned to $CL_{int,others}$ (additional systemic clearance). A value of 0.86 L/h was assigned to renal clearance based on the clinical study result (CLCI699C2101).

The in vitro K_i values for CYP1A2 (0.5 μ M), CYP2B6 (10 μ M), CYP2C9 (20 μ M), CYP2E1 (0.482 μ M), CYP2D6 (2 μ M) and CYP3A (3.25 μ M) were used in the osilodrostat model. The induction parameter values used in the model are 100 μ M and 18.7 for CYP1A2 $Ind_{C_{50}}$ and Ind_{max} respectively, and 136 μ M and 15.1 for CYP2B6 $Ind_{C_{50}}$ and Ind_{max} , respectively. The CYP3A4 induction parameter values used in the model were 196.7 μ M for $Ind_{C_{50}}$ and 12.38 for Ind_{max} , which were normalized based on the positive control rifampin induction parameters determined in vitro.

Metabolite LXB168

The minimal PBPK model was used with a predicted V_{ss} of 0.7175 L/kg and a K_p scalar of 0.5 to fit the LXB168 concentration-time profile in study CLCI699C2101. The B/P value was assumed to be the same as the parent drug, and the measured f_{up} value was 0.643. The total clearance was estimated based on the clinical PK data in study CLCI699C2101 and a value of 1 L/h was assigned to CL_{iv} . The CYP3A4 induction parameter values used in the model were 86.3 μ M for $Ind_{C_{50}}$ and 3.71 for Ind_{max} , which were normalized based on the positive control rifampin induction parameters determined in vitro. The CYP2B6 induction parameter values were 225 μ M and 3.96 for $Ind_{C_{50}}$ and Ind_{max} , respectively, which were determined in vitro and were not normalized.

Victim drug models

The default PBPK models of midazolam, caffeine, omeprazole, dextromethorphan, bupropion and warfarin in SimCYP were used without any modification for DDI prediction.

FDA's assessment

- The mass balance study showed that the metabolite LXB168 is the most abundant metabolite in human plasma after oral administration of 50 mg osilodrostat, contributing on average 51% (41.8-60.9%) to the total plasma radioactivity (AUC_{0-48h}) and the relative exposure of LXB168 was greater than 100% of osilodrostat. In the Applicant's original submission, the enzyme responsible for LXB168 formation was not identified. The in vitro study results may not provide adequate information to justify that LXB168 was not formed in the in vitro systems given the metabolite formation rate was low, while the in vitro incubation time was short, and very low amount of all other metabolites generated in the in vitro incubation systems. An information request was issued requesting the Applicant to identify the main enzyme that contributes to the formation of LXB168 and evaluate the DDI potential between osilodrostat and the modulators of this enzyme following a single or multiple dose administration of osilodrostat. Refer to 'Results' for FDA's assessment of the Applicant's responses.
- Osilodrostat showed nonlinear PK profiles over the dose range of 0.5-200 mg following oral administration in healthy subjects. The proposed recommended starting dose of osilodrostat is 2 mg orally twice daily, and gradually titrated based on individual response and tolerability, with a maximum dose of 30 mg twice daily. The Applicant's model did not incorporate the mechanism to capture the observed nonlinear PK of osilodrostat. An information request was issued requesting the Applicant to explore the mechanism which contributed to the observed nonlinear PK of osilodrostat, incorporate the nonlinear PK mechanism in the model and reevaluate the DDI liability of osilodrostat. Refer to 'Results' for FDA's assessment of the Applicant's responses.
- The model simulated formation rate of LXB168 (osilodrostat's metabolite) was much faster than that observed and the model simulated T_{max} was significantly shorter as compared to that observed (12 h vs 24h) in study CLCI699C2101. An information request was issued requesting the Applicant to refine the model to capture the observed PK profile of LXB168, perform the simulations to simulate the LXB168 steady state PK following multiple dose administration of osilodrostat and re-evaluate the DDI liability of osilodrostat (LXB168). Refer to 'Results' for FDA's assessment of the Applicant's responses.

Applicant's model refinement

The Applicant's original model did not capture the observed osilodrostat nonlinear PK profiles in the clinical studies. In response to FDA's information request, the Applicant investigated the potential mechanism responsible for the nonlinear PK of osilodrostat and concluded that the nonlinear PK of osilodrostat can be primarily attributed to the saturation of metabolism enzymes based on the analysis of the dose-normalized osilodrostat PK data over a dose range of 3 to 200 mg following a single dose administration. Due to the available high $K_{m,u}$ values ($\sim 30 \mu M$) for CYP3A4, CYP2B6 and CYP2D6, these enzymes are not likely saturated at clinically relevant doses since C_{max} is about $0.88 \mu M$ following multiple dose administration of 30 mg osilodrostat twice daily. It was assumed that all other metabolic pathways were saturated. Since the K_m values for other metabolic pathways were not available, the K_m values were optimized to capture the nonlinear PK of osilodrostat and a K_m of $0.3 \mu M$ was used in the model.

FDA's assessment

- It appears reasonable to assume that the potential mechanism responsible for the nonlinear PK of osilodrostat is due to the saturation of the metabolism enzymes.
- As shown in Table 7, the Applicant's refined model was able to capture the PK of osilodrostat over a dose range of 3-200 mg relatively well, however, the model overpredicted the osilodrostat exposure at dose level lower than 3 mg by 50% to 2-fold. Since the proposed titration schedule for osilodrostat is from a starting dose of 2 mg bid to 3 mg or 4 mg bid, the reviewer further refined the model to capture the PK over a dose range of 0.5-200 mg (Figure 19). Refer to "FDA's Model refinement and verification" for the detailed model development and verification.
- The observed C_{max} and C_{trough} decreased with the multiple dosing of osilodrostat, indicating the enzyme mediated auto-induction of osilodrostat metabolism. The Applicant's refined model did not adequately capture the in vivo auto-induction profile of osilodrostat. The reviewer further refined the model to adequately capture the in vivo osilodrostat auto-induction profile. Refer to "FDA's Model refinement and verification" for the detailed model development and verification.
- After incorporation of the nonlinear mechanism in the model, there was an improvement in the performance of the Applicant's refined model in predicting osilodrostat metabolite PK profile as compared to the Applicant's original model (Figure 20A). However, the metabolite C_{max} was still underpredicted by about 16% and T_{max} was about 6 hours shorter than those observed in study C2101. It was shown that LXB168 exposure in plasma was twice that of the parent and accounted for 40-60% of the circulating radioactivity in plasma in study C2101. Appreciable metabolite (LXB168) accumulation in the systemic circulation would be expected with multiple doses of osilodrostat due to the low metabolite elimination rate (Figure 20B). In addition, there was no multiple dose metabolite data available to verify the model. It was therefore deemed important to fully characterize the single dose PK of metabolite in the assessment of osilodrostat DDI potential after multiple doses. The reviewer further refined the metabolite model to better capture the metabolite PK in an effort to characterize the metabolite-mediated enzyme induction effect after multiple dose administration of osilodrostat.

In response to FDA's Information Request, the Applicant re-evaluated the osilodrostat metabolism by using a long-lived human hepatocyte coculture system and confirmed that the metabolite LXB168 can be formed in human liver. The specific enzymes responsible for the formation of LXB168 were not determined. The Applicant's assumption that cytochrome P450 enzymes were unlikely involved in the formation of LXB168 may not be valid due to the following reasons: 1) LXB168 was formed by the oxidation of the imidazole ring of osilodrostat, and it was reported that the imidazole-containing compounds are primarily metabolized by P450¹, 2) the clinically observed auto-induction of osilodrostat metabolism would not be attained with such a low f_m CYP3A4 (0.10) and f_m CYP2B6 (0.05) assigned in the Applicant's refined model. The possibility that the involvement of CYP3A4 and/or CYP2B6 in the formation of LXB168 cannot be excluded.

¹ <https://pubs.acs.org/doi/pdf/10.1021/tx015574b>

Table 7 Observed and simulated osilodrostat mean C_{max} and AUC and the predicted/observed C_{max} and AUC ratios following a single or multiple dose administration of osilodrostat. The Applicant's refined model, FDA refined Model 1 and Model 2 were used to conduct simulations.

Osilodrostat		C _{max} (ng/mL)				AUC _{last} (ng*h/mL)				Sources
		Observed	Applicant refined model	FDA's refined Model 1	FDA's refined Model 2	Observed	Applicant refined model	FDA's refined Model 1	FDA's refined Model 2	
Single dose	2 mg	7.91	11.2 / 1.41	11.0 / 1.39	10.3 / 1.30	38.6	60.6 / 1.57	49.6 / 1.28	52.3 / 1.35	Study A2102
	3 mg	18.0	17.0 / 0.94	17.6 / 0.98	16.4 / 0.91	81.8	93.8 / 1.15	82.3 / 1.00	86.2 / 1.05	Study A2101
	10 mg	79.2	62.6 / 0.79	64.4 / 0.86	65.2 / 0.82	420	370 / 0.88	405 / 0.96	417 / 0.99	
	30 mg	250	311 / 1.24	221 / 0.88	217 / 0.87	1782	2133 / 1.20	1856 / 1.04	1856 / 1.04	
	50 mg	313	354 / 1.13	378 / 1.21	372 / 1.19	3050	3059 / 1.00	3711 / 1.22	3662 / 1.20	Study C2102
	50 mg ^a	400	391 / 0.98	414 / 1.04	408 / 1.02	3470	3303 / 0.95	4042 / 1.16	3975 / 1.15	Study A2101
	100 mg	939	742 / 0.79	772 / 0.82	765 / 0.81	9788	7064 / 0.72	9138 / 0.93	8919 / 0.91	
200 mg	1657	1529 / 0.92	1575 / 0.95	1567 / 0.95	18033	17339 / 0.96	21565 / 1.20	20949 / 1.16		
Multiple dose, QD	0.5 mg, day 1	1.81	2.67 / 1.48	2.32 / 1.28	2.19 / 1.21	7.30	14.2 / 1.95	9.92 / 1.36	10.5 / 1.44	Study A2101
	0.5 mg, day 14	1.80	2.68 / 1.49	2.30 / 1.27	2.18 / 1.21	9.52	14.4 / 1.51	9.77 / 1.03	10.4 / 1.10	
	1 mg, day 1	3.98	5.41 / 1.36	5.00 / 1.26	4.69 / 1.18	19.15	29.0 / 1.52	21.7 / 1.13	22.9 / 1.20	
	1 mg, day 14	4.46	5.44 / 1.22	4.93 / 1.11	4.61 / 1.03	21.94	29.24 / 1.33	21.0 / 0.96	22.3 / 1.02	
	3 mg, day 1	15.8	17.0 / 1.08	17.6 / 1.11	16.4 / 1.04	73.5	93.1 / 1.27	82.1 / 1.12	85.3 / 1.16	
	3 mg, day 14	14.7	17.2 / 1.17	17.1 / 1.16	15.6 / 1.06	75.3	93.8 / 1.25	75.5 / 1.00	78.7 / 1.05	
	10 mg, day 1	68.7	62.6 / 0.91	68.4 / 1.00	65.2 / 0.95	349	367 / 1.05	405 / 1.16	417 / 1.19	
Multiple dose, BID	30 mg, day 8 ^b	306	292 / 0.95	287 / 0.94	288 / 0.94	1680	1787 / 1.06	1832 / 1.09	1848 / 1.10	Study C2108

proportion of female subjects in the simulation was set as 0.5, which was matched to that in study C2102.

b: The proportion of female subjects in the simulation was set as 1, which was matched to that in study A2108.

a:
The

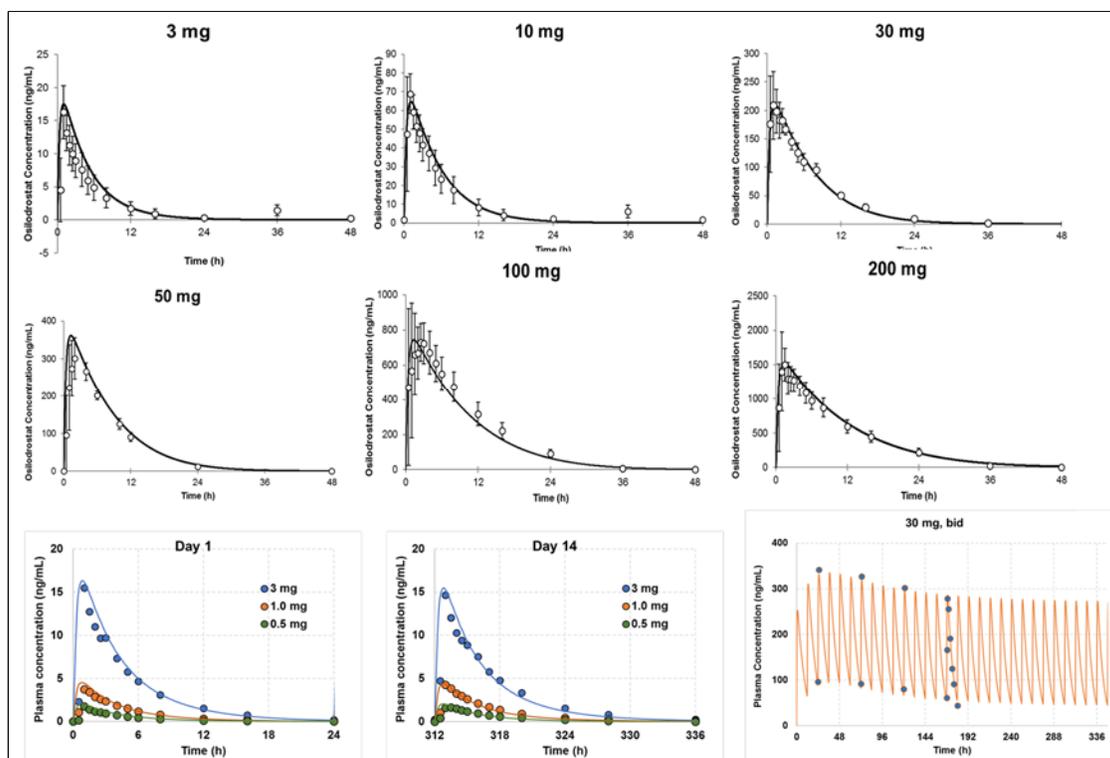


Figure 19 Observed (dots or circles) and simulated (lines) osilodrostat plasma concentration-time profiles following a single dose (3, 10, 30, 50, 100, or 200 mg) or multiple dose (0.5, 1 and 3 mg, qd or 30 mg, bid) administration of osilodrostat in healthy subjects. The osilodrostat PK profiles were simulated using FDA refined model 1.

Source: refer to Table 1.

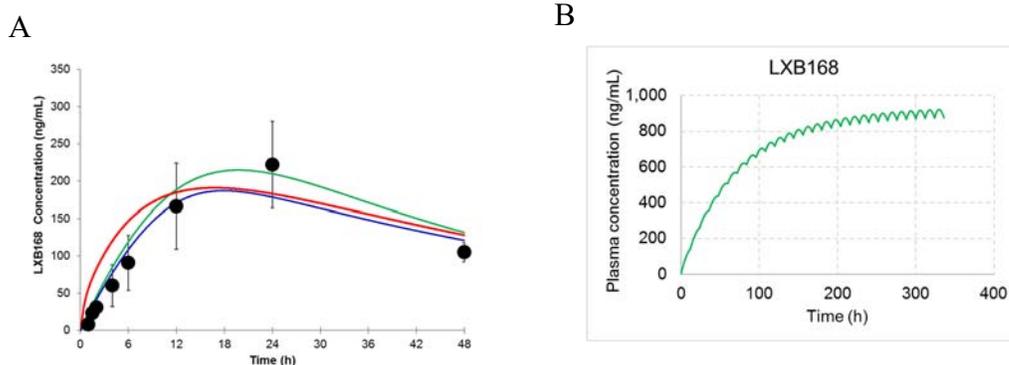


Figure 20 A: Observed (dots) and simulated (lines) concentration-time profiles of the metabolite LXB168 after a single dose administration of osilodrostat (50 mg) in healthy subjects. Red, blue and green lines represent the simulated metabolite LXB168 PK profiles using Applicant's original model, Applicant's refined model and FDA's refined model 1, respectively. B: Simulated concentration-time profiles of the metabolite LXB168 after multiple dose administration of osilodrostat (30 mg, bid) in healthy subjects using FDA refined Model 1.

Source: observed metabolite data were from clinical study C2101. The Applicant predicted results were from Report No. DMPK R1800128-01_ Updated physiologically-based pharmacokinetic (PBPK) model for osilodrostat (LCI699) to include metabolite LXB168 kinetics and drug interaction potential.

Table 8 Osilodrostat and metabolite LXB168 PBPK model parameter values in Applicant refined model and FDA refined Model 1 and Model 2. Only refined model parameters were listed.

Parameter	Applicant refined model	FDA refined model 1	FDA refined model 2
Absorption			
ka (1/h)	2.8 ^a	3.5 ^b	3.5 ^b
CYP3A4 V _{max} (pmol/min/pmol CYP) K _{m,u} (μM)	0.3458 ^c 36.1 ^d	0.3458 ^c 36.1 ^d	0.3458 ^c 36.1 ^d
CYP2D6 V _{max} (pmol/min/pmol CYP) K _{m,u} (μM)	3.443 ^c 30.4 ^d	3.443 ^c 30.4 ^d	3.443 ^c 30.4 ^d
CYP2B6_pathway 1 V _{max} (pmol/min/pmol CYP) K _{m,u} (μM)	1.4902 ^c 36.1 ^d	1.4902 ^c 36.1 ^d	1.4902 ^c 36.1 ^d
Additional HLM clearance (User ES microsomal kinetics) V _{max} (pmol/min/mg protein) K _{m,u} (μM)	1.5 ^e 0.3 ^e	0.2 ^f 0.07 ^f	0.3 ^g 0.07 ^g
CYP3A4_LXB168 formation V _{max} (pmol/min/pmol CYP) K _{m,u} (μM)	NA	0.008 ^f 0.07 ^f	NA
CYP2B6_LXB168 formation V _{max} (pmol/min/pmol CYP) K _{m,u} (μM)	NA	NA	0.115 ^g 0.07 ^g
User UGT1 HLM kinetics_LXB168 formation V _{max} (pmol/min/mg protein) K _{m,u} (μM)	1.5 ^e 0.3 ^e	NA	NA
Interaction			
CYP1A2 K _i , μM CYP1A2 Ind _{C50} , μM CYP1A2 Ind _{max} , fold	0.175 ⁱ 100 ^h 18.7 ^h	0.26 ⁱ	0.26 ⁱ
CYP2B6 K _i , μM CYP2B6 Ind _{C50} , μM CYP2B6 Ind _{max} , fold	10 ^h 136 ^h 15.1 ^h	Refer to Figure 3	
CYP2C9 K _i , μM	20 ^h	20 ^h	20 ^h
CYP2C19 K _i , μM CYP2C19 Ind _{C50} , μM CYP2C19 Ind _{max} , fold	1 ⁱ 52.3 ^h 1.56 ^h	Refer to Figure 5.	
CYP2D6 K _i , μM	2 ^h	2 ^h	2 ^h
CYP3A4 K _i , μM CYP3A4 Ind _{C50} , μM CYP3A4 Ind _{max} , fold	3.25 ^h 196.7 ^j 12.38 ^j	3.25 ^h	3.25 ^h
Metabolite LXB168 interaction			
CYP2B6 Ind _{C50} , μM CYP2B6 Ind _{max} , fold	225 ^h 3.96 ^h	NA	5.0 ^k 10 ^k
CYP3A4 Ind _{C50} , μM CYP3A4 Ind _{max} , fold	86.3 ^j 3.71 ^j	3.5 ^k 3.71 ^k	NA
Metabolite LXB168 clearance CL _{iv} (L/h)	1 ^b	1.3 ^b	1.3 ^b

NA: parameter values were not assigned.

- a: obtained from the fitting of the osilodrostat clinical PK data
- b: optimized based on the metabolite PK data
- c: adjusted to maintain the relative contributions of the enzymes to the elimination of osilodrostat
- d: determined in vitro
- e: optimized based on the osilodrostat nonlinear PK over the dose range of 3-200 mg following a single dose administration and assumed a non-CYP enzyme was responsible for the formation of LXB168
- f: optimized based on the osilodrostat nonlinear PK over the dose range of 0.5-200 mg following a single dose administration and assumed CYP3A was responsible for the formation of LXB168
- g: optimized based on the osilodrostat nonlinear PK over the dose range of 0.5-200 mg following a single dose administration and assumed CYP2B6 was responsible for the formation of LXB168
- h: determined in vitro
- i: optimized based on the single dose clinical DDI study results
- j: normalized based on the positive control rifampin induction parameters determined in vitro
- k: optimized based on the osilodrostat PK profile following multiple dose administration (30 mg, bid)

FDA's Model refinement and verification

Given the limitations identified in Applicant's modeling approach, the FDA's reviewer further refined the model by re-optimizing the model parameters to better capture the osilodrostat nonlinear PK over a dose range from 0.5-200 mg, osilodrostat auto-induction concentration-time profile, and metabolite concentration-time profile following a single dose or multiple dose administration.

Per the discussion in previous section, CYP3A4 and/or CYP2B6 are possibly involved in the formation of LXB168. However, based on the current available in vitro and in vivo information, it is impossible to determine which enzymes were responsible for the formation of LXB168 and the contribution of the enzyme to the overall osilodrostat clearance. Two scenarios were assumed, 1) CYP3A4 was the only enzyme involved in the formation of LXB168 and responsible for the auto-induction of osilodrostat metabolism (**Model 1**), and 2) CYP2B6 was the only enzyme involved in the formation of LXB168 and responsible for the auto-induction of osilodrostat metabolism (**Model 2**). It should be noted that these two scenarios would cover the situation that both CYP3A4 and CYP2B6 were involved in the formation of LXB168 and responsible for the auto-induction of osilodrostat metabolism. The osilodrostat enzyme kinetic parameters, enzyme induction parameters and LXB168 enzyme induction parameter and clearance were optimized to better recover the observed osilodrostat and LXB168 PK following a single and multiple dose administration (Table 8). The model was also verified to predict the clinical magnitude of a single dose osilodrostat (50mg) on probe substrates of CYP1A2 (observed AUCR=2.33), CYP2C19 (observed AUCR=1.91), CYP2D6 (observed AUCR=1.48) and CYP3A (observed AUCR=1.50) from a cocktail DDI study (Study C2102). The model verification results were similar between Model 1 and Model 2 and only results from Model 1 simulation was shown in Table 7, Figure 19 and Figure 20. After full characterization of osilodrostat nonlinear PK after a single dose administration, osilodrostat auto-induction PK profile after multiple dose administration and metabolite LXB168 PK profile after a single dose administration, and verification of the clinical DDI study results, the FDA's refined Model 1 and Model 2 were applied to assess the DDI

potential of osilodrostat as a perpetrator with CYP enzyme substrates.

PBPK model application

The developed PBPK model was used to simulate the DDIs for osilodrostat in the following scenarios.

- To predict the effect of osilodrostat (30 mg, BID) on midazolam (a CYP3A4 substrate), caffeine (a CYP1A2 substrate), omeprazole (a CYP2C19 substrate), and dextromethorphan (a CYP2D6 substrate), warfarin (a CYP2C9 substrate), and bupropion (a CYP2B6 substrate) at steady-state in healthy subjects.
- To predict the effect of osilodrostat on warfarin (a CYP2C9 substrate) and bupropion (a CYP2B6 substrate) following a single dose administration of osilodrostat (50 mg) at steady-state in healthy subjects.

Results

1. Can FDA refined osilodrostat PBPK models describe osilodrostat PK in healthy subjects?

Yes. The model predictive performance of FDA refined models was a great improvement compared to the Applicant's original model and the Applicant's refined model and was able to capture the observed osilodrostat nonlinear PK over a dose range of 0.5-200 mg, and osilodrostat auto-induction concentration-time profile following a single or multiple dose administration (Figure 19 and Table 7).

2. Can FDA refined osilodrostat PBPK models describe LXB168 PK in healthy subjects?

Yes. The model predictive performance of FDA refined models was a great improvement compared to the Applicant's original model and the Applicant's refined model and captured the observed PK profile of LXB168 reasonably well following a single dose administration of osilodrostat (Figure 20).

3. Can FDA refined osilodrostat PBPK models predict its effect on caffeine (a CYP1A2 substrate) PK following multiple dose administration of osilodrostat (30mg, bid)?

Yes. In vitro studies indicated that osilodrostat is a CYP1A2 competitive inhibitor and a CYP1A2 inducer. The in vivo osilodrostat CYP1A2 Ki value was optimized based on the single dose clinical DDI study results with caffeine. A value of 0.26 μ M for CYP1A2 Ki was found to better recover the observed caffeine AUCR with and without a single dose of osilodrostat. Due to the uncertainty associated with the in vitro-in vivo extrapolation of osilodrostat mediated CYP1A2 induction potentials, a risk assessment was conducted to explore the magnitude of osilodrostat mediated induction on CYP1A2.

Because CYP1A2 induction may attenuate CYP1A2 inhibition effect, the caffeine exposure changes after multiple dose of osilodrostat (30mg, bid) at steady state with CYP1A2 inhibition only (no CYP1A2 induction) represents the highest possible caffeine AUC ratio with osilodrostat.

The predicted caffeine AUCR with osilodrostat at steady state in the absence of CYP1A2 induction is 1.91. Then simulations were performed to deconvolute the CYP1A2 induction parameter values to attain a caffeine AUCR of 1.00 in the presence of both osilodrostat mediated CYP1A2 induction and inhibition effect at steady state. The deconvoluted CYP1A2 IndC₅₀ is 3.6 μM, while in vitro determined Ind_{max} value (18.7) remained unchanged in the analysis. Then caffeine plasma concentration-time profile was simulated in the presence of single dose osilodrostat mediated by both CYP1A2 inhibition and induction effect. As shown in Figure 21, the simulated caffeine elimination rate was much faster than clinically observed. As such, osilodrostat mediated CYP1A2 induction effect at steady state was deemed unlikely to be higher than that predicted using the deconvoluted induction parameter values (Figure 22). Therefore, it was concluded that the caffeine AUC ratio with osilodrostat (30mg, bid) at steady state ranged from 1.00 to 1.91 (Table 10).

The effect of lower dose osilodrostat on caffeine PK was also explored using Model 1 with osilodrostat mediated CYP1A2 inhibition effect only or with osilodrostat mediated by both CYP1A2 induction and inhibition effect. The predicted highest and lowest caffeine AUCR showed a trend toward 1 with the decrease in osilodrostat dose, indicating a lower DDI risk with lower dose osilodrostat (Figure 24).

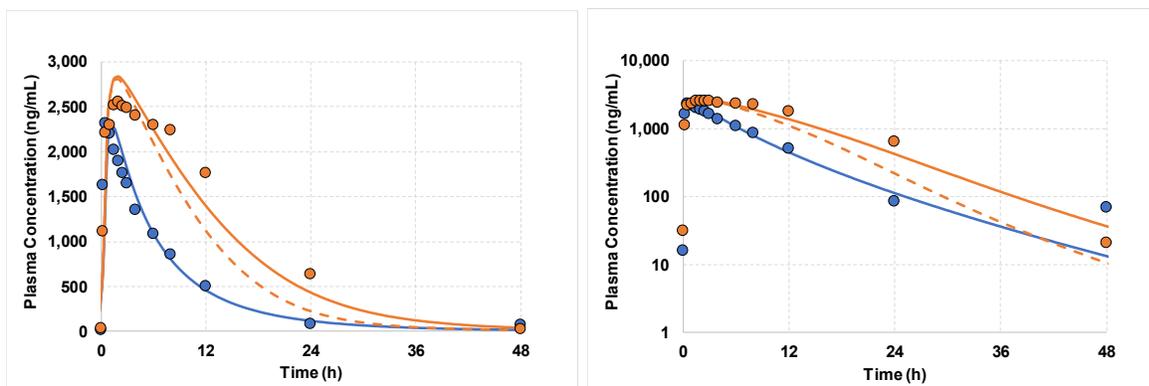


Figure 21 Observed (dots) and simulated (lines) caffeine concentration-time profiles in the presence (orange dots and lines) and absence (blue dots and lines) of single dose osilodrostat (50 mg). Orange solid line: simulated caffeine PK profile in the presence of osilodrostat mediated CYP1A2 inhibition effect only. Orange dashed line: simulated caffeine PK profile in the presence of osilodrostat mediated CYP1A2 inhibition and induction effect. The induction parameter values were deconvoluted to attain a caffeine AUCR of 1.00 in the presence of both osilodrostat mediated CYP1A2 induction and inhibition effect at steady state.

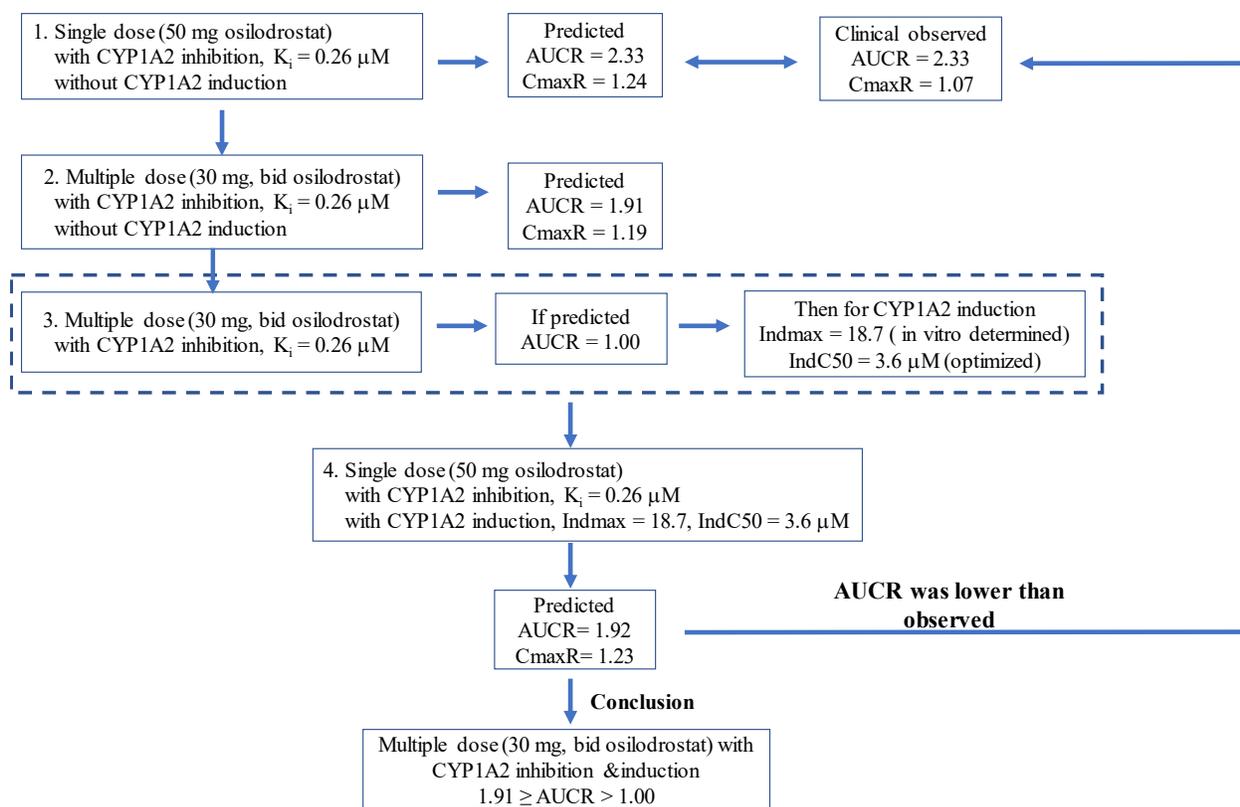


Figure 22 Assessment of DDI potential of osilodrostat as a perpetrator with caffeine. AUCR and CmaxR are the caffeine AUC and Cmax ratios in the presence and absence of osilodrostat mediated CYP1A2 inhibition effect, or both CYP1A2 induction and inhibition effect.

4. Can FDA refined osilodrostat PBPK models predict its effect on midazolam (a CYP3A substrate) PK following multiple dose administration of osilodrostat (30mg, bid)?

Yes. In vitro studies indicated that osilodrostat is a CYP3A4 substrate, a CYP3A4 competitive inhibitor and a CYP3A4 inducer. The in vitro osilodrostat CYP3A4 $IC_{50/2}$ value ($3.25 \mu\text{M}$) was found to provide adequate prediction of the observed midazolam AUCR with and without a single dose of osilodrostat. With respect to the osilodrostat mediated CYP3A4 induction effect, due to the uncertainty associated with the in vitro-in vivo extrapolation of osilodrostat mediated CYP3A4 induction potentials, two scenarios were assumed to explore the possible lower and higher end of midazolam exposure change with osilodrostat at steady state by using Model 1 and Model 2, respectively. Model 1 (with maximum CYP3A4 induction) assumed CYP3A4 was the only enzyme responsible for the auto-induction of osilodrostat metabolism while Model 2 (without CYP3A4 induction) assumed that CYP2B6 was the only enzyme responsible for the auto-induction of osilodrostat metabolism. As shown in Table 10, the estimated midazolam possible higher AUCR with osilodrostat (30mg, bid) at steady state is 1.28 using Model 1, while the estimated midazolam possible lower AUCR with osilodrostat (30mg, bid) at steady state is 0.52 using Model 2.

The effect of lower dose osilodrostat on midazolam PK was also explored using Model 1 and Model 2. The predicted highest and lowest midazolam AUCR showed a trend toward 1 with the decrease in osilodrostat dose, indicating a lower DDI risk with lower dose osilodrostat (Figure 24).

5. Can FDA refined osilodrostat PBPK models predict its effect on bupropion (a CYP2B6 substrate) PK following multiple dose administration of osilodrostat (30mg, bid)?

No. In vitro studies indicated that osilodrostat is a CYP2B6 substrate, a CYP2B6 competitive inhibitor, a CYP2B6 inducer, a CYP2D6 substrate, and a CYP2D6 competitive inhibitor. Bupropion is a CYP2B6 substrate and the metabolites of bupropion (hydroxybupropion, threohydrobupropion and erythrohydrobupropion) have been shown to be competitive inhibitors of CYP2D6. The osilodrostat and bupropion models are not adequate to assess the effect of osilodrostat on the PK of bupropion due to the following reasons.

- There is uncertainty associated with the in vitro-in vivo extrapolation of osilodrostat mediated CYP2B6 inhibition and CYP2B6 induction effect. There are no clinical data available for model verification.
- Bupropion metabolites were not included in the Applicant's model to account for the effect of bupropion metabolites on the osilodrostat PK.
- The fm of CYP2D6 toward overall osilodrostat metabolism has not been validated.
- The effect of modulator on CYP2B6 may be complicated by the overlapping metabolism of competing pathways such as CYP3A4, CYP2C19 and reductase for bupropion. Bupropion metabolites need to be included in the model to assess the overall effect of modulator on bupropion metabolism given the metabolites may contribute significantly to the efficacy and/or toxic effect of bupropion in human.

6. Can FDA refined osilodrostat PBPK models predict its effect on omeprazole (a CYP2C19 and CYP3A substrate) PK following multiple dose administration of osilodrostat (30mg, bid)?

Yes. In vitro studies indicated that osilodrostat is a CYP2C19 competitive inhibitor and a CYP2C19 time dependent inhibitor (TDI). Due to the uncertainty associated with the in vitro-in vivo extrapolation of osilodrostat mediated CYP2C19 TDI potential, the possible magnitude of osilodrostat mediated CYP2C19 TDI was estimated based on the available clinical study results and corresponding DDI between osilodrostat and omeprazole was evaluated. The clinical DDI study with omeprazole showed that omeprazole AUC increased about 1.9-fold with 50 mg single dose osilodrostat. As both competitive inhibition and TDI of CYP2C19 mediated by osilodrostat may increase the omeprazole exposure, two scenarios were investigated to assess the potential DDI risk of osilodrostat with omeprazole at steady state; Scenario 1) only osilodrostat mediated CYP2C19 competitive inhibition, or Scenario 2) only osilodrostat mediated CYP2C19 TDI was responsible for the observed DDI between osilodrostat and omeprazole following a single dose

administration of osilodrostat.

The in vivo osilodrostat CYP2C19 K_i (Scenario 1) or CYP2C19 K_i and k_{inact} (Scenario 2) values (Figure 23) were optimized separately based on the single dose clinical DDI study results with omeprazole. Thereafter, the DDI between osilodrostat and omeprazole following multiple dose administration of osilodrostat and single dose of omeprazole was predicted by using Model 1 and Model 2.

It should be noted that omeprazole is also a CYP2C19 TDI and the omeprazole model in the Applicant's submission which is the default omeprazole model in Simcyp did not account for omeprazole mediated CYP2C19 TDI. The reviewer refined the Simcyp omeprazole model by incorporating omeprazole mediated CYP2C19 TDI. The in vitro determined omeprazole CYP2C19 K_i (8.2 μM) and k_{inact} (1.74h^{-1}) values² were optimized to better recover the clinical omeprazole multiple dose PK study results (Table 9). The DDI between osilodrostat and omeprazole following multiple dose administration of both osilodrostat and omeprazole was also evaluated by using Model 1 and Model 2 to account for the effect of omeprazole mediated CYP2C19 TDI.

In summary, in an attempt to assess the potential DDI risk between osilodrostat and omeprazole, the highest possible omeprazole AUC ratio with osilodrostat was estimated by assuming CYP2B6 was the only enzyme responsible for the auto-induction of osilodrostat metabolism (Model 2) and only osilodrostat mediated CYP2C19 TDI was responsible for the observed DDI between osilodrostat and omeprazole. The lowest possible omeprazole AUC ratio with osilodrostat was estimated by assuming CYP3A4 was the only enzyme responsible for the auto-induction of osilodrostat metabolism (Model 1) and only osilodrostat mediated CYP2C19 competitive inhibition was responsible for the observed DDI between osilodrostat and omeprazole. As shown in Figure 23 and Table 10, the estimated omeprazole AUCR is between 1.06 to 2.28 following multiple dose administration of osilodrostat (30mg, bid) and single dose administration of omeprazole (20 mg) and the estimated omeprazole AUCR is between 0.86 to 1.52 following multiple dose administration of osilodrostat (30mg, bid) and omeprazole (20 mg, qd).

The effect of lower dose osilodrostat on omeprazole PK was also explored using Model 1 and Model 2. The predicted highest and lowest omeprazole AUCR showed a trend toward 1 with the decrease in osilodrostat dose, indicating a lower DDI risk with lower dose osilodrostat (Figure 24).

²Shirasaka Y, Sager JE, Lutz JD, Davis C, Isoherranen N. Inhibition of CYP2C19 and CYP3A4 by omeprazole metabolites and their contribution to drug-drug interactions. *Drug Metab Dispos.* 2013 Jul;41(7):1414-24.

Table 9 Optimized omeprazole mediated CYP2C19 TDI parameter values and observed and predicted AUC changes with time following multiple dose administration of omeprazole in healthy subjects.

Optimized omeprazole parameter values	AUCR ^c Day5/Day1		AUCR ^c Day7/Day1	
	Observed ^a	Predicted	Observed ^b	Predicted
CYP2C19 K _I = 0.25 μM k _{inact} = 3h ⁻¹	1.90	1.82	2.00	1.85

a: observed ratio of AUC on day 5 to AUC on day 1 following multiple oral administration of omeprazole (20 mg, qd) to healthy subjects. Data were obtained from Hassan-Alin 2000³.

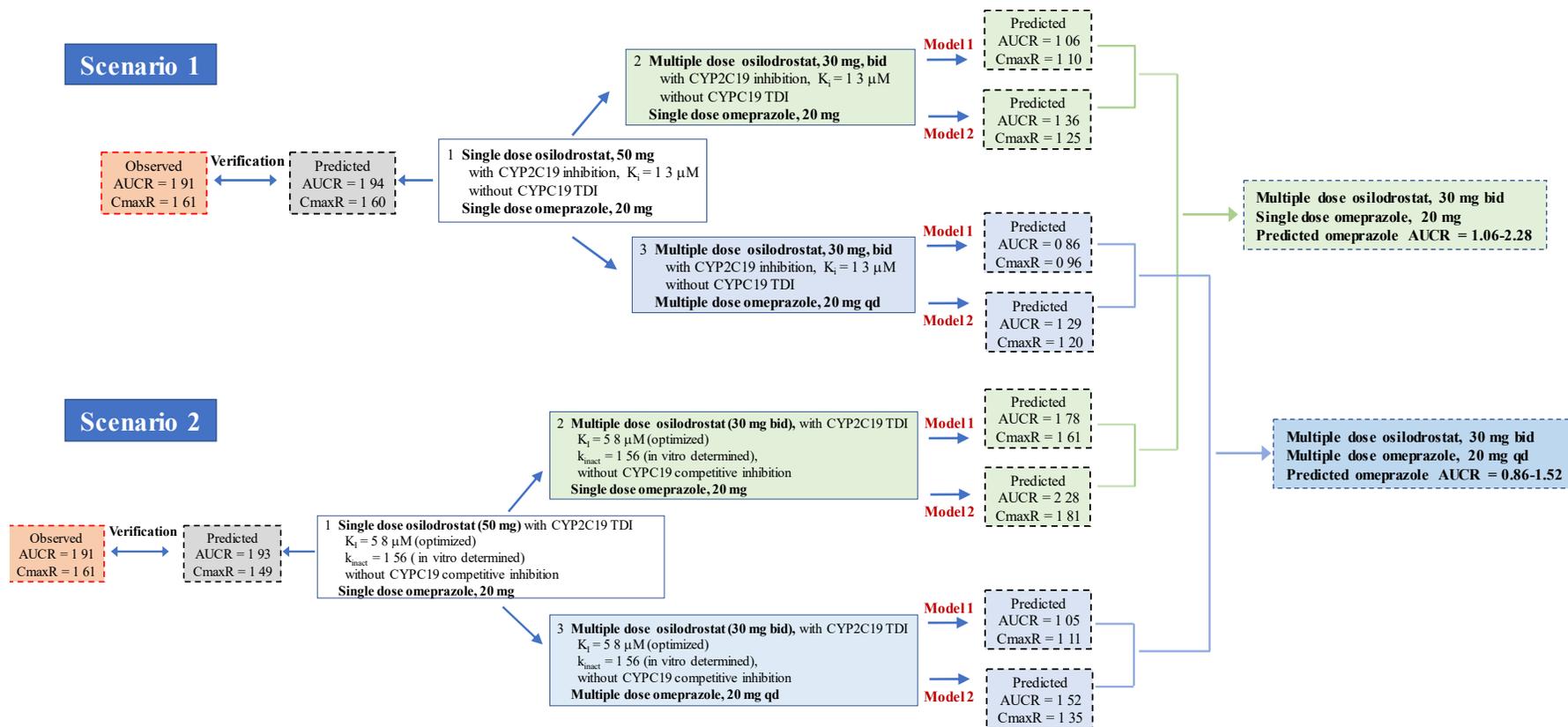
b: observed ratio of AUC on day 7 to AUC on day 1 following multiple oral administration of omeprazole (20 mg, qd) to healthy subjects. Data were obtained from Andersson 1998⁴.

c: Geometric mean ratio

3 Hassan-Alin M1, Andersson T, Bredberg E, Röhss K. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. Eur J Clin Pharmacol. 2000 Dec;56(9-10):665-70.

4 Andersson T1, Holmberg J, Röhss K, Walan A. Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. Br J Clin Pharmacol. 1998 Apr;45(4):369-75.

Figure 23 Assessment of DDI potential of osilodrostat as a perpetrator with omeprazole. The single or multiple dose omeprazole AUCR and CmaxR with multiple dose osilodrostat were predicted in Scenario 1 and Scenario 2 using Model 1 and Model 2.



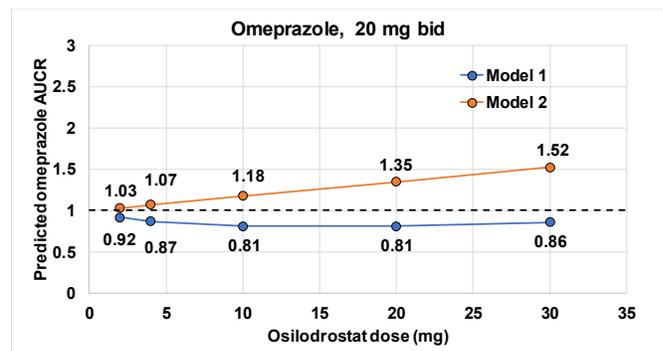
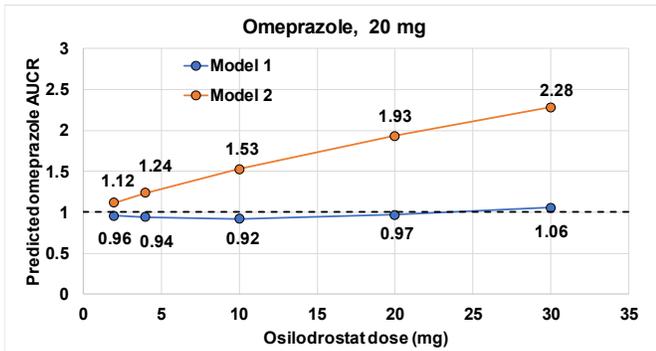
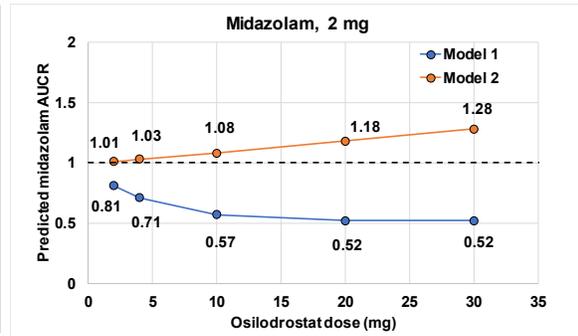
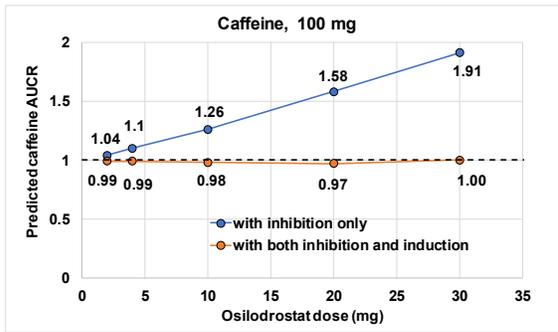


Figure 24 Predicted possible highest (orange lines and dots) and lowest (blue lines and dots) AUC ratios for caffeine (100 mg, single dose), midazolam (2 mg, single dose) and omeprazole (20 mg, single dose and 20 mg bid) with concomitant use of different doses of osilodrostat (2, 4, 10, 20 or 30 mg, bid) at steady state

7. Can FDA refined osilodrostat PBPK models predict its effect on dextromethorphan (a CYP2D6 substrate) PK following multiple dose administration of osilodrostat (30mg, bid)?

Yes. In vitro studies indicated that osilodrostat is a CYP2D6 competitive inhibitor. The in vitro osilodrostat CYP2D6 Ki value (2 µM) was found to provide adequate prediction of the observed dextromethorphan AUCR with and without a single dose of osilodrostat. The model predicted that dextromethorphan exposure would increase by 23% with osilodrostat (30 mg, bid) at steady state (Table 10).

8. Can FDA refined osilodrostat PBPK models predict its effect on warfarin (a CYP2C9 substrate) PK following multiple dose administration of osilodrostat (30mg, bid)?

Yes. In vitro studies indicated that osilodrostat is a CYP2C9 competitive inhibitor with an in vitro determined Ki value of 20 µM. The model predicted warfarin exposure was not significantly affected by concomitant osilodrostat by using the in vitro determined CYP2C9 Ki value (Table 10). The reviewer further conducted a sensitivity analysis of osilodrostat CYP2C9 Ki to assess the effect on the predicted warfarin exposure. The simulated warfarin AUC ratio was 1.14 with 10-fold lower CYP2C9 Ki value than the in vitro determined value, indicating that the inhibition effect of osilodrostat is low towards CYP2C9.

Table 10 Model predicted (osilodrostat 30 mg bid) and observed (osilodrostat 50 mg single dose) effect of osilodrostat and its metabolite on the exposure of caffeine, midazolam, omeprazole, dextromethorphan, and warfarin after multiple dose administration of osilodrostat (30 mg, bid).

Substrates	Predicted AUCR	Observed AUCR
Caffeine (CYP1A2), 100 mg	1.00-1.91	2.33
Midazolam (CYP3A), 2 mg	0.52-1.28	1.50
Omeprazole (CYP2C19), 20 mg, single dose	1.06-2.28	1.91
Omeprazole (CYP2C19), 20 mg, multiple dose	0.86-1.52	NA
Dextromethorphan (CYP 2D6), 30 mg	1.23	1.48
Warfarin (CYP2C9), 10 mg	1.02	NA

NA: not available

Additional Comments

With respect to the DDI potential of osilodrostat as a victim with CYP modulators, the Applicant stated in the Summary of Clinical Pharmacology and in response to the FDA's information request that "osilodrostat is unlikely to be a victim for DDI". Clinical DDI study has not been conducted to assess the DDI potential of osilodrostat as a victim with CYP modulators. After reviewing the totality of clinical pharmacology information, we determined that the statement "osilodrostat is unlikely to be a victim for DDI" may not be adequate at this time for the following reasons.

- The autoinduction property of osilodrostat metabolism indicated that the contribution of CYP3A4 and/or CYP2B6 to the overall osilodrostat clearance was underestimated.
- The possibility that the involvement of CYP3A4 and/or CYP2B6 in the formation of LXB168 cannot be excluded.
- The formation clearance of LXB168 was estimated to be about 14% of the total clearance of osilodrostat in the Summary of Clinical Pharmacology and response to the FDA's information request, which may be underestimated as evidenced by over 50% of the total clearance of osilodrostat that was assigned to the formation clearance of LXB168 in both Applicant's and FDA refined models to recover the LXB168 PK.

In conclusion, the DDI potential of osilodrostat as a victim of CYP modulators cannot be excluded.

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/s/

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