CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215092Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	215092
Link to EDR	\View submission in docuBridge
Submission Date	11/19/2020
Submission Type	NDA 505(b)(1); Standard
Brand Name	To be determined
Generic Name	Omidenepag isopropyl
Dosage Form and Regimen	Ophthalmic solution containing 0.02 mg/mL (0.002%) of omidenepag isopropyl; one drop in the affected eye(s) once daily in the evening
Route of Administration	Ophthalmic
Proposed Indication	For the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Applicant	Santen, Inc.
Associated IND	IND 111518
OCP Review Team	Suneet Shukla, Ph.D.; Bhawana Saluja, Ph.D.; Ping Ji, Ph.D.

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1 EXECUTIVE SUMMARY

Santen Inc (the Applicant) submitted an original NDA on November 19th, 2020, seeking marketing approval for omidenepag isopropyl (OMDI) ophthalmic solution for the proposed indication of reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The proposed drug product is supplied as a sterile, isotonic, buffered aqueous solution of omidenepag isopropyl; each mL of the drug product contains 0.02 mg of omidenepag isopropyl (0.002%). The proposed dosing regimen is one drop in the affected eye(s) once daily in the evening.

The drug product contains omidenepag isopropyl (OMDI), a prodrug of the pharmacologically active metabolite, omidenepag. Omidenepag is a prostaglandin E2 (EP2) receptor agonist and has a non-prostaglandin structure.

The clinical pharmacology program for the proposed product included a Phase 1 plasma PK and safety study (01171502). In addition, the submission contained seven in vitro studies characterizing metabolism, protein binding, partitioning in blood cells and in vitro metabolic/transporter-based drug interactions. Further, three dose-finding studies (33-001, 33-002, 33-003, and 01171503 Stage 1) and one dose regimen-finding study (011712IN) were conducted to optimize the dosing. However, PK parameters were not assessed in these studies.

The clinical pharmacology review is focused on the appropriateness of the proposed dosing regimen of one drop of omidenepag isopropyl ophthalmic solution, 0.002% in the affected eye(s) once daily in the evening.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of NDA 215092, and finds the application acceptable to support approval from a clinical pharmacology perspective. The key review issues with specific clinical pharmacology recommendations and comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of effectiveness is based on three randomized controlled trials (01171505, 011710IN, 011709IN) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). Supportive evidence of effectiveness is based on five dose or regimen-finding studies (33-001, 33-002, 33-003, 01171503 Stage 1 and 011712IN). No PK was collected in these studies.
General dosing instructions	One drop of omidenepag isopropyl ophthalmic solution, 0.002% in the affected eye(s) once daily in the evening.
Dosing in patients (intrinsic and extrinsic factors)	No dose adjustment is recommended for patients based on intrinsic and extrinsic factors.

Labeling	The proposed labeling concepts are generally acceptable.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. There is no difference between the clinical trial formulation and the to be marketed formulation.

1.2 Post Marketing Requirement

None

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

PK of OMDI ophthalmic solution 0.0025% was evaluated in healthy subjects (Study 01171502). The study was a single-arm open-label study where OMDI ophthalmic solution 0.0025% was administered into both eyes of 7 Japanese and 7 Caucasian subjects for 7 consecutive days. Plasma concentrations of omidenepag were measured before instillation and at 5, 15, 30, 60, 120, 240, and 480 minutes after instillation on Days 1, 3, and 7. It should be noted that the dosing strength of OMDI 0.0025% used to assess PK is different from OMDI 0.002% which was evaluated in Phase 3 pivotal studies and being proposed as final regimen.

Absorption

Following instillation of one drop of OMDI ophthalmic solution 0.0025% in both eyes once daily in healthy subjects for 7 days, plasma omidenepag concentration on Days 1, 3, and 7 reached maximum concentration (Cmax) of 34.36 to 35.51 pg/mL at times within the range of 0.17 to 0.25 h after instillation. The area under the concentration curve at time 0 to 8 hours ($AUC_{0\text{-}8h}$) and area under the concentration curve at infinity (AUC_{inf}) were 20.72 to 22.41 pg·h/mL and 21.43 to 22.42 pg·h/mL, respectively.

Distribution

No distribution data is available for OMDI. The plasma protein binding ratios at plasma omidenepag concentrations of 2.5 and 20 ng/mL were both 97.8%, indicating no concentration-dependent changes in the plasma protein binding ratios.

Metabolism

After topical ocular administration, OMDI is rapidly metabolized in the eye to omidenepag (active moiety) by carboxylesterase-1. Omidenepag, the pharmacologically active form, is further metabolized by liver through oxidation, *N*-dealkylation, glucuronidation, sulfate conjugation or taurine conjugation. CYP3A4 is involved in the metabolism of omidenepag.

Excretion

The terminal plasma elimination half-life of omidenepag following once-daily dosing in both eyes for seven days was in the range of 0.449 to 0.507 h. Following ocular instillation or subcutaneous injection of ^{14}C-OMDI to rats, most of the administered radioactive dose was excreted through bile into feces.

2.1.1 Dosing and Therapeutic Individualization

2.1.2 General Dosing

The recommended dosing regimen is one drop of OMDI ophthalmic solution, 0.002% in the affected eye(s) once daily in the evening. This dosing regimen was evaluated in three randomized controlled clinical trials (01171505, 011710IN, and 011709IN) with patients with primary OAG and OHT. These studies were designed to assess safety and efficacy, and specifically to demonstrate the non-inferiority of the IOP-lowering effect of DE-117 0.002% QD relative to the active control over the 3-month comparative treatment period.

2.1.3 Therapeutic Individualization

Therapeutic individualization is not applicable for OMDI ophthalmic solution because it is locally administered with minimum systemic exposure.

2.1.4 Outstanding Issues

None.

2.1.5 Summary of Labeling Recommendations

A summary of labeling recommendations that will be provided to the Applicant is below.

Omidenepag is absorbed through the cornea where prodrug omidenepag isopropyl is hydrolyzed to become biologically active metabolite, omidenepag. After once daily ocular administration of one drop of omidenepag isopropyl 0.0025% eye drops to both eyes in humans for 7 days, plasma concentrations of omidenepag reached Cmax at 10-15 minutes.

The pharmacologically active form, omidenepag is further metabolized by liver through oxidation, N-dealkylation, glucuronidation, sulfate conjugation or taurine conjugation. (b) (4)

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Omidenepag Isopropyl (OMDI) ophthalmic solution 0.002% is a selective EP2 receptor agonist with OMDI, a prodrug of omidenepag, with a non-prostaglandin structure, as the active ingredient. Omidenepag is an IOP-lowering agent that reduces elevated IOP by increasing the outflow of aqueous humor through the trabecular and uveoscleral pathways.

A summary of key clinical pharmacology-related discussions and correspondence with the Applicant are listed in Table 1 below.

Table 1: Summary of Key Clinical Pharmacology-related and Communication/Meetings with the Applicant

IND 111518 (July 2012)	▪ Recommended evaluation of the systemic exposure to OMDI and/or its major active acid metabolite, omidenepag following topical ocular administration of OMDI ophthalmic solution in humans during drug development program.
IND 111518 (August 2012)	▪ The Sponsor agreed on evaluating the systemic exposure systemic exposure to OMDI and/or its major active acid metabolite (i.e., omidenepag, UR-7276)
EOP1/2 June 2015)	▪ Agreed that the Phase 2 studies provide sufficient exploration of the concentration (0.003% and 0.0025% OMDI). ▪ (b) (4) ▪ Concurred on the selection of the 0.0025% dose for the Phase 3 studies.
EOP1/2 Nov 2017)	▪ The Agency recommended studying BID vs. QD dosing, in at least one arm of one clinical trial, since the Sponsor did not have any clinical data on BID dosing.

Source: Reviewer's summary based on meeting minutes (DARRTS; IND 111518)

3.2 General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and PK of OMDI and its active metabolite, omidenepag were evaluated in Phase 1 study (01171502) in healthy subjects. The clinical pharmacology and pharmacokinetics information of OMDI are summarized below.

Table 2: Summary of clinical pharmacology and pharmacokinetics

Pharmacology	
Mechanism of Action	Omidenepag is an EP2 receptor agonist which reduces elevated IOP by stimulating the outflow of aqueous humor through both the trabecular and uveoscleral pathways; the Applicant stated that this dual pathway is a mechanism

	of action that is distinct from that of latanoprost and most other agents that lower IOP via stimulation of aqueous humor outflow.
Active Moieties	Omidenepag is a selective EP2 receptor agonist which is an active metabolite of the prodrug, OMDI. OMDI after ocular instillation, is rapidly metabolized to omidenepag by esterases that are present in the cornea.
QT Prolongation	Omidenepag at 10 µmol/L had no effect on hERG currents in hERG transfected CHO cells. The concentration is well above the plasma concentrations detected in the clinical PK study (see summary below). Thus, the risk of QT prolongation with topical ocular administration of OMDI appears low.
General Information	
Bioanalysis	Validated LC/MS/MS methods to determine concentrations of omidenepag in the plasma.
Healthy vs. Patients	Systemic exposure of omidenepag was assessed in healthy subjects only.
Drug exposure at steady state following the therapeutic dosing regimen	Following instillation of one drop of OMDI ophthalmic solution 0.0025% in both eyes once daily in the evening (20:00) for 7 days, plasma omidenepag (UR-7276 concentration on Days 1, 3, and 7 reached maximum concentration (Cmax) of 34.3571 to 35.5071 pg/mL at times within the range of 0.1667 to 0.2500 h after instillation. $AUC_{0\text{-}8h}$ and AUC_{inf} were 20.7243 to 22.4143 pg·h/mL and 21.4286 to 22.4231 pg·h/mL, respectively.
Range of effective dose or exposure	Based on mean IOP reduction from baseline, a positive dose-response relationship was observed across four concentrations of OMDI (0.0012%, 0.0016%, 0.002%, and 0.0025%). Further, the IOP-lowering effect was slightly numerically greater (0.3 mmHg) in the 0.002% group as compared to the 0.0025% group. Both the 0.002% and 0.0025% concentrations were well tolerated. Since the higher of these 2 concentrations (0.0025%) did not demonstrate a greater magnitude of IOP-lowering effect, 0.002% was selected for pivotal Phase 3 trials.
Maximally tolerated dose or exposure	Maximum human dose (strength) evaluated was OMDI 0.03% QD.
Dose Proportionality	Not determined.
Accumulation	No systemic accumulation detected.
Variability (%)* ***Reviewer calculated from PK data in Study 01171502***	Cmax: 49.441 (Day 1), 45.332 (Day 3), 37.915 (Day 7) $AUC_{0\text{-}8h}$: 36.239 (Day 1), 34.172 (Day 3), 27.567 (Day 7)
Absorption	
Bioavailability	Not determined
Median T_{max} (h)	0.1667 (Day 1), 0.2500 (Day 3), 0.2500 (Day 3)
Distribution	
Volume of Distribution	NA
Plasma Protein Binding	97.8%, binding is independent of concentration between 2.5 and 20 ng/mL.
Substrate transporter systems [*in vitro*]	OMDI is not a substrate for MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, and BSEP. Omidenepag is a substrate for OAT3, OATP1B1, OATP1B3, and P-gp.

Elimination	
Terminal Elimination half-life (SD)	0.4488 (0.1339) (Day 1), 0.4813 (0.1029) (Day 3), 0.5072 (0.0803) (Day 7).
Effective Elimination half-life	NA
Excretion	
Primary excretion pathways (% dose) ±SD	Not determined in humans.
In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	Omidenepag at 10 µmol/L (4790,000 pg/mL) inhibited CYP3A4/5 activity by 27% and CYP3A4/5 activity by 64%, each with an IC_{50} of 5.04 µmol/L. Omidenepag at 10 µmol/L also inhibited CYP2C19 activity by 17%; however, omidenepag had no measurable impact on the metabolic activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, or CYP2D6. When omidenepag at 10 µmol/L was pre-incubated with human liver microsomes in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), an enhanced metabolism by CYP1A2 was observed, demonstrating metabolism dependent inhibition of CYP1A2 metabolic activity by omidenepag. Metabolism-dependent inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2D6, or CYP3A4/5 metabolic activities were not observed. The potential of systemic DDIs appears minimal because of low plasma concentrations of omidenepag following topical ocular administration.
Inhibition/Induction of transporter systems	OMDI is not a substrate for any of the studied transporters MATE1, MATE2-K, OAT1, OCT1, OCT2, BCRP, and BSEP. However, the data suggested that omidenepag could be a substrate for OAT3, OATP1B1, OATP1B3, and P-gp. OMDI inhibited the transport activities of MATE1 (IC_{50} >5 µmol/L), MATE2-K (IC_{50} = 5 µmol/L), OAT3 (IC_{50} = 8.96 µmol/L), OCT1 (IC_{50} = 2.26 µmol/L), OATP1B1 (IC_{50} = 1.89 µmol/L), OATP1B3 (IC_{50} >5 µmol/L), and BSEP (IC_{50} >5 µmol/L). Omidenepag inhibited the transport activities of MATE2-K (IC_{50} >5 µmol/L), OAT3 (IC_{50} = 7.13 µmol/L), OATP1B1 (IC_{50} = 1.80 µmol/L), OATP1B3 (IC_{50} >5 µmol/L), and P-gp (IC_{50} >5 µmol/L). The Cmax of omidenepag in plasma is 35 pg/mL (0.073 nmol/L) after repeated bilateral ocular instillation of 0.0025% OMDI ophthalmic solution in humans QD for 7 days which is order of magnitude lower than the concentration at which omidenepag inhibits metabolic enzymes or drug transporters (mostly at the µmol/L level). Therefore, inhibition or induction of these enzymes will not be possible at observed plasma drug concentration of omidenepag.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

There were no PK samples collected in three randomized and controlled clinical trials (01171505, 011710IN, 011709IN), which provided the primary evidence of effectiveness. Consequently, there was no analysis conducted to evaluate the relationship between omidenepag exposure and efficacy

endpoints. The three randomized and controlled clinical trials demonstrated a consistent IOP-lowering effect of 5.4 to 7.4 mmHg, similar to latanoprost 0.005% dosed once daily and timolol 0.5% dosed twice daily, respectively in subjects with open-angle glaucoma or ocular hypertension with average baseline IOP of 24-26 mmHg.

The effectiveness was also supported by the five dose or regimen-finding studies (33-001, 33-002, 33-003, 01171503 Stage 1 and 011712IN). No PK data were collected in these trials. Please refer to the clinical and statistical reviews for more information on efficacy and safety assessments.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of one drop of [redacted] (b) (4) (omidenepag isopropyl ophthalmic solution, 0.002%) in the affected eye(s) once daily in the evening were evaluated in three randomized and controlled clinical trials, in which the efficacy data supported this application based on consistent IOP-lowering effect relative to active control.

The selection of omidenepag isopropyl ophthalmic solution at 0.002% given once daily in the randomized and controlled clinical trials was based on five dose/regimen-finding studies, in which 9 concentrations of OMDI ophthalmic solution were evaluated: 0.0003%, 0.001%, 0.0012%, 0.0016%, 0.002%, 0.0025%, 0.003%, 0.01%, and 0.03% (Table 3). Three dose ranging studies (33-001, 33-002, 33-003) were conducted in patients with primary OAG or OHT exploring daily doses from 0.0003% to 0.03% administered QD in the evening. Taken together from above three dose ranging studies, a positive dose-response relationship for efficacy (i.e., increased IOP-lowering with increased dose) was observed across the 3 lower concentrations (0.0003%, 0.001%, and 0.002%). Further, the highest concentration of OMDI assessed 0.03% demonstrated safety issues and the IOP reduction at 0.002% strength was numerically the greatest when compared to the lower strengths (0.0003%, 0.001%) and higher strength (0.003%). A dose regimen finding study (011712IN) was also conducted comparing OMDI 0.002% BID with OMDI 0.002% QD in POAG or OHT patients. OMDI 0.002% ophthalmic solution administered QD in the evening demonstrated clinically meaningful IOP-lowering effect in POAG or OHT patients. Therefore, it was selected for confirmation in the Phase 3 program.

Table 3: Comparison of Designs of Dose-Finding Studies

Design Aspect		Dose-Finding Studies				Phase 3 Studies, Masked Period	
		33-001	33-002	33-003	01171503 Stage 1	011710IN=10 011709IN=09 01171505=1505	
Region		US	US	US	Japan	US (**09, 10**); Asia (**1505**)	
Design		Randomized, observer-masked[a], placebo- and active-controlled, parallel-group.	Randomized, observer-masked[a], placebo- and active-controlled, parallel-group.	Randomized, observer-masked[a], active-controlled, parallel-group.	Randomized, double-masked[a], placebo-controlled, parallel-group.	Randomized, observer/double-masked[a], active-controlled, parallel-group.	
Population		POAG or OHT	POAG or OHT	POAG or OHT	POAG or OHT	POAG, OHT, or other OAG (1-2%)	
Treatment duration		4 weeks	4 weeks	3 months	4 weeks	3 months	
DE-117 concentrations assessed (one drop per eye QD)	0.0003%	-	X	-	-	-	
	0.001%	-	X	-	-	-	
	0.0012%	-	-	X	-	-	
	0.0016%	-	-	X	-	-	
	0.002%	-	X	X	X	X	
	0.0025%	-	-	X	X	-	
	0.003%	X	X	X	-	-	
	0.01%	X	-	-	-	-	
	0.03%	X (discont.[b])	-	-	-	-	
Control(s)		placebo and tafluprost	placebo and latanoprost	latanoprost	placebo	timolol (**09, 10**) or latanoprost (**1505**)	
Number of subjects per arm, range		14-16[b]	14-17	29-32	19-22	204-215 (**09, 10**); 185 (**1505**)	
IOP assessment timepoints		08:00 10:00 12:00 16:00	08:00 10:00 12:00 16:00	08:00 10:00 12:00 16:00 18:00	09:00 13:00 17:00	**09, 10:** 08:00 10:00 16:00	**1505:** 09:00 13:00 17:00
Baseline IOP requirement in study eye		22-35 mmHg at 3 of 4 timepoints; 26-35 mmHg at 08:00	22-35 mmHg at all timepoints	22-35 mmHg at all timepoints	22-34 mmHg at all timepoints	22-34 mmHg at all timepoints[c]	
Follow-up visits		W1, W2, W4	W1, W2, W4	W1, W2, M1, M2, M3	W1, W2, W4	W1, W6, M3	

Abbreviations: M1 = Month 1, M2 = Month 2, etc.; W1 = Week 1, W2 = Week 2, etc.
a Double-masked and observer-masked both referred to the same masking technique: In brief, masking was achieved by ensuring that only authorized (unmasked) study staff could dispense/collect study drugs.
b DE-117 (OMDI) 0.03% QD arm discontinued for safety after 3 subjects had dosed for ≤ 2 weeks (IOP-lowering activity in this arm was observed); the number of subjects per arm in the table is based on the 0.003% and 0.01% study arms.
c Criteria for adults
Source: Module 2.7.3 Summary of Clinical Efficacy, Table 32, \\CDSESUB1\evsprod\nda215092\0001\m2\27-clin-sum\summary-clin-efficacy-glaucoma.pdf

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

An alternative dosing regimen is not needed. As the site of drug delivery and action for OMDI ophthalmic solution is the eye, the extent of systemic exposure does not correlate with its efficacy. From a perspective of safety, given minimal systemic exposure following topical administration, dose adjustment is not warranted in subpopulations based on the commonly known intrinsic factors.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The drug product is an ophthalmic solution; therefore, the issue of a food-drug interaction is not relevant. However, topically administered drugs in the eye may get to systemic circulation by entering the nasolacrimal duct before being absorbed from the nasal mucosa or GI tract. Considering this as a possible scenario, theoretical absorption of omidenepag was assessed. Assuming that, after ocular instillation of 0.002% OMDI ophthalmic solution at the proposed dose (1.2 μg/person given as single bilateral administration of one drop = approximately 30 μL/eye), all administered OMDI is transited to the GI tract and then metabolized to omidenepag, the estimated omidenepag concentration in the GI lumen will be approximately 72 nmol/L if the gastric fluid volume is assumed to be 35 mL. This estimated concentration, even if maintained in the blood supply to the liver, is lower by more than one order of magnitude than what was demonstrated for half-maximal inhibitory activity of omidenepag for CYP3A4/5 (IC_{50} = 5.04 μmol/L). In addition, the Cmax of the omidenepag concentration in plasma was approximately 35 pg/mL (≈ 0.073 nmol/L) after repeated bilateral ocular instillation of 0.0025% OMDI ophthalmic solution in humans QD for 7 days, indicating that drug-drug interactions resulting from inhibition of CYP-mediated metabolism by omidenepag are unlikely to be significant (SEE DDI below, Sections 4.26.and 4.2.7).

4 APPENDICES

4.1 Clinical PK Assessment

4.1.1 Study # 01171502: A Pharmacokinetic Study of OMDI (DE-117) Ophthalmic Solution in Healthy Adult Male Subjects.

The study was conducted to assess the safety and plasma pharmacokinetics of OMDI ophthalmic solution 0.0025% (one drop once daily for 7 days) in healthy male adults. It was a single-arm open-label based where OMDI ophthalmic solution 0.0025% (Batch No.: C020502) was administered at 9:00 am by ocular instillation into both eyes of 7 Japanese and 7 Caucasian subjects for 7 consecutive days. The plasma drug concentration was measured only for omidenepag in pharmacokinetic studies. Plasma concentrations of omidenepag were measured before instillation and at 5, 15, 30, 60, 120, 240, and 480 minutes after instillation on Days 1, 3, and 7. The following plasma pharmacokinetic parameters of omidenepag were evaluated: AUC, Cmax, Tmax, $T_{1/2.}$

4.1.1.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical method used for quantification of UR-7276 was validated (TRC Study No. P15-42601) The concentration of UR-7276 was determined using liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. The method validation is summarized as below.

Table 4: Bioanalytical method assessment

Information Requested	Data
Bioanalytical method validation report location	\\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\p15-42601\p1542601-analytical-report.pdf
Analyte	UR-7276
Internal Standard (IS)	UR-8087 (UR-7276-d6)
Limit of quantitation (pg/mL)	1.00 to 1000 pg/mL
Average recovery of drug at each QC (% CV)	HQC: 101 MQC: 97 LQC: 88
Average recovery of IS (%)	83
Standard curve concentrations (µg/mL)	1.00, 2.00, 5.00, 10.0, 50.0, 200, 500, 1000 pg/ml
QC concentrations (µg/mL)	LLQC: 1.00 pg/mL LQC: 2.00 pg/mL MQC: 100 pg/mL HQC: 800 pg/mL
QC intraday precision range (%)	1 % to 17 %
QC intraday accuracy range (%)	115% to 88 %
QC interday precision range (%)	4 % to 16 %
QC interday accuracy range (%)	96 % to 103 %
Bench-top stability (hrs)	24 hours (room temperature))
Stock stability (days)	32 days (1°C-10°C), and 6 hrs (room temperature)
Processed stability (hrs)	73 hours (at 10°C)
Freeze-thaw stability (cycles)	5 cycles (at -65°C)
Long-term storage stability (days)	91 days at -65°C and -15°C
Dilution Integrity	Not done
Selectivity	No interference at the retention times of analyte and internal standard

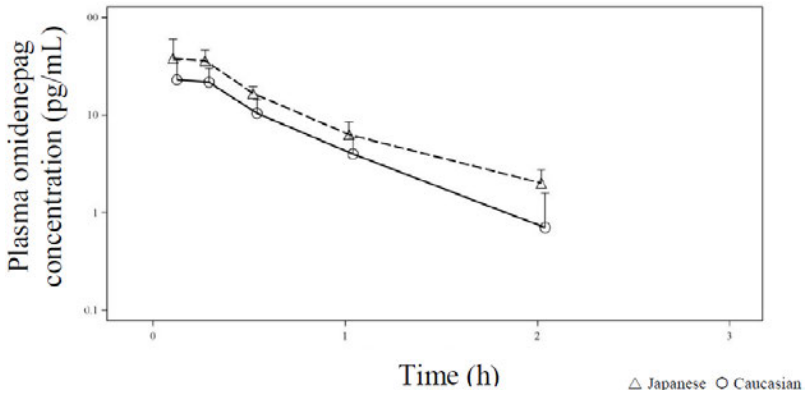
Reviewer's comments:

- *Plasma concentrations of UR-7276 was determined using a validated LC-MS/MS method.*
- *The % recovery of analyte is consistent across QC concentrations, also is comparable to the corresponding internal standards (IS).*
- *Heparin sodium was used as anticoagulant both the bioanalysis of samples from Study 01171502 and in pre-study bioanalytical method validation.*
- *Per bioanalytical method validation guidance, precision and accuracy run (within-run and between-run) were not performed at four (4) QC levels (LLOQ, LQC, MQC, and HQC) and at least five (5) replicates per QC level. The long-term storage stability of 91 days at -65°C and -15°C is sufficient to cover the sample storage at -65°C for a duration of 98 days (January 22, 2016-March 31, 2016). Pre-Study Method Validation is adequate.*
- *It is to be noted that that the Applicant did not have sufficient QC samples to assess the integrity of study sample analysis. The calibration curve concentration range was 1.0 - 1000 pg/mL with three QC samples (i.e., 2.00, 100, and 800 pg/mL for the LQC, MQC and HQC, respectively) while the concentrations of all but three study samples were below 50 pg/mL. However, considering that linearity is demonstrated in the range tested and incurred sample reanalysis of 34 incurred samples was within ±20.0%. between original and repeat analyses, the bioanalytical method validation and analysis will be considered acceptable.*

4.1.1.2 PK/PD results

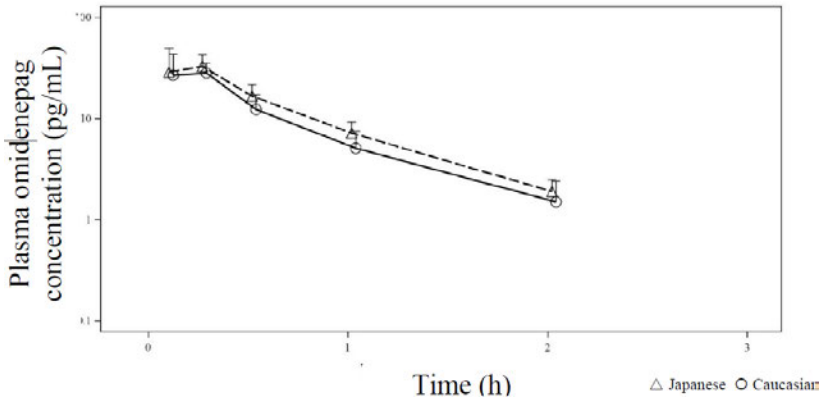
Mean plasma concentration of omidenepag, over time on Days 1 and 7 after repeated ocular instillation are shown in Figure 1 and Figure 2, respectively.

Figure 1: Mean Plasma Omidenepag Concentration over Time after Repeated Ocular Instillation (Day 1)



Source: CSR 01171502, Figure 14.3.1
Values are shown as mean + SD in 7 subjects.
Plasma omidenepag concentrations before administration and at 240 and 480 minutes after administration were below the lower limit of quantitation (< 1.00 pg/mL).
\\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\01171502\01171502-csr-body.pdf

Figure 2: Mean Plasma Omidenepag Concentration over Time after Repeated Ocular Instillation (Day 7)



Source: CSR 01171502, Figure 14.3.1
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The pharmacokinetic (PK) parameters on all analyzed days are shown in Table 5 below

Table 5: Plasma Pharmacokinetic Parameters of Omidenepag

Parameter	**Analysis Visit**		**Japanese**	**Caucasian**	**Overall**
Cmax (pg/mL)	Day 1	n	7	7	14
		Mean (SD)	41.5000 (20.0656)	27.2143 (10.1729)	34.3571 (16.9864)
		Median	33.1000	29.7000	31.9000
		Min, Max	24.6000, 82.1000	12.1000, 38.2000	12.1000, 82.1000
	Day 3	n	7	7	14
		Mean (SD)	38.8000 (15.1304)	32.2143 (17.5251)	35.5071 (16.0962)
		Median	33.6000	32.3000	32.9500
		Min, Max	20.1000, 64.7000	9.1000, 59.9000	9.1000, 64.7000
	Day 7	n	7	7	14
		Mean (SD)	37.5286 (15.5231)	33.3143 (11.8101)	35.4214 (13.4302)
		Median	34.0000	33.7000	33.8500
		Min, Max	13.5000, 60.4000	13.9000, 53.9000	13.5000, 60.4000
Parameter	**Analysis Visit**		**Japanese**	**Caucasian**	**Overall**

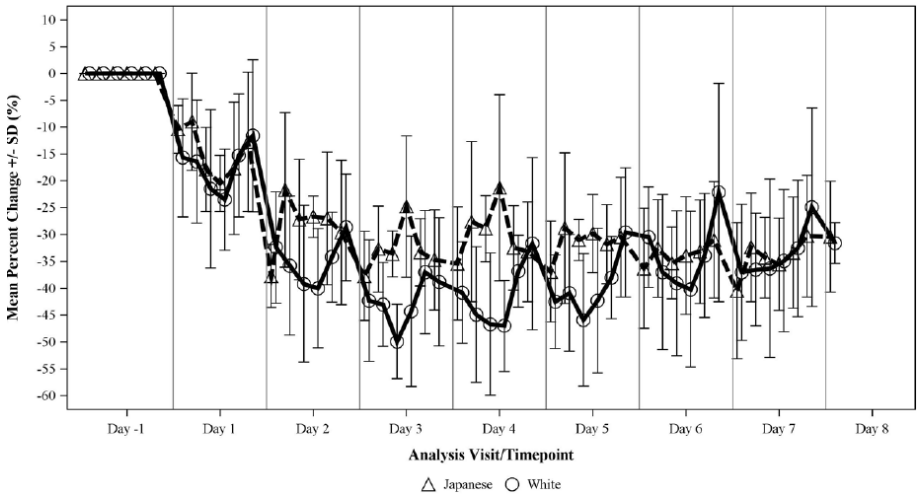
AUC_{0-8h} (pg·h/mL)	Day 1	n	7	7	14
		Mean (SD)	26.1286 (5.6818)	15.3200 (4.6668)	20.7243 (7.5103)
		Median	26.5000	16.3000	20.2000
		Min, Max	19.7000, 34.2000	8.8000, 21.0000	8.8000, 34.2000
	Day 3	n	7	7	14
		Mean (SD)	24.3000 (6.2156)	19.4571 (8.2941)	21.8786 (7.4763)
		Median	23.9000	17.8000	21.6500
		Min, Max	14.2000, 31.5000	11.0000, 35.6000	11.0000, 35.6000
	Day 7	n	7	7	14
		Mean (SD)	25.0143 (6.6031)	19.8143 (4.8316)	22.4143 (6.1789)
		Median	27.0000	18.4000	22.7500
		Min, Max	12.0000, 30.8000	13.7000, 27.6000	12.0000, 30.8000
Parameter	**Analysis Visit**		**Japanese**	**Caucasian**	**Overall**
AUC_{inf} (pg·h/mL)	Day 1	n	7	5	12
		Mean (SD)	25.6429 (5.6193)	15.8020 (4.7496)	21.5425 (7.1487)
		Median	26.4000	16.7000	20.1500
		Min, Max	19.2000, 33.6000	8.6100, 20.4000	8.6100, 33.6000
	Day 3	n	7	7	14
		Mean (SD)	23.8000 (6.1030)	19.0571 (8.0961)	21.4286 (7.3143)
		Median	23.3000	17.3000	21.1000
		Min, Max	13.9000, 30.9000	10.8000, 34.9000	10.8000, 34.9000
	Day 7	n	7	6	13
		Mean (SD)	24.4857 (6.4323)	20.0167 (4.8118)	22.4231 (5.9759)
		Median	26.4000	19.5000	23.6000
		Min, Max	11.8000, 30.2000	13.7000, 27.0000	11.8000, 30.2000
Parameter	**Analysis Visit**		**Japanese**	**Caucasian**	**Overall**
T_{max} (h)	Day 1	n	7	7	14
		Mean (SD)	0.1547 (0.0891)	0.1786 (0.0891)	0.1667 (0.0865)
		Median	0.0833	0.2500	0.1667
		Min, Max	0.0833, 0.2500	0.0833, 0.2500	0.0833, 0.2500

	Day 3	n	7	7	14
		Mean (SD)	0.2262 (0.0630)	0.1547 (0.0891)	0.1905 (0.0829)
		Median	0.2500	0.0833	0.2500
		Min, Max	0.0833, 0.2500	0.0833, 0.2500	0.0833, 0.2500
	Day 7	n	7	7	14
		Mean (SD)	0.2024 (0.0813)	0.1786 (0.0891)	0.1905 (0.0829)
		Median	0.2500	0.2500	0.2500
		Min, Max	0.0833, 0.2500	0.0833, 0.2500	0.0833, 0.2500
Parameter	**Analysis Visit**		**Japanese**	**Caucasian**	**Overall**
$T_{1/2}$ (h)	Day 1	n	7	5	12
		Mean (SD)	0.4935 (0.0994)	0.3864 (0.1616)	0.4488 (0.1339)
		Median	0.4537	0.3880	0.4407
		Min, Max	0.3907, 0.6661	0.2160, 0.6251	0.2160, 0.6661
	Day 3	n	7	7	14
		Mean (SD)	0.4860 (0.0443)	0.4765 (0.1447)	0.4813 (0.1029)
		Median	0.5001	0.4555	0.4896
	Day 7	n	7	6	13
		Mean (SD)	0.4911 (0.0691)	0.5261 (0.0946)	0.5072 (0.0803)
		Median	0.4727	0.5189	0.5018
		Min, Max	0.3799, 0.5809	0.4010, 0.6773	0.3799, 0.6773

Source: CSR 01171502, Table 14.3.2
Abbreviations: AUC0-8h = area under the concentration curve at time = 0 to 8 hours; AUCinf = area under the concentration curve at time = infinity; Cmax =maximum concentration; Min = minimum, Max = maximum, pg= picogram(s); SD = standard deviation; Tmax = time to maximum concentration. Data from subjects whose pharmacokinetic parameters were not calculated were excluded from mean and SD calculation.
\\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\01171502\01171502-csr-body.pdf

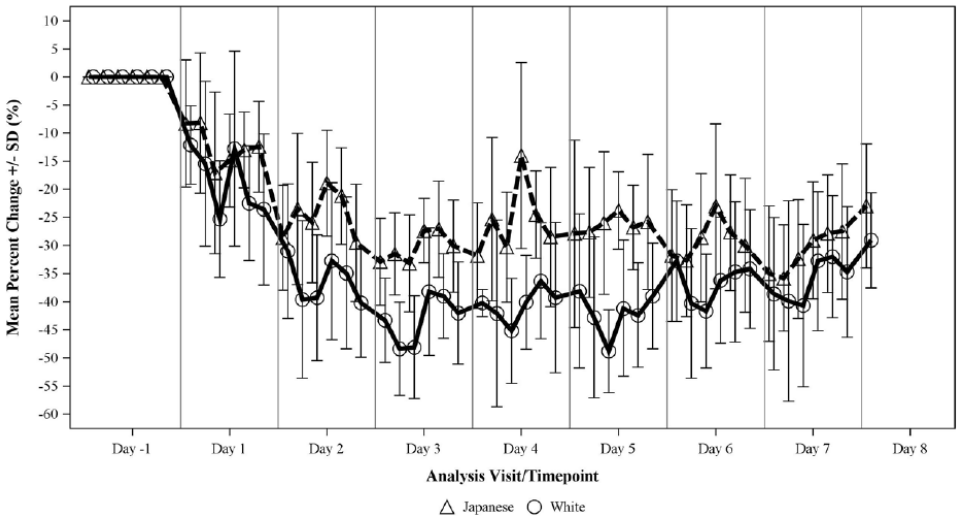
Mean diurnal IOP (SD) at baseline was 14.8 (1.49) mmHg for Japanese subjects and 15.1 (1.84) mmHg for Caucasian subjects. Reduction from baseline in mean IOP was observed starting from approximately 2 hours after the start of dosing on Day 1 (Figure 3 and Figure 4). The maximum IOP-lowering effect occurred by Day 3, and this was then sustained through the end of dosing. Following 7 days of dosing, mean (SD) diurnal IOP reduction from baseline was 4.92 (1.37) mmHg (33.2%) for the Japanese subjects and 5.41 (1.67) mmHg (35.8%) for the Caucasian subjects.

Figure 3. Intraocular Pressure: Raw Mean (+-SD) of Percent Change from Baseline over Time (Right Eye)



Source: CSR 01171502, Table 14.2.2.3.1
\\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\01171502\01171502-csr-body.pdf

Figure 4. Intraocular Pressure: Raw Mean (+-SD) of Percent Change from Baseline over Time (Left Eye)



Source: CSR 01171502, Table 14.2.2.3.2
\\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\01171502\01171502-csr-body.pdf

A total of 7 adverse events (in 14 subjects) were reported in this study. All adverse events were judged to be related to study drug administration; were of mild severity, non-serious, did not require dose adjustment/discontinuation and resolved without treatment.

Reviewer's comments: Plasma omidenepag concentration after ocular instillation of 0.0025% OMDI ophthalmic solution reached maximum concentration (Cmax) at 0.1667 to 0.2500 h after instillation, decreased with terminal half-lives ($T_{1/2}$) of 0.449 to 0.5072 h, and was below the lower limit of quantitation (LLOQ<1.00 pg/mL) after 4 hours post-instillation. in the overall population on Days 1, 3, and 7. The reviewer confirmed the PK parameters reported by the Applicant by performing NCA analysis using plasma concentration data from this study and observed similar values. Pharmacokinetic parameters of omidenepag were similar between Japanese and Caucasian subjects. There was no systemic accumulation of omidenepag after 7 days of dosing of OMDI 0.0025% QD. OMDI also demonstrated reduction in IOP over seven days' time period tested in this study.

It should be noted that this was only clinical study of OMDI in which the reduction in IOP was assessed immediately after the start of dosing (the earliest post dosing IOP assessments in other studies were at 1-week post dosing). Therefore, this study also provides information regarding the time to the onset of IOP-lowering and the time to the maximum IOP-lowering effect of OMDI. The dose used in this study, 0.0025% QD, is slightly higher than the dose in the regimen being proposed in this NDA, 0.002% QD. The Applicant justified the use of this dose by stating that dose-finding study 01171503 Stage 1 compared QD dosing of 0.0025% and 0.002% and found no clinically significant difference in IOP lowering. They further claim that approximate time to onset and maximum IOP lowering for OMDI 0.0025% QD are considered relevant to OMDI 0.002% QD. The Applicant has not conducted dose-response and exposure-response analysis. However, based on above justification about similar IOP lowering effect between 0.0025% and 0.002% QD dosing, the justification appears reasonable.

4.2 In Vitro Metabolism

4.2.1 Study 543Lg02A- In vitro plasma protein binding of omidenepag (UR-7276)

The protein binding of omidenepag in the plasma of human was determined by equilibrium dialysis for 6 hours at initial concentrations of 0.25, 2.5 and 20 ng/mL in plasma chamber. Plasma protein binding was also studied for male rat, male rabbit, monkey plasma but results from only human plasma protein are discussed below The concentrations of omidenepag in buffer chamber for 0.25 ng/mL concentration was BLQ. For 2.5 and 20 ng/mL concentrations, omidenepag was highly bound to plasma protein from human (Table 6), with mean percent bound 97.8% demonstrating that omidenepag was highly bound to plasma proteins. The binding was independent of concentration between 2.5 and 20 ng/mL.

Table 6: Protein binding of UR-7276 in human plasma after dialysis

Initial concentration (pg/mL)	Concentration (pg/mL)			Protein binding ratio (%)		Recovery (%)
	Plasma chamber	Buffer chamber		Unbound	Bound	
250	215	< 12.55*		< 5.8	> 94.2	> 86.0
	206	< 12.55*		< 6.1	> 93.9	> 82.4
	231	< 12.55*		< 5.4	> 94.6	> 92.4
			Mean	< 5.8	> 94.2	> 86.9
2500	2100	47.4		2.3	97.7	86.8
	2100	44.9		2.1	97.9	86.7
	2120	45.6		2.2	97.8	87.5
			Mean	2.2	97.8	87.0
20000	18700	422		2.3	97.7	96.7
	19700	411		2.1	97.9	101.6
	18400	396		2.2	97.8	95.0
			Mean	2.2	97.8	97.8

* Below lower limit of quantification

Source: Table 7, Study 543Lg02A Nonclinical Study Report. \\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\422-pk\4223-distrib\543lg02a\543lg02a-pre-clinical-study-report.pdf

4.2.2 Study 8309291- In vitro blood-to-plasma partitioning of omidenepag (^{14}C-UR-7276)

Following whole blood incubations in vitro, omidenepag (^{14}C-UR-7276) was observed to be stable and primarily partitions into the extracellular component of blood with minimal association with the cellular component. The mean blood to plasma concentration ratios were ranging from 0.505 to 0.634 (Table 7). No concentration dependence was observed over the target concentration range of 1 to 100 ng/mL of ^{14}C-UR-7276.

Table 7: The blood-to-plasma partitioning of ^{14}C-UR-7276 in human blood

Species	Concentration (ng/mL)	Blood-to-Plasma Concentration Ratio			Percent Associated with Cellular Components		
		Replicate	Mean	SD	Replicate	Mean	SD
Human 1	1	0.520	0.567	0.0768	0.00	1.05	1.82
Hct = 36.5%		0.656			3.15		
		0.526			0.00		
	10	0.670	0.641	0.0441	5.27	3.14	2.78
		0.663			4.15		
		0.590			0.00		
	100	0.560	0.520	0.0498	0.00	0.00	0.00
		0.536			0.00		
		0.464			0.00		
Human 2	1	0.617	0.625	0.00725	3.54	4.82	1.11
Hct = 40.5%		0.629			5.37		
		0.630			5.56		
	10	0.576	0.562	0.103	0.00	3.20	5.54
		0.658			9.60		
		0.453			0.00		
	100	0.567	0.532	0.0384	0.00	0.00	0.00
		0.539			0.00		
		0.491			0.00		
Human 3	1	0.563	0.571	0.00723	1.78	3.20	1.23
Hct = 44.8%		0.575			3.96		
		0.575			3.87		
	10	0.680	0.634	0.0401	18.8	12.6	5.34
		0.607			8.96		
		0.615			10.2		
	100	0.507	0.505	0.0268	0.00	0.00	0.00
		0.531			0.00		
		0.477			0.00		

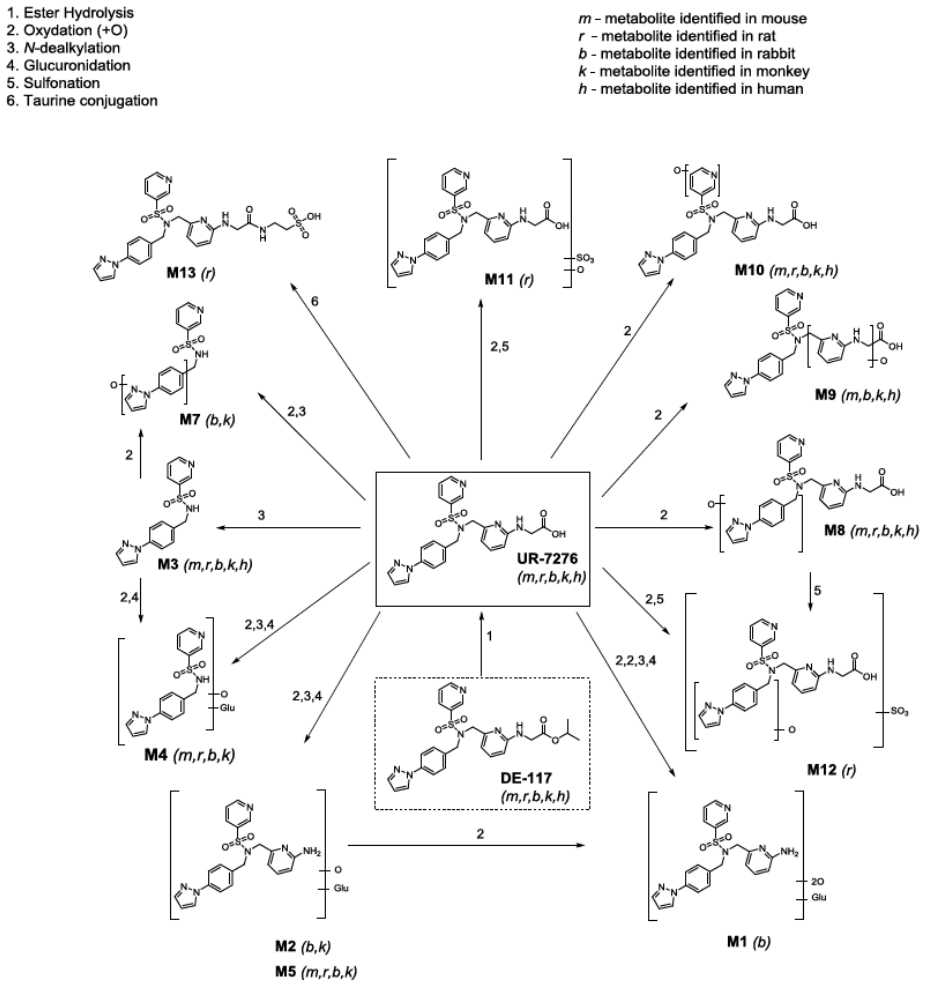
Hct Hematocrit.
SD Standard deviation.

Source: Table 2, Study 8309291 Nonclinical Study Report. \\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\422-pk\4223-distrib\8309291\8309291-pre-clinical-study-report.pdf

4.2.3 Study 8309287- In vitro metabolites of ^{14}C-OMDI in Hepatocytes

The metabolism of ^{14}C-OMDI was studied in in vitro assays using mouse, rat, rabbit, monkey, and human hepatocytes. ^{14}C-OMDI was incubated with hepatocytes at 1 or 10 µM for 0, 30, 60, or 120 minutes. The metabolism of 14C-OMDI in all species was nearly complete (< 7.5% remaining) at the first time point at 30 minutes at both concentrations. The major metabolite at 30 minutes was the hydrolysis product, UR-7276, for all species. Further, thirteen metabolites were identified; the hydrolysis product UR-7276, M3 (N-dealkylation), M8 (oxidation of UR-7276), and M10 (oxidation of UR-7276) were the major metabolites present in all species. The metabolism of 14C-OMDI involved hydrolysis, oxidation, N-dealkylation, glucuronidation, sulfonation, and taurine conjugation. Metabolism of UR-7276 was lowest in human hepatocytes. The proposed biotransformation pathways of OMDI in hepatocytes from mouse, rat, rabbit, monkey and human based on identified metabolites are presented below.

Figure 5. OMDI metabolite profiling



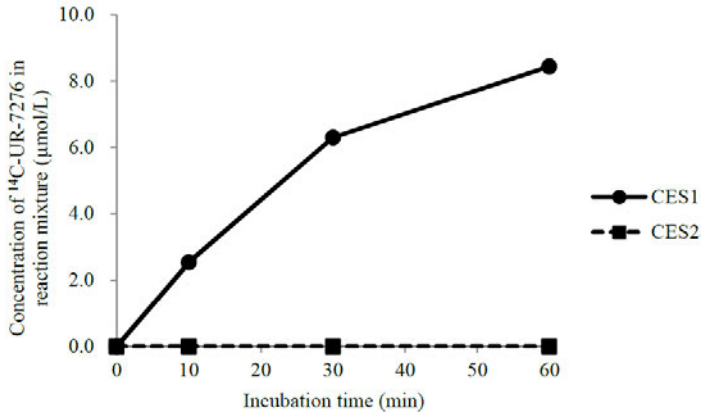
Source: Study 8309287 Final report, page 8. \\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\422-pk\4224-metab\8309287\8309287-pre-clinical-study-report.pdf

4.2.4 Study 387LI01A- In Vitro Metabolism of ^{14}C-OMDI by Human Carboxylesterases CES1 and CES2

In vitro metabolism of ^{14}C-OMDI (10 µmol/L) by human carboxylesterase (CES1 and CES2)-was assessed in bactosomes expressing CES1 and CES2 by incubating them with CES1 or CES2 for 0, 10, 30 and 60 minutes. A decrease in the concentration of OMDI in the reaction mixture and generation of omidenepag were observed only in the presence of CES1 (

Figure 6)

Figure 6. Time-dependent concentrations of omidenepag in reaction mixtures incubated with recombinant human CES1 or CES2 enzyme

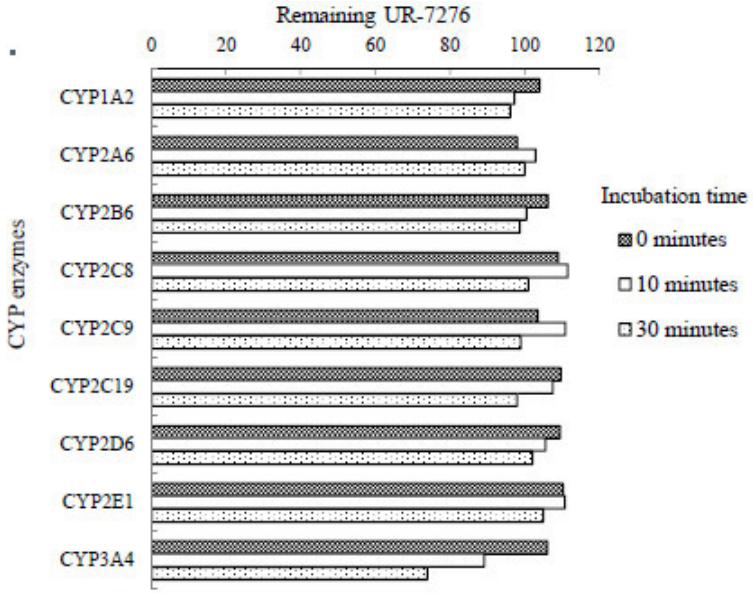


Source: 387Ll01A-analytical report, Figure 1. \\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\387ll01a\387ll01a-analytical-report.pdf

4.2.5 Study 516Lj03A- Identification of CYP Isozymes Involved in the Metabolism of Omidenepag

The metabolism of omidenepag (UR-7276, 5 nmol/L) with CYP enzymes was assessed using recombinant human CYP enzymes. As shown in Figure 7, UR-7276 was mainly metabolized by human CYP3A4 while other CYP enzymes, CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1, had little metabolic activity.

Figure 7. Metabolism of omidenepag by recombinant human CYP enzymes



Source: Study 516Lj03A Final report, Figure 4. \\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\516lj03a\516lj03a-analytical-report.pdf

4.2.6 Study 8309289- Inhibition of Drug Metabolizing Enzymes

Direct and metabolism-dependent inhibition potential of omidenepag using the P450 isozymes-selective marker activities was assessed for cytochromes P450 CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5, and CYP3A4/5 subgroups, respectively as recommended by the FDA guidance. The data showed that omidenepag was observed to inhibit CYP3A4/5 activity with a calculated IC_{50} value of 5.04 μM (Table 8). Additionally, omidenepag was a mild direct inhibitor of CYP2C19 andCYP3A4/5 activity (Table 8) while it did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2D6 isoform selective activities. Further, omidenepag did not demonstrate metabolism-dependent inhibition of any of the cytochrome P450 activities tested under the conditions of this study (Table 8).

Table 8. Summary of inhibition on human hepatic CYP isoenzymes by omidenepag

P450 Isoenzyme	Activity Assay	Direct Inhibition (Maximum inhibition %)	Metabolism-Dependent Inhibition
CYP1A2	Phenacetin *O*-deethylase	<10	NA
CYP2B6	Bupropion hydroxylase	<10	NA
CYP2C8	Amodiaquine *N*-deethylase	<10	NA
CYP2C9	Diclofenac 4′-hydroxylase	<10	NA
CYP2C19	*S*-Mephenytoin 4′-hydroxylase	17.0	NA
CYP2D6	Bufuralol 1′-hydroxylase	<10	NA
CYP3A4/5	Testosterone 6β-hydroxylase	27.0	NA
CYP3A4/5	Midazolam 1′-hydroxylase	64.0 (IC_{50}=5.04 μM)	NA

IC_{50} The concentration of the test article that inhibits 50% of the activity of an isoenzyme specific assay. NA Not applicable.

Source: Table 1, Study 8309289 analytical report. \\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\8309289\8309289-analytical-report.pdf

Reviewer's comments:

- *Omidenepag at 10 μmol/L inhibited the metabolic activities of CYP2C19 by 17% and inhibited the metabolic activities of CYP3A4/5 (IC_{50} = 5.04 μmol/L). In the assessment of metabolism-dependent inhibition, omidenepag inhibited the metabolic activities of CYP1A2 by 68.9% only at 10 μmol/L. Based on literature search, the Applicant stated that the mRNA for these CYP isozymes was not detected locally in the eye.*

- *Assuming that, after ocular instillation of 0.002% OMDI ophthalmic solution at the proposed dose (1.2 μg/person given as single bilateral administration of one drop = approximately 30 μL/eye), all administered OMDI is transited to the GI tract since, the estimated omidenepag concentration in the GI lumen is approximately 72 nmol/L if the gastric fluid volume is assumed to be 35 mL. In addition, the Cmax of the omidenepag concentration in plasma was approximately 35 pg/mL (≈ 0.073 nmol/L) after repeated bilateral ocular instillation of 0.0025% OMDI ophthalmic solution in humans QD for 7 days. These systemic (approximately 0.073 nmol/L) and estimated gastric concentrations (approximately 72 nmol/L) of omidenepag are order of magnitude lower than the concentration at which interactions are likely to occur (mostly at the μmol/L level).*

Therefore, from a safety perspective clinically significant differences in the systemic PK of omidenepag were studied due to DDI appears minimal.

- *The intended site of drug delivery and action is the eye, and both clinically relevant drug transporter and metabolizing enzymes are not present in the eye. Therefore, the extent of systemic exposure does not relate with the proposed drug product's efficacy.*

4.2.7 Study 8313224: Inhibitory Effects of OMDI and Omidenepag on Transporter Activities

OMDI and UR-7276 were assessed for potential interactions with human transporters including MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, and BSEP. As shown in Table 9, 14C-OMDI is not a substrate of the transporters tested. OMDI showed inhibition of MATE1, MATE2-K, OAT3, OATP1B1, OATP1B3, OCT1, and BSEP, but not other transporters tested. IC_{50} values were estimated to be approximately 5 μM for MATE2-K and >5 μM for MATE1, OATP1B3, and BSEP. IC50 values were determined to be 8.96, 2.26, and 1.89 μM, respectively, for OAT3, OCT1, and OATP1B1. 14C-UR-7276 is a substrate of OAT3, OATP1B1, OATP1B3, and P-gp, but not other transporters tested (Table 9). UR-7276 showed inhibition of MATE2-K, OAT3, OATP1B1, OATP1B3, and P-gp, but not other transporters tested (Table 9). IC50 values were estimated to be >5 μM for MATE2-K, OATP1B3, and P-gp. IC50 values were determined to be 7.13 and 1.80 μM, respectively, for OAT3 and OATP1B1 (Table 9).

Table 9. Summary of OMDI or UR-7276 as a substrate or inhibitor of human drug transporters

Transporter	Substrate	Inhibitor	IC_{50} (µM)
		OMDI	
MATE1	No	Yes	>5
MATE2-K	No	Yes	~5
OAT1	No	No	NA
OAT3	No	Yes	8.96
OCT1	No	Yes	2.26
OCT2	No	No	NA
OATP1B1	No	Yes	1.89
OATP1B3	No	Yes	>5
P-gp	No	No	NA
BCRP	No	No	NA
BSEP	No	Weak	>5
		UR-7276	
MATE1	No	No	NA
MATE2-K	No	Yes	>5
OAT1	No	No	NA
OAT3	Yes	Yes	7.13
OCT1	No	No	NA
OCT2	No	No	NA
OATP1B1	Yes	Yes	1.80
OATP1B3	Yes	Yes	>5
P-gp	Yes	Weak	>5
BCRP	No	No	NA
BSEP	No	No	NA

NA Not applicable, ~ Approximately.

Source: Table 1, Study 8313224 analytical report. \\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\8313224\8313224-analytical-report.pdf

Reviewer's comments:

- *In vitro assays demonstrated that while OMDI was not a substrate for the tested transporters, omidenepag is a substrate for OAT3, OATP1B1, OATP1B3, and P-gp. In addition, OMDI inhibited MATE1, MATE2-K, OAT3, OCT1, OATP1B1, OATP1B3, and BSEP, and omidenepag inhibited MATE2-K, OAT3, OATP1B1, OATP1B3, and P-gp.*

- *The Applicant assessed the drug interactions mediated by drug transporters using a literature search (using the ADME Database from Fujitsu Kyushu Systems) to determine if the transporters were affected by potential concomitant use of drugs for glaucoma and OHT with OMDI ophthalmic solution. FP receptor agonists (Latanoprost, Travoprost, and Bimatoprost), β-Blockers (Timolol), and CAIs (Acetazolamide) have been reported to be substrates of P-gp; CAIs (Acetazolamide and Methazolamide) have been reported to be inhibitors of P-gp and OAT3. It was reported that neither P-gp protein nor its mRNA and no OAT3 mRNA are found in the human cornea, which is known to be an intraocular pathway for drugs instilled via the ocular route.*

- *Further, as discussed above, the systemic (approximately 0.073 nmol/L) and estimated gastric concentrations (approximately 72 nmol/L) of omidenepag are much lower than the inhibitory concentrations of omidenepag for P-gp (IC_{50} > 5 μmol/L) and OAT3 (IC_{50} = 7.13 μmol/L), or that of OMDI for OAT3 (IC_{50} = 8.96 μmol/L). Furthermore, the incidence of systemic adverse drug reactions is very low after bilateral ocular instillation of OMDI ophthalmic solution to humans. Therefore, the possibility of transporter-mediated drug-drug interaction of omidenepag either in the eyes or in the rest of the body appears low.*

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