

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 215092

Supporting SD 1 (new NDA, submitted 11/19/2020)

document/s: SD 6 (response to Nonclinical Information Request (IR), submitted 1/15/2021)

SD 9 (response to Nonclinical IR, submitted 3/09/2021)

SD 12 (response to Nonclinical IR, submitted 4/15/2021)

CDER stamp date: November 19, 2020

Product: Omidenepag isopropyl ophthalmic solution, 0.002%

Indication: Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension

Applicant: Santen Incorporated
Emeryville, California 94608

Review Division: Division of Pharmacology Toxicology (DPT) for Rare Diseases, Pediatrics, Urology & Reproductive Medicine and Specialty Medicine (DPT-RURPM/SM)

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1 Executive Summary

1.1 Introduction

- Santen Incorporated (Santen) submitted an original new drug application under the 505(b)(1) pathway for omidenepag isopropyl (DE-117) ophthalmic solution, 0.002% (0.02 mg/ml) for reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.
 - o DE-117 was developed under IND 111518.
 - o Reportedly, omidenepag isopropyl ophthalmic solution 0.002% received approval in Japan in 2018 for treatment of glaucoma and ocular hypertension.¹

1.2 Brief Discussion of Nonclinical Findings

Omidenepag isopropyl is a small molecule pro-drug; its main metabolite, omidenepag, exhibits intended pharmacology (lowering of intraocular pressure (IOP) in animal models.

Primary pharmacology: EP2

- The prostaglandin E receptor family has four known members: EP1, EP2, EP3, and EP4.
- EP2 is a G protein-coupled transmembrane protein with wide tissue expression, including the eye (corneal epithelium, corneal choriocapillaris, conjunctiva, trabecular meshwork and Schlemm's canal, iris and ciliary body, retina), gastrointestinal (GI) tract, lung, heart, liver, kidneys, and bone.
- EP2 has high affinity for endogenous prostaglandin E2 (PGE2, dinoprostone). Dinoprostone is also an FDA-approved drug.
- Current approved anti-glaucoma medicines (e.g., latanoprost, bimatoprost, travoprost, carboprost) are agonists for the prostaglandin F2 α receptor (PGF2 α).

Pharmacology: *in vitro* data

- Omidenepag isopropyl has moderate binding affinity for EP2 (IC₅₀ = 52.06 ng/ml).
- Omidenepag is a high-potency agonist of EP2 (IC₅₀ and EC₅₀ values ranging from 4.79 to 3.45 ng/ml), and weak affinity for other prostaglandin receptors (EP4 and DP1).
- A secondary pharmacology screen did not detect other specific binding for either omidenepag isopropyl or omidenepag.

Pharmacology: *in vivo* data

- Topical ocular omidenepag isopropyl decreased IOP in ocular normotensive rabbits and monkeys, and in a monkey model of ocular hypertension.

¹ Duggan S. 2018. Omidenepag isopropyl ophthalmic solution 0.002%: first global approval. *Drugs*. 78(18):1925-1929. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/30465134/>

- A mechanistic study in monkeys observed that topical ocular omidenepag isopropyl did not affect the aqueous flow rate.
- Intravitreal administration of omidenepag isopropyl to monkeys exhibited IOP lowering with slow clearance.
- An inhalation safety pharmacology study in the dog was conducted, and submitted to the NDA for completeness of record. The inhalation doses tested are too high to be achieved by topical ocular dosing.

PK/ADME

- Omidenepag bound tightly to plasma protein, with no apparent species differences among human, monkey, rabbit; binding was slightly lower for the rat.
- Omidenepag did not preferentially partition to the cellular components of blood.
- A comparative hepatocyte metabolism study observed rapid metabolism, without unique human metabolites.
- A monkey topical ocular single dose study was conducted to evaluate ocular distribution.
 - o Cornea > bulbar conjunctiva > trabecular meshwork > palpebral conjunctiva > sclera > aqueous humor > iris > ciliary body > choroid-retinal pigmented epithelium (RPE) > plasma > blood
 - o Systemic exposure (i.e. plasma) was detected, with rapid clearance ($t_{1/2}$ = 23 minutes).
 - o Exposure of the retina to omidenepag was detected, but the clearance half-life could not be calculated.
- A rat excretion study evaluated topical ocular dosing.
 - o Fecal excretion was the primary route of elimination; urine was minor (3-4%), and no radiolabel was detected in expired air.
 - o Elimination was rapid, with most of the label cleared within 24 hours-post dose, and all label cleared by 72 hours post-dose.
 - o Testing bile duct cannulated rats observed that 50% of the excreted dose following topical ocular dosing was biliary (i.e. at least 50% of administered dose reached systemic circulation and was then cleared by the liver into bile).
- In rats, no placental transfer or lactational exposure was detected.
 - o Because the lower limits of quantitation (LLOQ) for analytes in the placental transfer study were close to the in vitro IC_{50} and EC_{50} values, it is not clear that gestational exposure is negligible.

Toxicology

Nonclinical exposure margins for labeling were based on the NDA reporting of a clinical AUC of 27.0 pg*h/ml for omidenepag, following bilateral once daily topical ocular dosing of omidenepag isopropyl 0.0025% eye drops.

The general toxicology study package spans two species: two topical ocular monkey studies, and a series of subcutaneous-route studies in the Sprague Dawley rat.

SD rat subcutaneous-route repeat dose toxicity studies

- The GLP rat 13-week subcutaneous toxicity study with omidenepag isopropyl identified a high-dose NOAEL, 0.003 mg/kg/day, excepting that the ophthalmoscopy and ocular histopathology were not fully adequate.
- The GLP rat 26-week subcutaneous toxicity study with omidenepag isopropyl did not identify a NOAEL, because rare tumors were observed with treatment. The low-dose was 0.003 mg/kg. This study had the same limitations as the 13-week sc study, for ophthalmoscopy and ocular histopathology not being not fully adequate.
- The rat sc studies did not include histopathology of the nasal turbinates / nasal cavity.

Cynomolgus monkey topical ocular repeat dose toxicity studies

- The GLP monkey 13-week topical ocular toxicity study with omidenepag isopropyl did not identify a NOAEL. The low-dose, 0.9 µg/eye/day (0.003% administered left eye (OS) only once daily for 90 days (QDx90)) caused:
 - o Respiratory nasal cavity olfactory epithelium metaplasia, recovery not demonstrated
 - o Vestibular nasal cavity increased goblet cell respiratory epithelium mucosa. Recovery was apparent after cessation of dosing.
 - o Pharmacological activity (decreased IOP), recovery observed.
 - o Miosis and increased corneal thickness, recovery observed.
- The GLP monkey 39-week topical ocular toxicity study with omidenepag isopropyl did not identify a NOAEL. The low-dose, 0.9 µg/eye/day (0.003% administered left eye (OS) only once daily for 90 days (QDx90)) caused:
 - o Increased incidence and severity of nasal cavity epithelial metaplasia; recovery not demonstrated
 - o Recoverable decreased IOP, miosis, and increased corneal thickness.
- Reporting for both monkey topical ocular studies was inadequate to evaluate the potential effects of omidenepag on iris color.

Genetic toxicology for omidenepag isopropyl

- Inadequate bacterial reverse mutation test
- Positive *in vitro* mouse lymphoma assay (MLA)
- Inadequate rat micronucleus assay

Carcinogenicity plan

- Rodent bioassays have not been conducted.
- The results of the 26-week rat subcutaneous toxicity study, and the monkey topical ocular studies, are concerning.

Developmental and reproductive toxicity (DART) studies

Submitted studies are adequate and support labeling:

- GLP rat fertility and early embryofetal development (FEED) study
- GLP rat and rabbit embryofetal development (EFD) studies
- GLP rat pre- and post-natal development (PPND) studies
- Rat study omidenepag placental transfer and lactation study

Other toxicity studies

- The ultraviolet absorption profile of omidenepag isopropyl indicates it may be phototoxic. Miosis was observed in monkeys. The Applicant reports that photophobia is a common adverse event. Therefore, the value of further photosafety testing is obviated.
- Omidenepag isopropyl 0.003% applied to the upper eyelids of pigmented mice did not affect eyelash growth.

1.3 Recommendations

1.3.1 Approvability

P/T has no objection to approval, presuming concurrence is reached for labeling.

1.3.2 Additional Non Clinical Recommendations

Information Requests (IR)

[Review note: On May 27, 2021, P/T requested that these IRs be conveyed to the Applicant. Resolution of these issues is pending]

1. *Regarding the bacterial reverse mutation test of UR-7385 (report # (b) (4) 102-224), the S9 metabolic activation system was obtained from the (b) (4) lot # 11052002. The study report did not include information showing that the S9 was active. We do not consider 2-aminoanthracene as the sole positive control +S9 to be an indicator of the potency of the S9 mix. Each batch of S9 should also be characterized with a mutagen that requires metabolic activation by microsomal enzymes, e.g., benzo(a)pyrene, dimethylbenzanthracene.*

If data are available demonstrating the activity of the S9 mix, submit them to the NDA.

2. *Regarding monkey aqueous humor dynamics study (report # 502Qm030), outflow facility and uveoscleral outflow data were withheld for 7/15 treated monkeys. If available, please provide all numerical fluorescein scanning data. Please provide step-by-step explanations of each data transformation / calculation.*
3. *Regarding the rabbit embryofetal development (EFD) historical control data submitted to the NDA on April 15, 2021 to support review of the rabbit EFD study (report # (b) (4) 102-294), the fetal anomaly data for each endpoint show the total number of fetuses, dams, and studies, and the number of fetuses with each observation. It is not clear from the tabulation what the terms "Mean", "Mean frequencies (%)", and "Max" represent. Numerically, the "Mean" values do not*

appear to be the mean incidences or percentages on a per fetus, per litter, or per study basis. Generally, we would expect "Max" to represent the maximum number of observations in a study, or the number of affected litters in a study (i.e. a whole number). Please explain.

Recommendations for postmarketing requirements (PMRs)

1. If the previously submitted bacterial reverse mutation assay cannot be shown to be adequate, P/T would recommend requiring submission of an adequate test for gene mutation in bacteria, consistent with ICH M3(R2) and ICH S2(R1). As discussed below, ICH S2(R1) cites Gatehouse et al. 1994, which explains and stresses the importance of not using 2-aminoanthracene as the only positive control to check the metabolizing capacity of S9 mix.
2. The *in vivo* rat micronucleus test (report # (b) (4) 02-226) dose selection was inadequate. The authors considered the 4 mg/kg/day high-dose to be the maximum feasible dose (MFD), based on solubility: 0.4 mg/ml (0.04%) solution, administered subcutaneously at a volume of 10 ml/kg. However, the Applicant has subsequent nonclinical data testing other formulations, up to 1% omidenepag isopropyl, which would allow a 25-fold increase in dose. Additionally, omidenepag isopropyl is soluble in dimethylsulfoxide (DMSO) at 483 mg/ml (actual, 500 mg/ml nominal). Depending on the dose of DMSO considered tolerable for the rodent study, a top dose at or near the limit dose of 5000 mg/kg may be feasible.

P/T recommends that an adequate *in vivo* test for genotoxicity be required, consistent with ICH S2(R1).

1.3.3 Labeling

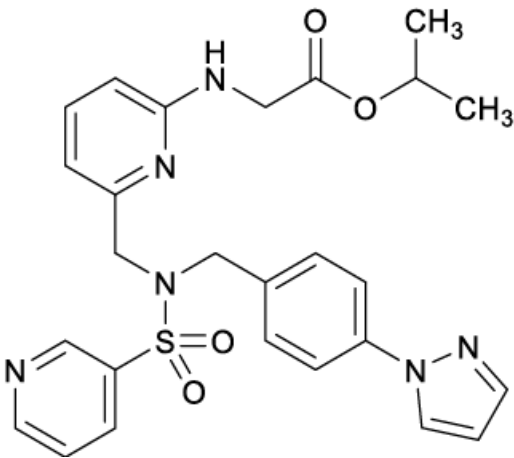
The Applicant provided draft labeling in the original (11/19/2020) NDA submission. Notes:

- The abbreviation EP2 should be explained the first time it appears.
- Dinoprostone is the naturally occurring form of prostaglandin E2 (PGE2), and is an FDA approved drug. From a scientific perspective, PGE2 is well-known as an EP2 receptor agonist; however, this is not explicitly state in labeling.
- Omidenepag isopropyl is a functional (but not structural) prostaglandin analog, and will be the first-in-class EP2 receptor agonist with a non-prostaglandin structure .
- The term 'prostaglandin analogs' has historically referred to approved F2 α prostaglandin analogs. Once drugs against other prostaglandin receptors are approved (e.g., this NDA), more precise terminology is warranted.

(b) (4)

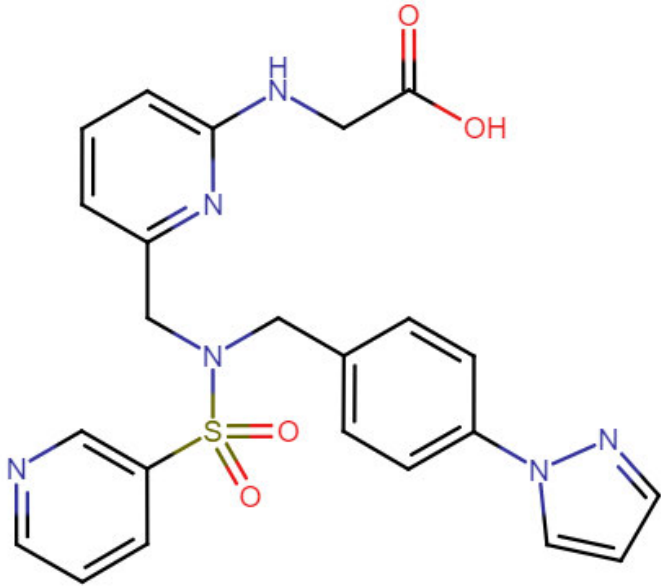
2 Drug Information

2.1 Drug

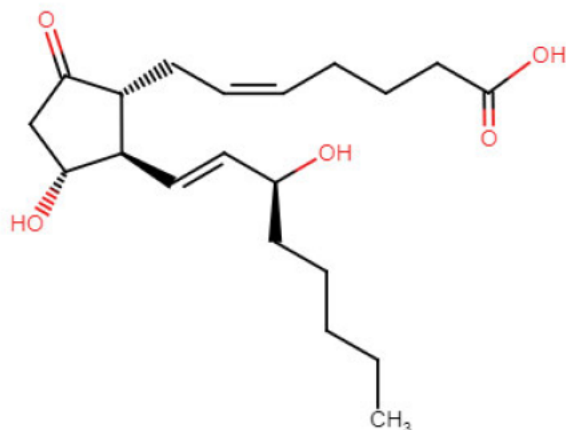
CAS Registry Number	187451-19-9
Generic Name	Omidenepag isopropyl
Code Names	DE-117, DE-117A, UR-7385
Chemical Name	- Glycine, N-[6-[[[4-(1H-pyrazol-1-yl)phenyl]methyl](3-pyridinylsulfonyl)amino]methyl]-2-pyridinyl]-, 1-methylethylester - Propan-2-yl N-{6-[(N-{[4-(1H-pyrazol-1-yl)phenyl]methyl}pyridine-3-sulfonamido)methyl]pyridin-2-yl}glycinate
Molecular Formula	C ₂₆ H ₂₈ N ₆ O ₄ S
Molecular Weight	520.61 g/mol
Structure	Figure 1: Structure of omidenepag isopropyl 
Pharmacological Class	Prostaglandin E2 (EP2) receptor agonist

2.1.1 Active Metabolite

Omidenepag isopropyl is the prodrug of omidenepag.

CAS Registry Number	1187451-41-7
Generic Name	Omidenepag
Code Names	UR-7276
Chemical Name	N-(6-((N-((4-(1H-pyrazol-1-yl)phenyl)methyl)pyridine-3-sulfonamido)methyl)pyridin-2-yl)glycine
Molecular Formula	C ₂₃ H ₂₂ N ₆ O ₄ S
Molecular Weight	478.5 g/mol
Structure	Figure 2: Structure of omidenepag  The chemical structure of omidenepag is shown. It features a central sulfonamide group (SO₂NH-) connecting three main fragments: a 4-(1H-pyrazol-1-yl)phenyl group, a 6-((N-((4-(1H-pyrazol-1-yl)phenyl)methyl)pyridine-3-sulfonamido)methyl)pyridin-2-yl group, and a glycine moiety (CH₂CH₂COOH). The pyridine ring is substituted at the 2-position with the sulfonamide group and at the 6-position with a methyl group. The phenyl ring is substituted at the 4-position with a 1H-pyrazol-1-yl group. The glycine moiety is attached to the nitrogen of the sulfonamide group via its amine nitrogen.

- The Applicant considers the structure of omidenepag to be “non-prostaglandin structure”. This is technically accurate. For context, the structure for prostaglandin E₂ (PGE₂; CAS # 353-24-6) is:

Figure 3: Structure of PGE2

2.2 Relevant INDs and DMF

- DE-117 ophthalmic solution was developed under IND 111518. The NDA includes a cross-reference² to the information previously submitted to the IND. (<\\CDSESUB1\\evsprod\\IND111518\\111518.enx>).
- Santen opened (b) (4)
- The NDA has a letter of authorization from (b) (4) authorizing reference to their entire DMF (b) (4) for the manufacture of the omidenepag isopropyl drug substance.

² Accessed via: <\\CDSESUB1\\evsprod\\nda215092\\0001\\m1\\us\\14-references\\cross-reference-to-previously-submitted-information-ind-1115.pdf>

2.3 Drug Formulation

The drug product formulation is reported in multiple NDA modules, including module 2.3.P Drug Product:

Table 1: Omidenepag isopropyl ophthalmic solution 0.002% formulation

Ingredient	Final concentration (%w/v)	Quantity (mg/ml)
Omidenepag isopropyl	0.002	0.02
Sodium citrate (b) (4)	(b) (4)	
(b) (4)		
Citric acid monohydrate		
Polyoxyl 35 castor oil		
Benzalkonium chloride (BAK)		
Edetate disodium		
Glycerin		
Sodium hydroxide / hydrochloric acid	Adjust pH (b) (4)	Adjust pH (b) (4)
Water for injection	(b) (4)	

- “The drug product is a sterile, isotonic, aqueous solution (b) (4)
(b) (4)
- The history of the drug product formulation is summarized in NDA module 3.2.P.2 Drug Product – Pharmaceutical Development – Drug Product.³
 - The formulation used in the GLP 13-week topical ocular monkey study (report # (b) (4) 102-212) matched the formulation used for the US Phase 1 and 2 clinical trials.
 - The formulation used in the GLP 39-week topical ocular monkey study (report # B-7689) matches the formulation used for the Phase 3 clinical trials.
- The main difference in the formulations (b) (4)
(b) (4)

³

(b) (4)

- The Applicant reports:
 - The omidenepag isopropyl drug substance “is practically insoluble in water”. (b) (4)
 - BAK (b) (4)% is added as an antimicrobial preservative.
 - The edetate disodium (b) (4)
 - Glycerin is (b) (4)

2.4 Comments on Novel Excipients

No concerns identified; the drug product does not have any novel excipients. The Applicant reports that all of the excipients are USP or NF grade.

2.5 Comments on Impurities/Degradants of Concern

No concerns identified.

- (b) (4) is the only identified impurity.

2.6 Proposed Clinical Population and Dosing Regimen

From the Applicant’s proposed Prescribing Information:

Indications and usage	<i>“(omidenepag isopropyl ophthalmic solution, 0.002%) is a prodrug of omidenepag, a selective EP2 receptor agonist, indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension”</i>
Dosage and administration	<i>“The recommended dosage is one drop in the affected eye(s) once daily in the evening.”</i>
Dosage form and strength	Ophthalmic solution containing 0.02 mg/mL of omidenepag isopropyl
Notable warning and precaution	The drug product <i>“should be used with caution in patients</i> (b) (4)

- Because omidenepag is itself a prostaglandin analog (targeting the EP2) receptor, P/T recommends that the warning and precaution wording specify F2α

2.7 Regulatory Background

- Santen opened IND 111518 for topical ocular omidenepag isopropyl in 2012.
- Santen submitted the original new NDA 215092 on November 19, 2020.
- In response to P/T information requests (IRs), Santen sent three responses: SD 6 on January 15, 2021; SD 9 on March 9, 2021; and SD 12 on April 15, 2021. The responses are acceptable.

3 Studies Submitted

3.1 Studies Reviewed

Table 2: Ten primary/secondary pharmacology study reports

Report #	Title
(b) (4)-4424-G	Binding Study of UR-7276 to Various Receptors
(b) (4)-4727-G	Binding study of UR-7275 and UR-7385 to prostanoid receptors
584Qm040	Binding Affinities of DE-117 and UR-7276 to Prostanoid Receptors
584Qm050	Agonistic Activities of DE-117 and UR-7276 to EP1, EP2, EP4 and FP Receptors
597Qm020	Binding Affinities of DE-117 and UR-7276 to DP2 Receptor
416Qg030	Effect of UR-7385 ophthalmic solution in GLP candidate formulation on intraocular pressure in ocular normotensive rabbits
416Qg070	Effect of UR-7385 ophthalmic solution on intraocular pressure with repeated dosing for 7 days in ocular normotensive monkeys
416Qg080	Effect of UR-7385 ophthalmic solution on intraocular pressure in laser-induced ocular hypertensive monkeys
502Qm030	Effect of DE-117, a selective EP2 receptor agonist, on aqueous humor dynamics in monkeys
SPI-14074	Intraocular pressure measurement following a single dose administration of omidenepag isopropyl solution via intravitreal and subconjunctival injection in normotensive cynomolgus monkeys

Table 3: Two safety pharmacology study reports

Report #	Title
(b) (4) 048-022	Effect of UR-7276 on potassium currents in hERG transfected CHO cells (non-GLP study)
YVQ0004	UR-7276: Maximum Tolerated Dose and Preliminary Cardiovascular Pharmacology Study by Inhalation Administration to Beagle Dogs

Table 4: Eight pharmacokinetics (distribution and metabolism) study reports

Report #	Title
8253494	Ocular Tissue Distribution of Radioactivity Following Topical Ocular Administration of ¹⁴ C-UR-7385 to Cynomolgus Monkeys
8309292	Absorption, Distribution, Metabolism, and Excretion of ¹⁴ C-DE-117 Following Topical Ocular or Subcutaneous Administration to Rats
AE-7762-G	Distribution to fetus via placenta and excretion to breast milk following subcutaneous administration of ¹⁴ C-DE-117 to SD rats
535WI060	Ocular Pharmacokinetic Evaluation after Single Intravitreal Administration of UR-7385 Sustained Release Formulation in Albino Rabbits ~ Citrate Ester~

543Lg02A	Determination of <i>in vitro</i> plasma protein binding ratio of UR-7276 in rat, rabbit, monkey and human
8309291	<i>In Vitro</i> Blood-to-Plasma Partitioning of ¹⁴ C-UR-7276 in Mouse, Rat, Rabbit, Monkey, and Human
543Lm07A	Metabolite profile of DE-117 in ocular tissues after ocular instillation of 0.03% ¹⁴ C-DE-117 ophthalmic solution to rabbits
8309287	Metabolism of ¹⁴ C-DE-117 in Mouse, Rat, Rabbit, Monkey, and Human Primary Hepatocytes

Table 5: One single-dose toxicity study report

Report #	Title
469Ff050	Measurement of systemic exposure following single topical ocular administration UR-7385 in monkeys

Table 6: Six repeat-dose toxicity study reports

Report #	Title
(b) (4) 102-212	A 13-Week Ocular Toxicity Study of UR-7385 Ophthalmic Solution in Cynomolgus Monkeys Followed by a 4-Week Recovery Period
B-7689	A 39-week ocular toxicity study of DE-117 ophthalmic solution in cynomolgus monkeys with a recovery period of 4 weeks
529Ff030	A 2-week repeated subcutaneous dose toxicity study of UR-7385 in rats
112201	A 4-Week Repeated Subcutaneous Dose Toxicity Study of UR-7385 in Rats
112203	A 4-Week Repeated Subcutaneous Dose Toxicity Study of UR-7385 in Rats - Additional Study
B-7645	A 13-week subcutaneous toxicity study of UR-7385 in rats with a recovery period of 4 weeks
B-7774	A 26-week subcutaneous toxicity study of UR-7385 in rats with a recovery period of 4 weeks

Table 7: Three genotoxicity study reports

Report #	Title
(b) (4) 102-224	A Bacterial Reverse Mutation Test of UR-7385
02-225	A Mouse Lymphoma TK Assay of UR-7385
102-226	A Micronucleus Test of UR-7385 in Rats

Table 8: Four developmental and reproductive toxicology (DART) study reports

Report #	Title
(b) (4) 102-333	A Study for Effects of DE-117 on Fertility and Early Embryonic

	Development up to Implantation by Subcutaneous Administration in Rats
(b) (4) 102-295	Study for Effects of UR-7385 on Embryo-Fetal Development by Subcutaneous Administration in Rats
102-294	A Study for Effects of UR-7385 on Embryo-Fetal Development by Subcutaneous Administration in Rabbits
102-349	A study for effects of DE-117 on pre- and postnatal development, including maternal function by subcutaneous administration in rats

Table 9: Three other toxicity study reports

Report #	Title
104Fm090	A research study of DE-117 on eyelash growth in mice
603Qn020	Effects of omidenepag and prostaglandin F2 α on adipogenesis in 3T3-L1 cells
104Fq080	A research study of the anterior chamber flare measurement after repeated instillation of DE-117 ophthalmic solution alone or in combination with tafluprost ophthalmic solution, latanoprost ophthalmic solution, travoprost ophthalmic solution, and bimatoprost ophthalmic solution for 1 week in cynomolgus monkeys

Table 10: Report on absorption spectrum to support the assessment of phototoxic potential

Wakabayashi, Y. (2018). Certificate of Analysis: UR-7385 and UR7276.
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3.2 Studies Not Reviewed

- Six PK analytical methods and validation reports were submitted to the NDA. With reference to the P/T reviews conducted under IND, these reports are not fully re-reviewed for the NDA.

Table 11: Six nonclinical pharmacokinetics (PK) analytical methods and validation reports

Report #	Title
515Lg01A	Validation of a LC-MS/MS Analytical Method for the Determination of UR-7276 in Rat Plasma
515Lg03A	Partial validation of a LC-MS/MS Analytical Method for the Determination of UR-7276 in Rat Plasma - Change in the analytical instrument
(b) (4) 102-281	Partial validation of an Analytical Method for the Determination of UR-7276 in Rat Plasma by LC-MS/MS
102-293	Validation of an analytical method for the determination of UR-7276

	in rabbit plasma
(b) (4) 102-213	Validation of an Analytical Method for the Determination of UR-7276 in Cynomolgus Monkey Plasma by LC-MS/MS
543Lg01A	Validation of a LC-MS/MS analytical method for the determination of UR-7276 in phosphate buffered saline (PBS) and plasma of rat, rabbit, monkey and human

3.3 Previous Reviews Referenced

- The P/T reviews under the IND 11518 are referenced: Wild 6/14/2011; Aziz 7/11/2012; Bebenek 6/05/2015; Bebenek 12/17/2015; McDougal 10/03/2017.

4 Pharmacology

4.1 Primary Pharmacology

Omidenepag isopropyl is a pro-drug of omidenepag. Omidenepag is an EP2 receptor agonist; its intended mechanism of action is to lower intraocular pressure (IOP).

Background on prostaglandins

- The eicosanoid superfamily is comprised of metabolites of arachidonic acid (AA), a 20-carbon unsaturated fatty acid, or other structurally-similar fatty acids. Prostanoids are a subfamily, consisting of the prostaglandins, prostacyclin (often classified as a prostaglandin), and thromboxanes (e.g., thromboxane A2 (TXA2) and thromboxane B2).
- The prostaglandins have 20 carbon atoms, including the 5-carbon ring. The four main prostaglandins are:
 - Prostaglandin E2 (PGE2; dinoprostone)
 - Prostaglandin F_{2α} (PGF_{2α})
 - Prostaglandin D₂ (PGD₂)
 - Prostaglandin I₂ (PGI₂, prostacyclin, epoprostenol)
- PGE2 (prostaglandin E2) is dinoprostone. It is reportedly the most abundant endogenous prostaglandin. PGE2 has four known receptors, the prostaglandin E (EP) receptor family: EP1, EP2, EP3, and EP4.
- Dinoprostone is currently approved under three NDAs:
 - NDA 20411 (dinoprostone 10 mg vaginal extended release insert)⁴ indicated for "initiation and/or continuation of cervical ripening in pregnant women at or near term in whom there is a medical or obstetrical indication for the induction of labor"

⁴ NDA 020411 / Supplement 31 labeling dated 7/07/2020, accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020411Orig1s031lbl.pdf

- o NDA 19617 (dinoprostone cervical gel) “indicated for ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction.”⁵
- o NDA 17810 (diprostone vaginal suppository) has indications including “termination of pregnancy...” and “evacuation of uterine contents in the management of missed abortion or intrauterine fetal death...”⁶
- PGF_{2α} (prostaglandin F_{2α}), is an endogenous prostalandin, and binds one known receptor, prostaglandin F receptor (FP). The medicines latanoprost, bimatoprost, travoprost, carboprost are structural analogs of PGF_{2α} and are FP agonists.
- PGI₂ (prostaglandin I₂, prostacyclin, epoprostenol) binds one known receptor, prostaglandin I₂ receptor (prostacyclin receptor, IP).
- PGD₂ (prostaglandin D₂) binds two receptors. DP1 and DP2 (prostaglandin D₂ receptor 2; CD294).

Background: EP2

- Prostaglandin *E2 receptor EP2 subtype* has several synonyms:
 - o EP2
 - o Prostaglandin E2 receptor
 - o Prostaglandin E2 receptor 2
 - o Prostaglandin E2 receptor 2, subtype 2
 - o PGE receptor EP2 subtype
 - o PGE2 receptor EP2 subtype
 - o Prostanoid EP2 receptor
- The encoding gene for EP2 is designated PTGER2.
- EP2 is a G protein-coupled transmembrane protein.
- EP2 is widely distributed, including: corneal epithelium, corneal choriocapillaries, sclera, GI, lung, heart, brain, liver, kidneys, bone.
- EP2 is activated by PGE2 > PGF_{2α} > PGI₂ > PGD₂.
- “PGE2 activates multiple prostanoid receptors”
- Butaprost is a PE2 agonist described in the published literature (used for mechanistic studies, no clinical data identified)
- As background information, the Applicant submitted published papers describing the expression of EP2 in the eye⁷ (reportedly prominent and abundant expression in

⁵ NDA 19617 / Supplement 17 labeling dated 7/05/2017, accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019617s017bl.pdf

⁶ NDA 17810 / Supplement 19 labeling dated 7/05/2017, accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017810s019bl.pdf

⁷ Biswas S, Bhattacharjee P, Paterson CA. Prostaglandin E2 receptor subtypes, EP1, EP2, EP3 and EP4 in human and mouse ocular tissues--a comparative immunohistochemical study. Prostaglandins Leukot Essent Fatty Acids. 2004 Nov;71(5):277-88. doi: 10.1016/j.plefa.2004.03.021. PMID: 15380814. Submitted to the NDA: [\\CDSESUB1\evsprod\nda215092\0001\m4\43-lit-ref\biswas-2004.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/043litrefbiswas-2004.pdf) Also accessible via: <https://pubmed.ncbi.nlm.nih.gov/15380814/>

human and mouse ocular tissues, including: trabecular meshwork and Schlemm's canal, conjunctiva, cornea, iris and ciliary body, retina) and gastrointestinal tract.⁸

- Confidentially, a DARRTS search by this reviewer identified other INDs for small molecule drug candidates that are also putative agonists for EP2: NON-RESPONSIVE

The Applicant did not mention these drugs or claim right of reference. This review did not use data for these products to support the safety of NDA 215092.

Review of *in vitro* primary pharmacology studies

Table 12: *In vitro* PD summary table

Report #	Test article	Target	Result	
			Molar basis	Mass basis
(b) (4)-4427-G	Omidenepag	EP2	IC ₅₀ = 10 nM	IC ₅₀ = 4.79 ng/ml
		EP4	IC ₅₀ = 5.48 µM	IC ₅₀ = 2.62 µg/ml
	Omidenepag isopropyl	EP2	IC ₅₀ = 100 nM	IC ₅₀ = 52.06 ng/ml
584Qm040	Omidenepag	EP2	IC ₅₀ = 7.2 nM	IC ₅₀ = 3.45 ng/ml
		DP1	IC ₅₀ = 6.8 µM	IC ₅₀ = 3.52 µg/ml
584Qm050	Omidenepag	EP2	EC ₅₀ = 8.3 nM	EC ₅₀ = 3.97 ng/ml

Title	Binding Study of UR-7276 to Various Receptors	
Report #	(b) (4)-4424-G	
Key findings	- Omidenepag was screened for binding at a single concentration (10 µM) to 127 receptors (105 human, 21 rat or rabbit), using competitive binding assays - Specific binding was detected for human EP2 (94.66% inhibition) and human EP4 (66.04%)	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-

⁸ Dey I, Lejeune M, Chadee K. Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. Br J Pharmacol. 2006 Nov;149(6):611-23. doi: 10.1038/sj.bjp.0706923. Epub 2006 Oct 2. PMID: 17016496; PMCID: PMC2014644. Submitted to the NDA: \\CDSESUB1\evsprod\nda215092\0001\m4\43-lit-ref\dey-2006.pdf Also accessible via: <https://pubmed.ncbi.nlm.nih.gov/17016496/>

		rep\421-pharmacol\4211-prim-pd\ (b) (4) -4424-g\ (b) (4) 4424g-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	March 30, 2010
	GLP status	No
	Test article	Omidenepag (UR-72760), purity 99.3%
Assay	- The specific types and sources of the human recombinant receptors, human tissue (for non-recombinant receptors), and animal tissues (for non-recombinant rat and rabbit receptors) and ligands are detailed in the study report. - For both EP2 and EP4, the ligand was prostaglandin E2. - The authors considered 50% inhibition of ligand binding as the threshold for a positive response	
Note	Although inhibition did not reach 50% for other receptors, the screening was notable for the following human receptors: - Prostanoid CRTH2: 12.75% - Prostanoid DP: 24.09% - Prostanoid EP3: 5.14% - Dopamine D1: 23.32% - Dopamine transporter: 34.32% - Na channel site 2: 24.99%	

Title	Binding study of UR-7275 and UR-7385 to prostanoid receptors
Report #	(b) (4) -4727-G
Key findings	- Endogenous prostaglandins bind the prostaglandin receptors with different specificities. - This was a preliminary assay to screen the test articles for specific binding (competitive inhibition of endogenous ligand binding) to DP1 receptor, EP1 receptor, EP2 receptor, EP3 receptor, EP4 receptor, FP receptor, and IP receptor. - Omidenepag isopropyl (DE-117) was designed as a prodrug of omidenepag. - For omidenepag isopropyl: - Initial screen at 1 μM: weak specific binding to EP1 (13.81%), EP3 (12.74%) and DP1 (7.98%) - Titration: EP₂ IC₅₀ = 100 nM [52.06 ng/ml] - For omidenepag: - Initial screen at 1 μM: weak specific binding to DP1 (26.98%) and EP3 (7.74%)

	o Titration: EP2 IC ₅₀ = 10 nM [4.785 ng/ml], EP4 IC ₅₀ = 5.48 µM [2.62 µg/ml]	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0006\m4\42-stud-rep\421-pharmacol\4211-prim-pd\ (b) (4) -4727-g\ (b) (4) 4727g-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	February 7, 2011
	GLP status	No
	Test articles	- UR-7385 (DE-117; omidenepag isopropyl) - UR-7276 (omidenepeg)

Title	Binding Affinities of DE-117 and UR-7276 to Prostanoid Receptors	
Report #	584Qm040	
Key findings	- This study was intended to confirm the preliminary experiments (report # (b) (4) -4227-G, reviewed above); the Applicant explained that they consider these results more reliable <i>In vitro</i>, DE-117 (omidenepeg isopropyl) showed specific binding to EP1 receptor (IC₅₀ = 3.3 µM; K_i = 1.7 µM). - DE-117 showed very weak binding to DP1, EP2, and FP (not biologically relevant) - Omidenepeg (UR-7276) shows potent specific binding: - to EP2, IC₅₀ = 7.2 nM (3.445 ng/ml), K_i = 3.6 nM - moderate binding to DP1, IC₅₀ = 6.8 µM (3.52 µg/ml); K_i not calculable	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\584qm040\584qm040-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	March 30, 2017
	GLP status	No
	Test articles	- DE-117 (omidenepeg isopropyl) - UR-7276 (omidenepeg)
Assay	Each receptor was recombinant human protein, expressed by transfected HEK-293 cells or 1321N1 cells. Cell membrane preparations were used for the competition assays.	

	- Radiolabeled human agonists were used over a range of five concentrations: - PGD2 for DP1 - PGE2 for EP1, EP2, EP3, and EP4 - PGF2α for FP - Iloprost for IP (PGI₂)
Note	- No specific binding was observed for the other receptors, for either test article. - The molecular weight of omidenepag isopropyl is 520.61 g/mol. For EP1 receptor, IC₅₀ = 3.3 μM (1718 ng/ml), K_i = 1.7 μM (885 ng/ml) - The molecular weight of omidenepag is 478.5 g/mol. - For EP2, IC₅₀ = 7.2 nM (3.445 ng/ml), K_i = 3.6 nM (1.72 ng/ml) - For DP1 IC₅₀ = 6.8 μM (3253.8 ng/ml)

Title	Agonistic Activities of DE-117 and UR-7276 to EP1, EP2, EP4 and FP Receptors	
Report #	584Qm050	
Key findings	In a cell-based <i>in vitro</i> assays for functional activity: - Omidenepag isopropyl (DE-117) did not activate EP1, EP2, or FP. - Omidenepag (UR-7276) was an agonist for EP2, EC₅₀ = 8.3 nM (3.972 ng/ml), and did not activate EP4, (not tested against EP1 or FP).	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\584qm050\584qm050-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	March 30, 2017
	GLP status	No
	Test article	- DE-117 (omidenepag isopropyl) - UR-7276 (omidenepag)
Method notes	- HECK-293 or CHO cells expressing recombinant human receptor (EP1, EP2, EP4, or FP) were used - For EP1 and FP, the assay measured intracellular calcium - For EP2 and EP4, the assay measured intracellular cAMP	

Review of *in vivo* proof of concept studies

Title	Effect of UR-7385 ophthalmic solution in GLP candidate formulation on intraocular pressure in ocular normotensive rabbits
Report #	416Qg030

Key findings	- Topical ocular administration of omidenepag isopropyl (0, 0.001%, 0.01%, 0.03%) to Japanese White rabbits caused a dose-response for decreasing intraocular pressure (IOP), with activity lasting at least 6 hours - No safety endpoints were reported.	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0006\m4\42-stud-rep\421-pharmacol\4211-prim-pd\416qg030\416qg030-pre-clinical-study-report.pdf)
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara Prefecture, 630-0101, Japan
	Report date	October 31, 2011
	GLP status	No
	Test article	Omidenepag isopropyl (UR-7385)
Method notes	Animal model	Healthy male Japanese White (Kbs:JW) rabbits - Rabbits were screened for IOP bilaterally, and only normotensive animals were used - Rabbits were habituated to the IOP measurement procedure for 2 days before dosing.
	Vehicle	Not reported (0.03% was the limit of solubility)
	Drop size	50 µl (administered using a micropipette)
	Dosing and IOP	- Animals received a single topical ocular dose (right eye only, OD) dose with 0, 0.001, 0.01, or 0.03% omidenepag isopropyl, at ~ 1 pm (to capture diurnal data). - OD IOP was measured pre-dose (and after dosing at 2, 4, and 6 hours.

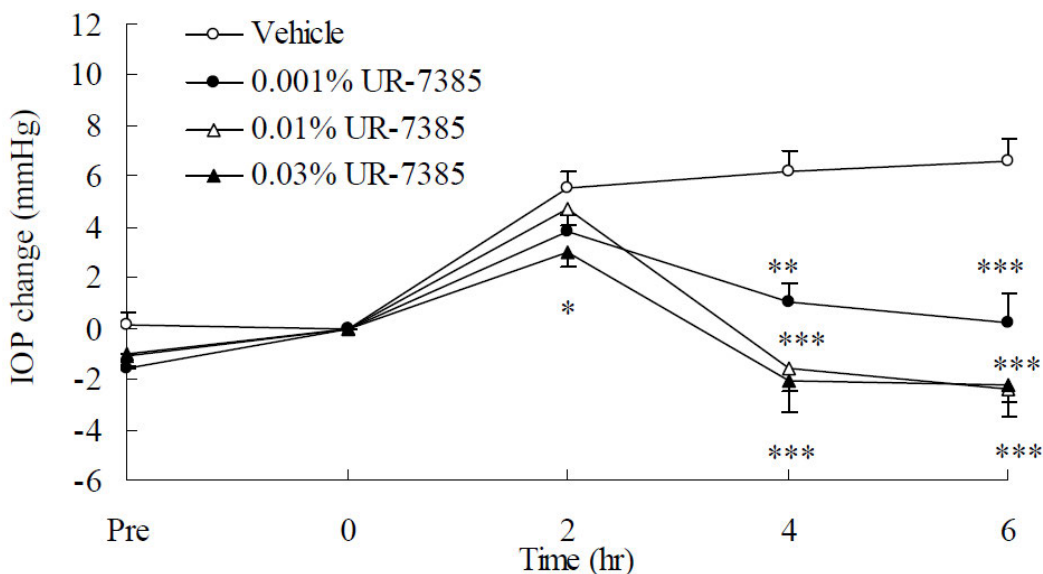
Results: Same data presented in the table and figure below:

Table 13: Omidenepag isopropyl caused IOP lowering in the eyes of normotensive rabbits (report # 416Qg030)

Concentration of omidenepag isopropyl	Treated eye (OD) IOP change (mm Hg) from baseline		
	2 hr	4 hr	6 hr
0	5.5 ± 0.7	6.2 ± 0.8	6.6 ± 0.9
0.001%	3.8 ± 0.7	1.0 ± 0.8**	0.2 ± 1.2***
0.01%	4.7 ± 0.6	-1.6 ± 0.9***	-2.4 ± 0.5***
0.03%	3.0 ± 0.6*	-2.1 ± 1.2***	-2.2 ± 1.3***

Statistically significant by Dunnett's test: * < 0.05, ** < 0.01, *** < 0.001

Figure 4: Omidenepag isopropyl caused IOP lowering in the eyes of normotensive rabbits (report # 416Qg030)

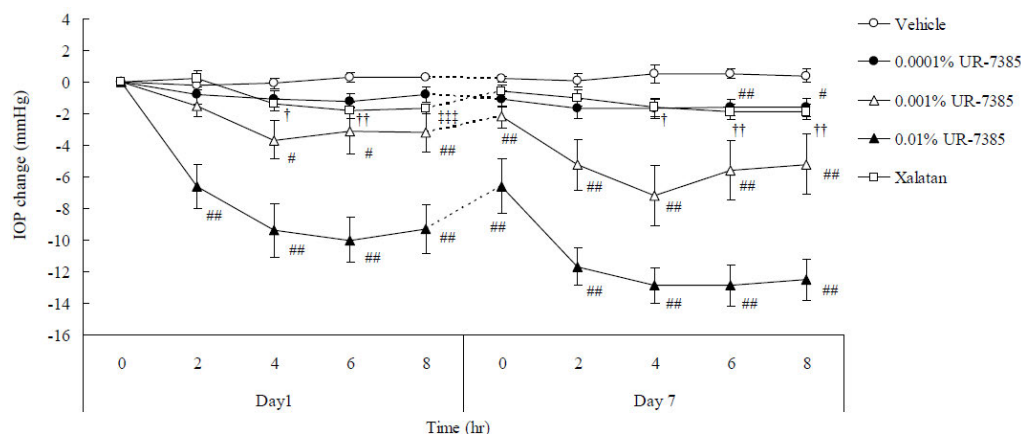


Title	Effect of UR-7385 ophthalmic solution on intraocular pressure with repeated dosing for 7 days in ocular normotensive monkeys	
Report #	416Qg070	
Key findings	- QDx7 topical ocular omidenepag isopropyl (0.001% and 0.01%) decreased IOP in the eyes of normotensive monkeys. - The vehicle was not reported. - No safety data were reported.	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\416qg070\416qg070-pre-clinical-study-report.pdf)
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara Prefecture, 630-0101, Japan
	Report date	December 14, 2011
	GLP status	No
	Test articles	- Omidenepag isopropyl (UR-7385) - Xalatan (0.005% latanoprost) as a positive control
Methods	Species	Male cynomolgus monkeys (returned to colony at end of study)

		8 males/dose group
	Dose groups	- Omidenepag isopropyl: 0, 0.0001%, 0.001%, 0.01% - Latanoprost 0.005%
	Dosing	Topical ocular dosing, 20 µl/eye, OD only, QD for 7 days
	Vehicle	Not reported
	Endpoints:	- IOP was measured on D1 and D7: pre-dose (1 hour prior and immediately prior), post-dose at 2, 4, 8, and 8 hours - General animal observations were made once/day on D1, 7, and 8 (appearance, behavior, feces). Local observation of the eye was made prior to each IP measurement (eye closure, hyperemia, pupil state). No results were reported.

Results

- The low-dose (0.0001%) omidenepag isopropyl did not affect IOP.
- The mid- and high-doses (0.001% and 0.01%) appeared more active than 0.005% latanoprost.



Statistically different from vehicle: # < 0.05, ## < 0.01 by Steel multiple comparison test. [the other marks are less stringent statistical tests).

Title	Effect of UR-7385 ophthalmic solution on intraocular pressure in laser-induced ocular hypertensive monkeys
Report #	416Qg080
Key findings	- A single topical ocular dose of 0.1% omidenepag isopropyl lowered IOP in monkey hypertensive eyes. The effect lasted through the last time point reported (6 hours post-dose). - The vehicle was not reported.

	No safety data were reported.	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\416qg080\416qg080-pre-clinical-study-report.pdf)
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara Prefecture, 630-0101, Japan
	Report date	December 19, 2011
	GLP status	No
	Test article	- Omidenepag isopropyl (UR-7385) 0.01% - Xalatan (0.005% latanoprost)
Method notes	Species	Male cynomolgus monkeys 11 monkeys with OS lasered eye (cross-over design with at least one week washout) - Animals were returned to colony at the end of study.
	Disease model: elevated IOP	- Under anesthesia, "Trabecular meshwork region of the left eye of each animal was photocoagulated with laser (360°, 1000 mW, 0.2 sec, 150 spots) under gonioscope" - Beginning two weeks after the initial laser, IOP was measured periodically until OS IOP dropped below 25 mm Hg. Eyes were then lasered again (1000 mW x 0.2 sec/spot), with the number of spots varied, with the goal of achieving similar IOP elevation results (no details provided for how the authors calculated the number of laser spots for each eye.
	Dosing	Single dose; one topical ocular drop (20 µl) of 0 or 0.01% omdinenepag isopropyl, or 0.005% latanoprost.
	Vehicle	Not reported
	Endpoints	- IOP twice pre-dose and post-dose at 2, 4, and 6 hours. - The general condition of the animal, and local ocular observations (eye closure, hyperemia, pupil condition) were noted at dosing and prior to each IOP measurement (no abnormalities noted).
Results - Predose IOP means were 34.6 to 35.2 mm Hg. - Omidenepag isopropyl reduced IOP by 16.3 mm Hg at 2 hours-post dose, and the effect was still apparent at 6 hours post-dose.		

Table 14: 0.1% omidenepag isopropyl lowered IOP in a monkey model for hypertensive eyes (report # 416Qg080)

Treatment	IOP (mm Hg)			
	0 hr	2 hr	4 hr	6 hr
Vehicle	34.9 ± 2.1	34.3 ± 2.3	33.9 ± 2.2	33.2 ± 1.9
0.1% omidenepag isopropyl	34.6 ± 2.3	18.3 ± 3.0 *	15.2 ± 2.7 *	14.8 ± 2.8 *
0.005% latanoprost	36.2 ± 2.7	28.8 ± 3.0	27.3 ± 3.2	26.9 ± 3.1

* Statistically different from vehicle by Student's t-test, $p < 0.001$

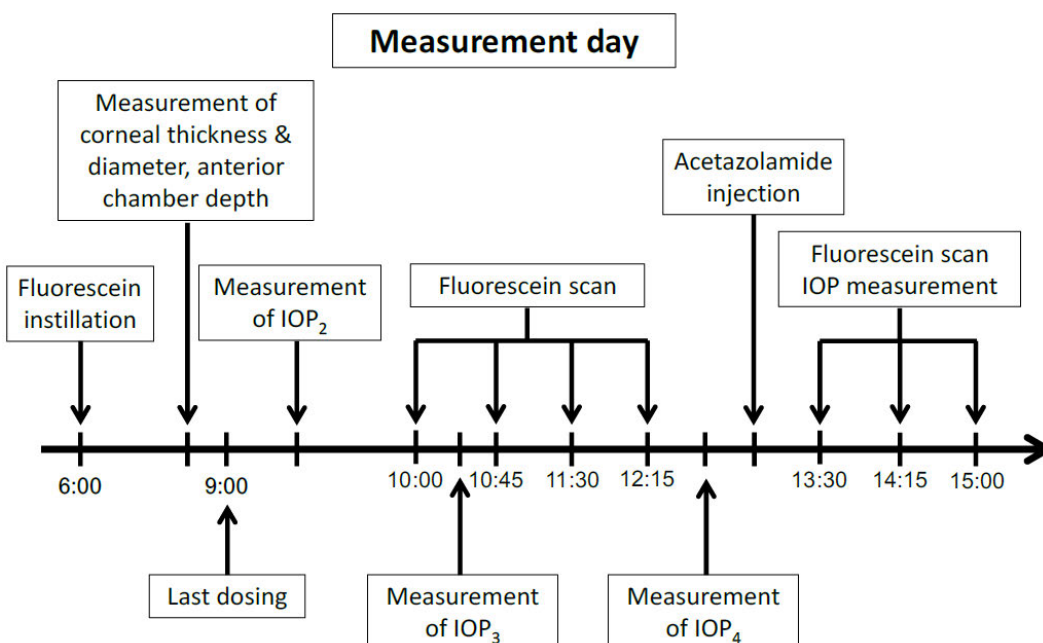
Title	Effect of DE-117, a selective EP2 receptor agonist, on aqueous humor dynamics in monkeys	
Report #	502Qm030	
Key findings	15 monkeys were tested, but results were only reported for 8 (53%). Therefore, the overall results are inconclusive. (b) (4) (b) (4) An IR has been drafted, and may resolve this issue. - In a colony of monkey with laser-induced unilateral ocular hypertension, monkeys received topical ocular omidenepag isopropyl 0.002% QD x7. On D7, aqueous humor dynamics were evaluated by fluorophotometry. - Omidenepag isopropyl did not affect aqueous flow (indicating a lack of activity on production of aqueous humor), and did decrease IOP in both the healthy (unlasered) eye and the hypertensive eye. - Based on fluorophotometry, the authors concluded that omidenepag isopropyl increased outflow via the trabecular and uveoscleral pathways. However, the information provided in the study report are not adequate to verify this conclusion.	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\502qm030\502qm030-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	May 12, 2017

Method notes	Experimental period	November 4, 2016 to December 22, 2016
	GLP status	No
	Test article	Omidenepag isopropyl (DE-117) 0.002%, lot # MTD2770
	Species	15 female cynomolgus monkeys (cross-over design, with at least one week-washout). - The animals were not treatment-naïve. The lasering procedures had been performed 5 to 16 years prior to this experiment. - Animals were returned to colony after the experiment
	Disease model	- Unilateral laser-induced glaucoma - The left eye (OS) had 50 to 100 argon laser photocoagulation burns “applied to the mid-portion of the trabecular meshwork for 350°, with spot size of 50 µm, power of 1000 mW, and exposure time of 0.5 second”, done between 2003 and 2013. - The right eye (OD) was left untreated. - Fluorescein was measured using a Fluorotron ocular fluorophotometer. - Review note: (b) (4)
	Dosing	One 20 µl drop per eye OU, QD x 7 of 0 or 0.002% omidenepag isopropyl.
	Formulation	Not reported
	Endpoints and procedure	- General health of the animals, and general ocular observations, were made at the time of dosing and each procedure (the authors report no abnormalities were noted). - On D1 of dosing, IOP was measured twice. - On D7: - Topical ocular fluorescein was applied to the cornea in excess (3 to 4 drops of 10% fluorescein), 3 hours prior to the omidenepag isopropyl dosing. - Central corneal thickness and anterior chamber depth were measured by ultrasound pachymetry shortly before test article administration - IOP was measured 4 times post-dose.

(b) (4)

- o Fluorescein scanning was conducted from 2-3 hours post-dose.
- o After the 4th IOP measurement, systemic acetazolamide was administered to inhibit aqueous humor product.
- o Fluorescein scanning was continued for another hour, and 3 more IOP measurements were made.
- The authors calculated aqueous outflow, outflow facility, and uveoscleral outflow.

Schematic for D7 procedures:



Results:

- The authors reported means, but not individual animal data.
- IOP and aqueous flow (Fa) were measured for all (15) monkeys.
- Outflow facility (Cfl) and uveoscleral outflow (Fu) were reported for 8 (53%) of the monkeys.
 - o Cfl and Fu could not be measured bilaterally for two monkeys (animals excluded).
 - o Data were not reported for 5 animals. The authors' explanation was: *"During the analysis process, both Cfl and Fu values of five animals (Animal numbers: 3, 5, 7, 11, and 14) were excluded because they could not satisfy the condition for executing Student's paired t-test."*
- The omission of individual eye data is a reporting limitation. Omitting collected Cfl and Fu results for test-article treated eyes is a reporting failure.
 - o Issues of statistical analysis are not an acceptable basis to omit reporting of pivotal data.

- o From a regulatory perspective, conclusions regarding the overall effect of omidenepag on Cfl and Fu cannot yet be reached.

Table 15: Authors reported outflow and outflow facility data for only 8 out of 15 monkeys with unilateral ocular hypertension treated with 0.02% omidenepag isopropyl QDx7 (report # 502qm030). The reliability of this partial data set is unclear.

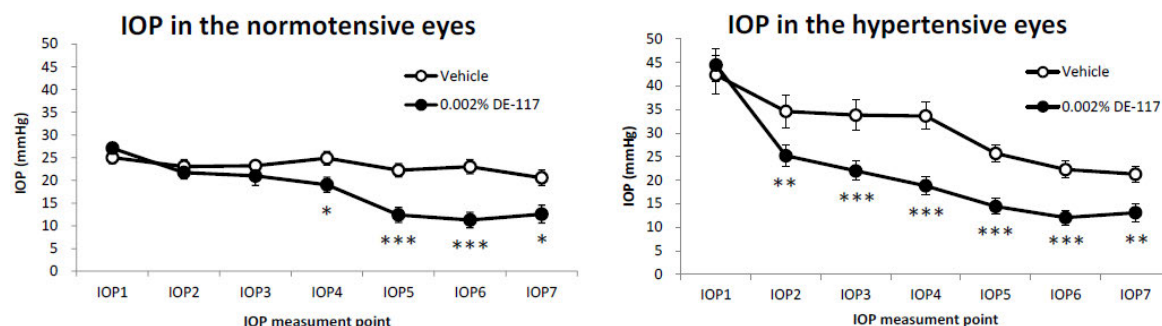
AHD parameter	Results reported for	Vehicle	0.002% DE-117	% increase
Aqueous flow (Fa, $\mu\text{l}/\text{min}$)	15/15 monkeys	2.928 ± 0.257	3.031 ± 0.182	3.5%
Outflow facility (Cfl, $\mu\text{l}/\text{min}/\text{mmHg}$)	8/15 monkeys	0.105 ± 0.026	$0.179 \pm 0.039^*$	71.2%
Uveoscleral outflow (Fu, $\mu\text{l}/\text{min}$)	8/15 monkeys	1.066 ± 0.495	$2.944 \pm 0.550^*$	176.2%

Results are mean $\pm$ standard error (SEM)

* Statistically different from control by two tailed Student's t-test, $p < 0.05$.

Test article reduced IOP in both the unlasered normotensive eye, and in the lasered hypertensive eye.

Table 16: 0.02% omidenepag isopropyl QDx7 decreased IOP in normotensive and hypertensive monkey eyes (report # 502qm030)



Statistically different from control by two tailed Student's t-test: * < 0.05 , ** < 0.01 , *** < 0.001 .

Paper	Fuwa M, Toris CB, Fan S, Taniguchi T, Ichikawa M, Odani-Kawabata N, Iwamura R, Yoneda K, Matsugi T, Shams NK, Zhang JZ. Effects of a Novel Selective EP2 Receptor Agonist, Omidenepag Isopropyl, on Aqueous Humor Dynamics in Laser-Induced Ocular Hypertensive Monkeys. J Ocul Pharmacol Ther. 2018 Sep;34(7):531-537. doi: 10.1089/jop.2017.0146. Epub 2018 Jul 10. PMID: 29989843.
File location	NDA module 4.3 Nonclinical Literature References (\\CDSESUB1\evsprod\nda215092\0001\m4\43-lit-ref\fuwa-2018.pdf)
Review note	• This published paper describes the same experiment summarized in report # 502Qm030 (reviewed above). • The paper was fully reviewed; no additional results were provided. The introduction and discussion provide context.

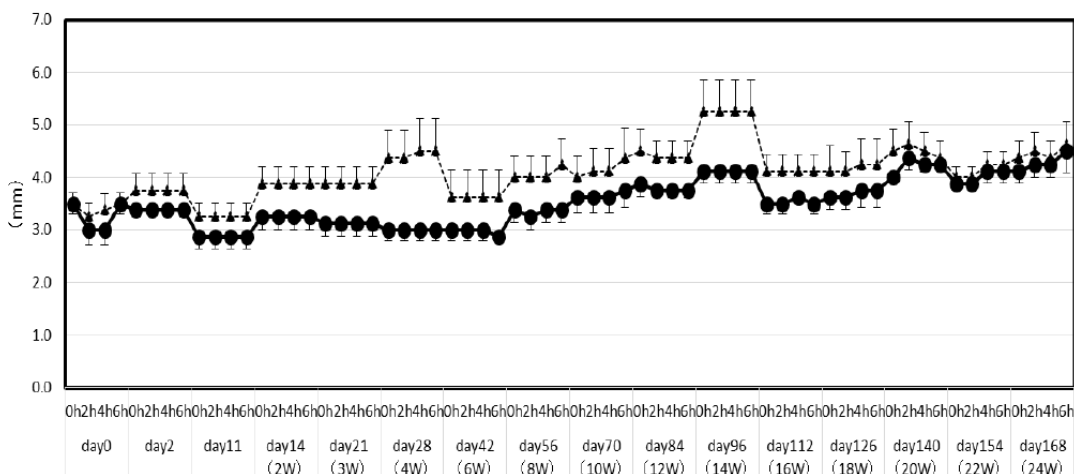
Title	Intraocular pressure measurement following a single dose administration of omdenepag isopropyl solution via intravitreal and subconjunctival injection in normotensive cynomolgus monkeys	
Report #	SPI-14074	
Key findings	• P/T requested submission of this intravitreal-route study report to the NDA, to verify the lack of any theoretical safety concerns. • Healthy (ocular normotensive) cynomolgus monkeys received a single intravitreal (ivt) injection of 0.2% omdenepag, or a single subconjunctival injection of 0, 0.04, 0.09, 0.2, or 1% omdenepag isopropyl solution. • Ivt dosing caused prolonged IOP lowering and pupil miosis (> 6 months) - o The study provides further support for the IOP-lowering proof of concept. - o The relevance of the miosis finding to patients following topical ocular dosing is unclear. - o These data are consistent with the slow clearance from the eye reported for the rabbit ivt ocular distribution study (report # 525w1060), reviewed below.	
Report details	NDA location	Submitted 3/09/2021 (SD # 9) to the NDA's module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0009\m4\42-stud-rep\421-pharmacol\4211-prim-pd\spi-14074\spi-14074-pre-clinical-study-report.pdf)

	Study laboratory	(b) (4)
	Report date	March 15, 2016
	GLP status	No
	Test article	Omidenepag isopropyl (no batch # or purity information reported)
Method notes	Species	Male cynomolgus monkeys, 2 to 12 years of age 4 males/group
	Design	Single 50 µl injection. Test article right eye (OD), vehicle (formulation not reported) left eye (OS)
	Groups	- Ivt: 0.04, 0.09, 0.2% [20, 45, 100 µg/eye] - Subconjunctival: 1% [500 µg/eye]
	Length of follow-up	- The first cohort consisted of: - the 0.2% ivt group, followed for 6 months - the 1% subconjunctival group, discontinued early (at 2 months) due to lack of activity - The second cohort consisted of: - the 0.04% ivt group, followed for 3 months. - The 0.09 ivt group, followed for 6 months.
	Endpoints	- Clinical observations once daily - Body weight measured monthly - IOP was measured pre-dose (D0), and after dosing on D2, 11, 14, 21, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, and 168 - Ophthalmoscopy (slit lamp and indirect) evaluated pre-dose and once monthly post-dose - For the three ivt groups, 2 monkeys/dose were sacrificed for ocular histopathology [not clear if selection was random]
Results	Clinical signs	- One monkey in the subconjunctival group exhibited an ocular infection [no details regarding the affected eye, onset, or recoverability] - No other abnormal clinical signs reported
	Body weight	Authors report "no abnormalities" for body weight (numerical results not reported)
	Ophthalmoscopy	The only reported effect was pupil miosis (unrelated to induced mydriasis for fundoscopy)
	Ocular histopathology	Authors report no findings for the ivt-dosed eyes evaluated (at 3 or 6 months post-dose).
Pupil miosis For the first cohort (0.2% ivt and 1% subconjunctival), the D28 ophthalmoscopy evaluation observed "remarkable" miosis for all treated (OD) eyes of the 2% ivt		

group, 1 to 2 mm compared to the untreated eye. The effect showed reduced severity (to 1 mm difference) by week 12, but persisted through 24 weeks.

- For the second cohort (0.04 and 0.09% ivt), miosis was measured quantitatively, and showed a persistent change.
- For 0.09% ivt, the miosis persisted through week 18 (i.e. recovery apparent).

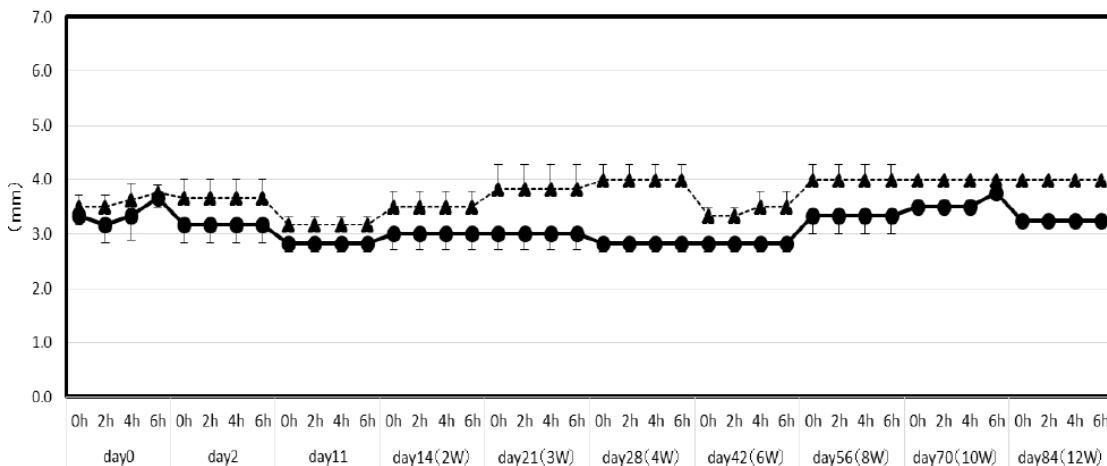
Figure 5: prolonged pupil miosis in monkeys after a single ivt dose 0.09% (45 µg/eye) of omidenepag isopropyl (report # SPI-14074)



- o The triangles (top lines) are for the vehicle-treated OS eyes. The circles are for the 0.09%-treated OD eyes.

- For 0.04% ivt, the miosis persisted through the end of evaluation (week 12).

Figure 6: prolonged pupil miosis in monkeys after a single ivt dose 0.04% (20 µg/eye) of omidenepag isopropyl (report # SPI-14074)

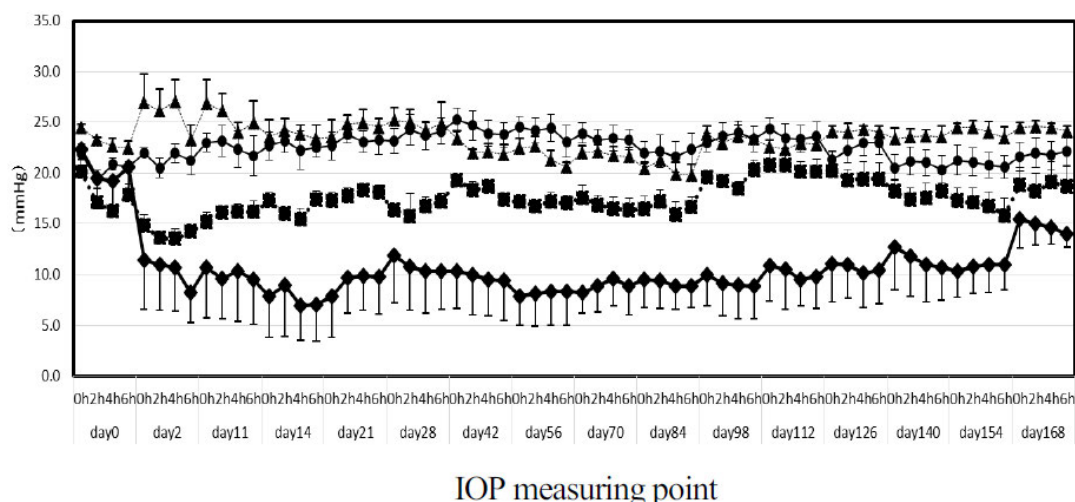


- o The triangles (top lines) are for the vehicle-treated OS eyes. The circles are for the 0.04%-treated OD eyes.

IOP

- The 1% subconjunctival dose reduce IOP (~ -10 mm Hg) for D0-2 post-dose, but eyes had recovered by D11.
- The ivt doses showed prolonged activity:
- For 0.04%: showed IOP reduction ~ -5 mmHg, through the 3 month evaluation period
- For 0.09%: showed IOP reduction ~ 5 mm Hg, with gradual recovery (resolved by D84)
- For 0.02%: greater magnitude of IOP reduction (~ -10 mm Hg), through D168.

Figure 7: Single ivt dosing of monkey eyes with omidenepag isopropyl caused prolonged reductions in intraocular pressure (report # SPI-14074)



- o The diamonds (bottom line) are the 0.2%-treated OD eyes
- o The squares (second line from bottom) are the 0.009%-treated OD eyes
- o The triangles are the OS eyes treated with the vehicle for the 0.2% formulation.
- o The circles are the OS eyes treated with the vehicle for the 0.009% formulation.

4.2 Secondary Pharmacology

- Report # (b) (4)-4424-G (reviewed above) was a screening assay for primary and secondary pharmacology.
- Additionally, report # 597Qm020 (reviewed below) screened for secondary pharmacology.

Title	Binding Affinities of DE-117 and UR-7276 to DP2 Receptor	
Report #	597Qm020	
Key findings	- No binding of omidenepag or omidenepag isopropyl to human prostaglandin D2 receptor (DP2, CRTH2) was detected in an <i>in vitro</i> binding assay - This finding is consistent with the other primary pharmacology study results.	
Report details	NDA location	NDA module 4.2.1.1 Primary Pharmacodynamics (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\416gg070\416gg070-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	March 22, 2017
	GLP status	No
	Test articles	- DE-117 (omidenepag isopropyl) - UR-7276 (omidenepag) - Prostaglandin D2 (positive control)
Methods	- Test article solvent was dimethylsulfoxide (DMSO) - Commercial "CRTH2 prostanoid membrane preparation" was used as the target, and an assay concentration of 200 µg/ml - Test articles were tested over a range of five concentrations from 10 nM to 1 µM, for their ability to compete cold or ³H-labeled prostaglandin D2	
Results	- No specific binding to CRTH2 was detected for omidenepag or omidenepag isopropyl - The positive control gave the expected response: under the conditions tested, the K_d for DP2 binding to CRTH2 was 8.4 nM.	

4.3 Safety Pharmacology

- In addition to the safety pharmacology endpoints built into the general toxicology studies, two stand-alone safety pharmacology studies were submitted to the NDA.
- The results are not concerning for the systemic exposures detected clinically after topical ocular dosing.

Title	Effect of UR-7276 on potassium currents in hERG transfected CHO cells (non-GLP study)	
Report #	(b) (4) 048-022	
Key findings	Omidenepag did not inhibit hERG at 10 μ M (4785 ng/ml)	
Report details	NDA location	NDA module 4.2.1.3 Safety Pharmacology (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4213-safety-pharmacol\ (b) (4) 048-022 (b) (4) 048022-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	April 28, 2009
	GLP status	No
	Test article	Omidenepag (UR-7276), lot # 2, purity 99.5%
	Vehicle	DMSO
	Cell line	Chinese hamster ovary (CHO) cells transfected with the human ether-a-go-go related gene (hERG)
	hERG assay	- Preliminary assay: auto patch clamp method – omidenepag was reportedly negative (no details provided) - Follow-up assay: manual patch clamp method
	Doses:	- Vehicle - Omidenepag at a single concentration (10 μM) - Positive control (E-4031) at a single concentration (300 nM)
Results	- Omidenepag did not inhibit hERG at 10 μM - The negative and positive controls gave the expected responses. - The ICH S7B guidance¹⁰ was consulted for the review of this study.	

Title	UR-7276: Maximum Tolerated Dose and Preliminary Cardiovascular Pharmacology Study by Inhalation Administration to Beagle Dogs
Report #	YVQ0004
Key findings	- The authors explain that omidenepag was tested for potential bronchodilator activity. - Omidenepag was administered to dogs by inhalation; no NOAEL was identified (based on heart and lung histopathology)

¹⁰ Guidance for Industry ICH S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.
 Accessed via: <https://www.fda.gov/media/72043/download>

	• Observation of the dogs observed “irregular breathing” at all dose-levels during exposure. Higher doses caused “deep” and “labored breathing”. • These respiratory effects did not cause detectable changes in respiratory rate or tidal volume. • Histopathology detected lung perivascular inflammatory cells, aggregations of alveolar macrophages, and interstitial pneumonitis in 3/8 dogs. • For in-life cardiovascular safety pharmacology endpoints, 0.268 mg/kg/day did not have an apparent effect. Doses $\geq$ 1.02 mg/kg of omidenepag caused increased heart rate, shortened PR interval, decreased blood pressure, and prolonged QTc. • Group 1 dogs (ascending dose, 0.0369 to 2.60 mg/kg/day)) exhibited gross left ventricle diffuse hemorrhage. The effect was not observed in group 2 (0.5 mg/kg/day) • These results are not concerning for topical ocular dosing, based on the systemic exposure margin (approximately 150 x from the low-dose TK means to the clinical PK means for both C_{max} and AUC).	
Report details	NDA location	NDA module 4.2.1.3 Safety Pharmacology (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\421-pharmacol\4213-safety-pharmacol\yvq0004\yvq0004-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	July 28, 2010
	GLP status	No
	Test article	Omidenepag (UR-7276), purity 99.3% (lot # not provided)
Preliminary study	• On report page 10, the authors summarize a previous nonclinical study: 14-day inhalation repeat-dose study in rats. The dose of 5.9 mg/kg reduced weight gain. • This rat study was not submitted to the NDA. Based on the other data available, P/T concludes that the rat study is not pivotal to understanding the safety of omidenepag isopropyl.	
Methods	Species	• Beagle dogs, age 22 to 25 weeks at start of dosing. • A total of 4 males and 4 females were used
	Test article preparation and vehicle	• Omidenepag was dissolved in water, and then mixed with (b) (4) and pH balanced, to achieve a final concentration of (b) (4)

		- A nebulizer used ultrasonic vibration to generate aerosol. A 14 liter aerosol conditioning chamber was used to control the droplet coalescence and deposition rate. All four dogs/group were exposed simultaneously to aerosol from the conditioning chamber. - Air flow rate of 2 liters/minute																							
	Dosing and vehicle	- Inhalation via a rubber face mask (covering the nose and mouth) 60 minutes/day - Particle size distribution was measured; the means ranged from 2.5 to 3.4 μm.																							
	Design	- Group 1: ascending dose. Two males and two females were exposed: Table 17: Dog inhalation safety pharmacology study (report # YVQ004): group 1 dosing design <table> <tr> <th>Days of dosing</th><th>Nominal dose (mg/kg/day)</th><th>Actual dose (mg/kg/day)</th></tr> <tr> <td>1-3</td><td>0.03</td><td>0.0369</td></tr> <tr> <td>4-6</td><td>0.3</td><td>0.268</td></tr> <tr> <td>7-9</td><td>3</td><td>2.60</td></tr> <tr> <td>10-12</td><td>Dosing holiday</td><td>0</td></tr> <tr> <td>13-15</td><td>1.0</td><td>1.02</td></tr> </table> - Group 2: Two males and two females were exposed for 14 days Table 18: Dog inhalation safety pharmacology study (report # YVQ004): group 2 dosing design <table> <tr> <th>Days of dosing</th><th>Nominal dose (mg/kg/day)</th><th>Actual dose (mg/kg/day)</th></tr> <tr> <td>1-15</td><td>0.5</td><td>0.568</td></tr> </table>	Days of dosing	Nominal dose (mg/kg/day)	Actual dose (mg/kg/day)	1-3	0.03	0.0369	4-6	0.3	0.268	7-9	3	2.60	10-12	Dosing holiday	0	13-15	1.0	1.02	Days of dosing	Nominal dose (mg/kg/day)	Actual dose (mg/kg/day)	1-15	0.5
Days of dosing	Nominal dose (mg/kg/day)	Actual dose (mg/kg/day)																							
1-3	0.03	0.0369																							
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13-15	1.0	1.02																							
Days of dosing	Nominal dose (mg/kg/day)	Actual dose (mg/kg/day)																							
1-15	0.5	0.568																							
Clinical observations, body weight, food consumption	Endpoints	- Animals were checked twice daily, and examined once weekly for general health - Clinical signs were observed immediately pre-dose, during dosing, and 2 and 4 hours after dosing - Body weight was measured weekly, and on the first day of each dose - Daily food consumption was evaluated qualitatively.																							
	Results	No early decedents																							

		• “Irregular breathing” was observed for group 1 (during exposure, at all dose levels) and group 2 • “Gasping and deep breathing were observed during exposure at 1.02 mg/kg • ≥ 0.268 mg/kg caused reddening of the sclera, ears, muzzle and abdomen (beginning at 30 minutes into dosing, resolving by 2 hours after the end of dosing). • For group 2 (0.5 mg/kg/day), “reddening of the whole body was evident from Day 3 in females and Day 4 in males from approximately 30 minutes into dosing until end of exposure” • No clear effects on body weight or food consumption.
Respiratory parameters	Endpoints	• Respiratory rate and tidal volume were measured using a pneumotachograph attached to the facemask; respiratory minute volume was calculated • Respiration recordings were collected from 15 minutes pre-dose until at least 30 minutes after the end of the 1 hour exposure period • Respiration rate data were also collected from the induction bands in the telemetry jackets
	Results	• The authors did not consider any of the respiratory parameters (respiratory rate measured by pneumotachograph or induction band; tidal volume, or respiratory minute) to show treatment-related effects • This reviewer concurs, but considers the clinical signs (observing effects on respiration) to be dispositive
Cardiovascular parameters	Endpoints	• Jacketed telemetry for electrocardiography (ECG, EKG) from 2 hours prior to the start of dosing until 24 hours post-dose • Blood pressure, using plethysmography cuffs secured around the base of the tail. Data collected in 1 minute intervals: 3 time points pre-dose, every 15 minutes during dosing, post-dose at 2 and 4 hours
	Results	• No treatment effect apparent at the low-dose, 0.0369 mg/kg/day. • For higher doses, the authors noted decreased PR interval corresponding with increased heart rate. • The authors reported no clear effects on ECG waveform morphology.

Clinical pathology	Endpoints	For group 2 only, blood was collected once pre-dose, and at termination. Standard hematology, coagulation, and clinical chemistry parameters were assayed.																																																	
	Results	No treatment-related clinical pathology effects apparent.																																																	
TK	Sampling	- Blood was collected from group 1 animals on the second day of each dose (i.e. D2, 5, 8, and 14) and from group 2 animals on D1 and 14. - Time points for blood collection: pre-dose, immediately after the end of dosing, and post-dose at 0.5, 1, 2, 4, 8 and 23 hours.																																																	
	Results:																																																		
	Table 19: Serum TK results for the dog inhalation safety pharmacology study (report # YVQ004)																																																		
	<table><tr><th rowspan="2">Nominal dose (mg/kg/day)</th><th colspan="2">C_{max} (ng/ml)</th><th colspan="2">AUC₀₋₂₄ (ng*h/ml)</th></tr><tr><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td colspan="5">Group 1</td></tr><tr><td>0.03</td><td>5.86</td><td>5.07</td><td>4.59</td><td>4.15</td></tr><tr><td>0.3</td><td>66.7</td><td>122</td><td>52.4</td><td>97.0</td></tr><tr><td>1</td><td>543</td><td>202</td><td>422</td><td>170</td></tr><tr><td>3</td><td>662</td><td>496</td><td>534</td><td>415</td></tr><tr><td colspan="5">Group 2</td></tr><tr><td>0.5 (D1)</td><td>80.4</td><td>153</td><td>69.3</td><td>129</td></tr><tr><td>0.5 (D14)</td><td>54.4</td><td>149</td><td>56.1</td><td>121</td></tr></table>		Nominal dose (mg/kg/day)	C _{max} (ng/ml)		AUC ₀₋₂₄ (ng*h/ml)		M	F	M	F	Group 1					0.03	5.86	5.07	4.59	4.15	0.3	66.7	122	52.4	97.0	1	543	202	422	170	3	662	496	534	415	Group 2					0.5 (D1)	80.4	153	69.3	129	0.5 (D14)	54.4	149	56.1	121
	Nominal dose (mg/kg/day)	C _{max} (ng/ml)		AUC ₀₋₂₄ (ng*h/ml)																																															
M		F	M	F																																															
Group 1																																																			
0.03	5.86	5.07	4.59	4.15																																															
0.3	66.7	122	52.4	97.0																																															
1	543	202	422	170																																															
3	662	496	534	415																																															
Group 2																																																			
0.5 (D1)	80.4	153	69.3	129																																															
0.5 (D14)	54.4	149	56.1	121																																															
- The authors noted exposure was higher than dose-proportional. - For group 2, accumulation was not apparent.																																																			
As summarized below (Table 93), the clinical C_{max} = 34 pg/ml and AUC = 27.0 pg*h/ml for the drug product. From the 0.03 mg/kg/day dose, the exposure margins are 149 x (by C_{max}) and 153.7 x (by AUC).																																																			
Gross necropsy and organ weights	Endpoints	All dogs underwent standard gross necropsy.																																																	
	Results	3/4 Group 1 dogs had heart – left ventricle diffuse hemorrhage - One dog had one area of hemorrhage (no histopathology correlate) - A second dog had “multiple areas” of hemorrhage (no histopathology correlate)																																																	

		- o A third dog had “few” areas of hemorrhage, corresponding to histopathology (minimal myocardial hemorrhage) • No heart gross pathology noted for Group 2 dogs
Histopathology	Endpoints	Histopathology was conducted for animals, limited to: • heart, lungs (sections from four major lobes, including bronchi), larynx (3 levels), pharynx, trachea (including bifurcation), nasal passages (4 levels), and tracheobronchial lymph nodes. • Notably, the list of tissues did not include the eye, optic nerve, or ocular adnexa
	Results	• Both dose groups (most lungs) had: - o minimal perivascular inflammatory cells - o minimal-to-slight aggregations of alveolar macrophages • Minimal or slight interstitial pneumonitis was observed in group 1 (1/4 dogs) and group 2 (2/4 dogs)
Review note	The ICH S7A guidance ¹¹ was consulted for the review of this study	

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 *In vitro* ADME studies

The Applicant submitted two *in vitro* distribution study reports, and one *in vitro* metabolism study report.

Title	Determination of <i>in vitro</i> plasma protein binding ratio of UR-7276 in rat, rabbit, monkey and human	
Report #	543Lg02A	
Key findings	Omidenepag bound tightly to plasma proteins. • No apparent difference among human, monkey and rabbit binding (76.9 to 97.8% at 20 ng/ml); binding to rat plasma protein was lower (94.4% at 20 ng/ml).	
Report details	NDA location	4.2.2.3 Pharmacokinetics – Distribution (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\422-pk\4223-distrib\543lg02a\543lg02a-pre-clinical-study-report.pdf)

¹¹ Guidance for Industry S7A Safety Pharmacology Studies for Human Pharmaceuticals. Accessed via: <https://www.fda.gov/media/72033/download>

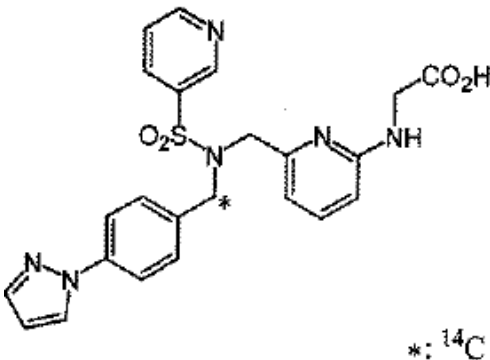
	Study laboratory	Santen Pharmaceutical Co., Ltd., Nara Research and Development Center, 8916-16 Takayama-cho, Ikoma-shi, Nara 630-0101, Japan
	Report date	March 28, 2021
	GLP status	No
	Test article	Omidenepag (UR-7276), lot # 20, purity 99.6%
Methods	Plasma sources	Commercially supplied frozen plasma from: • Male Sprague Dawley rats • Plasma from male Japanese White rabbits • Male and female cynomolgus monkeys • Male and female human volunteers
	Assay	• Omidenepag was dissolved in methanol (stock solution 500 µg/ml) and diluted • Final concentrations of 0.25, 2.5 and 20 ng/ml were tested • A preliminary experiment tested a single concentration (20 ng/ml) over range of incubation times (4, 8, 8, and 24 hours), with no apparent differences. The authors selected the 6 hour time point for the confirmatory assay. • Equilibrium dialysis, 6 hour incubation of plasma and test article at 37°C with vigorous shaking • After incubation, plasma proteins were pelleted by centrifugation at 11,000 rpm for 5 minutes.
	Detection	LC-MS/MS

Results:

Table 20: results of the in vitro comparative plasma protein binding study (report # 543Lg02A)

	Plasma protein % bound		
	0.25 ng/ml	2.5 ng/ml	20 ng/ml
Human	> 94.2	97.8	97.8
Monkey	> 94.1	97.2	97.1
Rat	> 94.5	94.1	94.4
Rabbit	> 94.4	97.0	96.9

Data are the means of three replicates.

Title	<i>In Vitro</i> Blood-to-Plasma Partitioning of ¹⁴C-UR-7276 in Mouse, Rat, Rabbit, Monkey, and Human	
Report #	8309291	
Key findings	Omidenepag did not show particular affinity for the cellular components of blood. No species differences were apparent.	
Report details	NDA location	4.2.2.3 Pharmacokinetics – Distribution
	Study laboratory	(b) (4)
	Report date	March 4, 2015
	GLP status	Yes
	Test article	Radiolabeled ¹⁴C-omidenepag (¹⁴C-UR-7276), lot # CP-4125, purity 99.4%, specific activity 2.23 GQq/mmol Figure 8: location of 14C-radiolabel for the <i>in vitro</i> blood partitioning study (report # 8309291)  *: ¹⁴C
Methods	Blood sources	Unfrozen blood with heparin anticoagulant obtained commercially and used immediately upon receipt: • Unpooled blood from three healthy human volunteers • Pooled blood from at least 3 animals/species for: C57/BL6 mice, Sprague Dawley rats, New Zealand White rabbits, and cynomolgus monkeys • The hematocrit was reported for each sample. The authors concluded, and this reviewer concurs, that the hematocrits were acceptable for the purpose of this assay.
	Assay	• A preliminary time course with human blood was conducted, to verify that 60 minute incubation was adequate. • Radiolabeled omidenepag was tested at 3 concentrations (1, 10, 100 ng/ml), 60 minute incubation at 37°C for each blood sample. • Aliquots were either solubilized (to obtain total levels), or centrifuged to separate cells from plasma.

	Detection	Liquid scintillation counting (LSC). The lower limit of quantitation (LLOQ) was not reported.	
Results:			
Table 21: Results for the <i>in vitro</i> blood partitioning study (report # 8309291)			
Species	% associated with cellular components		
	1 ng/ml	10 ng/ml	100 ng/ml
Human	3.03 ± 2.05	6.33 ± 6.27	0
Monkey	0	7.50 ± 0.977	0
Mouse	0.363 ± 0.630	7.20 ± 6.71	1.38 ± 2.39
Rat	0.916 ± 1.59	6.15 ± 8.82	0
Rabbit	0	0.422 ± 0.731	0
Results presented as mean ± SD			

Title	Metabolism of ¹⁴C-DE-117 in Mouse, Rat, Rabbit, Monkey, and Human Primary Hepatocytes	
Report #	8309287	
Key findings	- Radiolabeled omidenepag isopropyl was incubated with hepatocytes from humans, monkey, mouse, rat, and rabbit. - No unique human metabolites were identified. Metabolism was rapid (< 7.5% remaining by 30 minutes), hydrolysis to omidenepag (UR-7276). - Rabbits showed more rapid metabolism of omidenepag to M10 (oxidation product) than other species. - The major metabolites of omidenepag were detected in all species: M10, M8 (another oxidation product), and M3 (dealkylation product). - A total of 13 metabolites of omidenepag were detected (3 were rat only, 1 was rabbit only).	
Report details	NDA location	4.2.2.4 Pharmacokinetics – Metabolism
	Study laboratory	(b) (4)
	Report date	August 3, 2015
	GLP status	No
	Test article	Radiolabeled ¹⁴ C-omidenepag isopropyl (¹⁴ C-DE-117), lot # CP-4079, purity 98.3% [Label in the same position as shown in the figure above for report # 8309291]
Methods	Hepatocyte sources	Commercial cryopreserved pooled hepatocytes were obtained for:

		- o Humans (both sexes pooled) - o Cynomolgus monkey - o C57/BL6 mice - o Sprague Dawley rat - o NZW rabbit • Metabolic activity was verified
	Assay	• Radiolabeled omidenepag isopropyl was tested at two concentrations, 1 and 10 μM. Incubated with hepatocytes at 37°C for 0, 30, 60, or 120 minutes. • Detection by "HPLC equipped with a radioactivity detector"; metabolites characterized by LC-MS/MS.

1. Ester Hydrolysis
2. Oxidation (+O)
3. N-dealkylation
4. Glucuronidation
5. Sulfonation
6. Taurine conjugation

m - metabolite identified in mouse
r - metabolite identified in rat
b - metabolite identified in rabbit
k - metabolite identified in monkey
h - metabolite identified in human

5.2 *In vivo* ADME and PK

The Applicant submitted 4 *in vivo* ADME/PK study reports.

Title	Ocular Tissue Distribution of Radioactivity Following Topical Ocular Administration of ^{14}C-UR-7385 to Cynomolgus Monkeys	
Report #	8253494	
Key findings	- Cynomolgus monkeys received a single topical ocular dose of ^{14}C-omidenepag isopropyl. Distribution was: cornea > bulbar conjunctiva > trabecular meshwork > palpebral conjunctiva > sclera > aqueous humor > iris > ciliary body > choroid-retinal pigmented epithelium (RPE) > plasma > blood. - Exposure of the retina was detected following topical ocular dosing, but the clearance half-life ($t_{1/2}$) from the retina could not be calculated. - Systemic exposure (i.e. plasma) was also detected, with rapid clearance ($t_{1/2}$ = 23 minutes).	
Report details	NDA location	Module 4.2.2.3 Pharmacokinetic – Distribution (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\422-pk\4223-distrib\8253494\8253494-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	March 8, 2012
	GLP status	Yes
	Test article	Radiolabeled ^{14}C -omidenepag isopropyl (^{14}C -UR-7385), lot # CP-3786, purity 99.9% [Label in the same position as shown in the figure above for report # 8309291]
Methods	Vehicle	“Solution A” (b) (4) and BAK in water; excipient concentrations not reported). [Review note: this early formulation differs from the clinical trial formulation]
	Species	14 male cynomolgus monkeys, treatment-naïve, 2 to 4 years of age
	Dosing	- Single OU dose of 0.307 mg/ml labeled omidenepag isopropyl (0.0307%) 30 μl drop volume (corresponds to a dose of 9.21 $\mu\text{g}/\text{eye}$)
	In-life safety endpoints	Animals were checked twice daily for mortality and moribundity; cage side observations were noted once daily.

		Ophthalmoscopy (slit lamp biomicroscopy and indirect ophthalmoscope) pre-dose only.
	Sample collection	2 monkeys/time point were sacrificed post-dose at 0.25, 1, 2, 4, 8, 12 and 24 hours. - Blood was collected immediately prior to sacrifice. - After ocular enucleation, aqueous humor, bulbar and palpebral conjunctiva were collected. The rest of each eye was flash frozen. - The choroid with RPE, ciliary body, cornea, iris, lens, retina, sclera, trabecular meshwork, and vitreous humor were isolated. - Review note: the "choroid (including RPE)" was collected first. The remaining retina tissue was collected with filter paper. - Samples were weighed and processed. Analysis by liquid scintillation counting. - The lower limits of quantitation (LLOQ) varied by tissue. The assay was most sensitive for plasma (0.366 ng/mg) and blood (0.491 ng/g), and least sensitive for retina (10 ng/g), ciliary body (11.0 ng/g) and iris (77.0 ng/g).
Results	Test article analysis	Test article characterization for concentration, homogeneity and stability appears adequate.
	In-life endpoints	- The animals selected for this study had normal ophthalmoscopy results. - No treatment-related effects on clinical signs were apparent.

Table 22: PK summary for the monkey single topical ocular dose PK study (testing formulation "solution A") (report # 825394)

Sample	t _{1/2} (hours)	T _{max} (hours)	C _{max} (ng eq/g)	AUC _(0-t) ng eq* h/g)	AUC _(0-infinity) ng eq*h/g)
Blood	NC	0.25	2.58	1.44	NC
Plasma	0.387	0.25	4.79	3.35	3.46
Aqueous humor	3.99	4	22.1	185	188
Choroid-RPE	NC	2	8.40	25.7	NC
Ciliary body	NC	4	14.0	69.8	NC
Conjunctiva (bulbar)	10.6	0.25	541	1570	1920
Conjunctiva (palpebral)	6.54	0.25	139	668	767

Cornea	4.52	0.25	1250	5690	5820
Iris	NC	1	29.0	72.5	NC
Sclera	10.2	1	54.3	132	147
Trabecular meshwork	7.72	0.25	467	1310	1400

Eq: equivalents of ^{14}C -UR-7385

NC: not calculated

- Radiolabel was detected in the trabecular meshwork of all (4/4 eyes) at 15 minutes through 12 hours post-dose, and in 3/4 eyes at 24 hours post-dose
- For the choroid-RPE, radiolabel was not detected at 15 minutes post-dose; it was detected at 1 hour (3/4 eyes), 2 hours (3/4 eyes), 4 hours (1/4 eyes), 8 hours (1/4 eyes), but not at 12 or 24 hours post-dose.
- For the residual retina (after removal of the choroid and RPE; LLOQ = 10 ng/g) and vitreous humor (LLOQ = 0.712 ng/g), no radiolabel was detected at any time point.

Title	Absorption, Distribution, Metabolism, and Excretion of ^{14}C-DE-117 Following Topical Ocular or Subcutaneous Administration to Rats
Report #	8309292
Key findings	The Applicant proposed to summarize these results in labeling (section 12 Clinical Pharmacology) • An excretion study following topical ocular dosing, and multiple subcutaneous route studies, were conducted in male Sprague Dawley rats. • Following a single bilateral topical ocular dose of 1.5 μg/eye of omidenepag isopropyl, fecal excretion was the primary route of elimination; urinary excretion was minor (3-4%). - o 0.254% of label was detected in face wipe (4 hours post-dose), 0.139% in collar wipe (4 hours post-dose), and 1.0% of label was detected in cage rinse (24 hours post-dose). This radiation may reflect the administered dose that splashed out of the eye. - o No label was detected in expired air. - o Most of the label was cleared in the first 24 hours post-dose, and all of the label was cleared within 72 hours post-dose. - o In bile duct cannulated (BDC) rats, 50% of the excreted dose was detected in biliary secretion. - o Pooled fecal and urinary samples were analyzed for metabolites. • For subcutaneous dosing:

		- o The pattern of elimination (fecal > urine) was similar to topical ocular dosing. - o The whole body distribution experiment found label distributed throughout the body, with highest concentrations in the gastrointestinal tract, liver, and kidney. Distribution to the eye was detected, but not to the brain or testes. - o As expected, the main metabolite of omidenepag isopropyl was omidenepag. Other metabolites were also identified.
Report details	NDA location	Module 4.2.2.3 Pharmacokinetic – Distribution (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\422-pk\4223-distrib\8309292\8309292-pre-clinical-study-report.pdf)
	Study laboratory	(b) (4)
	Report date	March 27, 2015
	GLP status	Yes • The metabolite profiling and identification were not GLP compliant.
	Test article	Radiolabeled ¹⁴ C-omidenepag isopropyl (¹⁴ C-DE-117), lot # CP-4079, purity 98.3% [Label in the same position as for the previous ¹⁴ C-radiolabel studies]
Method notes	Vehicle	• For topical ocular dosing: “Solution A” (b) (4) and BAK in water; excipient concentrations not reported). [Review note: this early formulation differs from the clinical trial formulation] • For subcutaneous dosing: (b) (4) in saline
	Animal model	Male Sprague Dawley rats, 11 weeks old at dosing • A subgroup of rats were bile-duct cannulated (BDC) at week 7. BDC rats were fitted with a collection jacket for bile collection.
	Dosing	• 4 normal and 4 BDC rats received a single OU topical ocular dose of 1.5 µg/eye (5 µl/eye via micropipette) – excretion experiment only - o For the normal rats, excreta were collected at 24 hour intervals for 7 days. - o For the BDC rats, excreta were collected for 0-2, 2-6, 6-24, and 24-48 hours post-dose. • 36 normal rats received a single 0.03 mg/kg dose (5 ml/kg) by subcutaneous injection – multiple experiments.

	Observations	Animals were checked twice daily for mortality and distress, and once daily for clinical observations. No abnormal findings were noted.
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Results for the topical ocular groups:

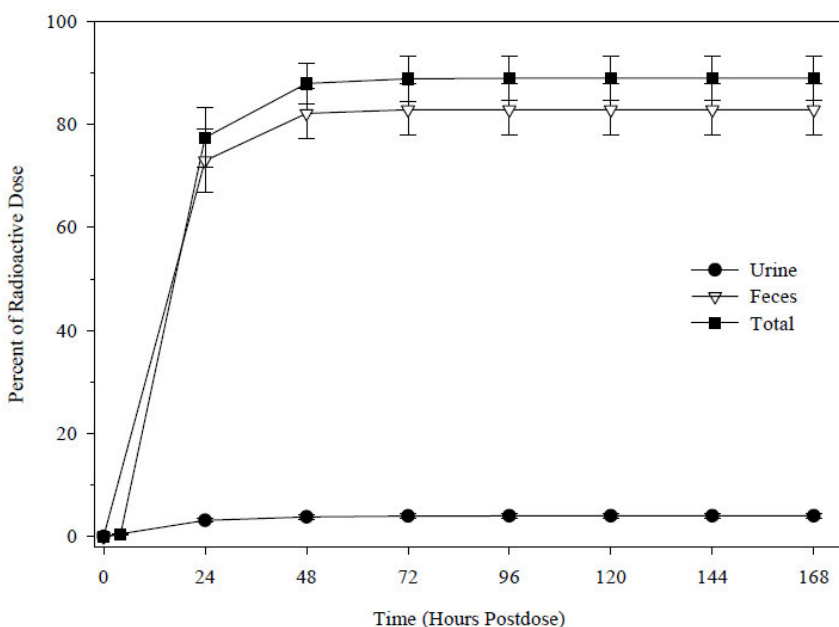
- For the normal rats receiving a single topical ocular dose:
 - No radiation was detected in expired air, volatiles, cage wash, or cage wipe.
 - Face wipe at 4 hours post-dose detected radiation for all (4/4) rats, 0.254 ± 0.0401 % of the total radiation.
 - Collar wipe at 4 hours post-dose detected radiation for 2/4 rats, $0.139 \pm 0.164\%$ of total radiation.
 - Carcass evaluation (at 168 hours) did not detect radiation.
 - For feces: radiation was detected for 4/4 at 0-24 and 24-48 hours; for 2/4 rats at 48-72 hours, and not thereafter (72-168 hours)
 - For urine: radiation was detected for 4/4 rats at 0-24 and 24-48 hours; for 3/4 rats at 48-72 hours, and not thereafter (72-168 hours).
 - For cage rinse, radiation was detected for 4/4 rats at 0-24 and 24-48 hours, and not thereafter (48-168 hours).
 - Only 88.9% of the administered radiation was recovered. Therefore, this reviewer considers it appropriate to normalize the recovery percentages.

Table 23: Excretion results following a single topical ocular dose of omidenepag isopropyl to normal rats (report # 8309292)

	% Radioactive dose administered [normalized]		
Time (hours)	Feces	Urine	Cage rinse
0-24	72.9 ± 6.21 [82.0%]	3.13 ± 0.353 [3.52%]	1.00 ± 0.523 [1.12%]
24-48	9.19 ± 8.02 [10.3%]	0.692 ± 0.283 [0.78%]	0.590 ± 0.797 [0.66%]
48-72	0.698 ± 0.807 [0.79%]	0.170 ± 0.139 [0.19%]	0

Results: percent mean $\pm$ SD, with normalized mean in brackets

Figure 9: mean cumulative excretion after a single topical ocular dose of omidenepag isopropyl to normal rats (report # 8309292)



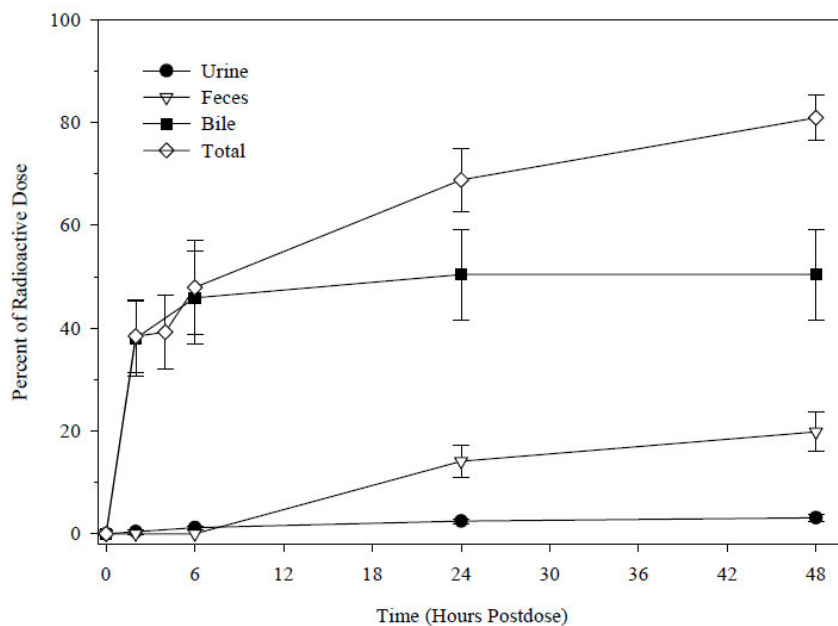
- For the BDC rats:
 - o Radiation was detected in urine: 2/4 rats at 0-2 hours, 4/4 rats thereafter.
 - o Radiation was detected in fetus: 0/4 from 0-2 and 2-6 hours, 4/4 from 6-24 and 24-48 hours.
 - o Radiation was detected in bile: for 4/4 rats from 0-2 hours, 2-6 hours, and 6-24 hours; but not for 24-48 hours.
 - o The face wipe at 4 hours post-dose detected radiation for 4/ 4 rats: 0.485 ± 0.139 % of radiation.
 - o The collar wipe at 4 hours post-dose detected radiation for 2/4 rats: 0.278 ± 0.322 % of radiation.
 - o The cage rinse at 24 hours detected 1.08 ± 0.460 % of radiation.
 - o The cage wash at 48 hours detected 3.32 ± 0.443 % of radiation.
 - o The cage wipe at 48 hours detected 2.43 ± 0.999 % of radiation.
 - o No radiation was detected for the bile cannula, jacket rinse. Air and volatiles were not measured.
 - o Only 80.9% of the administered radiation was recovered: 73.338% in bile, feces, and urine combined; the remainder from the cage, face, and collar wipes. Therefore, this reviewer considers it appropriate to normalize the recovery percentages (by 80.9%):

	% Radioactive dose administered
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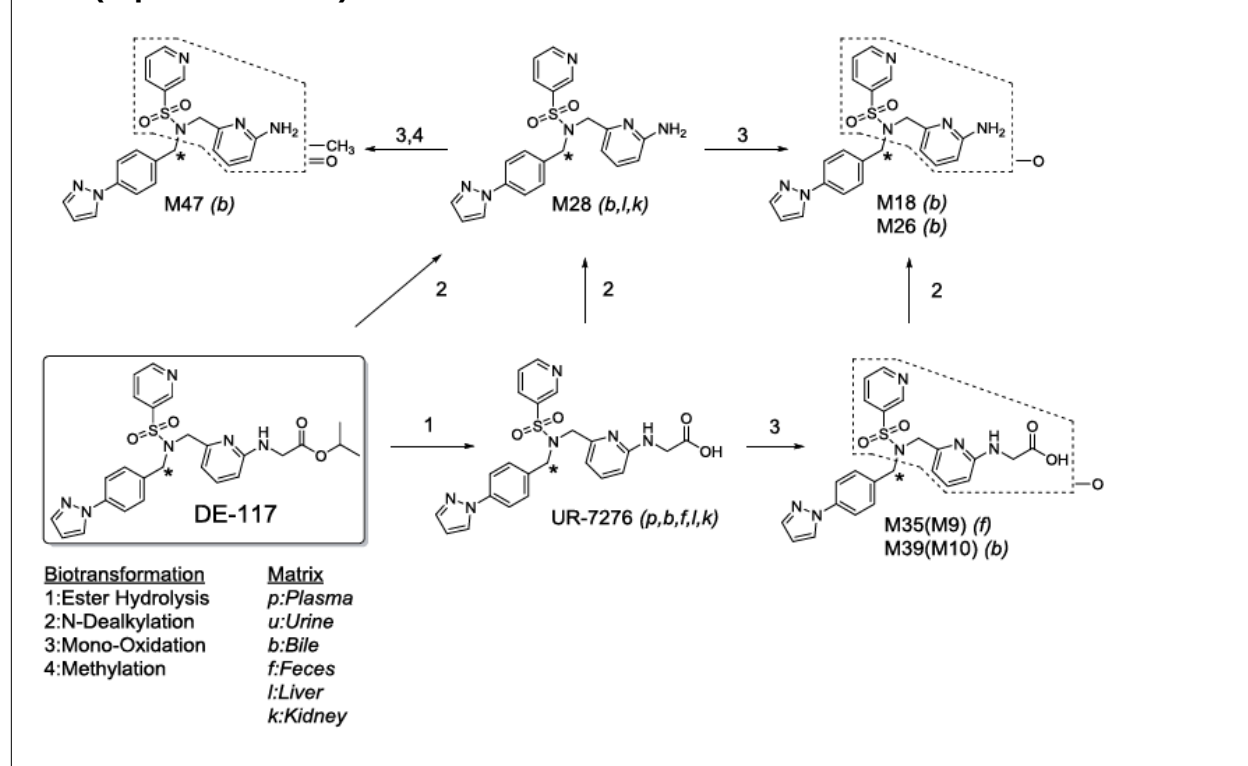
	[normalized]		
Time (hours)	Feces	Bile	Urine
0-2	0	38.0 ± 7.38 [47.0 %]	0.394 ± 0.463 [0.49 %]
2-6	0	7.89 ± 1.95 [9.8 %]	0.783 ± 0.421 [0.97 %]
6-24	14.1 ± 3.11 [17.4 %]	4.49 ± 0.752 [5.6 %]	1.28 ± 0.369 [1.58 %]
24-48	5.72 ± 0.969 [7.1 %]	0	0.651 ± 0.456 [0.80 %]

Results: percent mean $\pm$ SD, with normalized mean in brackets

Figure 10: mean cumulative excretion after a single topical ocular dose of omidenepag isopropyl to bile duct cannulated rats (report # 8309292)



Authors proposed the following biotransformation pathway:

Figure 11: Proposed biotransformation pathway of omidenepag isopropyl in rats (report # 830292)

Title	Distribution to fetus via placenta and excretion to breast milk following subcutaneous administration of 14C-DE-117 to SD rats	
Report #	AE-7762-G	
Key findings	(b) (4) - A single sc dose of 0.03 mg/kg of labeled omidenepag isopropyl was administered to pregnant rats on GD18, or lactating rats on PND 10. Label was detected in maternal blood, but not in placenta, amniotic fluid, fetal tissues, or milk. - Omidenepag is an agonist for EP2, with competitive binding IC_{50} and activation EC_{50} values in the range of 3.45 to 4.79 ng/ml - Comparing the LLOQs for this study to the primary PD results, it is reasonable to conclude that biologically relevant exposures may not be achieved from milk. However, it is not clear that gestational exposure is negligible, given inadequacy of primary PD studies to characterize embryofetal drug activity.	
Report details	NDA location	Module 4.2.2.3 Pharmacokinetic – Distribution (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-

		rep\422-pk\4223-distrib\ae-7762-g\ae7762g-pre-clinical-study-report.pdf
	Study laboratory	(b) (4)
	Report date	February 20, 2017
	GLP status	No
	Test article	Radiolabeled ¹⁴ C-omidenepag isopropyl (¹⁴ C-DE-117), lot # CP-4234, 4.33 MBq/mg, purity 98.2%
Species	Female Sprague Dawley rats were mated at 9 or 10 weeks of age	
Pregnant rat dosing and sampling	- On gestation day 18, sixteen pregnant rats received a single sc dose of 0.03 mg/kg of labeled omidenepag isopropyl (dose volume 5 ml/kg; dose of radioactivity = 0.13 MBq/kg) 4 pregnant rats/time point were sacrificed post-dose at 0.5, 4, 12, and 24 hours. - Tissues sampled: plasma, blood, cerebrum, heart, lung, liver, kidney, uterus, ovary, mammary gland, placenta, amniotic fluid, and fetal tissues (whole body of one fetus/litter; plasma, blood, brain, heart, lung, liver, and kidney from another one fetus/litter) - LLOQ was 0.748 to 1.55 ng/ml (varying slightly based on weight of sample collected) - For maternal and fetal blood and plasma, LLOQ was 1.36 to 1.52 ng/ml - For maternal organs, LLOQ ranged from 0.811 to 1.38 ng/g - For placenta, LLOQ ranged from 0.931 to 1.08 ng/g - For amniotic fluid, LLOQ ranged from 1.36 to 1.52 ng/g - For fetal tissues, LLOQ ranged from 0.748 to 1.55 ng/ml	
Lactating rat dosing and sampling	- On PND 10, four nursing rats received a single sc dose of 0.03 mg/kg of labeled omidenepag isopropyl (same volume and radioactivity). 1 rat/time point sampled: post-dose at 0.5, 4, 12, and 24 hours. - Tissues sampled: milk, blood, plasma - LLOQs: - Milk: 1.26 ng/ml - Blood: 1.28 ng/ml - Plasma: 1.46 ng/ml - Assay notes: litters had been weaned to 5 pups/litter. Pups were separated from their dams 1 hour pre-dose. Nursing rats received an intraperitoneal injection of oxytocin 30 minutes prior to sampling.	
Detection method	LSC and HPLC	
PK results for GD18	Following the single sc dose on GD18, radiolabel was detected in maternal plasma, blood, lung, liver, and kidney, but not in any other tissue.	

	These results show no evidence of placental transfer. Table 24: Rat placental transfer experiment results (report # AE7762g) <table><tr><td>Tissue</td><td>0.5 h</td><td>4 h</td><td>12 h</td><td>24 h</td></tr><tr><td>Plasma (ng/ml)</td><td>4.41 ± 0.66</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>Blood (ng/ml)</td><td>2.47 ± 0.46</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>Lung</td><td>1.29 ± 0.95</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>Liver</td><td>19.6 ± 0.95</td><td>4.27 ± 0.71</td><td>1.02 ± 0.68</td><td>ND</td></tr><tr><td>Kidney</td><td>36.6 ± 3.5</td><td>4.06 ± 0.98</td><td>ND</td><td>ND</td></tr></table> Results presented as mean ± SD ND: not detected Table 25: Rat placental transfer experiment: blood and plasma PK parameters (report # AE7762g) <table><tr><td>PK parameter</td><td>Plasma</td><td>Blood</td></tr><tr><td>C_{max} (ng eq/ml)</td><td>4.41</td><td>2.47</td></tr><tr><td>T_{max} (h)</td><td>0.50</td><td>0.50</td></tr><tr><td>AUC_{0-last} (ng eq*h/ml)</td><td>1.10</td><td>0.618</td></tr></table>	Tissue	0.5 h	4 h	12 h	24 h	Plasma (ng/ml)	4.41 ± 0.66	ND	ND	ND	Blood (ng/ml)	2.47 ± 0.46	ND	ND	ND	Lung	1.29 ± 0.95	ND	ND	ND	Liver	19.6 ± 0.95	4.27 ± 0.71	1.02 ± 0.68	ND	Kidney	36.6 ± 3.5	4.06 ± 0.98	ND	ND	PK parameter	Plasma	Blood	C _{max} (ng eq/ml)	4.41	2.47	T _{max} (h)	0.50	0.50	AUC _{0-last} (ng eq*h/ml)	1.10	0.618
Tissue	0.5 h	4 h	12 h	24 h																																							
Plasma (ng/ml)	4.41 ± 0.66	ND	ND	ND																																							
Blood (ng/ml)	2.47 ± 0.46	ND	ND	ND																																							
Lung	1.29 ± 0.95	ND	ND	ND																																							
Liver	19.6 ± 0.95	4.27 ± 0.71	1.02 ± 0.68	ND																																							
Kidney	36.6 ± 3.5	4.06 ± 0.98	ND	ND																																							
PK parameter	Plasma	Blood																																									
C _{max} (ng eq/ml)	4.41	2.47																																									
T _{max} (h)	0.50	0.50																																									
AUC _{0-last} (ng eq*h/ml)	1.10	0.618																																									
PK results for PPND 20	- Following the single sc dose on PMD20, radiolabel was detected in maternal plasma, but not in maternal blood or maternal milk. - These results show no evidence of secretion into milk. Table 26: Rat lactation experiment results (report # AE7762g) <table><tr><td>Tissue</td><td>0.5 h</td><td>4 h</td><td>12 h</td><td>24 h</td></tr><tr><td>Plasma (ng/ml)</td><td>2.33 ± 0.29</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>Blood (ng/ml)</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr><tr><td>Milk (ng/ml)</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr></table> Results presented as mean ± SD ND: not detected Table 27: Rat lactation experiment: plasma PK parameters (report # AE7762g) <table><tr><td>PK parameter</td><td>Plasma</td></tr></table>	Tissue	0.5 h	4 h	12 h	24 h	Plasma (ng/ml)	2.33 ± 0.29	ND	ND	ND	Blood (ng/ml)	ND	ND	ND	ND	Milk (ng/ml)	ND	ND	ND	ND	PK parameter	Plasma																				
Tissue	0.5 h	4 h	12 h	24 h																																							
Plasma (ng/ml)	2.33 ± 0.29	ND	ND	ND																																							
Blood (ng/ml)	ND	ND	ND	ND																																							
Milk (ng/ml)	ND	ND	ND	ND																																							
PK parameter	Plasma																																										

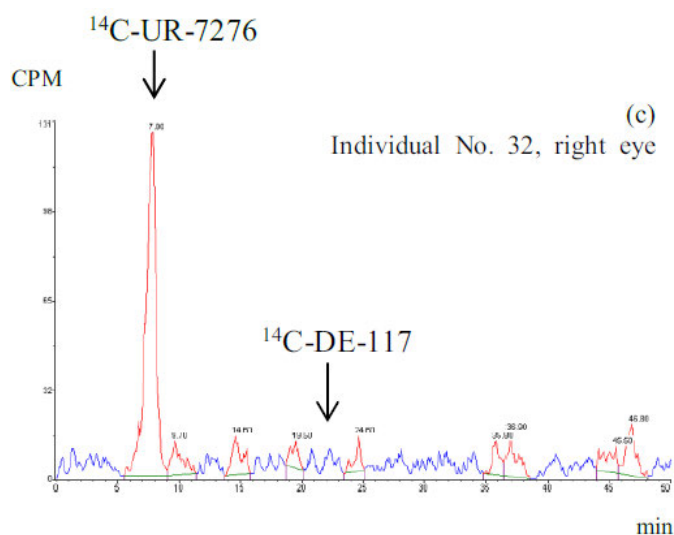
	$C_{\max}$ (ng eq/ml)	2.33 ± 0.29
	$T_{\max}$ (h)	0.50
	$AUC_{0-\text{last}}$ (ng eq*h/ml)	0.582 ± 0.073

Title	Metabolite profile of DE-117 in ocular tissues after ocular instillation of 0.03% ^{14}C-DE-117 ophthalmic solution to rabbits	
Report #	543Lm07A	
Key findings	- Following a single topical ocular administration of radiolabeled omidenepag isopropyl, three ocular tissues (aqueous humor, cornea, iris-ciliary body) were measured. - Low amounts of the parent omidenepag isopropyl were detected in the cornea and aqueous humor (but not in the iris-ciliary body). The main metabolite detected was omidenepag. - Distribution of radioactivity was cornea > aqueous humor > iris-ciliary body	
Report details	NDA location	4.2.2.4 Pharmacokinetics – Metabolism
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research & Development Center, 8916-16 Takayama-cho, Ikoma-shi, Nara 630-0101, Japan
	Report date	September 6, 2017
	GLP status	No
	Test article	Radiolabeled ^{14}C -omidenepag isopropyl (^{14}C -DE-117), lot # CP-4234, purity 99.0% [Label in the same position as shown in the figure above for report # 8309291]
Methods	Vehicle	Polyoxyethylene 35 castor oil (0.0511 g/ml) in water
	Species	Male Japanese White rabbits
	Dosing and sampling	- Single topical ocular instillation in both eyes (OU) of 0.03% ^{14}C-omidenepag isopropyl - Drop size of 50 μl (nominal dose = 15 $\mu\text{g}/\text{eye}$) - Two rabbits/time point were sacrificed 1, 2, or 4 hours after dosing. - Aqueous humor, cornea, and iris-ciliary body were isolated. - Analysis by LSC and HPLC for omidenepag isopropyl, omidenepag, and unidentified metabolites (i.e. other peaks).
Results	<i>“Radioactivity was distributed to the cornea, aqueous humor, and iris-ciliary body, and the maximum radioactivity concentration was highest in the cornea at 7220 ng eq./g, followed by aqueous humor at 205 ng eq./g and iris-ciliary body at 141 ng eq./g. The radioactivity concentrations in these tissues peaked at 1.0, 2.0, and 1.0 hours,</i>	

respectively, after dosing. In each tissue, the concentration of omidenepag was the highest of all metabolites. The concentration of omidenepag isopropyl was" at or below the limit of quantitation in all tissues measured.

- The following is a representative image of the radiochromatogram for aqueous humor at 4 hours post-dose, showing the peaks for omidenepag (UR-7276), omidenepag isopropyl (DE-117), and 8 other peaks (i.e. other metabolites):

Figure 12: representative radiochromatogram showing metabolites in the rabbit aqueous humor after topical ocular dosing (report # 543Im07a)



Title	Measurement of systemic exposure following single topical ocular administration UR-7385 in monkeys	
Report #	469Ff050	
Key findings	- A single topical ocular dose of 0.1% omidenepag isopropyl caused slight conjunctival congestion, which lasted 4 hours post-dose. - This study did not test the clinical ophthalmic formulation	
Report details	NDA location	Module 4.2.3.1 Single-dose toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4231-single-dose-tox\469ff050\469ff050-pre-clinical-study-report.pdf)

	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara, 630-0101, Japan
	Report date	November 16, 2017
	GLP status	No
	Test article	Omidenepag isopropyl (UR-7385), lot # 5
Methods	Vehicle	“Ophthalmic formulation: (b) (4) CO35, (b) (4) EDTA, (b) (4) glycerin, (b) (4) BAK, pH (b) (4)
	Species	sexually mature cynomolgus monkeys (6 years of age)
	Dosing	3 female monkeys received a single topical ocular dose of 0.1% omidenepag isopropyl into the left eye (OS) - Drop size = 30 µl (300 µg/eye dose)
	Endpoints	- Cage side observations once daily - On the day of dosing, cage-side observations: pre-dose, post-dose at 15 and 30 minutes, 1, 2, 4, and 24 hours - Ophthalmoscopy (slit lamp examination: pre-dose, post-dose at 30 minutes and 4 hours - Blood collection for TK: pre-dose and post-dose at 15 and 30 minutes, 1, 2, 4 and 2 hours - Animals were returned to colony at end of experiment
Results	Cage side observations	No observations noted for any animal
	Slit lamp exam	- No changes noted for the untreated right eye - For the treated left eye: - Slight (score 1) conjunctival congestion at 5 minutes (3/3), 30 minutes (2/3) and 4 hours (1/3) post-dose
	PK	- Omidenepag isopropyl (UR-7385) was detected in plasma at 15 minutes only (3/3 monkeys): 0.0480 ± 0.0029 ng/ml. - Omidenepag was detected in all plasma samples from 15 minutes through 4 hours (but not at 24 hours post-dose). $C_{\max} = 2.02 \pm 0.99$ ng/ml $AUC = 0.804 \pm 0.261$ ng*h/ml $T_{\max} = 15$ minutes $T_{1/2} = 1.07$ hours

Title	Ocular Pharmacokinetic Evaluation after Single Intravitreal Administration of UR-7385 Sustained Release Formulation in Albino Rabbits ~ Citrate Ester~	
Report #	535WI060	
Key findings	- Rabbits received a single ivt dose of 1% omidenepag isopropyl. The parent and omidenepag were detected in rabbit ocular tissues 12 months later. - The relevance of these data to the topical ocular formulation is unclear.	
Report details	NDA location	NDA module 4.2.2.3 Distribution (\\CDSESUB1\evsprod\nda215092\0009\m4\42-stud-rep\422-pk\4223-distrib\535w1060\535w1060-pre-clinical-study-report.pdf)
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research & Development Center 8916-16 Takayama-cho, Ikoma-shi, Nara, Japan
	Report date	February 28, 2017
	GLP status	No
	Test article	1% Omidenepag isopropyl (UR-7385) in (b) (4) formulation (b) (4) - The relevance of this formulation to the clinical topical ocular formulation is unclear.
Method notes	Test species	Male Japanese White (Kbs:JW) rabbits
	Design	6 rabbits received a single bilateral (OU) ivt dose of 1% omidenepag isopropyl in 50 µl (0.5 mg/eye). - Two rabbits/time point were sacrificed at 12 weeks, 24 weeks, or 48 weeks post-dose for collection of ocular tissues (aqueous humor, iris-ciliary body, cornea, retina-choroid, and vitreous body) - The authors report that body weight and clinical signs were monitored (no results reported). - Vitreous opacity was reported for 1/12 dosed eyes (no other details reported). - No reporting of IOP (or any other safety data)
Results Authors calculate the residual amount of the omidenepag isopropyl (prodrug) was 45.9% at month 3, 21.2% at month 6, and 2.4% at month 12.		

¹² Accessed via:<https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=BasicSearch.page>

- Omidenepag (UR-7276) was detectable in the iris-ciliary body and retina-choroid 12 months after the single ivt dose.
- From the study report:

Table 28: rabbit intravitreal single-dose study (report# 535w1060): ocular distribution results

Product	Periods	Residual amount (µg)		Residual amount ratio (%)	Concentration (ng/g or mL)							
					Cornea		Iris-ciliary body		Retina-choroid		Aqueous humor	
		(month)	UR-7276	DE-117	DE-117	UR-7276	DE-117	UR-7276	DE-117	UR-7276	DE-117	UR-7276
1%UR/ (b) (4) (500µg/eye)	3M	0.534	259	51.8	35.6	26.1	108	4.59	182	108	0.420	BLQ
		0.619	221	44.2	245	272	NS	NS	655	748	0.488	BLQ
		0.302	168	33.6	3.76	0.519	51.8	8.33	102	964	0.612	BLQ
		0.444	270	54.1	15.6	2.22	118	7.51	83.1	39.3	0.690	BLQ
	Mean	0.475	230	45.9	74.9	75.3	92.7	6.81	255	465	0.553	NC
	SD	0.136	46	9.3	114.1	131.8	35.8	1.97	270	461	0.121	NC
	6M	0.122	131	26.2	3.29	BLQ	37.9	2.14	20.9	6.19	0.171	BLQ
		0.236	215	43.0	3.99	2.52	64.2	49.8	58.4	26.6	0.244	BLQ
		0.111	77.7	15.5	1.97	BLQ	39.7	0.579	34.0	3.28	0.198	BLQ
		BLQ	0.368	0.1	BLQ	BLQ	0.328	BLQ	0.612	12.3	BLQ	BLQ
	Mean	0.117	106	21.2	2.31	NC	35.5	13.1	28.5	12.1	0.153	NC
	SD	0.097	90	18.1	1.76	NC	26.4	24.5	24.2	10.4	0.107	NC
	12M	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		BLQ	17.9	3.6	0.465	2.78	13.8	52.3	9.48	22.8	BLQ	BLQ
		BLQ	8.28	1.7	0.525	BLQ	1.91	BLQ	3.94	1.82	BLQ	BLQ
		BLQ	9.13	1.8	BLQ	BLQ	4.84	BLQ	4.13	1.22	BLQ	BLQ
Mean	NC	11.8	2.4	0.330	NC	6.86	NC	5.85	8.61	NC	NC	
SD	NC	5.4	1.1	0.287	NC	6.22	NC	3.14	12.29	NC	NC	
LLOQ(3M-6M):		0.056	0.056	0.0	0.140	0.140	0.165	0.165	0.320	0.320	0.0800	0.0800
LLOQ(12M):		0.070	0.070	0.0	0.351	0.351	0.413	0.413	0.801	0.801	0.200	0.200

NC: Not calculated

NR: No results

BLQ: Below the limit of quantification

6 General Toxicology

6.1 Topical Ocular Route Toxicity

Two GLP topical ocular studies were submitted to the NDA.

Study title: A 13-Week Ocular Toxicity Study of UR-7385 Ophthalmic Solution in Cynomolgus Monkeys Followed by a 4-Week Recovery Period

Study no.:	(b) (4) 102-212
Study report location:	NDA module 4.2.3.2 Repeat Dose Toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox (b) (4) 02-212 (b) (4) 02212-pre-clinical-study-report.pdf)
Conducting laboratory and location:	In-life test site: Santen Pharmaceutical Co., Ltd. Nara Research & Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101, Japan

Site for histopathology:

(b) (4)

Site for TK:

(b) (4)

Report date:	May 22, 2012
Date of study initiation:	August 30, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot #s 11002-02, -03, and -04 (0.003%, 0.01% and 0.03% respectively), purity $\geq$ 97.7%

Key Systemic Findings

- No systemic NOAEL, based on nasal cavity histopathology. Since the test article is administered by topical ocular instillation, drainage through the nasolacrimal duct system results in exposure of the nasal cavity lining.
 - Histopathology of the respiratory nasal cavity found respiratory olfactory epithelium metaplasia at 0.9 $\mu\text{g}/\text{eye}$ (1/3 males), 3 $\mu\text{g}/\text{eye}$ (1/3 males), and 9 $\mu\text{g}/\text{eye}$ (1/3 males). Metaplasia was observed at recovery for the 36 $\mu\text{g}/\text{eye}$ dose (1/2 males and 1/2 females).
 - Histopathology of the vestibular nasal cavity found increased goblet cell respiratory epithelium mucosa all omidenepag isopropyl levels: 0.9 $\mu\text{g}/\text{eye}$ (2/3 males, 1/3 females), 3 $\mu\text{g}/\text{eye}$ (2/3 males), 9 $\mu\text{g}/\text{eye}$ (2/3 males, 2/3 females), and 36 $\mu\text{g}/\text{eye}$ (2/3 males, 2/3 females). Recovery was apparent (i.e. finding not observed in recovery animals).

Key Ocular Study Findings

- Test article lowered IOP (intended pharmacology), which recovered after cessation of dosing.
- The authors considered 0.003% QD (9 $\mu\text{g}/\text{eye}/\text{day}$) to be the ocular NOAEL, and 0.003% 2 drops/dose BID (36 $\mu\text{g}/\text{eye}/\text{day}$) to be the ocular LOAEL, based on treatment-related increased corneal thickness. This reviewer concurs.

- o Treatment-related miosis was observed at the high-dose (clinical signs; recovery apparent after cessation of dosing), and for all doses (pupil size measured as part of the ERG assay).
- o The Applicant considers both responses (corneal thickness and miosis) to be related to primary pharmacology, and non-adverse.
- o With deference to the Clinical review team, the Applicant reported increased corneal thickening and photophobia as adverse events in clinical studies.¹³
- All treatment levels caused clear, ERG changes; the authors considered this secondary to the treatment-related miosis.
 - o *Review note:* ERG detected changes at all dose levels, and therefore appears to be a more sensitive endpoint than clinical signs, to detect pupil change.
- No apparent treatment-effect on body weight, food consumption, electrocardiography, blood pressure, clinical pathology (hematology, coagulation, clinical chemistry, urinalysis), or organ weights.

Methods

Concentrations: 0, 0.003, 0.01, or 0.03%

Doses:

Group #	%	# of drops per day	Dose (µg/eye/day)
1	0	4	0
2	0.003%	1	0.9
3	0.01%	1	3
4	0.03%	1	9
5	0.03%	4	36

- Frequency of dosing:
- Left eye (OS) only, daily for 13 weeks
 - Groups 1 and 5 received 2 drops per dose, at least 5 minutes apart. These two groups were dosed twice daily (BID), eight hours apart (morning and afternoon)
 - Groups 2-4 received 1 drop/dose, once daily (QD), in the afternoon.

Route of administration: Topical ocular instillation onto the cornea

Dose volume: Each drop = 30 µl (administered using a micropipette)

¹³ NDA module 5.3.5.3 Integrated Summary of Safety – Safety Data Display of Adverse Events, accessed via: <\\CDSESUB1\evsprod\nda215092\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\glaucoma\5353-rep-analys-data-more-one-stud\iss\iss-safety-data-aes.pdf>

Formulation/Vehicle: The Applicant clarified the formulation in the NDA, module 3.2.P.2.1 Drug product formulation development.¹⁴

Ingredient	Amount (% w/v)
Omidenepag isopropyl	(b) (4)
(b) (4)	
Polyoxyl 35 castor oil	
BAK	
(b) (4)	
Edetate disodium	
Glycerin	
Water	

pH adjusted to (b) (4)

This formulation matches the formulation used for the US Phase 1/2 clinical study # 33-001. It is different than the Phase 2 or 3 clinical formulations.

Species/Strain: Cynomolgus monkeys (*Macaca fascicularis*)

Number/Sex/Group: • Main-groups: 3/sex/dose [dosed for 90 days, sacrificed on D91]
 • Recovery groups: for groups 4 and 5 only (i.e. not controls), 2/sex/dose [sacrificed on D118]

Age: 3 to 6 years of age

Weight: At assignment to groups, males were 2.83 to 4.559 kg, females were 2.58 to 3.35 kg

Deviation from study protocol: This reviewer considers the deviations described in the report to be minor; they would not have affected overall study results.

Observations and Results

Mortality

- No premature deaths occurred.

Clinical Signs

- Animals were checked for mortality and clinical signs, including observation of the conjunctivae, cornea, and iris.
 - o Three times per day during dose
 - o Once per day during recovery

¹⁴ Accessed via: [\\CDSESUB1\evsprod\nda215092\0001\m3\32-body-data\32p-drug-prod\de117 \(b\) \(4\) 32p2-pharm-dev\pharmaceutical-development-dp.pdf](\\CDSESUB1\evsprod\nda215092\0001\m3\32-body-data\32p-drug-prod\de117 (b) (4) 32p2-pharm-dev\pharmaceutical-development-dp.pdf)

- The only treatment-related clinical sign reported was anisocoria (miosis) of the treated left eye for the high-dose group.
 - Observed for all high-dose animals beginning D1, after the second daily dose, through the end of treatment.
 - For the high-dose recovery animals, it was observed on recovery D1 (3/4) or recovery D1 and 2 (1/4), but not thereafter.
- Although the anisocoria as a clinical sign was only noted for high-dose animals, all dose-levels affected ERG (and pupil size differences observed at ERG). The authors considered these effects treatment-related (primary pharmacology) and not adverse.

Body Weights

- No treatment-related effect apparent for body weight.
- Body weight was measured weekly.

Feed Consumption

- No treatment-related effect apparent for food consumption.
- Animals were single-housed. Food consumption was measured daily.

Ophthalmoscopy

- Evaluations were done blinded to treatment, OU.
- The orders of procedures were:
 - gross examination, anesthesia, observation of iris color, corneal thickness measurement, mydriatic administration, slit lamp examination, examination for fluorescein staining of the cornea, ocular fundus examination.
 - anesthesia and surface anesthetic, IOP examination, specular microscopy.
- Gross and slit lamp examinations, fluorescein staining, fundoscopy: pre-dose, D22, D85; and for recovery animals on recovery D23
 - Gross observations of the position and movement of the eyeball and eyelids
 - Slit lamp examination of the iris (including photography for iris color), cornea, conjunctiva, anterior chamber, lens, and vitreous body.
 - Corneal thickness measured by ultrasound pachymetry
 - Corneal fluorescein staining evaluated by slit lamp twice: 1-4 hours after the last daily dose, and again 14-17 hours later
 - Fundoscopy using an indirect ophthalmoscope, with fundus photography
- IOP and specular microscopy: pre-dose, D18, 81 (at least 1 hour after the last daily dose), and for recovery animals on recovery D19
 - IOP was measured with a pneumotonometer
 - Specular microscope was used to evaluate the cornea: cell count, cell density, and mean dimensions of corneal endothelial cells were reported.

Slit lamp results

- All eyes were reported normal at all time points, except for one female (0.03% QD group): the left eye iris color was normal pre-dose, and was reported "iris pigmentation, brown" at week 4 and 13.
- Since the individual eye colors were not reported, it is not clear how sensitive the assay is (i.e. pigmentation changes are easier to detect in lighter irises)

Fundoscopy and specular microscopy results

No treatment-related effects apparent.

Corneal thickness

- The authors noted increased corneal thickness of the treated left eye at all dose levels, with recovery apparent, considering the effect $\leq 0.003\%$ QD (9 $\mu\text{g}/\text{eye}/\text{day}$) to be the ocular NOAEL for this effect.
- The literature suggests that increased corneal thickness may be at least partially due to decreased IOP.
- [Review note: no corneal cloudiness was detected for any eye at any time point]

Table 29: Corneal thickness results for the 13-week topical ocular monkey toxicity study (report # (b) (4) 102212)

Pachymetry		Ratio of treated (OS) cornea thickness / untreated (OD) corneal thickness				
Day	Time after the last dose (1-4 hours, or 14-17 hours)	0	0.9 $\mu\text{g}/\text{eye}$	3 $\mu\text{g}/\text{eye}$	9 $\mu\text{g}/\text{eye}$	36 $\mu\text{g}/\text{eye}$
Males						
D22	1-4	+0.1%	+3.6%	+4.9%	+5.2%	+9.5%
	14-17	-0.4%	+1.9%	+4.7%	+4.4%	+8.2%
D85	1-4	+0.7%	+4.3%	+5.5%	+4.3%	+8.2%
	14-17	-0.07%	+2.3%	+4.6%	+4.1%	+6.4%
Recovery D23	1-4	-	-	-	+2.7%	+0.7%
	14-17	-	-	-	+0.3%	-1.9%
Females						
D22	1-4	+0.4%	+5.5%	+6.7%	+5.9%	+8.1%
	14-17	-0.07%	+4.1%	+4.8%	+4.6%	+8.0%
D85	1-4	+0.9%	+5.9%	+5.0%	+4.6%	+7.9%
	14-17	+0.3%	+4.1%	+5.2%	+4.3%	+7.9%
Recovery D23	1-4	-	-	-	-0.7%	+1.1%
	14-17	-	-	-	+1.5%	+2.2%

Table 29 compiled by this reviewer

IOP

- Consistent with intended primary pharmacology, all dose levels decreased IOP, with recovery apparent.
- The effect at the high-dose is considered adverse, based on magnitude of effect.

Table 30: Treated eye IOP for the 13-week topical ocular monkey toxicity study (report # (b) (4) 102212)

Day	Treated eye (OS) IOP (mm Hg)				
	0	0.9 µg/eye	3 µg/eye	9 µg/eye	36 µg/eye
Males					
D18	22.00±11.00	20.17±2.89	6.67 ± 1.15 **	6.88 ± 1.80 **	< 5 (MV)
D81	20.83±0.76	17.17±1.04 *	9.83 ± 2.36 **	8.50 ± 1.08 **	6.67 ± 1.53 **
Recovery D19	-	-	-	19.00	21.25
Females					
D18	21.83 ± 0.76	9.33±3.06 **	10.00±2.83 **	11.00±3.63 **	< 5 (MV)
D81	20.67±1.44	9.75±5.30	9.00±3.46 *	10.20±4.69 *	10.75±7.42 a
Recovery D19	-	-	-	21.75	20.00

Data presented as mean ± SD

MV: missing values, IOP was not measurable (below the 5 mm Hg LLOD)

^a For high-dose females at D81, the measurement was measurable for 2/5 eyes, and MV for 3/5 eyes.

Statistically different from control by Dunnett's test, * p < 0.05, ** p < 0.01

Electroretinography (ERG)

- A single scotopic measurement: after dark adaption for at least 30 minutes, +25dB.
 - o After dark adaptation, animals were anesthetized, and a topical ocular mydriatic was applied. A contact lens-type electrode was used as part of the ERG apparatus.
 - o After ERG on D83 and recovery D21, pupil diameter was measured.

- ERG was conducted pre-dose, on D20 and 83 (at least 1 hour after the last dose), and for recovery animals on recovery D21.
- Amplitudes and latency of a, b, and oscillation waves (O-1, O-2, O-3, and O-4) were reported. Waveforms were charted and evaluated.
- After ERG, pupil diameter was measured at D83 and recovery D21 only (not D20).
- The only remarkable observation was for males at D83, affecting both the untreated (right) eye and the treated (left) eye. A dramatic increase in O-2 amplitude, and slight (but statistically significance) latencies in O-2, O-3, and O-4 were detected.
- The authors considered these ERG (and pupil) changes related to the anisocoria observed as a clinical sign.

Table 31: Treatment-related ERG changes for male monkeys in the 13-week topical ocular toxicity study (report # (b) (4) 102212)

Male 12 week ERG	0	0.9 µg/eye	3 µg/eye	9 µg/eye	36 µg/eye
Right eye					
O-2 amplitude (µV)	4.47±3.25	39.0±7.0*	28.6±5.7*	40.9±10.2*	39.5±8.9*
O-2 latency (mSec)	19.7±0.9	24.2±0.9*	23.4±0.5*	23.4±1.1*	22.8±0.7*
O-3 latency (mSec)	25.0±1.2	29.5±1.4*	27.9±0	28.4±1.1*	27.4±0.7
O-4 latency (mSec)	29.8±1.2	34.3±2.1*	33.2±0.5*	34.6±1.5*	33.7±1.4*
Left eye					
O-2 amplitude (µV)	2.6±1.7	32.7±4.1*	22.6±3.3*	38.3±11.9*	30.1±5.4*
O-2 latency (mSec)	19.2±1.4	24.2±0.9*	23.1±0.8*	23.4±1.1*	23.1±0.8*
O-3 latency (mSec)	25.0±1.2	29.0±0.9*	27.9±0.8*	28.5±1.3*	27.9±0.8*

O-4 latency (mSec)	29.8±1.2	34.0±2.0*	33.8±1.2*	34.8±1.3*	33.3±1.3*
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Data presented as mean ± SD

Data analyzed for homogeneity of variance by Bartlett's test. When variances were homogenous, Dunnett's test was applied. * Statistically different from vehicle by Dunnett's test, $p < 0.01$

Table 32: Pupil diameter (measured after instillation of a mydriatic agent to cause dilatation) in the 13-week topical ocular monkey study (report # (b) (4) 102212)

			Pupil diameter (mm)				
Sex	Week	Eye	0	0.9 µg/eye	3 µg/eye	9 µg/eye	36 µg/eye
M	12	R	7.17	7.33	7.50	7.20	7.00
		L	7.17	6.83	7.00	6.00	5.50
	RW3	R	-	-	-	7.50	6.75
		L	-	-	-	6.25	5.75
F	12	R	7.17	7.17	7.00	7.00	7.10
		L	7.17	6.17	5.83	5.70	5.60
	RW13	R	-	-	-	7.25	7.00
		L	-	-	-	7.25	6.25

ECG

- No treatment-related effects apparent for ECG.
- ECG leads and blood pressure cuff were placed without anesthesia: pre-dose, D16, and D17 (at least 1 hour after the last dose), and for recovery animals on recovery D15. ECG parameters evaluated: heart rate, PR interval, QRS duration, QT interval, and QTc. Blood pressure parameters evaluated: systolic pressure, diastolic pressure, and mean blood pressure.

Hematology

- No treatment-related effect apparent for hematology.
- Blood was drawn for hematology, coagulation, and clinical chemistry once pre-dose, on D28 and D29, and for recovery animals on recovery day 28.

- A standard panel of endpoints was evaluated for hematology. For coagulation, two parameters (PT and APTT) were measured.

Clinical Chemistry

- No treatment-related effect apparent for clinical chemistry.
- A standard panel of endpoints was evaluated.

Urinalysis

- No treatment-related effect apparent for urinalysis.
- Urine collection trays were used to collect fresh urine over a two hour collection period: once pre-dose, D27, and D90.
- A standard panel of endpoints was evaluated.

Gross Pathology

- Gross pathology was conducted for all animals.
- One high-dose male (#31) had a grossly apparent left kidney cyst (diagnosed as a papillary cyst by histopathology). This effect is not clearly treatment related *per se*, but is remarkable light of the other study findings.

Organ Weights

- The authors concluded no treatment-related effects were apparent for organ weights. The lung weights weakly suggest a slight treatment-effect (notably in context of the results of the 39-week monkey study).
- At necropsy, organ weights were collected for: lungs, submandibular glands, pancreas, liver with gallbladder, heart, kidneys, testes, epididymides, prostate, seminal vesicles, ovary, uterus, brain, spleen, thymus, pituitary, thyroids, and adrenals. Left and right organs were weighed separately.

Table 33: Lung weight results for the 13-week monkey topical ocular toxicity study (report # (b) (4) 02212)

	0	0.9 µg/eye	3 µg/eye	9 µg/eye	36 µg/eye
Main-group males					
Body wt (kg)	3.98 ± 0.99	4.30 ± 0.99	3.81 ± 1.12	3.69 ± 0.56	3.60 ± 0.28
Lung wt (g)	19.20±0.87	17.57±1.25	17.00±4.76	18.20±4.01	15.80±1.04
Lung/body wt	4.85 ± 0.35	4.20 ± 0.79	4.48 ± 0.062	4.90 ± 0.37	4.39 ± 0.18
Recovery males					
Body wt (kg)	-	-	-	4.07	3.81
Lung wt (g)	-	-	-	17.55	15.65

Lung/body wt	-	-	-	4.32	4.12
Main-group females					
Body wt (kg)	3.09 ± 0.30	2.93 ± 0.20	3.28 ± 0.40	3.01 ± 0.24	3.18 ± 0.22
Lung wt (g)	15.10±1.78	14.07±1.36	15.57±0.64	15.43±2.75	14.53±1.43
Lung/body wt	4.88 ± 0.21	4.81 ± 0.52	4.78 ± 0.56	5.12 ± 0.61	4.56 ± 0.25
Recovery-group females					
Body wt (kg)	-	-	-	2.78	2.80
Lung wt (g)	-	-	-	14.60	14.00
Lung/body wt	-	-	-	5.25	5.00

Data presented as mean ± SD

Histopathology

- The authors concluded no treatment-related histopathology effects were apparent. This reviewer disagrees: treatment is clearly associated with nasal cavity changes.
- All female monkeys were sexually mature (evidenced by cage side observation of menstruation, and uterine histopathology)
- For the males, sexual maturity was evident by histopathology for 0/3, 1/3, 2/3, 2/3, and 2/3 monkeys for the 0, 0.9, 3, 9, and 36 µg/eye groups respectively.
- The study pathologist was (b) (4)
- Adequate Battery:** Yes, for systemic organs. A standard systemic battery of tissues was evaluated, including:
 - Eyes with optic nerve and bulbar conjunctiva [fixed in a mixture of 2.5% paraformaldehyde and 3% glutaraldehyde)
 - Superior and inferior eyelids with palpebral conjunctiva
 - Lacrimal glands
 - Lungs with bronchi
 - “Nasal cavities (vestibular, respiratory, and olfactory areas)”

The adequacy of the histopathology to assess ocular structures was not documented; this is a study limitation.

Peer Review: No.

Histological Findings

- Histopathology of the respiratory nasal cavity found respiratory olfactory epithelium metaplasia at 0.9 µg/eye (1/3 males), 3 µg/eye (1/3 males), and 9 µg/eye (1/3 males). Metaplasia was observed in recovery animals at 36 µg/eye (1/2 males).
- Histopathology of the vestibular nasal cavity found increased goblet cell respiratory epithelium mucosa at 0.9 µg/eye (2/3 males, 1/3 females), 3 µg/eye (2/3 males), 9 µg/eye (2/3 males, 2/3 females), and 36 µg/eye (2/3 males, 2/3 females). Recovery was apparent (i.e. not observed in recovery animals).
- Based on control incidence, the observations of vestibular nasal cavity found respiratory squamous epithelium hyperplasia are not clearly treatment-related.

Table 34: Selected male histopathology findings for the 13-week monkey topical ocular toxicity study (report # (b) (4) 02212)

Tissue and lesion	Severity	0	0.9 µg/eye	3 µg/eye	9 µg/eye	36 µg/eye
Main-group males (3/dose)						
Left eyelid: conjunctival fornix cyst	Present	0/3	0/3	0/3	0/3	1/3
Lung, hyperplasia, bronchiolo- alveolar epithelium, focal	Very slight	0/3	0/3	0/3	1/3	0/3
Nasal cavity, <i>bilateral</i> , respiratory- metaplasia, respiratory, olfactory, epithelium, focal	Very slight	0/3	1/3	1/3	0/3	0/3
Nasal cavity, <i>left only</i> respiratory – metaplasia, respiratory, olfactory, epithelium, focal	Very slight	0/3	0/3	0/3	1/3	0/3
Nasal cavity, <i>bilateral</i> vestibular – hyperplasia, respiratory / squamous epithelium, mucosa	Very slight	0/3	0/3	1/3	0/3	1/3
Nasal cavity, <i>left only</i> vestibular –	Very slight	0/3	0/3	2/3	0/3	0/3

hyperplasia, respiratory / squamous epithelium, mucosa						
Nasal cavity, <i>bilateral</i> vestibular – increase, goblet cell, respiratory epithelium, mucosa	Very slight	0/3	2/3	2/3	2/3	2/3
Nasal cavity, left – vestibular – crust, intranasal	Very slight	0/3	0/3	0/3	0/3	2/3
Recovery males (2/dose for the 9 and 36 µg/eye groups only)						
Nasal cavity, left, respiratory – metaplasia, squamous, respiratory epithelium, focal	Very slight	-	-	-	0/2	1/2 (# 33 affected)
Nasal cavity, <i>bilateral</i> , vestibular – hyperplasia, respiratory / squamous epithelium, mucosa	Very slight	-	-	-	-	1/2 (# 32 affected)

Note: the authors used the scale ± (very slight), + (slight), 2+ (moderate), 3+ (marked).

- Notably, all the cases of male increased goblet cell mucosa were bilateral (i.e. not limited to the left nasal cavity).

Table 35: Selected female histopathology findings for the 13-week monkey topical ocular toxicity study (report # (b) (4) 102212)

Tissue and lesion	Severity	0	0.9 µg/eye	3 µg/eye	9 µg/eye	36 µg/eye
Main-group females (3/dose)						
Left eyelid: conjunctival fornix cyst	Present	0/3	0/3	1/3	0/3	0/3
Nasal cavity, <i>bilateral</i> vestibular – hyperplasia, respiratory / squamous	Very slight	1/3	1/3	0/3	0/3	0/3

epithelium, mucosa						
Nasal cavity, <i>bilateral</i> vestibular – increase, goblet cell, respiratory epithelium, mucosa	Very slight	0/3	1/3	0/3	2/3	2/3
Nasal cavity, <i>bilateral</i> – vestibular – crust, intranasal	Very slight	0/3	0/3	1/3	0/3	0/3
Recovery females (2/dose for the 9 and 36 µg/eye groups only)						
Nasal cavity, <i>right</i> <i>only</i> , respiratory – metaplasia, squamous, respiratory epithelium, focal	Very slight	-	-	-	0/2	1/2 (# 38 affected)
Nasal cavity, <i>right</i> <i>only</i> , vestibular – hyperplasia, respiratory / squamous epithelium, mucosa	Very slight	-	-	-	0/2	1/2 (# 37 affected)
Nasal cavity, <i>right</i> <i>only</i> , vestibular – increase, goblet cell, respiratory epithelium, mucosa	Very slight	-	-	-	1/2 (# 28 affected)	0/2

Toxicokinetics

- Blood was collected for TK from all animals after dosing on D1, D28, and D91: post-dose at 5, 15, 30 minutes; 1, 2, 4 hours. [For D28 and D91 only, pre-dose blood was also collected].

Table 36: plasma omidenepag TK for the 13-week monkey topical ocular toxicity study (report # (b) (4) 102212)

Parameters		Day 1 of Dosing	Day 28 of Dosing	Day 91 of Dosing
0.003%UR-7385 q.d. group (0.9 µg/body/day)				
Males (n=3)	t _{max} (h)	0.0833	0.0833	0.0833
	C _{max} (pg/mL)	368	279	268
	AUC _{0-4h} (pg·h/mL)	99.8	82.0	73.2
Females (n=3)	t _{max} (h)	0.0833	0.0833	0.0833
	C _{max} (pg/mL)	337	402	331
	AUC _{0-4h} (pg·h/mL)	71.4	73.4	66.6
0.01% UR-7385 q.d. group (3 µg/body/day)				
Males (n=3)	t _{max} (h)	0.0833	0.0833	0.0833
	C _{max} (pg/mL)	850	781	773
	AUC _{0-4h} (pg·h/mL)	223	224	190
Females (n=3)	t _{max} (h)	0.0833	0.0833	0.0833
	C _{max} (pg/mL)	703	623	623
	AUC _{0-4h} (pg·h/mL)	169	143	154
0.03% UR-7385 q.d. group (9 µg/body/day)				
Males (n=5)	t _{max} (h)	0.117	0.117	0.117
	C _{max} (pg/mL)	1740	1740	1380
	AUC _{0-4h} (pg·h/mL)	638	654	535
Females (n=5)	t _{max} (h)	0.0833	0.0833	0.117
	C _{max} (pg/mL)	1750	1870	1400
	AUC _{0-4h} (pg·h/mL)	565	602	479
0.03% UR-7385 b.i.d. group (36 µg/body/day)				
Males (n=5)	t _{max} (h)	0.0833	0.0833	0.117
	C _{max} (pg/mL)	3300	3990	3210
	AUC _{0-4h} (pg·h/mL)	1290	1520	1300
Females (n=5)	t _{max} (h)	0.0833	0.0833	0.0833
	C _{max} (pg/mL)	2090	2250	2020
	AUC _{0-4h} (pg·h/mL)	764	1000	747

Dosing Solution Analysis

- Test article characterization was included in the report, and appears adequate. Actual doses were within 6.1% of nominal.

Study title: A 39-week ocular toxicity study of DE-117 ophthalmic solution in cynomolgus monkeys with a recovery period of 4 weeks

Study no.:	B-7689
Study report location:	NDA module 4.2.3.2 Repeat Dose Toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\b-7689\b7689-pre-clinical-study-report.pdf)
Conducting laboratory and location:	(b) (4)
Report date:	October 30, 2015
Date of study initiation:	July 11, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (DE-117) - Lot # 140001-03, purity 96.4.0% - Lot # 140001-04, purity 98.3%

Key Study Findings

- No systemic NOAEL. Treatment increased the incidence and severity of nasal cavity epithelial squamous metaplasia. Recovery was not demonstrated.
- The ocular NOAEL is the high dose, 0.01% one drop QD (3 µg/eye/day).
 - Both dose levels decreased IOP, decreased pupil diameter, and increased corneal thickness. Recovery was apparent after cessation of dosing.
- Treated main-group females had lower lung weight (absolute and lung/body weight) compared to controls; the difference is not clearly treatment-related. Treatment-related effects were apparent for clinical signs, body weight, food consumption, ocular irritation, ERG, ECG, hematology, clinical chemistry, or urinalysis.

Methods

Doses:	0, 0.003%, or 0.01% [0, 0.9, or 3 µg/eye/day]
Frequency of dosing:	Left eye (OS) only, one drop per day (QD), daily for 39 weeks (273 days)
Route of administration:	Topical ocular instillation (onto the cornea)
Dose volume:	30 µl (single drop, administered by micropipette)

Formulation/Vehicle: The Applicant clarified the formulation in the NDA, module 3.2.P.2.1 Drug product formulation development.¹⁵

Ingredient	Amount (% w/v)
Omidenepag isopropyl	(b) (4)
(b) (4)	
Polyoxyl 35	
castor oil	
BAK	
Edetate disodium	
Glycerin	
Water	

pH adjusted to (b) (4)

This formulation matches the formulation used for the US Phase 2a clinical study # 33-002. It is slightly different than the Phase 2b or Phase 3 clinical formulations.

Species/Strain: Cynomolgus monkeys

Number/Sex/Group: • Main group: 3/sex/dose [necropsy on D274]
• Recovery group: 2/sex/dose [necropsy on D302]

Age: 3-4 years of age at start of dosing

Weight: Males 2.33 to 3.80 kg, females 2.45 to 3.14 kg, at start of dosing

Deviation from study protocol: Histopathology did not include the retina for multiple eyes (report pages 9-10, 34). The failure to evaluate the fovea of treated (left eyes) for two low-dose monkeys and 3 high-dose monkeys is a serious study limitation.

Observations and Results

Mortality

- No premature deaths occurred.

Clinical Signs

- Excepting observations for one high-dose male (# 3004) and detection of menses (in all females), no other clinical signs were reported.
- Animals were checked twice daily (approximately 30 minutes before and 30 minutes after dosing) on dosing days, and once daily during recovery. Observations also included visual observation of the conjunctivae, corneas and irises of both eyes at time of dosing.

¹⁵ Accessed via: <\\CDSESUB1\evsprod\nda215092\0001\m3\32-body-data\32p-drug-prod\de117-32p2-pharm-dev\pharmaceutical-development-dp.pdf>

- For monkey # 3004, necropsy found pancreas gross white discoloration; histopathology detected moderate necrosis and moderate diffuse acinar atrophy. [Pancreas organ weight not affected.] The authors attributed the clinical signs, reduced food consumption, weight loss, and clinical chemistry changes to incidental pancreatic disease.
 - o Clinical chemistry changes were apparent at week 23 and 36 (decreased total protein, decreased albumin, decreased albumin:globulin ratio). Weight loss began week 30, and reduced food consumption began week 33. Bilateral cheek swelling was first noticed during week 37, and persisted until scheduled sacrifice (week 39).
 - o Since the pancreas has not been identified as a target organ in other animals (this report or others), and since this monkey's TK was not usual, the authors considered the effect incidental, and this reviewer concurs.
 - o [These observations for monkey # 3004 are omitted from the entries below, for readability]

Body Weights

- No treatment effect apparent for body weights.
- Body weight was measured weekly.

Feed Consumption

- No treatment effect apparent for food consumption.
- Food consumption was measured daily.

Ophthalmoscopy

- Ophthalmoscopy pre-dose, D86, D177, and D267 (at least one hour after dosing), and for recovery animals on recovery day 23.
 - o The order of procedures was: visual observation, anesthesia, photography of iris color, corneal thickness measurement, administration of topical mydriatic agent, slit lamp examination, fluorescein staining and examination for the cornea (via slit lamp), ocular fundus examination (with fundus photography).
 - o Eye irritation was scored using the McDonald-Shadduck scale.
- IOP and specular microscopy (for corneal endothelial cell count, density, and mean dimensions): pre-dose, D90, D181, D269 or 271, and for recovery animals on recovery day 26 or 27.
 - o The order of procedures was: anesthesia, specular microscopy, surface anesthetic, IOP.
- The orders of procedures were:
 - o gross examination, anesthesia, observation of iris color, corneal thickness measurement, mydriatic administration, slit lamp examination, examination for fluorescein staining of the cornea, ocular fundus examination.

- o anesthesia and surface anesthetic, IOP examination, specular microscopy.

Ophthalmoscopy results:

- No treatment-related effects apparent by slit lamp, fundoscopy, or specular microscopy.
- Review note: no comments on iris color or iris pigmentation were documented (e.g. pre-dose, after start of dosing).
- The treated left eyes exhibited reduced IOP, decreased pupil size, and increased corneal thickness, with recovery apparent after cessation of dosing.
- The authors considered the changes in corneal thickness to be incidental. This reviewer disagrees; the effect is clearly treatment-related for both levels, and consistent across both GLP monkey topical ocular studies.

Table 37: Omidenepag isopropyl decreased IOP in the 39-week monkey topical ocular toxicity study (report # B7689)

OS IOP (mm Hg)	Males			Female		
	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye/)	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye/)
Pre-dose	20.4 ± 1.8	20.9 ± 1.7	21.0 ± 1.4	19.8 ± 0.7	20.8 ± 1.5	20.7 ± 1.7
D90	19.0 ± 1.8	11.1 ± 4.7*	7.3 ± 4.8 **	20.1 ± 0.8	12.7 ± 4.1*	5.3 ± 6.5*
D181	19.1 ± 2.3	10.3 ± 3.3**	9.0 ± 2.3 **	18.5 ± 1.4	13.4 ± 4.4	7.0 ± 6.8**
D269/271	19.2 ± 1.2	18.5 ± 2.9	11.8 ± 7.9	18.6 ± 1.6	20.4 ± 1.3	13.4 ± 4.7*
Recovery D26/27	19.5	19.5	19.0	19.2	22.6	19.1

Mean ± SD. Statistically different from control by Dunnett's test, * ≤ 0.05, ** ≤ 0.01

- For high-dose animals, OS IOP values were below the limit of quantitation (5 mm Hg):
 - o Males: 1/5 at week 13, 1/5 at week 39.
 - o Females: 2/5 at week 13, and 2/5 at week 26.
- It is remarkable that the IOP-lowering effect appears smaller at week 39 compared to week 26.

Table 38: Omidenepag isopropyl caused slight increases in corneal thickness in the 39-week monkey topical ocular toxicity study (report # B7689)

OS corneal thickness (change from baseline)	Males			Female		
	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye/)	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye/)
D86	- 0.21%	+ 3.6%	+ 4.3%	- 0.68%	+ 3.4%	+ 7.2%
D177	+ 0.42%	+ 3.8%	+ 3.6%	- 0.23%	+ 4.3%	+ 5.3%
D267	+ 0.21%	+ 2.9%	+ 3.6%	+ 1.33%	+ 2.7%	+ 6.8%
Recovery D23	+ 1.67%	+ 4.0%	+ 1.81%	+ 2.49%	- 0.45%	+ 8.7%

Table 39: Omidenepag isopropyl caused slightly reduced pupil size in the 39-week monkey topical ocular toxicity study (report # B7689)

OS pupil diameter (mm)	Males			Female		
	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye/)	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye/)
Pre-dose	7.8 ± 0.3	7.8 ± 0.3	7.8 ± 0.3	7.6 ± 0.2	7.5 ± 0	7.7 ± 0.3
D86	8.0 ± 0	7.9 ± 0.2	7.5 ± 0	8.0 ± 0	7.5 ± 0.5	7.1 ± 0.2
D177	8.0 ± 0	7.6 ± 0.4	7.3 ± 0.4	8.0 ± 0	7.4 ± 0.5	6.9 ± 0.2
D267	8.0 ± 0	7.3 ± 0.6	6.6 ± 0.4	8.0 ± 0	6.6 ± 0.7	6.3 ± 0.4
Recovery D23	8.0	8.0	7.8	8.0	8.0	8.0

Mean ± SD

Electroretinography (ERG)

- No treatment-related ERG effects apparent. [Review note: this reviewer expected the treatment-related miosis to have affected ERG. Therefore, the lack of apparent scotopic ERG changes is remarkable.]
- ERG was measured pre-dose (D-9), D135, D240 (at least one hour after dosing), and for recovery animals on recovery day 15 or 16.

Measured	Calculated
Dark adaptation	Rod response (RR)
	Latency and amplitude of b-wave
	Standard combined rod-cone response (SR)
Light adaptation	Latency and amplitude of a-b wave
	Oscillatory potentials (OP)
	Latency and amplitude of OP2-wave
	Cone response (CR)
	Latency and amplitude of b-wave
	30Hz Flicker response (FR)
	Interval between b1 and b2 waves, and amplitude of b1 wave

- Order of procedures: dark adaptation for at least 30 minutes; preparing the skin, mydriasis, anesthesia, pupil size measurement (using a red light pupillometer), placement of electrodes, surface anesthetic, placement of contact lens, ERG measurement under dark adapted conditions (at least 1 minute of darkness between measurements), 10 minute light adaptation, ERG measurements under light adaption

Figure 13: ERG measurement conditions for the 39-week monkey topical ocular toxicity study (report # B7689)

1) ERG under dark adaptation					
ERG	Measurement conditions of the instrument for evoked potential				
	Band-pass filter		Present count	Analysis (/div)	Stimulus frequency
	High	Low			
RR	500 Hz	0.5 Hz	5	30 msec.	0.1 Hz
SR	500 Hz	0.5 Hz	1×2	30 msec.	—
OP	500 Hz	50 Hz	1×2	10 msec.	—
ERG	Measurement conditions of the instrument for LED luminescent device				
	Stimulus luminance (cd/m ²)		Background luminance (cd/m ²)		Duration
RR	100		—		0.1 msec
SR	1000		—		3 msec
OP	1000		—		3 msec
2) ERG under light adaptation					
ERG	Measurement conditions of the instrument for evoked potential				
	Band-pass filter		Present count	Analysis (/div)	Stimulus frequency
	High	Low			
CR	500 Hz	0.5 Hz	5	20 msec.	0.1 Hz
FR	500 Hz	0.5 Hz	20	20 msec.	30 Hz
ERG	Measurement conditions of the instrument for LED luminescent device				
	Stimulus luminance (cd/m ²)		Background luminance (cd/m ²)		Duration
CR	1000		31.6		3 msec
FR	1000		31.6		3 msec

ECG

- No treatment-related effects apparent for ECG or blood pressure.
- ECG and blood pressure (chair restraint without anesthesia) were measured pre-dose, D135, D240 (at least one hour after dosing), and for recovery animals on recovery day 15 or 16. Heart rate, PR, QT, QRS, and QTc were calculated. Systolic and diastolic blood pressure were measured (upper left arm cuff).

Hematology and Clinical Chemistry

- No treatment-related effects apparent for hematology, coagulation, or clinical chemistry.
- After overnight fasting, blood was collected for hematology, coagulation, and clinical chemistry pre-dose, D75/76, D250/251, and for recovery animals on recovery day 19/20. Standard endpoints were evaluated.

Urinalysis

- No treatment-related effects apparent for urinalysis.
- Overnight fasted urine samples were collected pre-dose, D72/73, D156/157, D247/248 [not evaluated during recovery]
- Review note: generally, P/T recommends collecting urinalysis with blood collection for clinical pathology, to avoid the need for multiple days of fasting close together. Standard endpoints were evaluated.

Gross Pathology

- No treatment-related effects apparent.
- As noted above, high dose male # 3004 had grossly visible pancreas white discoloration.
- All animals were fasted overnight prior to sacrifice, and underwent gross examination for pathology.

Organ Weights

- Organ weights were measured for the brain, pituitary, thyroid (with parathyroid), submandibular gland, spleen, heart, lung, liver with gall bladder, pancreas, kidney, male reproductive organs (testis, epididymis, prostate), female reproductive organs (ovary, uterus). [the thymus was not weighed]
- The authors noted a decrease in lung weight for the low-dose female group, and attributed it to lung observations (granuloma for # 2101, inflammatory changes for # 2103). The authors considered these effects incidental.
 - o Notably, the male relative lung/body weights are 0.47, 0.49, and 0.54 for the main-group control, low-dose, and high-doses respectively. Together with the female recovery lung weight, these data suggest that the control lung weights might be outliers. This reviewer concurs that a treatment-effect is not clearly apparent.

Table 40: Female lung weight for the 39-week monkey topical ocular toxicity study (report # B7689)

Group	Wt	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye/)
Main group	Body wt (kg)	3.02 ± 0.27	3.22 ± 0.07	2.92 ± 0.14
	Lung wt (g)	17.9 ± 1.6	15.5 ± 0.8 [-13.4%]	14.4 ± 1.1 * [-19.6%]
	Lung /body wt	0.59 ± 0.01	0.48 ± 0.02 ** [-18.6%]	0.50 ± 0.05 * [-15.2%]
Recovery group	Body wt (kg)	3.26	3.96	3.31
	Lung wt (g)	16.0	16.2	14.8
	Lung /body wt	0.49	0.44	0.45

Mean ± SD. Statistically different from control by Dunnett's test, * ≤ 0.05, ** ≤ 0.01

Histopathology

Adequate Battery

- Histopathology was limited to: eyeball, optic nerve, conjunctiva (palpebral, superior, inferior), nasal cavity (vestibular, respiratory, and olfactory), sciatic nerve, lacrimal gland, thyroid and parathyroid, adrenal, submandibular lymph node, submandibular gland, sublingual gland, parotid gland, kidney, testis, epididymis, ovary, femur (including bone marrow), and femoral skeletal muscle.
- Based on the cheek observations noted for one monkey, cheek skin (left and right, including the nasal bridge) was collected and examined for all control and high-dose males.
- "macula retinae containing fovea were not present on the slide for the animals numbered 1002 (right), 2002 (left), 3003 (right and left), 1102 (left), 2013 (left), 3103 (right and left), 3005 (left))." The failure to evaluate the fovea of treated (left eyes) for two low-dose monkeys and 3 high-dose monkeys is a serious study limitation.

Study Pathologist: (b) (4) (credentials not reported). No peer review documented.

Histopathology reporting deficiency: The study report does not include a separate pathology report. The histopathology summary tables (tables 13-1 to 13-12, report pages 407-418) are incomplete. The individual animal listings (report pages 419-448) have additional information pivotal to the review of this study.

Histological Findings

- All of the females were sexually mature (based on clinical signs of menses).
- Based on histopathology, only one male was sexually mature, # 2003 (high dose group).
- No treatment-related effects apparent for eyes or ocular adnexa.
- Histopathology results were reported for the vestibular, respiratory, and olfactory areas together (i.e. pooled, not separately listed).
 - o The summary table presented nasal cavity respiratory inflammation. The individual animal data sheets clarified that the finding was “chronic respiratory inflammation”.
 - o Additionally, the individual animal sheets (but not the summary data tables) clarified that the nasal cavity chronic respiratory inflammation was observed with squamous metaplasia: 1/10 controls, 3/10 low-dose, and 4/10 high-dose animals.
 - o Severity increased with dose: the single control observation was minimal; the metaplasia was graded mild for all 3 of the low-dose observations, and 2 of the high-dose observations.
 - o This reviewer concludes that the incidence of nasal cavity squamous metaplasia is treatment-related and adverse.

Table 41: Selected histopathology result for the 39-week monkey topical ocular toxicity study (report # B7689)

Finding	Severity	Male			Female		
		0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye)	0	0.003% (0.9 µg/eye)	0.01% (3 µg/eye)
Main groups							
Pancreas: acinar atrophy; necrosis	Moderate	0/3	0/3	1/3	0/3	0/3	0/3
Right nasal cavity – chronic respiratory inflammation	Minimal	2/3	1/3	1/3	0/3	1/3	1/3
	Mild	1/3	2/3	0/3	3/3	2/3	2/3
Left nasal cavity – chronic respiratory inflammation	Minimal	2/3	1/3	1/3	0/3	1/3	1/3
	Mild	1/3	2/3	0/3	3/3	2/3	2/3

Nasal cavity chronic respiratory inflammation with unilateral (L or R) <i>squamous metaplasia</i>	Mild	0/3	1/3 (R)	0/3	0/3	0/3	1/3 (L)
Nasal cavity chronic respiratory inflammation with <i>bilateral squamous metaplasia</i>	Minimal	0/3	0/3	1/3	1/3	0/3	0/3
	Mild	0/3	1/3	0/3	0/3	0/3	0/3
Lung – fibrosis, alveolar septa, with alveolar cell hyperplasia	Minimal	1/3	0/3	1/3	0/3	0/3	0/3
Lung – granuloma	Minimal	0/3	0/3	0/3	0/3	1/3	0/3
Lung – inflammation, chronic	Minimal	1/3	1/3	0/3	0/3	1/3	0/3
Recovery groups							
Right nasal cavity – chronic respiratory inflammation	Minimal	0/2	1/2	1/2	1/2	1/2	1/2
	Mild	1/2	1/2	1/2	0/2	1/2	1/2
Left nasal cavity – chronic respiratory inflammation	Minimal	0/2	1/2	1/2	1/2	1/2	1/2
	Mild	1/2	1/2	1/2	0/2	1/2	1/2
Lung – fibrosis, alveolar septa	Minimal	0/2	0/2	1/2	0/2	0/2	0/2
Lung inflammation	Minimal	0/2	0/2	1/2	0/2	0/2	0/2
Nasal cavity chronic respiratory inflammation with <i>bilateral squamous metaplasia</i>	Minimal	0/2	0/2	0/2	0/2	0/2	1/2
	Mild	0/2	1/2	0/2	0/2	0/2	1/2

Toxicokinetics

- Blood was collected for TK for D1, 35, 98, 189, 273: pre-dose (on all days except D1), and post-dose at 5, 15, 30 minutes, 1, 2, 4 hours.
- Detection method was LC-MS/MS.

Table 42: Plasma Omidenepag TK results for the 39-week monkey topical ocular toxicity study (report # B7689)

	Males		Females	
Group	0.003% DE-117group	0.01% DE-117 group	0.003% DE-117group	0.01% DE-117group
T _{max} (h)				
Day 1	0.0833	0.0833	0.0833	0.150
Week 5	0.0833	0.0833	0.0833	0.150
Week 14	0.117	0.117	0.0833	0.117
Week 27	0.117	0.217	0.0833	0.0833
Week 39	0.117	0.183	0.0833	0.117
C _{max} (pg/mL)				
Day 1	447	1030	375	913
Week 5	439	937	414	1160
Week 14	444	946	433	1370
Week 27	385	963	461	1380
Week 39	323	911	329	1140
AUC _{0-4h} (pg·h/mL)				
Day 1	145	534	111	420
Week 5	172	425	133	459
Week 14	170	450	155	496
Week 27	158	502	145	525
Week 39	131	484	113	445

*

Dosing Solution Analysis

The test article characterization appears adequate. Doses were 96.4 to 98.3% of nominal.

6.2 Subcutaneous Injection Route Toxicity

Title	A 2-week repeated subcutaneous dose toxicity study of UR-7385 in rats	
Report #	529Ff030	
Key findings	- The authors concluded, and this reviewer concurs, that this non-GLP subcutaneous dose range-finding study did not identify a NOAEL. - At the low-dose LOAEL (0.4 mg/kg): clinical signs (skin flushing, loose stool), increased reticulocyte counts; injection site foamy cell infiltration and fibrous tissue proliferation	
Report details	NDA location	4.2.3.1 Single-Dose Toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4231-single-dose-tox\529ff030\529ff030-pre-clinical-study-report.pdf) [Review note: this is a repeat-dose study]
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center, 8916-16, Takayama-cho, Ikoma-shi, Nara, 630-0101 Japan
	Report date	November 16, 2017 - Study initiation 11/04/2010 - Necropsy 12/03/2010
	GLP status	No
	Test article	Omidenepag isopropyl (UR-7385), lot # 7
Methods	Vehicle	(b) (4) in physiological saline
	Species	Sprague Dawley rat 5 weeks old at start of dosing
	Doses	0, 0.4, 1.3, or 4 mg/kg/day for 14 days by subcutaneous injection (10 ml/kg)
	Group sizes	- Main-group: 3/sex/dose - TK groups: 3/sex/dose for the 0.4, 1.3, and 4 mg/kg doses
	Endpoints	Standard general toxicology design including ophthalmoscopy (slit lamp examination and funduscopy) for control and high-dose animals on D13; blood and urine collection for clinical pathology

		on D15; blood collection for TK following dosing on D1 and D14. Necropsy on D15, with limited organ weight measurement and limited systemic histopathology (not including the eyes or ocular adnexa)
Results	Clinical signs	- All omidenepag isopropyl-treated rats exhibited slight flushing of the pinna, limbs and tail from 1 to 5 hours post-dose - Beginning D4 for 0.4 and 1.3 mg/kg groups - Beginning D1 for the 4 mg/kg group (all high-dose rats affected on all days of treatment) - All animals recovered on D15 (i.e. last dose on D14) - All Omidenepag isopropyl treated groups exhibited loose stool, beginning on D4 (3/6 low-dose rats, 6/6 mid-dose and 6/6 high-dose rats affected)
	Body weight	Authors noted reduced weight gain at 1.3 and 4 mg/kg
	Food consumption	No treatment-effect apparent
	Ophthalmology	One high-dose rat (1/6) had a unilateral lens opacity (nuclear) on D13. Without pre-dose ophthalmoscopy, the relationship to treatment cannot be determined or excluded.
	Hematology	Authors noted increased reticulocyte counts for all omidenepag isopropyl dose levels
	Coagulation	Authors noted shortened plasma prothrombin time (PT) and activated plasma thromboplastin time (APTT) at 1.3 and 4 mg/kg/day
	Gross necropsy	One high-dose male (1/6) had unilateral kidney pelvis dilatation
	Histopathology	- All omidenepag isopropyl dose levels caused injection site foamy cell accumulation and fibrous tissue proliferation - Kidney damage at 1.3 mg/kg (3/3 males) and 4 mg/kg (6/6 rats): eosinophilic material in the proximal tubules (suggestive of protein resorption), "brush border derangement" of urinary tubules - Heart damage at 1.3 mg/kg (myocardium degeneration in 2/6) and 4 mg/kg (myocardial hypertrophy in 2/6) - Liver damage at 4 mg/kg: diffuse hypertrophy, bile duct hypertrophy, microgranuloma
	Dose formulation	Testing appears adequate, test article was within 2.2% of nominal.
TK:		

Table 43: Serum TK data for the non-GLP 2-week rat subcutaneous route toxicity study (report # 529ff030)

Day	Sex	Parameter	0.4 mg/kg/day	1.3 mg/kg/day	4 mg/kg/day
1	Male	C _{max} (ng/ml)	87.1 ± 29.3	293 ± 23	902 ± 166
		AUC _{0-last} (ng*hr/ml)	169 ± 16	648 ± 20	1960 ± 320
		T _{1/2} (hr)	0.705	0.605	0.625
1	Female	C _{max} (ng/ml)	64.2 ± 11.6	210 ± 30	842 ± 163
		AUC _{0-last} (ng*hr/ml)	145 ± 20	483 ± 52	1810 ± 180
		T _{1/2} (hr)	0.833	1.00	0.833
14	Male	C _{max} (ng/ml)	84.5 ± 8.3	286 ± 18	910 ± 65
		AUC _{0-last} (ng*hr/ml)	201	651 ± 60	2160 ± 150
		T _{1/2} (hr)	NC	0.594	NC
14	Female	C _{max} (ng/ml)	83.5 ± 18.1	194 ± 17	825 ± 23
		AUC _{0-last} (ng*hr/ml)	184 ± 39	542 ± 29	1880 ± 80
		T _{1/2} (hr)	0.380	0.665 ± 0.038	NC

Data presented as means ± SD (or without SD when SD not calculated)

NC: not calculated

Study title: A 4-Week Repeated Subcutaneous Dose Toxicity Study of UR-7385 in Rats

Study no.:	112201
Study report location:	4.2.3.2 Repeat-Dose Toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\112201\112201-pre-clinical-study-report.pdf)
Conducting laboratory and location:	Santen Pharmaceutical Co., Ltd. Nara Research & Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101, Japan
Report date:	March 21, 2012
Date of study initiation:	May 19, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot 28, purity 99.9%

Key Study Findings

- The authors concluded that the GLP 4-week rat sc toxicity study did not identify a NOAEL based on liver and kidney toxicity.
 - This reviewer concurs with the conclusion that a NOAEL was not identified, based on liver gross pathology (dark and large liver), and clinical signs (skin flushing, loose stool). The description of the liver and kidney histopathology findings are unclear.
 - The study was repeated with lower doses (report # 112203, reviewed below).
- The high-dose, 1 mg/kg/day, caused retinal hyperreflexia (detected by in-life ophthalmoscopy), corresponding to the histopathology finding of slight focal retinal degeneration.
- Only a limited battery of systemic tissues was evaluated. Notably, histopathology of the nasal cavity was not conducted; this limits the value of this systemic route study to interpret the topical ocular monkey study results.

Methods

Doses:	0, 0.04, 0.2, 1.0 mg/kg/day
Frequency of dosing:	Once daily for 28 days
Route of administration:	Subcutaneous injection
	Injection site rotated among for dorsal sites
Dose volume:	5 ml/kg
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	Main group: 10/sex/dose [necropsy on D29] TK group: 4/sex/dose
Age:	5 weeks old at start of dosing
Deviation from study protocol:	The pancreas is listed as an organ for histopathology, but was only evaluated when gross lesions were noted. This protocol deviation is not addressed, and is a study limitation.

Observations and Results

Mortality

- No animals died early.

Clinical Signs

- Cage side observations were made twice daily during dosing (once pre-dose, and once approximately 1 hour post-dose). Animals with findings were removed from cage for detailed clinical signs.
- No clinical signs were apparent at 0.04 mg/kg/day.
- Slightly flushing of the pinna, tail and extremities were observed at 1 hour post-dose, and had resolved the next day (when animals were observed pre-dose).

- o At 0.2 mg/kg: 9/10 males and 10/females affected, beginning on D3.
 - o At 1.0 mg/kg: all animals affected, beginning D1.
- Loose stool:
 - o At 0.2 mg/kg: observed in 1 male and 1 female (beginning D7)
 - o At 1 mg/kg: observed in 10/10 males and 5/10 females, beginning D1

Body Weights

- No treatment-effect on body weight apparent.
- Body weight was measured weekly.

Feed Consumption

- No treatment-effect on food consumption apparent.
- Rats were single-housed. Food consumption was measured on a weekly basis.

Ophthalmoscopy

- Ophthalmoscopy (slit lamp and fundoscopy) was scheduled for the control and high-dose only on D25 (i.e. not pre-dose). Based on high-dose findings, ophthalmology was also conducted for the 0.2 mg/kg/day group.
- Two high-dose animals had a retinal finding, "hyperreflexia" (bilateral in male # 040036, OS only in female # 04100).
 - o The finding in both the male (report page 176) and female (report page 184) corresponded histopathological with slight focal retinal degeneration.
- The background incidence of corneal opacity and lens opacity was high (i.e. observed in the control and treated groups); no treatment effect apparent.

Hematology and Clinical Chemistry

- No treatment-effect apparent for hematology, coagulation, or clinical chemistry.
- Blood was collected on D29 for hematology, coagulation, and clinical chemistry. Standard parameters were measured.

Urinalysis

- No treatment-effect apparent for urinalysis.
- For 5/sex/dose, rats were placed in metabolism cages on D28, to collect overnight urine with fasting. Standard parameters were measured. Separately, subsequent urine (from the first collection until necropsy) was collected and preserved.

Gross Pathology

- Main-group animals were sacrificed on D29, and underwent full gross pathology.
- Large and dark liver: males at 0.04, 2 and 1 mg/kg, females at 1 mg/kg only.
- Large and dark kidney: males at 1 mg/kg
- Large thyroid: males at 0.2 and 1 mg/kg.

Table 44: selected gross pathology for the first GLP 4-week rat sc toxicity study (report # 112201)

Gross finding	0	0.04 mg/kg	0.2 mg/kg	1.0 mg/kg
Number/sex/group examined	10	10	10	10
Males				
Liver – large	0	1	2	4
Liver – dark	0	1	3	10
Kidney – large	0	0	0	5
Kidney – dark	0	0	0	4
Thyroid – bilateral, large	0	0	1	2
Females				
Liver – large	0	0	0	2
Liver – dark	0	0	0	5
Liver – diaphragmatic nodule	0	1	0	0
Kidney – unilateral cyst	0	0	0	1

- The liver nodule observed for the low-dose female (# 02073). Liver histopathology for this animal found very slight peripheral fatty change, slight focal necrosis, and an increase in hepatocyte nuclear chromatin. The authors did not directly address whether any of these changes correspond to the nodule.

Organ Weights

- Kidney weight was increased slightly for high-dose males: +5.8% (absolute organ weight), + 8.7% kidney/body weight.
- Limited battery of organs weighed, notably including the eyes but not the pancreas, prostate, or epididymis. Organs weighed were: liver, kidneys, eyes, submandibular gland, thymus, heart, lung with bronchi, spleen, testes, ovaries, uterus, adrenals, thyroid with parathyroid, brain, pituitary.
- Review note:* the control mean eye weights were 281 mg (males) and 264 mg (females). The control mean eye/body weights were 7.3 mg/kg body weight (males) and 12.5 mg/kg (females).

Histopathology

- The study personnel for histopathology are Osamu Katsuta and Miwa Yohsima (credentials not reported). No mention made of peer-review.

Adequate Battery

- The list of systemic tissues was limited: liver, kidneys, eyes, submandibular gland, thymus, heart, lungs with bronchi, spleen, testes, ovaries, uterus, adrenals, thyroid with parathyroid, brain, pituitary, stomach, duodenum, jejunum, ileum, cecum, colon.
 - The pancreas was listed for histopathology (report page 30), but no results were reported for any animal.

- o Notably, the battery omitted nasal cavity or nasal turbinates, trachea, esophagus, bone, bone marrow, epididymis, mammary glands, skeletal muscle, skin, spinal cord, urinary bladder, and vagina
- o Details for sectioning and evaluation of the eyes was not reported; this is a study limitation.
- o The report appears to have omitted standard histopathology results [hematoxylin and eosin (H&E) staining] for the liver and kidneys. This is not a critical study limitation (since toxicity is clearly evident from the gross pathology results]
- Immunohistochemistry for proliferating cell nuclear antigen (PCNA) was conducted for the liver and jejunum (the latter tissue used as a positive control).
- After standard sectioning, the left kidney for 3 rats/sex/dose were processed for transmission electron microscopy (TEM) and examined.

Histological Findings

Table 45: selected male histopathology for the first GLP 4-week rat subcutaneous toxicity study (report # 112201)

Male Lesion	Severity	0	0.04 mg/kg	0.2 mg/kg	1.0 mg/kg
Number/sex/group examined	0	10	10	10	10
Liver – focal necrosis	Very slight to slight	10	10	10	8
	Moderate	0	0	0	1
Liver – microgranuloma	Very slight	6	9	6	6
	Slight	0	1	1	0
Liver – hepatocyte increased nuclear chromatin	Very slight	0	0	3	3
	Slight	0	0	1	5
Stomach – limiting ridge vacuolation	Slight	0	0	0	3
	Moderate	0	0	0	4
Stomach – glandular hyaline inclusion	Slight	0	0	0	4
	Moderate	0	0	0	5
Heart – myocardial degeneration	Very slight	2	1	1	3
	Slight	1	1	1	0
	Moderate	0	0	1	0
Spleen – hypertrophy, red pulp, histiocytic cell	Very slight	0	2	0	1
	Slight	0	0	1	0
Lung – artery mineralization	Very slight	0	2	1	2
Lung – hemorrhage	Very slight	2	1	0	1
	Slight	0	1	0	1
Eyes – focal retinal degeneration	Slight	0	0	0	1
Skin (injection site) - proliferation of subcutaneous fibrous tissue	Very slight to slight	10	7	10	6
	Moderate	0	3	0	4
Skin (injection site) – subcutaneous foamy cell	Slight	0	4	2	2
	Moderate	10	6	8	8

Kidney – proximal tubule basophilia	Very slight	4	2	4	4
	Slight	1	0	0	1
	Moderate	0	0	0	1
Kidney – interstitial fibrosis	Very slight	0	0	0	1
	Slight	0	0	0	1
Kidney – proximal tubule eosinophilic substance	Very slight	0	0	2	1
	Slight	0	1	1	7
	Moderate	0	0	0	2

Table 46: selected female histopathology for the first GLP 4-week rat subcutaneous toxicity study (report # 112201)

Female Lesion	Severity	0	0.04 mg/kg	0.2 mg/kg	1.0 mg/kg
Number/sex/group examined	0	10	10	10	10
Liver – focal necrosis	Very slight to slight	7	7	9	8
Liver – peripheral fatty change	Very slight	1	2	4	6
	Slight	0	2	2	0
	Moderate	1	0	1	0
Liver – hepatocyte increased nuclear chromatin	Very slight	0	2	3	4
	Slight	0	0	1	4
Stomach – glandular hyaline inclusion	Slight	0	0	0	1
	Moderate	0	0	0	6
Heart – myocardial degeneration	Very slight	0	0	0	1
Thyroid – follicular dilatation colloid	Very slight	0	0	0	3
Lung – artery mineralization	Very slight	0	0	1	0
Lung – hemorrhage	Very slight	0	0	0	1
Eyes – focal retinal degeneration	Slight	0	0	0	1
Skin (injection site) - proliferation of subcutaneous fibrous tissue	Very slight to slight	9	7	8	8
	Moderate	1	3	1	2
Skin (injection site) – subcutaneous foamy cell	Very slight	1	0	2	0
	Slight	3	7	5	8
	Moderate	6	3	3	2
Kidney – proximal tubule basophilia	Very slight	0	0	1	3
Kidney – proximal tubule eosinophilic substance	Very slight	0	1	1	4

Table 47: Transmission electron microscopy found substance in the renal proximal tubular epithelial cells of the first GLP rat 4-week subcutaneous toxicity study (report # 112201)

Kidney TEM: substance in the proximate tubular epithelial cells	Severity	0	0.04 mg/kg	0.2 mg/kg	1.0 mg/kg
Males (described as crystalline substance)	Present	0/3	1/3	2/3	3/3
Females (described has high electron density substance)	Present	0/3	3/3	2/3	3/3

Toxicokinetics

- For the TK group, blood was collected for the D1 and D28 doses: pre-dose on D28; and for both days, post-dose at 15 and 30 minutes; 1, 2, 4 and 8 hours. Plasma was analyzed by LC-MS/MS for omidenepag (UR-7276).
- Clinical signs and body weight data were reportedly collected for the TK animals, but not reported.

Table 48: Omidenepag plasma TK results for the first GLP rat 4-week subcutaneous toxicity study (report # 112201)

Day	Sex	Parameter	0.04 mg/kg/day	0.2 mg/kg/day	1 mg/kg/day
1	Male	C _{max} (ng/ml)	6.03 ± 0.55	45.3 ± 9.2	257 ± 57
		AUC _{0-8h} (ng*hr/ml)	11.2 ± 0.8	71.0 ± 6.6	456 ± 44
		T _{1/2} (hr)	0.582	0.481	0.596
1	Female	C _{max} (ng/ml)	5.86 ± 1.00	28.6 ± 2.8	203 ± 26
		AUC _{0-8h} (ng*hr/ml)	10.6 ± 1.8	50.4 ± 4.7	356 ± 33
		T _{1/2} (hr)	0.648	0.555	0.553
28	Male	C _{max} (ng/ml)	7.41 ± 1.58	33.2 ± 3.5	201 ± 25
		AUC _{0-8h} (ng*hr/ml)	18.1 ± 1.9	86.9 ± 5.5	483 ± 57
		T _{1/2} (hr)	1.26	1.04	0.735
28	Female	C _{max} (ng/ml)	5.09 ± 1.21	22.5 ± 3.8	166 ± 26

		AUC _{0-8h} (ng*hr/ml)	13.9 ± 5.1	51.5 ± 5.7	356 ± 33
		T _{1/2} (hr)	NC	0.700	0.791

Data presented as means ± SD. NC = not calculated

Dosing Solution Analysis

Test article analysis appears adequate. Concentrations were within 4.4% of nominal.

Study title: A 4-Week Repeated Subcutaneous Dose Toxicity Study of UR-7385 in Rats - Additional Study

Study no.:	112203
Study report location:	4.2.3.2 Repeat-Dose Toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\112203\112203-pre-clinical-study-report.pdf)
Conducting laboratory and location:	Santen Pharmaceutical Co., Ltd. Nara Research & Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101, Japan
Report date:	April 27, 2012
Date of study initiation:	October 19, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot 28, purity 99.9%

Key Study Findings

- This GLP 4-week rat sc toxicity study did not identify a clear NOAEL, based on kidney interstitial tissue fibrosis (very slight to slight) in males at the low-dose (0.01 mg/kg), and increased severity of liver peripheral fatty change in females at 0.01 mg/kg.
- The authors considered the mid-dose, 0.02 mg/kg/day, to be the NOAEL.
- The authors noted high-dose effects: increased incidence of increased hepatocyte nuclear chromatin in females, and increased kidney proximal tubular epithelium eosinophilic material in both sexes. This review concurs that these effects may be treatment-related, but they are not clearly adverse.
- Histopathology was limited to the liver, kidneys, and grossly observed lesions (i.e. relying on the previous 4-week rat sc study (report # 112201) for other histopathology). Taking these two studies together, the histopathology would not be considered adequate to identify a NOAEL to support clinical dosing.

Methods

Doses:	0, 0.01, 0.02, or 0.04 mg/kg/day
Frequency of dosing:	Daily for 28 days
Route of administration:	Subcutaneous injection
Dose volume:	5 ml/kg
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	Main group: 10/sex/dose [necropsy on D29] TK satellite: 4/sex/dose [necropsy on D64 for females and D65 for males – i.e. used as recovery animals]
Age:	5 weeks old at start of dosing

Key Observations and Results

- No animals died early.
- No treatment-related effects were apparent for clinical signs, body weight, food consumption.
- Ophthalmology was not performed.
- Blood and urine samples were not collected for clinical pathology endpoints.

Gross Pathology & Organ weights

- Main-group rats were necropsied on D29; the TK (recovery) rats were necropsied on D64.
- Only the liver and kidneys were weighed.
- No treatment-related effects were apparent for gross pathology and organ weights.

Histopathology

- The study personnel for histopathology are (b) (4) (credentials not reported). No mention made of peer-review.

Adequate Battery

- Histopathology was limited to liver, kidneys, and grossly observed lesions from all animals.

Histopathology findings

- No kidney or liver effects for the low- and mid-dose.
- The authors noted treatment effects at the high-dose:
 - o Increased hepatocyte nuclear chromatin in females
 - o Kidney proximal tubular epithelium eosinophilic material

- This reviewer concludes that no clear NOAEL was identified, based on kidney interstitial tissue fibrosis (very slight to slight) in males at 0.04 mg/kg, and increased severity of liver peripheral fatty change in females at 0.04 mg/kg.

Table 49: Selected male kidney histopathology for the second GLP 4-week rat subcutaneous toxicity study (report # 112203)

Male Lesion	Severity	0	0.01 mg/kg	0.02 mg/kg	0.04 mg/kg
Main-group (10/dose)					
Kidney: proximal tubule basophilia	Very slight	2/10	2/10	4/10	4/10
	Slight	2/10	2/10	1/10	0/10
Kidney: proximal tubular epithelium – eosinophilic substance	Very slight	0/10	0/10	0/10	1/10
Kidney: fibrosis, interstitial tissue	Very slight	0/10	1/10	0/10	1/10
	Slight	0/10	1/10	0/10	0/10
TK (recovery)-group (4/dose)					
Kidney: proximal tubule basophilia	Very slight	2/4	0/4	0/4	1/4
	Slight	0/4	2/4	0/4	2/4

Table 50: Selected female kidney and liver histopathology for the second GLP 4-week rat subcutaneous toxicity study (report # 112203)

Male Lesion	Severity	0	0.01 mg/kg	0.02 mg/kg	0.04 mg/kg
Main-group (10/dose)					
Liver – peripheral fatty change	Very slight	6/10	6/10	3/10	4/10
	Slight	0/10	1/10	1/10	1/10
Liver – hepatocyte increase in nuclear chromatin	Very slight	0/10	0/10	0/10	3/10
Kidney: proximal tubule basophilia	Very slight	2/10	1/10	0/10	3/10
	Slight	0/10	0/10	1/10	0/10
Kidney: proximal tubular epithelium – eosinophilic substance	Very slight	0/10	0/10	0/10	1/10
TK (recovery)-group (4/dose)					
Liver – peripheral fatty change	Very slight	0/4	0/4	0/4	1/4
	Slight	0/4	1/4	1/4	0/4
Kidney: proximal tubule basophilia	Very slight	2/4	0/4	0/4	1/4
	Slight	0/4	2/4	0/4	2/4

Toxicokinetics

- Similar to the previous 28-day rat study, blood was collected from TK animals for the D1 and D28 doses: pre-dose on D28; and for both days, post-dose at 15 and 30 minutes; 1, 2, 4 and 8 hours. Plasma was analyzed by LC-MS/MS for omidenepag (UR-7276).

Table 51: Omidenepag plasma TK results for the second GLP rat 4-week subcutaneous toxicity study (report # 112203)

Day	Sex	Parameter	0.01 mg/kg/day	0.02 mg/kg/day	0.04 mg/kg/day
1	Male	C _{max} (ng/ml)	1.58 ± 0.29	2.68 ± 0.21	10.9 ± 4.3
		AUC _{0-8h} (ng*hr/ml)	2.54 ± 0.14	5.11 ± 0.48	14.7 ± 3.5
		T _{1/2} (hr)	0.625	0.750	0.625
1	Female	C _{max} (ng/ml)	0.964 ± 0.080	2.45 ± 0.57	3.85 ± 0.62
		AUC _{0-8h} (ng*hr/ml)	1.80 ± 0.14	4.53 ± 1.54	8.48 ± 1.02
		T _{1/2} (hr)	1.35	0.810	0.791
28	Male	C _{max} (ng/ml)	1.55 ± 0.15	3.77 ± 0.68	6.75 ± 1.64
		AUC _{0-8h} (ng*hr/ml)	3.96 ± 0.30	8.41 ± 0.32	18.6 ± 0.9
		T _{1/2} (hr)	1.10	0.875	1.25
28	Female	C _{max} (ng/ml)	1.19 ± 0.16	4.03 ± 2.09	8.83 ± 3.29
		AUC _{0-8h} (ng*hr/ml)	2.57 ± 0.32	6.59 ± 0.92	15.9 ± 7.3
		T _{1/2} (hr)	NC	0.777	0.636

Data presented as means ± SD. NC = not calculated

Dosing Solution Analysis

The test article characterization appears adequate; concentrations were 95.6 to 101.2% of nominal.

Study title: A 13-week subcutaneous toxicity study of UR-7385 in rats with a recovery period of 4 weeks

Study no.:	B-7645
Study report location:	4.2.3.2 Repeat-Dose Toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\b-7645\b7645-pre-clinical-study-report.pdf)
Conducting laboratory and location:	(b) (4)
TK analysis:	(b) (4)
Report date:	February 27, 2015
Date of study initiation:	March 26, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot # PPS110673, purity 99.5%

Key Study Findings

- The authors considered the high-dose, 0.003 mg/kg/day, to be the NOAEL. This reviewer concurs.
- The study has serious study limitations – inadequate ophthalmoscopy, inadequate ocular histopathology, and inadequate histopathology of paired organs.
 - o Ophthalmoscopy (slit lamp and biomicroscopy) was performed pre-dose, prior to group assignments. One rat with severe lesions was removed from the study, and others were used for TK.
 - o Ophthalmoscopy was performed for the recovery group rats (i.e. 5/sex/dose) on D22, D89, and recovery D26 (report page 23). The decision to omit the main-group rats from ophthalmoscopy was not explained, and is a serious study limitation.
 - o Three rats (1/5 mid-dose males and 2/5 high-dose males) had retinal folds detected (D22, D89, recovery D26).
 - The authors considered these effects incidental (i.e. either missed pre-dose, or developing spontaneously).
 - This reviewer concurs that a clear relationship to treatment is not established.
 - o For all paired organs (including the eyes), only unilateral histopathology was performed; this is a study limitation.

- As with the 4-week rat sc studies, no histopathology was conducted for the nasal cavity or nasal turbinates; this limits the value of this systemic route study to interpret the topical ocular monkey study results.

Methods

Doses:	0, 0.003, 0.01, or 0.03 mg/kg/day
Frequency of dosing:	Once daily for 91 days
Route of administration:	Subcutaneous injection
	Dosing was rotated among four dorsal injection sites
Dose volume:	5 ml/kg/day
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	Main-group: 10/sex/dose [necropsy on D92] Recovery-group: 5/sex/dose [necropsy on D120] TK group: 4/sex/dose
Age:	6 weeks of age at start of dosing
Weight:	Males 203 to 233 g, females 141 to 176 g, at start of dosing
Deviation from study protocol:	No deviations reported which would have affected the outcome or interpretability of the study

Observations and Results

Mortality

- No early deaths occurred.

Clinical Signs

- No treatment-related clinical signs apparent.
 - Review note:* the only clinical sign recorded was a broken incisor for one animal.
- During dosing, cage side observations were recorded three times daily: prior to dosing, immediately after dosing, and post-dose (1-3 hours). During recovery, cage side observations were recorded once daily.

Body Weights

- No treatment-related changes in body weight were apparent.
- Body weight was measured weekly and prior to necropsy.

Feed Consumption

- No treatment-related changes in food or water consumption were apparent.

- Animals were single-housed. Food consumption was measured weekly. During week 13 and recovery week 4, water intake was measured for one day (using water bottles, during the urine collection).

Ophthalmoscopy

- Slit lamp microscopy and indirect ophthalmoscopy: pre-dose, D22, D89, and recovery day 26.
- Pre-dose ophthalmoscopy was conducted for all animals.
 - Pre-dose, one male was removed from the study (severe iris hemorrhage with aqueous flare). 17 males and 12 females were found to have less severe abnormalities (e.g., lens opacity, vitreous hemorrhage, retinal folds, hyperreflectivity of the fundus, anterior chamber residue; data not tabulated) and were used to fill the TK groups.
- Ophthalmoscopy at D22, 89 and recovery day 26 was limited to the recovery rats (5 rats/sex/dose; report page 23). This is an important study limitation.
- Treatment-related effects were not clearly apparent.
 - At D22 onward, retinal folds were detected for one mid-dose male and two high-dose males.

Hematology and Clinical Chemistry

- No treatment-related effects apparent for clinical pathology.
- Blood was collected for hematology, coagulation, and clinical chemistry prior to necropsy, with overnight (16 to 21 hours) fasting. Standard clinical pathology parameters were evaluated.

Urinalysis

- No treatment-related effects apparent for urinalysis.
- The results of the 4-week rat studies identified the kidney as a sensitive target organ. Urine was collected over D85-86, and recovery D22-23. 44-hour urine samples (fasting with access to water) were collected into urine-collection trays, then the following 20-hour urine samples were collected (free access to food and water).
- Standard urinalysis endpoints measured.

Gross Pathology

- No treatment-related effects apparent. The injection sites (controls and treated) had subcutaneous brown or dark red foci for most main-group animals, with a lower incidence among recovery animals.
- Standard full gross necropsy was conducted for all main-group and recovery group animals.

Organ Weights

- No treatment-related effect apparent for organ weight results.
- The following organs were weighed (paired organs weighed separately noted with *): “brain, pituitary, thyroid (including parathyroid)*, adrenal*, thymus, spleen, heart, lung (including bronchus), salivary gland*, liver, kidney*, testis*, prostate, seminal vesicle, ovary* and uterus”.
- *Review note:* the omission of the pancreas weight is a study limitation, given its omission from the 4-week sc rat studies.

Histopathology

- The study pathologist was (b) (4). No mention of peer-review.

Adequate Battery

- From report page 27, “Paired organs indicated by * were removed bilaterally, but microscopically examined unilaterally.

cerebrum, cerebellum, spinal cord (thoracic), sciatic nerve, eyeball*, optic nerve*, harderian gland*, pituitary, thyroid*, parathyroid*, adrenal*, thymus, spleen, submandibular lymph node, mesenteric lymph node, heart, thoracic aorta, trachea, lung (including bronchus), tongue, esophagus, stomach, duodenum, jejunum, ileum (including Peyer’s patch), cecum, colon, rectum, submandibular gland*, sublingual gland*, liver, pancreas, kidney*, urinary bladder, testis*, epididymis*, prostate, seminal vesicle*, ovary*, uterus*, vagina, mammary gland (inguinal region)*, sternum (including bone marrow), femur (including bone marrow)*, femoral skeletal muscle*, skin (inguinal region)* and injection site (subcutis, dorsal)”*

- The larynx and nasal cavity were preserved, but not evaluated.
- Histopathology was conducted for the controls and high-dose animals only
- *Review note:* no information documenting sectioning of the eyes or adequate assessment of ocular structures was reported; this is a study limitation.

Histological Findings

- The authors conclude, and this reviewer concurs, that no treatment-related histopathology findings were reported.
- *Review note:* this reviewer checked carefully, and verified the lack of findings associated with preneoplastic or neoplastic changes for the treated animals.

Toxicokinetics

- Blood was collected from 3/sex/dose satellite animals (with one reserve/sex/dose in case of accident).
- For the control TK group, blood was collected once/day for D1, D28, and D91.

- For the omidenepag isopropyl treated groups, blood was collected on pre-dose for D28 and D91 and post-dose for D1, D28 and D91 at: 15 and 30 minutes, 1, 2, 4, and 8 hours.

Table 52: Omidenepag serum TK for the 13-week rat subcutaneous toxicity study (report # B7645)

Day	Dose level (mg/kg/day)	Sex	T _{max} (h)	C _{max} (ng/ml)	AUC _{0-8h} (ng*h/ml)
1	0.003	M	0.4	0.765	0.701
		F	0.4	0.622	0.560
	0.01	M	0.4	2.45	2.67
		F	0.3	1.48	1.33
	0.03	M	0.5	9.41	9.97
		F	0.3	6.53	6.32
28	0.003	M	0.6	0.746	1.08
		F	0.4	0.889	0.789
	0.01	M	0.5	3.51	4.68
		F	0.4	2.15	2.37
	0.03	M	0.5	12.7	14.9
		F	0.4	7.86	8.91
91	0.003	M	0.8	1.01	1.81
		F	0.4	0.878	0.992
	0.01	M	0.8	3.39	6.76
		F	0.4	2.02	2.73
	0.03	M	0.5	13.5	22.4
		F	0.4	9.94	12.2

Data presented as mean TK parameter.

Dosing Solution Analysis

Test article characterization appears adequate. Concentrations were 98.0 to 102.0% of nominal.

Study title: A 26-week subcutaneous toxicity study of UR-7385 in rats with a recovery period of 4 weeks

Study no.:	B-7774
Study report location:	4.2.3.2 Repeat-Dose Toxicity (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\b-7774\b7774-pre-clinical-study-report.pdf)
Conducting laboratory and location:	(b) (4)
Histopathology:	(b) (4)
TK analysis:	(b) (4)
Report date:	November 11, 2015
Date of study initiation:	November 11, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot # RGC1403010, purity 99.2%

Key Study Findings

- No NOAEL identified. The low-dose is the LOAEL.
 - o A concerning finding (spermatic cord nodule) was detected grossly in one low-dose male (histopathology was not performed).
 - o Despite tumors observed in the high-dose group for the pituitary, kidney, pancreas, and mammary, histopathology of these organs was not performed for the low- and mid-doses, or for any recovery animals. Therefore, NOAEL values for these tumors was not established.
- This study has additional deficiencies which limit its usefulness to support safety:
 - o Ophthalmoscopy after start of dosing was only performed for recovery-group animals (i.e. not main-group animals). [No concerns identified]
 - o As with the 4-week and 13-week rat sc studies, pancreas not weighed. [This is a study deficiency, in light of the high-dose pancreas adenoma]

- o As with the 4-week and 13-week rat sc studies, no histopathology was conducted for the nasal cavity or nasal turbinates; this limits the value of this systemic route study to interpret the topical ocular monkey study results.
- o The reporting does not explicitly document histopathologic examination of all structures of the eye. Moreover, histopathology was only performed for one eye/animal (for the main-group control and high-dose animals).

Methods

Doses:	0, 0.003, 0.01, or 0.03 mg/kg/day
Frequency of dosing:	Once daily for 182 days (26 weeks)
Route of administration:	Subcutaneous injection
	Dosing was rotated among four dorsal injection sites
Dose volume:	5 ml/kg/day
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	Main-group: 15/sex/dose [necropsy on D183] Recovery-group: 5/sex/dose [necropsy on D211] TK group: 4/sex/dose
Age:	6 weeks of age at start of dosing
Weight:	At start of dosing: male range 206 to 249 g, females 155 to 196 g
Deviation from study protocol:	No deviations reported which would have affected the outcome or interpretability of the study

Observations and Results

Mortality

- One rat was found dead; no rats exhibited moribundity; none were sacrificed early.
- Low-dose male # 2005 was found dead on D122 (week 18). The authors noted, “no abnormalities were noted in the clinical observations or gross pathology”, and considered the histopathology unremarkable.
 - o The authors did not determine a cause of death, but considered the death incidental based on weight of evidence (e.g., no deaths at higher doses). This reviewer concurs.
 - o This reviewer verified that the in-life data (e.g. body weight data, urinalysis) were unremarkable.
 - o Urine and blood were not collected from the carcass for clinical pathology, due to autolysis.
- *Review note:* the failure to check animals twice per day approximately 12 hours apart for moribundity and morbidity is a study design deficiency.

Clinical Signs

- No treatment-related clinical signs apparent.
- During dosing, cage side observations were generally recorded three times daily (prior to dosing, immediately after dosing, and once approximately 1-3 hours post-dose). During recovery, cage side observations were recorded once daily.

Body Weights

- No treatment-related changes in body weight were apparent.
- Body weight was measured weekly and prior to necropsy.

Feed Consumption

- No treatment-related changes in food or water consumption were apparent.
- Animals were single-housed. Food consumption was measured weekly. During weeks 13, 26, and recovery week 4, water intake was measured for one day (using water bottles, during the urine collection).

Ophthalmoscopy

- No treatment-related changes apparent for ophthalmoscopy.
- Like the 13-week rat sc study, slit lamp microscopy and indirect ophthalmoscopy were only conducted for the recovery group animals: pre-dose, D90, D179, and recovery day 26. Failure to evaluate main-group animals is a serious study limitation.
- Pre-dose ophthalmoscopy was conducted for all animals.
 - Pre-dose, eight males and 5 females were removed from study due to severe ophthalmological abnormalities. Another 14 males and 18 females with minor abnormalities were used to fill the TK groups.

Hematology and Clinical Chemistry

- Low-dose male # 2006 (nephroblastoma) was an outlier for high white blood cell (WBC) counts (+76%), neutrophil counts (+4.03-fold increase), fibrinogen (+92%), and blood urea nitrogen (BUN, +2.09-fold increase) compared to control male means at necropsy.
- No other remarkable observations for clinical pathology.
- Blood was collected for hematology, coagulation, and clinical chemistry prior to necropsy, with overnight (16 to 21 hours) fasting. Standard clinical pathology parameters were evaluated.

Urinalysis

- Low-dose male # 2006 (nephroblastoma) was an outlier for high urinary volume at week 26: 35.6 ml (+73% compared to the control male mean at week 26). Other urine parameters for this animals were unremarkable.
- No other remarkable urinalysis results.
- Urine was collected overnight (fasting with access to water) on D85/86, D176/177, and recovery D22/23. 44-hour urine samples (fasting with access to water) were collected into urine-collection trays, then the following 20-hour urine samples were collected (free access to food and water).
- Standard urinalysis endpoint measured.

Gross Pathology

- Standard full gross necropsy was conducted for all main-group and recovery group animals. Remarkably, the study design did not trigger histopathology for all grossly observed lesions, and this is a serious study deficiency.
- One low-dose male (# 2013) had grossly detected “fat tissue, spermatic cord nodule”, 25 x 20 x 10 mm; “No tissues examined” for histopathology (report page 728).
 - o Organ weights (e.g. testis, prostate, seminal vesicle) were unremarkable for this rat.
 - o In this absence of histopathology, it is unclear if this finding was a benign or malignant.
 - o Reportedly^{16,17,18}, ~ 75% of spermatic cord tumors in patients are benign (e.g., sarcoma), and ~ 25% are malignant (e.g., liposarcoma, rhabdomyosarcoma).
- One low-dose male (# 2006) had gross left kidney nodule, correlating with the histopathology finding of nephroblastoma (report page 721)
- One high-dose female (# 4101) had pituitary nodule (2x2x2 mm), correlating with the histopathology finding of pars distalis adenoma, and pars distalis hyperplasia (report page 836). This animal also had a histopathology finding of mammary gland adenocarcinoma.

¹⁶ Moschini M, Mattei A. Diagnosis and management of spermatic cord tumors. Curr Opin Urol. 2017 Jan;27(1):76-79. doi: 10.1097/MOU.0000000000000318. PMID: 27262142. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/27262142/>

¹⁷ Rodríguez, Dayron, and Aria F Olumi. 20212. Management of spermatic cord tumors: a rare urologic malignancy. Therapeutic Advances in Urology 4(6): 325-3 34. doi:10.1177/1756287212447839. Accessed via: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3491755/>

¹⁸ Dagur, G., Gandhi, J., Kapadia, K., Inam, R., Smith, N. L., Joshi, G., & Khan, S. A. 2017. Neoplastic diseases of the spermatic cord: an overview of pathological features, evaluation, and management. Translational Andrology and Urology, 6(1), 101–110. <https://doi.org/10.21037/tau.2017.01.04> Accessed via: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5313312/>

Table 53: selected gross pathology for the GLP 26-week rat subcutaneous toxicity study (report # B7774)

Lesion	Severity	0	0.003 mg/kg	0.01 mg/kg	0.03 mg/kg
Main-group males (15/dose)					
Kidney nodule	Present	0	1	0	0
Spleen cyst	Present	0	0	1	1
Fat tissue, spermatic cord, nodule	Present	0	1	0	0
Main-group females (15/dose)					
Pituitary nodule	Present	0	0	0	1
Kidney cyst	Present	0	1	0	0
Liver dark red focus	Present	0	0	0	1

Organ Weights

- Low-dose rat # 2006 (nephroblastoma) had a normal right kidney weight; the left kidney was 47.18 g (+25.0-fold increase compared to the male control mean).
- High-dose female # 4101 (pituitary adenoma) was an outlier for increased pituitary weight: 43.4 mg (+2.12-fold the female control mean absolute pituitary weight, 2.07-fold increase over control for organ/body weight).
- No other remarkable observations for organ weight results.
- The following organs were weighed (paired organs weighed separately noted with *): "brain, pituitary, thyroid (including parathyroid)*, adrenal*, thymus, spleen, heart, lung (including bronchus), salivary gland*, liver, kidney*, testis*, prostate, seminal vesicle, ovary* and uterus".
- Review note:* the omission of the pancreas weight is a study limitation, given the omission of pancreas weight data from the 4- and 13-week rat sc studies.

Histopathology

- The study pathologist was (b) (4) No mention of peer-review.

Adequate Battery

- From report page 27, "Paired organs indicated by * were removed bilaterally, but microscopically examined unilaterally.
cerebrum, cerebellum, spinal cord (thoracic), sciatic nerve*, eyeball*, optic nerve*, harderian gland*, pituitary, thyroid*, parathyroid*, adrenal*, thymus, spleen, submandibular lymph node, mesenteric lymph node, heart, thoracic aorta, trachea, lung (including bronchus), tongue, esophagus, stomach, duodenum, jejunum, ileum (including Peyer's patch), cecum, colon, rectum,

submandibular gland, sublingual gland*, liver, pancreas, kidney*, urinary bladder, testis*, epididymis*, prostate, seminal vesicle*, ovary*, uterus*, vagina, mammary gland (inguinal region)*, sternum (including bone marrow), femur (including bone marrow)*, femoral skeletal muscle*, skin (inguinal region)* and injection site (subcutis, dorsal)."*

- The larynx and nasal cavity were preserved, but not evaluated.
- Histopathology was conducted for the main-group controls, high-dose animals, and one early decedent only. *"For the other animals including the low and middle dose groups in the main group and all recovery animals, histopathological examination was not done, because there were no treatment related changes in the high dose group in the main group."*
- *Review note:* the note that paired organs were examined unilaterally is inadequate for the eye; both eyes should be examined microscopically to support an ophthalmic indication. No information documenting sectioning of the eyes or adequate assessment of ocular structures was reported. These are study limitations.

Histological Findings

- This reviewer considers the tumor incidence among omidenepag isopropyl treated animals concerning.

Table 54: tumorigenicity summary for the GLP 26-week rat subcutaneous toxicity study (report # B7774)

Lesion	Both sexes combined			
	0	0.003 mg/kg/day	0.01 mg/kg/day	0.03 mg/kg/day
Pancreas acinar cell carcinoma	1/30	0/0	0/0	0/30
Nephroblastoma	0/30	1/1	0/0	0/30
Spermatic cord nodule (males only)	0/15	1/1	0/0	0/15
Pituitary pars distalis adenoma	0/30	0/30	0/30	2/30
Mammary adenocarcinoma (females only)	0/15	0/15	0/15	1/15

Note: this table likely underpredicts risks, since histopathology was not conducted for the low- and mid-dose groups, or for recovery animals.

Table 55: selected histopathology findings for the GLP 26-week rat subcutaneous toxicity study (report # B7774)

Dose group (mg/kg/day)	Rat #	Tissue	Notes
0	M 1001	Pancreas	- No gross finding - Histopathology: pancreas acinar cell carcinoma
0	M 1015	Pituitary	- No gross finding - Histopathology: pituitary mild pars distalis cyst
0.003	M 2006	Kidney	- Grossly detected left kidney nodule - Histopathology identified nephroblastoma
0.003	F 2104	Kidney	- Grossly detected left kidney cyst, 2x2x1 mm - Histopathology not conducted
0.003	M 2013	Spermatic cord	- Grossly detected "fat tissue, spermatic cord nodule" - Histopathology not conducted
0.01	M 3006	Spleen	- Grossly detected spleen cyst, 3x3x3 mm - Histopathology not conducted
0.03	F 4101	Pituitary	- Gross pituitary nodule (2x2x2 mm), - Histology detected - Pituitary pars distalis focal hyperplasia - Pituitary pars distalis adenoma
		Mammary gland	- This female also exhibited pituitary adenoma - No gross mammary gland finding - Histopathology: mammary gland adenocarcinoma (detected in the inguinal region)
0.03	M 4013	Pituitary	- No gross finding - Histopathology: pituitary pars distalis adenoma
0.03	M4113	Liver	- Gross liver focus, dark red, 2x2 mm - Liver mild angiectasis
0.03	M 4011	Spleen	- Spleen gross cyst, 1x2 mm - Spleen, minimal capsular lymphangiectasis
0.03	F 4106	Pituitary	- No gross finding - Histopathology: pituitary mild pars intermedia cyst
0.03	F 4114	Pituitary	- No gross finding - Histopathology: pituitary mild pars intermedia cyst

- The study report authors noted the lack of pituitary hyperplasia (in rats other than # 4101), and considered this supporting evidence of a lack of treatment-effect (page 38).
- The main-group rats were 32 weeks of age at necropsy (i.e. 6-weeks at start of dosing + 26 weeks of treatment). The authors (page 38) noted that "*Adenomas of pars distalis in the pituitary are reported to occur spontaneously in Sprague-Dawley rats (both sexes) at 32 weeks of age*", citing Ikezaki et al. 2011.¹⁹

¹⁹ Ikezaki S, Takagi M and Tamura K. Natural occurrence of neoplastic lesions in young

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(b) (4)

Table 56: published laboratory historical control data for tumors in 32-week old Sprague Dawley rats (Ikezaki et al. 2011)

Tumor	Observations in 19-week old rats	Observations in 32 week old rats
Pancreas carcinoma	0/1735	0/1716
Pituitary anterior adenoma	1/1735 (0.0576%)	4/1716 (0.233%)
Mammary gland adenocarcinoma	0/878 female rats	6/874 female rats (0.686%)
Kidney nephroblastoma	1/1735 (0.0576%)	0/1716

- o This reviewer disagrees with the authors, and considers the paper's data support for a conclusion of treatment-relatedness.
- As a benchmark, comparing the incidence of 2/30 versus 4/1716 by the Chi-Square test, the difference is statistically significant ($p < 0.00001$).

Toxicokinetics

- Blood was collected from 3/sex/dose satellite animals (with one reserve/sex/dose in case of accident).
- For the control TK group, blood was collected once/day for D1, D28, and D91.
- For the omidenepag isopropyl treated groups, blood was collected on pre-dose for D28 and D91 and post-dose for D1, D28 and D91 at: 15 and 30 minutes, 1, 2, 4, and 8 hours.

Table 57: Omidenepag serum TK for the 26-week rat subcutaneous toxicity study (report # B-7774)

Day	Dose level (mg/kg/day)	Sex	T _{max} (h)	C _{max} (ng/ml)	AUC _{0-8h} (ng*h/ml)
1	0.003	M	0.4	0.794	0.771
		F	0.4	0.661	0.600

Sprague-Dawley rats. J Toxicol Pathol 2011; 24: 37-40. Accessible via: <https://pubmed.ncbi.nlm.nih.gov/22272042/> Submitted to the NDA: <\\CDSESUB1\evsprod\nda215092\0001\m4\43-lit-ref\ikezaki-2011.pdf>

	0.01	M	0.5	2.90	3.08
		F	0.3	2.33	2.02
	0.03	M	0.3	9.10	8.97
		F	0.4	6.87	5.74
Day 88 (week 13)	0.003	M	0.7	1.13	2.03
		F	0.5	0.747	1.03
	0.01	M	0.5	3.73	6.66
		F	0.5	2.53	3.55
	0.03	M	0.8	12.9	21.1
		F	0.5	8.89	10.8
Day 180 (week 26)	0.003	M	0.7	1.24	2.01
		F	0.5	0.856	1.14
	0.01	M	0.7	4.71	7.36
		F	0.5	3.12	4.57
	0.03	M	0.5	16.9	23.9
		F	0.5	9.63	12.1

Data presented as mean TK parameter.

Dosing Solution Analysis

Test article characterization appears adequate. Concentrations were 99.5 to 103.5% of nominal.

7 Genetic Toxicology

- This review references:
 - the ICH M3(R2)²⁰ guidance (section 9 Genotoxicity Studies), which references ICH S2B²¹.

²⁰ 2010 Guidance for Industry ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. Accessed via: <https://www.fda.gov/media/71542/download>

²¹ 1997 Guidance for Industry ICH S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals. Accessed via: <https://www.fda.gov/media/71971/download>

- o ICH S2(R1)²², which combined and updated ICH S2A²³ and ICH S2B.
- Consistent with these guidances, Santen submitted a complete battery of genotoxicity assays for omidenepag isopropyl in 2012, to support opening IND 111518 for the treatment of ocular hypertension or open angle glaucoma.
- Review of these studies (documented below) under NDA found:
 - o Omidenepag isopropyl is clearly positive in the mouse lymphoma assay (MLA).
 - o The reverse mutation assay in bacteria is partially adequate.
 - Omidenepag isopropyl was negative in the absence of metabolic activation (-S9)
 - The assay was inadequate to evaluate potential genotoxicity in the presence of metabolic activation (+S9). This issue is particularly important, since omidenepag isopropyl is a prodrug of omidenepag, with different ADME and PD activity.
 - o The *in vivo* rat micronucleus assay is inadequate (insufficient dose levels).

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: A Bacterial Reverse Mutation Test of UR-7385

Study no.:	(b) (4) 102-224
Study report location:	NDA module 4.2.3.3.1 Genotoxicity <i>in vitro</i> (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro (b) (4) 102-224 (b) (4) 02224-pre-clinical-study-report.pdf)
Conducting laboratory and location:	(b) (4)
Report date:	February 15, 2012
Date of study initiation:	September 9, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot # 28, purity 99.9% by HPLC

Key Study Findings

- Omidenepag isopropyl was not associated with any positive responses, up to the limit test (5000 µg/plate).

²² 2010 Guidance for Industry ICH S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. Accessed via: <https://www.fda.gov/media/71980/download>

²³ 1996 Guideline for Industry ICH S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals. Accessed via: <https://www.fda.gov/media/71959/download>

- The potency of the S9 was not verified (i.e. with a positive control requiring metabolic activation). Therefore, the results +S9 are of limited regulatory value.

Methods

Strains:	<i>Salmonella typhimurium</i>: TA100, TA1535, TA98, and TA1537 <i>Escherichia coli</i>: WP2uvrA
Concentrations in definitive study:	- Without metabolic activation - TA100, TA1535, and TA98: 39.1, 78.1, 156, 313, 625, 1250, 2500, and 5000 µg/plate - TA1537 and WP2uvrA: 156, 313, 625, 1250, 2500, and 5000 µg/plate (TA1537 and WP2uvrA) - With metabolic activation (all test strains): 156, 313, 625, 1250, 2500, and 5000 µg/plate
Basis of concentration selection:	Range-finder: - no growth inhibition +S9 - Growth inhibition -S9 ≥ 625 µg/plate for strains TA100, TA1535, and TA98 - Growth inhibition -S9 at 2500 and 5000 µg/plate for TA1537 - No growth inhibition for WP2uvrA
Negative control:	Vehicle (DMSO)
Positive controls:	+S9: 2-aminoanthracene (2-AA) for all strains -S9: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide [AF-2] for TA100, TA98, and WP2uvrA - Sodium azide (NaN₃) for TA1535 9-Aminoacridine hydrochloride hydrate (9AA) for TA1537
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Pre-incubation method (48 hours)

Study Validity

- The study appears adequate to evaluate genotoxicity without metabolic activation (i.e. -S9), but is of limited value to evaluate genotoxicity +S9. This study used 2-AA as the only positive control +S9. The report does not mention verification of the S9 metabolic activity.
 - The S9 metabolic activation system was manufactured by (b) (4), lot # 11052002, production date May 20, 2011, stored frozen.
 - S9 liver microsomes were prepared from male Sprague Dawley rats dosed with intraperitoneal (ip) phenobarbital and 5,6-benzoflavone.

- o For the bacterial reverse mutation assay, ICH S2(R1) section 3.2.2 recommends “appropriate positive and negative controls”, without further details.
- o For the bacterial reverse mutation test, the recommendation “2-Aminoanthracene should not be used as the sole indicator of the efficacy of the S9 mix. If 2-aminoanthracene is used, each batch of S9 should also be characterized with a mutagen that requires metabolic activation by microsomal enzymes, e.g., benzo(a)pyrene, dimethylbenzanthracene” is worded the same in FDA/CFSAN’s Redbook 2000 (section IV.C.1.a)²⁴, the US Environmental Protection Agency (EPA)’s Health Effects Test Guidelines OPPTS 870.5100 Bacterial Reserve Mutation Test²⁵, and the OECD Test Guideline 471 Bacterial Reverse Mutation Test²⁶.
- o Notably, 2-AA was not tested -S9 for any strain (i.e. no results that might demonstrate an increase in genotoxicity after metabolic activation)
- For the design of the bacterial reverse mutation assay, ICH S2A and ICH S2(R1) cite Gatehouse et al. 1994.^{27, 28}
- Gatehouse et al. 1994 recommend, “Positive controls requiring metabolic
- activation should be used for experiments performed in the presence of an exogenous metabolising system. It is suggested that **2-aminoanthracene should not be recommended as the ONLY positive control included in the assay to check the metabolising capacity of S9 mix**, although it may be used for some of the strains. This is because 2-aminoanthracene may be activated by enzyme systems other than the microsomal cytochrome P450 family (Ayrton et al., 1992).” [bolding and capitalization in the original]
- Ayrton et al. 1992²⁹ explains that 2-aminoanthracene is a stronger mutagen when activated S9, but has activity in the absence of S9.

²⁴ Accessed via: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivc1a-bacterial-reverse-mutation-test>

²⁵ Accessed via: <https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0156-0022>

²⁶ Accessed via: https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

²⁷ Gatehouse, D., S. Haworth, T. Cebula, E. Gocke, L. Kier, T. Matsushima, C. Melcion, T. Nohmi, T. Ohta, S. Venitt, and E. Zeiger, “Report from the working group on bacterial mutation assays: International workshop on standardisation of genotoxicity test procedures,” Mutation Research, 312:217-233, 1994.

²⁸ Review note: Gatehouse et al. 1994 is generally cited as Gatehouse D, Haworth S, Cebula T, Gocke E, Kier L, Matsushima T, Melcion C, Nohmi T, Ohta T, Venitt S, et al. Recommendations for the performance of bacterial mutation assays. Mutat Res. 1994 Jun;312(3):217-33. doi: 10.1016/0165-1161(94)90037-x. PMID: 7514736. The full text is available via: <https://pubmed.ncbi.nlm.nih.gov/7514736/>

²⁹ Ayrton AD, Neville S, Ioannides C. Cytosolic activation of 2-aminoanthracene: implications in its use as diagnostic mutagen in the Ames test. Mutat Res. 1992 Jan;265(1):1-8. doi: 10.1016/0027-5107(92)90034-y. PMID: 1370238. The full text is available via: <https://pubmed.ncbi.nlm.nih.gov/1370238/>

- The test article characterization appears adequate.

Results

- Omidenepag isopropyl had no positive results.
- The negative and positive controls gave the expected responses.
- Precipitation was observed ≥ 150 $\mu\text{g}/\text{plate}$ – S9 and ≥ 313 $\mu\text{g}/\text{plate}$ + S9.

7.2 In Vitro Assays in Mammalian Cells

Study title: A Mouse Lymphoma TK Assay of UR-7385

Study no.:	(b) (4) 102-225
Study report location:	NDA module 4.2.3.3.1 Genotoxicity <i>in vitro</i> (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro (b) (4) 02-225 (b) (4) 02225-pre-clinical-study-report.pdf)
Conducting laboratory and location:	(b) (4)
Report date:	February 28, 2012
Date of study initiation:	September 8, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot # 28, purity 99.9% by HPLC

Key Study Findings

- Omidenepag was positive in the mouse lymphoma assay (MLA), with 3 hour incubation in the absence of metabolic activation (3 h -S9). The frequency of small colonies (S-MF) was increased.
- For labeling³⁰, the Applicant proposed, “Omidenepag was not mutagenic ...in (b) (4) ... micronucleus test. (b) (4)”
 - P/T concludes omidenepag was mutagenic under the conditions tested.
 - The assay is a hazard identification following very short (3 or 24 hour) exposure; it is not designed to characterize a dose-response.

³⁰ Annotated draft labeling text submitted 11/19/2020 accessed via:
<\\CDSESUB1\evsprod\nda215092\0001\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text.docx>

- (b) (4) the assay's ability to detect clastogenic damage (manifesting as small colonies, due to slower proliferation rate).
- The results show clear dose-responses for increasing small colony frequency (i.e. clastogenic damage). (b) (4)
- From the report's summary: *"It was concluded from these results that, under the conditions of this study, UR-7385 induced gene mutation in mouse lymphoma cells in absence of metabolic activation, (b) (4) P/T concurs that omidenepag induced gene mutations, (b) (4)*

Methods

Cell line:	L5178Y (Tk ^{+/-} -3.7.2.c) mouse lymphoma cells
Basis of concentration selection:	Cytotoxicity. The dose-finding test included the dose limit, 5000 µg/ml
Negative control:	DMSO
Positive control:	Methy methanesulfonate (MMS), cyclophosphamide monohydrate (CP)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	• Test article exposure: 3 hours ± S9; 24 hours -S9 • Mutant expression period: 2 days (with daily determination of relative suspension growth (RSG)) • For the cytotoxicity evaluation, plates were incubated for 12-14 days • For detection of mutation frequency, plates were incubated for 12 days

Mouse Lymphoma Assay (MLA) Principle

- L5178Y cells are heterozygous for functional thymidine kinase (TK^{+/-}). Exposure to the pyrimidine analog trifluorothymidine (TFT) is lethal to cells with a functional TK. The test is designed to detect forward mutations (i.e. loss of function to TK^{-/-}). TK^{-/-} cells are unable to incorporate TFT, and therefore survive and proliferate. Cell survival and growth is detected by the formation of colonies. Large colonies indicate normal cell proliferation, considered evidence of point mutations. Small colonies indicate slow growth, attributed to chromosomal damage.
- L5178Y cells have inadequate endogenous metabolic activity; the assay requires metabolic activation (i.e. S9).
- In addition to statistical analysis of results, the biological relevance of increased mutation frequency (MF) is judged based on a predefined Global Evaluation Factor (GEF). Responses that exceed the concurrent control by more than the GEF are considered positive.

Study Validity

- The study used the MLA microwell method. The study met the standard MLA microwell method acceptability criteria for MF, cloning efficiency (CE; cloning frequency), and suspension growth (SG).
- The study design appears consistent with ICH S2(R1) recommendations for MLA. The guidance (section 3.3.1) notes, "For the MLA, at the top dose there should be 80-90% cytotoxicity as measured by an RTG between 20-10% (note 9)." Note 9 explains "very few chemicals that were positive in MLA only at concentrations with less than 20% RTG ... caution is appropriate in interpreting results when increases in mutation are seen only below 20% RTG, and a result would not be considered positive if the increase in mutant fraction occurred only at $\leq 10\%$ RTG."
- Two additional guidance documents were consulted for this review:
 - o For the mouse lymphoma thymidine kinase assay, FDA/CFSAN's Redbook 2000 (section IV.C.1.c) provides guidance updated in 2006.³¹
 - o OCED³² 490 In vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene was consulted for this review.
- The authors did not explicitly state the GEF they apply to evaluate the study results; this is a minor reporting oversight, because the authors cite Moore et al. 2006³³
 - o ICH S2(R1) was finalized in 1997, and does not address the GEF concept for MLA.
 - o For the GEF, OECD 490 and Redbook, both citing Moore et al. 2006, recommend a GEF of 90×10^{-6} for the MLA agar assay, and a GEF of

³¹ Accessed via: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivc1c-mouse-lymphoma-thymidine-kinase-gene-mutation-assay>

³² Accessed via: https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

³³ Moore MM, Honma M, Clements J, Bolcsfoldi G, Burlinson B, Cifone M, Clarke J, Delongchamp R, Durward R, Fellows M, Gollapudi B, Hou S, Jenkinson P, Lloyd M, Majeska J, Myhr B, O'Donovan M, Omori T, Riach C, San R, Stankowski LF Jr, Thakur AK, Van Goethem F, Wakuri S, Yoshimura I. 2006. Mouse lymphoma thymidine kinase gene mutation assay: follow-up meeting of the International Workshop on Genotoxicity Testing--Aberdeen, Scotland, 2003--Assay acceptance criteria, positive controls, and data evaluation. Environ Mol Mutagen. 47(1):1-5. doi: 10.1002/em.20159. PMID: 15991242. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/15991242/>

126x10⁻⁶ for the microwell MLA assay. Likewise, Lloyd and Kidd 2012³⁴ cite the same GEFs.

- o This review uses 126x10⁻⁶ ("126") for the MLA microwell assay.

Results

- Precipitation was observed ≥ 156 $\mu\text{g/ml}$
- Test article was not toxic -S9. At 3 hours +S9, doses ≥ 1250 $\mu\text{g/ml}$ were too cytotoxic (by relative growth or relative survival).
- In the table below, the positive results (based on MF exceeding the control + GEF) values not excluded due to excessive cytotoxicity are bolded (i.e. 1400 and 1500 $\mu\text{g/ml}$, 3h -S9).
 - o Lack of concordance between the two experiments is expected, because the second experiment prudently focused on a narrower range of concentrations for 3h -S9. [Ideally, the test would have had more concentrations between 1400 and 1600 $\mu\text{g/ml}$, to more clearly delineate the dose-response.]
 - o Similarly, from a scientific perspective, it would have been helpful to have more concentrations 3h+S9 between 1000 and 1050 $\mu\text{g/ml}$, and 24h-S9 between 900 and 1000 $\mu\text{g/ml}$.

Table 58: Mouse lymphoma assay summary table (report # (b) (4) 102225)

Condition	Dose (µg/ml)	RTG	Data excluded due to RTG < 10%	S-MF	T-MF	Positive (T-MF exceeds control + GEF)
First assay						
3 h S-9	0	100	none	44.4	112.5	No
	1250	83.4		74.3	83.9	
	1768	18.5	10-20% range	112.3	87.4	
	2500	91.5	None	69.6	130.9	
	5000	95.4		37.1	109.3	
24 h S-9	0	100	none	40.9	70.7	
	625	30.5		84.0	142.3 *	
	884	22.3		144.2	158.8 *	
Confirmatory assay						
3 h S-9	0	100	None	28.5	78.5	No
	1100	97.9		60.6	132.7	
	1200	63.0		75.5	149.9 *	

³⁴ Lloyd M, Kidd D. The mouse lymphoma assay. Methods Mol Biol. 2012;817:35-54. doi: 10.1007/978-1-61779-421-6_3. PMID: 22147567. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/22147567/>

	1300	45.9		106.7	178.2 *	Yes
	1400	32.6		113.8	205.8 *	
	1500	16.6		145.5	224.7 *	
	1600	8.2	< 10%	197.9	323.3 †	
3 h +S9	0	100	None	48.2	81.4	No
	1000	16.7	10-20% range	52.4	100.7	
	1050	2.3	< 10%	77.4	225.6 †	Yes
	1100	0.8		124.0	239.4 †	
24 h -S9	0	100	No	22.2	70.6	No
	500	43.0		56.8	131.0 *	
	600	34.7		61.6	105.6	
	700	20.8		60.2	130.7 *	
	800	12.5	10-20% range	69.4	135.0 *	
	900	15.3		69.7	129.0	
	1000	6.2	< 10%	199.1	246.7 †	Yes
	1100	3.5		378.1	494.4 †	

* Statistically different from control by Dunnett's multiple comparison test, $p < 0.05$

† Authors excluded from analysis because RTG < 10%

Table 59: MLA: first assay results - mutation frequency and colony sizing (report # (b) (4) 10225)

Treatment condition	Test and control articles	Dose (µg/mL)	Positive well number				Well number		PE2 (%)	MF ($\times 10^{-6}$)			%SC
			L	S	L/S	Total	Total	Negative		L-MF	S-MF	T-MF	
Short-term (3 h) -S9 mix	NC (DMSO)	0	44	32	0	76	384	308	98	62.1	44.4	112.5	39.5
	UR-7385	313	19	11	0	30	192	162	101	51.5	29.1	83.9	34.7
		442	21	18	0	39	192	153	130	44.6	37.9	87.4	43.4
		625	27	17	2	46	192	146	105	78.3	49.8	130.9	38.0
		884	14	22	0	36	192	156	95	39.9	64.1	109.3	58.6
		1250	17	34	1	52	192	140	135	36.4	74.3	116.6	63.7
		1768	16	46	1	63	192	129	125	37.1	112.3	159.1	70.6
		2500	18	31	2	51	192	141	135	40.6	69.6	114.0	61.1
		5000	26	16	1	43	192	149	125	60.6	37.1	101.5	36.6
	PC (MMS)	10	33	57	4	94	192	98	101	105.7	188.8	332.1	56.8
Short-term (3 h) +S9 mix	NC (DMSO)	0	36	37	2	75	384	309	116	44.9	46.2	93.6	49.3
	UR-7385	313	17	16	0	33	192	159	125	37.1	34.8	75.5	46.1
		442	23	22	1	46	192	146	148	45.1	43.1	92.6	46.6
		625	29	22	2	53	192	139	112	78.6	59.6	144.2	41.3
		884	24	28	0	52	192	140	141	47.2	55.8	111.7	49.9
		1250	Not tested ¹⁾										
		1768	Not tested ²⁾										
	PC (CP)	3	47	95	5	147	192	45	45	353.8	824.1	1625.1	50.7
Continuous (24 h) -S9 mix	NC (DMSO)	0	21	31	0	52	384	332	103	27.3	40.9	70.7	57.8
	UR-7385	156	16	17	0	33	192	159	130	33.5	35.7	72.6	49.2
		313	15	20	0	35	192	157	116	35.1	47.4	86.7	54.7
		442	16	19	1	36	192	156	98	47.3	56.1	105.9	53.0
		625	20	34	0	54	192	138	116	47.4	84.0	142.3	* 59.0
		884	4	46	0	50	192	142	95	11.1	144.2	158.8	* 90.8
		1250	Not tested ¹⁾										
	PC (MMS)	10	43	98	7	148	192	44	89	168.9	443.2	824.9	53.7

NC: Negative control, DMSO: Dimethyl sulfoxide

PC: Positive controls, MMS: Methyl methanesulfonate, CP: Cyclophosphamide monohydrate

L: Well number containing 1 or more large colonies, S: Well number containing 1 or more small colonies,

L/S: Well number containing 1 or more both large and small colonies, PE: Plating efficiency, MF: Mutation frequency

L-MF: Mutation frequency of large colonies, S-MF: Mutation frequency of small colonies, T-MF: Total mutation frequency

%SC: Ratio of S-MF to T-MF

1) The cell death occurred during the 2-day mutation expression period.

2) The number of cells was insufficient; therefore, the procedure was not performed.

Test article precipitation in the treatment medium was observed at 156 µg/mL and greater and 1768 µg/mL and greater at the start and end of treatment, respectively.

* Statistically significantly increased from negative control ($p < 0.05$, Dunnett's multiple comparison test)

Dose-dependency was noted ($p < 0.05$, Trend test with regression analysis).

- For 24 h -S9, the two highest concentrations both had statistically significant increases in MF, but their MF did not exceed the GEF (i.e. 70.7 for the concurrent control + 126 = 196.7). A dose-response is apparent for both small colony frequency (S-MF) and total mutation frequency (T-MF).

- o These data are not positive results, because the GEF was not exceeded. However, it raises concern, and is relevant to the interpretation of the confirmatory assay.
- o The authors concluded for 24 h -S9, "A statistically significant increase in the T-MF was noted at 625 and 884 µg/mL when compared with the negative control group (70.7×10^{-6}), but it did not exceed the GEF-applied value and this determination was evaluated as negative with this criterion, and the results were judged to be equivocal." P/T considers this conclusion reasonable from a scientific perspective; from a regulatory perspective, these data are classified as negative.

Table 60: MLA: confirmatory assay results - mutation frequency and colony sizing (report # (b) (4) 10225)

Treatment condition	Test and control articles	Dose (µg/mL)	Positive well number				Well number		PE2 (%)	MF ($\times 10^{-6}$)			%SC
			L	S	L/S	Total	Total	Negative		L-MF	S-MF	T-MF	
Short-term (3 h) -S9 mix	NC (DMSO)	0	37	22	1	60	384	324	108	48.2	28.5	78.5	36.4
	UR-7385	1100	28	27	1	56	192	136	130	63.0	60.6	132.7	45.7
		1200	27	31	2	60	192	132	125	65.5	75.5	149.9 *	50.3
		1300	26	47	3	76	192	116	141	57.9	106.7	178.2 *	59.9
		1400	29	44	2	75	192	117	120	73.2	113.8	205.8 *	55.3
		1500	23	54	1	78	192	114	116	57.5	145.5	224.7 *	64.7
		1600	24	41	7	72	192	120	73	121.1	197.9	323.3 †	61.2
		1700	Not tested ¹⁾										
		1800	Not tested ¹⁾										
	PC (MMS)	10	32	50	4	86	192	106	98	105.9	168.4	303.0	55.6
Short-term (3 h) +S9 mix	NC (DMSO)	0	24	37	1	62	384	322	108	31.1	48.2	81.4	59.2
	UR-7385	850	23	24	0	47	192	145	105	61.0	63.8	134.2	47.6
		900	25	18	0	43	192	149	108	64.5	45.5	117.2	38.8
		950	16	15	1	32	192	160	125	37.1	34.8	73.0	47.7
		1000	18	21	1	40	192	152	116	44.9	52.4	100.7	52.1
		1050	34	21	0	55	192	137	75	130.3	77.4	225.6 †	34.3
		1100	16	18	1	35	192	157	42	110.3	124.0	239.4 †	51.8
		1150	Not tested ²⁾										
		1200	Not tested ²⁾										
		1250	Not tested ²⁾										
		1300	Not tested ²⁾										
	PC (CP)	3	31	97	3	131	192	61	35	279.9	1056.6	1646.8	64.2

Continuous (24 h) -S9 mix	NC (DMSO)	0	40	20	0	60	384	324	120	45.7	22.2	70.6	31.5
	UR-7385	400	18	15	2	35	192	157	101	54.3	45.8	99.4	46.1
		500	21	18	0	39	192	153	87	66.8	56.8	131.0 *	43.4
		600	13	20	0	33	192	159	89	39.3	61.6	105.6	58.3
		700	18	17	0	35	192	157	77	63.9	60.2	130.7 *	46.1
		800	17	20	0	37	192	155	79	58.5	69.4	135.0 *	51.4
		900	14	16	2	32	192	160	71	61.6	69.7	129.0	54.0
		1000	7	33	0	40	192	152	47	39.2	199.1	246.7 †	80.7
		1100	12	46	1	59	192	133	37	94.4	378.1	494.4 †	76.5
	PC (MMS)	10	40	77	5	122	192	70	65	205.8	429.3	777.7	55.2

NC: Negative control, DMSO: Dimethyl sulfoxide

PC: Positive controls, MMS: Methyl methanesulfonate, CP: Cyclophosphamide monohydrate

L: Well number containing 1 or more large colonies, S: Well number containing 1 or more small colonies,

L/S: Well number containing 1 or more both large and small colonies, PE: Plating efficiency, MF: Mutation frequency

L-MF: Mutation frequency of large colonies, S-MF: Mutation frequency of small colonies, T-MF: Total mutation frequency

%SC: Ratio of S-MF to T-MF

1) The cell death occurred immediately after treatment. 2) The cell death occurred during the 2-day mutation expression period

Test article precipitation in the treatment medium was observed at 400 µg/mL and greater and 1300 µg/mL and greater

at the start and end of treatment, respectively.

† This datum was not used for evaluation because the RTG was less than 10%.

* Statistically significantly increased from negative control ($p < 0.05$, Dunnett's multiple comparison test)

Dose-dependency was noted ($p < 0.05$, Trend test with regression analysis).

- **The results 3 h -S9 are clearly positive.**
 - o The authors considered these results positive, and P/T concurs.
 - o For the concurrent control, adding the GEF (126) to the small colony frequency and total mutation frequency = 154.4 and 204.5 respectively.
 - o **The 1400 and 1500 µg/ml results exceed the control responses by more than the GEF, without reducing RTG < 10%.**
 - o A dose-response is apparent for T-MF.
 - o Review note: in accordance with ICH S2(R1), the results for 1600 µg/ml (3 h -S9) are not considered relevant to humans, due to excessive cytotoxicity. The relative suspension growth was 0.12; the RTG was 8.2.
- The results 3 h + S9 are not considered positive. Although the top two concentrations increased MF above the GEF, they are not considered relevant to humans, due to cytotoxicity.
- The results 24 h – S9 are not clearly positive.
 - o The authors considered these results equivocal. P/T considers this conclusion reasonable from a scientific perspective; from a regulatory perspective, these data are classified as negative.
 - o For the concurrent control, adding the GEF (126) to the small colony frequency and total mutation frequency = 148.2 and 196.6 respectively.
 - o The 1000 and 1000 µg/ml are not considered relevant to humans, due to excessive toxicity

- 1000 µg/ml: RSG of 0.16, RTG 6.2
- 1100 µg/ml: RS of 0.11, RTG 3.5
- o The lower concentrations do not exceed the GEF.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: A Micronucleus Test of UR-7385 in Rats

Study no:	(b) (4) 102-226
Study report location:	NDA module 4.2.3.3.2 Genotoxicity <i>in vivo</i> (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4233-genotox\42332-in-vivo\ (b) (4) 102-226 (b) (4) 102226-pre-clinical-study-repor .pdf)
Conducting laboratory and location:	(b) (4)
Report date:	February 15, 2012
Date of study initiation:	September 7, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Omidenepag isopropyl (UR-7385), lot # 28, purity 99.8% by HPLC

Key Study Findings

- The study is wholly inadequate. The high dose was 4 mg/kg/day (QD x 2) by subcutaneous (sc) injection.
 - o High dose selection was not limited by toxicity.
 - o For the vehicle selected ((b) (4) in saline), the maximum concentration was reportedly 0.04% (4 mg/ml), which limited the dose for this vehicle to 4 mg/kg.
 - o However, the P/T package has *in vivo* data testing 1% (10 mg/ml) omidenepag isopropyl (not limited by toxicity). Therefore, the maximum feasible dose (MFD) is at least 100 mg/kg.
 - o Additionally, omidenepag isopropyl was soluble in DMSO up to 483 mg/ml. Different laboratories have different SOPs for the maximum tolerable dose of DMSO in rats. As a benchmark, using 100% DMSO (10 ml/kg) would support a MFD of 4830 mg/kg.
 - o Because the MFD is somewhere in the range of 25 to 1200 fold higher than the high dose; this study clearly did not test the MFD.

Methods

Doses in definitive study:	0, 0.4, 1.3, and 4 mg/kg/day
Frequency of dosing:	Twice (2-hour interval)
Route of administration:	Subcutaneous injection (dorsal area, shaved skin)
Dose volume:	10 ml/kg/day
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	Male Sprague Dawley rat (8 weeks old at dosing)
Number/Sex/Group:	5 male rats/dose
Satellite groups:	None
Basis of dose selection:	The authors provided two justifications: • Solubility limit (b) (4) in saline is 0.4 mg/ml. Limiting the dose volume to 10 ml/kg = 4 mg/kg/day dose. • The rat 2-week sc study (report # 529F030) observed “a slight flush in the auricle” at 4 mg/kg/day. “Therefore, the highest dose level was set at 4 mg/kg/day. The lower doses were set at 1.3 and 0.4 mg/kg/day.”
Negative control:	Vehicle
Positive control:	Single oral gavage dose (on D2) of 20 mg/kg cyclophosphamide monohydrate (CP) [dose volume of 10 ml/kg]

Assay Principle

- As bone marrow erythroblasts (of humans and rodents) develop into reticulocytes (immature erythrocytes), the main nucleus is excluded. This allows for the visualization of remaining nuclear material (micronuclei) with staining and microscopy.
- An increase in the frequency of immature erythrocytes with micronuclei indicates chromosomal damage (structural or numerical changes).

Study Design

- Clinical signs were noted before dosing, post-dose at 1, 2, 4, and 6 hours, and prior to sacrifice. Body weight was measured prior to dosing, and prior to sacrifice (i.e. QDx3 for the test-article treated rats).
- 24 hours after the last dose, right femurs were removed to isolate marrow. Two slides per animal were prepared.
- Microscopic examination was performed blinded to treatment.
- For each animal, two thousand (2000) immature erythrocytes (IE) were counted, and the number of micronucleated immature erythrocytes (MNIE) were counted. Five hundred (500) total erythrocytes were counted, and the proportion of mature erythrocyte (ME) to IE was noted as an indicator of bone marrow toxicity.

Clinical signs and body weight results

- No clinical signs were observed for the 0.4 mg/kg group or the positive control group.
- The test article caused reddening skin and soft stool:
 - At 1.3 mg/kg: reddening skin was observed in 2/5 rats on D1 of dosing (1-2 hours post-dose), and in 5/5 rats on D2 (1-4 hours post-dose)
 - At 4 mg/kg/day: all (5/5) rats exhibited reddening skin and soft stool on D1 and D2 (2 to 4 hours post-dose)
 - No clinical signs were observed at 6 hours post-dose (on D1 and D2), or on D3, indicating the reddening skin and soft stool were transient effects.
 - The authors noted “a tendency toward a suppression of body weight gain” from D1 to D2 for the 4 mg/kg group. This reviewer does not consider the effect clearly apparent (i.e. may be normal variability).

Table 61: Body weight data for the rat micronucleus study (report # (b) (4) 102-226)

Body weight (mean $\pm$ SD)	0	0.4 mg/kg/day	1.3 mg/kg/day	4 mg/kg/day	Positive control
D1	339.0 $\pm$ 19.2	339.6 $\pm$ 13.1	342.0 $\pm$ 9.8	341.0 $\pm$ 14.8	-
D2	338.0 $\pm$ 18.9	341.8 $\pm$ 14.6	341.0 $\pm$ 12.5	337.4 $\pm$ 14.2	348.8 $\pm$ 10.5
D3	344.2 $\pm$ 6.2	349.4 $\pm$ 7.6	348.0 $\pm$ 12.7	347.0 $\pm$ 17.8	354.4 $\pm$ 9.6
Body weight gain (D1 to D3)	+1.53%	+2.89%	+1.75%	+1.76%	-

Study Validity

- The study is wholly inadequate to evaluate potential clastogenicity, because dose selection was too low to adequately characterize potential activity.
- The author's dose selection justification (report page 13) reads, “*The maximum soluble level for the test article was 0.4 mg/mL in (b) (4) in physiological saline. A dose volume of 10 mL/kg is acceptable for subcutaneous administration to rats; therefore, the maximum practicable dose level is 4 mg/kg/day. In the preliminary study in rats (Study number: 529Ff030, subcutaneous administration for 2 weeks), a slight flush in the auricle was detected in males at 4 mg/kg/day from the dosing initiation, in clinical signs. Therefore, the highest dose level was set at 4 mg/kg/day. The lower doses were set at 1.3 and 0.4 mg/kg/day.*”
- Neither of these justifications (maximum feasible dose (MFD) or toxicity) are acceptable. ICH S2(R1) section 4.3 Dose Selection for In Vivo Assays provides several options.

- o For short-term dosing (as was done for this study), it recommends a high dose *“as the dose producing signs of toxicity such that higher dose levels, based on the same dosing regimen, would be expected to produce lethality”*
- o A limit dose of 2000 mg/kg
- o *“The maximum feasible dose (MFD) based on physico-chemical properties of the drug in the vehicle”*
- o The guidance advises, *“Selection of a top dose based only on an exposure margin (multiple over clinical exposure) without toxicity is not considered sufficient justification.”*
- Other guidances provided similar advice.
 - o FDA/CFSAN’s Redbook 2000 (section IV.C.1.d)³⁵ also recommends a maximum volume (oral or ip injection) of 20 ml/kg.
 - o OECD³⁶ 474 Mammalian Erythrocyte Micronucleus Test was consulted for this review.
- As the clinical signs and body weight data show, the high-dose was not limited by toxicity.
- The laboratory’s decision to use (b) (4) in saline vehicle is inadequate because another solvent with greater solubility would have afforded a higher MFD
 - o The concentration tested in this assay, 4 mg/ml, is 0.04%. Notably, the monkey PD study (report # 416Qg080) tested 0.1% omidenepag isopropyl. A subsequent monkey PD study (report # SPI-14074) tested 1% omidenepag isopropyl (subconjunctival injection); a rabbit ivt study (report # 535WI060) also tested 1% ivt. 1% = 10 mg/ml. As a benchmark calculation 10 mg/ml concentration X 10 ml/kg dose volume = **100 mg/kg**.
 - o The P/T package reports in the certificate of analysis for report # (b) (4) 10224 (the bacterial reverse mutation assay) that omidenepag isopropyl was soluble and stable in DMSO at a concentration of 483 mg/ml. Likewise, the MLA assay (report # (b) (4) 102-225) reported omidenepag isopropyl was soluble and stable in DMSO at a concentration of 478 mg/ml.
 - 100% DMSO is relatively non-toxic. The literature varies regarding the amount of DMSO tolerated by rats. As a benchmark calculation, 483 mg/ml concentration X 10 ml/kg dose volume = **4830 mg/kg** (near the dose limit test).
 - Hayashi et al. 1994³⁷ was cited by the report authors (not cited by ICH S2(R1)). This paper recommended water or saline vehicle,

³⁵ Accessed via: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivc1d-mammalian-erythrocyte-micronucleus-test>

³⁶ Accessed via: https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

³⁷ Hayashi M, Tice RR, MacGregor JT, Anderson D, Blakey DH, Kirsh-Volders M, Oleson FB Jr, Pacchierotti F, Romagna F, Shimada H, Sutou S, Vannier B. 1994. In

and specifically recommended “Organic solvents such as dimethyl sulfoxide (DMSO) are not generally recommended.” The basis for these recommendations was not discussed.

- In contrast, Hayashi et al. 2000³⁸ and Hayashi et al. 2007³⁹ (both cited by ICH S2(R1)) do not provide solvent recommendations (or mention DMSO).
- The test article characterization appears adequate.

Dose margin/exposure margin justification is not an acceptable to accept the doses tested

- The clinical topical ocular dose, local and systemic exposures are important considerations for risk evaluation. However, these are not relevant to evaluating the adequacy of this assay to detect potential genotoxicity.
- The NDA’s Toxicology Written Summary (module 2.6.6)⁴⁰ does not directly address the inadequacy of the high dose for the micronucleus study.
- The *in vivo* micronucleus test is designed to induced detectable chromosomal aberrations quickly (48 hours), by administering a sub-lethal dose of test article, to achieve as high as feasible exposure of the bone marrow to test article. The design is for hazard identification, not quantitative risk estimate. The appropriate assay to quantify risk by exposure would be the rodent carcinogenicity bioassays.
- As quoted above, ICH S2(R1) notes, “*Selection of a top dose based only on an exposure margin (multiple over clinical exposure) without toxicity is not considered sufficient justification.*”

Results

vivo rodent erythrocyte micronucleus assay. Mutat Res. 312(3):293-304. doi: 10.1016/0165-1161(94)90039-6. PMID: 7514741. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/7514741/>

³⁸ Hayashi M, MacGregor JT, Gatehouse DG, Adler ID, Blakey DH, Dertinger SD, Krishna G, Morita T, Russo A, Sutou S. 2000. In vivo rodent erythrocyte micronucleus assay. II. Some aspects of protocol design including repeated treatments, integration with toxicity testing, and automated scoring. Environ Mol Mutagen. 35(3):234-52. PMID: 10737958. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/10737958/>

³⁹ Hayashi M, MacGregor JT, Gatehouse DG, Blakey DH, Dertinger SD, Abramsson-Zetterberg L, Krishna G, Morita T, Russo A, Asano N, Suzuki H, Ohyama W, Gibson D. 2007. In Vivo Micronucleus Assay Working Group, IWGT. In vivo erythrocyte micronucleus assay III. Validation and regulatory acceptance of automated scoring and the use of rat peripheral blood reticulocytes, with discussion of non-hematopoietic target cells and a single dose-level limit test. Mutat Res. 627(1):10-30. doi: 10.1016/j.mrgentox.2006.08.010. Epub 2006 Dec 6. PMID: 17157053. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/17157053/>

⁴⁰ Accessed via: [\CDSESUB1\evsprod\nda215092\0001\m2\26-nonclin-sum\toxicology-written-summary.pdf](#)

- Test article was negative and non-toxic for each treated rat (i.e. no positives).
- The positive and negative controls gave the expected responses.

Table 62: Erythrocyte results of the rat micronucleus study (report # (b) (4) 102-226)

Bone marrow parameters	0	0.4 mg/kg/day	1.3 mg/kg/day	4 mg/kg/day	Positive control
MNIE (total # out of 10,000 IE total counted for 5 rats/group)	10	12	10	12	201
MNIE %	0.01 ± 0.04	0.12 ± 0.06	0.10 ± 0.05	0.12 ± 0.04	2.01 ± 0.54
IE %	47.12 ± 2.77	49.64 ± 2.05	44.72 ± 5.26	46.20 ± 3.37	32.96 ± 3.72

MNIE % and IE % presented as mean ± SD

7.4 Structure-activity relationship (SAR) considerations for genotoxicity

- Within CDER, the Office of Translational Sciences (OTS) Office of Clinical Pharmacology (OCP)'s Division of Applied Regulatory Science (DARS) provides a quantitative structure activity relationship (QSAR) computational toxicology consult service [(Q)SAR/CompTox]⁴¹ for DPT review divisions. This reviewer sent a consult request for (Q)SAR/CompTox prediction on April 27, 2021.
- The consult response was received May 13, 2021.
 - o "Omidenepag (API) and Omidenepag isopropyl (prodrug) from NDA 215092 were evaluated by the CDER/OTS/OCP/DARS Computational Toxicology Consultation Service for ICH S2 genetic toxicity using
 - o (Q)SAR models. Three software programs were used: Derek Nexus 6.1.0 (DX), Leadscope Model Applier version 3.0.2-4 (LMA), and CASE Ultra version 1.8.0.2 (CU)." DARS experts
- For omidenepag and omidenepag isopropyl, "*No prediction could be made for the mouse lymphoma assay due to the lack of structurally relevant training set chemicals in the models.*"
- For the *in vitro* chromosomal aberration assay prediction, "the presence of the pyrazole group" was noted as a potential concern.

⁴¹ The internal webpage accessed via:

<https://intranetapps.fda.gov/scripts/CompToxRequest/index.cfm>

8 Carcinogenicity

- Carcinogenicity testing has not been performed with omidenepag isopropyl or omidenepag.
- As justification for not conducting carcinogenicity studies, the Applicant:
 - o Cited ICH S1A⁴², “*Pharmaceuticals administered by the ocular route may not need carcinogenicity studies unless there is cause for concern or unless there is significant systemic exposure.*”

⁴² ICH S1A. Guideline for Industry The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals. Accessed via: <https://www.fda.gov/media/71921/download>

- o Noted the administered daily dose, 1.2 µg/person/day, is lower than the threshold for toxicological concern (1.5 µg/person/day) discussed in ICH M7(R1).⁴³
 - o Noted the clinical C_{max} of 28.3 pg/ml
 - o Noted the lack of apparent accumulation following sc or topical ocular dosing.
- As noted above, the 26-week sc rat study detected rare tumors after dosing with omidenepag isopropyl, and the monkey topical ocular studies detected nasal cavity metaplasia. From a safety perspective, the presence of these lesions in chronic testing raises questions.
- The carcinogenic potential of omidenepag isopropyl is an active topic of discussion and review; P/T has not yet reached a final decision.

9 Reproductive and Developmental Toxicology

- The Applicant submitted one fertility and early embryonic development (FEED) study (rat), two embryofetal development (EFD) studies (rat and rabbit), and one pre-/post-natal development (PPND) study (rat).
- The Applicant also submitted a study of placental transfer and lactation in the rat (report # AE-7762-G), reviewed above (section 5 of this review).

9.1 Fertility and Early Embryonic Development

Study title: A Study for Effects of DE-117 on Fertility and Early Embryonic Development up to Implantation by Subcutaneous Administration in Rats

Study no.: (b) (4) 102-333
Study report location: NDA module 4.2.3.5.1 Fertility and early embryonic development:

Study report:
[\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev \(b\) \(4\) 102-333 \(b\) \(4\) 102333-pre-clinical-study-report.pdf](\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev (b) (4) 102-333 (b) (4) 102333-pre-clinical-study-report.pdf)

Historical control data:
[\\CDSESUB1\evsprod\nda215092\0012\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev \(b\) \(4\) 102-333 \(b\) \(4\) 102333-background-rat-feed-2013-2017.pdf](\\CDSESUB1\evsprod\nda215092\0012\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42351-fert-embryo-dev (b) (4) 102-333 (b) (4) 102333-background-rat-feed-2013-2017.pdf)

Report date: May 12, 2017

⁴³ ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk. Accessed via: <https://www.fda.gov/media/85885/download>

Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 21, 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	DE-117 (omidenepag isopropyl), lot # RGC1403010, purity 100%

Key Study Findings

- The NOAEL for effects on both male and female male fertility is the high dose, 1 mg/kg/day.
- The 1.0 mg/kg group was associated with non-adverse effects on clinical signs (increased soft stool after dosing), transient increases in male and female body weight gain, and slightly increased food consumption.

Methods	
Doses:	0, 0.01, 0.1, or 1 mg/kg/day
Frequency of dosing:	Once daily
	• Males were dosed for 28 days before mating, through the mating period (2 consecutive weeks, D29-42 of dosing) until the day before necropsy (D42 or D43) • Females were dosed for 14 days before mating, through the mating period (no longer than 2 weeks, D15 to 28 of dosing), through Gestation Day (GD) 6 • "the day on which copulation was confirmed" designated as GD 0.
Dose volume:	10 ml/kg
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	Sprague Dawley rat (confirmed sexually mature during acclimation – testicular descent and palpation for males, estrous cycle examinations for females)
Number/Sex/Group:	20/sex/dose
Satellite groups:	None
Study design:	No study design deficiencies identified.
Deviation from study protocol:	The authors report no protocol deviations.

Observations and Results

Mortality

- All rats survived to scheduled sacrifice.

Clinical Signs

- Rats were checked twice daily on dosing days, and once daily on non-dosing days, for clinical signs and mortality.
- At 1 mg/kg, soft stool 1-2 hours after dosing was observed for 17/20 males and 6/20 females. The authors note (report page 16) that the loose stool was expected, based on the results of the 4-week repeat-dose rat sc toxicity study (report # 112201), which observed loose stool at this dose-level.
- No other remarkable clinical signs were noted.

Body Weight

- Male body weight was measured twice weekly.
- Females were weighted twice weekly before copulation, and on GD 0, 3, 6, 9, 12, and 15.
- No remarkable effects on body weight or weight gain for the low- and mid-dose.
- The authors noted an increase in mid- and high-dose animals, and provided the following data summary (report pages 43-47).
- Based on the individual animal data, this review concurs that the increase for 0.1 and 1 mg/kg is treatment-related, non-adverse, and notes the effect was transient for males, but apparently not for females.

Table 63: Rat fertility study – transient increased male body weight gain at 0.1 and 1 mg/kg (report # (b) (4) 102-333)

Males	Body weight gain			
Day	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
1-15	17.0 ± 11.5	21.4 ± 12.1	25.9 ± 10.0 *	24.8 ± 9.0
15-20	30.0 ± 8.9	29.3 ± 7.8	29.7 ± 9.5	29.3 ± 7.5

*: statistically significant difference from controls, $p < 0.05$ by Dunnett's test

- Similarly, the authors noted a pre-mating increase for females, and provided the following data summary (report page 45):

Table 64: Rat fertility study – increased male body weight gain at 0.1 and 1 mg/kg (report # (b) (4) 102-333)

Females	Body weight gain			
Day	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
1-15 (pre-mating)	6.3 ± 7.5	6.1 ± 8.2	8.8 ± 7.8	12.9 ± 6.0 *

[females not weighed during mating]				
GD 0-6	24.7 ± 6.5	29.7 ± 7.8	26.5 ± 8.1	27.2 ± 6.1
GD 6-15	45.8 ± 6.5	43.4 ± 5.5	45.3 ± 8.5	40.0 ± 7.6 *

*: statistically significant difference from controls, $p < 0.05$ by Dunnett's test

- No treatment-effect was apparent for female body weight or weight gain from GD0-15.

Feed Consumption

- Male and female rats were housed individually, except during mating.
- For males, food consumption was measured twice weekly pre-mating (i.e. D1-28).
- For females, food consumption was measured twice weekly pre-mating (i.e. D1-14), and every 3 days from GD 0-15.
- Food consumption was not measured during mating (i.e. one male and one female in the same cage).
- Males at 0.1 and 1 mg/kg exhibited a clear slight (+10 to 15%) increase in food consumption pre-mating, apparent from D8 to D28.
- Females at 1 mg/kg exhibited a clear slight (+7 to +10%) increase in food consumption pre-mating, apparent D4-11 (but not D11-14). No apparent effect on food consumption for females during gestation (GD0-GD15).

Estrous cycle examination

- For all females, vaginal smears were taken using cotton swabs daily from 4 weeks prior to initiation of mating, until confirmation of copulation. Light microscopy was used to classify smears as proestrus, estrus, metestrus, or diestrus. After initiation of mating, the presence or absence of sperm in the vaginal smear was evaluated.
- No apparent treatment-effect on estrus cycle. For the 2-week pre-mating dosing period, females has 3 or 4 estrus cycles (excepting one animal, #10113 in the mid-dose group, which only had 2 estrus cycles during the 2-week pre-mating dosing period). Female # 10113 copulated on the first day of mating (i.e. copulatory plug found on D16 of dosing). These data are not concerning.

Mating

- Males and females of the same dose group were paired 1:1, in the afternoon (D29 for males, D15 for females). For this study, no animals were re-paired.
- Copulation was confirmed in the morning, by either presence of a copulatory plug or presence of sperm in vaginal smear.
- The copulatory index was calculated as the number of days from the first day of mating until the confirmation of copulation.
- The copulation rate and fertility rate were 100% for all groups (no treatment-effect apparent).
- The authors did not consider the numerical differences for copulatory interval to be treatment-related, and this reviewer concurs.
 - o Most rats copulated by D3.

- o The control group had one outlier pair, that did not achieve copulation until mating day 14 (male # 10016, female # 10036). When this outlier is removed, no difference across groups is apparent.

Table 65: Rat fertility study: copulatory interval (report # (b) (4) 102-333)

Copulatory interval (day)	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
Mean ± SD	2.6 ± 2.9 [1.9 ± 1.0]	2.0 ± 1.5	2.2 ± 1.2	2.4 ± 1.4

Value in brackets is the control mean with one outlier removed.

Toxicokinetics

- No blood samples were collected for TK.

Male Necropsy

- No treatment-related effects apparent for male necropsy.
 - o One high-dose male (# 10135) had “testis: soft” and “epididymis, caput: yellowish white focus”. The L/R testis and epididymis weights for this animal were not remarkable. This male copulated on mating D1.
 - o No findings noted for other males.
- For males, gross necropsy was performed on D43 or 44 or dosing. Testes and epididymides were weighed and fixed (histopathology not performed).

Female Necropsy

- No abnormalities were noted for any female at necropsy.
- For females, gross necropsy was performed on GD15. The number of corpora lutea and implantation were determined. Ovaries and uteri (after removal of embryos) were fixed (histopathology not performed).

Female Ovary and C-section Parameters

- At GD15, the number of corpora lutea and implantations were determined.
- All embryos and placentae were collected. “The number of live embryos, and number of postimplantation losses and their condition (classified as implantation site, placental remnant, or dead embryo) were determined.”

Review notes regarding the term “placental remnant”

- o During the review process, this reviewer was asked to clarify how the study laboratory, (b) (4), uses the term “placental remnant” across the DART studies for omidenepag isopropyl.

- o Review note: the term “placental remnant” is listed by the study authors as a type of postimplantation loss, but is not otherwise defined in the study report. The Applicant did not use the term “postimplantation loss” or “placental remnant” in the Toxicology Written Summary (NDA module 2.6.6) or Toxicology Tabulated Summary (NDA module 2.6.7).
- o From context, this reviewer understands that the study laboratory uses the term “placental remnant” synonymously with “late resorption”, and “implantation site” synonymously with early resorption.
- o In some cases⁴⁴, authors have defined the term early resorption as a “conceptus in which only placental remnants (metrial gland) are visible” and a late resorption as having “both placental and fetal remnants visible”
- o A literature search did not find the term “placental remnant” in common usage to describe rat FEED or EFD study data.
- o A search of published FDA/OND documents found the term “placental remnant”.
 - It was used once (NDA 22275) to describe a type of early resorption, once (NDA 22406) to describe a type of late resorption, and once (NDA 214514) to describe signs of abortion.
 - Other uses were for C-section results, without explicit definition or discussion.
 - From context, use of the term generally appears to be used to describe C-section findings, and appears consistent with considering it a synonym for “late resorption.
 - These data were not used to support the safety of NDA 215092, and are noted here for context and clarity of review.

Table 66: Search of publicly available data for P/T use of the term “placental remnant”

Selected use in OND reviews	Notes
NDA 214514	• FDA approved NDA 214154 for Nextstellis on 4/15/2021. The multi-disciplinary review is publicly available on Drugs@FDA.⁴⁵ • “<i>Signs of abortion (blood, fetal/placental remnants in bedding) for 6 MD dams...</i>” – the phrase is not being used to describe a C-section finding.

⁴⁴ Erb C. 2006. Embryology and Teratology. Chapter 28 of The Laboratory Rat, edited by Mark A. Suckow, Steven H. Weisbroth, Craig L. Franklin. Academic Press. Accessed online via: <https://books.google.com>

⁴⁵ Accessed via: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214154Orig1s000MultidisciplineR.pdf

NDA 211349	• FDA approved NDA 211349 for Xospata on 11/28/2018. The multi-disciplinary review is publicly available on Drugs@FDA.⁴⁶ • The term “placental remnant” appears once, for a rat EFD study, and is tabulated as a type of post implantation loss. For 3/5 dose groups, all “postimplantation loss (%)” are “placental remnant (%)”. For the two high-dose groups (2/5), postimplantation loss % is higher than placental remnant % (i.e. some other type of postimplantation loss was documented). • The finding appears to be labeled⁴⁷ under section 8.1, as “embryo-fetal death (postimplantation loss)”
NDA 210854	• FDA approved NDA 210854 for Xofluza on 10/24/2018. The P/T review by Dr. Deacqunita Diggs (9/21/2018) is publicly available on Drugs@FDA.⁴⁸ • The term “placental remnant” appears once, as part of a narrative description of C-section results for a dose-range finding rabbit EFD study. <i>“Post-implantation loss rates, mainly observed as placental remnant, in the 300 and 1000 mg/kg groups (10.7% and 13.9%, respectively) were higher than those in the controls (5.5%) and historical controls (0.0% to 9.6%).”</i>
NDA 209176	• FDA approved NDA 209176 for Radicava on 5/05/2017. The P/T review by Dr. David Carbone is publicly available on Drugs@FDA.⁴⁹ • The term “placental remnant” is used once, to describe the C-section results of a pregnant rat sacrificed during a rat PPND study: <i>“One HDF did not deliver by GD 24; uterine contents included retention of dark red fluid, 2 resorbed embryos, 1 placental remnant, and 2 dead fetuses.”</i>
NDA 22406	• This is the second earliest public example found by this reviewer.

⁴⁶ Accessed via:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211349Orig1s000MultidisciplineR.pdf

⁴⁷ NDA 211349 / S-01 labeling dated 5/29/2019, accessed via:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211349s001lbl.pdf

⁴⁸ Accessed via:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210854Orig1s000PharmR.pdf

⁴⁹ Accessed via:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209176Orig1s000PharmR.pdf

	• FDA approved NDA 22406 for Xarelto on 7/01/2011. The P/T review by Dr. Yash Chopra (5/12/2009) is publicly available on Drugs@FDA.⁵⁰ • The term “placental remnant” is used twice: - o To describe a rat EFD study: “<i>The uterus and placenta were weighed (individual weight and appearance), number of early resorptions (only implantation site visible) and late resorptions (fetal or placental remnant visible), and dead fetuses (fetuses without signs of life, but without maceration), number of live fetuses, fetal sex and their weights were taken.</i>” - o To describe a rabbit EFD study: “<i>The uterus and placenta were weighed (individual weight and appearance), number of early (only implantation site visible) and late resorptions (fetal or placental remnant visible), and dead fetuses (fetuses without signs of life, but without maceration), number of live fetuses, fetal sex and their weights were determined.</i>”
NDA 22275	• This is the earliest public example found by this reviewer. • FDA approved NDA 22275 for Samsca on 5/19/2009. The P/T review by Dr. Joseph Xavier (6/24/2008) is publicly available on Drugs@FDA.⁵¹ • The term “placental remnant” is used once, to describe findings for a rabbit EFD study. “<i>The numbers of corpora lutea, implantations, early resorptions (implantation scars, placental remnants or amorphous embryos), late resorptions (macerated fetuses with distinct extremities), dead (fetuses without maceration) and live fetuses were counted.</i>” [Review note: this appears on page 132 (pdf page 41/97). The version on Drugs@FDA is not text-searchable.]

Female Ovary and C-section Parameter Results

- The authors concluded no treatment-related effects were apparent for # of corpora lutea and C-section results.
- This reviewer concurs that no treatment-related adverse effects are apparent.

⁵⁰ Accessed via:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406Orig1s000PharmR.pdf

⁵¹ Accessed via:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022275s000_PharmR_P2.pdf

- The numbers of corpora lutea, implantations, and live embryos are slightly higher for the 1 mg/kg group compared to the control group.
 - o Based on the historical control data, this difference appears incidental (i.e. not due to pharmacologic EP2 receptor agonist activity of omidenepag isopropyl)
 - o Historical control data were provided by (b) (4) for 18 studies (2013 to 2017), totaling 368 males and 368 females.
 - Mean corpora lutea = 14.8 ± 0.6
 - Mean # of implantations = 14.1 ± 0.6
 - % implantations = 95.3 ± 2.1

Table 67: Rat fertility study – ovary examination and C-section results (report # (b) (4) 102-333)

Parameter (mean $\pm$ SD)	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of pregnant dams	20	20	20	20
Corpora lutea	13.7 ± 1.3	14.2 ± 1.8	13.8 ± 2.0	14.6 ± 1.5
# Implantations	13.1 ± 1.9	13.7 ± 2.0	13.5 ± 2.3	14.0 ± 1.6
% Implantations ^a	95.3 ± 8.2	96.5 ± 4.9	97.4 ± 6.4	95.9 ± 6.4
# Preimplantation loss	0.6 ± 0.9	0.5 ± 0.6	0.3 ± 0.7	0.6 ± 1.0
% Preimplantation loss ^b	4.7 ± 8.2	3.5 ± 4.9	2.6 ± 6.4	4.1 ± 6.4
# Postimplantation losses	1.0 ± 1.1	1.7 ± 1.9	1.0 ± 1.1	1.0 ± 1.4
% Postimplantation loss	8.1 ± 9.7	12.7 ± 14.9	9.0 ± 14.9	6.8 ± 10.4
Postimplantation loss type: implantation site %	0	0	0	0
Postimplantation loss type: placental remnant %	8.1 ± 9.7	11.9 ± 13.0	8.7 ± 15.1	6.8 ± 10.4
Postimplantation loss type: dead embryo %	0	0.9 ± 3.8	0.3 ± 1.3	0
Live embryos	12.1 ± 2.3	12.0 ± 2.8	12.5 ± 2.9	13.1 ± 1.9
% Embryonic viability	91.9 ± 9.7	87.3 ± 14.9	91.1 ± 14.9	93.3 ± 10.4

Data are presented as mean $\pm$ SD

^a Percent implantations = $100 \times \text{number of implantations} / \text{number of corpora lutea}$

^b Percent preimplantation loss = $100 \times (\text{number of corpora lutea} - \text{number of implantations}) / \text{number of corpora lutea}$

^c Percentage postimplantation loss = $100 \times \text{number of postimplantation losses} / \text{number of implantations}$

^d percentage embryonic viability = $\text{number of live embryos} / \text{number of implantations}$

Table 68: Rat fertility study – additional selected data (report # (b) (4) 102-333)

Parameter	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
Totals per group				
Pregnant dams	20	20	20	20
Corpora lutea	274	283	276	292
Implantations	262	274	270	280
Preimplantation loss	12	9	6	12
Live embryo	242	240	250	261
Placental remnant	20	32	19	19
Dead embryo	0	2	1	0
Postimplantation loss	20	34	20	19

Dosing Solution Analysis

- Results are acceptable
- Concentration was verified at the start of dosing and during the last week of dosing; concentrations were 97.5 to 107.6% of nominal.

9.2 Embryonic Fetal Development

Study title: A Study for Effects of UR-7385 on Embryo-Fetal Development by Subcutaneous Administration in Rats

Study no.:	(b) (4) 102-295
Study report location:	NDA module 4.2.3.5.2 Embryo-fetal development
Study report:	\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\102-295\102295-pre-clinical-study-report.pdf
Historical control data:	\\CDSESUB1\evsprod\nda215092\0012\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev\102-295\102295-background-rat-efd-2011-2015.pdf
Conducting laboratory and location:	(b) (4)
TK:	(b) (4)
Report date:	June 23, 2015
Date of study initiation:	December 8, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	UR-7385 (omidenepag isopropyl), lot # RGC1403010, purity 99.2%

Key Study Findings

- No treatment-related toxicity was observed. The high dose, 1 mg/kg/day, is the NOAEL for maternal toxicity and developmental toxicity.

Methods

Doses:	0, 0.01, 0.1, 1 mg/kg/day
Frequency of dosing:	Once daily from GD6-17 (total of 12 doses)
Dose volume:	10 ml/kg (based on the body weight at GD6)
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	Sprague Dawley rat

Number/Sex/Group:	• 20 mated females/dose for toxicology • 4 mated females/dose for TK
Study design:	The design appears adequate; this reviewer did not identify deficiencies.
Deviation from study protocol:	The authors reported no deviations from the study protocol.

Observations and Results

Mortality

- All dams survived to scheduled sacrifice.

Clinical Signs

- No clinical signs were noted for any dam.
 - As justification for dose-selection, the authors report that the 2-week repeat-dose rat sc toxicology study (report # 529Ff030) observed clinical signs at all dose levels (slight transient flushing of the pinna, extremities and tail, loose stool); the high-dose (4 mg/kg) was considered to be above the NOAEL.
- The toxicology group animals were checked twice daily during the dosing period (before dosing and 1-2 hours post-dose), and once daily during non-dosing days.
- The TK satellite animals were checked once daily.

Body Weight

- No effect on body weight or body weight gain apparent.
- Body weight was measured on GD0, 6, 9, 12, and 15. For the toxicology group only, body weight was also measured on GD20.

Feed Consumption

- No effect on food consumption apparent.
- Females were single-housed after mating. Food consumption was measured for the toxicology group animals, from GD5-19.

Toxicokinetics

- The laboratory dosed 4 rats/dose for TK.
- Blood was collected from controls once on GD6 and GD17.
- From the treatment-groups, blood was collected on GD6 at and GD17 (post-dose at 15, 30 minutes; 1, 2, 4, 8 hours). Additionally, blood was also collected pre-dose on GD17.
- Plasma was prepared, frozen, and shipped.
- Plasma concentrations of omidenepag isopropyl were measured using a validated LC-MS/MS assay.

- For TK animals, pregnancy status was confirmed on GD18, but no further evaluation was performed.

Table 69: Rat EFD study: plasma TK results (report # (b) (4) 102-295)

Gestation Day	Dose level (mg/kg/day)	T _{max} (h)	C _{max} (ng/ml)	AUC _{0-8h} (ng*h/ml)
6	0.01	0.8	1.70	4.00
	0.1	1.2	13.9	44.7
	1	1.0	179	585
17	0.01	1.2	0.807	2.88
	0.1	1.7	7.13	32.6
	1	1.7	66.2	307

- The authors noted the decrease in exposure at GD17 compared to GD6, and this reviewer concurs.
- The authors proposed two possible causes: increased body size (since doses were based on body weight at GD6) or distribution of test article from maternal circulation into the placenta and fetus.

Necropsy

- No gross necropsy findings were noted for any dam.
- Toxicology group animals were sacrificed on GD20. "Determination of pregnancy, and examinations of external appearance, and internal organs and tissues were conducted macroscopically.
- Three toxicology group animals were found to be non-pregnant (1 control, 1 low-dose, 1 high-dose). All of the TK animals were pregnant.
- No abortions were observed.

Table 70: Rat EFD study – no abortions observed (report # (b) (4) 102-295)

Parameter	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of copulated females	20	20	20	20
# of pregnant females	19	19	20	19
# of abortions	0	0	0	0

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

- At the GD20, “The numbers of corpora lutea and implantations were determined, and the percentage implantation and the percentage preimplantation loss were calculated.”
- The authors report no treatment-related effects; this reviewer concurs.
- The laboratory classified embryofetal deaths as “implantation site, placental remnant, or dead fetus”

Table 71: Rat EFD study – GD20 C-section results (report # (b) (4) 102-295)

Parameter	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
Corpora lutea	14.8 ± 2.2	13.7 ± 2.2	14.6 ± 2.0	13.8 ± 1.4
Implantations	13.4 ± 3.3	13.1 ± 3.2	13.6 ± 3.3	12.9 ± 1.7
% Implantations ^a	89.3 ± 16.0	93.4 ± 14.7	91.9 ± 16.8	93.4 ± 7.3
% Implantation loss ^b	10.7 ± 16.0	6.7 ± 14.9	8.2 ± 16.8	6.6 ± 7.3
Embryofetal deaths	1.2 ± 1.7	0.5 ± 0.8	0.6 ± 0.8	0.7 ± 0.8
% Postimplantation loss ^c	9.3 ± 13.6	4.9 ± 8.8	5.5 ± 8.4	5.2 ± 6.2
Postimplantation loss: % Implantation site	0	0	0	0
Postimplantation loss: % placental remnant	8.8 ± 13.8	4.9 ± 8.8	4.8 ± 8.1	5.2 ± 6.2
Postimplantation loss: % dead fetus	0.4 ± 1.8	0	0.7 ± 2.0	0
Live fetuses	12.2 ± 3.8	12.5 ± 3.2	13.0 ± 3.3	12.2 ± 1.8
% fetal viability ^d	90.7 ± 13.6	95.1 ± 8.8	94.6 ± 8.4	94.8 ± 6.2
Sex ratio (% male)	45.2 ± 14.9	56.5 ± 18.5	48.6 ± 19.0	41.9 ± 12.8
Male fetal body weight (g)	3.66 ± 0.24	3.75 ± 0.33	3.73 ± 0.32	3.80 ± 0.17
Female fetal body weight (g)	3.47 ± 0.29	3.47 ± 0.23	3.53 ± 0.32	3.52 ± 0.21
Male placental weight (g)	0.55 ± 0.10	0.53 ± 0.15	0.49 ± 0.05	0.56 ± 0.10
Female placental weight (g)	0.55 ± 0.15	0.49 ± 0.05	0.49 ± 0.06	0.56 ± 0.12

Data are presented as mean ± SD

^a % implantations = corpora lutea / implantations

^b % implantation loss = (corpora lutea – implantations) / implantations

^c % postimplantation loss = 100 * embryofetal deaths / implants

^d % fetal viability = 100 * live fetuses / implants

Offspring (Malformations, Variations, etc.)

- At GD20 C-section, all fetuses and placenta were classified (live, implantation site, placental remnant, or dead fetus). For live fetuses, the fetal and placenta weight were recorded, external features (including the placenta and oral cavity) were evaluated, and fetuses were sexed.
- Approximately half of each litter was fixed in formalin for visceral examination. Remaining fetuses were processed for skeletal examination.
 - o For visceral examinations, *“Fetuses were examined for visceral abnormalities and variations in the cephalic, thoracic, and abdominal organs with a stereoscopic microscope by Wilson’s method, the method described by Barrow et al., and Nishimura’s method (heart).”*
 - o For skeletal evaluation, *“Fetuses from all groups fixed in ethyl alcohol were stained with Alizarin red S in accordance with Dawson’s method, and examined for skeletal abnormalities and variations, and ossification. The numbers of ossified sternebrae and sacral and caudal vertebrae were examined as indices of ossification.”*

Fetal results

- No treatment-related fetal malformations were observed.
 - o No malformations (external, visceral, skeletal) were reported for any fetus. No external variations were reported for any fetus.
 - o The incidences of visceral findings (thymic remnant in the neck, dilated ureter), and skeletal findings (short rib, short supernumerary rib, dumbbell ossification of thoracic centrum, and/or splitting of thoracic centrum), and increased ossification (sacral and caudal vertebrae) do not show a treatment-effect.
- Three dams had abnormal placentae (enlargement of placenta):
 - o One dam (# 10003) in the control group (the placenta for one fetus showed enlargement)
 - o One dam (# 10027) in the 0.01 mg/kg group (placentas for two fetuses showed enlargement)
 - o One dam (# 10062) in the 1 mg/kg group (the placenta for one fetus showed enlargement).
 - o The placentae were formalin fixed but did not undergo histopathology.
 - o The four fetuses with enlarged placentae did not exhibit structural anomalies.
 - o The authors did not consider the placental enlargement observations treatment-related, and this reviewer concurs.

Table 72: Rat EFD study – external and placental findings (report # (b) (4) 102-295)

Parameter	Litter / fetal incidence	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of litters	L	19	19	20	19
Total # of fetuses	F	232	238	259	232
Fetal external anomalies	L	0	0	0	0
	F	0	0	0	0
Placental enlargement	L	1 (5.3%)	1 (5.3%)	0	1 (5.3%)
	F	1	2	0	1

Table 73: Rat EFD study – fetal visceral findings (report # (b) (4) 102-295)

Parameter	Litter / fetal incidence	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of litters	L	19	19	20	19
Total # of fetuses	F	111	115	124	111
Thymic remnant in neck	L	0	1 (5.3%)	0	2 (10.5%)
	F	0	1	0	3
Dilated renal pelvis	L	1 (5.3%)	0	0	0
	F	1	0	0	0
Dilated ureter	L	2 (10.5%)	1 (5.3%)	1 (5.0%)	3 (15.8%)
	F	2	1	1	4
Other visceral abnormalities	L	0	0	0	0
	F	0	0	0	0

Table 74: rat EFD study – fetal skeletal findings (report # (b) (4) 102-295)

Parameter	Litter / fetal incidence	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of litters	L	19	19	20	19
Total # of fetuses	F	121	123	135	121
Short rib	L	0	0	1 (5.0%)	0
	F	0	0	1	0
Short supernumerary rib	L	9 (47.4%)	5 (26.3%)	8 (40.0%)	7 (36.8%)
	F	14	11	14	11
Dumbbell ossification of thoracic centrum	L	0	2 (10.5%)	1 (5.0%)	0
	F	0	2	1	0
Splitting of thoracic centrum	L	0	3 (15.8%)	1 (5.0%)	0
	F	0	3	1	0
Litter mean # of ossified sternebrae	L	5.0 ± 0.6	5.0 ± 0.5	5.3 ± 0.6	5.3 ± 0.5
Litter mean # of ossified sacral and caudal vertebrae	L	7.6 ± 0.8	7.8 ± 0.5	8.1 ± 0.6	8.0 ± 0.3

Dosing Solution Analysis

- Results are acceptable
- Concentration and stability were verified; test articles were 94.6 to 100% of nominal.

Study title: A Study for Effects of UR-7385 on Embryo-Fetal Development by Subcutaneous Administration in Rabbits

Study no.: (b) (4) 102-294

Study report location: NDA module 4.2.3.5.2 Embryo-fetal development

Study report at:

[\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev \(b\) \(4\) 102-294 \(b\) \(4\) 102294-pre-clinical-study-report.pdf](\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev (b) (4) 102-294 (b) (4) 102294-pre-clinical-study-report.pdf)

Historical control data at:

[\\CDSESUB1\evsprod\nda215092\0012\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev \(b\) \(4\) 102-294 \(b\) \(4\) 102294-background-rabbit-efd-2011-2015.pdf](\\CDSESUB1\evsprod\nda215092\0012\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42352-embryo-fetal-dev (b) (4) 102-294 (b) (4) 102294-background-rabbit-efd-2011-2015.pdf))

Conducting laboratory and location:

(b) (4)

TK:

(b) (4)

Report date: June 24, 2015

Date of study initiation: January 7, 2015

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: UR-7385 (omidenepag isopropyl), lot # RGC1403010, purity 99.2%

Key Study Findings

- No NOAEL for fetal skeletal malformations were observed, based on observations of rare skeletal malformations in multiple litters at each dose level.
 - o The low-dose, 0.008 mg/kg, exhibited increased incidences in two litter: misaligned thoracic centrum with thoracic hemivertebra.
 - o Sternebral malformations were observed in 3 mid-dose litters (fused sternebra); thoracic malformations were observed in 1 mid-dose litter and 1 high-dose litter (absent thoracic arch with hemicentric thoracic centrum, fused thoracic arch).

- o Cervical vertebral malformations were observed in 1 mid-dose litter (misaligned cervical vertebra with or without misshapen cervical vertebra).
 - o Rib malformations (absent rib, branched rib, fused rib) were also observed at all omidenepag isopropyl dose levels.
- The high-dose group is associated with lower incidences of full supernumerary rib and short supernumerary rib.
 - o Because the control fetal incidence of these variations is > 50%, these ribs represent normal for these rabbits, and the lack of the 'supernumerary rib' is a clear treatment-related difference from controls (i.e. absent rib).
 - o This effect is not per se adverse, but supports the conclusion that treatment-related fetal skeletal effects occurred.
- Omidenepag isopropyl did not cause fetal external or visceral malformations in rabbits at any dose level tested.
- The NOAEL for embryofetal loss is the mid-dose, 0.08 mg/kg; the LOAEL is the high-dose, 0.8 mg/kg.
 - o The authors concluded that the high-dose caused increased postimplantation loss (increased placental remnants), resulting in decreased number of live fetuses/litter and decreased litter % fetal viability. This reviewer concurs.
- The NOAEL for toxicity to fertility is the mid-dose, 0.08 mg/kg; the LOAEL is the high-dose, 0.8 mg/kg.
 - o Because dosing was initiated on GD6, the test article had the potential to affect implantation. The high-dose clearly reduced the mean number of implants, resulting in a lower % of implantation, higher preimplantation loss, and higher % preimplantation loss.
 - o The authors did not consider these effects treatment-related; this reviewer disagrees.
- The high dose, 0.8 mg/kg/day, was the maternal NOAEL. This dose level was associated with non-adverse findings:
 - o sporadic iris hyperemia,
 - o slightly decreased body weight gain during dosing (GD6-18 body weight gain for the 0.8 mg/kg group was 79% of the control mean), with a slight rebound increased weight gain post-dose (GD18-28 body weight gain for 0.8 mg/kg group was + 9.3% compared to the control mean).
 - o Slightly decreased food consumption during dosing (GD6-18), with a slight rebound increase in food consumption post-dose.

Methods

Doses: 0, 0.008, 0.08, 0.8 mg/kg/day
 Frequency of dosing: Once daily from GD6 to GD18 (total 13 doses)
 Dose volume: 2 ml/kg (doses based on weight at GD6)

Route of administration:	Subcutaneous injection
Formulation/Vehicle:	(b) (4) in physiological saline
Species/Strain:	New Zealand White (NZW) rabbit
Number/Sex/Group:	20 mated females/dose group
Study design:	- o The design appears adequate; this reviewer did not identify deficiencies. - o Individual fetuses were not uniquely identified, and the report did not provide a tabulation of fetal anomalies for each fetus. This complicates review (i.e. unclear whether particular observations were observed in one fetus or different fetuses in the same litter). This did not affect the overall interpretation of the study.
Deviation from study protocol:	The authors reported no deviations from the study protocol.

Observations and Results

Mortality

- All does survived to scheduled sacrifice.
- Does were checked once daily on non-dosing days, and twice daily on dosing days for mortality and clinical signs.
-

Clinical Signs

- Does were checked once daily on non-dosing days, and twice daily on dosing days for clinical signs.
- Iris hyperemia was observed 1-2 hours post-dose in 12/20 high-dose animals.
 - o The range was GD 6-17.
 - o Of those affected, 9 exhibited iris hyperemia on GD6 (the first day of dosing). Five only exhibited the sign once, and four only on two days.
 - o The three does most affected were # 10070 (7 days), # 10071 (7 days), and 10073 (6 days).
- This reviewer considers this effect treatment-related.
 - o The NZW rabbit eye is a useful model for observing iris hyperemia.
 - o The only other rabbit study submitted to the NDA (report # 542Lm07A) was a single-dose metabolism study that did not report safety endpoints.
 - o

Body Weight

- Body weights were measured on GD0, daily from GD6-18; GD 22, 26 and 28.
- The authors concluded treatment did not affect body weight. This reviewer disagrees – a slight decrease in body weight gain was apparent for the high-dose (summary table on report page 39, individual data on report pages 52-63).

- Based on the small magnitude of effect, these changes in body weight gain are not considered adverse.

Table 75: Rabbit EFD study – doe body weight gain (report # (b) (4) 102-294)

Gestation day	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
0- 6	0.255±0.068	0.308±0.053	0.239±0.079	0.270±0.076
6-12	0.116±0.051	0.121±0.055	0.128±0.051	0.074±0.063
12-18	0.123±0.050	0.152±0.047	0.136±0.041	0.114±0.064
6-18	0.239±0.082	0.272±0.083	0.264±0.080	0.189±0.108
18-28	0.166±0.101	0.166±0.096	0.159±0.089	0.181±0.072
0-28	0.661±0.145	0.746±0.132	0.662±0.147	0.640±0.154

Data presented as mean ± SD

Feed Consumption

- Food consumption was measured daily from GD5-27.
- The authors concluded treatment did not affect food consumption. This reviewer disagrees – a slight decrease in food consumption is apparent for mid-dose and high-dose animals compared to controls during the dosing period, followed by slight rebound weight gain GD21-28 (summary table on report page 30, individual data pages 64-71).
- Based on the small magnitude of effect, these changes in food consumption are not considered adverse.

Table 76: Rabbit EFD study: food consumption results (report # (b) (4) 102-294)

Gestation day	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
5- 6	176.1±22.5	188.1±10.9	166.4±30.2	172.8±21.9
6- 7	163.4±33.2	177.4±19.6	160.8±31.3	152.3±29.6
7- 8	170.7±22.4	178.9±14.9	166.9±22.4	151.8±28.7*
8- 9	172.5±18.8	178.2±13.9	166.2±19.7	154.8±30.9
9-10	167.9±24.1	177.6±14.4	161.8±19.3	152.8±29.3
10-11	163.2±28.2	173.4±16.8	163.8±19.6	152.1±28.1
11-12	159.4±25.9	170.8±19.1	153.5±24.5	139.4±35.8
12-13	145.1±28.4	163.3±19.0	141.6±24.0	133.6±39.8
13-14	134.8±28.7	156.1±24.7	129.1±27.5	125.4±54.7
14-15	140.2±32.4	156.3±29.7	137.6±25.9	122.7±51.7

15-16	145.7±26.5	161.0±24.2	145.9±25.6	128.7±54.1
16-17	152.3±26.3	168.7±18.3	143.5±25.4	138.9±48.3
17-18	164.9±21.4	163.3±19.5	150.4±31.1	149.7±36.3
18-19	159.1±25.1	155.0±34.1	140.2±45.4	151.1±27.1
19-20	164.3±22.3	161.4±22.1	143.4±30.8*	167.7±26.4
20-21	159.3±24.6	171.5±17.1	147.5±26.0	157.3±40.5
21-22	141.1±31.8	156.4±36.3	137.4±26.2	165.8±24.4*
22-23	129.7±31.3	147.4±28.5	113.9±37.4	157.7±24.1*
23-24	118.6±35.6	142.1±34.4	106.3±31.5	154.8±31.0**
24-25	115.7±25.7	131.1±38.5	110.2±32.1	148.2±28.3**
25-26	115.3±27.3	124.6±39.5	113.5±36.8	142.8±30.3*
26-27	109.5±31.4	125.2±40.6	121.2±27.9	136.3±35.0
27-28	118.6±41.9	131.4±35.7	123.1±24.5	138.3±30.2

Data presented as mean ± SD

Statistically different from control by Dunnett's test, * p < 0.05, ** p < 0.01

Toxicokinetics

- Blood was analyzed for 3 animals/dose/time point on GD6 and GD18.
- For controls, only one blood sample was taken per day.
- For the test-article groups, blood was measured post-dose at 15 and 30 minutes; 1, 2, 4, and 8 hours. For GD18 only, blood was also collected pre-dose.
- Plasma was frozen, shipped, and analyzed by a validated LC-MS/MS method.
- The authors noted that C_{max} and AUC were near dose proportional for both GD6 and GD18.

Table 77: Rabbit EFD study – TK results (report # (b) (4) 102-294)

Gestation Day	Dose (mg/kg/day)	T _{max} (h)	C _{max} (ng/ml)	AUC _{0-8h} (ng*h/ml)
6	0.008	0.4	1.59	3.94
	0.08	0.7	14.9	46.5
	0.8	0.8	161	531
18	0.008	0.8	0.655	2.68
	0.08	0.8	6.92	25.5
	0.8	0.7	99.8	315

Necropsy

- Does were sacrificed on GD28. Gross necropsy was performed, including determination of pregnancy and counting of corpora lutea and implantation sites.
- Eight animals were found not to be pregnant (1 control, 2 low-dose, 3 mid-dose, 2 high-dose)
- No abortions were detected during in-life (i.e. no does sacrificed early). Two animals were found to have either “abortion or total resorption of litter”.
 - o Low dose # 10021 had 5 corpora lutea, 4 implantations sites, 0 placental remnants, 0 live fetuses.
 - o High dose # 10069 had 5 corpora lutea, 4 implantation sites, 1 placental remnant, 0 live fetuses. [Review note: the laboratory classifies “implantation site” and “placental remnant” as type of postimplantation loss. This reviewer understands the term “placental remnant” to be synonymous with late resorption, and “implantation site” to be synonymous with early resorption.]
 - o The authors did not consider these effects treatment-related, and this reviewer concurs.
- No gross abnormalities were noted for any doe.

Table 78: Rabbit EFD study – pregnancy status (report # (b) (4) 102-294)

Parameter	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
# of copulated females	20	20	20	20
# of pregnant females	19	18	17	18
# of “abortion or total resorption of litter”	0	1	0	1
Gross necropsy findings	0	0	0	0

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

- C-sections were performed on GD28.
- The authors noted treatment-related adverse effects at 0.8 mg/kg: decreased number of live fetuses and percentage fetal viability; increased number of embryofetal deaths, postimplantation loss, and percentage placental remnants. This reviewer concurs.
- The authors concluded no treatment-related effect was apparent for implantation and preimplantation loss, live fetus body weight, live fetus placental weight, or sex ratio.
- This reviewer disagrees:
 - The high-dose is associated with decreased implants/litter, corresponding to higher preimplantation loss.
 - For placenta weight: the high-dose group showed a slight increase in placenta weight for live fetuses (presumably secondary to reduced litter sizes).

Table 79: Rabbit EFD study: C-section endpoints (report # (b) (4) 102-294)

Litter means ± SD	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
# of does examined on GD28	19	18	17	18
corpora lutea	8.4 ± 1.9	8.6 ± 1.6	8.9 ± 2.1	7.6 ± 1.7
implants	7.8 ± 2.1	7.8 ± 2.0	8.4 ± 2.2	6.3 ± 2.2
% implants	92.7 ± 8.9	90.1 ± 11.6	93.1 ± 10.0	82.3 ± 18.7
preimplantation loss	0.5 ± 0.6	0.8 ± 0.9	0.6 ± 0.9	1.3 ± 1.3
% preimplant. loss	7.4 ± 9.0	10.0 ± 11.6	6.9 ± 10.0	17.7 ± 18.7

Embryofetal deaths				
Postimplant embryofetal loss	0.4 ± 0.7	1.0 ± 1.6	0.2 ± 0.4	1.4 ± 1.5 *
% postimplantation loss	6.2 ± 12.9	14.6 ± 27.6	2.5 ± 4.6	25.0 ± 29.8*
Implant sites	0	0.2 ± 0.9	0	0.2 ± 0.7
% Implant sites	0	5.6 ± 23.6	0	4.2 ± 17.7
Placental remnant	0.2 ± 0.5	0.7 ± 1.5	0.1 ± 0.2	1.2 ± 1.4
% placental remnant	3.4 ± 11.7	7.8 ± 17.9	0.6 ± 2.7	19.9 ± 23.7*
Dead fetus	0.2 ± 0.5	0.1 ± 0.3	0.2 ± 0.4	0.1 ± 0.2
% dead fetus	2.8 ± 7.0	1.3 ± 3.8	1.8 ± 4.1	0.9 ± 4.0
Live fetuses				
live fetuses	7.5 ± 2.4	6.8 ± 2.6	8.1 ± 2.1	4.8 ± 2.8**
% fetal viability	93.8 ± 12.9	85.5 ± 27.6	97.5 ± 4.6	75.1 ± 29.8*
Fetal sex ratio (% male)	55.7 ± 18.6	47.4 ± 15.6	60.0 ± 19.1	51.7 ± 24.7
Male fetal body wt (g)	34.2 ± 2.8	35.2 ± 3.3	34.5 ± 4.3	36.6 ± 4.4
Female fetal body wt (g)	34.4 ± 3.1	34.1 ± 4.2	34.1 ± 4.7	36.3 ± 4.5
Male placenta wt (g)	5.61 ± 0.60	5.15 ± 0.42	5.60 ± 0.77	6.12 ± 0.98
Female placenta wt (g)	5.41 ± 0.87	4.93 ± 0.60	5.27 ± 0.73	6.02 ± 0.95
Placental abnormalities	0	0	0	0

Data presented as mean ± SD

% implantations = 100 * implants / corpora lutea

% preimplantation loss = 100 * (corpora lutea – implants)/ corpora lutea

Postimplant embryofetal loss = sum of implant sites, placental remnants, and dead fetuses

% postimplantation loss = 100 * number of embryofetal death / implantations

% fetal viability = live fetuses / implantations

Statistically different from control by Dunnett's test, * p < 0.05, ** p < 0.01

Table 80: Rabbit EFD study: C-section endpoints (report # (b) (4) 102-294)

Totals per dose group	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
# of does examined on GD28	19	18	17	18
corpora lutea	159	155	152	136
implants	149	141	142	113
Preimplantation loss	10	14	10	23
Live fetuses	142	123	138	87
Embryofetal death – implantation sites	0	4	0	3
Embryofetal death – placental remnants	3	12	1	22
Embryofetal death – dead fetus	4	2	3	1

- In response to an Information Request (IR) from P/T, the Applicant provided historical control data to the NDA on April 15, 2021 (SD # 12). For the laboratory, (b) (4) (2011 to 2015), rabbit GD28 litter data were provided for 60 studies (656 dams, 4854 fetuses).

Table 81: Rabbit EFD study: selected GD28 litter historical control data

Parameter	Historical control data
	Litter mean $\pm$ SD
Corpora lutea	8.4 $\pm$ 0.6
Implants	7.7 $\pm$ 0.8
% implantation rate	91.4 $\pm$ 5.4
Mean post-implant embryofetal loss	0.4 $\pm$ 0.2
% postimplantation loss	4.5 $\pm$ 2.4
Live fetuses	7.4 $\pm$ 0.8
% Fetal viability	95.5 $\pm$ 2.4

Discussion of pre/peri-implantation loss in a rabbit EFD study

- ICH S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals⁵² recommends initiation of dosing for the rabbit EFD study on “GD6/7”.
- For reference, ICH S5(R2) states, “ Unless shown otherwise it is assumed that, for rats, mice and rabbits implantation occurs on day 6-7 of pregnancy”
- The review article by Wise et al. 2009⁵³ cited ICH S5(R2)’s recommendation for initiating dosing of the rabbit EFD study on GD7, but did not cite other sources. Likewise, timing is not addressed in reviews by Barrow and Clemann 2021⁵⁴ or Ishihar-Hattori and Barrow 2016.⁵⁵
- Nishimura 2001⁵⁶ reported on NZW rabbit data. Rabbits were mated for a 1 hour (8:00 to 9:00 am) window (designated as GD0).
 - o On GD6 (sacrificed 8:30 to 11:00 am), blastocysts were present in the uterus but no implantation was detected.
 - o On GD7 (8:30 to 11), + 1 hour, onset of implantation was observed.
 - o On GD8, “Ob-placental implantation” was advanced, and placental implantation was detected.
- Sivaram et al. 2008⁵⁷ reported, “In both the New Zealand White and Japanese White rabbit strains, implantation was initiated on GD 6.5 and was completed on GD 7.”
 - o The authors defined the day on which mating was observed as GD0.
 - o Rabbits were mated for 1 hour (11 to 12 am).
 - o C-sections were performed on GD5 (3:30 pm), GD 6 (9:30 am, 5 pm), GD7 (9 am and 3:30 pm), and GD8 (9 am).
 - o From the paper:

⁵² Accessed from the ICH website via: https://database.ich.org/sites/default/files/S5-R3_Step4_Guideline_2020_0218_1.pdf

⁵³ Wise LD, Buschmann J, Feuston MH, Fisher JE, Hew KW, Hoberman AM, Lerman SA, Ooshima Y, Stump DG. 2009. Embryo-fetal developmental toxicity study design for pharmaceuticals. Birth Defects Res B Dev Reprod Toxicol. 86(6):418-428. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/20025038/>

⁵⁴ Barrow P, Clemann N. 2021. Review of embryo-fetal developmental toxicity studies performed for pharmaceuticals approved by FDA in 2018 and 2019. Reprod Toxicol. 99:144-151. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/32593570/>

⁵⁵ Ishihara-Hattori K, Barrow P. 2016. Review of embryo-fetal developmental toxicity studies performed for recent FDA-approved pharmaceuticals. Reprod Toxicol. 64:98-104. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/27112525/>

⁵⁶ Nishimura, Michiyo. 2001. Timing of implantation in New Zealand White rabbits. Congenital Abnormalities. 41:198-203. Accessed from the FDA Bioscience Library via: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1741-4520.2001.tb00833.x>

⁵⁷ Sivaraman L, Horimoto M, Tassinari M, Hurtt M, Cappon G. 2008. Timing of implantation and closure of the palatal shelf in New Zealand white and Japanese white rabbits. Drug Chem Toxicol. 31(2):255-261. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/18330786/>

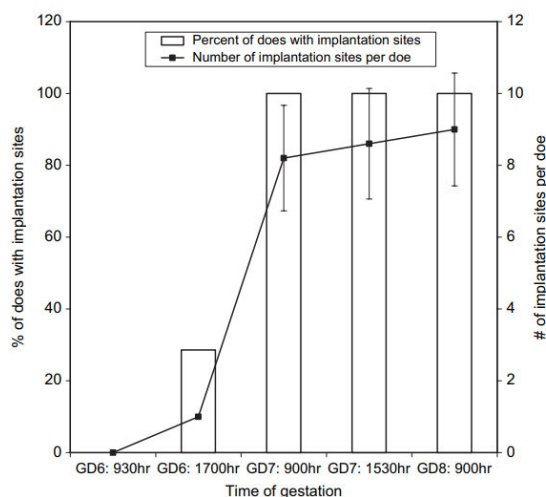
Figure 15: NZW rabbit conceptus implantation data from Sivaram et al. 2008

Figure 2: Timing of implantation in New Zealand White rabbits. The bars represent the percent of does with any implantation sites. The line graph represents the average number of implantation sites per doe (does without implantation sites were not included in mean), the error bars represent the standard deviation (a standard deviation was not calculated for the GD 6:1700 h sample, as only two does had implantation sites). Also, the data from GD 5 1530 h is not plotted because the number of implants was zero.

- Garside and Heath 1996⁵⁸ designated the day of mating as GD1. For convenience, this review subtracts 1 day from the results summarized below (i.e. to convert their results to day of mating as GD0. For Dutch belted and NZW rabbits, they reported:
 - o GD5: no implantations, morula in Fallopian tube.
 - o GD6: no implantations, blastocysts detected in the uterine lumen unattached to the uterine epithelium
 - o GD7: established implantation sites detected, supporting normal embryonic development
- Taking these data and recommendations together, this reviewer concludes that administration of omidenepag isopropyl to rabbits on GD6 had the potential to affect implantation. As the data above show, the high-dose is associated with pre/peri-implantation loss.

Offspring (Malformations, Variations, etc.)

- At GD28 C-section, all fetuses and placenta were classified (live, implantation site, placental remnant, or dead fetus). For live fetuses, the fetal and placenta weight were recorded, external features (including the placenta and oral cavity) were evaluated, and fetuses were sexed.
- Visceral and skeletal examination for all fetuses.

⁵⁸ Garside DA, Charlton A, Heath KJ. 1996. Establishing the timing of implantation in the Harlan Porcellus Dutch and New Zealand White rabbit and the Han Wistar rat. *Regul Toxicol Pharmacol*. 23(1 Pt 1):69-73. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/8628922/>

Fetal external and visceral anomalies**Table 82: Rabbit EFD study – no treatment-related external or visceral fetal anomalies (report # (b) (4) 102-294)**

Parameter	Litter / fetal incidence	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
# of dams	L	19	17	17	17
# of fetuses	F	142	123	138	87
External findings					
Cleft lip	L	1 (5.3%)	0	1 (5.9%)	0
	F	3	0	2	0
Cleft palate	L	0	0	1 (5.9%)	0
	F	0	0	1	0
Visceral findings					
Membranous ventricular septum defect (VSD)	L	1 (5.3%)	0	0	0
	F	1	0	0	0
Small lung	L	1 (5.3%)	0	0	0
	F	1	0	0	0
Diaphragmatic hernia	L	1 (5.3%)	0	0	0
	F	1	0	0	0

- o For the mid-dose group, one litter (# 10042) had two fetuses with cleft lip. The same litter had the cleft palate (not clear from the reporting whether one fetus had both findings, or whether they occurred in three separate fetuses in the same litter).

- o For the control group, one litter (# 10002) had three fetuses with cleft lip, and one fetus with the VSD (not clear if one fetus had both findings). Another litter (# 10011) had both the small lung and diaphragmatic hernia (not clear from reporting whether one fetus had both findings, or whether they occurred in separate fetuses in the same litter).
- o This reviewer concurs that no treatment-related external or visceral fetal anomalies are apparent.

Fetal skeletal malformations

- The authors concluded no treatment-related effects fetal effects were apparent. This reviewer does not concur: Treatment-related rare skeletal malformations occurred at all dose-levels.
 - o Based on incidence and severity, with consideration of the concurrent and historical control data, attribution to treatment is appropriate and consistent with ICH S5(R3) section 9 *Principles of Risk Assessment*⁵⁹, and the CDER 2011 Guidance for Industry Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns⁶⁰.

Table 83: Rabbit EFD study – fetal skeletal malformations (report # (b) (4) 102-294)

Parameter	Litter / fetal incidence	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
# of dams	L	19	17	17	17
# of fetuses	F	142	123	138	87
Fused rib	L	0	0	0	2 (11.8%)
	F	0	0	0	3
Misaligned cervical vertebrae	L	0	0	0	2 (11.8%)
	F	0	0	0	2
Misshapen cervical vertebra	L	0	0	0	1 (5.9%)
	F	0	0	0	1

⁵⁹ ICH S5(R3) accessed via: https://database.ich.org/sites/default/files/S5-R3_Step4_Guideline_2020_0218_1.pdf

⁶⁰ Guidance accessed via: <https://www.fda.gov/media/72231/download>

Fused thoracic arch	L	0	0	0	1 (5.9%)
	F	0	0	0	1
Absent thoracic arch	L	0	0	1	0
	F	0	0	1	0
Hemicentric thoracic centrum	L	0	0	1 (5.9%)	0
	F	0	0	1	0
Misaligned thoracic centrum	L	0	1 (5.9%)	0	0
	F	0	1	0	0
Thoracic hemivertebra	L	0	1 (5.9%)	0	0
	F	0	1	0	0
Misshapen premaxilla	L	1 (5.3%)	0	1 (5.9%)	0
	F	3	0	2	0
Fused sternebra	L	0	1 (5.9%)	1 (5.9%)	0
	F	0	1	1	0
Thready fusion of sternebra	L	0	0	2 (11.8%)	0
	F	0	0	2	0
Absent rib	L	0	1 (5.9%)	1 (5.9%)	0
	F	0	1	1	0
Branched rib	L	0	1 (5.9%)	0	0
	F	0	1	0	0

Table 84: Rabbit EFD study: individual fetus skeletal malformation results (report # (b) (4) 102-294)

Dose level (mg/kg)	Doe #	# of fetuses affected	Findings
0	10002	3	Misshapen premaxilla
0.008 mg/kg	10022	1	Fused sternebra
	10030	1	Absent rib, branched rib, misaligned thoracic centrum, thoracic hemivertebra
0.08 mg/kg	10042	2	Misshapen premaxilla
	10055	1	Absent rib, absent thoracic arch, hemicentric thoracic centrum
	10057	1 ^a	Fused sternebra
		1 ^a	Thready fusion of sternebra
	10047	1	Thready fusion of sternebra
0.8 mg/kg	10062	1	Fused rib
	10067	1	Fused rib, misaligned cervical vertebra, misshapen cervical vertebra, fused thoracic arch
	10068	1	Fused rib
	10080	1	Misaligned cervical vertebrae

^a Not clear from the reporting whether these effects were in the same fetus, or different fetuses in the same litter.

- o The skeletal finding of "misshapen premaxilla" correlates with the external findings of cleft lip. These anomalies do not appear treatment-related, based on detection in 1 control litter and 1 low-dose litter.
- o The authors considered "fused sternebra" to be a malformation. The authors considered "fusion of sternebra" and "thready fusion of sternebra" to be variations.
- In response to an Information Request (IR) from P/T, the Applicant provided historical control data to the NDA on April 15, 2021 (SD # 12). Fetal skeletal data were provided for the study laboratory, (b) (4) for 49 studies (2011 to 2015), for 564 litters (4139 fetuses).
 - o For each observation, the total # of fetuses with the finding were reported, as well as "mean ± SD". It is not clear what the "mean" is referred to (by back-calculation, they are not the mean # of litters with the observation, or the number of studies with the observation). An IR has been drafted to request clarification.

Table 85: Rabbit EFD – selected laboratory fetal skeletal historical control data (2011-2015, for 564 litters)

Fetal skeletal anomaly	Laboratory historical control data		
	# of observations	% fetal incidence ^a	Mean ± SD
Misshapen premaxilla	6	0.145%	0.07 ± 0.33
Fused sternebra	9	0.217%	0.20 ± 0.11
Thready fusion of sternebra	28	0.676%	0.75 ± 1.10
Absent rib	5	0.121%	0.07 ± 0.23
Branched rib	1	0.024%	0.01 ± 0.08
Misaligned thoracic centrum	1	0.024%	0.01 ± 0.08
Thoracic hemivertebra	0	0	0
“Hemicentric thoracic centrum” ^b	4	0.0966%	0.05 ± 0.18
Fused rib	13	0.314%	0.34 ± 0.85
Misaligned cervical vertebra	0	0	0
“Misaligned cervical centrum” ^b	1	0.024%	0.01 ± 0.08
Misshapen cervical vertebra	0	0	0
“Misshapen cervical arch” ^{b c}	1	0.024%	0.02 ± 0.11
Fused thoracic arch ^c	2	0.0483%	0.06 ± 0.36

^a % fetal incidence = 100 * total number of historical control fetuses with the observations / total number (4139) of fetuses examined

^b Closest term in the historical control data to the reported fetal anomaly.

^c These means do not appear to match the others, based on fetal incidence; basis of calculation unclear

- Review note: after receiving this 2011-2015 historical control data from the Applicant, this reviewer noted that the Applicant had provided in the original NDA submission laboratory historical control data for rabbit fetal skeletal findings, 2009 to 2013 (429 litters, 3242 fetuses) under module 4 Literature References⁶¹.
 - o The data overlap (i.e. 2011 to 2013) for the data tabulated above; some of the data are slightly different numerically, but none would change the interpretation for any observation. The 2011-2015 data are more relevant to this study.

⁶¹ [\\CDSESUB1\evsprod\nda215092\0001\m4\43-lit-ref\control-background-data-2013-rabbits.pdf](#)

Fetal skeletal variations**Table 86: Rabbit EFD study – fetal skeletal variations (report # (b) (4) 102-294)**

Parameter	Litter / fetal incidence	0	0.008 mg/kg	0.08 mg/kg	0.8 mg/kg
# of dams	L	19	17	17	17
# of fetuses	F	142	123	138	87
Supernumerary lumbar vertebra	L	6 (31.6%)	6 (35.3%)	4 (23.5%)	8 (47.1%)
	F	11	12	6	21
Full supernumerary rib	L	19 (100%)	17 (100%)	15 (88.2%)	15 (88.2%)
	F	71	78	64	65
Short supernumerary rib	L	16 (84.2%)	15 (88.2%)	14 (82.4%)	8 (47.1%)
	F	45	38	35	18
Knobby rib	L	0	0	0	1 (5.9%)
	F	0	0	0	1
Litter mean – number of ossified sternbrae	L	5.69 ± 0.28	5.72 ± 0.24	5.68 ± 0.27	5.68 ± 0.29
Litter mean – number of ossified sacral and caudal vertebrae	L	19.24 ± 0.43	19.41 ± 0.47	19.42 ± 0.43	19.32 ± 0.35

- o Generally, this reviewer would consider supernumerary lumbar vertebra to be a malformation. However, the relatively high incidence in the concurrent control group supports considering the effect, in this case, to be a variation. A treatment effect is not clearly apparent.
- o Because the fetal incidence of full and short supernumerary rib are so high, these should be considered the baseline for these rabbits. A treatment effect for short

supernumerary rib is clearly apparent for the high-dose group. Therefore, the apparent decrease in supernumerary ribs (full and short combined) for the high-dose group is the equivalent of missing ribs.

Table 87: Rabbit EFD – selected fetal skeletal historical control data

Fetal skeletal variation	Laboratory historical control data		
	# of observations	% fetal incidence ^a	Mean ± SD
Supernumerary lumbar vertebra	336	8.12%	7.30 ± 6.98
Full supernumerary rib	2052	49.58%	50.25 ± 12.17
Short supernumerary rib	1185	28.63%	28.73 ± 6.67
Knobby rib	8	0.193%	0.25 ± 0.74

Dosing Solution Analysis

- Results are acceptable
- Concentration was verified on the first day of dosing and during the final week of dosing; concentrations were 99.6 to 102.1% of nominal.

9.3 Prenatal and Postnatal Development

Study title: A study for effects of DE-117 on pre- and postnatal development, including maternal function by subcutaneous administration in rats

Study no.: (b) (4) 102-349

Study report location: NDA module 4.2.3.5.3 Prenatal and postnatal development

Study report:

[\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42353-pre-postnatal-dev \(b\) \(4\) 102-349 \(b\) \(4\) 102349-pre-clinical-study-report.pdf](\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42353-pre-postnatal-dev (b) (4) 102-349 (b) (4) 102349-pre-clinical-study-report.pdf)

Historical control data:

[\\CDSESUB1\evsprod\nda215092\0012\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42353-pre-postnatal-dev \(b\) \(4\) 102-349 \(b\) \(4\) 102349-background-rat-ppnd-2010-2019.pdf](\\CDSESUB1\evsprod\nda215092\0012\m4\42-stud-rep\423-tox\4235-repro-dev-tox\42353-pre-postnatal-dev (b) (4) 102-349 (b) (4) 102349-background-rat-ppnd-2010-2019.pdf)

Conducting laboratory and location:

(b) (4)

Report date: February 19, 2019

Date of study initiation: July 2, 2018

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: DE-117 (UR-7385, omidenepag isopropyl), lot # RGC1403010, purity 100.0%

Key Study Findings

- No treatment-related toxicity was observed. The NOAEL for pre- and postnatal development was the high-dose, 1 mg/kg/day. The NOAEL for maternal toxicity was also the high-dose, 1 mg/kg/day.
 - o High-dose females exhibited sporadic loose stool for a few days at the start of dosing. This effect is not considered adverse.
 - o For F1 pups, the percentage with fully open eyelids on PND 14 showed a dose-response, for both males and females. All F1 pups had fully open eyelids on PND16. In the absence of other apparent treatment-related differences, this effect is not considered adverse.
- Based on omidenepag isopropyl's mechanism of action (EP2 receptor activation), theoretical effects on parturition and delivery were potential concerns. The empirical results did not identify any basis for concern.

Methods

Doses: 0, 0.01, 0.1, or 1 mg/kg/day
Frequency of dosing: Daily from GD6 to postnatal day (PND) 20
Dose volume: 10 ml/kg (based on most recent body weight)
Route of administration: Subcutaneous injection
Formulation/Vehicle: (b) (4) in physiological saline
Species/Strain: Sprague Dawley rat
Number/Sex/Group: 20 mated females/dose group (F0)
Study design:

- o Dams were allowed to delivery naturally.
- o Litters (F1) were culled on PND 4 (keeping 4/sex/litter; keeping 8/litter if there were fewer than 4 of each sex, and not culling if litter size was < 8)
- o On PND 21, 2/sex from each litter (F1) were kept after weaning for growth endpoints. 1/sex from each litter were used for the reproductive performance test.
- o Pregnant F1 females underwent C-section on GD15.

Deviation from study protocol: The authors report no protocol deviations.

F₀ Dams Observations and Results

- Three dams were not pregnant: 1 in the low-dose group (# 10028), and 2 in the high-dose group (# 10065 and # 10069). These animals were excluded from analysis.

Survival

- All dams survived to scheduled necropsy.
- Dams were checked once daily on non-dosing days, and twice daily on dosing days (pre-dose and 1-2 hours post-dose), for mortality and clinical signs.

Clinical signs

- The only clinical sign reported was for the high-dose group: 11/18 exhibited soft stool over GD7-15 (only once for 7, twice for 3, and five days for one, # 10068).
- Notably, no clinical signs were reported for any dam during the lactation period.

Body weight

- No apparent differences for body weight or body weight gain.
- Dams were weighed on GD0, 6, 9, 12, 15, 18 and 20, and on PND 0, 4, 7, 10, 14, 17 and 21.

Food consumption

- No apparent differences for food consumption.
- Dams were single-housed (except for pre-dose mating; dams and litters were housed together). Food consumption was measured twice weekly from GD0 through PND 20.

Parturition

- No treatment-related effects. Results tabulated below (as part of the F1 outcome table).
- Dams were allowed to delivery naturally. The date and time of confirmation of delivery was recorded. Dams were allowed to nurse their own litters through PND 21.

Necropsy

- Dams were sacrificed on PND 21. Full gross necropsy was conducted. All dams were reported normal (no findings).
- The number of implants were determined (tabulated above).

Toxicokinetics

- o No samples were collected for TK.

Dosing Solution Analysis

- Results are acceptable
- Concentration was verified on the first day of dosing and during the final week of dosing; concentrations were 98.1 to 106.5% of nominal.

F₁ Generation Observations and Results**Design**

- On PND 4, pups were weighed, and then litters were culled randomly, with the goal of selecting 4 males and 4 females litter. When fewer than 4 of either sex was available, additional pups of the other sex were kept, with the goal of reaching a litter size of 8. When the total number of pups/litter was 8 or fewer, no pups were culled.
- No necropsy of culled pups was performed (report page 21).
- Tests for physical and functional development were conducted after culling, and before weaning.
- On PND 21, 2/sex/litter were selected for weaning. Pups sacrificed on PND 21 underwent gross necropsy.
- Post-weaning rats were evaluated for external genitalia morphology
- Behavior, and learning were conducted for 1/sex/litter. The other 1/sex/litter was used for the reproductive performance test.
- At 11-12 weeks after birth, 1/sex/litter were selected for reproductive performance testing. Pregnant F1 females were sacrificed at GD15. The surviving F1 animals underwent gross necropsy after reproductive performance evaluation was complete.

Survival

- No treatment-related effects apparent for F0 reproduction parameters, or F1 survival.

- o Summary table on report page 58, individual animal data on report pages 121-124.
- o For the high-dose, numerical decreases in the numbers of implantations/litter, pups born live/litter, and pups live at weaning/litter are apparent, but are not clearly treatment-related.

Figure 16: Rat PPND study: F0 pregnancy outcome data and F1 survival data (report # (b) (4) 102-349)

Parameter	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of pregnant animals	20	19	20	18
Gestation period (days)	22.00 ± 0.36	22.05 ± 0.37	21.95 ± 0.32	22.00 ± 0.24
# of pregnant animals that delivered	20	19	20	18
Delivery index (%)	100	100	100	100
# of implantations	14.9 ± 2.2	14.9 ± 2.2	14.8 ± 1.3	14.0 ± 3.0
At Birth				
# born	13.8 ± 2.0	13.9 ± 2.6	13.6 ± 1.4	12.9 ± 2.9
# live	13.5 ± 2.0	13.7 ± 2.6	13.5 ± 1.4	12.7 ± 2.9
Live birth index (%)	90.96 ± 7.65	91.57 ± 10.80	91.63 ± 7.45	90.57 ± 9.21
Viability index (%)	97.79 ± 3.49	98.11 ± 3.30	99.65 ± 1.59	98.43 ± 3.90
Sex ratio (male/total)	0.47 ± 0.15	0.55 ± 0.13	0.53 ± 0.11	0.56 ± 0.11
External malformations	0	0	0	0
At PND 4				
# live	13.1 ± 2.1	13.5 ± 2.5	13.1 ± 1.6	12.3 ± 3.0
Viability index (%)	97.02 ± 4.43	98.60 ± 3.43	96.73 ± 6.53	97.34 ± 5.51
Sex ratio (male/total)	0.48 ± 0.14	0.55 ± 0.13	0.55 ± 0.14	0.56 ± 0.12
Number of pups after D4 culling	8.0 ± 0.0	7.9 ± 0.5	8.0 ± 0.0	7.8 ± 0.9

At weaning				
# live	7.9 ± 0.3	7.8 ± 0.6	8.0 ± 0.0	7.7 ± 1.0
Weaning index (%)	98.75 ± 3.85	98.68 ± 5.74	100.00 ± 0.00	99.31 ± 2.95
Sex ratio (male/total)	0.50 ± 0.06	0.52 ± 0.09	0.52 ± 0.04	0.51 ± 0.07

Data presented as mean ± SD

Live birth index% = 100 * number born live / number of implants

Viability index % at birth = live birth index / number born

Viability index % at PND 4 = number of pups live at PND 4 / number of pups born live

Table 88: Rat PPND study: additional F0 pregnancy outcome data and F1 survival data (report # (b) (4) 102-349)

Parameter	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of litters	20	19	20	18
# of implants	298	283	295	252
# of pups born	276	265	271	232
# of pups born live	270	260	270	228
# of pups born not live	6	5	1	4
# of litters with deaths PND0-4	7	3	5	4
# of pup deaths PND0-4	8	4	9	6
# of pups live after PND 4 cull	160	150	160	140
# of pups live at weaning	158	148	160	139
# of litters with deaths post-culling (PND4) to weaning (PND21)	2	1	0	1
Pup deaths post-culling (PND4) to weaning (PND21)	2	2	0	1

Evaluations at birth

- No external malformations were noted for any pup.
- It is not clear how the laboratory identified pups born dead, versus pups that died after birth. No mention of checking decedent pups for inflated lungs or belly milk.

- No cause(s) of pup death reported.

Clinical signs

- No clinical signs were noted for any F1 pup.
- F1 animals were observed for clinical signs and mortality once daily, as part of the dam observations.

Body weight

- No treatment-related effects on body weight are apparent.
- F1 pups were weighted on PND 0, 4 (pre-cull), 7, 10, 14, 17, and 21. After weaning, remaining pups were weighed on PND 28 and then weekly until PND 70. Pregnant F1 females were weighed on GD0, 7, and 15.

Physical and Functional Development During the Lactation Period

- After the PND 4 culling, pups were evaluated for:
 - o Pinna detachment (PND 4, daily until completion on PND 5)
 - o Incisor eruption (PND 11 and 13) [when both pairs of incisors have erupted from the upper and lower jaws]
 - o Eyelid opening (PND 14 and 16) [when both eyelids open completely]
 - o Functional development on PND 20:
 - pupillary reflex (dark acclimation of at least 30 seconds, followed by light exposure to cause constriction of the pupil)
 - Preyer reflex (pinna reflex in response to a Galton's whistle, 5 to 15 kHz)
 - Pain response (reaction to softly pinching the tail)
 - Air righting reflex (normal response is landing limbs down when dropped dorsal side down from a height of 30 cm).

Physical development results

- Results were reported on a per litter basis, as the percent of the litter achieving the milestone.
- For eyelid opening on PND 14, there is trend for increased incidence with increasing dose (summary table on report page 61, individual data on pages 145-152)

Table 89: Rat PPND study: physical development of F1 pups (report # (b) (4) 102-349)

	Day	0	0.01 mg/kg	0.1 mg/kg	1 mg/kg
# of litters	L	20	19	20	18
MALES					
Pinna detachment %	4	98.8 ± 5.6	100	100	100
	5	100	100	100	100
Incisor eruption %	11	83.5 ± 29.0	69.2 ± 35.3	85.5 ± 25.2	80.0 ± 26.9
	13	100	100	100	100
Eyelid opening %	14	59.5 ± 40.3	68.9 ± 32.9	80. ± 32.6	84.7 ± 25.9
	16	100	100	100	100
FEMALES					
Pinna detachment %	4	100	100	100	100
Incisor eruption %	11	83.8 ± 21.1	73.3 ± 29.5	91.3 ± 16.8	90.8 ± 13.6
	13	100	100	100	100
Eyelid opening %	14	60.4 ± 38.9	66.7 ± 33.3	82.5 ± 32.5	80.6 ± 26.5
	16	100	100	100	100

- For males on PND14, 0% (i.e. no eyelids fully open) was observed for 4 control litters (10003, 10006, 10014, 10017), 2 low-dose litters (10032, 10033), 1 mid-dose litter (10046), and 0 high-dose litters.
- For females on PND14, 0% (no eyelids open) was observed for 4 control litters (10003, 10006, 10011, 10017 – i.e. partial overlap with males), 2 low-dose litters (10031 and 10032 – partial overlap), 1 mid-dose litter 10046 – the same litter as for the males), and 0 high-dose litters.
- Historical control data were provided for the study laboratory, (b) (4) (2010 to 2019), for 24 rat PPND studies (440 litters). For eyelids open, the % means are:
 - o PND 14: 61.2 ± 14.0
 - o PND 16: 99.4 ± 1.6
 - o PND 17: 100.0 ± 0.0
- The concurrent control data are consistent with the historical control data, and support the conclusion of a treatment-effect for earlier eyelid opening.

Functional development results

- No treatment-related effects apparent.
- All animals exhibited the functional endpoint (i.e. 100% for all rats at PND 20).

F1 necropsy at weaning

- Pups sacrificed at weaning underwent gross necropsy. No observations were reported for any animal.

Examination for Morphological Differentiation of External Genitalia

- No treatment-related effects apparent.
- The post-weaning 2 males/litter were examined for cleavage of the balano-preputal gland from PND 45 daily until completion (PND 63)
- The post-weaning 2 females/litter females were examined for vaginal opening on PND 35 and 40.

Behavioral assessment

- No treatment-related effects apparent.
- An open field test was performed for 1/sex/litter, 4-5 weeks after birth. The rat was placed in a 60 cm diameter circle, marked with 25 compartments, for 3 minutes. The rat was scored for ambulation (each time all limbs from one compartment into another), rearing, grooming and preening, and defecation.

Learning assessment (Biel type water maze test)

- 1/sex/litter, at 6 to 7 weeks after birth, daily for 4 days
- *“On the first day of the test, each animal was made to swim in a straight channel (3 trials). The number of backing errors and the time from the start to the goal were measured. Each trial was conducted for a maximum of 2 minutes. From the second to the fourth day, each animal was made to swim in the multiple water maze (3 trials per day). The numbers of selection and backing errors, and the time from the start to the goal were measured. Each trial was conducted for a maximum of 3 minutes. Data on swimming time and the number of errors from the animals that failed to reach the goal were excluded from the data analysis.”*

Reproduction

- No treatment-related effects apparent.
- 1 male and 1 female from each litter were mated (paired at the same dose level, not siblings). The copulatory interval, copulation rate, and fertility rate were calculated.
- Pregnant F1 females were sacrificed on GD15 for C-section to determine numbers of corpora lutea, implantations, live embryos, and postimplantation losses (classified as implantation site, placental remnant, or dead fetus).

Necropsy post-weaning

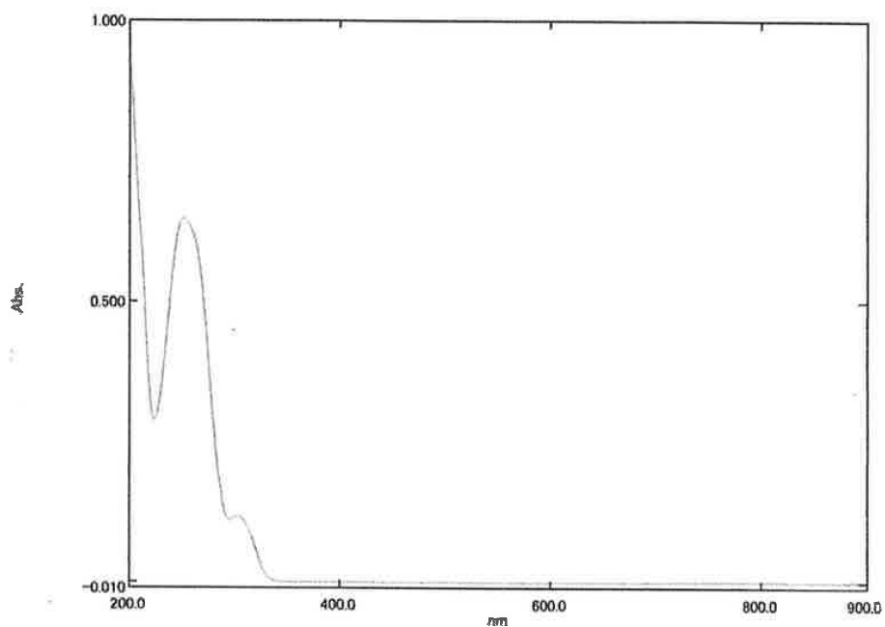
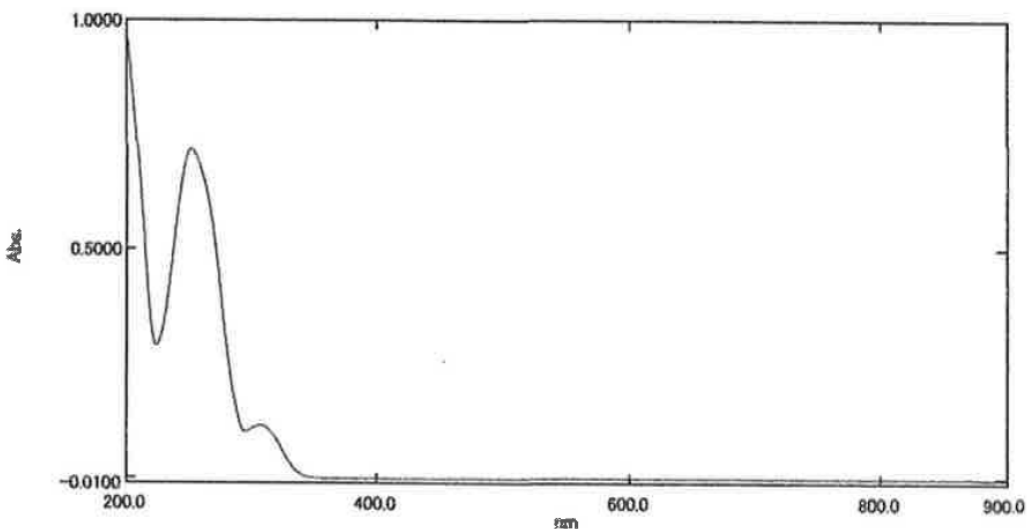
- No gross findings were reported for any animal (i.e. the pregnant F1 females, or the other F1 animals).

F₂ Generation Observations and Results

- Survival: No treatment-related effects apparent through the GD15 C-section.
- Body weight: Not determined
- External evaluation: Not performed
- Male/Female ratio: Not sexed
- Review note: The F2 data provided are adequate to show safety in this case.
- The ICH S5(R3) guidance does not explicitly recommend assessment of F1 parturition, or F2 fetal evaluation for sex, weight, structural anomalies, or survival at/after birth.
 - Notably, the laboratory historical control database includes data for F2 sex ratio, viability at birth, PND 4 and PND 7 (but not weight or external anomaly evaluation).

10 Special Toxicology Studies

Report title	Wakabayashi, Y. (2018). Certificate of Analysis: UR-7385 and UR7276.	
Key finding	• The Applicant provided a certificate of analysis for omidenepag isopropyl (UR-7385) and omidenepag (UR-72752) for UV absorption. • Data raise concern for phototoxicity. This is consistent with the Applicant’s reporting that photophobia is a common adverse event (5.3%) associated with omidenepag isopropyl 0.002%.	
File location	NDA module 4.3 Nonclinical References (\\CDSESUB1\evsprod\nda215092\0001\m4\43-lit-ref\wakabayashi-2018.pdf)	
Summary:		
Table 90: UV spectral results for omidenepag isopropyl and omidenepag		
Test article	$\Lambda_{\max}$ (290-700 nm)	$\epsilon_{\max}$
omidenepag isopropyl (UR-7385)	303.4 nm	4910 L/mol*cm (at 303.4 nm)
omidenepag (UR-72752)	306.2 nm	4430 L/mol*cm (at 306.2 nm)

Figure 17: UV absorbance spectrum for omidenepag isopropyl**Figure 18: UV absorption spectrum for omidenepag**

- Both compounds absorb wavelengths in the range of natural sunlight (290-700 nm) and have molar extinction coefficients (MECs) greater than 100 L/mol*cm. As discussed in the 2015 Guidance for Industry ICH S10 Photosafety

Evaluation of Pharmaceuticals⁶², these properties raise safety questions for potential direct phototoxicity. • Ideally, experimental data to evaluate binding to lens protein would be available. In the absence of other data, binding activity can be inferred from the <i>in vitro</i> plasma protein binding study (report # 5431Lg02A), which observed binding of 97.1 to 97.2% for human plasma protein. • Per ICH M3(R2) section 14 <i>Photosafety Testing</i>, direct clinical testing of the drug product in the eye clinically can provide an adequate assessment. - o With deference to the Clinical Review team regarding review of clinical data, the Applicant's NDA module 2.7.4 Summary of Clinical Safety⁶³ reports : ▪ The most common AE for omidenepag isopropyl 0.002% was conjunctival hyperemia (8.5%), followed by photophobia (5.3%) ▪ Phase 2 clinical trial 33-002, 28 days, "Increased incidences of ocular side effects of hyperemia, photophobia, and itching were observed at concentrations of 0.002% and 0.003%" omidenepag isopropyl ▪ Phase 3 clinical trial 011751505 (PEONY), 3 months, 0.002% omidenepag isopropyl, "Conjunctival hyperemia, dry eye, and photophobia identified as frequent AEs" ▪ Phase 3 clinical trial 011709IN (Spectrum 3), 9 months, 0.002% omidenepag isopropyl, "Conjunctival hyperemia, vision blurred, and photophobia identified as frequent AEs"	• The Applicant addressed photosafety in the Toxicology Written Summary (NDA module 2.6.6, section 8.1)⁶⁴: - o Acknowledged "<i>Both compounds had MEC values greater than the threshold MEC of 1000 L/mol ·cm which requires photosafety evaluation.</i>" - o Despite this point, the Applicant concluded omidenepag isopropyl ophthalmic solution was "<i>very unlikely to cause phototoxicity during clinical use in humans, and it was considered unnecessary to take particular light-protective measures.</i>"
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⁶² Accessed via: <https://www.fda.gov/media/85076/download>

⁶³ Accessed via: <\\CDSESUB1\evsprod\nda215092\0001\m2\27-clin-sum\summary-clin-safety.pdf>

⁶⁴ Accessed via: <\\CDSESUB1\evsprod\nda215092\0001\m2\26-nonclin-sum\toxicology-written-summary.pdf>

Title	A research study of DE-117 on eyelash growth in mice	
Report #	104Fm090	
Key findings	(b) (4) • Omidenepag isopropyl 0.003% applied to the upper eyelid of mice for 2 weeks did not affect eyelash or thickness. • The positive control, 0.03% bimatoprost ophthalmic solution, increased mouse eyelash growth. Bimatoprost is reportedly a prostaglandin F2α receptor antagonist.	
Report details	NDA location	NDA module 4.2.3.7 Other Toxicity Studies (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42373-mechan-stud\104fm090\104fm090-pre-clinical-study-report.pdf)
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center, 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101 Japan
	Report date	July 26, 2019
	GLP status	No
	Test articles	• Omidenepag isopropyl (DE-117) ophthalmic solution 0.003%, lot # LEPA161226-01 • Lumigan ophthalmic solution 0.03% (bimatoprost)
Methods	Species	Female C57BL/6JmsSlc mice, 4 weeks old at dosing • This strain is pigmented
	Doses	• 10 female mice/group • Saline, bimatoprost 0.03%, or omidenepag isopropyl 0.003% • One 3 μl drop applied to the right upper eyelid, once daily for 14 days
	Eyelid evaluation	• On D15, mice were sacrificed. • "From the temporal corner to the nasal corner of the eyelid, the number of eyelashes was counted in each animal using a stereoscopic microscope." • For each mouse, 3 eyelashes of short length (approximately 250 μm), medium length (approximately 450 μm), and long length (approximately 2500 μm) were identified; and their width measured (measuring device not specified). • Histopathology: eyelids were formalin fixed and embedded. Fifty consecutive 3 μm sections from the middle part of the upper eyelid were evaluated

		to identify the eyelash hair cycle (telogen, anagen, or catagen). Hairs in anagen were measured to papillae and hair bulb thickness. Review note: anagen is the hair growth phase; catagen is the regression phase; telogen is the resting phase; and exogen is the release/detachment phase.		
Results:				
Table 91: Omidenepag isopropyl 0.003% QDx14 did not affect mouse eyelash growth				
Parameters	Categories	Saline	Bimatoprost 0.03%	Omidenepag isopropyl 0.003%
# of rats		10	9	10
# of eyelashes		144.2 ± 5.7	166.7 ± 7.0 *	143.5 ± 6.2
Thickness of eyelashes (µm)	Short (-250 µm)	7.03 ± 0.31	9.51 ± 0.47 *	7.17 ± 0.44
	Medium (-450 µm)	11.89 ± 0.91	14.79 ± 0.59 *	12.16 ± 0.79
	Long (- 2500 µm)	22.79 ± 0.91	22.58 ± 0.85	22.98 ± 0.51
Histology: number of eyelashes in each hair cycle	Telogen	22	7	15
	Anagen	44 (51.7%)	54 * (77.0%)	49 (54.4%)
	Catagen	19	13	26
	Total	85	74	90
Histology: thickness (µm) of the anagen eyelash papilla and hair bulb	Dermal papilla	26.8 ± 9.2	31.5 ± 6.7	24.6 ± 6.4
	Hair bulb	68.8 ± 10.0	74.8 ± 10.9	67.8 ± 13.6
* Statistically different from saline, by t-test (number and thickness) and z-test (for fraction in each stage of the hair growth cycle), p < 0.01				
Safety endpoints	- Clinical signs (cage side observations) were evaluated once daily. No abnormalities were noted for any animal. - Mice were weighed once pre-dose (D-5) and on D14 (prior to sacrifice on D15). No treatment-effect on body weight was apparent.			

Title	Effects of omidenepag and prostaglandin F2α on adipogenesis in 3T3-L1 cells	
Report #	603Qn020	
Key findings	(b) (4) (b) (4) The relevance of the assay to fat tissue <i>in vivo</i>, and to clinical DUES, is not established by the information submitted to the NDA.	
	- The authors hypothesize that FP receptor agonist-induced DUES is caused by inhibition of adipogenesis, leading to atrophy of orbital fat in the eyelid. - The authors report that mouse embryonic fibroblast cells can be induced to differentiate into adipocytes. Omidenepag (0.1 to 40 μM) did not inhibit this differentiation. - The relevance to patients is unclear.	
Report details	NDA location	NDA module 4.2.3.7 Other Toxicity Studies (\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-rep\423-tox\4237-other-tox-stud\42373-mechan-stud\603qn020\603qn020-pre-clinical-study-report.pdf)
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center, Address 8916-16 Takayama-cho, Ikoma-shi, Nara, Japan
	Report date	June 26, 2019
	GLP status	No
	Test articles	- Omidenepag (UR-7276), lot # ST-1 - Latanoprost free acid - Prostaglandin F2α
Model	3T3-L1 mouse embryonic fibroblast cells were obtained commercially. - The authors report that these cells can be induced to differentiate into adipocytes. Induction used a D0 induction medium (including insulin, dexamethasone, and 3-isobutyl-1-emethylxanthine) for 2 days, followed by D1 induction medium (including heat-inactivated 10% calf serum, and insulin) for 8 days. - Verification of adipocyte differentiation was verified by microscopy with Oil Red-O staining, and by PCR for three markers: <i>ppary</i>, <i>c/ebpa</i>, and <i>c/ebpβ</i>. - Cell viability was measured (assay not reported).	
Dose groups	- Undifferentiated cells (untreated with test article or induction media) - Normal (untreated) - Vehicle (0.1% DMSO) control	

	• 0.1, 1, 10, or 40 μM omidenepag • 100 nM latanoprost free acid • 100 nM prostaglandin F2α	
Dosing	Cells were incubated with test article, with or without the induction media, for 10 days.	
Results	Cell viability	• Induction media caused a 2-fold increase in cell growth, versus undifferentiated cells • Omidenepag had no effect on cell growth • Cell viability was increased, compared to vehicle control, by latanoprost free acid (+17.9%) and PGF2α (+8.4%)
	Oil Red O staining	• Induction media caused a 6.6-fold increase in oil Red O staining. • Omidenepag had no effect • Latanoprost free acid and PGF2α completely inhibited the increase in staining
	Gene marker expression	• PCR was performed at D0, 2, 4, and 10. • Omidenepag had no effect • The biological significance is unclear for the effects between undifferentiated and differentiated cells, and the effects caused by latanoprost free acid or PGF2α versus vehicle-treated cells.

Title	A research study of the anterior chamber flare measurement after repeated instillation of DE-117 ophthalmic solution alone or in combination with tafluprost ophthalmic solution, latanoprost ophthalmic solution, travoprost ophthalmic solution, and bimatoprost ophthalmic solution for 1 week in cynomolgus monkeys	
Report #	104Fq080	
Key findings	• The rationale for this study was the clinical observation (in clinical study # 33-001) that the combination of omidenepag isopropyl (0.003 to 0.03%) in combination with tafluoprost ophthalmic solution 0.0015% caused greater ocular inflammation than the omidenepag isopropyl monotherapy group. • Four FP receptor agonists were tested in combination with omidenepag isopropyl; all four combinations increased anterior chamber flare compared to omidenepag isopropyl monotherapy. Recovery was apparent after cessation of dosing. • The authors noted that the mechanism of this combination is unknown.	
Report details	NDA location	NDA module 4.2.3.7 Other Toxicity Studies (\\CDSESUB1\evsprod\nda215092\0001\m4\42-stud-

		rep\423-tox\4237-other-tox-stud\42377-other\104fq080\104fq080-pre-clinical-study-report.pdf
	Study laboratory	Santen Pharmaceutical Co., Ltd. Nara Research and Development Center 8916-16, Takayama-cho, Ikoma-shi, Nara 630-0101 Japan
	Report date	July 16, 2019
	GLP status	No
	Test articles	• Omidenepag isopropyl ophthalmic solution 0.002% (DE-117), lot # ET0005 • Tapros (tafuprost ophthalmic solution 0.0015%) • Xalatan (latanoprost ophthalmic solution 0.005%) • Travatan Z (travoprost ophthalmic solution 0.004%) - Lumigan (bimatoprost ophthalmic solution 0.03%)
Methods	Species	10 female cynomolgus monkeys, age 3-4 years • Returned to colony at end of study
	Dosing	• 5 one week-treatment cycles (of all 10 monkeys), with a 7-18 day washout period between cycles • For each treatment cycle: - o omidenepag isopropyl ophthalmic solution 0.002% was instilled once daily (OU QDx7), one drop per dose. - o 5 minutes after the omidenepag isopropyl dose, the left eye (OS) only was dosed with one drop of an approved product (OS QDx7): tafuprost in cycle 1, latanoprost in cycle week 2, travoprost in cycle 3, bimatoprost in cycle 4, and tafuprost again for cycle 5.
	Endpoints	• Daily clinical signs • Body weight was only measured at the start and end of the experiments • Limited ophthalmic examinations: prior to the start of each cycle; on D1, 4, and 7 of each cycle (pre-dose and 6 hours post-dose on dosing days); and recovery after each cycle (D8 and 11/12). Slit lamp biomicroscopy without fluorescein staining (scored using the McDonald-Shadduck method), anterior chamber flare scoring, recorded: anterior segment irritation signs, anterior chamber flare using a laser flare meter and slit lamp, corneal thickness by ultrasound pachymetry.

Results

- No clinical signs abnormalities noted.
- No apparent effects on body weight; no ocular irritation (other than anterior chamber flare) reported; no effects on corneal thickness apparent.
- Aqueous flare by slit lamp was mostly scored as 0, with sporadic scores of 1 (very slight).
- For aqueous flare by laser flare meter, results were reported as photon counts per millisecond.
- For omidenepag isopropyl ophthalmic solution 0.002% monotherapy (OD): the D1 score was not increased compared to the pre-dose measurement; D4 and D7 results were higher than D1 (but not different from each other). Partial recovery was apparent at D8, and full recovery was apparent by D11/12.
- For the combination treatments, aqueous flare was higher (statistically significant) for D4 and 7 post-dose.

Table 92: Monkey topical ocular combination study: aqueous flare results (report# 104fq080)

OS treatments	Day 4 (6 hours post-dose)		Day 7 (6 hours post-dose)	
	OD (monotherapy)	OS (combination)	OD (monotherapy)	OS (combination)
Tafluprost	42.0 ± 24.2	45.0 ± 19.4	28.9 ± 15.4	45.1 ± 20.6
Latanoprost	35.1 ± 21.4	48.2 ± 24.3	22.5 ± 6.2	33.4 ± 11.3 *
Travoprost	29.6 ± 10.8	59.0 ± 31.2 *	25.7 ± 10.3	45.0 ± 16.1 **
Bimatoprost	36.5 ± 16.2	54.8 ± 24.0	29.3 ± 12.9	48.5 ± 21.2 *
Tafluprost	39.3 ± 24.6	61.2 ± 30.1	25.6 ± 9.1	42.3 ± 22.7

Values reported as means ± SD

Statistically different OS versus OD [analytical method not reported], * p < 0.05, ** p < 0.01

11 Integrated Summary and Safety Evaluation

11.1 Omidenepag clinical exposure

- Omidenepag isopropyl ophthalmic solution 0.002% contains 0.02 µg/µl of omidenepag isopropyl.
- The Applicant proposes labeling for “one drop in the affected eye(s) once daily”
- The drop size study is summarized in the NDA section 3.2.P.2 Pharmaceutical Development.⁶⁵ (b) (4)
- The daily dose is (b) (4) µg/eye/day.
- Assuming both eyes are dosed, (b) (4) µg/person/day.
 - The 2005 CDER Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers⁶⁶ provides guidance for interspecies scaling based on body surface area (BSA). Assuming 100% absorption following topical ocular dosing, using a reference human body weight of 60 kg, and a reference BSA conversion factor (CF) of 37x for adult humans, (b) (4)
- Omidenepag isopropyl is a prodrug. The nonclinical PK/TK assays and the clinical PK assay measured omidenepag, the active metabolite.
- The Applicant’s proposed labeling reports: “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 C_{max} (b) (4) (b) (4) Systemic exposure was similar between days 1 and 7, indicating no systemic accumulation.”
 - The NDA’s Summary of Clinical Pharmacology Studies (module 2.7.2)⁶⁷ summarizes one clinical pharmacology study, phase 1 study # 01171502.
 - With deference to the Clinical Pharmacology review team, (b) (4) (b) (4)
 - The Applicant did not propose to describe AUC in labeling. The highest median AUC_{0-8h} was 27.0 pg*h/ml. The highest maximum AUC value reported was 35.6 pg*h/ml.
 - The longest median T_{1/2} was 0.5189 hour. The maximum T_{1/2} reported was 0.6773 hours.
- This reviewer did not identify clinical PK results for the to-be-marketed 0.002% drug product. The 0.0025% test article has 25% more omidenepag isopropyl. Given the

⁶⁵ Accessed via: [\\CDSESUB1\evsprod\nda215092\0001\m3\32-body-data\32p-drug-prod\de117 \(b\) \(4\) \32p2-pharm-dev\pharmaceutical-development-dp.pdf](\\CDSESUB1\evsprod\nda215092\0001\m3\32-body-data\32p-drug-prod\de117 (b) (4) \32p2-pharm-dev\pharmaceutical-development-dp.pdf)

⁶⁶ Accessed via: <https://www.fda.gov/media/72309/download>

⁶⁷ Accessed via: <\\CDSESUB1\evsprod\nda215092\0001\m2\27-clin-sum\summary-clin-pharm.pdf>

range of clinical exposures, using the highest reported median $C_{\max}$ and AUC for 0.0025% is a reasonably protective approach for calculating nonclinical exposure margins.

Table 93: Omidenepag daily dose and clinical PK estimates used to calculate nonclinical dose margins and exposure margins to support labeling

Clinical	Value used to calculate nonclinical exposure margins
Daily dose of omidenepag isopropyl	(b) (4)
Omidenepag $C_{\max}$	34 pg/ml
Omidenepag AUC	27.0 pg*h/ml

11.2 Summary of Omidenepag isopropyl GLP monkey topical ocular toxicity study results and margins for labeling

- The Applicant submitted two GLP topical ocular toxicity studies, both in monkeys. They tested different formulations, both slightly different from the final to-be-marketed formulation.
- Both studies treated the left eye (OS) only.
- The 13-week monkey topical ocular toxicity study (report # (b) (4) 102-212) tested doses of 0, 0.9, 3, 9, or 36 µg/eye/day.
 - No NOAEL. The low dose, 0.9 µg/eye/day is the LOAEL, based on two findings in the nasal cavity:
 - Respiratory nasal cavity olfactory epithelium metaplasia. Metaplasia was observed for 2/4 high-dose recovery animals (i.e. recovery not demonstrated).
 - Vestibular nasal cavity increased goblet cell respiratory epithelium mucosa. Recovery was apparent.
 - The incidence was increased bilaterally and left-side only, following left eye dosing. P/T attributes these changes to exposure resulting from nasolacrimal clearance following topical ocular dosing (i.e. unlikely to be due to systemic toxicity).
 - All dose levels:
 - decreased IOP (expected pharmacology), with recovery apparent after cessation of dosing.
 - caused miosis (observed as a clinical sign, and by pupillometry), increased corneal thickness. The Applicant considers these effects non-adverse, and related to primary pharmacology.

- affected electroretinography (ERG): dramatically increasing oscillatory wave (O-2) amplitude, and causing slight increases in O-2, O-3, and O-4 latency. The authors considered these ERG changes secondary to the treatment-related miosis.
 - For the low dose, 0.9 µg/eye/day, the lowest mean omidenepag plasma TK parameters were $C_{max} = 268$ pg/ml, $AUC_{0-4h} = 66.6$ pg*h/ml.
- The 39-week monkey topical ocular toxicity study (report # B-7689) tested doses of 0, 0.9, or 3 µg/eye/day.
 - No NOAEL. The low dose, 0.9 µg/eye/day is the LOAEL, based on increased incidence and severity of nasal cavity epithelial metaplasia. Recovery was not demonstrated.
 - The data were reported for the nasal cavity as a whole (i.e. not respiratory, vestibular, and olfactory epithelium results separately).
 - The incidence was primarily bilateral, suggesting an indirect (or systemic) response to exposure.
 - It is notable that hyperplasia and increased goblet cell activity were not observed.
 - As with the 13-week study:
 - all dose levels decreased IOP, decreased pupil size, and increased corneal thickness.
 - No slit lamp or fundoscopy effects were observed (e.g., not irritating).
 - However, no ERG changes were detected (might reflect differences in the assay design, compared to the 13-week study).
 - For the low dose, 0.9 µg/eye/day, the lowest mean omidenepag plasma TK parameters were $C_{max} = 323$ pg/ml, $AUC_{0-4h} = 111$ pg*h/ml.

Table 94: Dose margin and exposure margin calculations from the monkey topical ocular LOAEL (13- and 39-week studies)

	13-week monkey topical ocular study (report # (b) (4) 102-212)	39-week monkey topical ocular study (report # B-7689)
LOAEL (no NOAEL identified)	0.9 µg/eye/day (OS only)	0.9 µg/eye/day (OS only)
Effect observed at all dose levels	Nasal cavity epithelial metaplasia; increased goblet cell respiratory epithelium mucosa	Nasal cavity epithelial metaplasia
Dose margin (from the clinical dose (b) (4))	1.07449 x	1.07449 x
Monkey C_{max} (pg/ml)	269	323

Exposure margin (from the clinical C _{max} of 34 pg/ml)	7.912 x	9.50 x
Monkey AUC (pg*h/ml)	66.6	111
Exposure margin (from the clinical AUC of 27.0 pg*h/ml)	2.41 x	4.11 x

11.3 Summary of omidenepag isopropyl repeat-dose subcutaneous toxicity testing in rats

- The rat non-GLP sc 2-week range-finder did not identify a NOAEL; the low-dose LOAEL determination of 0.4 mg/kg/day was based on clinical signs (skin flushing, loose stool, injection site foamy cell accumulation and fibrous tissue proliferation).
- The first GLP sc rat 4-week toxicity study did not identify a NOAEL; the low-dose LOAEL determination of 0.04 mg/kg was based on clinical signs (skin flushing, loose stool), liver gross pathology (dark and large liver), liver and kidney histopathology.
 - Retinal hyperreflexia (with corresponding retinal degeneration) was observed at the high-dose, 1 mg/kg/day.
- The second GLP sc rat 4-week toxicity study did not identify a clear NOAEL, based on kidney interstitial tissue fibrosis (very slight to slight) in males at 0.01 mg/kg, and increased severity of liver peripheral fatty change in females at 0.04 mg/kg. The authors considered the mid-dose, 0.02 mg/kg/day, to be the NOAEL.
- The GLP sc rat 13-week toxicity study identified a high-dose NOAEL, 0.003 mg/kg/day. Ophthalmoscopy and ocular histopathology were inadequate.
- The GLP rat 26-week toxicity study did not identify a NOAEL, based on detection of rare tumors at the low-dose (0.003 mg/kg/day) and the high-dose (0.03 mg/kg/day). Because histopathology was only performed for control and high-dose main group animals, the results may underpredict the true tumorigenic potential of omidenepag isopropyl at 6 months. Ophthalmoscopy and ocular histopathology were inadequate.

11.4 Summary of omidenepag isopropyl developmental and reproductive toxicology (DART) results and exposure margins for labeling

Table 95: Omidenepag DART summary table

Report #	Study type	Dose level (mg/kg/day)	Effect	Mean TK values ^a
(b) (4) 102-333	Rat sc FEED	1	NOAEL for male and female fertility	No TK
(b) (4) 102-295	Rat sc EFD	1	NOAEL for developmental toxicity and maternal toxicity	C _{max} = 66.2 ng/ml; AUC _{0-8hr} = 307 ng*hr/ml

(b) (4) 102-294	Rabbit sc EFD	0.008	LOAEL for fetal skeletal malformations	$C_{\max} = 0.655 \text{ ng/ml}$; $AUC_{0-8\text{hr}} = 2.68 \text{ ng*hr/ml}$
		0.08	NOAEL for female fertility	$C_{\max} = 6.92 \text{ ng/ml}$; $AUC_{0-8\text{hr}} = 25.5 \text{ ng*hr/ml}$
		0.8	NOAEL for maternal toxicity; LOAEL for preimplantation loss and post-implantation loss	$C_{\max} = 99.8 \text{ ng/ml}$; $AUC_{0-8\text{hr}} = 315 \text{ ng*hr/ml}$
(b) (4) 102-349	Rat sc PPND	1	NOAEL for pre- and postnatal development, maternal NOAEL	No TK

The EFD studies collected TK data for GD6 and GD17 (rat) or GD18 (rabbit). This table uses the lower values (i.e. GD 17/18), as a protective approach for patient safety.

Table 96: DART dose and exposure margins considered for labeling

Species	Rat	Rabbit		
Dose (mg/kg/day)	1	0.008	0.08	0.8
Dose (mg/m ² /day) ^a	6	0.096	0.96	9.6
Dose margin (from the clinical dose of 0.00103304 mg/m ² /day)	5808 x	92.93 x	929.3 x	9293 x
$C_{\max}$ (ng/ml)	66.2	0.655	6.92	99.8
Exposure margin from the clinical $C_{\max}$ (0.034 ng/ml)	1947.0 x	19.264 x	203.53 x	2935.3 x
$AUC_{0-8\text{h}}$ (pg*h/ml)	307	2.68	25.5	315
Exposure margin from the clinical AUC (0.027 ng*h/ml)	11,370.4 x	99.259 x	944.4 x	11,666.7 x

^a For rat, reference body weight of 0.150 kg, reference BSA CF of 6x. For rabbit, reference body weight of 1.8 kg, reference BSA CF of 12x. For monkey, reference body weight of 3 kg, reference BSA CF of 12x.

- Regarding P/T recommendations for DART labeling:
 - o The table above shows that using dose margins would underpredict risk substantially.
 - o Per ICH S5(R3), it is generally appropriate to use the TK parameter that results in a lower (more protective) exposure margin.
 - o The 2020 CDER/CBER Draft Guidance Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry⁶⁸ (PLLR guidance) recommends summarizing nonclinical preimplantation loss under labeling sections for fertility (i.e. section 8.3 Females and Males of Reproductive Potential, Section 13.1 Impairment of Fertility).

11.3 Omidenepag isopropyl nonclinical published literature

- The Applicant published some of the primary PD result^{69, 70} and the other toxicology assay results^{71, 72, 73}. Two PD papers were published in 2021 (after

⁶⁸ Accessed via: <https://www.fda.gov/media/90160/download>

⁶⁹ Kiriara T, Taniguchi T, Yamamura K, Iwamura R, Yoneda K, Odani-Kawabata N, Shimazaki A, Matsugi T, Shams N, Zhang JZ. 2018. Pharmacologic Characterization of Omidenepag Isopropyl, a Novel Selective EP2 Receptor Agonist, as an Ocular Hypotensive Agent. Invest Ophthalmol Vis Sci. 59(1):145-153. doi: 10.1167/iovs.17-22745. PMID: 29332128. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/29332128/>

⁷⁰ Fuwa M, Toris CB, Fan S, Taniguchi T, Ichikawa M, Odani-Kawabata N, Iwamura R, Yoneda K, Matsugi T, Shams NK, Zhang JZ. 2018. Effects of a Novel Selective EP2 Receptor Agonist, Omidenepag Isopropyl, on Aqueous Humor Dynamics in Laser-Induced Ocular Hypertensive Monkeys. J Ocul Pharmacol Ther. 34(7):531-537. doi: 10.1089/jop.2017.0146. Epub 2018 Jul 10. PMID: 29989843. Submitted to the NDA. Abstract accessible via: <https://pubmed.ncbi.nlm.nih.gov/29989843/>

⁷¹ Ida Y, Hikage F, Umetsu A, Ida H, Ohguro H. Omidenepag, a non-prostanoid EP2 receptor agonist, induces enlargement of the 3D organoid of 3T3-L1 cells. 2020. Sci Rep. 0(1):16018. doi: 10.1038/s41598-020-72538-x. PMID: 32994409; PMCID: PMC7524797. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/32994409/>

submission of the NDA)^{74,75}. Except as noted in the body of the review (above), these (abstracts or full papers) were cursorily reviewed to verify the lack of safety concerns and overlap with the submitted study reports, but were not all fully reviewed yet.

- The clinical published literature is beyond the scope of this review.

⁷² Yamamoto Y, Taniguchi T, Inazumi T, Iwamura R, Yoneda K, Odani-Kawabata N, Matsugi T, Sugimoto Y, Shams NK. 2020. Effects of the Selective EP2 Receptor Agonist Omidenepag on Adipocyte Differentiation in 3T3-L1 Cells. *J Ocul Pharmacol Ther.* 36(3):162-169. doi: 10.1089/jop.2019.0079. Epub 2020 Jan 14. PMID: 31934812; PMCID: PMC7175626. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/31934812/>

⁷³ Esaki Y, Katsuta O, Kamio H, Noto T, Mano H, Iwamura R, Yoneda K, Odani-Kawabata N, Morishima K, Shams NK. 2020. The Antiglaucoma Agent and EP2 Receptor Agonist Omidenepag Does Not Affect Eyelash Growth in Mice. *J Ocul Pharmacol Ther.* 36(7):529-533. doi: 10.1089/jop.2020.0003. Epub 2020 May 17. PMID: 32412835; PMCID: PMC7482127. Abstract accessed via: <https://pubmed.ncbi.nlm.nih.gov/32412835/>

⁷⁴ Fuwa M, Shimazaki A, Odani-Kawabata N, Kirihaara T, Taniguchi T, Iwamura R, Yoneda K, Kato M, Morishima K, Shams NK. Additive Intraocular Pressure-Lowering Effects of a Novel Selective EP2 Receptor Agonist, Omidenepag Isopropyl, Combined with Existing Antiglaucoma Agents in Conscious Ocular Normotensive Monkeys. *J Ocul Pharmacol Ther.* 2021 Feb 17. doi: 10.1089/jop.2020.0071. Epub ahead of print. PMID: 33600237. Abstract accessed via: <https://pubmed.ncbi.nlm.nih.gov/33600237/>

⁷⁵ Ichioka H, Ida Y, Watanabe M, Ohguro H, Hikage F. Prostaglandin F2 α and EP2 agonists, and a ROCK inhibitor modulate the formation of 3D organoids of Grave's orbitopathy related human orbital fibroblasts. *Exp Eye Res.* 2021 Apr;205:108489. doi: 10.1016/j.exer.2021.108489. Epub 2021 Feb 12. PMID: 33587909. Accessed via: <https://pubmed.ncbi.nlm.nih.gov/33587909/>

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