CTD 第 2 部

2.6　非臨床試験の概要文及び概要表

2.6.6　毒性試験の概要文

MSD 株式会社

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LIST OF ABBREVIATIONS, ACRONYMS AND DEFINITION OF TERMS

Abbreviation/Acronym	Definition
3TC	Lamivudine
AUC	Area Under the Curve
$AUC_{0\text{-}24\ hr}$	Area Under the Curve (0 to 24 hours)
CHO	Chinese Hamster Ovary
C_{max}	Maximal Concentration
DOR	Doravirine
EFV	Efavirenz
ETR	Etravirine
EU	European Union
F	Female
FOB	Functional Observational Battery
GD	Gestation Day
GLP	Good Laboratory Practice
hr	Hour
HIV-1	Human Immunodeficiency Virus Type 1
HPMCAS	Hydroxypropyl methylcellulose-acetate succinate
ICH	International Council on Harmonisation
IM	Intramuscular
LAP	Long Acting Parenteral
LE	Long Evans
LLQ	Lower Limit of Quantitation
LNC	Lymph Node Cells
M	Male
MN-PCE	Micronucleated Polychromatic Erythrocytes
N/A	Not Applicable
NC	Not Calculated
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level

Abbreviation/Acronym	Definition
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PND	Postnatal Day
PNW	Postnatal Week
PSD	Particle Size Distribution
QD	Once Daily
RT	Reverse Transcriptase
SC	Subcutaneous
SE	Standard Error
[redacted]F	[redacted] Formulation
TDF	Tenofovir Disoproxil Fumarate
TK	Toxicokinetics
T_{max}	Time to Reach C_{max}
UVR	Ultraviolet Radiation
w/v	Weight/volume

1 BRIEF SUMMARY

Doravirine (also referred to as DOR or MK-1439) is a novel and potent non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Because of its potential to offer important advantages over currently marketed NNRTIs, including safety, tolerability, activity against prevalent NNRTI-resistant mutants, limited drug-drug interactions and convenience of use, DOR was developed as a single entity to be co-administered with other anti-HIV agents and as part of a fixed dose combination (FDC) tablet. The FDC consists of DOR, and two NRTIs, lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) for use as a complete regimen for the treatment of HIV-1 infection in treatment-naive adult patients. The recommended human dose of DOR is 100 mg, as a single entity and in the FDC tablet: DOR (100 mg)/3TC (300 mg)/TDF (300 mg). Nonclinical exposure margins of DOR to humans were based on population pharmacokinetics analysis from DOR Phase 3 trials (P018 and P021), where a 100 mg QD DOR clinical dose resulted in systemic geometric mean systemic $AUC_{0\text{-}24hr}$ exposures of 37.8 μM•hr and a C_{max} of 2.26 μM.

1.1 DOR Toxicity Profile

DOR has been evaluated in a comprehensive nonclinical safety assessment program to support oral administration to humans that included in vitro and in vivo genetic toxicity assays and repeat-dose oral tolerability and toxicity studies of up to 3 months duration in mice, up to 6 months duration in rats, and up to 9 months duration in dogs [Table 2.6.6: 1]. Developmental and reproductive toxicology studies conducted with DOR included a male and female rat fertility study, embryo-fetal developmental toxicity studies in rats and rabbits, a pre- and post-natal toxicity study in rats, and juvenile toxicity studies in rats. In addition, a six-month oral carcinogenicity study in rasH2 transgenic mice, a two-year oral carcinogenicity study in rats, a rat phototoxicity study, a one-month oral rat combination toxicity study, and three-month oral rat toxicity studies evaluating potential impurities were completed.

To explore the feasibility of novel Long Acting Parenteral (LAP) formulations of DOR given via the intramuscular or subcutaneous route of administration, LAP micro-particulate suspension formulations of DOR were evaluated in single-dose exploratory local tolerability and toxicokinetics studies in dogs and in repeat-dose toxicity and toxicokinetic studies in rats. These studies are included in this application to provide the collective nonclinical experience with DOR; however, the results from these LAP studies using a non-relevant route of administration for oral clinical dosing and exploratory formulations do not impact the nonclinical risk assessment of the oral DOR program. DOR systemic exposures achieved in LAP studies were far lower than those achieved in the oral program.

The rat and dog were selected as the rodent and non-rodent species for DOR toxicity assessment based on in vitro and in vivo metabolic profiles and the demonstration of satisfactory pharmacokinetics. Nonclinical formulation development studies were performed prior to the conduct of pivotal toxicity studies to maximize DOR exposures in animal species [Sec. 2.6.4.3]. In the pivotal GLP studies in dogs, DOR doses were orally administered

once-daily as suspensions of DOR jet-milled base compound suspended in 10% polysorbate 80 in deionized water, or vehicle, at a dosing volume of 5 mL/kg and up to the limit dose of 1000 mg/kg/day. In the pivotal GLP studies in mice, rats, and rabbits, DOR was orally administered as a [redacted] formulation [consisting of [redacted]% DOR base form and [redacted]% of hydroxypropyl methylcellulose-acetate succinate (HPMCAS), suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water] in deionized water, or control article [consisting of HPMCAS at concentrations of up to 120 to 180 mg/mL in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water], once-daily at a dosing volume of 10 mL/kg. HPMCAS is an inert cellulose-based polymer extensively used in solid dispersion formulations to improve test article absorption and systemic exposure clinically and nonclinically [Ref. 4.3: 04NSFN]. In the DOR toxicity studies using [redacted] formulation, the HPMCAS polymer was present in control article at the same concentration as present in the highest tested doses of DOR [redacted] formulation.

The maximum feasible oral dose of the DOR [redacted] formulation, based on the maximum feasible concentration and a 10 ml/kg dosing volume, was 450 mg/kg/day in adult-aged rats, mice and rabbits, and was 300 mg/kg/day when administered to juvenile rats due to inability to give higher doses using smaller oral gavage needles selected for neonatal and juvenile-aged rats. Orally administered DOR in the [redacted] formulation showed superior systemic exposures (AUC and C_{max}) in these species as compared to conventional formulations using the base compound. A plateau in exposure was determined to occur at DOR [redacted] formulation at doses ≥300 mg/kg/day in mice and rabbits, and therefore 300 mg/kg/day was administered as the highest dose in the pivotal rabbit embryo-fetal development study and in the mouse carcinogenicity study. In dogs, oral administration of the DOR base compound (non-[redacted]) in a formulation containing 10% polysorbate 80 was determined to provide acceptable exposure using the limit dose of 1000 mg/kg/day, given the longer half-life for DOR in dogs as compared to other nonclinical species and accumulation with repeat-dose administration.

Table 2.6.6: 1 DOR Toxicology Program

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day, unless otherwise specified)	NOAEL (mg/kg/day, unless otherwise specified)	Study No. (GLP Status)
Repeat-dose Toxicity					
One-Month Range-Finding with TK	Oral (gavage)	rasH2 Wild-Type Mice (Hybrid)	0, 30, 100, 300, 450	≥450	TT #[redacted]-6010 (GLP)[a]
Three-Month Range-Finding with TK	Oral (gavage)	Mice CRL:CD1(ICR)	0, 3, 30, 150, 300, 450	≥450	TT #[redacted]-6013 (GLP)
Exploratory Seven-Day Tolerability with TK	Oral (gavage)	Rats (Female) Crl:WI(Han)	0, 5, 100, 750 (total) (given as b.i.d. doses)	≥750	TT #[redacted]-2518 (Non-GLP)
Seven-Day TK	Oral (gavage)	Rats Crl:WI(Han)	1.5, 15, 175, 225 (given as b.i.d. doses) 30, 175, 225 (QD)	N/A	TT #[redacted]-0019 (GLP)
Two-Week Toxicity with FOB & TK	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 75, 450	≥450	TT #[redacted]-6029 (GLP)
Three-Month Toxicity with TK	Oral (gavage)	Rats Crl:WI(Han)	0, 3, 30, 450	≥450	TT #[redacted]-6040 (GLP)
Six-Month Toxicity with TK	Oral (gavage)	Rats Crl:WI(Han)	0, 3, 30, 450	≥450	TT #[redacted]-6019 (GLP)[b]
Two-Week Toxicity with TK	Oral (gavage)	Dogs (Beagle)	10	≥10	TT #[redacted]-6030 (GLP)
Three-Month Toxicity with TK	Oral (gavage)	Dogs (Beagle)	0, 1,10, 1000	≥1000	TT #[redacted]-6039 (GLP)
Nine-Month Toxicity with TK	Oral (gavage)	Dogs (Beagle)	0, 1, 10, 1000	≥1000	TT #[redacted]-6018 (GLP)[c]
Genotoxicity –In Vitro					
Exploratory Microbial Mutagenesis Assay	In vitro	*Salmonella typhimurium* TA97a, TA98, TA100, and TA1535 and *Escherichia coli* WP2 uvrA pKM101	30 to 5000 µg/plate	Negative	TT #[redacted]-8021 (Non-GLP)
Microbial Mutagenesis Assay			100 to 5000 µg/plate		TT #[redacted]-8099 (GLP) (reported with TT #[redacted]-8021)
Microbial Mutagenesis Assay		TA100	100 to 5000 µg/plate		TT #[redacted]-8113 (GLP) (reported with TT #[redacted]-8021)

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day, unless otherwise specified)	NOAEL (mg/kg/day, unless otherwise specified)	Study No. (GLP Status)
Exploratory Range Finding In Vitro Assay for Chromosomal Aberrations In Vitro Assay for Chromosomal Aberration	In vitro	Chinese hamster ovary cells	75 to 500 µM	Negative	TT #[redacted]-8662 (Non-GLP) TT #[redacted]-8666 (GLP) (reported with TT #[redacted]-8662)
Genotoxicity - In Vivo					
Exploratory Assay for Micronucleus Induction in Rat Bone Marrow	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 100, 750 (total) (given as b.i.d. doses)	Negative	TT #[redacted]-8707 (Non-GLP) (In conjunction with a 7-Day Tolerability Study TT #[redacted]-2518)
Assay for Micronucleus Induction in Rat Bone Marrow	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 75, 450	Negative	TT #[redacted]-8725 (GLP) (In conjunction with 2-WK Oral Toxicity Study TT #[redacted]-6029)
Carcinogenicity					
Six-Month Carcinogenicity with TK	Oral (gavage)	rasH2 Transgenic Mice	0, 10, 60, 300	≥300 No evidence of carcinogenic potential	TT #[redacted]-6005 (GLP)
Two-Year Carcinogenicity with TK	Oral (gavage)	Rat Crl:WI(HAN)	0, 3, 30, or 450	≥450 for neoplastic & non-neoplastic findings	TT #[redacted]-6029 (GLP)[d]
Reproductive & Developmental Toxicity					
Fertility	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 30, 450	≥450	TT #[redacted]-7300 (GLP)[e]
Exploratory Range-Finding (Pregnant)	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 45, 450	≥450	TT #[redacted]-7045 (Non-GLP)
Embryo-Fetal Developmental Toxicity with TK	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 45, 450	≥450 (for both maternal and developmental toxicity)	TT #[redacted]-7040 (GLP)[f]
Exploratory Single-Dose TK (Non-Pregnant)	Oral (gavage)	Rabbits (Dutch Belted)	1, 10, 100, 1000	N/A	TT #[redacted]-7206 (Non-GLP)

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day, unless otherwise specified)	NOAEL (mg/kg/day, unless otherwise specified)	Study No. (GLP Status)
Exploratory Single-Dose TK (Non-Pregnant)	Oral (gavage)	Rabbits (Dutch Belted)	15, 50, 150, 450	N/A	TT #[redacted]-7207 (Non-GLP)
Exploratory 5-Day TK (Non-Pregnant)	Oral (gavage)	Rabbits (Dutch Belted)	15, 50, 300, 150, 450	N/A	TT #[redacted]-7277 (Non-GLP)
Exploratory Oral Range-Finding (Pregnant)	Oral (gavage)	Rabbits (Dutch Belted)	0, 1, 15, 450	≥450	TT #[redacted]-7055 (Non-GLP)
Embryo-Fetal Developmental Toxicity with TK	Oral (gavage)	Rabbits (Dutch Belted)	0, 2, 15, 300	15 (maternal toxicity); ≥300 (developmental toxicity)	TT #[redacted]-7050 (GLP)[f]
Pre- and Postnatal Development	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 45, 450	≥450 (for both maternal and F_1 generation toxicity)	TT #[redacted]-7010 (GLP)[e]
Exploratory Toxicity with TK Range-Finding Juveniles	Oral (gavage)	Rats Crl:WI(Han)	0, 5, 45, 150, 300	300	TT #[redacted]-7005 (Non-GLP)
Toxicity with TK in Juveniles	Oral (gavage)	Rats Crl:WI(Han)	0, 10, 45, 300	≥300	TT #[redacted]-7140 (GLP)[e]
Local Tolerance					
Bovine Corneal Opacity and Permeability Test	In vitro	Bovine Corneas	0.75 mL ([redacted]% DOR solution)	N/A	TT #[redacted]-7857 (GLP)
MatTek EpiDerm™ MTT Viability Assay	In vitro	MatTek EpiDerm™ tissue samples	100 mg	N/A	TT #[redacted]-7858 (GLP)
Other Toxicity Studies					
- Immunotoxicity					
Local Lymph Node Assay	Topical	Mouse (CBA/J)	5, 10 and 25% (w/v) DOR in DMF	N/A	TT #[redacted]-7859 (GLP)
- Impurity Studies					
Three-Month Toxicity (API Batch Qualification Study)	Oral (gavage)	Rats Crl:WI(HAN)	0, 115	≥115	TT #[redacted]-6035 (GLP)
Three-Month Toxicity (Phenol Degradate Qualification Study)	Oral (gavage)	Rats Crl:WI(HAN)	30	≥30 (0.12 of DOR phenol degradate)	TT #[redacted]-6017 (GLP)
Three-Month Toxicity with a Micronucleus Assay (DOR or TDF Degradate G Qualification Study)	Oral (gavage)	Rats Crl:WI(HAN)	Group 1: DOR & TDF Degradate G Control Group 2: DOR at 30 mg/kg/day Group 3: TDF Degradate G	≥30 DOR (with impurities of interest) ≥0.3 TDF Degradate	TT #[redacted]-6010 (GLP)

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day, unless otherwise specified)	NOAEL (mg/kg/day, unless otherwise specified)	Study No. (GLP Status)
			[fumaric acid ester] 0.3 mg/kg/day	G [fumaric acid ester]	
- Other Toxicity Studies – Other					
Phototoxicity	Oral (gavage)	Rats Crl:LE (Long-Evans)	0, 30, 450	≥450	TT #[redacted]-9011 (GLP)
Exploratory Ten-Day Urine Examination	Oral (gavage)	Rats (Female) Crl:WI(Han)	450	N/A	TT #[redacted]-1095 (Non-GLP)
One-Month Combination Toxicity Study *(with MK-8591)*	Oral (gavage)	Rats Crl:WI(Han)	0, 0+3 MK-8591; 30+1 MK-8591, 30+3 MK-8591	≥30 +3 MK-8591	TT #[redacted]-1012 (GLP)
Long-Acting Parenteral (LAP) Formulations (No impact on oral DOR toxicity profile)					
LAP: Exploratory 34-Day Local Tolerability (Day 1 and 30) & TK	IM	Rats (Males) Crl:WI(HAN)	Doses of two formulations each administered on Study Day 1 and Study Day 30 only Formulation 1: 200 mg of DOR/mL aqueous suspension containing 3% polyethylene glycol 3350 isotonic Formulation 2: 150 mg of DOR/mL solution in N-methyl pyrrolidone	N/A	TT #[redacted]-6034 (Non-GLP)
LAP: Exploratory 15-Day Tolerability & TK	SC or IM	Rats Crl:WI(HAN)	60 mg/kg/dose (8 µm d50 PSD formulation) given as three once weekly doses	N/A	TT #[redacted]-1033 (Non-GLP)
LAP: 3-Week Toxicity with 1-Week Treatment Free Period	IM	Rats Crl:WI(HAN)	15, 30, 60 mg/kg/dose (2 and 8 µm d50 PSD formulation) given as three once weekly doses	N/A	TT #[redacted]-6016 (GLP)
LAP: 3-Week Toxicity with 1-Week Treatment Free Period	SC	Rats Crl:WI(HAN)	15, 30, 60 mg/kg/dose (2 and 8 µm d50 PSD formulation) given as three once weekly doses	N/A	TT #[redacted]-6015 (GLP)
LAP: Exploratory Intermittent Dose (Days 1, 8, 15) with 2-Month Treatment-Free Period	IM	Rats Crl:WI(HAN)	10 or 40 mg/kg/dose (0.25 µm [nano-formulation] d50 PSD)	N/A	TT #[redacted]-1065 (Non-GLP)

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day, unless otherwise specified)	NOAEL (mg/kg/day, unless otherwise specified)	Study No. (GLP Status)
LAP: Exploratory TK (13-Week Observation Period)	IM	Dogs (Beagle)	200 mg [1 injection of 1.0 mL 2.0 µm or 2 injections of 0.5 mL each of 8.0 µm d50 PSD formulation]	NA	TT #[redacted]-1081 (Non-GLP)
LAP: Exploratory TK (13-Week Observation Period)	IM or SC	Dogs (Beagle)	Single dose of 200 mg and 300 mg IM or SC (d50 PSD of 8.0 µm)	NA	TT #[redacted]-1061 (Non-GLP)
LAP: Exploratory TK (13-Week Observation Period)	IM	Dogs (Beagle)	Single dose of 200 mg (d50 PSD of 0.3 µm)	NA	TT #[redacted]-1106 (Non-GLP)
LAP: Exploratory Single-Dose TK Study (with ~8.5 month observation period)	IM	Dogs (Beagle)	Single dose of 200 mg (d50 PSD of 16.0 µm)	NA	TT #[redacted]-1064 (Non-GLP)

NA = Not Applicable

[a] With the exception of confirmatory genotyping of female study animals.

[b] With the exception of urinary crystal identification and metabolite profiling.

[c] With the exception of metabolite profiling.

[d] With the exceptions of physical stability of the [redacted] formulation of DOR in the vehicle and the exploratory metabolite profiling.

[e] With the exception of determination of the physical stability of the formulation.

[f] With the exception of the skeletal evaluation by micro-CT and determination of the physical stability of the formulation.

Test article batches used in the nonclinical studies are provided in [Sec. 2.6.7.4]. Pivotal toxicology studies were conducted in compliance with Good Laboratory Practice (GLP) as denoted in [Table 2.6.6: 1] and were consistent with the ICH guidances. Studies were conducted at Merck Research Laboratories, West Point, Pennsylvania, U.S.A.; Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherche, Riom, France, or [redacted], U.S.A. The U.S.A. and France are members of the Organisation for Economic Co-operation and Development (OECD) and therefore part of the OECD Mutual Acceptance of Data system. GLP compliance statements are included in all GLP study reports. All pivotal studies were supported by toxicokinetic evaluation of DOR within the study or from studies conducted under the same conditions utilizing identical doses administered using the same formulation [Sec. 2.6.7.2]; [Sec. 2.6.7.3].

DOR treatment was well tolerated in all animal toxicity studies up to the highest doses tested, corresponding to systemic no-observed-adverse-effect level (NOAEL) exposure multiples in mouse, rat, and dog versus human exposures at the clinical 100 mg QD dose to be approximately 5.5X, 7.5X and 18X, respectively. No target organs were identified. There

was no genetic or carcinogenic risk identified with DOR. There were no findings in male and female rat fertility toxicity studies, nor were there adverse findings in rat and rabbit embryo-fetal development studies, in a rat pre- and post-natal development study, or in rat juvenile toxicity studies up to the highest doses tested.

1.2 Lamivudine and Tenofovir Disoproxil Fumarate Toxicity Profiles

No nonclinical toxicity studies were conducted with 3TC or TDF by the Sponsor. A three-month study was however conducted where rats were dosed with deg G (also known as fumaric acid ester), a TDF degradation product in the FDC, which was qualified in this study. Both 3TC (referred to as EPIVIR®) and TDF (referred to as VIREAD®) are marketed approved compounds with well-characterized nonclinical and clinical safety profiles. Lamivudine and TDF have been clinically used as part of HIV-1 therapy for over 22 years and 15 years, respectively.

Comprehensive nonclinical testing programs for 3TC and TDF, evaluated as individual agents, have been previously conducted by their respective sponsors to support their original marketing registrations. Extensive clinical experience exists for both agents when used in combination with other agents as part of anti-retroviral therapy. A brief summary is provided below of the nonclinical toxicology public domain data obtained from the approved prescribing information, the scientific literature and public domain regulatory review documents associated with marketing approvals, where ICH-compliant toxicity bioassays are described. The doses of 3TC and TDF in the DOR/3TC/TDF FDC tablet are similar to the respective marketed single entity doses (300 mg daily dose for both 3TC and TDF).

1.2.1 Lamivudine (3TC)

For supporting nonclinical data for 3TC collected from ICH-compliant safety assessment studies, the Sponsor refers to EPIVIR® US Prescribing Information [Ref. 4.3: 04P95N], TRIUMEQ® US Prescribing Information [Ref. 4.3: 04RMRC], the EPIVIR® NDA 20-564 [Ref. 4.3: 03TKG7] and the EU Marketing Authorization (MA) for EPIVIR EMEA/H/C/000107 [Ref. 4.3: 03RRT8]. The nonclinical safety of 3TC has been evaluated in a variety of studies that have been conducted to determine its potential genotoxicity, general toxicity profile following acute and repeated dose studies in rats and dogs of up to 12 months duration, developmental and reproductive toxicity, juvenile toxicity, and carcinogenic potential in rat and mouse carcinogenicity studies of 2 years duration. In the prescriber information and from regulatory reviews, 3TC was documented to have low acute toxicity in rodents and was adequately tolerated in repeat dose studies in dogs and rats. In repeat dose rat studies, doses up to 2000 mg/kg/BID were evaluated and adequately tolerated, and a 450 mg/kg/bid (900 mg/kg daily) dose was identified as the no-observed-effect level (NOEL); AUC exposure at NOEL dose was approximately 17-fold higher than the human therapeutic AUC at 300 mg. Treatment-related effects included minor hematological (mainly red cell parameters), clinical chemistry and urinalysis changes, and mucosal hyperplasia of the cecum. In dogs, deaths were seen in female dogs dosed with 1500 mg/kg b.i.d. in a 3-month study but not at 1000 mg/kg b.i.d when administered for 12-months. A 3TC daily dose of 45 mg/kg was identified in dogs as a NOEL; AUC exposure at this dose was

approximately 9-fold higher than the human therapeutic AUC. Treatment-related changes in animals administered 3TC were restricted to reductions in red cell blood cell counts, observed on occasion with increased mean corpuscular volume, hemoglobin reductions, and decreases in total lymphocyte counts, but with no effect on bone marrow cytology.

Long-term carcinogenicity studies of 3TC in mice and rats showed no evidence of carcinogenic potential relevant to humans at exposures up to 12 times (mice) and 57 times (rats) those achieved in humans at the 300 mg daily 3TC therapeutic dose. Lamivudine was negative in a microbial mutagenicity screen and an in vitro cell transformation assay, but showed weak in vitro mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, 3TC showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended treatment dose for HIV-1 infection.

Developmental and reproduction studies have been performed with 3TC in rats and rabbits at orally administered doses up to 4000 mg/kg/day and 1000 mg/kg/day, respectively, producing plasma levels up to approximately 32-fold relative to exposure at the adult daily therapeutic HIV dose of 300 mg. No evidence of teratogenicity due to 3TC was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at plasma levels up to 32 times those in humans. Studies in both pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. Lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 112 times higher than those in humans.

In juvenile rat toxicity studies with 3TC, decreases in red blood cell parameters were observed, similar to findings in repeat dose adult animal studies. The only finding observed not also seen in adult animals administered 3TC was reduction in testes weight corresponding to slight to moderate dilation of the seminiferous tubules in high dose animals. The safety margin for this finding was estimated to be > 80-fold when compared to a 300 mg daily human dose of 3TC.

In conclusion, the nonclinical safety profile of 3TC was well characterized. The identified target organs were limited to bone marrow (reduction in red and, on occasion white blood cell counts without effects on bone marrow cytology) and lower GI (cecum). There was no identified overlapping toxicity profile to DOR.

1.2.2 Tenofovir Disoproxil Fumarate (TDF)

For supporting nonclinical data for TDF collected from ICH-compliant safety assessment studies, the Sponsor refers to the VIREAD® Prescribing Information [Ref. 4.3: 04P95P], STRIBILD® Prescribing Information [Ref. 4.3: 04G9B5], VIREAD® NDA 21-356 [Ref. 4.3: 0438FY] and the EU Marketing Authorization (MA) for VIREAD EMEA/H/C/000419 [Ref. 4.3: 0438G4]. The nonclinical safety of TDF has been evaluated in a variety of studies to determine its potential genotoxicity, general toxicity profile following acute and repeated dose studies in dogs, rats, and monkeys, developmental and

reproductive toxicity, juvenile toxicity, and carcinogenic potential in rat and mouse carcinogenicity studies of 105 weeks duration. Tenofovir disoproxil fumarate was administered in toxicology studies to rats and dogs up to 42 weeks, and in monkey studies up to 24 months.

The target organs of TDF in animal species was kidney (tubular dilatation and karyomegaly, interstitial nephritis), bone (osteomalacia and/or reduced bone mineral density), and the gastrointestinal tract (seen in rats only).

Gastrointestinal lesions were only observed in rats at approximately 3-fold the human exposure at a 300 mg daily therapeutic dose, but no signs were reported in either monkeys or in dogs at up to 5-10-fold the human therapeutic dose. Changes in serum chemistry parameters in rats, including dose-related slight to moderate changes in cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine, were also reported at approximately 3-fold the human exposure. All these effects were reversible after treatment discontinuation. The NOEL was ≤30 mg/kg, with exposures similar to that at the therapeutic human dose; therefore no overall safety margins in rat could be established.

Evidence of TDF-related renal toxicity was noted in all animals species tested, with NOEL margins to kidney findings in dogs, monkeys, and rats to be 1X, 5X and 6X, respectively. Dose-related histopathological changes in dogs included tubular dilatation and interstitial nephritis reported in the 10 and/or 30 mg/kg/day dose groups and slight to moderate renal tubular karyomegaly in all treated groups. Proteinuria, glycosuria, increased urinary creatinine, and increased urine volume were observed in the 30 mg/kg/day dose group throughout the study. The NOAEL in dog was ≤3 mg/kg, with exposures at or below the therapeutic human exposure, and no overall safety margin could be established. In rat, mouse, and monkey, increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed. These toxicities were noted at AUC exposures approximately 2 to 20 times higher than those observed in humans at the therapeutic dose. Clinical use of TDF is reported to result in new onset or worsening renal impairment that can include acute renal failure and Fanconi syndrome.

Bone has been identified in nonclinical studies as a target of TDF toxicity. Tenofovir exposures (based on AUCs) ≥ 6-fold those observed in humans caused bone toxicity in nonclinical species. In monkeys, the bone toxicity was described as osteomalacia, and was reversible upon dose reduction or discontinuation of TDF. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown. Decreased bone mineral density has been observed in humans following chronic TDF administration.

Long-term oral carcinogenicity studies of TDF in mice and rats were conducted at exposures up to approximately 10 times (mice) and four times (rats) those observed in humans at the therapeutic adult dose 300 mg dose. Liver adenomas were increased in high-dose female mice (exposures 10 times that of the human therapeutic dose). In rats, the study was negative

for carcinogenic findings at exposures up to five times that observed in humans at the therapeutic dose. Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). Tenofovir disoproxil fumarate was negative when administered to male mice in an in vivo mouse micronucleus assay.

Reproduction studies have been performed with TDF in rats and rabbits at doses up to 14 and 19 times (based on body surface area) the human therapeutic dose, respectively, and revealed no evidence of impaired fertility or harm to the fetus. There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose (based on body surface area comparisons) for 28 days prior to mating and to female rats for 15 days prior to mating through gestational day seven. Alteration of the estrous cycle in female rats was observed but was without apparent functional consequence on fertility.

In conclusion, the reviewed nonclinical safety evaluations indicate that the toxicity profile of TDF has been well characterized. The target organs identified in nonclinical studies were kidney, bone, and gastrointestinal tract. These toxicities were noted in rats, dogs and/or monkeys at AUC exposures approximately 1 to 20 times higher than those observed in humans at the therapeutic dose. Worsening renal impairment and decreases in bone mineral density has been observed clinically with TDF. Assessment of TDF data in the public domain indicated there was no identified overlapping toxicity profile to DOR.

1.3 Doravirine, Lamivudine, and Tenofovir Disoproxil Fumarate Combination

Nonclinical toxicity studies evaluating oral administration of the combination of DOR, 3TC and TDF have not been performed. This is in accordance with regulatory guidances (ICH M3 [R2]: *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment FDA Guidance for Industry, Center for Drug Evaluation and Research, November 2015, Revision 1), where for combinations involving marketed or late-stage entities, nonclinical combination toxicity studies would generally not be recommended to support clinical studies or registration unless data from nonclinical studies or clinical trials for an investigational agent suggest a potential for serious synergistic toxicity with an approved therapeutic drug combination.

DOR administration was well-tolerated in all animal species evaluated up to the highest doses tested, corresponding to systemic NOAEL exposure multiples versus humans at the clinical 100 mg QD dose ranging from 5.5X to 18X [Sec. 2.6.6.3]. No target organs were identified. There was no genetic or carcinogenic risk identified with DOR. There were no findings in the male and female rat fertility study, nor were there adverse effects identified in rat juvenile studies, rat and rabbit embryo-fetal development studies or a rat pre- and post-natal development study, up to the highest doses tested.

No toxicologic concern (e.g., similar target organ toxicity) or potential for synergistic toxicity was identified in the nonclinical safety programs of DOR, 3TC and TDF. All

therapeutic agents target the non-mammalian HIV-1 reverse transcriptase enzyme with high specificity, minimizing the potential for off-target activity. The approved marketed agents comprising the FDC, TDF and 3TC, have been used clinically in combination with a large number of HIV-1 antiretroviral agents for greater than 15 (TDF) and 22 years (3TC) with acceptable safety profiles. In addition, clinical experience of DOR/3TC/TDF combination through ≥48 weeks of dosing has not exhibited any evidence of safety concern.

The nonclinical toxicity studies conducted with DOR are detailed in [Sec. 2.6.6.2] through [Sec. 2.6.6.8] below. As mentioned above, no nonclinical toxicity studies were conducted with 3TC, TDF, or with the DOR/3TC/TDF combination.

2 SINGLE-DOSE TOXICITY

No formal acute toxicity studies have been conducted with DOR. However, consistent with ICH M3(R2) guidance, the toxicity after a single dose can be assessed from the repeat-dose oral toxicity studies in mice (up to 450 mg/kg/day), rats (up to 750 mg/kg/day) and dogs (up to 1000 mg/kg/day) as discussed below in [Sec. 2.6.6.3]. A dog oral pharmacology study testing single doses of DOR ranging from 2 mg/kg to 750 mg/kg was performed as described in the pharmacology written summary [Sec. 2.6.2], and single dose toxicokinetic studies in rabbits to support embryo-fetal toxicity studies were performed as described in [Sec. 2.6.6.6]. Overall, there was no evidence of acute toxicity in these species.

3 REPEAT-DOSE TOXICITY

DOR was evaluated in repeated-dose oral tolerability and toxicity studies at durations up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs. In the pivotal GLP studies in rats and mice, animals were orally administered DOR as a [redacted] formulation [consisting of [redacted]% DOR base form and [redacted]% of HPMCAS, suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water] or control article [consisting of HPMCAS at a concentration of up to 180 mg/mL in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water] once-daily at a dosing volume of 10 mL/kg. In all toxicity studies using the [redacted] formulation, the HPMCAS polymer was present in control article at the same concentration as present in the highest tested dose of DOR [redacted] formulation. This enabled formulation of DOR was selected to improve the plasma exposures in rodents and rabbits, compared to other evaluated formulations [Sec. 2.6.5]. The DOR high dose, 450 mg/kg/day, was the maximum feasible oral dose of DOR [redacted] formulation under the conditions of the pivotal GLP studies. In dogs, DOR doses were orally administered as suspensions of the (jet-milled) base compound in 10% polysorbate 80 or vehicle at a dosing volume of 5 mL/kg. The high dose of the 3- and 9-month dog studies was the limit dose, 1000 mg/kg/day, per ICH M3(R2) guidance. The plasma toxicokinetics of both DOR and its major human metabolite (M9) was assessed in chronic rat and dog oral toxicity studies.

3.1 Mice

3.1.1 One-Month Oral Range-Finding and Toxicokinetic Study in rasH2 Wild-Type Mice (Hybrid) (TT #[redacted]-6010)

The purpose of this study was to determine the potential toxicity and toxicokinetic profile of DOR when administered orally, once a day, to rasH2 wild-type mice for approximately 1 month (TT #[redacted]-6010) [Sec. 2.6.7.6], in support of the dose selection of a 6-month rasH2 transgenic mouse carcinogenicity study.

Jic:CB6F1-nonTgrasH2@Jcl mice were assigned to five groups; four groups of 21 females and 21 males each that received 30, 100, 300 or 450 mg/kg/day of DOR [as a [redacted] formulation], and one group of 15 females and 15 males that received the control article only. The amount of HPMCAS administered to the control group was the same amount of the polymer present at the 450 mg/kg/day DOR dose level. The first 10 mice/sex of each group were dedicated to the range-finding arm of the study and the remaining mice to the toxicokinetic arm of the study [5 mice/sex in the control group and 11 mice/sex (including two replacement animals) in the DOR-treated groups].

Assessment of toxicity was based on mortality, clinical observations, body weights, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined in treated and control samples.

There were no test article-related unscheduled deaths nor test article-related antemortem or postmortem findings.

The toxicokinetic parameters are presented in [Table 2.6.6: 2].

Table 2.6.6: 2 Summary Mean (±SE) Plasma DOR Toxicokinetic Parameters in Mice Following Dosing of DOR: Study Week 4 (TT #[redacted]-6010)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
30	Female	56.1 ± 5.39	7.58 ± 0.244	2.0 ± NC
	Male	53.4 ± 5.76	8.17 ± 0.599	1.0 ± NC
	All	54.7 ± 3.58	7.57 ± 0.392	1.0 ± NC
100	Female	143 ± 8.26	14.7 ± 1.08	1.0 ± NC
	Male	90.8 ± 7.53	13.0 ± 1.52	1.0 ± NC
	All	117 ± 11.5	13.9 ± 0.914	1.0 ± NC
300	Female	288 ± 28.3	27.0 ± 1.62	1.0 ± NC
	Male	151 ± 16.7	23.6 ± 2.21	1.0 ± NC
	All	220 ± 28.2	25.3 ± 1.44	1.0 ± NC
450	Female	264 ± 22.3	22.1 ± 2.76	2.0 ± NC
	Male	171 ± 23.7	22.3 ± 1.91	1.0 ± NC
	All	217 ± 22.4	21.0 ± 1.43	2.0 ± NC

There were no substantial sex-related differences in mean systemic exposure to DOR or in mean C_{max} at all doses in Study Week 4. Mean systemic exposure and mean C_{max} were less than dose-proportional across 30, 100, and 300 mg/kg/day doses, and were similar at 300 mg/kg/day and 450 mg/kg/day.

Based on the absence of test article-related findings, the NOEL was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 217 µM•hr; approximately 5.5-fold above the DOR exposure at the human 100 mg daily dose).

3.1.2 Three-Month Oral Range-Finding and Toxicokinetic Study in CD1 Mice (TT #[redacted]-6013)

The purpose of this study was to evaluate the potential toxicity and toxicokinetic profile of DOR when administered once daily, by oral gavage, to CD1 mice for approximately 3 months (TT #[redacted]-6013), in support of the dose selection of a potential long-term mouse carcinogenicity study [Sec. 2.6.7.7A].

CRL:CD1(ICR) mice were assigned to six groups for the toxicity arm and six groups for the toxicokinetic arm. In the toxicity arm of the study, the six groups consisted of 10 females and 10 males each that received 3, 30, 150, 300, or 450 mg/kg/day of DOR [[redacted] formulation] or control article only. In the toxicokinetic arm of the study, there were five groups of 11 females and 11 males each (including two replacement animals/sex/group) that received the same doses of 3, 30, 150, 300, or 450 mg/kg/day of DOR as the same [redacted] formulation in the same vehicle and one group of five females and five males (including two replacement animals/sex) that received control article only. The amount of HPMCAS administered to the control group was the same amount administered to the high-dose group.

Assessment of toxicity was based on mortality, clinical observations, body weights, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined in DOR-treated groups from the toxicokinetic arm.

There were no test article-related unscheduled deaths.

Antemortem test article-related findings were limited to decreases in body weight gain in both sexes at 450 mg/kg/day (compared to controls, -16% in females in Study Week 13 and -22% to -37% in males from Study Week 8 onward). At the end of the study, mean body weights in both males and females at 450 mg/kg/day differed by ≤-1.3 grams from corresponding mean male and female control body weights. This weight difference was not considered toxicologically significant.

There were no postmortem test article-related changes.

The toxicokinetic parameters are presented in [Table 2.6.6: 3].

Table 2.6.6: 3. Summary Mean (±SE) Plasma DOR Toxicokinetic Parameters in Mice Following Dosing of DOR: Study Week 13 (TT #[redacted]-6013)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
3	Female	21.9 ± 2.11	3.23 ± 0.460	1.0 ± NC
	Male	17.7 ± 3.23	3.24 ± 0.101	0.50 ± NC
	All	19.8 ± 2.18	3.19 ± 0.288	1.0 ± NC
30	Female	94.7 ± 6.39	12.0 ± 1.40	0.50 ± NC
	Male	64.3 ± 9.23	11.6 ± 0.564	1.0 ± NC
	All	79.5 ± 6.64	10.4 ± 1.22	0.50 ± NC
150	Female	206 ± 21.4	22.2 ± 2.03	1.0 ± NC
	Male	135 ± 10.7	14.6 ± 3.59	0.50 ± NC
	All	170 ± 19.7	18.3 ± 2.04	1.0 ± NC
300	Female	244 ± 42.5	23.4 ± 2.93	1.0 ± NC
	Male	157 ± 9.70	22.8 ± 0.731	1.0 ± NC
	All	201 ± 26.3	23.1 ± 1.36	1.0 ± NC
450	Female	236 ± 18.9	25.1 ± 2.23	2.0 ± NC
	Male	156 ± 5.52	23.2 ± 1.47	1.0 ± NC
	All	196 ± 14.1	20.3 ± 2.85	2.0 ± NC

NC = Not Calculated

There were no substantial sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and in mean C_{max} values for DOR at all doses in Study Week 13. Mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and mean C_{max} were less than dose proportional between 3 mg/kg/day and 150 mg/kg/day, and were similar at 150, 300, and 450 mg/kg/day.

Based on the slight decreases in body weight gain, the NOEL was 300 mg/kg/day. The only finding observed at 450 mg/kg/day was a very slight non-toxicologically significant decreased body weight gain (≤-1.3 gram total body weight difference compared to controls) which may have been related to the potential bulk local gastrointestinal effects of increased amount of test article and HPMCAS polymer excipient compared to the 300 mg/kg/day dose. Saturation of AUC exposure was seen at doses ≥300 mg/kg/day. Based on the lack of a toxicologically significant body weight change, any other antemortem findings, and absence of postmortem findings, the NOAEL was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 196 µM•hr, approximately 5-fold above the DOR exposure at the human 100 mg daily dose).

3.2 Rats

3.2.1 Exploratory 7-Day Oral Tolerability Study in Female Rats (TT #[redacted]-2518)

The purpose of this study was to assess the potential toxicity and toxicokinetic profile of DOR when administered twice daily (6 hours apart) by oral gavage to female rats for 7 days (TT #[redacted]-2518) [Sec. 2.6.7.6] in support of dose selection for subsequent repeat-dose toxicity studies.

Crl:WI(HAN) 6-week-old rats were assigned to four groups of five females each that received 0 (vehicle), 2.5, 50, or 375 mg/kg/b.i.d. of DOR (base compound) in vehicle (10% polysorbate 80 in deionized water) at a dose volume of 5 mL/kg.

Assessment of toxicity was based on deaths, physical signs, body weights, clinical pathology (serum biochemistry and hematology), and limited anatomic pathology evaluation (including liver weights, gross and histomorphologic examinations of liver, heart, kidneys, brain, skeletal muscle, small intestine, large intestine, bone marrow, spleen, stomach, and lung). Plasma drug concentration analyses were conducted.

No test article-related mortality, physical signs, effects on body weight, gross or histomorphologic changes, or changes in liver weight were noted at ≤375 mg/kg/day b.i.d. (750 mg/kg/day). Hematological findings at 2.5 mg/kg/ b.i.d (5 mg/kg/day) consisted of very slight decreases in red blood cell counts, hemoglobin and % hematocrit. At doses of 50 mg/kg/ b.i.d. (100 mg/kg/day) and 375 mg/kg / b.i.d., very slight decreases in red blood cells and slight decreases in hemoglobin and % hematocrit were noted (up to approximately -10%). Serum biochemistry findings were only observed at 375 mg/kg/ b.i.d., and consisted of very slight decreases (up to approximately -7%) in albumin and total protein.

The toxicokinetic parameters are presented in [Table 2.6.6: 4].

Table 2.6.6: 4 DOR Toxicokinetic Parameters in Rats - Study Day 7 (TT #[redacted]-2518)

Dose (mg/kg b.i.d.)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
2.5	50.3 ± 7.41	3.27 ± 0.50	9 ± 0
50	207 ± 54.8	13.6 ± 2.4	9 ± 0
375	235 ± 21.8	15.0 ± 1.1	7.6 ± 3.1
Data presented as the mean ± standard deviation, n=5. DOR was administered twice daily, approximately 6 hours apart.			

Based on slight to very slight clinical pathology findings that were not considered adverse based on their limited magnitude of change, the NOAEL for this study was ≥750 mg/kg/day [375 mg/kg/ b.i.d.], ($AUC_{0\text{-}24\ hr}$: 235 µM•hr, approximately 6-fold above the DOR exposure at the human 100 mg daily dose).

3.2.2 Seven-Day Oral Toxicokinetic Study in Rats (TT #[redacted]-0019)

The purpose of this study was to evaluate the toxicokinetic profile of DOR when administered daily or twice daily by oral gavage for seven days (TT #[redacted]-0019), in support of dose selection for subsequent repeat-dose toxicity studies [Sec. 2.6.7.6].

Crl:WI(HAN) rats were assigned to seven groups of four females and four males. Rats were administered either a single daily oral dose (30, 175, or 225 mg/kg/day), or a twice daily oral dose (1.5, 15, 175, or 225 mg/kg b.i.d., approximately 5 hours between doses) of DOR for 7

days. DOR was administered as a [redacted] formulation [consisting of [redacted]% DOR base form and [redacted]% of HPMCAS, suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water].

Antemortem assessment was limited to mortality. Test article concentrations in plasma samples collected on Study Day 7 were determined.

There was no test-article related mortality at any dose level.

The toxicokinetic parameters are presented in [Table 2.6.6: 5].

Table 2.6.6: 5 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Female and Male Rats Following Dosing of DOR: Study Day 7 (TT #[redacted]-0019)

Dose	Sex	$AUC_{0\text{-}24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
1.5	Female	25.0 ± 4.34	1.62 ± 0.282	4.3 ± 1.7
(mg/kg b.i.d.)	Male	13.5 ± 1.69	0.966 ± 0.122	1.0 ± 0.0
	All	19.3 ± 3.31	1.29 ± 0.201	2.7 ± 1.1
15	Female	117 ± 5.96	7.02 ± 1.07	6.3 ± 0.33
(mg/kg b.i.d.)	Male	79.4 ± 6.31	5.50 ± 0.365	6.7 ± 0.33
	All	98.3 ± 9.33	6.26 ± 0.609	6.5 ± 0.22
30	Female	126 ± 21.3	9.11 ± 0.539	2.3 ± 0.88
(mg/kg/day)	Male	94.9 ± 9.24	8.33 ± 0.618	1.7 ± 0.33
	All	110 ± 12.4	8.72 ± 0.406	2.0 ± 0.45
175	Female	193 ± 25.2	13.2 ± 1.34	1.7 ± 0.33
(mg/kg/day)	Male	116 ± 14.2	9.07 ± 1.60	3.0 ± 1.5
	All	155 ± 21.6	11.1 ± 1.31	2.3 ± 0.76
175	Female	260 ± 15.7	14.9 ± 1.08	6.3 ± 0.33
(mg/kg b.i.d.)	Male	169 ± 4.20	9.61 ± 0.100	4.7 ± 1.9
	All	214 ± 21.7	12.2 ± 1.28	5.5 ± 0.92
225	Female	195 ± 16.2	13.6 ± 1.91	2.0 ± 1.0
(mg/kg/day)	Male	139 ± 2.03	9.35 ± 0.683	2.0 ± 0.0
	All	167 ± 14.1	11.5 ± 1.31	2.0 ± 0.45
225	Female	296 ± 21.0	16.1 ± 1.37	2.7 ± 1.7
(mg/kg b.i.d.)	Male	192 ± 14.4	10.6 ± 1.33	1.0 ± 0.0
	All	244 ± 26.0	13.4 ± 1.49	1.8 ± 0.83

For the b.i.d dose groups, the second daily dose was administered approximately 5 hours after the first daily dose.

Following once daily dosing of DOR, mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and mean C_{max} were less than dose proportional between 30 mg/kg/day and 175 mg/kg/day and were similar at 175 mg/kg/day and 225 mg/kg/day. Following twice daily dosing of DOR, mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and mean C_{max} were less than dose proportional between 1.5 mg/kg b.i.d. and 175 mg/kg b.i.d., and were similar at 175 mg/kg b.i.d. and 225 mg/kg b.i.d.

Exposure after 175 or 225 mg/kg/day and 175 or 225 mg/kg twice daily, respectively, were not considered meaningfully different. Following dosing at 175 mg/kg b.i.d. and 225 mg/kg b.i.d., the mean systemic exposures ($AUC_{0\text{-}24\ hr}$) were approximately only 1.5-fold greater than following dosing of 175 mg/kg/day and 225 mg/kg/day. The mean C_{max} were similar following dosing of 175 mg/kg/day, 225 mg/kg/day, 175 mg/kg b.i.d. and 225 mg/kg b.i.d.

3.2.3 Two-Week Oral Toxicity Study in Rats with a Functional Observational Battery Assay (TT #[redacted]-6029)

The purpose of this study was to evaluate the potential toxicity and toxicokinetic profile of DOR when administered to rats once daily by oral gavage for approximately 2 weeks and to assess its potential nervous system effects after the first dose (TT #[redacted]-6029) [Sec. 2.6.7.7B].

Wistar Han rats were assigned to four groups of 10 females and 10 males each that received 5, 75, or 450 mg/kg/day of DOR or control article only. DOR was used as a [redacted] formulation [consisting of [redacted]% DOR base form and [redacted]% of HPMCAS, suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water] or control article [consisting of HPMC-AS at a concentration at 180 mg/mL in 0.5% methylcellulose (the same HPMCAS polymer concentration as present in the highest tested dose of DOR [redacted] formulation) with 5 mM hydrochloric acid in deionized water] once-daily at a dosing volume of 10 mL/kg.

Assessment of toxicity was based on mortality, physical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations in treated and control groups were determined. In addition, a functional observational battery assay was conducted to evaluate potential nervous system effects in male rats after a single oral dose on Study Day 1.

There were no test article-related functional observation battery assay findings.

Antemortem test article-related findings observed at 450 mg/kg/day were limited to postdosing salivation in both sexes and the presence of crystals in the urine of females. The urinary crystals were shown to be formed ex vivo in the exploratory ten-day oral-dose urine examination study in female rats (TT #[redacted]-1095) [Sec. 2.6.6.8.7.2] and were not associated with any evidence of kidney or urinary bladder toxicity.

There were no postmortem test article-related findings.

The toxicokinetic parameters are presented in [Table 2.6.6: 6].

Table 2.6.6: 6 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Rats Following Dosing of DOR: Study Week 2 (TT #[redacted]-6029)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5	Female	45.1 ± 1.85	3.5 ± 0.288	1.0 ± NC
	Male	31.1 ± 2.36	3.15 ± 0.212	2.0 ± NC
	All	38.1 ± 2.18	3.2 ± 0.180	2.0 ± NC
75	Female	189 ± 2.47	14.8 ± 0.523	1.0 ± NC
	Male	123 ± 5.57	10.5 ± 0.768	1.0 ± NC
	All	156 ± 9.49	12.6 ± 1.04	1.0 ± NC
450	Female	272 ±17.4	16.7 ± 0.841	6.0 ± NC
	Male	194 ± 11.1	13.8 ± 0.283	6.0 ± NC
	All	233 ± 15.2	15.2 ± 0.757	6.0 ± NC

NC = Not Calculated
All DOR concentrations in plasma from control group animals at 4 hours postdose were below the lower limit of quantitation (LLQ = 0.029 µM).

There were no substantial (i.e., more than 2-fold) sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and in mean C_{max} values for DOR at all doses in Study Week 2. Absorption of DOR was rapid at 5 and 75 mg/kg/day doses in Study Week 2 with mean near C_{max} concentration or C_{max} attained within 2 hours postdose, and prolonged until 6 hours postdose at 450 mg/kg/day. Mean systemic exposure was less than dose proportional over the dose range. Mean C_{max} was less than dose proportional between 5 mg/kg/day and 75 mg/kg/day and similar between 75 mg/kg/day and 450 mg/kg/day.

Based on antemortem findings of postdosing salivation and ex vivo presence of urinary crystals, the NOEL was 75 mg/kg/day. Based on the lack of postmortem findings or adverse antemortem findings, the NOAEL for this study was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 233 µM•hr; approximately 6-fold above the DOR exposure at the human 100 mg daily dose).

3.2.4 Three-Month Oral Toxicity Study in Rats (TT #[redacted]-6040)

The purpose of this study was to determine the potential toxicity and toxicokinetic profile of DOR when administered once daily by oral gavage to rats for approximately 3 months (TT #[redacted]-6040) [Sec. 2.6.7.7C].

Crl:WI(HAN) rats were assigned to four groups of 10 females and 10 males each that received 3, 30, and 450 mg/kg/day of DOR or control article only. DOR was used as a [redacted] formulation [consisting of [redacted]% DOR base form and [redacted]% of HPMCAS, suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water] or control article [consisting of HPMCAS at a concentration at 180 mg/mL in 0.5% methylcellulose (the same

HPMCAS polymer concentration as present in the highest tested dose of DOR [redacted] formulation) with 5 mM hydrochloric acid in deionized water] once-daily at a dosing volume of 10 mL/kg.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined in all groups.

Test article-related antemortem changes at ≥30 mg/kg/day were limited to post-dose salivation in both sexes at 450 mg/kg/day, and the presence of urinary crystals in the urine of the majority of females at 450 mg/kg/day, and in a single female at 30 mg/kg/day. The urinary crystals were shown to be formed ex vivo in the exploratory ten-day oral-dose urine examination study in female rats (TT #[redacted]-1095) [Sec. 2.6.6.8.7.2] and were not associated with any evidence of kidney or urinary bladder toxicity.

There were no test article-related postmortem findings.

The toxicokinetic parameters in Study Week 13 are presented in [Table 2.6.6: 7].

Table 2.6.6: 7 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Rats Following Dosing of DOR: Study Week 13 (TT #[redacted]-6040)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
3	Female	29.7 ± 1.23	2.40 ± 0.162	1.0 ± NC
	Male	17.9 ± 0.636	1.73 ± 0.0397	1.0 ± NC
	All	23.8 ± 1.66	2.07 ± 0.168	1.0 ± NC
30	Female	136 ± 7.38	11.1 ± 0.663	2.0 ± NC
	Male	101 ± 9.31	9.85 ± 1.07	2.0 ± NC
	All	119 ± 7.04	10.5 ± 0.631	2.0 ± NC
450	Female	310 ± 20.2	22.8 ± 3.71	2.0 ± NC
	Male	195 ± 11.8	16.6 ± 1.89	1.0 ± NC
	All	253 ± 19.7	19.4 ± 1.65	1.0 ± NC

NC = Not Calculated

All MK-1439 concentrations in plasma from control group animals at 2 hours postdose were below the lower limit of quantitation (LLQ = 0.029 µM)

Rapid absorption and rapid to moderately rapid elimination of DOR in plasma were observed in Study Week 13. There were no substantial (i.e., more than 2-fold) sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and in mean C_{max} values for DOR at all doses in Study Week 13. In Study Week 13, mean systemic exposure and mean C_{max} were less than dose proportional between 3 mg/kg/day and 450 mg/kg/day, with a more pronounced effect between 30 mg/kg/day and 450 mg/kg/day.

Based on the occurrence of test article-related antemortem changes consisting of postdosing salivation and ex vivo presence of urinary crystals at ≥30 mg/kg/day in females and

450 mg/kg/day in males, the NOEL was 3 mg/kg/day in females and 30 mg/kg/day in males. Based on the lack of postmortem findings or adverse antemortem findings, the NOAEL for this study was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 253 µM•hr; approximately 6.5-fold above the DOR exposure at the human 100 mg daily dose).

3.2.5 Six-Month Oral Toxicity Study in Rats (TT #[redacted]-6019)

The purpose of this study was to determine the potential toxicity of DOR when administered orally, once daily, to rats for approximately 6 months and to evaluate the toxicokinetic profile of DOR when administered orally, once daily, to rats for approximately 3 months (TT #[redacted]-6019) [Sec. 2.6.7.7D].

Crl:WI(HAN) rats were assigned to four groups of 15 females and 15 males each that received 3, 30, or 450 mg/kg/day of DOR or control article only. DOR was used as a [redacted] formulation [consisting of [redacted]% DOR base form and [redacted]% of HPMCAS, suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water] or control article [consisting of HPMCAS at a concentration at 180 mg/mL in 0.5% methylcellulose (the same HPMCAS polymer concentration as present in the highest tested dose of DOR [redacted] formulation) with 5 mM hydrochloric acid in deionized water] once-daily at a dosing volume of 10 mL/kg.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined in DOR and control samples. In addition, exploratory urinary crystal identification was performed and exploratory semi-quantitative analysis of plasma was performed to assess levels of the M9 metabolite.

There were no test article-related unscheduled deaths. Test article-related antemortem findings were observed in males at ≥30 mg/kg/day and in females at 450 mg/kg/day. At 450 mg/kg/day, post-dose salivation was observed in both sexes. At ≥30 mg/kg/day, very slight increases in prothrombin time and activated partial thromboplastin time in males were observed [very slight, statistically significant ($p \leq 0.05$) increases in prothrombin time and activated partial thromboplastin time (+9 to +10% and +5 to +10%, respectively]. Urinary parameter findings at 450 mg/kg/day consisted of very slight transient decreases in urinary volume (-56%), very slight increases in urine specific gravity, low individual urinary pH values in females (3 out of 13 values at pH=5.5), and the presence of yellow-brown, needle-like urinary crystals in both sexes. These observations were considered non-adverse due to the slight magnitude of change, lack of correlating postmortem effects, and absence of toxicologic significance. The proton NMR spectra of the urine sediments showed that the sediment contained one major component with spectral characteristics identical to the DOR standard analyzed under the same conditions. Accurate mass and collision-induced dissociation fragmentation data obtained by liquid chromatography-mass spectrometry confirmed the identification of DOR as the urinary crystal component.

An exploratory ten-day oral-dose urine examination study in female rats (TT #[redacted]-1095) [Sec. 2.6.6.8.7.2] was conducted to further assess urinary crystals. Absence of urine crystal

observation in DOR-treated animals after urine collection by cystocentesis in vivo, despite presence of urine crystal formation from urine collected ex vivo, was confirmed in a separate investigative study in rats [Sec. 2.6.6.8.7.2].

There were no test article-related postmortem findings.

The toxicokinetic parameters are presented in [Table 2.6.6: 8].

Table 2.6.6: 8 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Rats Following Dosing of DOR: Study Week 13 (TT #[redacted]-6019)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
3	Female	25.2 ± 1.21	1.86 ± 0.0640	2.0 ± NC
	Male	13.0 ± 0.682	1.37 ± 0.102	1.0 ± NC
	All	19.1 ± 1.86	1.59 ± 0.136	1.0 ± NC
30	Female	108 ± 5.51	10.3 ±1.49	1.0 ± NC
	Male	66.7 ± 2.19	7.24 ± 0.407	1.0 ± NC
	All	87.3 ± 5.67	8.76 ± 0.969	1.0 ± NC
450	Female	352 ± 14.8	28.1 ± 0.767	2.0 ± NC
	Male	206 ± 16.6	16.0 ± 1.77	2.0 ± NC
	All	279 ± 22.0	22.0 ± 2.84	2.0 ± NC

NC = Not Calculated
DOR concentrations from all control group animals at 1 hour were below the lower limit of quantitation (LLQ = 0.029 µM) of the bioanalytical method.

Exploratory analysis was performed to assess levels of the M9 metabolite in pooled plasma samples from male and female rats from the mid- and high-dose. The data indicated that M9 is present in rat plasma. Area ratios of analyte over internal standard (PAR) was performed and indicated M9 presence in rat plasma at M9/DOR PAR ratios of 0.0028 (female) to 0.0032 (male) in the 450 mg/kg/day dose group. The data indicated that M9 was present in rat plasma at levels that were in average 52% relative to levels observed in human plasma after 10 daily administrations of 240 mg DOR. As the unbound fraction of M9 was found to be approximately 2.2-fold higher in rat plasma relative to that in human plasma, therefore unbound concentrations of M9 in rat plasma are approximately similar to those expected in humans at the clinical dose of 100 mg [Sec. 2.6.4.5.6].

Based on antemortem findings consisting of post-dose salivation and very slight to slight coagulation and urinalysis clinical pathology findings, the NOEL was 30 mg/kg/day in females and 3 mg/kg/day in males. Based on the absence of postmortem findings and lack of adverse antemortem findings, the NOAEL was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 279 µM•hr approximately 7.5-fold above the DOR exposure at the human 100 mg daily dose).

3.3 Dogs

3.3.1 Fourteen-Day Oral Toxicity Study in Dogs (TT #[redacted]-6030)

The purpose of this study was to evaluate the potential toxicity and toxicokinetic profile of DOR when administered to dogs once daily by oral gavage for 14 days (TT #[redacted]-6030) [Sec. 2.6.7.6].

Beagle dogs (two females and two males) received 10 mg/kg/day of DOR in 10% polysorbate 80 in deionized water.

Assessment of toxicity was based on mortality, physical observations, body weights, food consumption, electrocardiographic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined.

There were no antemortem or postmortem test article-related findings.

The toxicokinetic parameters are presented in [Table 2.6.6: 9] and [Table 2.6.6: 10].

Table 2.6.6: 9 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Dogs Following Dosing of 10 mg/kg/day of DOR: Study Day 1 (TT #[redacted]-6030)

Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
Female	153 ± ID	8.82 ± ID	2.0 ± ID
Male	156 ± ID	7.67 ± ID	6.0 ± ID
All	155 ± 19.3	8.24 ± 1.09	4.0 ± 1.4

ID = Insufficient Data

Table 2.6.6: 10 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Dogs Following Dosing of 10 mg/kg/day of DOR: Study Day 14 (TT #[redacted]-6030)

Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
Female	289 ± ID	17.0 ± ID	2.0 ± ID
Male	313 ± ID	14.4 ± ID	1.5 ± ID
All	301 ± 30.2	15.7 ± 1.70	1.8 ± 0.25

ID = Insufficient Data

Mean DOR systemic exposure ($AUC_{0\text{-}24\ hr}$) and mean C_{max} were approximately 1.9-fold greater on Study Day 14 than on Study Day 1.

Based on the absence of antemortem or postmortem findings, the NOEL was ≥10 mg/kg/day (Study Day 14 mean $AUC_{0\text{-}24\ hr}$: 301 µM•hr, approximately 8-fold above the DOR exposure at the human 100 mg daily dose).

3.3.2 Three-Month Oral Toxicity Study in Dogs (TT #[redacted]-6039)

The purpose of this study was to evaluate the potential toxicity and toxicokinetic profile of DOR when administered orally to dogs, once a day, for approximately 3 months (TT #[redacted]-6039) [Sec. 2.6.7.7E]. Beagle dogs were assigned to four groups of three females and three males each that received 1, 10, and 1000 mg/kg/day of DOR in 10% polysorbate 80 in deionized water, or vehicle only.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic and electrocardiographic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined in all samples.

Test article-related antemortem findings were limited to a discoloration (pale brown or white) of the feces in both sexes at 1000 mg/kg/day, most likely due to the non-absorbed whitish DOR formulation. There were no test article-related postmortem changes.

The toxicokinetic parameters are presented in [Table 2.6.6: 11] and [Table 2.6.6: 12]. There were no substantial sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) or in mean C_{max} values for DOR at 1, 10, or 1000 mg/kg/day. On Study Day 1 and in Study Week 13, mean systemic exposure and mean C_{max} were less than dose proportional between 1 mg/kg/day and 1000 mg/kg/day, with a more pronounced effect between 10 mg/kg/day and 1000 mg/kg/day. Mean systemic exposure and mean C_{max} were approximately 1.7-fold greater in Study Week 13 than on Study Day 1.

Based only on the non-adverse discoloration of the feces observed at 1000 mg/kg/day, the NOEL was 10 mg/kg/day. Based on the lack of postmortem or adverse antemortem findings, the NOAEL for this study was ≥1000 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 683 µM•hr, approximately 18-fold above the DOR exposure at the human 100 mg daily dose).

Table 2.6.6: 11 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Dogs Following Dosing of DOR: Study Day 1 (TT #[redacted]-6039)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
1	Female	38.0 ± 5.87	2.24 ± 0.250	2.7 ± 0.67
	Male	46.2 ± 6.49	2.51 ± 0.265	3.3 ± 0.67
	All	42.1 ± 4.32	2.37 ± 0.174	3.0 ± 0.45
10	Female	220 ± 52.2	11.8 ± 2.54	2.7 ± 0.67
	Male	161 ± 14.5	7.88 ± 0.783	4.7 ± 1.3
	All	190 ± 27.6	9.86 ± 1.48	3.7 ± 0.80
1000	Female	413 ± 15.0	22.5 ± 0.606	24 ± 0.0
	Male	364 ± 36.6	19.9 ± 2.72	24 ± 0.0
	All	389 ± 20.8	21.2 ± 1.37	24 ± 0.0

All MK-1439 concentrations in plasma from control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).

Table 2.6.6: 12 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Dogs Following Dosing of DOR: Study Week 13 (TT #[redacted]-6039)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
1	Female	72.8 ± 15.4	4.27 ± 0.901	2.7 ± 0.67
	Male	79.6 ± 12.2	4.46 ± 0.591	2.3 ± 0.88
	All	76.2 ± 8.91	4.37 ± 0.484	2.5 ± 0.50
10	Female	350 ± 20.8	17.9 ± 1.17	4.0 ± 1.2
	Male	295 ± 48.2	16.0 ± 2.64	2.0 ± 0.0
	All	323 ± 26.5	17.0 ± 1.36	3.0 ± 0.68
1000	Female	754 ± 59.1	36.7 ± 3.12	2.7 ± 0.67
	Male	613 ± 66.7	31.2 ± 3.02	2.7 ± 0.67
	All	683 ± 50.8	34.0 ± 2.30	2.7 ± 0.42

All MK-1439 concentrations in plasma from control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).

3.3.3 Nine-Month Oral Toxicity Study in Dogs (TT #[redacted]-6018)

The purpose of this study was to evaluate the potential toxicity profile of DOR in dogs when administered orally once daily for 9 months, and to evaluate the toxicokinetic profile of DOR when administered once daily for approximately 3 months (TT #[redacted]-6018) [Sec. 2.6.7.7F].

Beagle dogs were assigned to four groups of four females and four males each that received 1, 10, and 1000 mg/kg/day of DOR or vehicle only.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic and electrocardiographic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations were determined in all samples.

There were no test article-related unscheduled deaths. Test article-related clinical signs observed at all dose levels (both sexes) consisted of discoloration of feces and sporadic increased incidence of unformed stools. Sporadic salivation was observed at 1000 mg/kg/day in both sexes and in males at 10 mg/kg/day and 1 mg/kg/day. At doses ≥ 10 mg/kg/day, transient unilateral or bilateral clear eye discharge was sporadically observed during the study. These findings were not considered adverse as it did not impact the health status of the animals and did not correlate with postmortem findings.

Upon postmortem evaluation, there were no test article-related gross, organ weight or histomorphologic changes at final necropsy.

The toxicokinetic parameters are presented in the [Table 2.6.6: 13] and [Table 2.6.6: 14].

Table 2.6.6: 13 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Dogs Following Dosing of DOR: Study Day 1 (TT #[redacted]-6018)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
1	Female	37.9 ± 2.13	2.06 ± 0.137	4.5 ± 0.96
	Male	40.1 ± 3.25	2.16 ± 0.127	4.8 ± 1.3
	All	39.0 ± 1.85	2.11 ± 0.0886	4.6 ± 0.73
10	Female	205 ± 22.7	10.4 ± 1.11	4.5 ± 1.3
	Male	169 ± 24.0	8.43 ± 1.38	6.0 ± 0.82
	All	187 ± 16.7	9.39 ± 0.896	5.3 ± 0.75
1000	Female	518 ± 77.6	24.8 ± 3.16	11 ± 4.6
	Male	579 ± 11.5	27.5 ± 1.04	7.5 ± 0.50
	All	548 ± 38.1	26.1 ± 1.62	9.0 ± 2.2

Table 2.6.6: 14 Summary Mean (±SE) Plasma Toxicokinetic Parameters in Dogs Following Dosing of DOR: Study Week 13 (TT #[redacted]-6018)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
1	Female	80.7 ± 9.03	4.14 ± 0.535	4.5 ± 0.96
	Male	83.8 ± 10.3	4.39 ± 0.522	4.5 ± 0.50
	All	82.2 ± 6.35	4.27 ± 0.349	4.5 ± 0.50
10	Female	365 ± 35.6	18.5 ± 1.69	2.8 ± 0.75
	Male	402 ± 14.5	19.9 ± 0.621	4.0 ± 0.82
	All	383 ± 19.1	19.2 ± 0.873	3.4 ± 0.56
1000	Female	643 ± 60.9	30.7 ± 2.57	3.3 ± 1.1
	Male	704 ± 9.28	34.8 ± 0.502	5.0 ± 0.58
	All	673 ± 30.8	32.7 ± 1.44	4.1 ± 0.67

Exploratory semi-quantitative analysis was performed to assess levels of the M9 metabolite in pooled plasma samples from male and female dogs from the mid- and high-dose. The data indicated that M9 is present in dog plasma. Area ratios of analyte over internal standard (PAR) were performed and indicated M9 presence in dog plasma at M9/DOR PAR ratios of 0.0034 in females and 0.0035 in males in the 1000 mg/kg/day dose group. The data indicated that M9 was present in dog plasma at levels that were up to 51% relative to levels observed in human plasma after 10 daily administrations of 240 mg DOR [Sec. 2.6.4.5.6]. In addition, the unbound fraction of M9 in dog plasma was found to be approximately 2.8-fold relative to that in human plasma. Therefore, unbound concentrations of M9 in dog plasma are approximately greater than those expected in humans at the clinical dose of 100 mg.

The NOEL was <1 mg/kg/day based on antemortem observations of discolored feces and sporadic increased incidence of unformed stool and salivation. Based on the absence of postmortem findings and lack of adverse antemortem findings, the NOAEL was

≥1000 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 673 µM•hr, approximately 18-fold above the DOR exposure at the human 100 mg daily dose).

4 GENOTOXICITY

DOR was not mutagenic or genotoxic in a standard core battery of *in vitro* [Sec. 2.6.7.8A], [Sec. 2.6.7.8B] and *in vivo* [Sec. 2.6.7.9A], [Sec. 2.6.7.9B] genetic toxicity assays conducted in accordance with ICH S2 [R1] *Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*.

4.1 In Vitro

4.1.1 Microbial Mutagenesis Assay (TT #[redacted]-8021, TT #[redacted]-8099, and TT #[redacted]-8113)

DOR was evaluated for mutagenic potential in a microbial mutagenesis test system using mutant strains of *Salmonella typhimurium* (TA1535, TA97a, TA98, and TA100) and *Escherichia coli* (WP2 uvrA pKM101) [Sec. 2.6.7.8A]. In this test system, mutation was measured as reversion to histidine prototrophy of *Salmonella* test strains which are histidine auxotrophs and as reversion to tryptophan prototrophy of an *E. coli* test strain which is a tryptophan auxotroph. The test article was tested with and without a liver S-9 activation system prepared from rats treated with phenobarbital and beta-naphthoflavone. The human metabolite M9 was demonstrated to be formed by the liver S-9 activation system. The test article was tested using triplicate plates with and/or without metabolic activation for each strain tested.

DOR was used as a solution in dimethyl sulfoxide (DMSO). The final concentrations tested were 30 (TT #[redacted]-8021 only), 100, 300, 1000, 3000 and 5000 µg/plate with and without S-9 metabolic activation. The high dose was the limit dose per ICH S2(R1) guidance.

The results of the exploratory Microbial Mutagenesis Assay (TT #[redacted]-8021) indicated that DOR did not produce any 2-fold or greater increases in revertants relative to control. The positive control compound, 2-aminoanthracene (2AA), produced the expected increases in revertants in all test strains in the presence of metabolic activation. Precipitate was seen on the plates at test concentrations of 300 µg/plate or higher and interfered with scoring of the plates at 5000 µg/plate in most test strains. No inhibition of bacterial lawn growth was noted at any concentration tested. Inhibition of revertant growth was noted at some doses in TA97a without metabolic activation and in TA98 with metabolic activation.

To confirm these negative results, a second Microbial Mutagenesis Assay (TT #[redacted]-8099) was performed. The results confirmed that DOR did not produce any 2-fold or greater increases in revertants relative to control. The positive control and diagnostic mutagens showed appropriate S-9- and strain-dependent increases in revertants. Precipitate was seen on the plates at test concentrations of 300 µg/plate or higher and interfered with scoring of the plates without metabolic activation at 5000 µg/plate in most test strains and at 3000 µg/plate in the *E. coli* strain. No inhibition of bacterial lawn growth was noted at any concentration tested. Inhibition of revertant growth was noted at some doses in TA100;

however, the spontaneous revertant rate was outside the historical range for this strain. This strain was repeated.

The results for the repeat assay of TA100 (TT #[redacted]-8113) confirmed that DOR did not produce any 2-fold or greater increases in revertants relative to control. The positive control and diagnostic mutagens showed appropriate S-9- and strain-dependent increases in revertants. Precipitate was seen on the plates at test concentrations of 1000 µg/plate or higher, but did not interfere with scoring of the plates. No inhibition of bacterial lawn or revertant growth was noted at any concentration tested.

DOR did not induce 2-fold or greater dose-related increases in revertants relative to the solvent control in any of the test strains in 2 separate assays and thus is not detectably mutagenic in the Microbial Mutagenesis Assay.

4.1.2 Assay for Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells (TT #[redacted]-8662 and TT #[redacted]-8666)

DOR was evaluated for its potential to cause chromosomal aberrations in Chinese hamster ovary (CHO) cells (subclone WBL) [Sec. 2.6.7.8B].

DOR was prepared as a solution in Dimethyl Sulfoxide (DMSO) and diluted 100-fold into medium. DOR was tested with and without a metabolic activation system (S-9) prepared from the livers of rats treated with beta-naphthoflavone and phenobarbital. A range-finding assay was done to select a dose range for the chromosome aberration assay. Cytotoxicity was assessed as reductions in cell growth or monolayer confluence. The range-finding and aberration assays involved two treatment durations; 3-hour treatment with or without S-9 and a continuous treatment without S-9 (about 20 hours). The concurrent solvent control cells were treated with 1% v/v DMSO. Positive controls (cyclophosphamide with S-9 activation or mitomycin C without S-9) were included. The cells were fixed for analysis of chromosome aberrations about 20 hours from the beginning of treatment (about 1.5 normal cell cycle lengths).

Precipitate was found in the range-finding assay, TT #[redacted]-8662, and the top doses for the chromosomal aberration assay were based on test article solubility in cultures.

In the chromosomal aberration assay, TT #[redacted]-8666, the top doses of DOR scored for aberrations were selected such that reductions in cell growth did not greatly exceed about 50% of concurrent solvent controls, and to test to the limit of test article solubility in cultures. The treatment levels of DOR scored for aberrations were 200, 250, and 300 µM with and without S-9 (3-hour treatments) or 100, 150, and 200 µM after the 20-hour treatment without S-9. At the top doses scored, precipitate was evident with and without S-9 and cell growth at 20 hours was 98, 92, and 74% of concurrent solvent controls, respectively.

The high-dose positive controls induced significant increases in aberrations over the concurrent solvent controls. There was no increase in structural chromosome aberrations, so that the assay of DOR was negative.

4.2 In Vivo

4.2.1 Assay for Micronucleus Induction in Rat Bone Marrow from an Exploratory 7-Day Oral Tolerability Study (TT #[redacted]-8707)

DOR was negative in the micronucleus test in the bone marrow of female rats up to 750 mg/kg/day (given as 375 mg/kg/bid) [Sec. 2.6.7.9A]. The frequencies of micronucleated polychromatic erythrocytes (MN-PCE) for each treatment group were within the historical range for vehicle control-treated females. There was also no apparent effect of DOR on the proportions of PCE among total erythrocytes in the bone marrow.

4.2.2 Assay for Micronucleus Induction in Rat Bone Marrow from a 2-Week Oral Toxicity Study (TT #[redacted]-8725)

DOR was tested to determine its potential to induce micronuclei in bone marrow polychromatic erythrocytes [Sec. 2.6.7.9B] of female and male rats from the oral toxicity study TT #[redacted]-6029 [Sec. 2.6.6.3.2.3].

Female and male Crl:WI(HAN) rats, approximately 10 weeks old at start of the toxicity study, received a once daily oral dose of 5, 75, or 450 mg/kg of DOR or the control article, HPMCAS-LF polymer in 0.5% (w/v) Methylcellulose with 5 mM hydrochloric acid in deionized water, for at least 14 days. The high dose was the maximum feasible dose.

Rats were sacrificed for harvest of bone marrow cells the day after their final dose in this 16 day duration study. Slides were prepared from bone marrow cells that were harvested at sacrifice and stained with acridine orange. Positive control slides from male rats previously treated with mitomycin C were included in the coded slides scored. Two thousand polychromatic erythrocytes (PCE) per rat were scored for micronuclei (MN-PCE) from coded slides from 10 control article treated rats per sex, each of five low- and high-dose positive control male rats, and from each of five DOR treated rats per group per sex. The frequencies of PCE and of mature, normochromatic erythrocytes (NCE) were also recorded among 1000 erythrocytes per rat.

The dose levels of DOR scored for micronuclei were 5, 75, and 450 mg/kg/day for both males and females. The study was negative. The frequencies of micronucleated PCE (MN-PCE) for each DOR treatment group were similar to the concurrent controls and within the range for historical vehicle controls. There was also no apparent effect on the proportions of PCE among total erythrocytes in the bone marrow. The NOEL for micronucleus induction was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 233 µM•hr; approximately 6-fold above the DOR exposure at the human 100 mg daily dose).

5 CARCINOGENICITY

To assess the carcinogenicity potential of DOR, transgenic Tg.rasH2 mice and Wistar Hannover rats were administered DOR as a [redacted] formulation at three dose levels, with at least two identically treated control groups (HPMCAS in vehicle) via oral gavage, once a day for 6 months and 24 months, respectively. In rats, an additional 0.5% methylcellulose

control group was used for comparison to the two HPMCAS control groups. In the transgenic mouse study, a positive control (urethane) was used. DOR exposures attained in these studies reflected maximum achievable systemic exposures in test species and exceeded those exposures expected clinically at the 100 mg dose.

The top dose chosen in the 2 year rat carcinogenicity bioassay was considered to be the maximal feasible oral dose (MFD), based on the maximum daily dose volume (10 ml/kg) and maximum feasible concentration of 45 mg/mL for the [redacted] formulation, administered to adult animals. There were no adverse test article-related findings in rats treated with DOR (3, 30 or 450 mg/kg) for 3 or 6 months. The doses for the 6-month carcinogenicity study in Tg.rasH2 mice were 10, 60 and 300 mg/kg/day. Data to support dose selection for the 6-month carcinogenicity study in Tg.rasH2 transgenic mice was provided by a 4-week oral gavage study in Jic:CB6F1-nonTgrasH2@Jcl (hybrid, wild-type littermates) mice at DOR doses of 30, 100, 300 or 450 mg/kg (TT #[redacted]-6010) [Sec. 2.6.6.3.1.1]. There were no test article-related adverse findings in the study. The NOAEL was 450 mg/kg. Saturation of exposure was observed between 300 and 450 mg/kg; these data were used to set the proposed high dose of 300 mg/kg in the 6-month Tg.rasH2 transgenic mouse carcinogenicity study.

5.1 Six-Month Oral Carcinogenicity Study in rasH2 Transgenic Mice (TT #[redacted]-6005)

The purpose of this study was to evaluate the potential carcinogenicity of DOR when administered daily, by oral gavage to rasH2 transgenic mice for approximately 6 months (TT #[redacted]-6005) [Sec. 2.6.7.10A].

Jic:CB6F1-TgrasH2@Jcl mice were assigned to five groups of 25 females and 25 males each that received 10, 60, and 300 mg/kg/day of DOR or control article only (two control groups of 25 mice/sex/group). The amount of HPMCAS administered to the control groups (1200 mg/kg/day) was equivalent to the amount of polymer present in the high-dose group formulation. In addition, a positive control group of 10 females and 10 males was given urethane in 0.9% sodium chloride at 1000 mg/kg, by the intraperitoneal route, once a day, on Study Days 1, 3, and 5. In the six study groups, 2 mice/sex/group were added to be used as potential replacement animals during the first 2 weeks. Unused replacement animals were sacrificed and discarded without postmortem examination after the first 2 weeks.

Assessment of toxicity or carcinogenicity was based on mortality, clinical observations (including palpation for presence of masses except in the positive control group), body weights, and anatomic pathology evaluations. DOR concentrations in plasma samples from DOR-treated and control animals were determined.

There were no test article-related unscheduled deaths and no test article-related findings in clinical observations or body weights.

There was no test article-related increase in mortality and no evidence of a carcinogenic potential in any sex up to 300 mg/kg/day.

The toxicokinetic parameters are presented in the following table [Table 2.6.6: 15].

Table 2.6.6: 15 Summary Mean (± SE) Plasma DOR Toxicokinetic Parameters in Mice Following Dosing of DOR: Study Week 27 (TT #[redacted]-6005)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
10	Female	40.0 ± 3.98	10.8 ± 1.67	0.50 ± NC
	Male	33.5 ± 5.35	8.24 ± 0.861	0.50 ± NC
	All	36.7 ± 3.36	9.51 ± 1.01	0.50 ± NC
60	Female	123 ± 16.6	20.5 ± 3.50	0.50 ± NC
	Male	79.3 ± 7.13	18.9 ± 1.08	1.0 ± NC
	All	98.0 ± 10.7	19.2 ± 1.91	0.50 ± NC
300	Female	273 ± 24.2	40.1 ± 2.01	2.0 ± NC
	Male	182 ± 12.6	37.7 ± 1.83	1.0 ± NC
	All	228 ± 19.9	33.6 ± 2.15	1.0 ± NC

NC = Not calculated
DOR concentrations in plasma from all control mice at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.00935 µM) of the bioanalytical method.

There were no substantial (i.e., greater than 2-fold) sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) to DOR or mean C_{max} at any dose in Study Week 27. Mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and mean C_{max} were less than dose proportional between 10 mg/kg/day and 300 mg/kg/day.

In conclusion, there were no test article-related antemortem or postmortem findings, no test article-related increase in mortality, and no evidence of a carcinogenic potential up to 300 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 228 µM•hr; approximately 6-fold above the DOR exposure at the human 100 mg daily dose) after 6 months of daily oral administration of DOR.

5.2 Two-Year Oral Carcinogenicity Study in Rats with a Six-Month Toxicokinetic Evaluation (TT #[redacted]-6029)

The purpose of this study was to determine the potential carcinogenicity and toxicokinetic profile of DOR when administered chronically, once daily, to rats by oral gavage (TT #[redacted]-6029) [Sec. 2.6.7.10B].

Crl:WI(Han) rats were assigned to nine groups separated into carcinogenicity and toxicokinetics study arms. Groups 1 to 5 (carcinogenicity arm) included 50 females and 50 males each that received 3, 30, or 450 mg/kg/day of DOR. The two control groups received the control article equivalent to the amount present in the formulation administered to the 450 mg/kg/day DOR dose group. Groups 6 to 9 (toxicokinetics arm) included

4 animals/sex that received 3, 30, or 450 mg/kg/day of DOR or control article as described above.

Assessment of toxicity or carcinogenicity was based on mortality, clinical observations, palpable masses, body weights, and anatomic pathology evaluations. Plasma DOR concentrations were determined in Study Weeks 14 and 27 in treated and control samples. In addition, exploratory non-GLP semi-quantitative metabolite analysis for assessment of DOR M9 metabolite was performed by high performance liquid chromatography coupled with high resolution mass spectrometry (HPLC-HRMS) in plasma and urine samples from 30 and 450 mg/kg/day groups.

There was no statistically significant effect on unscheduled death rate.

Test article-related antemortem findings were limited to intermittent salivation in both sexes at 450 mg/kg/day and were considered of minimal toxicologic significance.

There was no DOR-related increased tumor incidence. Test article-related non-neoplastic changes were limited to very slight centrilobular hypertrophy of hepatocytes in the livers from males at 450 mg/kg/day which, in the absence of associated degenerative, neoplastic or preneoplastic liver changes, were considered of minimal toxicologic significance.

The plasma concentrations are presented in the following tables [Table 2.6.6: 16] and [Table 2.6.6: 17].

Table 2.6.6: 16 Summary Mean (± SE) Plasma DOR Concentrations (µM) in Rats Following Dosing of DOR: Study Week 14 (TT #[redacted]-6029)

			Time (hr)	
Week	**Dose (mg/kg/day)**	**Sex**	**1**	**24**
14	3	Female	3.10 ± 0.215	0.431 ± 0.0695
		Male	2.67 ± 0.183	0.0871 ± 0.0162
		All	2.89 ± 0.158	0.259 ± 0.0833
	30	Female	16.9 ± 1.23	1.82 ± 0.196
		Male	12.6 ± 0.736	0.412 ± 0.0504
		All	14.7 ± 1.15	1.12 ± 0.328
	450	Female	47.5 ± 4.11	2.73 ± 0.231
		Male	31.1 ± 2.43	2.01 ± 1.15
		All	39.3 ± 4.25	2.37 ± 0.548

DOR concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.0284 µM) of the bioanalytical method.

Table 2.6.6: 17 Summary Mean (± SE) Plasma DOR Concentrations (µM) in Rats Following Dosing of DOR: Study Week 27 (TT #[redacted]-6029)

			Time (hr)	
Week	**Dose (mg/kg/day)**	**Sex**	**1**	**24**
27	3	Female	3.23 ± 0.150	0.461 ± 0.0355
		Male	3.16 ± 0.0609	0.118 ± 0.00713
		All	3.20 ± 0.0740	0.290 ± 0.0783
	30	Female	15.9 ± 1.14	2.16 ± 0.139
		Male	13.0 ± 1.22	0.666 ± 0.146
		All	14.4 ± 0.992	1.41 ± 0.346
	450	Female	44.1 ± 1.72	3.08 ± 0.289
		Male	32.8 ± 1.15	2.33 ± 0.816
		All	38.4 ± 2.68	2.71 ± 0.421

DOR concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.0287 µM) of the bioanalytical method.

Mean DOR plasma concentrations at 1 hour and 24 hours postdose (identified as C_{max} and C_{min} timepoints from the toxicokinetics results from a previous chronic DOR rat toxicity study) increased in a dose related manner and were similar in Study Weeks 14 and 27. Following HPLC-HRMS analysis, the data indicated that metabolite M9 is present in plasma from males and females at 1 hour and 24 hours (except for females at 24 hours in the 30 mg/kg/day group). M9 was also present in urine; the concentrations of M9 in rat urine samples were above 10 µM at both 30 and 450 mg/kg/day dose levels.

In conclusion, the NOEL was ≥450 mg/kg/day for neoplastic changes, and the NOAEL was ≥450 mg/kg/day for non-neoplastic changes in this study. Based on assessment of DOR C_{min} and C_{max} exposures in this study, the projected AUC exposures would have equaled or exceeded that achieved in the chronic rat toxicity study [Sec. 2.6.6.3.2.5]; ≥7.5-fold above the DOR AUC exposure at the human 100 mg daily dose.

6 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Developmental and reproductive toxicology studies conducted with DOR included a male and female rat fertility study, embryo-fetal developmental toxicity studies in rats and rabbits, a pre- and post-natal toxicity study in rats, and juvenile toxicity studies in rats. The high dose of the studies conducted in rats was the maximum feasible dose of DOR in the [redacted] formulation. The toxicokinetic profile of DOR in rabbits was evaluated in exploratory oral single-dose and multiple dose toxicokinetic studies preceding the pivotal rabbit embryo-fetal studies. In rabbits, the DOR [redacted] formulation showed superior exposures (AUC) at lower dose levels when compared to the DOR base compound; a plateau in exposure was

demonstrated to occur at [redacted] formulation doses ≥300 mg/kg/day DOR. Consequently, 300 mg/kg/day was selected as the high dose of the pivotal embryofetal developmental study in rabbits.

There were no developmental toxicities identified in rat or rabbit embryofetal developmental studies or in the rat pre-postnatal developmental study at any dose levels tested. In the rabbit embryo-fetal developmental toxicity and toxicokinetic study, the top dose of 300 mg/kg/day resulted in DOR AUC exposures of 315 µM•hr (approximately 8.5-fold above the DOR exposure at the human 100 mg daily dose); in the rat embryo-fetal developmental toxicity and toxicokinetic study, AUC exposure at the top dose of 450 mg/kg/day DOR was 345 µM•hr (approximately 9-fold above the DOR exposure at the human 100 mg daily dose). No reproductive toxicity was observed in the oral male and female rat fertility study (where doses up to 450 mg/kg/day were evaluated), and no juvenile toxicity was observed in rats up to the top dose tested of 300 mg/kg/day (maximum feasible dose for juvenile rats).

6.1 Fertility and Early Embryonic Development

6.1.1 Oral Fertility Study in Female and Male Rats (TT #[redacted]-7300)

The potential effects of DOR on the fertility of F0 female and male rats were evaluated following once daily oral administration for 15 days prior to cohabitation, during cohabitation, and through Gestation Day (GD) 7 for the females and until the day prior to scheduled sacrifice for the males (approximately 6 weeks total) (TT #[redacted]-7300) [Sec. 2.6.7.12].

CRL:WI(HAN) rats were assigned to four groups of 20 rats per sex each that received 5, 30, or 450 mg/kg/day of DOR, supplied as [redacted] form, in 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water or hydroxypropyl methylcellulose acetate succinate (HPMCAS) polymer in vehicle. One additional group of 20 females and 20 males was untreated throughout the duration of the study and served as mating partners for the high-dose males and females, respectively, during the cohabitation interval. The dosing volume for all animals was 10 mL/kg.

Assessment of toxicity in the females and males was based on mortality, physical signs, body weights, food consumption, and gross examination of the thoracic and abdominal viscera. For the evaluation of mating and reproductive performance, females were housed with males in a 1:1 ratio following 15 days of treatment for a maximum of 20 nights. The high-dose females were housed with untreated males, high-dose males were housed with untreated females, while the females from the control, low-dose, and mid-dose groups were housed with the males from the corresponding dose group. On GD 15 to 17, mated females were euthanized, uterine contents were examined for embryonic/fetal viability, and corpora lutea were counted. Assessment of reproductive toxicity in males also included evaluations of sperm count, sperm motility, and testicular weights.

There were no test article-related deaths, physical signs, changes in mean body weight gain or food consumption, or gross examination findings.

There was no test article-related reproductive toxicity at any dose level.

Based on the absence of findings, the NOEL for general toxicity and for fertility parameters in female and male rats was ≥450 mg/kg/day. Based on female and male rats in general toxicity studies at the 450 mg/kg/day NOEL dose [Sec. 2.6.6.3.2], the following DOR systemic exposures were considered attained: $AUC_{0\text{-}24\ hr}$: 279 µM•hr, approximately 7.5-fold above the DOR exposure at the human 100 mg daily dose.

6.2 Embryo-fetal Development

6.2.1 Exploratory Oral Range-Finding Toxicity Study in Pregnant Rats (TT #[redacted]-7045)

The purpose of this study was to evaluate the potential for developmental toxicity of DOR ([redacted] formulation) in rats following oral administration on Gestation Days (GD) 6 through 20 (TT #[redacted]-7045) [Sec. 2.6.7.11].

On GD 0 (day of confirmed breeding), female Crl:WI(HAN) rats were assigned to four groups of six presumed pregnant females each. From GD 6 through 20, females received 5, 45, or 450 mg/kg/day of DOR, supplied as the [redacted] formulation or the control article only in the same vehicle. The amount of HPMCAS administered to the control animals was the same as the amount present in the 450 mg/kg/day dose. The dosing volume for all animals was 10 mL/kg.

Assessment of maternal toxicity was based on mortality, physical signs, body weights, and food consumption. On GD 21, all females were euthanized and uterine contents examined. Number of corpora lutea and gross placental morphology were evaluated. Assessment of developmental toxicity was based on embryonic/fetal viability, fetal weights, sex ratios, and external fetal morphology.

There were no unscheduled deaths. There were no test article-related physical signs or changes in mean maternal body weight gain or mean food consumption. There was no evidence of developmental toxicity at any dose level.

In conclusion, there was no evidence of maternal or developmental toxicity in rats up to the maximum feasible dose of 450 mg/kg/day in the exploratory range-finding study.

6.2.2 Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats (TT #[redacted]-7040)

The potential developmental toxicity of DOR was evaluated in rats following oral administration from Gestation Days (GD) 6 through 20 (TT #[redacted]-7040) [Sec. 2.6.7.13A]. In addition, the toxicokinetic profile of DOR was evaluated on GD 15.

On GD 0 (day of confirmed breeding), presumed pregnant female Crl:WI(HAN) rats were assigned into three groups of 28 females each and one control group of 24 females. From GD 6 through 20, females received 5, 45, or 450 mg/kg/day of DOR, supplied as the [redacted]

[redacted] formulation of DOR or the control article only in the same vehicle. The amount of HPMCAS administered to the control animals was the same as the amount present in the 450 mg/kg/day dose. The dosing volume for all animals was 10 mL/kg.

Assessment of maternal toxicity was based on mortality, physical signs, body weights, food consumption, and gross examination. Plasma drug concentrations in samples from non-fasted treated and control female rats were determined on GD 15; these animals were euthanized after the last sample was collected. On GD 21, all surviving females (18 to 20/group) were euthanized and uterine contents examined. Number of corpora lutea and gross placental morphology were evaluated. Assessment of developmental toxicity was based on embryonic/fetal viability, fetal weights, sex ratios, and external, visceral, coronal, and skeletal morphology, the latter by evaluation of both alizarin red stained and micro computed tomography scanned specimens.

There were no test article-related unscheduled deaths at any dose level.

There were no test article-related physical signs or changes in mean maternal body weight gain, mean food consumption, or gross findings.

There was no evidence of developmental toxicity at any DOR dose level. The toxicokinetic parameters are presented in [Table 2.6.6: 18].

Table 2.6.6: 18 Summary Mean (±SE) Maternal Plasma DOR Toxicokinetic Parameters in Rats Following Dosing of DOR: Gestation Day 15 (TT #[redacted]-7040)

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5	61.2 ± 2.50	5.08 ± 0.592	1.0 ± NC
45	243 ± 8.14	18.5 ± 0.222	2.0 ± NC
450	345 ± 16.3	26.1 ± 0.716	2.0 ± NC

NC = Not Calculated

All MK-1439 concentrations in maternal plasma from control group animals at 4 hours postdose were below the lower limit of quantitation (LLQ = 0.029 µM).

Based on the results of this study, the NOEL for both maternal and developmental toxicity were ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 345 µM•hr; approximately 9-fold above the DOR exposure at the human 100 mg daily dose).

6.2.3 Exploratory Oral Single-Dose Toxicokinetic Study in Nonpregnant Rabbits (TT #[redacted]-7206)

The objective of this study was to determine the toxicokinetic profile of DOR following single dose oral administration of the base compound to nonpregnant rabbits (TT #[redacted]-7206) [Sec. 2.6.7.11].

Twelve Dutch Belted female rabbits were assigned to four groups of three animals each. Female rabbits received a single dose of 1, 10, 100, or 1000 mg/kg of the base form of DOR in 10% polysorbate 80 in deionized water. The dosing volume for all animals was 5 mL/kg.

The rabbits were observed for mortality daily. Plasma drug concentrations were evaluated.

All rabbits survived until study termination and were returned to the animal colony.

The toxicokinetic parameters of DOR are presented in [Table 2.6.6: 19].

Table 2.6.6: 19 Mean Plasma DOR Toxicokinetic Parameters in Nonpregnant Rabbits – Single Dose (TT #[redacted]-7206)

	DOR (mg/kg)			
	1	10	100	1000
$AUC_{0\text{-}24\ hr}$ (μM•hr)[a]	10.3 ± 1.44	29.1 ± 2.17	63.3 ± 7.38	80.5 ± 11.3
C_{max} (μM)[a]	0.755 ± 0.12	2.13 ± 0.07	3.24 ± 0.21	4.14 ± 0.59
T_{max} (hr)[a]	2.3 ± 0.88	1.0 ± 0.0	9.0 ± 7.5	16 ± 7.7
[a] Mean ± SEM.				

6.2.4 Exploratory Oral Single-Dose Toxicokinetic Study in Nonpregnant Rabbits (TT #[redacted]-7207)

The objective of this study was to determine the toxicokinetic profile of DOR administered orally as a single dose of the [redacted] formulation to nonpregnant rabbits (TT #[redacted]-7207) [Sec. 2.6.7.11].

Twelve Dutch Belted female rabbits were assigned to four groups of three animals each. Female rabbits received a single dose of 15, 50, 150, or 450 mg/kg of the [redacted] form of DOR. The dosing volume for all animals was 10 mL/kg. The 450 mg/kg dose was the maximum feasible dose in this vehicle for this species.

The rabbits were observed for mortality daily. Plasma drug concentrations were evaluated.

All rabbits survived until study termination and were returned to the animal colony.

The toxicokinetic parameters of DOR are presented in [Table 2.6.6: 20].

Table 2.6.6: 20 Mean Plasma DOR Toxicokinetic Parameters in Nonpregnant Rabbits – Single Dose (TT #[redacted]-7207)

	DOR (mg/kg)			
	15	50	150	450
$AUC_{0\text{-}24\ hr}$ (µM•hr)[a]	156 ± 12.8	385 ± 52.3	335 ± 46.5	433 ±46.7
C_{max} (µM)[a]	11.2 ± 1.06	29.4 ± 3.99	21.7 ± 5.13	26.1 ± 2.04
T_{max} (hr)[a]	3.0 ± 1.0	1.0 ± 0.0	1.3 ± 0.33	4.7 ± 0.67
[a] Mean ± SEM.				

6.2.5 Exploratory Five-Day Oral Toxicokinetic Study in Nonpregnant Rabbits (TT #[redacted]-7277)

The objective of this study was to determine the toxicokinetic profile of DOR in nonpregnant rabbits following oral administration of a [redacted] formulation once daily for 5 days (TT #[redacted]-7277) [Sec. 2.6.7.11].

Fifteen Dutch Belted female rabbits were assigned to five groups of three animals each. Female rabbits received five DOR doses of 15, 50, 150, 300, or 450 mg/kg/day of the [redacted] formulation. The dosing volume for all animals was 10 mL/kg. The 450 mg/kg/day dose was the maximum feasible dose in this vehicle for this species.

The rabbits were observed for mortality daily. Plasma drug concentrations were evaluated.

All rabbits survived until study termination and were returned to the animal colony.

The toxicokinetic parameters of DOR are presented in [Table 2.6.6: 21].

Table 2.6.6: 21 Summary Mean (± SE) Plasma DOR Toxicokinetic Parameters in Rabbits Following Dosing of DOR: Study Day 5 (TT #[redacted]-7277)

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
15	107 ± 15.4	6.93 ± 1.09	4.0 ± 1.2
50	218 ± 3.81	13.5 ± 0.474	4.0 ± 1.2
150	291 ± 35.7	19.6 ± 2.77	1.7 ± 0.33
300	364 ± 53.4	20.7 ± 3.73	4.0 ± 0.0
450	336 ± 57.8	20.4 ± 2.47	4.7 ± 0.67

6.2.6 Exploratory Oral Range-Finding Toxicity Study in Pregnant Rabbits (TT #[redacted]-7055)

The purpose of this study was to evaluate the potential for developmental toxicity of DOR in rabbits following oral administration on Gestation Days (GD) 7 through 20 (TT #[redacted]-7055) [Sec. 2.6.7.11].

On GD 0 (day of confirmed breeding) female Dutch Belted rabbits were assigned to four groups of six presumed pregnant females in each group. From GD 7 through 20 females received 1, 15, or 450 mg/kg/day of DOR [redacted] formulation. The control group received 1800 mg/kg/day of the HPMCAS polymer in the same vehicle, the same amount of the polymer administered to the high-dose group. The dosing volume for all animals was 10 mL/kg.

Assessment of maternal toxicity was based on mortality, physical signs, body weights, and food consumption. On GD 28, all surviving females were euthanized and uterine contents examined. Number of corpora lutea and gross placental morphology were evaluated. Assessment of developmental toxicity was based on embryonic/fetal viability, fetal weights, and external fetal morphology.

There were no test article-related deaths. There were no test article-related physical signs or changes in mean maternal body weight gain or mean food consumption.

Non-test article related findings included two early sacrifices of pregnant females in the control group on GDs 15 and 17, and an early sacrifice of a pregnant female in the 450 mg/kg/day group on GD 17 due to excessive body weight loss. One rabbit in each of the control, 15 mg/kg/day and 450 mg/kg/day dose levels were determined not to have been pregnant, further limiting the number of litters that could be evaluated on the study.

There was no test article-related developmental toxicity at any dose level. In the 450 mg/kg/day group there was a slight decrease in mean fetal body weight (8.5% below control) and one litter with external findings consisting of open eyelids and cleft palate. These findings were not considered to be related to treatment due to the small number of litters evaluated at this dose level and in the control group (i.e., four and three litters, respectively).

Based on the results of this exploratory range-finding study, and accounting for the small number of litters able to be evaluated at 450 mg/kg/day and control groups in this study, there was no evidence of DOR-related maternal or developmental toxicity in rabbits.

6.2.7 Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits (TT #[redacted]-7050)

The potential developmental toxicity of DOR was evaluated in rabbits following oral administration from Gestation Days (GD) 7 through 20 (TT #[redacted]-7050) [Sec. 2.6.7.13B]. In addition, the toxicokinetic profile of DOR was evaluated on GD 15.

On GD 0 (day of confirmed breeding) female Dutch Belted rabbits were assigned to four groups of 22 presumed pregnant females each. From GD 7 through 20 females received 2, 15, or 300 mg/kg/day of the [redacted] form of DOR or control article only. The dosing volume for all animals was 10 mL/kg.

Assessment of maternal toxicity was based on mortality, physical signs, body weights, food consumption, and gross examination. Plasma drug concentrations in samples from non-fasted treated and control female rabbits were determined on GD 15; these animals were euthanized after the last sample was collected. On GD 28, surviving females were euthanized and uterine contents examined. Number of corpora lutea and gross placental morphology were evaluated. Assessment of developmental toxicity was based on embryonic/fetal viability, fetal weights, sex ratios; and fetal external, visceral, and skeletal morphology, the latter by evaluation of both alizarin red stained and micro computed tomography (micro-CT) scanned specimens.

There were no test article-related deaths. There were no test article-related physical signs or changes in mean food consumption. At 300 mg/kg/day there was a decrease in mean maternal body weight gain observed from GD 7 to 21 and from GD 7 to adjusted GD 28 (12% and 62% below control, respectively).

There was no evidence of developmental toxicity at any dose level.

The toxicokinetic parameters are presented in [Table 2.6.6: 22].

Table 2.6.6: 22 Summary Mean (±SE) Maternal Plasma DOR Toxicokinetic Parameters in Rabbits Following Dosing of DOR: Gestation Day 15 (TT #[redacted]-7050)

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
2	13.8 ± 1.75	1.06 ± 0.0858	2.7 ± 0.67
15	80.7 ± 5.39	5.73 ± 0.420	2.3 ± 0.88
300	315 ± 32.8	20.1 ± 2.95	3.3 ± 0.67

In summary, the NOEL for maternal toxicity was 15 mg/kg/day (approximately 2-fold above the DOR exposure at the human 100 mg daily dose) based on decreased mean maternal body weight gain at 300 mg/kg/day, and the NOEL for developmental toxicity was ≥300 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 315 µM•hr; approximately 8.5-fold above the DOR exposure at the human 100 mg daily dose).

6.3 Prenatal and Postnatal Development (including maternal function)

6.3.1 Oral Pre- and Postnatal Developmental Toxicity Study in Rats (TT #[redacted]-7010)

The potential effects of DOR on development, growth, behavior, reproductive performance, and fertility of the F_1 generation in rats following oral administration to F_0 females from Gestation Days (GD) 6 through Lactation Day (LD) 20 were evaluated (TT #[redacted]-7010) [Sec. 2.6.7.14].

On GD 0 (day of confirmed breeding), presumed pregnant female WI(Han) rats were assigned into four groups of 20 females/group. From GD 6 through LD 20, females received 5, 45, or 450 mg/kg/day of DOR, prepared as a suspension of a DOR [redacted] formulation or control article only. The dosing volume for all animals was 10 mL/kg.

Assessment of maternal toxicity was based on mortality, clinical signs, body weights, food consumption, and gross examination. All females were allowed to deliver naturally. Assessment of preweaning F_1 development was based on external morphology, mortality, body weights, and clinical signs. Assessment of postweaning F_1 development was based on mortality, clinical signs, body weights, developmental signs, behavioral tests (passive avoidance, auditory startle habituation, open-field motor activity), and reproductive performance.

There were no DOR-related unscheduled deaths at any dose level. There were no DOR-related clinical signs or changes in mean maternal body weight gain or mean food consumption.

There was no evidence of preweaning F_1 toxicity at any dose level. Upon assessment of postweaning F_1 development, there were no DOR-related clinical signs, changes in body weights, developmental signs, or findings upon passive avoidance or auditory startle habituation behavioral tests. Mean motor activity in F_1 females in the 45 and 450 mg/kg/day groups were higher than that of concurrent controls (38% and 41% above the concurrent control, respectively), however this was not considered adverse as there were only a limited number of DOR-treated females with basic movements greater than or equal to the highest values observed historically in control females in this laboratory. Additionally there was a general absence of dose-response across mid- and high-dose females, there was no increase in mean motor activity in males, and there was no evidence of toxicity in any other parameter in the F_1 females or males during the postweaning period.

Based on the results of this study, the NOEL for F_0 maternal toxicity was ≥450 mg/kg/day. Based on the absence of preweaning F_1 toxicity and lack of adverse postweaning toxicity, the NOAEL for F_1 generation toxicity was ≥ 450 mg/kg/day.

6.4 Studies in which the Offspring (Juvenile Animals) are Dosed and/or Further Evaluated

6.4.1 Exploratory Oral Range-Finding Toxicity and Toxicokinetic Study in Juvenile Rats (TT #[redacted]-7005)

The objective of this study was to assist in determining dose levels of DOR for a subsequent toxicity study in juvenile rats following once daily oral administration from Postnatal Day (PND) 14 through 55. In addition, the toxicokinetic profile of DOR was evaluated on PND 55 (TT #[redacted]-7005) [Sec. 2.6.7.11].

WI(Han) rats (14 days of age at study start) were assigned to five groups of 12 rats per sex each that received 5, 45, 150, or 300 mg/kg/day DOR, supplied as a [redacted] formulation or control article alone. The amount of HPMCAS administered to the control animals was the same as the amount present in the 300 mg/kg/day dose. Each dose group consisted of three litters with four fostered pups/sex/litter (i.e., each litter was comprised of pups from different litters, and all pups in a given litter received the same dose level or control article only). The dosing volume for all animals was 10 mL/kg. The 300 mg/kg/day dose is the maximum feasible dose of the DOR [redacted] formulation in this vehicle in the condition of dosing of juvenile rats (i.e., small oral gavage needles for neonatal animal dosing).

Assessment of toxicity was based on mortality, clinical signs, body weights, and food consumption. Plasma test article concentrations were determined from samples collected from treated rats on PND 55.

All animals survived until scheduled termination. There were no test article-related clinical signs or effects on female or male body weight or food consumption.

The PND 55 values for toxicokinetic parameters are presented in the following table [Table 2.6.6: 23].

Table 2.6.6: 23 Summary Mean (± SE) Plasma DOR Toxicokinetic Parameters in Rats Following Dosing of DOR: Postnatal Day 55 (TT #[redacted]-7005)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
5	Female	44.3 ± 1.27	4.00 ± 0.226	1.0 ± NC
	Male	30.6 ± 1.03	2.87 ± 0.119	2.0 ± NC
	All	37.4 ± 1.82	3.34 ± 0.285	1.0 ± NC
45	Female	175 ± 6.72	14.5 ± 0.985	2.0 ± NC
	Male	127 ± 7.36	11.9 ± 1.49	1.0 ± NC
	All	151 ± 7.44	13.0 ± 0.904	1.0 ± NC
150	Female	300 ± 13.3	26.9 ± 2.17	2.0 ± NC
	Male	207 ± 6.16	20.6 ± 0.678	2.0 ± NC
	All	253 ± 13.4	23.8 ± 1.59	2.0 ± NC
300	Female	340 ± 20.4	32.1 ± 2.11	1.0 ± NC
	Male	277 ± 9.70	25.1 ± 1.55	2.0 ± NC
	All	308 ± 12.7	27.8 ± 1.95	1.0 ± NC

NC = Not calculated
DOR was administered from PND 14 through 55.

There was no substantial sex-related difference in mean systemic exposure ($AUC_{0\text{-}24hr}$) or mean C_{max} values for DOR at all doses on PND 55. Mean systemic exposure ($AUC_{0\text{-}24hr}$) was less than dose-proportional between 5 and 300 mg/kg/day. Mean C_{max} was less than dose-proportional between 5 and 150 mg/kg/day, and comparable at 150 and 300 mg/kg/day.

Based on the results of this study, a high dose level of 300 mg/kg/day, the maximum feasible dose, was recommended for the subsequent definitive juvenile toxicity study in rats.

6.4.2 Oral Toxicity and Toxicokinetic Study in Juvenile Rats (TT #[redacted]-7140)

The objectives of this study were to evaluate the potential effects of DOR on juvenile rat development, growth, and behavior following once daily oral administration from Postnatal Day (PND) 14 through 55, to evaluate the toxicokinetic profile of DOR on PND 55, and to evaluate the potential recovery profile of any identified toxicities after an approximate 4-week treatment-free period [Sec. 2.6.7.15].

Crl:WI(Han) rats (14 days old) were assigned to four groups of 32 rat/sex/group and received 10, 45, or 300 mg/kg/day of DOR as a [redacted] formulation or the control article only. The amount of HPMCAS administered to the control animals was the same as the amount present in the 300 mg/kg/day dose. Each dose group consisted of eight litters with four fostered pups/sex/litter (i.e., each litter was comprised of pups from different litters). All pups in a given litter received the same dose level or control article only from PND 14 through 55

(Postnatal Week [PNW] 8). The dosing volume for all animals was 10 mL/kg. The 300 mg/kg/day dose is the maximum feasible dose of the DOR [redacted] formulation in this vehicle for juvenile rats.

Assessment of toxicity was based on mortality, clinical signs, body weights, food consumption, developmental landmarks, behavioral assessments of motor activity, and clinical and anatomic pathology evaluations. Blood samples were collected during PNW 8 for clinical pathology and plasma toxicokinetic evaluations, and urine samples were collected ex vivo by overnight urine collection caging in PNW 8 and 13 for urinalyses. Ten animals/sex/group were necropsied on PND 56-58 (interim necropsy; PNW 9) at the end of the dosing period, and ten animals/sex/group were necropsied following an approximate 4-week treatment-free period (PNW 13). Histomorphologic evaluation was limited to rats necropsied at the interim necropsy, as there were no toxicities identified that required postmortem evaluation of recovery.

There were no DOR-related deaths, clinical observations, or effects on body weight, food consumption, developmental landmarks (vaginal opening and preputial separation), open field motor activity, or alterations in hematology and serum biochemistry parameters. There was a dose-related increase in the incidence of DOR-treated rats with urine crystals observed ex vivo following overnight urine collection in all test article-treated groups in PNW 8; this finding was not correlated with any other clinical pathology observation or any anatomic pathology finding. The urine crystals were no longer present after a 4-week treatment-free period (PNW 13). There were no DOR-related gross observations, organ weight changes, or histomorphologic changes in rats at 300 mg/kg/day.

The PND 55 values for toxicokinetic parameters are presented in the following table [Table 2.6.6: 24].

Table 2.6.6: 24 Summary Mean (± SE) Plasma DOR Toxicokinetic Parameters in Rats Following Dosing of DOR: Postnatal Day 55 (TT #[redacted]-7140)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
10	Female	53.5 ± 2.24	5.40 ± 0.320	1.0 ± NC
	Male	43.7 ± 1.89	4.36 ± 0.135	2.0 ± NC
	All	48.5 ± 1.89	4.60 ± 0.134	2.0 ± NC
45	Female	159 ± 4.77	16.1 ± 0.486	1.0 ± NC
	Male	109 ± 4.39	11.5 ± 0.537	2.0 ± NC
	All	137 ± 7.97	13.6 ± 1.37	1.0 ± NC
300	Female	383 ± 16.1	35.3 ± 2.28	2.0 ± NC
	Male	283 ± 9.99	26.2 ± 0.548	2.0 ± NC
	All	333 ± 18.1	30.7 ± 2.30	2.0 ± NC

NC = Not calculated
DOR was administered from PND 14 to 55. DOR concentrations in plasma from all control group animals at 1 hour post-dose were below the lower limit of quantitation (LLQ = 0.0291 µM) of the bioanalytical method.

There was no substantial sex-related difference in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) or mean C_{max} for DOR at all doses on PND 55. The mean C_{max} values of DOR were achieved at 1 or 2 hours post-dose. Plasma DOR elimination was rapid at all doses with mean 24-hour concentrations that were less than 8% of their respective mean C_{max}. The mean $AUC_{0\text{-}24\ hr}$ and C_{max} values increased in a less than dose-proportional manner between 10 and 300 mg/kg/day.

The only study finding in DOR-treated rats was presence of urine crystals observed ex vivo following overnight urine collection. This was previously also observed in repeat dose rat toxicity studies, and was determined in a follow on investigative study to be the result of ex vivo formation [Sec. 2.6.6.8.7.2]. Based on the results of this study, excluding the ex vivo DOR-associated urine crystals, the NOEL was ≥300 mg/kg/day ($AUC_{0\text{-}24h}$: 333 µM.hr, approximately 9-fold above the DOR exposure at the human 100 mg daily dose).

7 LOCAL TOLERANCE

Local tolerance studies (bovine corneal opacity and permeability assay and MatTek EpiDerm™ MTT Viability Assay) were conducted in support of the occupational safety program.

7.1 Bovine Corneal Opacity and Permeability Test (BOCP) (TT #[redacted]-7857)

The objective of this study was to determine the potential for ocular irritation using an alternative to the Draize methodology (TT #[redacted]-7857) [Sec. 2.6.7.16]. Five corneas were dosed with 0.75 mL of a [redacted]% suspension of DOR. Opacity measurements and sodium fluorescein permeability were determined. DOR was classified as a non-irritant in this assay.

7.2 MatTek EpiDerm™ MTT Viability Assay (TT #[redacted]-7858)

The objective of this study was to provide an estimate of dermal irritation potential using an alternative to the Draize methodology (TT #[redacted]-7858) [Sec. 2.6.7.16]. The MatTek EpiDerm™ MTT Viability Assay has been demonstrated to be a quantitative method for assessing potential skin hazards. MatTek EpiDerm™ tissue samples were treated in duplicate with DOR (100 mg) for 1, 4 and 24 hours or with 1% Triton® X-100 (positive control) for 4 and 9 hours. A negative control (undosed tissue) was tested in the same manner for 4 hours only. Following treatment, the viability of the tissues was determined using Methyl thiazole tetrazolium (MTT) uptake and reduction. The absorbance of each sample was measured at 540 nm using a reference wavelength of 690 nm. The viability was then expressed as a percent of control values. The mean percent viability for each time point was used to calculate an ET_{50}, which represents the time at which the EpiDerm™ tissue viability was reduced 50% compared to negative control tissues. The ET_{50} scores were converted to an irritancy classification. DOR was classified as non-irritating (ET_{50} of >24.0 hours).

8 OTHER TOXICITY STUDIES

8.1 Antigenicity

There were no observations or changes considered to be due to potential antigenicity by DOR in the routine repeat-dose oral toxicity studies [Sec. 2.6.6.3]. Therefore, no antigenicity evaluations were conducted.

8.2 Immunotoxicity

There was no indication of immunotoxicity observed for DOR in the routine oral repeat-dose toxicity studies [Sec. 2.6.6.3] and there was no evidence of immunotoxicological risk. As such, in accordance with ICH Guidance S8 *Guidance on Immunotoxicity Studies for Human Pharmaceuticals*, no additional immunotoxicity studies were conducted. Results in the repeat dose oral studies in mouse, rat, or dog showed no evidence of autoimmune or inflammatory adverse effects, nor any adverse effects on lymphoid tissues. In these studies, the combination of hematologic, organ weight, and macroscopic and histopathologic evaluation provided compelling weight of evidence that DOR was not associated with cause for immunotoxicity concern.

A local lymph node assay (LLNA) in mice was conducted in support of the occupational safety program and is presented below in [Sec. 2.6.6.8.2.1].

8.2.1 Local Lymph Node Assay in Mice (LLNA) (TT #[redacted]-7859)

In a local lymph node assay conducted in mice, concentrations of DOR (5%, 10% and 25% (w/v) in N,N-dimethylformamide (DMF)), a positive control (25% v/v hexylcinnamaldehyde), or vehicle control (DMF) were administered by topical application to the dorsum of each ear of 5 female CBA/J mice once daily for three consecutive days (TT #[redacted]-7859) [Sec. 2.6.7.17]. Ear thickness measurements and individual animal observations indicated that none of the test article treatments resulted in excessive local dermal irritation. At sacrifice, the auricular lymph nodes were isolated, single-cell suspensions of lymph node cells (LNC) were generated, and the LNC suspensions were analyzed by flow cytometry for 5-bromo-2'-deoxyuridine (BrdU) incorporation. The amount of proliferating (BrdU+) LNC was determined as a measure of the proliferative response of the local lymph node. DOR was not considered a dermal sensitizer since there was no test-article related increase in the stimulation index compared to the vehicle control group.

8.3 Mechanistic Studies

The mechanism of action of DOR was assessed as part of the pharmacodynamics studies [Sec. 2.6.2]. No additional mechanistic studies were conducted.

8.4 Dependence

The results of the quantitative whole body autoradiography in male Wistar Han rats after a single IV dose (3 mg/kg) of [14C]MK-1439 (DOR) suggested that DOR does not readily cross the blood-brain-barrier [Sec. 2.6.4.4.1]. In addition, there was no indication that DOR has a pharmacologic profile consistent with drug abuse liability potential [Sec. 2.6.2], and there was no evidence in the CNS safety pharmacology study [Sec. 2.6.2.4] or in any of the other routine repeat-dose toxicity studies [Sec. 2.6.6.3] of psychoactive effects (i.e., sedative or stimulant effects). As such, no animal abuse potential studies were conducted.

8.5 Studies on Metabolites

All circulating metabolites that were detectable in human plasma or human excreta were also present in plasma and/or excreta of nonclinical species. The only metabolite which was observed at exposures greater than 10% of total drug-related exposure in a single dose radiolabeled clinical study was the oxidative metabolite M9, which represented 12.9% of total drug-related human exposure [Sec. 2.7.2.2.1.3]. Formation of M9 was also the main metabolic pathway in nonclinical species, and was detected in plasma and excreta (urine and/or feces) of all nonclinical species [Sec. 2.6.4.5].

Exploratory analyses were performed to assess levels of the M9 metabolite in plasma from rat and dog chronic toxicology studies relative to levels of M9 in clinical samples collected in healthy subjects that had received daily doses of 240 mg DOR as a fit for purpose formulation for 10 days (P008) [Sec. 2.7.2.2.1.3]. Plasma samples collected in a 24 hr period from the animals dosed chronically with DOR were pooled in an $AUC_{0\text{-}24hr}$ proportional manner such that the resulting peak area of M9, determined by UPLC-HRMS analysis, was directly proportional to the exposure of M9. A similar AUC-pooled sample was prepared from healthy subjects that had received daily doses of 240 mg DOR for 10 days. Comparison of the M9 peak area in rat and dog plasma to the peak area of M9 in the human plasma sample enabled the estimation of the abundance of M9 in the safety samples relative to its abundance in the clinical sample. The data indicated that M9 (total M9, consisting of unbound and bound levels) was present the plasma of rat and dog at levels that were approximately 52% and 51% respectively relative to levels observed in human plasma. Consequently, the total M9 exposure in rat and dog chronic toxicity studies was at least 50% of the total M9 exposure in humans at the recommended DOR dose of 100 mg. As the unbound fraction of M9 in rat and dog plasma was approximately 2.2 and 2.8-fold higher than in humans [Sec. 2.6.4.4.3], the unbound M9 exposure in rat and dog plasma was approximately similar to the unbound plasma exposure of M9 in humans after 10 daily administrations of 240 mg DOR. Therefore, the unbound systemic exposure of M9 in the chronic rat and dog studies is similar or slight greater to the M9 exposure in humans at the recommended DOR dose of 100 mg. As such, characterization of M9 toxicity is considered adequate, according to I*CH M3(R2) guidance, Questions and Answers (R2), Question 5 in "Metabolites"* section which states that characterization of metabolite toxicity would generally be considered adequate when animal exposure is at least 50% the exposure seen in humans. While M9 levels were not measured directly on mouse or rabbit safety assessment studies, data generated from single dose studies indicated M9 to be the major circulating

metabolite in mice and the predominant metabolite in excreta for both mice and rabbits [Sec. 2.6.4.5].

8.6 Studies on Impurities

DOR impurities and degradation products were qualified according to ICH Q3A(R2) and ICH Q3B(R2) guidances by virtue of their presence in the batches evaluated in the repeat-dose toxicity studies of ≥3-month in duration [Sec. 2.6.6.3] or in the 3-month toxicity studies in rats detailed below. In addition, TDF degradate G (also known as fumaric acid ester) which is specified at a level above the qualification threshold in the DOR/3TC/TDF FDC tablet was qualified in the three-month oral rat toxicity study (TT #[redacted]-6010) detailed below. The dose multiples for each DOR-related impurity or degradation products relative to the dose of impurity in a 100 mg human daily dose of DOR, or TDF degradate G relative to the dose of degradate in a 300 mg daily dose of TDF as part of the DOR/3TC/TDF fixed dose combination, are presented in [Table 2.6.6: 27]. Whether normalized to body surface area, dose multiples for each impurity were achieved compared to human exposures and are considered qualified at the acceptance limits found in the active pharmaceutical ingredient (API).

In addition, potential and actual impurities, including identified impurities in each starting material, intermediate, and drug substance/product, have been assessed for mutagenic potential according to ICH M7 guidance, as described in [Sec. 3.2.S.3.2] (Drug Substance) and [Sec. 3.2.P.5.5] (Drug Product). According to note 1 of ICH M7 guidance, no further qualification for mutagenic or genotoxic potential is required since none of the impurities exceeds a dose of impurity to the patients of 1 mg/day. TDF degradate G , was assessed in an impurity qualification study and was negative in a micronucleus assay [Sec. 2.6.6.8.6.3]

8.6.1 Three-Month Oral Toxicity Study in Rats (TT #[redacted]-6035)

The purpose of this study was to determine the potential toxicity and toxicokinetic profile of a new DOR batch lot when administered once daily by oral gavage to rats for approximately 3 months (TT #[redacted]-6035) [Sec. 2.6.7.17].

Crl:WI(HAN) rats were assigned to two groups of 10 females and 10 males each that received 0 or 115 mg/kg/day of DOR or control article only. The test article form was a [redacted] formulation [redacted] that consisted of [redacted]% of DOR base compound and [redacted]% of HPMCAS polymer. HPMCAS polymer in vehicle was administered to the control group at 460 mg/kg/day. This amount of HPMC-AS was equivalent to the amount of polymer administered to the 115 mg/kg/day dose group.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations in the test article-treated and control groups were determined.

There were no test article-related unscheduled deaths. There were no test article-related clinical signs, changes in body weight or food consumption, or ophthalmic findings.

The only test article-related clinical pathology changes were very slight decreases in mean serum triglyceride levels at 115 mg/kg/day in females and males (-26% and -40%, respectively) compared to mean control values at Study Week 12. These isolated decreases in triglycerides were considered of minimal toxicological significance because of the small magnitude of the changes.

There were no test article-related postmortem changes.

The mean plasma DOR toxicokinetic parameters in Study Week 13 are presented in the following table [Table 2.6.6: 25].

Table 2.6.6: 25 Summary Mean (± SE) Plasma DOR Toxicokinetic Parameters in Rats Following Dosing of DOR: Study Week 13 (TT #[redacted]-6035)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
115	Female	233 ± 12.8	24.0 ± 1.52	1.0 ± NC
	Male	170 ± 8.08	18.9 ± 1.24	1.0 ± NC
	All	202 ± 10.6	21.4 ± 1.45	1.0 ± NC

NC = Not Calculated
DOR concentrations in plasma from all control group animals at 2 hours postdose were below the lower limit of quantitation (LLQ = 0.0287µM) of the bioanalytical method

There were no substantial sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and mean C_{max}. Absorption of DOR was rapid with mean C_{max} attained at 1 hour postdose, and mean 24-hour level that was approximately 11% of the mean C_{max}.

Based on the absence of postmortem findings or adverse antemortem findings, the NOAEL for this DOR batch lot was ≥115 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 202 µM•hr).

8.6.2 Three-Month Oral Toxicity Study in Rats (TT #[redacted]-6017)

The purpose of this study was to determine the potential toxicity of a new batch lot of DOR containing an induced phenol degradate, and the toxicokinetic profile of DOR when this batch lot is administered orally, once daily, to rats for approximately 3 months (TT #[redacted]-6017) [Sec. 2.6.7.17].

Crl:WI(Han) rats were assigned to two groups, one test article-treated and one control) of 10 females and 10 males each. The test article-treated group received 30 mg/kg/day of DOR, supplied as a [redacted] formulation containing [redacted]% of its anhydrous free base II and [redacted]% of HPMCAS-LG polymer suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water. This [redacted] formulation was photo-stressed to induce DOR phenol degradation. At release, the photo-stressed [redacted] formulation contained 0.4% of DOR

phenol degradate. The control group received HPMCAS-LF polymer in the vehicle (the amount of HPMCAS-LF administered to control animals matched that given to test article-treated animals).

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma DOR concentrations in the test article-treated and control groups were determined.

There were no unscheduled deaths. There were no test article-related clinical signs, changes in body weight or food consumption, clinical pathology or ophthalmic findings. There were no test article-related postmortem findings.

The toxicokinetic parameters are presented in [Table 2.6.6: 26].

Table 2.6.6: 26 Summary Mean (± SE) Plasma DOR Toxicokinetic Parameters in Rats Following Dosing of DOR: Study Week 13 (TT #[redacted]-6017)

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
30	Female	176 ± 7.58	16.2 ± 0.683	1.0 ± NC
	Male	104 ± 5.79	12.9 ± 0.228	1.0 ± NC
	All	140 ± 11.4	14.5 ± 0.797	1.0 ± NC
NC = Not Calculated				

DOR concentrations in plasma from all control group animals at 2 hours postdose were below the lower limit of quantitation (LLQ = 0.0284 µM) of the bioanalytical method.

There was no substantial sex-related difference in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) and mean C_{max} following oral administration of DOR at 30 mg/kg/day.

Based on these findings, the NOEL was ≥30 mg/kg/day of DOR or 0.12 mg/kg/day of DOR phenol degradate.

8.6.3 Three-Month Oral Toxicity Study in Rats with a Micronucleus Assay (TT #[redacted]-6010)

The purpose of this study was to determine the potential toxicity profile of a new DOR batch lot and to determine the potential toxicity profile and micronucleus induction potential of Tenofovir Disoproxil Fumarate Degradate G (also known as fumaric acid ester) when each test article formulation is individually administered orally once daily to rats for approximately 3 months (TT #[redacted]-6010) [Sec. 2.6.7.17].

Crl:WI(Han) rats were assigned to three groups of 10 females and 10 males each that received 30 mg/kg/day of DOR (free base form) in 10% polysorbate 80 in deionized water, 0.3 mg/kg/day of Tenofovir Disoproxil Fumarate Degradate G (free acid form) in 10% polysorbate 80 in deionized water or vehicle only, at a dose volume of 5 mL/kg.

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Bone marrow was collected from the humerus at necropsy for micronucleus evaluation (in the Tenofovir Disoproxil Fumarate Degradate G dose group only).

All animals survived to scheduled termination.

There were no test article-related antemortem findings, clinical pathology changes or ophthalmic findings.

There were no test article-related postmortem findings for both test articles.

The micronucleus assay was negative for Tenofovir Disoproxil Fumarate Degradate G at 0.3 mg/kg/day.

Based on the absence of findings, the NOELs were ≥30 mg/kg/day and ≥0.3 mg/kg/day, for DOR and Tenofovir Disoproxil Fumarate Degradate G, respectively.

Table 2.6.6: 27 DOR Impurities and Dose Multiples

Impurity	Specification Limits	Impurity Level %	Rodent Total Daily Intake of Impurity (mg/kg)	Human Total Daily Intake of Impurity (mg/kg)[a]	Dose Multiple based on mg/kg[c]	Rodent Total Daily Intake of Impurity (mg/m^2)[d]	Human Total Daily Intake of Impurity (mg/m^2)[d]	Dose Multiple based on mg/m^2[e]
Drug Substance Impurities								
[redacted]	≤[redacted]%	[redacted][f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≤[redacted]%	[redacted][f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≤[redacted]%	[redacted][f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≤[redacted]%	[redacted][f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≤[redacted]%	[redacted][f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MK-1439 [redacted]	≤[redacted]%	[redacted][g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug Product Impurities								
Tenofovir Deg G (also known as fumaric acid ester)	≤[redacted]%	[redacted][g]	[redacted]	[redacted][b]	[redacted]	[redacted]	[redacted]	[redacted]
MK-1439 [redacted]	≤[redacted]%	[redacted][g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≤[redacted]%	[redacted][h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	≤[redacted]%	[redacted][h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a Based upon a total daily DOR dose of 100 mg and presuming a 60 kg patient

b Based upon a total daily TDF dose of 300 mg and presuming a 60 kg patient

c Dose multiple was calculated as a ratio of total daily intake in rats (mg/kg) divided by the total daily intake in humans (mg/kg).

d Based upon a mg/kg to mg/m^2 conversion factor of 6 for rat, 3 for mouse, and 37 for an adult human e.g. mg/kg X 37 equals adult human dose on basis of mg/m^2.

e Dose multiple was calculated as a ratio of total daily intake in rodents (mg/m^2) divided by the total daily intake in humans (mg/m^2).

f Based on the nonclinical Batch/Lot # [redacted] (consisting of [redacted]% [redacted] and [redacted]% of hydroxypropyl methylcellulose acetate succinate polymer) used in the GLP 3 month oral toxicity study in rats TT #[redacted]-6035 [Sec. 2.6.7.17].

g Impurities tested in DOR batch # [redacted] and Deg G (fumaric acid ester) Lot # [redacted] used in the GLP 3 month oral toxicity study in rats TT#[redacted]-6010 [Sec. 2.6.7.17].

h Impurities tested in DOR batch # [redacted] (consisting of [redacted]% [redacted] and [redacted]% of hydroxypropyl methylcellulose acetate succinate polymer) used in the GLP three-month oral range-finding and toxicokinetic study in CD1 mice TT #[redacted]-6013 [Sec. 2.6.7.7A].

8.7 Other Studies

Light absorbance was observed in the 290 to 700 nM range (at ~327 nM) with DOR with a Molar Extinction Coefficient (MEC) greater than 1000 L/mol/cm [Sec. 3.2.S.3.1.1]. Thus, a phototoxicity study was conducted in pigmented male rats (TT #[redacted]-9011). DOR (30 mg/kg/day and 450 mg/kg/day) was not phototoxic in the eye and skin of pigmented male rats, indicating that DOR does not pose a phototoxic concern.

8.7.1 Three-Day Oral (Gavage) Phototoxicity and Bioanalysis Evaluation of DOR in Male Pigmented Rats (TT #[redacted]-9011)

The objective of this study was to evaluate the potential phototoxic effects of DOR after it was administered orally (via gavage) for three consecutive days to Crl:LE (Long-Evans) pigmented male rats followed by exposure to radiation from a xenon lamp (to simulate sunlight) (TT #[redacted]-9011) [Sec. 2.6.7.17]. The study design was as follows in [Table 2.6.6: 28].

Table 2.6.6: 28 Phototoxicity Experimental Design (TT #[redacted]-9011)

						UVR	Exposure
Group No.	**No. of Animals**	**Test Material**	**Dosage Level (mg/kg/day)**	**Conc. (mg/mL)[a]**	**Dosage Volume (mL/kg)**	**Instrumental UVR Dosage (MED)[b]**	**Interval Between Formulation Administration and UVR Exposure (Minutes)[c]**
1	5 + 3[d]	Methyl-cellulose (Control Article)	0	0	10	0.5	60 ± 10
2	5 + 3[d]	DOR	30	3	10	0.5	60 ± 10
3	5 + 3[d]	DOR	450	45	10	0.5	60 ± 10

a Concentration of the active ingredient
b Minimal Erythema Dose is an instrumental UVR dose adequate to elicit a barely perceptible response in the skin.
c The timing of the start of the UVR exposure was based on the median dosing time for each group
d Rats assigned to the bioanalysis phase. These rats were not anesthetized or exposed to UVR

Fifteen Crl:LE (Long-Evans) pigmented male rats were randomly assigned to the phototoxicity phase, that consisted of three dose groups (Groups 1 through 3) of five rats per group. An additional nine rats were assigned to Groups 1 through 3, three rats per group, for bioanalysis sample collection. Formulations of DOR or the control article were administered orally via gavage once daily on study days 1 through 3 at doses of 0 (control article), 30 or 450 mg/kg/day. The top dose of 450 mg/kg/day DOR was considered to be the maximum feasible oral dose.

Prior to UVR exposure, the phototoxicity phase rats were lightly anesthetized via intramuscular injection of a mixture of ketamine/xylazine and then positioned on plastic trays. In order to expose the eyes to a UVR intensity comparable to that of the skin sites, the head of each rat was elevated so that the eyes were on a plane equivalent to the skin sites. The rats were placed 1.2 meters from the UVR source at the time of exposure. An instrumental UVR exposure dose equivalent to 0.5 minimal erythema dose (MED) was delivered to each rat over a period of 30 minutes.

Plasma DOR levels were determined at approximately 30 minutes, 1 and 2 hours post-dose (timepoints were selected based on bracketing the projected Tmax).

Phototoxicity phase rats were euthanized on Day 6 of the study after the completion of ophthalmic examinations. Eye and skin samples were collected.

The following parameters were evaluated: viability, clinical and skin reaction observations, body weights, ophthalmological examinations, bioanalysis and ocular histopathology.

All rats survived to scheduled sacrifice. Three daily oral (gavage) administrations of the control article or DOR at 30 or 450 mg/kg/day in the control article, followed approximately 60 minutes later by a single exposure to solar simulated ultraviolet radiation, resulted in no skin reactions indicative of phototoxicity.

There were no adverse clinical observations in the rats administered the DOR formulations. There were no DOR-related ocular findings in any rats administered doses of 30 or 450 mg/kg/day that were indicative of phototoxicity. There were no DOR-related necropsy findings in the eyes, optic nerves or skin and there were no DOR-related histopathologic findings in the eyes or optic nerves of the rats examined.

For study interval Day 1 - 3, a reduction in mean body weight gain at 450 mg/kg/day (4.6 g gain) as compared with the control article value gain was noted (11.2 g gain).

The bioanalytical results revealed that concentrations of the test article were not present in control rats (Group 1) and that DOR was quantifiable in all plasma samples of test article dosed rats (Groups 2 and 3) in a dosage-dependent manner.

In summary, a three-day oral (gavage) administration of DOR at 30 or 450 mg/kg/day followed approximately 60 minutes after the final administration by a single exposure to solar-simulated ultraviolet radiation (UVR exposure) did not result in any skin reactions or ocular observations (confirmed by histopathology of the eye tissues) indicative of phototoxicity. The NOEL for phototoxicity was ≥450 mg/kg/day, based on the lack of test-article related changes in the eyes and skin.

8.7.2 Exploratory Ten-Day Oral-Dose Urine Examination Study in Female Rats (TT #[redacted]-1095)

Urinary crystals composed of DOR were sporadically observed in rats predominantly at doses of 450 mg/kg/day in all repeat-dose rat toxicity studies after overnight ex vivo urine

collection. The purpose of this study was to investigate potential for urine crystal formation in vivo and ex vivo using various urine collection methods in female rats orally dosed with DOR, for 10 days (TT #[redacted]-1095) [Sec. 2.6.7.17].

Sixteen female Crl:WI(Han) rats received 450 mg/kg/day of DOR as a [redacted] formulation [consisting of [redacted]% DOR base form and [redacted]% of HPMCAS, suspended in 0.5% methylcellulose with 5 mM hydrochloric acid in deionized water]

Assessment of toxicity was based on mortality, clinical observations, body weights, and gross examinations of urinary bladder and kidney. Overnight urine collections via metabolism caging (*ex vivo* collection) were performed on all rats on Study Days 3 and 9. Urine collections via cystocentesis (*in vivo* collection) were performed on all rats on Study Days 4 and 10. Urine chemistry and microscopic examinations were performed to evaluate crystal formation. Drug concentrations in plasma, urine supernatant, and urine sediment were measured.

All animals survived to study termination. There were no test article-related clinical observations, body weight changes, or changes in gross examination of urinary bladder and kidney.

DOR urinary crystals were not observed in urine samples collected by cystocentesis. Urine crystals were, however, seen following ex vivo overnight metabolism cage collection in the same animals with negative urinary crystals evaluated by cystocentesis (9/16 urine samples on Study Day 3, and 16/16 urine samples on Study Day 9), the collection method used in repeat dose toxicity studies. Animal DOR urine concentrations reached as high as >[redacted]-fold the solubility levels reported for DOR in aqueous media. The observation of presence of urine crystal in ex vivo overnight urine collection, but not directly in in vivo collection (cystocentesis), indicates that urine crystal formation is likely due to changes in external environment (such as temperature decrease from 37°C to ambient temperature, volume decrease by evaporation, protein precipitation, and/or surface contact with urine collection containers) ex vivo and was not associated with in vivo crystal formation.

8.7.3 One-Month Oral Combination Toxicity Study in Rats (TT #[redacted]-1012)

The purpose of this study was to determine the potential toxicity and toxicokinetic profile of DOR and MK-8591 (an investigational human immunodeficiency virus nucleoside reverse transcriptase inhibitor [HIV NRTI]) when administered orally, either alone or in combination, to rats once daily for approximately 1 month (TT #[redacted]-1012) [Sec. 2.6.7.17].

Crl:WI(Han) rats were assigned to 5 groups of 10 females and 10 males each that received DOR alone, MK-8591 alone, a combination of both test articles at two dose levels, or control article for both test articles, as indicated in the table [Table 2.6.6: 29] below.

Table 2.6.6: 29 Study Design (TT #[redacted]-1012)

Dose Group	Test/Control Article		Females	Males
	Dose Group Identifier	Description		
1	Control	MK-1439 Control (HPMCAS in 0.5% MC/5 mM HCl) + MK-8591 Control (10% PS 80)	10	10
2	MK-8591 alone	(MK-1439 Control +) 3 mg/kg/day MK-8591	10	10
3	MK-1439 alone	30 mg/kg/day MK-1439 (+ MK-8591 Control)	10	10
4	Low-dose combination	30 mg/kg/day MK-1439 + 1 mg/kg/day MK-8591	10	10
5	High-dose combination	30 mg/kg/day MK-1439 + 3 mg/kg/day MK-8591	10	10

HPMCAS = Hydroxypropyl methylcellulose acetate succinate.
0.5% MC/5 mM HCl = 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water.
10% PS 80 = 10% (w/w) polysorbate 80 in deionized water.

Each test article was formulated separately, with DOR [redacted] formulation (composed of [redacted]% [w/w] DOR base compound and [redacted]% [w/w] hydroxypropyl methylcellulose acetate succinate [HPMCAS] excipient polymer) in a vehicle of 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water, and MK-8591 ([redacted]) in a vehicle of 10% (w/w) polysorbate 80 in deionized water. The DOR control group received the same amount of HPMCAS as was present in the 30 mg/kg/day DOR dose formulation. DOR (or DOR control) was administered first, immediately followed by MK-8591 (or MK-8591 Control). The dose volume for each test article was 5 mL/kg; thus, animals received a total daily dose volume of 10 mL/kg.

Assessment of toxicity was based on mortality observations, clinical observations, body weights, food consumption, ophthalmic examinations, and clinical and anatomic pathology evaluations. Plasma concentrations of DOR and MK-8591 in treated and control samples were determined.

There were no unscheduled deaths. There were no test article-related antemortem findings (clinical signs, or changes in body weight or food consumption) in the study. In addition, there were no test article-related ophthalmic findings or changes in clinical pathology parameters. There were no test article-related postmortem findings (gross necropsy, organ weight or histomorphological findings) in the study.

The mean plasma DOR and MK-8591 toxicokinetic parameters in rats in Study Week 5 following dosing of DOR/MK-8591 are presented in [Table 2.6.6: 30] and [Table 2.6.6: 31].

Table 2.6.6: 30 Summary Mean (± SE) Plasma DOR Toxicokinetic Parameters in Rats Following Dosing of DOR/MK-8591: Study Week 5 (TT #[redacted]-1012)

Analyte	Treatment	Sex	$AUC_{0\text{-}24\ hr}$ (µM●hr)	C_{max} (µM)	T_{max} (hr)
MK-1439	30 mg/kg/day MK-1439 + 1 mg/kg/day MK-8591	Female	173 ± 11.8	14.7 ± 0.646	2.0 ± NC
		Male	146 ± 3.97	12.2 ± 0.555	2.0 ± NC
		All	159 ± 6.68	13.5 ± 0.680	2.0 ± NC
MK-1439	30 mg/kg/day MK-1439 + 3 mg/kg/day MK-8591	Female	180 ± 7.54	12.5 ± 0.657	2.0 ± NC
		Male	136 ± 4.94	10.4 ± 0.304	2.0 ± NC
		All	158 ± 7.31	11.4 ± 0.582	2.0 ± NC

NC = Not Calculated
MK-1439 concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.0294 µM) of the bioanalytical method.

For DOR, there were no substantial (i.e., more than 2-fold) sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) or mean C_{max} values in Study Week 5; therefore, results are presented for sexes combined. In addition, mean systemic exposure and C_{max} values were similar following dosing of 30 mg/kg/day DOR in combination with 1 mg/kg/day or 3 mg/kg/day of MK-8591. The DOR exposures at 30 mg/kg/day in this study in combination with MK 8591 was considered similar to those DOR exposures observed in previous studies where DOR at a dose of 30 mg/kg/day was administered alone.

Table 2.6.6: 31 Summary Mean (± SE) Plasma MK-8591 Toxicokinetic Parameters in Rats Following Dosing of DOR/MK-8591: Study Week 5 (TT #[redacted]-1012)

Analyte	Treatment	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
MK-8591	3 mg/kg/day MK-8591	Female	3.06 ± 0.154	1.52 ± 0.405	0.50 ± NC
		Male	3.85 ± 0.334	1.33 ± 0.0887	0.50 ± NC
		All	3.45 ± 0.227	1.42 ± 0.190	0.50 ± NC
MK-8591	1 mg/kg/day MK-8591 + 30 mg/kg/day MK-1439	Female	0.814 ± 0.0589	0.325 ± 0.0258	0.50 ± NC
		Male	1.02 ± 0.142	0.361 ± 0.0393	1.0 ± NC
		All	0.916 ± 0.0771	0.339 ± 0.0236	1.0 ± NC
MK-8591	3 mg/kg/day MK-8591 + 30 mg/kg/day MK-1439	Female	3.28 ± 0.234	1.38 ± 0.170	0.50 ± NC
		Male	3.26 ± 0.308	1.04 ± 0.174	1.0 ± NC
		All	3.27 ± 0.181	1.19 ± 0.116	0.50 ± NC

NC = Not Calculated
MK-8591 concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.00170 µM) of the bioanalytical method.

For MK-8591, there were no substantial (i.e., more than 2-fold) sex-related differences in mean systemic exposure ($AUC_{0\text{-}24\ hr}$) or mean C_{max} values in Study Week 5; therefore, results are presented for sexes combined. Mean systemic exposure and C_{max} values were similar following dosing of 3 mg/kg/day MK-8591 alone or in combination with 30 mg/kg/day DOR. Mean systemic exposure and C_{max} values for MK-8591 increased in a dose proportional manner between 1 mg/kg/day (administered in combination with 30 mg/kg/day of DOR) and 3 mg/kg/day irrespective of whether MK-8591 was administered alone or in combination with 30 mg/kg/day of DOR.

Based on the lack of antemortem or postmortem findings in the study, the NOEL/NOAEL was ≥ 30 mg/kg/day DOR and 3 mg/kg/day MK-8591.

8.7.4 Long-Acting Parenteral (LAP) Formulation Studies

These studies are included in this application to provide the collective nonclinical experience with DOR; however, the exploratory results from these LAP studies using a non-relevant route of administration for clinical dosing and exploratory microparticulate suspension formulations do not impact nonclinical risk assessment of the oral DOR program. LAP development of DOR has been discontinued.

DOR systemic exposures achieved in LAP studies were far lower than those achieved in the oral program. LAP formulations of DOR were intramuscularly or subcutaneously

administered as single or repeated doses in rats and dogs to support potential clinical dosing of DOR formulations by these routes. There were no toxicities directly attributed to DOR when administered as particulate microsuspension LAP formulations. There was no relationship between DOR systemic exposures and local or systemic LAP formulation-related findings. Transient antemortem and postmortem injection-site related observations were observed with intramuscular and subcutaneous injections, consistent with injected polysorbate 80 response in dogs [Ref. 4.3: 046W89] and host response to injection of foreign body particulates (DOR API was milled to form microparticulate suspensions of various mass median diameter particle size distributions [d50 PSD]) which was commonly noted following LAP administration of marketed LAP formulations [Ref. 4.3: 046W6Y] [Ref. 4.3: 046W89]. Macrophage accumulation in tissues distant from injection sites (e.g. Harderian gland, ovaries, bone marrow, lung, adipose tissue) was sporadically observed in rats following repeated IM and SC dosing of the 2 µm d50 PSD DOR LAP and in one animal SC administered the 8 µm d50 PSD DOR LAP, but not in rats following IM injection of either the 8 µm d50 PSD or exploratory nanoformulation (0.25 µm) d50 PSD DOR LAP formulations. Systemic findings of macrophage accumulation were attributed to the particulate sizes of the administered LAP microsuspensions, the IM and/or SC dosing routes, and/or the frequency of administered injections. Intramuscular injection of the 8 µm d50 PSD DOR LAP and the exploratory nanoformulation (0.25 µm) d50 PSD DOR LAP was without systemic findings of macrophage accumulation, and there was no relationship between DOR systemic exposures and local or systemic LAP-related findings. LAP IM and SC studies in rats and dogs are listed in [Table 2.6.6: 32] below.

Table 2.6.6: 32 Long-Acting Parenteral (LAP) Formulation Studies with DOR

Long-Acting Parenteral (LAP) Formulations (No impact on oral DOR toxicity profile)					
Study Type/Duration	Route	Species	Dose Levels (mg/kg/day, unless otherwise specified)	NOAEL (mg/kg/dose)	Study No. (GLP Status)
LAP: Exploratory 34-Day Local Tolerability (Day 1 and 30) & TK	IM	Rats (Males) Crl:WI(HAN)	Doses of two formulations each administered on Study Day 1 and Study Day 30 only Formulation 1: 200 mg of DOR/mL aqueous suspension containing 3% polyethylene glycol 3350 isotonic Formulation 2: 150 mg of DOR/mL solution in N-methyl pyrrolidone	N/A	TT #[redacted]-6034 (Non-GLP)
LAP: Exploratory 15-Day Tolerability & TK	SC or IM	Rats Crl:WI(HAN)	60 mg/kg/dose (8 µm d50 PSD formulation) given as three once weekly doses	N/A	TT #[redacted]-1033 (Non-GLP)

Long-Acting Parenteral (LAP) Formulations (No impact on oral DOR toxicity profile)					
Study Type/Duration	Route	Species	Dose Levels (mg/kg/day, unless otherwise specified)	NOAEL (mg/kg/dose)	Study No. (GLP Status)
LAP: 3-Week Toxicity with 1-Week Treatment Free Period	IM	Rats Crl:WI(HAN)	15, 30, 60 mg/kg/dose (2 and 8 µm d50 PSD formulation) given as three once weekly doses	≥60 mg/kg/dose 8 µm d50 PSD formulation	TT #[redacted]-6016 (GLP)
LAP: 3-Week Toxicity with 1-Week Treatment Free Period	SC	Rats Crl:WI(HAN)	15, 30, 60 mg/kg/dose (2 and 8 µm d50 PSD formulation) given as three once weekly doses	30 mg/kg/dose 8 µm d50 PSD formulation	TT #[redacted]-6015 (GLP)
LAP: Exploratory Intermittent Dose (Days 1, 8, 15) with 2-Month Treatment-Free Period	IM	Rats Crl:WI(HAN)	10 or 40 mg/kg/dose (0.25 µm [nano-formulation] d50 PSD)	N/A	TT #[redacted]-1065 (Non-GLP)
LAP: Exploratory TK (13-Week Observation Period)	IM	Dogs (Beagle)	200 mg [1 injection of 1.0 mL 2.0 µm or 2 injections of 0.5 mL each of 8.0 µm d50 PSD formulation]	NA	TT #[redacted]-1081 (Non-GLP)
LAP: Exploratory TK (13-Week Observation Period)	IM or SC	Dogs (Beagle)	Single dose of 200 mg and 300 mg IM or SC (d50 PSD of 8.0 µm)	NA	TT #[redacted]-1061 (Non-GLP)
LAP: Exploratory TK (13-Week Observation Period)	IM	Dogs (Beagle)	Single dose of 200 mg (d50 PSD of 0.3 µm)	NA	TT #[redacted]-1106 (Non-GLP)
LAP: Exploratory Single-Dose TK Study (with ~8.5 month observation period)	IM	Dogs (Beagle)	Single dose of 200 mg (d50 PSD of 16.0 µm)	NA	TT #[redacted]-1064 (Non-GLP)

NA = Not Applicable

[g] d50 PSD = mass median diameter particle size distribution

9 DISCUSSION AND CONCLUSIONS

The safety of DOR administration to humans is supported by repeat-dose oral toxicity studies in mouse, rat and dog of up to 3 months, 6 months and 9 months duration, respectively. Genotoxicity and carcinogenicity potential was assessed in vitro and in vivo in bioassays up to two years duration. Developmental and reproductive toxicology studies conducted with DOR included a male and female rat fertility study, embryo-fetal developmental toxicity studies in rats and rabbits, a pre- and post-natal toxicity study in rats, and juvenile toxicity in rats. Doses were tested up to either maximal feasible oral doses, saturation of systemic DOR exposure, or the limit dose of 1000 mg/kg/day. DOR treatment was well tolerated in mouse,

rat, and dog. The NOAEL in the three-month mouse toxicity study was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 196 µM•hr). The NOAEL in the six-month rat toxicity study was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 279 µM•hr). The NOAEL in the nine-month oral dog toxicity study was ≥1000 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 673 µM•hr). There were no findings in rat fertility or juvenile toxicity studies, nor were there adverse findings in embryo-fetal development or pre- and post-natal development findings, up to the highest doses tested. Exposure comparisons in animals versus humans (based on the human DOR clinical dose of 100 mg QD associated with a systemic DOR $AUC_{0\text{-}24hr,ss}$ of 37.8 µM•hr) indicates DOR systemic NOAEL exposure multiples in mouse, rat and dog to be 5.5X, 7.5X and 18X, respectively. See [Table 2.6.6: 33] for exposure comparisons in animals versus humans.

Table 2.6.6: 33 DOR Systemic Exposure Multiples in Pivotal Studies

Species	Study	Dose Levels (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	Exposure Multiples[†]
Mouse (CD1)	Three Month Toxicity Study	3 30 150 300 450 (NOAEL)	19.8 79.5 170 201 196	<1X 2X 4.5X 5.5X 5.5X
Rat	Six Month Toxicity Study	3 30 450 (NOAEL)	19.1 87.3 279	<1X 2X 7.5X
Dog	Nine Month Toxicity Study	1 10 1000 (NOAEL)	82.2 383 673	2X 10X 18X
Rat	Male and Female Fertility Study	5 30 450 (NOEL)	NA[#]	~1X[#] 2X[#] 7.5X[#]
Rat	Embryo-Fetal Developmental Toxicity Study	5 45 450 (NOEL – Maternal and Developmental)	61.2 243 345	1.5X 6.5X 9.0X
Rabbit	Embryo-Fetal Developmental Toxicity Study	2 15 300 (NOAEL-Developmental and Maternal)	13.8 80.7 315	<1X 2X 8.5X
Rat	Pre- & Post-Natal Development	5 45 450 (NOAEL – Maternal and F_1 Generation)	NA^	1.5X 6.5X 9.0X
Rat	Juvenile Toxicity	10 45 300	48.5 137 333	1X 3.5X 9X

Species	Study	Dose Levels (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	Exposure Multiples[†]
450 mg/kg/day was the maximum feasible oral dose (MFD) of the DOR [redacted] formulation in adult mouse, rat, and rabbit studies and 300 mg/kg/day was the MFD in juvenile aged rats. A limit dose of 1000 mg/kg/day (DOR suspended in 10% polysorbate 80 formulation was used in dogs. [†] Exposure multiples were based on population pharmacokinetics analysis from DOR Phase 3 trials (P018 and P021), where a 100 mg QD DOR clinical dose resulted in systemic geometric mean exposures of $AUC_{0\text{-}24hr}$ of 37.8 µM•hr. [#]In the rat male and female fertility study, no toxicokinetics were performed; exposures were determined to those measured in the rat repeat-dose toxicity study. [^]In the rat pre- & post-natal development study, no toxicokinetics were performed; exposures were determined to those measured in the rat embryo-fetal developmental toxicity study.				

DOR repeat-dose oral administration to rats, mice and dogs up to either maximal feasible doses or a toxicity limit dose of 1000 mg/kg/day was well tolerated and did not result in adverse findings in general toxicity studies. In rodents, there were no adverse antemortem or postmortem findings when administered in one- and three-month toxicity studies in TgRas wild type mice and CD1 mice, respectively ($AUC_{0\text{-}24\ hr}$ exposures achieved of 220 and 201 µM•hr, respectively) approximately 5.5-fold above the DOR exposure at the human 100 mg daily dose). In the chronic 6-month rat toxicity study, test article-related non-adverse antemortem findings observed in males at ≥30 mg/kg/day and in females at 450 mg/kg/day consisted of very slight to slight increases in prothrombin time and activated partial thromboplastin (5-10%) coagulation parameters, and urinary findings of very slight decreases in urinary volume (-56%), very slight increases in urine specific gravity, and low individual pH values in females (pH values of 5.5 observed in a minority of animals). These were considered non-adverse based due to the slight magnitude of change, lack of correlating postmortem effects, and absence of toxicologic significance. Urinary crystals, described as yellow-brown, needle-like, were also sporadically observed in rats predominantly at doses of 450 mg/kg/day in all repeat-dose rat toxicity studies after overnight ex vivo urine collection. Exploratory analyses identified the urinary crystals as consisting of DOR only and considered due to apparent supersaturation of DOR in urine. These crystals were shown to be formed ex vivo during overnight urine collection and not in vivo in an investigative study in rats [Sec. 2.6.6.8.7.2]. In this study, there were no crystals in urine from DOR-treated animals after urine collection by cystocentesis in vivo, while there were crystals in urine from DOR-treated animals after overnight ex vivo urine collection.

In the two year rat carcinogenicity study, test article-related changes were limited to very slight centrilobular hypertrophy of hepatocytes in the livers from males at 450 mg/kg/day which, in the absence of associated degenerative, neoplastic or preneoplastic liver changes, were considered of minimal toxicologic significance. Based on the absence of postmortem findings and lack of adverse antemortem findings, the NOAEL in rats was ≥450 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 279 µM•hr, approximately 7.5-fold above the DOR exposure at the human 100 mg daily dose).

In the pivotal nine-month (chronic) dog study, test article-related clinical observations at all dose levels consisted of discoloration of feces (resembling test article) and increased incidence of unformed stools. Sporadic salivation was observed at 1000 mg/kg/day in both

sexes and in males at 1 mg/kg/day and 10 mg/kg/day. At doses ≥ 10 mg/kg/day, sporadic and transient unilateral or bilateral clear eye discharge was observed during the study. There were no test article-related gross, organ weight or histomorphologic changes at final necropsy upon postmortem evaluation. Clear eye discharge, salivation, and presence of discolored (resembling administered test article) and/or unformed stool was not considered adverse based on its sporadic incidence, lack of correlative or associated clinical or anatomic pathology findings, and limited biologic and toxicologic impact. Based on the absence of postmortem findings and lack of adverse antemortem findings, the NOAEL was ≥1000 mg/kg/day ($AUC_{0\text{-}24\ hr}$: 673 μM•hr, approximately 18-fold above the DOR exposure at the human 100 mg daily dose).

In summary, the findings observed in the repeat-dose studies in mice, rats, and dogs were limited to non-adverse antemortem findings of minimal amplitude which did not impact the physical conditions of the animals and did not correlate with postmortem observations. In the two year rat carcinogenicity study, very slight centrilobular hypertrophy of hepatocytes in the livers from males at 450 mg/kg/day was observed and considered of minimal toxicologic significance as it was not associated with associated degenerative, neoplastic or preneoplastic liver changes. As such, the NOAELs were the highest dose tested in all nonclinical repeat-dose studies.

DOR was not mutagenic or genotoxic in a battery of *in vitro* or *in vivo* studies carried out according to ICH guidances that included a microbial mutagenesis assay ("Ames" test), a chromosomal aberrations assay, and an *in vivo* assay for micronucleus induction in rat bone marrow. The top doses were the limit dose or were limited by solubility in the *in vitro* genetic toxicity studies, and the maximum feasible dose in the *in vivo* genetic toxicity study. No in vivo or in vitro genetic toxicity was identified, and no carcinogenic potential was identified in a six-month mouse rasH2 transgenic mice carcinogenicity study or a 2-year rat carcinogenicity study.

There were no effects on male and female fertility or on juvenile development in rats, or adverse findings in embryo-fetal development toxicity studies in rats or rabbits or in a pre- and post-natal development study in rats.

There was no evidence of phototoxicity in pigmented rats following repeat-dose oral DOR administration followed by exposure to solar-simulated ultraviolet radiation. DOR was classified as a non-irritant and as a non-dermal sensitizer in local tolerance assays. There were no toxicities upon one month combination toxicity assessment in rats with an investigational HIV NRTI candidate. There were no toxicities directly attributed to DOR when administered to rats or dogs as a particulate microsuspension LAP formulation. The LAP formulation studies are not relevant to the oral DOR nonclinical risk assessment.

No significant toxicologic concern (e.g., similar target organ toxicity) or potential for synergistic toxicity was identified concerning the co-administration of DOR with the well-characterized marketed approved compounds, 3TC and TDF. Impurities and degradation products were assessed according to ICH Q3A(R2), ICH Q3B(R2) and ICH M7 guidances.

In conclusion, the toxicological profile of DOR supports the safe use of DOR (100 mg) as a single entity and in the DOR/3TC/TDF FDC tablet for the treatment of HIV-1 infection in treatment-naive adult patients.

10 LIST OF REFERENCES

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[Ref. 4.3: 04RMRC] U.S. Prescribing Information: TRIUMEQ (dolutegravir, abacavir, and lamivudine) tablets for oral use: 2014.

CTD 第 2 部

2.6　非臨床試験の概要文及び概要表

2.6.7　毒性試験概要表

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Sec. 2.6.7.1 Toxicology: Overview

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Repeat-Dose Toxicity	rasH2 Wild-Type Mice (Hybrid)	Oral (gavage)	1 Month	0, 30, 100, 300, 450	Yes[b]	MRL-F	TT #[redacted]-6010	[Ref. 4.2.3.2: TT[redacted]6010FIN]
	Mice CRL:CD1(ICR)	Oral (gavage)	3 Months	0, 3, 30, 150, 300, 450	Yes	MRL-F	TT #[redacted]-6013	[Ref. 4.2.3.2: TT[redacted]6013FIN]
	Rats (Female) Crl:WI(Han)	Oral (gavage)	7 Days	0, 5, 100, 750 (total) (given as b.i.d. doses)	No	MRL-WP	TT #[redacted]-2518	[Ref. 4.2.3.2: TT[redacted]2518FIN]
	Rats Crl:WI(Han)	Oral (gavage)	7 Days (TK Study)	1.5, 15, 175, 225 (given as b.i.d. doses) 30, 175, 225 (QD)	Yes	MRL-WP	TT #[redacted]-0019	[Ref. 4.2.3.2: TT[redacted]0019FIN]
	Rats Crl:WI(Han)	Oral (gavage)	2 Weeks	0, 5, 75, 450	Yes	MRL-F	TT #[redacted]-6029	[Ref. 4.2.3.2: TT[redacted]6029FIN]
	Rats Crl:WI(Han)	Oral (gavage)	3 Months	0, 3, 30, 450	Yes	MRL-F	TT #[redacted]-6040	[Ref. 4.2.3.2: TT[redacted]6040FIN]
	Rats Crl:WI(Han)	Oral (gavage)	6 Months	0, 3, 30, 450	Yes[C]	MRL-F	TT #[redacted]-6019	[Ref. 4.2.3.2: TT[redacted]6019FIN]
	Dogs (Beagle)	Oral (gavage)	14 Days	10	Yes	MRL-F	TT #[redacted]-6030	[Ref. 4.2.3.2: TT[redacted]6030FIN]
	Dogs (Beagle)	Oral (gavage)	3 Months	0, 1,10, 1000	Yes	MRL-F	TT #[redacted]-6039	[Ref. 4.2.3.2: TT[redacted]6039FIN]
	Dogs (Beagle)	Oral (gavage)	9 Months	0, 1, 10, 1000	Yes[d]	MRL-F	TT #[redacted]-6018	[Ref. 4.2.3.2: TT[redacted]6018FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Genotoxicity	*Salmonella typhimurium* TA97a, TA98, TA100, and TA1535 and *Escherichia coli* WP2 uvrA pKM101	In vitro	48 hours ± S-9	30 to 5000 µg/plate	No	MRL-WP	TT #[redacted]-8021	[Ref. 4.2.3.3.1: TT[redacted]8 021FIN]
	Salmonella typhimurium TA97a, TA98, TA100, and TA1535 and *Escherichia coli* WP2 uvrA pKM101	In vitro	48 hours ± S-9	100 to 5000 µg/plate	Yes	MRL-WP	TT #[redacted]-8099	Reported with TT #[redacted]-8021 [Ref. 4.2.3.3.1: TT[redacted]8 021FIN]
	TA100	In vitro	48 hours ± S-9	100 to 5000 µg/plate	Yes	MRL-WP	TT #[redacted]-8113	Reported with TT #[redacted]-8021 [Ref. 4.2.3.3.1: TT[redacted]8 021FIN]
	Chinese hamster ovary cells	In vitro	3 hours (+S-9) 3 hours (-S-9) 20 hours (-S-9)	75 to 500 µM	No	MRL-WP	TT #[redacted]-8662	[Ref. 4.2.3.3.1: TT[redacted]8 662FIN]
	Chinese hamster ovary cells	In vitro	3 hours (+S-9) 3 hours (-S-9) 20 hours (-S-9)	75 to 500 µM	Yes	MRL-WP	TT #[redacted]-8666	Reported with TT #[redacted]-8662 [Ref. 4.2.3.3.1: TT[redacted]8 662FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Genotoxicity (continued)	Rat/Crl:WI(HAN)	Oral (gavage)	Harvested bone marrow cells the day after final dose in this 7-day study	0, 5, 100, 750 (total) (given as b.i.d. doses)	No	MRL-WP	TT #[redacted]-8707 (in conjunction with a 7-Day Oral Tolerability Study TT #[redacted]-2518)	[Ref. 4.2.3.3.2: TT [redacted]8707FIN]
	Rat/Crl:WI(HAN)	Oral (gavage)	Harvested bone marrow cells the day after final dose in this 16-day study	5, 75, 450	Yes	MRL-WP	TT #[redacted]-8725 (in conjunction with a Two-Week Oral Toxicity Study TT #[redacted]-6029)	[Ref. 4.2.3.3.2: TT [redacted]8725FIN]
Carcinogenicity	rasH2 Transgenic Mice	Oral (gavage)	6 Months	0, 10, 60, 300	Yes	MRL-F	TT #[redacted]-6005	[Ref. 4.2.3.4.1: TT [redacted]6005FIN]
	Rat/Crl:WI(HAN)	Oral (gavage)	2 Years	0, 3, 30, or 450	Yes[e]	MRL-F	TT #[redacted]-6029	[Ref. 4.2.3.4.1: TT [redacted]6029FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Reproductive and Developmental Toxicity	Rats Crl:WI(Han)	Oral (gavage)	15 days prior to cohabitation, during cohabitation, and through GD 7 or until day removed from cohabitation for the females, and until the day prior to scheduled sacrifice for the males (approximately 6 weeks total)	0, 5, 30, 450	Yes[f]	MRL-WP	TT #[redacted]-7300	[Ref. 4.2.3.5.1: TT [redacted]7300FIN]
	Rats Crl:WI(Han)	Oral (gavage)	GD 6-20	0, 5, 45, 450	No	MRL-WP	TT #[redacted]-7045	[Ref. 4.2.3.5.2: TT [redacted]7045FIN]
	Rats Crl:WI(Han)	Oral (gavage)	GD 6-20	0, 5, 45, 450	Yes[g]	MRL-WP	TT #[redacted]-7040	[Ref. 4.2.3.5.2: TT [redacted]7040FIN]
	Rabbits (Dutch Belted)	Oral (gavage)	1 day (single-dose TK)	1, 10, 100, 1000	No	MRL-WP	TT #[redacted]-7206	[Ref. 4.2.3.5.2: TT [redacted]7206FIN]
	Rabbits (Dutch Belted)	Oral (gavage)	1 day (single-dose TK)	15, 50, 150, 450	No	MRL-WP	TT #[redacted]-7207	[Ref. 4.2.3.5.2: TT [redacted]7207FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Reproductive and Developmental Toxicity (continued)	Rabbits (Dutch Belted)	Oral (gavage)	5 days (TK)	15, 50, 150, 300, 450	No	MRL-WP	TT #[redacted]-7277	[Ref. 4.2.3.5.2: TT[redacted]7277FIN]
	Rabbits (Dutch Belted)	Oral (gavage)	GD 7-20	0, 1, 15, 450	No	MRL-WP	TT #[redacted]-7055	[Ref. 4.2.3.5.2: TT[redacted]7055FIN]
	Rabbits (Dutch Belted)	Oral (gavage)	GD 7-20 (GD 7-15 for TK)	0, 2, 15 (maternal toxicity), 300 (developmental toxicity (for both maternal and F_1 generation toxicity)	Yes[g]	MRL-WP	TT #[redacted]-7050	[Ref. 4.2.3.5.2: TT[redacted]7050FIN]
	Rats Crl:WI(Han)	Oral (gavage)	GD 6-LD 20	0, 5, 45, 450 (for both maternal and F_1 generation toxicity)	Yes[f]	MRL-WP	TT #[redacted]-7010	[Ref. 4.2.3.5.3: TT[redacted]7010FIN]
	Rats Crl:WI(Han)	Oral (gavage)	PND 14-55	0, 5, 45, 150, 300	No	MRL-WP	TT #[redacted]-7005	[Ref. 4.2.3.5.4: TT[redacted]7005FIN]
	Rats Crl:WI(Han)	Oral (gavage)	PND 14-55	0, 10, 45, 300	Yes[f]	MRL-WP	TT #[redacted]-7140	[Ref. 4.2.3.5.4: TT[redacted]7140FIN]
Local Tolerance	Isolated Bovine Cornea	In vitro	4 hr	0.75 mL ([redacted]% DOR solution)	Yes	[redacted]	TT #[redacted]-7857	[Ref. 4.2.3.6: TT[redacted]7857FIN]
	MatTek EpiDerm™	In vitro	1, 4, 24 hr	100 mg	Yes	[redacted]	TT #[redacted]-7858	[Ref. 4.2.3.6: TT[redacted]7858FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Other Toxicity Studies								
Immunotoxicology	Mouse (CBA/J)	Topical, ear	3 days	5, 10 and 25% (w/v) DRO in DMF	Yes	[redacted]	TT #[redacted]-7859	[Ref. 4.2.3.7.2: TT[redacted]7859FIN]
Impurities	Rats Crl:WI(HAN)	Oral (gavage)	3 Months	0, 115 (Batch Study)	Yes	MRL-F	TT #[redacted]-6035	[Ref. 4.2.3.7.6: TT[redacted]6035FIN]
	Rats Crl:WI(HAN)	Oral (gavage)	3 Months	30 (0.4% Phenol Degradate)	Yes	MRL-F	TT #[redacted]-6017	[Ref. 4.2.3.7.6: TT[redacted]6017FIN]
	Rats Crl:WI(HAN)	Oral (gavage)	3 Months	Group 1: DOR & TDF Degradate G Control Group 2: DOR at 30 mg/kg/day Group 3: TDF Degradate G at 0.3mg/kg/day [fumaric acid ester]	Yes	MRL-F	TT #[redacted]-6010	[Ref. 4.2.3.7.6: TT[redacted]6010FIN]
Phototoxicity	Rats Crl:LE (Long-Evans)	Oral (gavage)	3 Days	0, 30, 450	Yes	[redacted]	TT #[redacted]-9011	[Ref. 4.2.3.7.7: TT[redacted]9011FIN]
Urine Study	Rats (Female) Crl:WI(Han)	Oral (gavage)	10 Days	450	No	MRL-WP	TT #[redacted]-1095	[Ref. 4.2.3.7.7: TT[redacted]1095FIN]
Combination Toxicity Study	Rats Crl:WI(HAN)	Oral (gavage)	1 Month	●MK-1439 Control + MK-8591 Control; ●(MK-1439 Control +) 3 mg/kg/day MK-8591; ●30 mg/kg/day MK-1439 (+ MK-8591 Control); ●30 mg/kg/day MK-1439 + 1 mg/kg/day MK-8591; ●30 mg/kg/day MK-1439 + 3 mg/kg/day MK-8591	Yes	MRL-WP	TT #[redacted]-1012	[Ref. 4.2.3.7.7: TT[redacted]1012FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
Other Toxicity Studies (continued)								
Long-Acting Parenteral (LAP) Formulation	Rats (Males) Crl:WI(HAN)	IM	Dosed on Day 1 & 30 Necropsy Day 34	Doses of 2 formulations each administered on SD 1and SD 30 only Formulation 1: 200 mg of DOR/mL aqueous suspension containing 3% PEG 3350 isotonic. Formulation 2: 150 mg of DOR/mL solution in N-methyl pyrrolidone Placebo Control 1: Suspension containing 3% PEG 3350 isotonic Placebo Control 2: N-methyl pyrrolidone	No	MRL-F	TT #[redacted]-6034	[Ref. 4.2.3.7.7: TT[redacted]6034FIN]
	Rats Crl:WI(HAN)	SC or IM	15 Day (once weekly for a total of 3 doses)	60 mg/kg/dose (8 µm d50 PSD formulation) given as three once weekly doses. Vehicle Control Article = 3.84% PEG 3350, 0.256% Polysorbate 80, 0.9% Sodium Chloride, and 0.176% Sodium Phosphate Monobasic Monohydrate Vehicle Control 1: SC; Vehicle Control 2: IM	No	MRL-WP	TT #[redacted]-1033	[Ref. 4.2.3.7.7: TT[redacted]1033FIN]
	Rats Crl:WI(HAN)	IM	3 Week (once weekly for 3 doses followed by a 1-week treatment free period)	15, 30, 60 mg/kg/dose (2 or 8 µm d50 PSD formulation in Placebo 1 or Placebo 2, respectively) given as three once weekly doses – Groups 4-6 Group 1 = Saline Control; Group 2 = Placebo 1: (1% Polysorbate 80) Group 3 = Placebo 2: (0.2% Polysorbate 80)	Yes	MRL-F	TT #[redacted]-6016	[Ref. 4.2.3.7.7: TT[redacted]6016FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
	Rats Crl:WI(HAN)	SC	3 Week (once weekly for 3 doses followed by a 1-week treatment free period)	15, 30, 60 mg/kg/dose (2 or 8 µm d50 PSD formulation in Placebo 1 or Placebo 2, respectively) given as three once weekly doses – Groups 4-6 Group 1 = Saline Control; Group 2 = Placebo 1: (1% Polysorbate 80); Group 3 = Placebo 2: (0.2% Polysorbate 80)	Yes	MRL-F	TT #[redacted]-6015	[Ref. 4.2.3.7.7: TT[redacted]6015FIN]
	Rats Crl:WI(HAN)	IM	Days 1, 8, 15 with 2-Month Treatment-Free Period	10 or 40 mg/kg/dose (0.25 µm [nano-formulation] d50 PSD) Control: 4% Vitamin E TPGS, 10 mM phosphate buffer, and 0.9% sodium chloride in water for injection	No	MRL-WP	TT #[redacted]-1065	[Ref. 4.2.3.7.7: TT[redacted]1065FIN]
	Dogs (Beagle)	IM	1 day (1 or 2 doses) with a 13-week observation period	200 mg/animal Group 2: 2 IM injections (0.5 mL each) of [redacted]% DOR API (d50 PSD of 8.0 µm) in 0.2% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/ 10 mM sodium phosphate monobasic monohydrate Group 3: Single IM injection (1.0 mL) of [redacted]% DOR API (d50 PSD of 2.0 µm) in 1.0% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/ 10 mM sodium phosphate monobasic monohydrate Vehicle Control (Group 1): 1.0% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/10 mM sodium phosphate monobasicmonohydrate	No	MRL-WP	TT #[redacted]-1081	[Ref. 4.2.3.7.7: TT[redacted]1081FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses[a]	GLP Compliance	Testing Facility	Study Number	Location Vol. Section
	Dogs (Beagle)	IM or SC	1 day (with a 13-week observation period)	Single dose of 200 mg [1.0 mL – SC or 0.66 mL or 1.0 mL – IM] or 300 mg [1.0 mL- IM] (d50 PSD of 8.0 µm) in vehicle Vehicle Control: Day 1 (IM); Day 2 (SC) - 0.2% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/10 mM sodium phosphate monobasic monohydrate)	No	MRL-WP	TT #[redacted]-1061	[Ref. 4.2.3.7.7: TT[redacted]1061FIN]
	Dogs (Beagle)	IM	1 day (with a 13-week observation period)	Single dose of 200 mg (1.0 mL/dose) (d50 PSD of 0.3 µm) in vehicle (4.0% (w/w) TPGS/0.9% sodium chloride/10mM sodium phosphate monobasic monohydrate)	No	MRL-WP	TT #[redacted]-1106	[Ref. 4.2.3.7.7: TT[redacted]1106FIN]
	Dogs (Beagle)	IM	1 day (with ~8.5 month observation period)	Single dose of 200 mg (d50 PSD of 16.0 µm) in 0.2% Polysorbate 80/3.0% PEG 3350/0.9% sodium chloride/0.137% sodium phosphate monobasic	No	MRL-WP	TT #[redacted]-1064	[Ref. 4.2.3.7.7: TT[redacted]1064FIN]

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Sec. 2.6.7.1 Toxicology: Overview (Continued)

Test Article: DOR

a Doses are mg/kg/day unless otherwise specified. For Repeat-Dose Toxicity, the highest NOAEL (No-Observed-Adverse-Effect Level) is underlined.
b GLP compliant with the exception of confirmatory genotyping of female study animals.
c GLP compliant with the exception that urinary crystal identification and metabolite profiling were performed non-GLP.
d GLP compliant with the exception that metabolite profiling was performed non-GLP.
e GLP compliant with the exceptions that physical stability of the [redacted] formulation of DOR in the vehicle and the exploratory metabolite profiling were performed using non-GLP assays.
f GLP compliant with the exception of determination of the physical stability of the formulation which was performed using a non-GLP assay.
g GLP compliant with the exception of the skeletal evaluation by micro-CT and determination of the physical stability of the formulation.

API = Active pharmaceutical ingredient; b.i.d. = Twice daily dosing; d50 PSD = mass median diameter particle size distribution; DMF = N,NDimethylformamide; DOR = Doravirine; GD = Gestation Day; IM = Intramuscular; LAP = Long-Acting Parenteral; LD = Lactation Day; OD = Once daily dosing; SC = Subcutaneous; SD = Study Day; TDF = Tenofovir Disoproxil Fumarate; TK = Toxicokinetic; TPGS = Vitamin E tocopherol polyethylene glycol succinate

[redacted] = [redacted], U.S.A.
MRL-F = Merck Research Laboratories, Mirabel, Riom, France.
MRL-WP = Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
[redacted] = [redacted], U.S.A

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Sec. 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies

Test Article: DOR

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)[a]	GLP Compliance	Study Number	Location Vol. Section
1-Month Range-Finding & TK	rasH2 Wild-Type Mice (Hybrid)	Oral (gavage)	0, 30, 100, 300, 450	Yes[b]	TT #[redacted]-6010	[Ref. 4.2.3.2: TT[redacted]6010FIN]
3-Month Range Finding & TK	Mice CRL:CD1(ICR)	Oral (gavage)	0, 3, 30, 150, 300, 450	Yes	TT #[redacted]-6013	[Ref. 4.2.3.2: TT[redacted]6013FIN]
7 Day Tolerability with TK	Rats (Female) Crl:WI(Han)	Oral (gavage)	0, 5, 100, 750 (total) (given as b.i.d. doses)	No	TT #[redacted]-2518	[Ref. 4.2.3.2: TT[redacted]2518FIN]
7 Day TK	Rats Crl:WI(Han)	Oral (gavage)	1.5, 15, 175, 225 (given as b.i.d. doses) 30, 175, 225 (QD)	Yes	TT[redacted]-0019	[Ref. 4.2.3.2: TT[redacted]0019FIN]
2-Week Toxicity with TK	Rats Crl:WI(Han)	Oral (gavage)	0, 5, 75, 450	Yes	TT #[redacted]-6029	[Ref. 4.2.3.2: TT[redacted]6029FIN]
3-Month Toxicity with TK	Rats Crl:WI(Han)	Oral (gavage)	0, 3, 30, 450	Yes	TT #[redacted]-6040	[Ref. 4.2.3.2: TT[redacted]6040FIN]
6-Month Toxicity with TK	Rats Crl:WI(Han)	Oral (gavage)	0, 3, 30, 450	Yes[c]	TT #[redacted]-6019	[Ref. 4.2.3.2: TT[redacted]6019FIN]
14-Day Toxicity with TK	Dogs (Beagle)	Oral (gavage)	10	Yes	TT #[redacted]-6030	[Ref. 4.2.3.2: TT[redacted]6030FIN]
3-MonthToxicity with TK	Dogs (Beagle)	Oral (gavage)	0, 1,10, 1000	Yes	TT #[redacted]-6039	[Ref. 4.2.3.2: TT[redacted]6039FIN]
9-Month Toxicity with TK	Dogs (Beagle)	Oral (gavage)	0, 1, 10, 1000	Yes[d]	TT #[redacted]-6018	[Ref. 4.2.3.2: TT[redacted]6018FIN]

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Sec. 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies (Continued)

Test Article: DOR

Type of Study	Test System	Method of Administration	Doses (mg/kg/day)[a]	GLP Compliance	Study Number	Location Vol. Section
6-Month Carcinogenicity with TK	rasH2 Transgenic Mice	Oral (gavage)	0, 10, 60, 300	Yes	TT #[redacted]-6005	[Ref. 4.2.3.4.1: TT[redacted]6005FIN]
2-Year Carcinogenicity with TK[e]	Crl:WI(HAN)	Oral (gavage)	0, 3, 30, 450	Yes[f]	TT #[redacted]-6029	[Ref. 4.2.3.4.1: TT[redacted]6029FIN]
Embryo-fetal Development with TK	Rats Crl:WI(Han)	Oral (gavage)	0, 5, 45, 450	Yes[g]	TT #[redacted]-7040	[Ref. 4.2.3.5.2: TT[redacted]7040FIN]
Exploratory Single Dose TK (Non-Pregnant)	Rabbits (Dutch Belted)	Oral (gavage)	1, 10, 100, 1000	No	TT #[redacted]-7206	[Ref. 4.2.3.5.2: TT[redacted]7206FIN]
Exploratory Single Dose TK (Non-Pregnant)	Rabbits (Dutch Belted)	Oral (gavage)	15, 50, 150, 450	No	TT #[redacted]-7207	[Ref. 4.2.3.5.2: TT[redacted]7207FIN]
Exploratory 5-Day TK (Non-Pregnant)	Rabbits (Dutch Belted)	Oral (gavage)	15, 50, 150, 300, 450	No	TT #[redacted]-7277	[Ref. 4.2.3.5.2: TT[redacted]7277FIN]
Embryo-fetal Development with TK	Rabbits (Dutch Belted)	Oral (gavage)	0, 2, 15, 300	Yes[g]	TT #[redacted]-7050	[Ref. 4.2.3.5.2: TT[redacted]7050FIN]
Exploratory Range-Finding with TK in Juveniles	Rats Crl:WI(Han)	Oral (gavage)	0, 5, 45, 150, 300	No	TT #[redacted]-7005	[Ref. 4.2.3.5.4: TT[redacted]7005FIN]
Toxicity and TK in Juveniles	Rats Crl:WI(Han)	Oral (gavage)	0, 10, 45, 300	Yes[h]	TT[redacted]-7140	[Ref. 4.2.3.5.4: TT[redacted]7140FIN]

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Sec. 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies (Continued)

Test Article: DOR

b.i.d = twice daily; DOR = Doravirine; QD = once daily; TK = Toxicokinetics

a Unless specified otherwise.
b GLP compliant with the exception of confirmatory genotyping of female study animals.
c GLP compliant with the exception that urinary crystal identification and metabolite profiling were performed non-GLP.
d GLP compliant with the exception that metabolite profiling was performed non-GLP.
e Two-Year Oral Carcinogenicity Study in Rats with a Six-Month Toxicokinetic Evaluation with TK at SW 14 & 27 (1 hr and 14 hr only) at C_{max} and C_{min}
f GLP compliant with the exceptions that physical stability of the [redacted] formulation of DOR in the vehicle and the exploratory metabolite profiling were performed using non-GLP assays.
g GLP compliant with the exception of the skeletal evaluation by micro-CT and determination of the physical stability of the formulation.
h GLP compliant with the exception of determination of the physical stability of the formulation which was performed using a non-GLP assay.

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Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data

Test Article: DOR

Steady-State AUC(0-24hr) µM/hr

Daily Dose (mg/kg/day)	Mice	Rats	Dogs	Rabbits	Humans*
1 (SD 1)			42.1[i], 39[j]	10.3[m]	
1 (SW 13)			76.2 [i], 82.2[j]		
2 (GD 15)				13.8[p]	
3 (SD 7) – given as 1.5 mg/kg b.i.d.		19.3[d]			
3 (SW 13)	19.8[b]	23.8[f], 19.1[g]			
5 (SD 7) - given as 2.5 mg/kg b.i.d		50.3[c]			
5 (SW 2)		38.1[e]			
5 (GD 15)		61.2[l]			
5 (PND 55)		37.4[q]			
10 (SD 1)			155[h], 190[i], 187[j]	29.1[m]	
10 (SD 14)			301[h]		
10 (SW 13)			323[i], 383[j]		
10 (SW 27)	36.7[k]				
10 (PND 55)		48.5[r]			
15 (SD 1)				156[n]	
15 (SD 5)				107[o]	
15 (GD 15)				80.7[p]	

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Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data (Continued)

Test Article: DOR

Steady-State AUC(0-24hr) µM/hr

Daily Dose (mg/kg/day)	Mice	Rats	Dogs	Rabbits	Humans*
30 (SD 7) – given as 15 mg/kg b.i.d.		98.3[d]			
30 (SD 7)		110[d]			
30 (SW 4)	54.7[a]				
30 (SW 13)	79.5[b]	119[f], 87.3[g]			
45 (GD 15)		243[l]			
45 (PND 55)		151[q], 137[r]			
50 (SD 1)				385[n]	
50 (SD 5)				218[o]	
60 (Week 27)	98[k]				
75 (SW 2)		156[e]			
100 (SD 1)				63.3[m]	
100 (SD 7) – given as 50 mg/kg b.i.d.		207[c]			
100 (SW 4)	117 [a]				
150 (SD 1)				335[n]	
150 (SD 5)				291[o]	
150 (SW 13)	170[b]				
150 (PND 55)		253[q]			
175 (SD 7)		155[d]			
225 (SD 7)		167[d]			

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Sec. 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data (Continued)

Test Article: DOR

Steady-State AUC(0-24hr) µM/hr

Daily Dose (mg/kg/day)	Mice	Rats	Dogs	Rabbits	Humans*
300 (SD 5)				364[o]	
300 (SW 4)	220[a]				
300 (SW 13)	201[b]				
300 (SW 27)	228[k]				
300 (GD 15)				315[p]	
300 (PND 55)		308[q], 333[r]			
350 (SD 7) given as 175 mg/kg b.i.d.		214[d]			
450 (SD 1)				433[n]	
450 (SD 5)				336[o]	
450 (SD 7) – given as 225 mg/kg b.i.d.		244[d]			
450 (SW 2)		233[e]			
450 (SW 4)	217[a]				
450 (SW 13)	196[b]	253[f], 279[g]			
450 (GD 15)		345[l]			
750 (SD 7) – given as 375 mg/kg b.i.d.		235[c]			
1000 (SD 1)		389[i], 548[j]		80.5[m]	
1000 (SW 13)		683[i], 673[j]			

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Sec 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data (Continued)

Test Article: DOR

Plasma DOR Concentrations (µM)[S]

Daily Dose (mg/kg/day)	Rats	
	1 hr	24 hr
3 (SW 14)	2.89	0.259
3 (SW 27)	3.20	0.290
30 (SW 14)	14.7	1.12
30 (SW 27)	14.4	1.41
450 (SW 14)	39.3	2.37
450 (SW 27)	38.4	2.71

*The clinical $AUC_{-24hr,ss}$ of 37.8 µM•hr is based on Phase 3 trials (P018 and P021) at a clinical dose of 100 mg/day.
b.i.d = twice daily; DOR = Doravirine; SD = Study Day; SW = Study Week
a = TT #[redacted]-6010 [Ref. 4.2.3.2: TT[redacted]6010FIN] One-Month Oral Range-Finding and Toxicokinetic Study in rasH2 Wild Type Mice (Hybrid)
b = TT #[redacted]-6013 [Ref. 4.2.3.2: TT[redacted]6013FIN] Three-Month Oral Range-Finding and Toxicokinetic Study in CD1 Mice
c = TT #[redacted]-2518 [Ref. 4.2.3.2: TT[redacted]2518FIN] Exploratory 7-Day Oral Tolerability Study in Female Rats
d = TT #[redacted]-0019 [Ref. 4.2.3.2: TT[redacted]0019FIN] Seven-Day Oral Toxicokinetic Study in Rats
e = TT #[redacted]-6029 [Ref. 4.2.3.2: TT[redacted]6029FIN] Two-Week Oral Toxicity Study in Rats with a Functional Observational Battery Assay
f = TT #[redacted]-6040 [Ref. 4.2.3.2: TT[redacted]6040FIN]Three-Month Oral Toxicity Study in Rats
g = TT #[redacted]-6019 [Ref. 4.2.3.2: TT[redacted]6019FIN] Six-Month Oral Toxicity Study in Rats
h = TT #[redacted]-6030 [Ref. 4.2.3.2: TT[redacted]6030FIN] Fourteen-Day Oral Toxicity Study in Dogs
i = TT #[redacted]-6039 [Ref. 4.2.3.2: TT[redacted]6039FIN] Three-Month Oral Toxicity Study in Dogs
j = TT #[redacted]-6018 [Ref. 4.2.3.2: TT[redacted]6018FIN] Nine-Month Oral Toxicity Study in Dogs
k = TT #[redacted]-6005 [Ref. 4.2.3.4.1: TT[redacted]6005FIN] Six-Month Oral Carcinogenicity Study in rasH2 Transgenic Mice
l = TT #[redacted]-7040 [Ref. 4.2.3.5.2: TT[redacted]7040FIN] Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats
m = TT #[redacted]-7206 [Ref. 4.2.3.5.2: TT[redacted]7206FIN] Exploratory Oral Single-Dose Toxicokinetic Study in Nonpregnant Rabbits
n = TT #[redacted]-7207 [Ref. 4.2.3.5.2: TT[redacted]7207FIN] Exploratory Oral Single-Dose Toxicokinetic Study in Nonpregnant Rabbits
o = TT #[redacted]-7277 [Ref. 4.2.3.5.2: TT[redacted]7277FIN] Exploratory Five-Day Oral Toxicokinetic Study in Nonpregnant Rabbits
p = TT #[redacted]-7050 [Ref. 4.2.3.5.2: TT[redacted]7050FIN] Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits
q = TT #[redacted]-7005 [Ref. 4.2.3.5.4: TT[redacted]7005FIN] Exploratory Oral Range-Finding Toxicity and Toxicokinetic Study in Juvenile Rats
r = TT #[redacted]-7140 [Ref. 4.2.3.5.4: TT[redacted]7140FIN] Oral Toxicity and Toxicokinetic Study in Juvenile Rats
s = TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] Two-Year Oral Carcinogenicity Study in Rats with a Six-Month Toxicokinetic Evaluation (at C_{max} and C_{min})

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Sec. 2.6.7.4 Toxicology: Drug Substance

Test Article: DOR

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, area %)[3] A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	Study Number	Type of Study
PROPOSED SPECIFICATION[1]:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	*	*	*	*	*	*	*	*	*	TT #[redacted]-8021	Microbial Mutagenesis Assay
[redacted]	*	*	*	*	*	*	*	*	*	TT #[redacted]-2518	Exploratory 7-Day Oral Tolerability Study in Female Rats
										TT #[redacted]-8707	Assay for Micronucleus Induction in Rat Bone Marrow from an Exploratory 7-Day Oral Tolerability Study
[redacted]	*	*	*	*	*	*	*	*	*	TT #[redacted]-7206	Exploratory Oral Single Dose Toxicokinetic Study in Nonpregnant Rabbits
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-6029	Fourteen-Day Oral Toxicity Study in Rats
										TT #[redacted]-6030	Fourteen-Day Oral Toxicity Study in Dogs
										TT #[redacted]-8099	Microbial Mutagenesis Assay
										TT #[redacted]-8113	Microbial Mutagenesis Assay
										TT #[redacted]-8725	Assay for Micronucleus Induction in Rat Bone Marrow from a Two-Week Oral Toxicity study in Rats Study
										TT #[redacted]-7207	Exploratory Oral Single Dose Toxicokinetic Study in Nonpregnant Rabbits

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Sec. 2.6.7.4 Toxicology: Drug Substance (Continued)

Test Article: DOR

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, area %)[3] A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	Study Number	Type of Study
PROPOSED SPECIFICATION[1]:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-6040	Three-Month Oral Toxicity Study in Rats
										TT #[redacted]-6039	Three-Month Oral Toxicity Study in Dogs
										TT #[redacted]-8662	Exploratory Assay For Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells
										TT #[redacted]-8666	Assay For Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells
										TT #[redacted]-7045	Exploratory Oral Range-Finding Toxicity Study in Pregnant Rats
										TT #[redacted]-7040	Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats
										TT #[redacted]-7277	Exploratory Oral 5-Day Toxicokinetic Study in Nonpregnant Rabbits
										TT #[redacted]-7055	Exploratory Oral Range-Finding Toxicity Study in Pregnant Rats

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Sec. 2.6.7.4 Toxicology: Drug Substance (Continued)

Test Article: DOR

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, area %)[3] A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	Study Number	Type of Study
PROPOSED SPECIFICATION[1]:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-1095	Exploratory Ten-Day Oral-Dose Urine Examination Study in Female Rats
										TT #[redacted]-7050	Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-6010	Three-Month Oral Toxicity Study in Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-9011	Three-Day Oral Phototoxicity Study in Rats
										TT #[redacted]-6010	One-Month Oral Range-Finding and Toxicokinetic Study in rasH2 Wild-Type Mice (Hybrid)
										TT #[redacted]-6013	Three-Month Oral Range-Finding and Toxicokinetic Study in CD1 Mice
										TT #[redacted]-6019	Six-Month Oral Toxicity Study in Rats
										TT #[redacted]-6018	Nine-Month Oral Toxicity Study in Dogs
										TT #[redacted]-7857	Bovine Corneal Opacity and Permeability Test (BCOP)
										TT #[redacted]-7858	MatTek EpiDermTM MTT Viability Assay
										TT #[redacted]-7859	Local Lymph Node Assay in Mice (LLNA)

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Sec. 2.6.7.4 Toxicology: Drug Substance (Continued)

Test Article: DOR

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, area %)[3] A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	Study Number	Type of Study
PROPOSED SPECIFICATION[1]:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-0019	Seven-Day Oral Toxicokinetic Study in Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-6005	6-Month Oral Carcinogenicity Study in Transgenic Mice
										TT #[redacted]-6029	Two-Year Oral Carcinogenicity Study in Rats
										TT #[redacted]-7300	Oral Fertility Study in Female and Male Rats
										TT #[redacted]-6034	Exploratory 34-Day Intramuscular Local Tolerance and Toxicokinetic Study in Male Rats
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-7010	Oral Pre- and Postnatal Developmental Toxicity Study in Rats
										TT #[redacted]-7005	Exploratory Oral Range-Finding Toxicity and Toxicokinetic Study in Juvenile Rats
										TT #[redacted]-7140	Oral Toxicity and Toxicokinetic Study in Juvenile Rats
										TT #[redacted]-6017	Three-Month Oral Toxicity Study in Rats
										TT #[redacted]-1012	One-Month Oral Combination (*with MK-8591*) Toxicity Study in Rats

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Sec. 2.6.7.4 Toxicology: Drug Substance (Continued)

Test Article: DOR

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, area %)[3] A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	Study Number	Type of Study
PROPOSED SPECIFICATION[1]:											
										TT #[redacted]-1033	Exploratory Fifteen-Day Subcutaneous and Intramuscular Tolerability and Toxicokinetic Study in Rats
										TT #[redacted]-1061	Exploratory Single-Dose Intramuscular and/or Subcutaneous Toxicokinetic Study in Dogs
										TT #[redacted]-1081	Exploratory Single-Dose Intramuscular Toxicokinetic Study in Dogs
										TT #[redacted]-6035	Three-Month Oral Toxicity Study in Rats
										TT #[redacted]-1106	Exploratory Single-Dose Intramuscular Toxicokinetic Study in Dogs
										TT #[redacted]-1065	Exploratory Intermittent-Dose Intramuscular Toxicity Study in Rats with a Two-Month Treatment-Free Period
										TT #[redacted]-6029	Two-Year Oral Carcinogenicity Study in Rats
										TT #[redacted]-6015	Three-Week Subcutaneous Toxicity Study in Rats with a 1-Week Treatment Free Period
										TT #[redacted]-6016	Three-Week Intramuscular Toxicity Study in Rats with a 1-Week Treatment Free Period
										TT #[redacted]-6015	Three-Week Subcutaneous Toxicity Study in Rats with a 1-Week Treatment Free Period
										TT #[redacted]-6016	Three-Week Intramuscular Toxicity Study in Rats with a 1-Week Treatment Free Period

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Sec. 2.6.7.4 Toxicology: Drug Substance (Continued)

Test Article: DOR

Batch No.	Purity (%)[2]	Specified Impurities (HPLC, area %)[3] A[4]	B[5]	C[6]	D[7]	E[8]	F[9]	G[10]	H[11]	Study Number	Type of Study
PROPOSED SPECIFICATION[1]:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TT #[redacted]-1064	Exploratory Single-Dose Intramuscular Toxicokinetic Study in Dogs

1 See [Sec. 3.2.S.4.1] for complete specification.
2 Purity: HPLC weight percent (dry basis) for proposed specified purity and HPLC weight percent or HPLC area percent for individual batch purity.
3 Specified impurities: HPLC area percent.
4 [redacted]
5 [redacted]
6 [redacted]
7 [redacted]
8 [redacted]
9 [redacted]
10 Individual, Unspecified impurity. For lots with multiple unspecified impurities, this value represents the worst case (i.e., the unspecified impurity present at the highest level).
11 Total impurities.
ND = None detected

* Early chemistry batch. Purity ~100%. Impurity profile not characterized.

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Sec. 2.6.7.5 Single-Dose Toxicity

Test Article: **DOR**

No formal acute toxicity studies have been conducted with DOR. However, the toxicity after a single dose can be assessed from the repeat-dose oral toxicity studies in mice (up to 450 mg/kg/day), rats (up to 750 mg/kg/day) and dogs (up to 1000 mg/kg/day) [Sec 2.6.7.6] and [Sec. 2.6.7.7]. A dog oral pharmacology study testing single doses of DOR ranging from 2 mg/kg to 750 mg/kg was performed as described in the pharmacology written summary [Sec. 2.6.2], and single dose toxicokinetic studies in rabbits to support embryo-fetal toxicity studies were performed as described in [Sec. 2.6.7.11].

C Confidential

Sec. 2.6.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies

Test Article: DOR

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	NOAEL[b] (mg/kg)	Noteworthy Findings	Study Number
rasH2 Wild-Type Mice (Hybrid)	Oral (gavage) (0.5% (w/v) methylcellulose with 5mM hydrochloric acid in deionized water)	1 Month	0, 30, 100, 300, 450	Toxicity Arm:10/sex/group; TK Arm: 5/sex/control group; 11/sex/test article-dosed group	≥ 450	No test article-related mortality or changes in clinical observations, body weights, clinical or anatomic pathology. There were no substantial sex-related differences in mean systemic exposure to DOR or in mean C_{max} at all doses in Study Week 4. Mean systemic exposure and mean C_{max} were less than dose-proportional across 30, 100, and 300 mg/kg/day doses, and were similar at 300 mg/kg/day and 450 mg/kg/day.	TT #[redacted]-6010 [Ref. 4.2.3.2: TT[redacted]6010FIN]
Rats (Female) Crl:WI(Han)	Oral (gavage) (10% Polysorbate 80 in deionized water)	7 Days	0, 5, 100, 750 (total) (given as b.i.d. doses)	5/sex/group	≥ 750	No test article-related mortality, physical signs, effects on body weight, gross or histomorphologic changes, or changes in liver weight were noted at doses ≤375 mg/kg/day b.i.d. (750 mg/kg/day). Hematological findings at 2.5 mg/kg/ b.i.d (5 mg/kg/day) consisted of very slight decreases in red blood cells, hemoglobin and % hematocrit. At doses of 50 mg/kg/ b.i.d. (100 mg/kg/day) and 375 mg/kg/ b.i.d. (750 mg/kg/day), very slight decreases in red blood cells and slight decreases in hemoglobin and % hematocrit were noted (up to approximately -10%). Serum biochemistry findings were only observed at 375 mg/kg/ b.i.d., and consisted of very slight decreases (up to approximately -7%) in albumin and total protein.	TT #[redacted]-2518 [Ref. 4.2.3.2: TT[redacted]2518FIN]

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Sec. 2.6.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies (Continued)

Test Article: DOR

Species/ Strain	Method of Administration (Vehicle/Formulation)	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	NOAEL[b] (mg/kg/day)	Noteworthy Findings	Study Number
Rats Crl:WI(Han)	Oral (gavage) (0.5% methylcellulose with 5mM hydrochloric acid in deionized water)	7 Days (TK Study)	1.5, 15, 175, 225 (given as b.i.d. doses) 30, 175, 225 (QD)	4/sex/group	N/A	There was no test article-related morality in this TK study. **Plasma MK-1439 toxicokinetic parameters:** 1.5 mg/kg b.i.d. in F/M, respectively: AUC_{0-24} (µM•hr): 25.0/13.5 C_{max} (µM): 1.62/0.966 T_{max} (hr): 4.3/1.0 15 mg/kg b.i.d. in F/M, respectively: AUC_{0-24} (µM•hr): 117/79.4 C_{max} (µM): 7.02/5.50 T_{max} (hr): 6.3/6.7 30 mg/kg/day in F/M, respectively: AUC_{0-24} (µM•hr): 126/94.9 C_{max} (µM): 9.11/8.33 T_{max} (hr): 2.3/1.7 175 mg/kg/day in F/M, respectively: AUC_{0-24} (µM•hr): 193 and 116 C_{max} (µM): 13.2 and 9.07 T_{max} (hr): 1.7 and 3.0 175 mg/kg b.i.d. in F/M, respectively: AUC_{0-24} (µM•hr): 260 and 169 C_{max} (µM): 14.9 and 9.61 T_{max} (hr): 6.3 and 4.7 225 mg/kg/day in F/M, respectively: AUC_{0-24} (µM•hr): 195 and 139 C_{max} (µM): 13.6 and 9.35 T_{max} (hr): 2.0 and 2.0 225 mg/kg b.i.d. in F/M, respectively: AUC_{0-24} (µM•hr): 296 and 192 C_{max} (µM): 16.1 and 10.6 T_{max} (hr): 2.7 and 1.0	TT[redacted]-0019 [Ref. 4.2.3.2 : TT[redacted]0019 FIN]

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Sec. 2.6.7.6 Repeat-Dose Toxicity: Non-Pivotal Studies (Continued)

Test Article: DOR

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	NOAEL[b] (mg/kg/day)	Noteworthy Findings	Study Number
Dogs (Beagle)	Oral (gavage) (10% Polysorbate 80 in deionized water)	14 Days	10	2/sex/group	10	There was no test article-related mortality. There were no test article-related clinical observations, or effects on body weights, food consumption, ophthalmology, ECGs, hematology, serum biochemistry, urinalysis, organ weights, and gross or histomorphologic examinations. **Toxicokinetic Parameters (F/M, respectively):** • Study Day 1 $AUC_{0\text{-}24\ hr}$ (µM•hr): 153/156 C_{max} (µM): 8.82/7.67 T_{max} (hr): 2.0/6.0 • Study Day 14 $AUC_{0\text{-}24\ hr}$ (µM•hr): 289/313 C_{max} (µM): 17.0/14.4 T_{max} (hr): 2.0/1.5	TT #[redacted]-6030 [Ref. 4.2.3.2: TT [redacted]6030FIN]

b.i.d. = twice daily; DOR = Doravirine; ECGs = Electrocardiograms; F = Female; N/A = Not Applicable; M = Male; QD = Once daily; TK = Toxicokinetics

a Unless otherwise noted
b No-Observed-Adverse-Effect Level

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Sec. 2.6.7.7A Repeat-Dose Toxicity: Three-Month Oral Range-Finding and Toxicokinetic Study in CD1 Mice (TT #[redacted]-6013)

Test Article: **DOR**

Species/Strain: Mouse, CRL:CD1(ICR)
Initial Age: ~6 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 3 Months
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)

Study Number: TT #[redacted]-6013
Location in CTD: Vol. Section [Ref. 4.2.3.2: TT[redacted]6013FIN]
GLP Compliance: Yes

Special Features:
No-Observed-Adverse-Effect Level: ≥ 450 mg/kg/day

Daily Dose (mg/kg)	0 (Control)		3		30		150		300		450	
Number of Animals	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Toxicokinetics[a] – SW 13	F:5	M:5	F:11	M:11	F:11	M:11	F:11	M:11	F:11 or 10	M:11	F:11	M:11
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	21.9	17.7	94.7	64.3	206	135	244	157	236	156
C_{max} (µM)	N/A	N/A	3.23	3.24	12.0	11.6	22.2	14.6	23.4	22.8	25.1	23.2
T_{max} (hr)	N/A	N/A	1.0	0.50	0.50	1.0	1.0	0.50	1.0	1.0	2.0	1.0

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Sec. 2.6.7.7A Repeat-Dose Toxicity

Study No.: TT #[redacted]-6013 [Ref. 4.2.3.2: TT[redacted]6013FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		3		30		150		300		450	
Number of Animals	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Noteworthy Findings												
Mortality (No. of Animals)	-	-	-	-	-	-	-	-	-	-	-	1[b]
Body Weight (%)[c]	31.4 g	43.6 g	+2.9	+5.0	+2.5	+7.8	+0.3	-3.0	+0.6	+3.0	-4.1	-2.8
Body Weight Change (%)[d]	5.6	7.3	+20	+19	+25	+37	+5.4	-15	+16	+8.2	[-16]	[-33%]
Clinical Observations	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-	-	-	-	-
Serum Biochemistry	-	-	-	-	-	-	-	-	-	-	-	-
Organ weights (%)	-	-	-	-	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-	-	-	-	-
Histomorphology	-	-	NE	NE	NE	NE	NE	NE	NE	NE	-	-

a TK samples from controls were not analyzed. TK Arm included 2 replacement animals/sex/group. Three males in the TK arm at 300 mg/kg/day were found dead on SDs, 11, 24, and 26 respectively. The cause of death in these animals was consistent with intubation accidents. One male in the TK arm at 150 mg/kg/day was found dead on SD 89. The cause of death in this animal was a consequence of anesthesia for blood sampling from orbital sinus.
b One male in the range-finding arm at 450 mg/kg/day was found dead on SD 9; cause of death consistent with intubation accident.
c At end of dosing period (Week 13). For controls, group means are shown. For dose groups, percent differences from controls are shown.
d Body weight change between pretest and Week 13. For controls, group means are shown. For dose groups, percent differences from controls are shown.

DOR = Doravirine; HPMCAS-LG = Hydroxypropyl methylcellulose acetate succinate – LG; N/A = Not applicable; NE = Group not examined.; [redacted]F = [redacted] Formulation
[ ] = Test article-related change based on incidence and/or severity.
- = No noteworthy findings.

Confidential

Sec. 2.6.7.7B Repeat-Dose Toxicity: Two-Week Oral Toxicity Study in Rats with a Functional Observational Battery Assay (TT #[redacted]-6029)

Test Article: DOR

Species/Strain: Rats Crl:WI(Han)
Initial Age: 10 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 2 Weeks
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)

Study Number: TT #[redacted]-6029
Location in CTD: Vol. Section [Ref. 4.2.3.2: TT[redacted]6029FIN]
GLP Compliance: Yes

Special Features: A functional observational battery assay was conducted to evaluate potential nervous system effects in male rats (first 6/group) after a single oral dose on Study Day 1.
No-Observed-Adverse-Effect Level: ≥ 450 mg/kg/day

Daily Dose (mg/kg)	0 (Control)[a]		5		75		450	
Number of Animals	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Toxicokinetics[b] – SW 2								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	45.1	31.1	189	123	272	194
C_{max} (µM)	N/A	N/A	3.50	3.15	14.8	10.5	16.7	13.8
T_{max} (hr)	N/A	N/A	1.0	2.0	1.0	1.0	6.0	6.0

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Sec. 2.6.7.7B Repeat-Dose Toxicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.2: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[a]		5		75		450	
Number of Animals	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Noteworthy Findings								
Mortality (No. of Animals)	0	0	0	0	0	0	0	0
Body Weight (%)[c]	200.5 g	330.4 g	+1.3	-2.5	+3.5	-1.9	+0.8	-3.5
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations								
Postdose Salivation	0	0	0	0	0	0	[3/10]	[9/10]
Urine Crystals – Ex vivo	0	0	0	0	0	0	[7/10][d]	0
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Biochemistry	-	-	-	-	-	-	-	-
Urinalysis/Urine Chemistry	-	-	-	-	-	-	-	-
Functional Observational Battery	N/A	-	N/A	-	N/A	-	N/A	-
Organ Weights	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Histomorphology	-	-	NE	NE	NE	NE	-	-

a Control = HPMCAS-LF polymer at 180 mg/mL in 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water.
b DOR concentrations from all control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).
c At end of dosing period (Week 2). For controls, group means are shown. For dose groups, percent differences from controls are shown.
d See TT #[redacted]-1095 [Ref. 4.2.3.7.7: TT[redacted]1095FIN] for discussion of ex vivo urine crystals.
DOR = Doravirine; HPMCAS-LG = Hydroxypropyl methylcellulose acetate succinate – LG; N/A = Not applicable; NE = Group not examined; [redacted]F = [redacted] Formulation.
[ ] = Test article-related change based on incidence and/or severity.
- = No noteworthy findings.

C Confidential

Sec. 2.6.7.7C Repeat-Dose Toxicity: Three-Month Oral Toxicity Study in Rats (TT #[redacted]-6040)

Test Article: **DOR**

Species/Strain: Rats Crl:WI(Han)
Initial Age: ~6 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 3 Months
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMC-AS-LG)

Study Number: TT #[redacted]-6040
Location in CTD: Vol. Section [Ref. 4.2.3.2: TT[redacted]6040FIN]
GLP Compliance: Yes

Special Features: N/A
No-Observed-Adverse-Effect Level: ≥ 450 mg/kg/day

Daily Dose (mg/kg)	0 (Control)[b]		3		30		450	
Number of Animals	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Toxicokinetics – SW 13[a]								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	29.7	17.9	136	101	310	195
C_{max} (µM)	N/A	N/A	2.4	1.73	11.1	9.85	22.8	16.6
T_{max} (hr)	N/A	N/A	1.0	1.0	2.0	2.0	2.0	1.0

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Sec. 2.6.7.7C Repeat-Dose Toxicity

Study No.: TT #[redacted]-6040 [Ref. 4.2.3.2: TT[redacted]6040FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[b]		3		30		450	
Number of Animals	F:10	M:10	F:10	M:10	F:10	M:10	F:10	M:10
Noteworthy Findings								
Mortality (No. of Animals)	0	0	1[c]	0	0	0	0	0
Body Weight (%)[d]	231.1 g	432.0 g	+2.8	+0.7	+2.6	+2.6	+6.5	+1.4
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations								
Postdose Salivation	0	2/10	0	1/10	0	0	[4/10]	[6/10]
Urine Crystals – Ex vivo	0	0	0	0	1/10	0	[7/9][e]	0
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Biochemistry	-	-	-	-	-	-	-	-
Urinalysis/Urine Chemistry	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Histomorphology	-	-	NE[f]	NE	NE	NE	-	-

a DOR concentrations from all control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).
b Control = HPMCAS-LF polymer at 180 mg/mL in 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water.
c One 3 mg/kg/day female was found dead following the Week 13 (8 hr) blood collection. Death was attributed to the blood collection procedure.
d At end of dosing period (Week 13). For controls, group means are shown. For dose groups, percent differences from controls are shown.
e See TT #[redacted]-1095 [Ref. 4.2.3.7.7: TT[redacted]1095FIN] for discussion of ex vivo urine crystals.
f Not Examined, with the exception of one 3 mg/kg-dosed female whose death was attributed to the blood collection procedure

DOR = Doravirine; HPMCAS-LG = Hydroxypropyl methylcellulose acetate succinate – LG; N/A = Not applicable; NE = Group not examined; [redacted]F = [redacted] Formulation.
[ ] = Test article-related change based on incidence and/or severity.
- = No noteworthy findings.

C Confidential

Sec. 2.6.7.7D Repeat-Dose Toxicity: Six-Month Oral Toxicity Study in Rats (TT #[redacted]-6019)

Test Article: **DOR**

Species/Strain: Rats Crl:WI(Han)
Initial Age: 5 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 6 Months
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)

Study Number: TT #[redacted]-6019
Location in CTD: Vol. Section [Ref. 4.2.3.2: TT[redacted]6019FIN]
GLP Compliance: Yes[a]

Special Features: Exploratory urinary crystal identification was performed and exploratory non-GLP semi-quantitative metabolite analysis for assessment of DOR M9 metabolite was performed using liquid chromatography – quadrupole time-of-flight mass spectrometry following protein precipitation with acetonitrile on pooled plasma samples (Day 87) and analyzed for rats in the 30 and 450 mg/kg/day groups.
No-Observed-Adverse-Effect Level: ≥ 450 mg/kg/day

Daily Dose (mg/kg)	0 (Control)[b]		3		30		450	
Number of Animals	F:15	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Toxicokinetics – SW 13[c]								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	25.2	13.0	108	66.7	352	206
C_{max} (µM)	N/A	N/A	1.86	1.37	10.3	7.24	28.1	16.0
T_{max} (hr)	N/A	N/A	2.0	1.0	1.0	1.0	2.0	2.0

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Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.:** TT #[redacted]-6019 [Ref. 4.2.3.2: TT[redacted]6019FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[b]		3		30		450	
Number of Animals	F:15	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Peak Area Ratios (PAR) of M9 Metabolite to Parent (DOR) – Day 88 (time proportional pool from 0-24 hr) – PAR(X1000)								
DOR	N/A	N/A	N/A	N/A	323	253	1150	735
M9 Metabolite	N/A	N/A	N/A	N/A	0.4	0.7	3.2	2.3
Ratio of M9/DOR[d]	N/A	N/A	N/A	N/A	0.0012	0.0029	0.0028	0.0032

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Sec. 2.6.7.7D Repeat-Dose Toxicity

Study No.: TT #[redacted]-6019 [Ref. 4.2.3.2: TT[redacted]6019FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[b]		3		30		450	
Number of Animals	F:15	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Noteworthy Findings								
Mortality (No. of Animals)	1[e]	0	0	0	0	1[f]	0	0
Body Weight (%)[g]	261.7 g	503.3 g	+1.9	-2.6	+3.5	+0.5	+4.4	+4.7
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations								
Postdose Salivation	0	1/15	0	1/15	0	0	[15/15]	[15/15]
Urine Crystals – Ex vivo	0	0	0	0	0	0	[7/13][h]	[5/15][h]
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology								
Prothrombin Time (sec) – Week 27	10.9	11.6	10.8	12.4*	10.5	[12.7*]	10.6	[12.6*]
Activated Partial Thromboplastin Time (sec) – Week 27	18.2	18.8	18.9	19.5	18.6	[19.8*]	19.3	[20.6*]
Serum Biochemistry	-	-	-	-	-	-	-	-

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Sec. 2.6.7.7D Repeat-Dose Toxicity

Study No.: TT #[redacted]-6019 [Ref. 4.2.3.2: TT[redacted]6019FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[b]		3		30		450	
Number of Animals	F:15	M:15	F:15	M:15	F:15	M:15	F:15	M:15
Urinalysis/Urine Chemistry								
Urine Volume								
Week 12	9	9	8	12	7	11	[4]	11
Week 24	9	9	8	11	9	12	[7]	11
Specific Gravity								
Week 12	1.024	1.033	1.029	1.029	1.029	1.028	[1.041]	1.032
Week 24	1.024	1.029	1.024	1.027	1.024	1.025	[1.031]	1.031
pH								
Week 12 (Individual values <5.5)	6.3 (Mean)	-	0	-	0	-	[3/13] samples	-
Organ Weights	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Histomorphology	-	-	NE	NE	NE	NE[i]	-	-

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Sec. 2.6.7.7D Repeat-Dose Toxicity **Study No.:** TT #[redacted]-6019 [Ref. 4.2.3.2: TT[redacted]6019FIN] (Continued)

a With the exception that crystal identification and metabolite profiling were performed non-GLP.
b Control = HPMCAS-LF polymer at 180 mg/mL in 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water.
c DOR concentrations from all control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).
d Assuming HRMS ionization of M9 equivalent to that of DOR, a ratio of 1 would indicate that levels of M9 would be expected to be essentially equivalent to DOR for that given sample.
e One control female was found dead on Study Day 165 following blood sampling for hematological and serum biochemical examinations (Study Week 24). This death was considered related to an anesthesia accident.
f One male dosed at 30 mg/kg was found dead on Study Day 85. No relevant clinical signs were observed prior to death. The main histomorphologic findings were seen in the kidneys (pelvis dilatation, papilla necrosis, and mineralization), urinary bladder (dilatation, inflammation, and mineralization), prostate and seminal vesicle (inflammation). Mineralization was also seen in the heart, aorta, and stomach. These changes generally correlated with the gross observations (kidney discoloration and pelvic dilatation, urinary bladder dilatation and discoloration, prostate discoloration) and supported urinary obstruction as a cause of death, unrelated to test article. The mineralization seen in several tissues was consistent with uremia secondary to urinary obstruction.
g At end of dosing period (Week 26). For controls, group means are shown. For dose groups, percent differences from controls are shown.
h See TT #[redacted]-1095 [Ref. 4.2.3.7.7: TT[redacted]1095FIN] for discussion of ex vivo urine crystals.
i Not Examined, with the exception of the one incidental death in the 30 mg/kg dose group.

DOR = Doravirine; HPMCAS-LG = Hydroxypropyl methylcellulose acetate succinate – LG; N/A = Not applicable; NE = Group not examined; [redacted]F = [redacted] Formulation
[ ] = Test article-related change based on incidence and/or severity.
- = No noteworthy findings.
* = P-value ≤.05

Confidential

Sec. 2.6.7.7E Repeat-Dose Toxicity: Three-Month Oral Toxicity Study in Dogs (TT #[redacted]-6039)

Test Article: **DOR**

Species/Strain: Dogs (Beagle)
Initial Age: 29 to 38 weeks
Date of First Dose: [redacted]
Dose Volume: 5 mL/kg

Duration of Dosing: 3 Months
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle Formulation: 10% (10:90 w/w) Polysorbate 80 in deionized water
DOR Formulation: Base compound in vehicle

Study Number: TT #[redacted]-6039
Location in CTD: Vol. Section [Ref. 4.2.3.2: TT[redacted]6039FIN]
GLP Compliance: Yes

Special Features: N/A
No-Observed-Adverse-Effect Level: ≥ 1000 mg/kg/day

Daily Dose (mg/kg)	0 (Control)[a]		1		10		1000	
Number of Animals	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Toxicokinetics – SD 1[b]								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	38.0	46.2	220	161	413	364
C_{max} (µM)	N/A	N/A	2.24	2.51	11.8	7.88	22.5	19.9
T_{max} (hr)	N/A	N/A	2.7	3.3	2.7	4.7	24	24

Confidential

Sec. 2.6.7.7E Repeat-Dose Toxicity

Study No.: TT #[redacted]-6039 [Ref. 4.2.3.2: TT[redacted]6039FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[a]		1		10		1000	
Number of Animals	F:3	M:3	F:3	M:3	F:3	M:3	F:3	M:3
Toxicokinetics – SW 13[b]								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	72.8	79.6	350	295	754	613
C_{max} (µM)	N/A	N/A	4.27	4.46	17.9	16.0	36.7	31.2
T_{max} (hr)	N/A	N/A	2.7	2.3	4.0	2.0	2.7	2.7
Noteworthy Findings								
Mortality (No. of Animals)	-	-	-	-	-	-	-	-
Body Weight (%)[c]	8.6 kg	10.6 kg	+3.5	-6.6	-4.7	-7.5	-4.7	-6.6
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations								
Discolored Feces (pale brown or white)	0	0	0	1/3	0	0	[3/3]	[3/3]
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiograms	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-
Serum Biochemistry	-	-	-	-	-	-	-	-
Urinalysis/Urine Chemistry	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Histomorphology	-	-	NE	NE	NE	NE	-	-

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Sec. 2.6.7.7E Repeat-Dose Toxicity **Study No.:** TT #[redacted]-6039 [Ref. 4.2.3.2: TT[redacted]6039FIN] (Continued)

a 10% (10:90 w/w) Polysorbate 80 in deionized water.
b DOR concentrations from all control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).
c At end of dosing period (Week 13). For controls, group means are shown. For dose groups, percent differences from controls are shown.

DOR = Doravirine; N/A = Not applicable; NE = Group not examined; SD = Study Day; SW = Study Week
[ ] = Test article-related change based on incidence and/or severity.
- = No noteworthy findings.

Confidential

Sec. 2.6.7.7F Repeat-Dose Toxicity: Nine-Month Oral Toxicity Study in Dogs (TT #[redacted]-6018)

Test Article: DOR

Species/Strain: Dog/Beagle
Initial Age: 25 to 29 weeks
Date of First Dose: [redacted]
Dose Volume: 5 mL/kg

Duration of Dosing: 9 months
Duration of Postdose: None
Method of Administration: Oral (gavage)
Vehicle and Control Formulation: 10% (w/w) Polysorbate 80 in deionized water
DOR Formulation: DOR (base compound) in 10% (w/w) Polysorbate 80 in deionized water

Study Number: TT #[redacted]-6018
Location in CTD: Vol. Section [Ref. 4.2.3.2: TT[redacted]6018FIN]
GLP Compliance: Yes[a]

Special Features: Exploratory non-GLP semi-quantitative metabolite analysis for assessment of DOR M9 metabolite was performed by high performance liquid chromatography coupled with high resolution mass spectrometry (HPLC-HRMS) using pooled plasma samples (Day 88) and analyzed for dogs in the 10 and 1000 mg/kg/day groups.
No-Observed-Adverse-Effect Level: ≥1000 mg/kg/day

Daily Dose (mg/kg)	0 (Control)[b]		1		10		1000	
Number of Animals	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Toxicokinetics – Study Day 1[c]								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	37.9	40.1	205	169	518	579
C_{max} (µM)	N/A	N/A	2.06	2.16	10.4	8.43	24.8	27.5
T_{max} (hr)	N/A	N/A	4.5	4.8	4.5	6.0	11	7.5
Toxicokinetics - Study Week 13[d]								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	80.7	83.8	365	402	643	704
C_{max} (µM)	N/A	N/A	4.14	4.39	18.5	19.9	30.7	34.8
T_{max} (hr)	N/A	N/A	4.5	4.5	2.8	4.0	3.3	5.0

Confidential

Sec. 2.6.7.7F Repeat-Dose Toxicity **Study No.:** TT #[redacted]-6018 [Ref. 4.2.3.2: TT[redacted]6018FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[b]		1		10		1000	
Number of Animals	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Peak Area Ratios (PAR) of M9 Metabolite to Parent (DOR) – Day 88 (time proportional pool from 0-24 hr) – PAR(X1000)								
DOR	N/A	N/A	N/A	N/A	426	463	667	734
M9 Metabolite	N/A	N/A	N/A	N/A	1.2	1.4	2.3	2.6
Ratio of M9/DOR[e]	N/A	N/A	N/A	N/A	0.0028	0.0031	0.0034	0.0035

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Sec. 2.6.7.7F Repeat-Dose Toxicity **Study No.:** TT #[redacted]-6018 [Ref. 4.2.3.2: TT[redacted]6018FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[b]		1		10		1000	
Number of Animals	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Noteworthy Findings								
Mortality (No. of Animals)	-	-	-	-	-	-	1/4[f]	-
Body Weight (%)[g]	8.5 kg	10.7 kg	-1.2	-7.5	-1.2	-0.9	-4.7	-4.7
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations								
Eye Discharge, Clear	1/4	-	-	-	[1/4]	[2/4]	[2/4]	[4/4]
Feces								
Discolored	-	-	1/4	1/4	2/4	1/4	[4/4]	[4/4]
Unformed	4/4	4/4	[4/4]	[3/4]	[4/4]	[4/4]	[4/4]	[4/4]
Other Substance in Pan	-	-	[1/4]	[1/4]	-	-	[4/4]	[4/4]
Salivation	-	-	-	[3/4]	-	[1/4]	[2/4]	[2/4]
Ophthalmoscopy	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-

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Sec. 2.6.7.7F Repeat-Dose Toxicity **Study No.:** TT #[redacted]-6018 [Ref. 4.2.3.2: TT[redacted]6018FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[b]		1		10		1000	
Number of Animals	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4
Noteworthy Findings (continued)								
Hematology	-	-	-	-	-	-	-	-
Coagulation	-	-	-	-	-	-	-	-
Serum Biochemistry	-	-	-	-	-	-	-	-
Urinalysis/Urine Chemistry	-	-	-	-	-	-	-	-
Organ weights	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Histomorphology	-	-	NE	NE	NE	NE	-	-

a GLP compliant with the exception that metabolite profiling was performed non-GLP.
b 10% (10:90 w/w) Polysorbate 80 in deionized water.
c DOR concentrations from all control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).
d DOR concentrations in plasma from control animals were above the lower limit of quantitation (LLQ = 0.029 µM) at all time points for 3/8 animals, at 6 hours for 1/8 animals and at 24 hours for 1/8 animals. These values were less than 1.3% of the mean Cmax of the low dose group and there is no impact on the quality and integrity of the study.
e Assuming HRMS ionization of M9 equivalent to that of DOR, a ratio of 1 would indicate that levels of M9 would be expected to be essentially equivalent to DOR for that given sample.
f Sacrificed early on Study Day 247 (Study Week 36); clinical signs were considered to be consistent with an intubation accident.
g At end of dosing period (Week 38). For controls, group means are shown. For dose groups, percent differences from controls are shown.
N/A = Not applicable; NE = Group not examined.
[ ] = Test article-related change based on incidence and/or severity.
- = No noteworthy findings.

Confidential

Sec. 2.6.7.8A Genotoxicity – In Vitro: Microbial Mutagenesis Assay (TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113)

Test Article: **DOR**

Test for Induction of: Reverse mutation to wild type in bacteria cells
Strains: *Salmonella typhimurium* (TA1535, TA97a, TA98, and TA100), *Escherichia coli* (WP2 uvrA pKM101)
Metabolizing System: Xenobiotic-induced rat liver S-9; 50 µL/plate
Treatment: Approximately 48 hours

No. of Independent Assays: 1
No. of Replicate Cultures: 3 per dose point
No. of Cells Analyzed/Culture: Not applicable
Vehicle for Positive Controls: Solutions in DMSO or water depending on compound
Vehicle for Test Article: DMSO

Study No.: TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113
Location in CTD: Section [Ref. 4.2.3.3.1: TT[redacted]8021FIN]
GLP Compliance: Yes, except TT #[redacted]-8021 range-finding (RF) study
Date of Treatment: [redacted] (TT #[redacted]-8021); [redacted] (TT #[redacted]-8099); [redacted] (TT #[redacted]-8113)

Cytotoxic Effects: No inhibition of bacterial lawn growth or revertant growth was noted.
Genotoxic Effects†: None

† Criteria for a positive result are (1) a 2-fold or greater increase in number of revertant colonies, and (2) a dose-related increase in number of revertant colonies.

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Sec. 2.6.7.8A Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT[redacted]8021FIN] (Continued)

TT #[redacted]-8021 (Range-Finding)

	TA100 [redacted]				TA1535 [redacted]				TA97a [redacted]			
	Without S-9		With S-9		Without S-9		With S-9		Without S-9		With S-9	
Conc./Plate	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	176.8	13.3	185.0	22.9	24.1	5.9	26.9	8.1	233.6	12.1	309.3	23.0
30 µg	168.3	23.8	165.3	7.0	23.0	3.6	29.7	6.0	250.7	18.0	279.3	4.5
100 µg	171.0	13.1	185.7	2.9	22.0	8.2	17.3	1.2	232.3	15.5	311.0	28.1
300 µg	176.7*	22.4	181.0	5.6	14.0*	2.6	22.3	2.5	222.7*	1.2	315.7	36.5
1000 µg	169.3*	19.3	184.0*	12.8	18.7*	6.7	21.3*	1.5	199.7*	14.0	321.7*	6.7
3000 µg	166.3*	17.5	170.7*	2.5	28.3*	8.7	18.3*	2.1	209.0*	24.4	277.7*	12.5
5000 µg	PPT		161.7*	18.6	PPT		17.7*	3.2	PPT		PPT	

	TA98 [redacted]				WP2 uvrA pKM101 [redacted]			
	Without S-9		With S-9		Without S-9		With S-9	
Conc./Plate	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	46.2	9.9	55.8	5.6	120.1	13.6	123.3	18.0
30 µg	51.0	6.1	42.7	8.0	108.0	7.0	117.0	19.2
100 µg	32.0	7.8	56.3	12.1	126.7	23.8	115.0	19.0
300 µg	47.0*	10.6	42.7	1.2	117.7*	29.0	121.7	14.5
1000 µg	34.3*	9.5	46.3*	3.2	111.3*	4.2	121.7*	4.6
3000 µg	PPT		48.0*	7.2	145.7*	15.6	113.3*	15.0
5000 µg	PPT		PPT		PPT		113.3*	19.9

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Sec. 2.6.7.8A Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT [redacted]8021FIN] (Continued)

TT #[redacted]-8021 (Range-Finding) - continued

	TA100 [redacted]				TA1535 [redacted]				TA97a [redacted]			
	Without S-9		With S-9		Without S-9		With S-9		Without S-9		With S-9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO	176.8	13.3	185.0	22.9	24.1	5.9	26.9	8.1	233.6	12.1	309.3	23.0
2AA 1.0 µg	191.7	21.2	607.0	23.1	29.7	11.0	88.7	9.6	239.0	13.9	581.7	125.3
2AA 2.0 µg	182.0	31.6	1103.3	75.8	29.0	9.0	164.3	17.7	237.3	7.5	814.3	90.6
ICR-191 1.5 µg									1973.7	183.6		
Distilled Water	175.7	13.3			20.3	2.1						
Sodium azide 0.75 µg	649.0	30.5			481.0	42.9						

	TA98 [redacted]				WP2 uvrA pKM101 [redacted]			
	Without S-9		With S-9		Without S-9		With S-9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO	46.2	9.9	55.8	5.6	120.1	13.6	123.3	18.0
2AA 1.0 µg	51.0	8.9	319.0	28.0				
2AA 2.0 µg	43.3	10.0	636.3	46.6	129.0	14.0	270.3	38.6
2AA 5.0 µg					119.3	18.7	764.7	74.5

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Sec. 2.6.7.8A Genotoxicity – In Vitro Study No.: TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT[redacted]8021FIN] (Continued)

TT #[redacted]-8021 (Range-Finding) - continued

	TA98[redacted]				WP2 uvrA pKM101[redacted]			
	Without S-9		With S-9		Without S-9		With S-9	
Conc./Plate	Mean	SD	Mean	SD	Mean	SD	Mean	SD
2NF 1.0 µg	388.3	57.4						
4NQO 1.0 µg					676.7	142.7		

Salmonella typhimurium/E. coli genotypes:
TA100 his G46 (base substitution) ΔuvrB rfa pKM101 (R factor).
TA1535 his G46 (base substitution) ΔuvrB rfa.
TA97a his D6610 (frameshift) ΔuvrB rfa pKM101 (R factor).
TA98 his D3052 (frameshift) ΔuvrB rfa pKM101 (R factor).
WP2 uvrA pKM101 (trp-) ΔuvrA pKM101 (R factor).

S-9 = Metabolic activation.
SD = Standard deviation.
* = Precipitate; did not interfere with scoring.
PPT = Precipitate; plate unreadable.
! = Not all plates used to calculate mean.

2AA = 2-Aminoanthracene
4NQO = 4-Nitroquinoline-N-oxide
DMSO = Dimethyl sulfoxide
2NF = 2-Nitrofluorene

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Sec. 2.6.7.8A Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT[redacted]8021FIN] (Continued)

TT #[redacted]-8099

	TA100 [redacted]				TA1535 [redacted]				TA97a [redacted]			
	Without S-9		With S-9		Without S-9		With S-9		Without S-9		With S-9	
Conc./Plate	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	265.1	26.1	257.6	16.6	10.6	3.4	9.8	3.2	181.6	10.0	242.2	14.3
100 µg	266.7	13.8	268.0	22.5	10.0	2.6	9.7	2.1	182.0	8.7	232.3	18.9
300 µg	252.3*	27.1	258.0	21.0	7.7*	4.6	11.7	3.1	187.0*	4.6	244.3	3.5
1000 µg	212.7*	6.4	261.7*	12.2	8.0*	2.6	10.7*	6.4	178.0*	14.7	250.3*	15.9
3000 µg	215.0!*	NSD	234.0*	22.9	9.3*	4.9	11.7*	2.1	173.0!*	NSD	228.7*	10.3
5000 µg	PPT		246.3*	20.8	9.7*	4.0	10.7*	4.0	PPT		231.3*	3.2

	TA98 [redacted]				WP2 uvrA pKM101 [redacted]			
	Without S-9		With S-9		Without S-9		With S-9	
Conc./Plate	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	45.1	10.3	49.8	5.4	133.6	13.4	131.6	14.8
100 µg	41.7	1.2	54.0	12.3	135.3	18.0	135.7	6.5
300 µg	30.0*	4.4	47.3	7.5	120.3*	11.7	140.3	18.3
1000 µg	36.3*	5.5	58.0*	8.7	124.7*	17.1	136.3*	5.0
3000 µg	31.7*	3.5	45.3*	2.1	PPT		125.3*	11.7
5000 µg	PPT		55.0*	7.0	PPT		132.3*	13.0

Salmonella typhimurium/E. coli genotypes:
TA100 his G46 (base substitution) ΔuvrB rfa pKM101 (R factor).
TA1535 his G46 (base substitution) ΔuvrB rfa.
TA97a his D6610 (frameshift) ΔuvrB rfa pKM101 (R factor).
TA98 his D3052 (frameshift) ΔuvrB rfa pKM101 (R factor).
WP2 uvrA pKM101 (trp-) ΔuvrA pKM101 (R factor).

S-9 = Metabolic activation.
SD = Standard deviation.
* = Precipitate; did not interfere with scoring.
! = Not all plates used to calculate mean.
PPT = Precipitate; plate unreadable.
NSD= No standard deviation.

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Sec. 2.6.7.8A Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT[redacted]8021FIN] (Continued)

TT #[redacted]-8099 – continued

			Salmonella typhimurium strains							
	S-9	Conc./	TA1535		TA97a		TA98		TA100	
Mutagen†	+/-	Plate	Fold Inc		Fold Inc		Fold Inc		Fold Inc	
Sodium azide	-	0.75 µg	23.6		1.0		0.8		1.5	
ICR-191	-	1.5 µg	1.7		6.7		1.1		1.0	
2-Nitrofluorene	-	1.0 µg	0.9		2.0		3.2		1.5	
4NQO	-	1.0 µg	11.3		5.4		5.4		8.4	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
DMSO	-	100 µL	10.6	3.4	181.6	10.0	45.1	10.3	265.1	26.1
2AA	-	1.0 µg	12.3	7.4	212.7	8.6	39.0	6.9	276.0	3.5
2AA	-	2.0 µg	10.7	3.8	206.7	4.0	42.7	6.7	286.0	26.0
DMSO	+	100 µL	9.8	3.2	242.2	14.3	49.8	5.4	257.6	16.6
2AA	+	1.0 µg	70.7	5.1	649.0	39.9	159.7	15.0	645.7	35.9
2AA	+	2.0 µg	147.3	13.0	1141.0	81.3	349.7	16.7	1305.0	51.2
Distilled Water	-	100 µL	14.3	5.5	201.0	13.1	46.7	11.9	260.7	21.0

C Confidential

Sec. 2.6.7.8A Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT[redacted]8021FIN] (Continued)

TT #[redacted]-8099 – continued

Mutagen†	S-9 +/-	Conc./ Plate	*Escherichia coli* strains WP2 uvrA pKM101 Fold Inc	
Sodium azide	-	0.75 µg	1.0	
ICR-191	-	1.5 µg	1.0	
2-Nitrofluorene	-	1.0 µg	0.8	
4NQO	-	1.0 µg	6.1	
			Mean	SD
DMSO	-	100 µL	133.6	13.4
2AA	-	2.0 µg	140.7	17.0
2AA	-	5.0 µg	124.7	3.2
DMSO	+	100 µL	131.6	14.8
2AA	+	2.0 µg	278.3	27.1
2AA	+	5.0 µg	663.0	11.5
Distilled Water	-	100 µL	143.3	2.9

† = Sodium azide was dissolved in water; all other compounds, in DMSO.
SD = Standard Deviation.
S-9 = Metabolic activation.
2AA = 2-Aminoanthracene; DMSO = Dimethyl sulfoxide; 4NQO = 4-Nitroquinoline-N-oxide

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Sec. 2.6.7.8A Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT[redacted]8021FIN] (Continued)

TT #[redacted]-8113

TA100 [redacted]

	Without S-9		With S-9	
Conc./Plate	Mean	SD	Mean	SD
0 µg	186.5	12.1	150.3	20.0
100 µg	180.3	21.5	167.0	14.0
300 µg	173.7	13.3	167.0	26.5
1000 µg	170.7*	12.6	149.7*	21.4
3000 µg	165.7*	13.1	168.7*	14.0
5000 µg	153.3*	4.5	156.0*	5.3

Salmonella typhimurium genotype:
TA100 his G46 (base substitution) ΔuvrB rfa pKM101 (R factor).

S-9 = Metabolic activation.
SD = Standard deviation.
* = Precipitate; did not interfere with scoring.

Confidential

Sec. 2.6.7.8A Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8021, TT #[redacted]-8099, TT #[redacted]-8113 [Ref. 4.2.3.3.1: TT[redacted]8021FIN] (Continued)

TT #[redacted]-8113 - continued

Mutagen†	S-9 +/-	Conc./ Plate	*Salmonella typhimurium* strains TA100 Fold Inc / Mean	SD
Sodium azide	-	0.75 µg	2.6	
ICR-191	-	1.5 µg	1.1	
2-Nitrofluorene	-	1.0 µg	1.9	
4NQO	-	1.0 µg	9.6	
DMSO	-	100 µL	186.5	12.1
2AA	-	1.0 µg	177.0	14.0
2AA	-	2.0 µg	185.3	10.0
DMSO	+	100 µL	150.3	20.0
2AA	+	1.0 µg	368.7	27.8
2AA	+	2.0 µg	760.7	43.2
Distilled Water	-	100 µL	196.7	2.5

† = Sodium azide was dissolved in water; all other compounds, in DMSO.
SD = Standard Deviation.
S-9 = Metabolic activation.
2AA = 2-Aminoanthracene; DOR = Doravirine; DMSO = Dimethyl sulfoxide; 4NQO = 4-Nitroquinoline-N-oxide

Confidential

Sec. 2.6.7.8B Genotoxicity – In Vitro: Assay for Chromosomal Aberrations In Vitro, in Chinese Hamster Ovary Cells (TT #[redacted]-8662, TT #8666)

Test Article: DOR

Test for Induction of: Chromosome Aberrations
Strains: Chinese Hamster Ovary cells, clone WBL
Metabolizing System: Beta-naphthoflavone and phenobarbital-induced rat liver S9, 1.5%
Vehicle for Test Article: Dimethylsulfoxide (DMSO)
Treatment: Continuous treatment for 20 hours without S9; pulse treatment 3 hours with and without S9. Harvested 20 hours after beginning of treatment.

No. of Independent Assays: 1
No. of Replicate Cultures: 1
No. of Cells Analyzed/Culture: 200 except high-dose positive controls
Vehicle for Positive Controls: Distilled water
Vehicle for Test Article: DMSO

Study No.: TT #[redacted]-8662 and TT #[redacted]-8666
Location in CTD: Section [Ref. 4.2.3.3.1: TT[redacted]8662FIN]
GLP Compliance: Yes, TT #[redacted]-8662 was a range-finding (RF) study
Date of Treatment: [redacted] (TT #[redacted]-8662) and [redacted] (TT #[redacted]-8666)

Cytotoxic Effects: TT #[redacted]-8662 (RF): Precipitate and no marked cell growth reduction. At the end of treatment, precipitate was evident at 500 µM and above for the 3-hour treatments (with and without S-9) and at 250 µM and above for the 20-hour treatment without S-9.

TT #[redacted]-8666: Precipitate and moderate cell growth reduction in the 20-hour treatment without S-9. Cell growth for the top dose scored at this treatment was reduced to 74% of concurrent solvent controls. At the end of treatment, precipitate was evident at 300 µM and above for the 3-hour treatments (with and without S-9) and at 200 µM and above for the 20-hour treatment without S-9.
Genotoxic Effects: None†.

† A test is considered positive if there are statistically significant increases ($p \leq 0.05$) over concurrent controls in the percentages of aberrant cells at 2 or more separate concentrations of test article without greatly exceeding a 50% reduction in growth. The analysis is a pairwise comparison of the percentage of cells with aberrations at each dose level with the controls by Fisher's Exact test with the p-values adjusted for multiple comparisons against a common control by the method of Dunnett. The tests with and without S-9 activation, and different treatment lengths are considered separately.

Additional Comments Regarding Test: There was no evidence for any consistent or dose-related increase in polyploidy, and the maximum level of polyploidy and endoreduplication combined, 2.0%, is within the typical historical control range for this laboratory, 0.0 to 9.00%. Endoreduplication does not represent chromosome breakage. It is a form of polyploidy, and polyploidy is known to occur in several normal tissues in vivo. Endoreduplication in cultured cells occurs spontaneously and as a result of treatment with various agents. Possible mechanisms for endoreduplication include inhibition of normal DNA synthesis and/or temporary cell-cycle block in the G2 phase.

C Confidential

2.6.7.8B Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8662; TT #[redacted]-8666 [Ref. 4.2.3.3.1: TT[redacted]8662FIN] (Continued)

TT #[redacted]-8666: Assay for Chromosomal Aberrations
Summary of Cytotoxicity and Aberrations at 20 Hours

Treatment	Cell Growth (PD, % Control)	% Aberrant Cells	Frequency Abs per 100 Cells[a]	% Endos[b]	% Polys[c]
With S-9 (3-Hour Treatment)					
DMSO (1%)	100	0.50	0.50	0.2	0.6
DMSO (1%)	100	1.00	1.00	0.0	1.2
Cyclophosphamide (10 µM)[d]	50	34.00**	98.00	NS	NS
Cyclophosphamide (30 µM)[e]	23	88.00**	336.00	NS	NS
MK-1439 (µM)					
200	107	0.50	0.50	0.2	1.6
250	103	1.00	2.00	0.0	0.8
300[f]	98	1.00	1.00	0.0	0.8
350[f]	Discarded	NS	NS	NS	NS
400[f]	Discarded	NS	NS	NS	NS
450[f]	Discarded	NS	NS	NS	NS
500[f]	Discarded	NS	NS	NS	NS

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2.6.7.8B Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8662; TT #[redacted]-8666 [Ref. 4.2.3.3.1: TT[redacted]8662FIN] (Continued)

TT #[redacted]-8666: Assay for Chromosomal Aberrations (Continued)
Summary of Cytotoxicity and Aberrations at 20 Hours

Treatment	Cell Growth (PD, % Control)	% Aberrant Cells	Frequency Abs per 100 Cells[a]	% Endos[b]	% Polys[c]
Without S-9 (3-Hour Treatment)					
DMSO (1%)	100	0.00	0.50	0.0	0.8
DMSO (1%)	100	2.00	2.00	0.0	1.8
Mitomycin C (0.5 µM)[d]	84	20.00**	28.00	NS	NS
Mitomycin C (1.5 µM)[e]	66	48.00**	68.00	NS	NS
MK-1439 (µM)					
200	95	0.50	1.00	0.0	0.4
250	93	0.59	1.50	0.2	1.2
300[f]	92	1.50	2.00	0.2	1.4
350[f]	Discarded	NS	NS	NS	NS
400[f]	Discarded	NS	NS	NS	NS
450[f]	Discarded	NS	NS	NS	NS
500[f]	Discarded	NS	NS	NS	NS

Confidential

2.6.7.A.8B Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8662; TT #[redacted]-8666 [Ref. 4.2.3.3.1: TT[redacted]8662FIN] (Continued)

TT #[redacted]-8666: Assay for Chromosomal Aberrations (Continued)
Summary of Cytotoxicity and Aberrations at 20 Hours

Treatment	Cell Growth (PD, % Control)	% Aberrant Cells	Frequency Abs per 100 Cells[a]	% Endos[b]	% Polys[c]
Without S-9 (20-Hour Treatment)					
DMSO (1%)	100	1.50	1.50	0.0	1.0
DMSO (1%)	100	1.00	1.00	0.0	1.0
MK-1439 (µM)					
75	93	NS	NS	NS	NS
100	90	1.00	1.00	0.0	2.0
125	85	NS	NS	NS	NS
150	82	0.50	0.50	0.0	2.0
175	72	NS	NS	NS	NS
200[f]	74	1.00	1.50	0.0	1.0
225[f]	Discarded	NS	NS	NS	NS
250[f]	Discarded	NS	NS	NS	NS

Footnotes on following page.

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2.6.7.8B Genotoxicity – In Vitro **Study No.:** TT #[redacted]-8662; TT #[redacted]-8666 [Ref. 4.2.3.3.1: TT[redacted]8662FIN] (Continued)

a The total number of aberrations per 100 cells, since a cell may have more than one aberration.
b The number of endoreduplicated metaphases based on 500 cells.
c The number of polyploid metaphases based on 500 cells.
200 cells scored for aberrations per point except where noted.
d 50 cells scored for aberrations.
e 25 cells scored for aberrations.
f Precipitate observed at the end of treatment.
** A positive point that is statistically significant $p \leq 0.01$ compared to the relevant control group using a one-sided Fisher's exact test and is also outside the historical solvent control range.
Cyclophosphamide (CP) and Mitomycin C (MMC) are positive controls.
DMSO = Dimethyl sulfoxide; NS = Not scored; PD = Population doubling, RF = Range Finding

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Sec. 2.6.7.9A Genotoxicity – In Vivo: Assay for Micronucleus Induction in Rat Bone Marrow from an Exploratory 7-Day Oral Tolerability Study (TT #[redacted]-8707)

(Non-Pivotal) **Test Article: DOR**

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Rats / Crl:WI(Han)	Oral gavage (10% (w/w) polysorbate 80 in deionized water/ Suspension)	7 days: bone marrow sampled the day after the final dose	0, 5, 100, 750 (total daily dose) (given as 2.5, 5.0, 375 mg/kg b.i.d.)	5F	Negative up to 750 mg/kg/day (given as 375 mg/kg b.i.d.)	TT #[redacted]-8707[a] [Ref. 4.2.3.3.2: TT[redacted] 8707FIN]

a Conducted in conjunction with an exploratory 7-day oral tolerability study: TT #[redacted]-2518 [Ref. 4.2.3.2: TT[redacted] 2518FIN]
b.i.d. = twice daily; F = Female.

Confidential

Sec. 2.6.7.9B Genotoxicity – In Vivo: Assay for Micronucleus Induction in Rat Bone Marrow from a 2-Week Oral Toxicity Study (TT #[redacted]-8725)

Test Article: DOR

Test for Induction of: Micronuclei in rat bone marrow polychromatic erythrocytes
Species/Strain: Rat/WI (HAN)
Age: Approximately 10 weeks at start of dosing
Cells Evaluated: Polychromatic erythrocytes (PCE)
No. of Cells Analyzed/Animal: 2000 PCE

Treatment Schedule: 2 weeks
Sampling Time: 24 hours after final dose.
Method of Administration: Oral gavage
Vehicle/Formulation: HPMCAS-LF/Acidified Methylcel

Study No.: TT #[redacted]-8725
Location in CTD: Section [Ref. 4.2.3.3.2: TT[redacted]8725FIN]
GLP Compliance: Yes
Date of Dosing: [redacted] to [redacted]

Dose Selection: See Final Report for TT #[redacted]-6029 [Ref. 4.2.3.3.2: TT[redacted]6029FIN], Two-Week Oral Toxicity Study in Rats with a Functional Observational Battery Assay. Both females and males were used for the micronucleus study.

Additional Comments Regarding Test: Rats from the toxicity study, TT #[redacted]-6029, from which samples were taken for micronucleus analysis were treated once daily for 2 weeks at a dosing volume of 10 mL/kg/day and sacrificed the day after final treatment. Positive control(s) bone marrow slides from male rats previously treated with a single dose of mitomycin C (5 mL/kg, from TT #[redacted]-8609) and sacrificed about 24 hours after treatment were coded and randomly incorporated into the slides scoring process. Bone marrow samples were processed in accordance with the SOP for Assay for Micronucleus Induction in Rat Bone Marrow.
Toxic/Cytotoxic Effects: For clinical signs see Final Report for TT #[redacted]-6029 [Ref. 4.2.3.3.2: TT[redacted]6029FIN], Two-Week Oral Toxicity Study in Rats with a Functional Observational Battery Assay. There was no suppression of bone marrow polychromatic erythrocytes observed.

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Sec. 2.6.7.9B Genotoxicity – In Vivo **Study No.:** TT #[redacted]-8725 [Ref. 4.2.3.3.2: TT[redacted]8725FIN] (Continued)

Genotoxic Effects: Negative. Statistical analysis was not done since the mean incidences of MN-PCE for the test-article treated groups were within the typical historical vehicle control range.

Evidence of Exposure: See Final Report for TT #[redacted]-6029 [Ref. 4.2.3.3.2: TT[redacted]6029FIN], Two-Week Oral Toxicity Study in Rats with a Functional Observational Battery Assay.

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Sec. 2.6.7.9B Genotoxicity – In Vivo **Study No.:** TT #[redacted]-8725 [Ref. 4.2.3.3.2: TT[redacted]8725FIN] (Continued)

		Females				Males			
Treatment Dose	Harvest Time (Hr)	Total PCE	Total MN-PCE	MN-PCE/ 1000 PCE[a]	Percent PCE[b]	Total PCE	Total MN-PCE	MN-PCE/ 1000 PCE[a]	Percent PCE[b]
HPMCAS-LF/Acidified Methylcel 10 mL/kg	FN	20,000	33	1.7 ± 0.3	61.4 ± 2.1	20,000	36	1.8 ± 0.4	56.2 ± 2.4
MK-1439 - 5 mg/kg	FN	10,000	21	2.1 ± 0.8	62.1 ± 1.9	10,000	13	1.3 ± 0.4	54.9 ± 3.2
MK-1439 - 75 mg/kg	FN	10,000	17	1.7 ± 0.4	59.3 ± 6.3	10,000	13	1.3 ± 0.5	60.3 ± 4.2
MK-1439 - 450 mg/kg	FN	10,000	18	1.8 ± 0.6	62.6 ± 3.2	10,000	23	2.3 ± 0.9	60.8 ± 5.2
Mitomycin C 0.8 mg/kg	24	N/A	N/A	N/A	N/A	10,000	57	5.7 ± 2.9	63.0 ± 1.8
Mitomycin C 2.0 mg/kg	24	N/A	N/A	N/A	N/A	10,000	353	35.3 ± 6.4	61.8 ± 3.1

a Group mean ± standard error.

b PCE as a percent of 1000 total erythrocytes.

PCE = Polychromatic erythrocytes; MN-PCE = Micronucleated PCE, FN = Final necropsy, N/A = Not applicable.

DOR = Doravirine; HPMCAS-LF/Acidified Methylcel = HPMCAS-LF polymer in 0.5% (w/v) Methylcellulose with 5 mM Hydrochloric Acid in Deionized Water.

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Sec. 2.6.7.10A Carcinogenicity: Six-Month Oral Carcinogenicity Study in rasH2 Transgenic Mice (TT #[redacted]-6005)

Test Article: DOR

Species/Strain: rasH2 Transgenic Mice
Initial Age: 8 to 9 weeks
Date of First Dose: [redacted]
DOR Formulation: [redacted] F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)

Duration of Dosing: 6 Months
Method of Administration: Oral (gavage) for all groups except Positive Controls
Vehicle/Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
Treatment of Controls: Control 1 and 2: HPMCAS (120 mg/mL) in 0.5% methylcellulose with 5 mM HCl in deionized water; **Positive Control:** Urethane (1000 mg/kg) intraperitoneally on Study Days 1, 3 and 5

Study No.: TT #[redacted]-6005
Location in CTD: Vol. Section [Ref. 4.2.3.4.1: TT[redacted]6005FIN]
GLP Compliance: Yes

Basis for High-Dose Selection: The high-dose was the maximum feasible dose.

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		Positive Control		10		60		300	
Gender	F	M	F	M	F	M	F	M	F	M	F	M
Toxicokinetics[a] – Week 27												
AUC (µg•hr/mL)	N/A	N/A	N/A	N/A	NE	NE	40.0	33.5	123	79.3	273	182
C_{max} (µg/mL)	N/A	N/A	N/A	N/A	NE	NE	10.8	8.24	20.5	18.9	40.1	37.7
Number of Animals[b]												
At Start	27	27	27	27	12	12	27	27	27	27	27	27
Died/Sacrificed Moribund	2	-	-	1	9	9	-	2	1	-	1	3
Terminal Sacrifice	23	25	25	24	1	1	25	23	24	25	24	22
Survival (%)	92	100	100	96	10	10	100	92	96	100	96	88
Body Weight	-	-	-	-	- c	-c	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-	-	-	-	-

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Sec. 2.6.7.10A Carcinogenicity **Study No.:** TT #[redacted]-6005 [Ref. 4.2.3.4.1: TT[redacted]6005FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		Positive Control		10		60		300	
No. of Animals	F:25	M:25	F:25	M:25	F:10	M:10	F:25	M:25	F:25	M:25	F:25	M:25
Postmortem Findings												
Animals with malignant neoplasms	2	1	3	2	10	10	1	3	1	5	5	1
Animals with benign neoplasms	0	1	1	0	7	5	0	0	0	0	0	2
Animals with neoplasms	2	2	4	2	10	10	1	3	1	5	5	3
Total malignant neoplasms	2	1	5	2	13	14	1	3	1	5	5	1
Total benign neoplasms	0	1	1	0	7	5	0	0	0	0	0	2
Total neoplasms	2	2	6	2	20	19	1	3	1	5	5	3

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Sec. 2.6.7.10A Carcinogenicity **Study No.:** TT #[redacted]-6005 [Ref. 4.2.3.4.1: TT[redacted]6005FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		Positive Control		10		60		300	
No. of Animals	F:25	M:25	F:25	M:25	F:10	M:10	F:25	M:25	F:25	M:25	F:25	M:25
Postmortem Findings												
Statistically Significant Increases in Tumor Incidence												
Harderian Gland												
Adenoma[d]	0	0	1	0	0	0	0	0	0	0	0	2
Lung,												
Adenoma[e]	0	1	0	0	7	5	0	0	0	0	0	0
Adenocarcinoma[f]	0	0	2	0	3	5	0	0	0	1	0	0
Spleen												
Hemangiosarcoma[g]	1	0	1	2	10	9	1	1	0	4	2	1
Other Tumor Incidnece												
Harderian Gland												
Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	1	0
Stomach, nonglandular mucosa, squamous cell												
Carcinoma	0	1	0	0	0	0	0	0	0	0	0	0

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Sec. 2.6.7.10A Carcinogenicity **Study No.:** TT #[redacted]-6005 [Ref. 4.2.3.4.1: TT[redacted]6005FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		Positive Control		10		60		300	
No. of Animals	F:25	M:25	F:25	M:25	F:10	M:10	F:25	M:25	F:25	M:25	F:25	M:25
Postmortem Findings												
Other Tumor Incidence												
Skin												
Hemangiosarcoma	0	0	0	0	0	0	0	0	0	0	1	0
Skin, squamous cell												
Carcinoma	0	0	0	0	0	0	0	1	0	0	0	0
Lung												
Hemangiosarcoma	1	0	2	0	0	0	0	0	0	0	0	0
Body cavity, peritoneum												
Hemangiosarcoma	0	0	0	0	0	0	0	0	0	0	1	0
Body cavity, mediastinum												
Hemangiosarcoma	0	0	0	0	0	0	0	1	1	0	0	0
Gross Pathology	-	-	-	-	-	-	-	-	-	-	-	-
Histomorphology – Non-neoplastic findings	-	-	-	-	NE	NE	-	-	-	-	-	-

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Sec. 2.6.7.10A Carcinogenicity **Study No.:** TT #[redacted]-6005 [Ref. 4.2.3.4.1: TT[redacted]6005FIN] (Continued)

a DOR concentrations in plasma from all control mice at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.00935 µM) of the bioanalytical method.
b 27 (25 +2) or 12 (10 + 2) since two animals/sex/group were used as potential replacement animals during the first 2 weeks. Unused replacement animals were sacrificed and discarded without postmortem examination after the first 2 weeks.
c There was a marked increase in mean body weight gain of urethane-treated females and males from ~Week 4. This has been observed previously in rasH2 transgenic mice in this laboratory.
d A statistically significant increasing trend in tumor incidence through the 300 mg/kg/day dose tested was found for adenoma in harderian glands in male mice prior to multiplicity adjustment (P=0.033). After the adjustment of multiplicity, the increasing trend was not statistically significant (Adj. P=0.063). The incidence of adenomas of the harderian gland was 2/25 in males of the 300-mg/kg/day group whereas none were present in males of the low- and mid-dose or the concurrent control groups**.** It is of particular note that similar or higher (up to 3 per group) incidences of this tumor type have been found in 5/34 vehicle-treated male rasH2 historical control groups.
Therefore, the incidence of 2/25 adenomas of the harderian gland noted in this study is considered unrelated to treatment with the test article.
e P<0.001 (males and females)
f P<0.001 (males); P=0.014 (females)
g P<0.001 (males and females)
- = No noteworthy findings.
DOR = Doravirine; HPMCAS-LG = hydroxypropyl methylcellulose acetate succinate-LG; NE = Not Evaluated or Not Examined; N/A = Not Applicable

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Sec. 2.6.7.10B Carcinogenicity: Two-Year Oral Carcinogenicity Study in Rats with a Six-Month Toxicokinetic Evaluation (TT #[redacted]-6029)

Test Article: DOR

Species/Strain: Rat/Crl:WI(HAN)
Initial Age: 5 weeks
Date of First Dose: [redacted]
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)

Duration of Dosing: 104 Weeks
Method of Administration: Oral (gavage)
Vehicle/Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
Treatment of Controls 1 and 2: HPMCAS (180 mg/mL) in 0.5% methylcellulose with 5 mM HCl in deionized water

Study No.: TT #[redacted]-6029
Location in CTD: Vol. Section [Ref. 4.2.3.4.1: TT[redacted]6029FIN]
GLP Compliance: Yes[a]

Special Features: Exploratory non-GLP semi-quantitative metabolite analysis for assessment of DOR M9 metabolite was performed by high performance liquid chromatography coupled with high resolution mass spectrometry (HPLC-HRMS) in plasma and urine samples from 30 and 450 mg/kg/day groups.

Basis for High-Dose Selection: The high-dose was the maximum feasible dose.

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
Number of Animals:	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Toxicokinetics:[b,c]	F:4	M:4	NE	NE	F:4	M:4	F:4	M:4	F:4	M:4
Week 14 – 1 hr (µM)	N/A	N/A	N/A	N/A	3.10	2.67	16.9	12.6	47.5	31.1
Week 14 – 24 hr (µM)	N/A	N/A	N/A	N/A	0.431	0.0871	1.82	0.412	2.73	2.01
Week 27 – 1 hr (µM)	N/A	N/A	N/A	N/A	3.23	3.16	15.9	13.0	44.1	32.8
Week 27 - 24 hr (µM)	N/A	N/A	N/A	N/A	0.461	0.118	2.16	0.666	3.08	2.33

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
Number of Animals:	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Semi-Quantitative Analysis: DOR Concentrations (µM)[d]										
Plasma 1 hr	N/A	N/A	N/A	N/A	NE	NE	15.5	13.8	34.1	30.2
Plasma 24 hr	N/A	N/A	N/A	N/A	NE	NE	2.7	0.8	3.9	3.2
Urine (0-24 hr)	N/A	N/A	N/A	N/A	NE	NE	>100	~100	>100	>100
Semi-Quantitative Analysis: M9 Metabolite Concentrations (µM)[d]										
Plasma 1 hr	N/A	N/A	N/A	N/A	NE	NE	0.1	0.2	0.6	0.6
Plasma 24 hr	N/A	N/A	N/A	N/A	NE	NE	0.0	0.1	0.1	0.1
Urine (0-24 hr)	N/A	N/A	N/A	N/A	NE	NE	>10	>10	>10	>10

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
At Start	50	50	50	50	50	50	50	50	50	50
Died/Sacrificed Moribund	13	18	17	19	13	10	19	13	18	13
Terminal Sacrifice	37	32	33	31	37	40	31	37	32	37
Survival (%)	74	64	66	62	74	80	62	74	64	74
Body Weight	-	-	-	-	-	-	-	-	-	-
Clinical Observations										
Salivation, intermittent	1	11	1	11	1	2	7	19	[50]	[50]
Postmortem Findings										
Animals with malignant neoplasms	12	9	9	13	5	12	9	10	9	14
Animals with benign neoplasms	38	28	35	25	36	29	41	22	34	24
Animals with neoplasms	42	33	40	31	39	36	43	27	38	32
Total malignant neoplasms	14	9	9	15	5	12	10	10	9	15
Total benign neoplasms	61	34	52	33	49	38	63	34	53	38
Total neoplasms	75	43	61	48	54	50	73	44	62	53

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Statistically Significant Increases in Tumor Incidence										
Thyroid, parafollicular cell										
Adenoma[e]	1	2	0	4	0	3	1	2	5	3
Other Tumor Incidence										
Brain										
Astrocytoma	1	0	0	0	0	0	1	1	0	1
Granular cell tumor, benign	0	1	2	1	1	1	1	3	0	1
Oligodendroglioma, benign	0	0	0	0	0	0	1	0	0	0
Oligodendroglioma, malignant	0	0	0	0	0	0	0	0	1	0
Pituitary										
Adenoma	29	15	23	13	30	13	35	10	30	14
Pituitary, pars intermedia										
Adenoma	0	0	1	2	0	0	1	0	1	1

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Adrenal										
Ganglioneuroma	0	1	0	0	0	0	0	0	0	0
Pheochromocytoma, benign	1	2	1	1	1	0	1	1	0	2
Pheochromocytoma, malignant	0	0	0	0	0	1	0	0	0	1
Adrenal, adrenocortical										
Adenoma	2	1	0	0	1	0	1	0	0	1
Carcinoma	1	1	0	1	0	0	0	0	0	0
Thyroid										
Ganglioneuroma	1	0	0	0	0	0	0	0	0	0
Thyroid, parafollicular cell										
Carcinoma	0	0	0	0	0	0	0	1	1	0
Thyroid, follicular cell										
Adenoma	1	1	1	0	3	3	2	1	1	1
Carcinoma	1	0	0	1	0	0	0	1	0	2

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Parathyroid										
Adenoma	0	0	1	1	0	0	0	0	0	0
Salivary gland										
Fibrosarcoma	0	0	0	1	0	0	0	0	0	0
Myoepithelioma, malignant	1	0	0	0	0	0	0	0	0	0
Heart										
Fibroma	0	0	0	0	0	1	0	0	0	0
Myxosarcoma	0	0	1	0	0	0	0	0	0	0
Small intestine										
Fibroma	0	0	1	0	1	0	0	0	0	0
Large intestine										
Adenoma	0	0	0	1	0	0	0	0	0	0
Fibrosarcoma	0	0	0	0	0	0	1	0	0	0
Hemangiosarcoma	0	0	0	0	0	0	1	0	0	0
Leiomyosarcoma	1	0	0	0	0	0	0	0	0	0

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Stomach										
Adenocarcinoma	0	0	0	0	0	0	0	0	0	1
Hemangioma	0	0	0	0	0	0	0	0	0	1
Leiomyosarcoma	0	0	0	0	0	1	0	0	0	0
Papilloma	0	0	0	1	0	1	1	0	0	0
Kidney										
Adenoma	0	0	0	1	0	0	0	0	0	1
Liposarcoma	1	0	0	1	0	0	0	0	0	0
Nephroblastoma	0	0	0	0	1	1	0	0	0	0
Skin										
Fibroma	0	0	0	0	0	2	0	1	0	0
Fibrosarcoma	0	1	0	1	0	0	0	1	0	2
Hemangiosarcoma	0	0	0	0	0	1	0	0	0	0
Keratoacanthoma, benign	0	3	0	2	1	2	0	2	1	5
Lipoma	0	0	0	1	0	0	0	0	0	0
Papilloma	0	2	0	0	0	1	0	0	0	1

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Skin										
Paraganglioma, benign	0	0	1	0	0	0	0	0	0	0
Rhabdomyosarcoma	0	1	0	0	0	0	0	0	0	0
Schwannoma, malignant	0	1	0	0	0	0	0	1	0	0
Histiocytoma, fibrous	0	1	0	0	0	0	0	0	0	0
Skin, basal cell										
Adenoma	0	1	0	0	0	1	0	3	0	0
Carcinoma	1	0	1	0	0	0	0	0	0	0
Skin, squamous cell										
Carcinoma	0	1	0	0	0	0	0	0	0	0
Mammary gland										
Adenocarcinoma	2	0	1	0	2	0	1	0	2	0
Adenoma	1	0	1	0	1	0	1	0	1	0
Fibroadenoma	6	0	5	0	1	0	4	0	5	0

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Liver										
Adenoma	0	0	1	0	1	2	0	0	1	1
Carcinoma, hepatocellular	0	0	0	1	0	0	0	0	0	0
Lung										
Adenoma	0	0	0	0	0	1	0	0	0	0
Spleen										
Hemangioma	0	1	0	0	0	0	1	2	0	0
Hemangiosarcoma	0	0	0	1	0	0	0	0	0	1
Thymus										
Thymoma, benign	7	2	1	1	2	2	4	3	0	0
Thymoma, malignant	0	0	0	0	1	0	0	0	0	0
Lymph node										
Hemangioma	0	1	0	2	1	0	0	2	0	1
Hemangiosarcoma	0	1	1	4	0	1	0	3	0	3

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Pancreas										
Carcinoma	0	0	0	0	0	1	0	0	0	0
Pancreas, islet cell										
Adenoma	0	1	0	1	0	2	0	2	1	0
Carcinoma	0	0	0	0	0	2	0	0	0	1
Testis										
Leydig cell tumor, benign	0	0	0	0	0	1	0	0	0	3
Uterus										
Adenocarcinoma	1	0	0	0	0	0	1	0	1	0
Adenoma	0	0	0	0	0	0	2	0	0	0
Leiomyoma	1	0	0	0	0	0	0	0	0	0
Schwannoma, malignant	0	0	1	0	0	0	0	0	0	0
Uterus, endometrial stromal										
Polyp	3	0	3	0	0	0	4	0	0	0
Uterus, endometrial										
Stromal sarcoma	1	0	0	0	0	0	0	0	1	0

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Ovary										
Adenoma	0	0	0	0	0	0	1	0	0	0
Granulosa cell tumor, benign	0	0	1	0	2	0	0	0	2	0
Granulosa cell tumor, malignant	0	0	1	0	0	0	1	0	1	0
Leiomyoma	1	0	1	0	0	0	0	0	0	0
Luteoma, benign	1	0	0	0	0	0	0	0	0	0
Stromal tumor, benign	0	0	0	0	0	0	0	0	1	0
Vagina										
Schwannoma, malignant	0	0	0	0	0	0	1	0	0	0
Polyp, vaginal	0	0	0	0	0	0	0	0	1	0
Bone										
Osteosarcoma	0	0	0	0	0	0	0	1	1	1
Ear, squamous cell										
Carcinoma	0	0	0	2	0	1	0	0	0	0

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Primary site undetermined										
Plasma cell tumor, malignant	0	1	0	0	0	0	0	0	0	0
Leukemia, granulocytic	1	0	0	0	0	0	0	0	0	0
Leukemia, lymphocytic	0	0	0	0	0	1	0	0	0	1
Lymphoma, lymphoblastic	0	0	0	1	0	0	1	0	0	1
Lymphoma, small lymphocytic	0	0	1	0	0	1	0	1	0	0
Sarcoma, histiocytic	0	0	0	0	0	1	1	0	0	0
Clitoral glands										
papilloma	0	0	1	0	0	0	0	0	0	0
Body cavity, peritoneal										
Lipoma	3	0	5	1	3	2	1	2	2	1
Paraganglioma, benign	0	0	0	0	0	0	0	0	0	1
Schwannoma, malignant	0	0	1	1	0	0	1	0	0	0

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Sec. 2.6.7.10B Carcinogenicity

Study No.: TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

Daily Dose (mg/kg/day)	0 (Control 1)		0 (Control 2)		3		30		450	
No. of Animals	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50	F:50	M:50
Postmortem Findings										
Other Tumor Incidence										
Cervix										
Fibroma	1	0	0	0	0	0	0	0	0	0
Granular cell tumor, benign	0	0	1	0	0	0	0	0	0	0
Schwannoma, malignant	0	0	1	0	0	0	0	0	1	0
Cervix, squamous cell										
Carcinoma	1	0	0	0	0	0	0	0	0	0
Cervix, endometrial stromal										
Polyp	2	0	1	0	0	0	1	0	1	0
Mediastinum										
Schwannoma, malignant	1	0	0	0	1	0	0	0	0	0
Nerve, optic										
Schwannoma, malignant	0	1	0	0	0	0	0	0	0	0
Gross Pathology	-	-	-	-	-	-	-	-	-	-
Histomorphology – Non-neoplastic findings										
Liver										
Hypertrophy, centrilobular (very slight)	0	0	0	0	0	0	0	0	0	[11][f]

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Sec. 2.6.7.10B Carcinogenicity **Study No.:** TT #[redacted]-6029 [Ref. 4.2.3.4.1: TT[redacted]6029FIN] (Continued)

a GLP with the exceptions that physical stability of the [redacted] formulation of DOR in the vehicle and the exploratory metabolite profiling were performed using non-GLP assays.

b DOR concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.0284 µM) of the bioanalytical method.

c Include 1 spare/sex/group. Animals from the toxicokinetic arm were sacrificed and discarded without postmortem examination following analysis of Study Week 27 samples.

d Rat plasma and urine samples (30 and 450 mg/kg/day), Day 184 for plasma and Day 185 for urine were pooled across animals. Concentrations of DOR and M9 were calculated based on the comparison with the mass spectrometry responses of control plasma and urine samples supplemented with known concentrations of MK-1439 and synthetic M9.

e The incidence of benign thyroid c-cell (parafollicular cell) adenomas in females from the 450 mg/kg/day group only (10%), was statistically significantly increased when analyzed by trend analysis (P=0.029 after adjustment for multiplicity of statistical tests) relative to the incidence in the concurrent control groups (0% and 2%) but was within the range observed in female vehicle treated controls from Merck's historical record (incidence up to and including 10% of benign thyroid c-cell adenomas in 10 control groups of 50 female Han Wistar rats each) and well within the range (1.25 – 22%) and close to the mean value (~7%) for female historical control Han Wistar rats, published by the supplier. Therefore, the increased incidence of benign thyroid c-cell adenomas in females from the 450 mg/kg/day group relative to concurrent control groups is consistent with spontaneously-occurring variability in tumor incidence and not test article related. No other statistically significant variations in tumor incidence, after correction for multiplicity of tests, were present in this study.

f Considered consistent with hepatic enzyme induction and of minimal toxicologic significance based on very slight degree and low incidence, absence at lower doses, absence in females, and absence of any associated degenerative, neoplastic or preneoplastic liver changes.

- = No noteworthy findings.
DOR = Doravirine; HPMCAS-LG = hydroxypropyl methylcellulose acetate succinate-LG; NE = Not Evaluated or Not Examined; N/A = Not Applicable

C Confidential

Sec. 2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies

Test Article: DOR

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	Noteworthy Findings	Study Number
Rat/ Crl:WI(Han) *(Pregnant, Exploratory Range-Finding)*	Oral gavage (Vehicle = 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water; Control = 1800 mg/kg/day HPMCAS-LF)	GD 6 through 20	0, 5, 45, 450	6F/group	**450 mg/kg/day:** No test article-related maternal or developmental toxicity. **45 mg/kg/day**: No test article-related maternal or developmental toxicity. **5 mg/kg/day**: No test article-related maternal or developmental toxicity.	TT #[redacted]-7045 [Ref. 4.2.3.5.2: TT[redacted]7045FIN]

DOR = Doravirine; F = Female; GD = Gestation Day; HPMCAS-LF = Hydroxypropyl methylcellulose acetate succinate – LF

Confidential

2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies (Continued)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	Noteworthy Findings	Study Number
Rabbit/ Dutch Belted	Oral gavage	Single Dose	1, 10, 100, 1000	3F/group	No deaths at any dose.	TT #[redacted]-7206 [Ref. 4.2.3.5.2: TT[redacted]7206FIN]
(Non-Pregnant, Exploratory Single-Dose TK)	(10% polysorbate 80 in deionized water)				MK-1439 Toxicokinetic Parameters	

	MK-1439 (mg/kg)			
	1	10	100	1000
$AUC_{0\text{-}24\ hr}$ (µM•hr)	10.3	29.1	63.3	80.5
C_{max} (µM)	0.755	2.13	3.24	4.14
T_{max} (hr)	2.3	1.0	9.0	16

F = Female; TK = Toxicokinetic; DOR = Doravirine

Confidential

2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies (Continued)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	Noteworthy Findings	Study Number
Rabbit/ Dutch Belted *(Non-Pregnant, Exploratory Single-Dose TK)*	Oral gavage (Vehicle = 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water	Single Dose	15, 50, 150, 450	3F/group	No deaths at any dose.	TT #[redacted]-7207 [Ref. 4.2.3.5.2: TT[redacted]7207FIN]

MK-1439 Toxicokinetic Parameters

	MK-1439 (mg/kg)			
	15	50	150	450
$AUC_{0\text{-}24\ hr}$ (µM•hr)	156	385	335	433
C_{max} (µM)	11.2	29.4	21.7	26.1
T_{max} (hr)	3.0	1.0	1.3	4.7

F = Female; TK = Toxicokinetic; DOR = Doravirine

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2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies (Continued)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	Noteworthy Findings	Study Number
Rabbit/ Dutch Belted *(Non-Pregnant, Exploratory 5-Day TK)*	Oral gavage (Vehicle = 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water)	5 days	15, 50, 150, 300, 450	3F/group	No deaths at any dose.	TT #[redacted]-7277 [Ref. 4.2.3.5.2: TT[redacted]7277FIN]

MK-1439 Toxicokinetic Parameters - Study Day 5

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
15	107	6.93	4.0
50	218	13.5	4.0
150	291	19.6	1.7
300	364	20.7	4.0
450	336	20.4	4.7

F = Female; TK = Toxicokinetic; DOR = Doravirine

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2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies (Continued)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	Noteworthy Findings	Study Number
Rabbit/ Dutch Belted	Oral gavage	GD 7 through 20	0, 1, 15, 450	6F/group		TT #[redacted]-7055 [Ref. 4.2.3.5.2: TT[redacted] 7055FIN]
(Pregnant, Exploratory Range-Finding)	(Vehicle = 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water; Control = 1800 mg/kg/day HPMCAS-LF polymer in the vehicle				**450 mg/kg/day:** No maternal or developmental effects. **15 mg/kg/day:** No maternal or developmental effects. **1 mg/kg/day:** No maternal or developmental effects.	

F = Female; HPMCAS-LF = Hydroxypropyl methylcellulose acetate succinate – LF; TK = Toxicokinetic; DOR = Doravirine

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2.6.7.11 Reproductive and Developmental Toxicity: Non-Pivotal Studies (Continued)

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg/day)	Gender and No. per Group	Noteworthy Findings	Study Number
Rats Crl:WI(Han)	Oral (gavage)	PND 14 through 55	0, 5, 45, 150, 300	12M & 12F /group	No effects on mortality, clinical signs, body weight or food consumption in males or females at any dose.	TT #[redacted]-7005 [Ref. 4.2.3.5.4: TT [redacted]7005FIN]
(Exploratory Range-Finding in Juveniles)	(Vehicle = 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water; Control = 120 mg/mL HPMCAS-LF polymer in the vehicle)					

MK-1439 Toxicokinetic Parameters

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM*hr)	C_{max} (µM)	T_{max} (hr)
5	Female	44.3	4.00	1.0
	Male	30.6	2.87	2.0
	All	37.4	3.34	1.0
45	Female	175	14.5	2.0
	Male	127	11.9	1.0
	All	151	13.0	1.0
150	Female	300	26.9	2.0
	Male	207	20.6	2.0
	All	253	23.8	2.0
300	Female	340	32.1	1.0
	Male	277	25.1	2.0
	All	308	27.8	1.0

PND = Postnatal Day; NC = Not Calculated; M = Male; F = Female; DOR = Doravirine

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Sec. 2.6.7.12 Reproductive and Developmental Toxicity – Oral Fertility Study in Female and Male Rats (TT #[redacted]-7300)

Fertility and Early Embryonic Development to Implantation

Test Article: DOR

Design Similar to ICH 4.1.1? Yes
Species/Strain: Rat/Crl:WI(Han)
Age at Study Start: Females ~9 weeks
Males: ~11 weeks
Study Start Date: [redacted]

Day of Mating: GD 0
Day of Cesarean-Section: GD 15-17
Method of Administration: Oral gavage
Dosing Volume: 10 mL/kg
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LF)
Control Article: 180 mg/mL HPMCAS-LF polymer
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water

Study Number: TT #[redacted]-7300
Location in CTD: Vol. Section [Ref. 4.2.3.5.1: TT[redacted]7300FIN]
GLP Compliance: Yes[a]

Special Features: For cohabitation, high-dose females housed with untreated males, high-dose males housed with untreated females, mid-dose females housed with mid-dose males, low-dose females housed with low-dose males, control females housed with control males.

Treatment Interval (females): 15 days prior to cohabitation, during cohabitation, and through GD 7 or until the day removed from cohabitation

Treatment Interval (males): 15 days prior to cohabitation, during cohabitation, and through one day prior to scheduled sacrifice (~6 weeks total)

No-Observed-Effect Level: ≥450 mg/kg/day (female and male fertility parameters; female and male general toxicity parameters)

No-Observed-Adverse-Effect Level: ≥450 mg/kg/day (female and male fertility parameters; female and male general toxicity parameters)

	Females				Males			
Daily Dose (mg/kg)	0 (Control)	5	30	450	0 (Control)	5	30	450
Toxicokinetics[b,c]								
$AUC_{0\text{-}24\ hr}$ (μM•hr)	N/A	N/A	108	352	N/A	N/A	66.7	206
C_{max} (μM)	N/A	N/A	10.3	28.1	N/A	N/A	7.24	16.0
T_{max} (hr)	N/A	N/A	1.0	2.0	N/A	N/A	1.0	2.0

C Confidential

2.6.7.12 Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7300 [Ref. 4.2.3.5.1: TT[redacted]7300FIN] (Continued)

Fertility and Early Embryonic Development to Implantation

	Females				Males			
Daily Dose (mg/kg)	0 (Control)	5	30	450	0 (Control)	5	30	450
Number of Animals	20	20	20	20	20	20	20	20
Noteworthy Findings								
Mortality	0	0	0	0	0	0	0	0
Physical Examination	-	-	-	-	-	-	-	-
Body Weight Change	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-

C Confidential

2.6.7.12 Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7300 [Ref. 4.2.3.5.1: TT[redacted]7300FIN] (Continued)

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control) F/ 0 (Control) M	5 mkd F/ 5 mkd M	30 mkd F/ 30 mkd M	450 F/ Untreated M	Untreated F/ 450 M
Number of Animals	20/20	20/20	20/20	20/20	20/20
Noteworthy Findings (continued)					
No. Females Cohabited	20	20	20	20	20
No. Females Bred	20	20	20	20	19
No. Pregnant Females	17	17	18	17	17
No. Nonpregnant Females	3	3	2	3	2
Time to Mating (4-day periods)	1.00	1.00	1.20	1.15	1.42
Mating Index (%)	100	100	100	100	95
Fecundity Index (%)	85	85	90	85	89
Fertility Index (%)	85	85	90	85	85

C Confidential

2.6.7.12 Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7300 [Ref. 4.2.3.5.1: TT[redacted]7300FIN] (Continued)

Fertility and Early Embryonic Development to Implantation

Daily Dose (mg/kg)	0 (Control) F/ 0 (Control) M	5 mkd F/ 5 mkd M	30 mkd F/ 30 mkd M	450 F/ Untreated M	Untreated F/ 450 M
Number of Animals	20/20	20/20	20/20	20/20	20/20
Noteworthy Findings (continued)					
Reproductive Parameters (Mean Values)					
No. Corpora lutea/pregnant female	14.0	13.9	13.9	14.6	13.9
No. Implantations/pregnant female	11.8	11.7	12.2	12.8	10.5
% Resorptions/implantations (L.M.)	9.1	14.1	16.1	4.0	7.6
% Dead fetuses/implantations (L.M.)	0	0	0	0	0
No. Live fetuses/pregnant female	10.8	10.7	10.9	12.1	9.9
% Peri-implantation loss (L.M.)	16.0	16.8	13.0	13.5	24.2
% Postimplantation loss (L.M.)	9.1	14.1	16.1	4.0	7.6
Sperm Parameters (Mean Values ± S.D.)					
Sperm count/g cauda epididymis ($\times 10^6$)	879.5 ± 129.7	NE	NE	N/A	780.4 ± 114.7
Sperm motility (%)	91.9 ± 3.4	92.4 ± 4.2	92.1 ± 2.8	N/A	90.3 ± 4.3
Gross Examination[d]	-	-	-	N/A	-
Organ Weight					
Testes	-	-	-	N/A	-

Confidential

2.6.7.12 Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7300 [Ref. 4.2.3.5.1: TT[redacted]7300FIN] (Continued)

Fertility and Early Embryonic Development to Implantation

a With the exception of determination of the physical stability of the formulation. Since physical stability was part of the formulation design activities and definitive chemical stability was performed (GLP), the use of non-GLP conditions for physical stability determinations did not impact the quality and conduct of the study.
b DOR concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.029 µM).
c Study Week 13 toxicokinetic data for doses of 30 and 450 mg/kg are from the 6-Month Repeat-Dose Toxicity Study in Rats (TT #[redacted]-6019) [Ref. 4.2.3.2: TT[redacted]6019FIN].
d Limited to examination of the thoracic and abdominal viscera of control and treated females and males.

– = No noteworthy findings.
DOR = Doravirine; F = Female; GD = Gestation Day; HPMCAS-LF = Hydroxypropyl methylcellulose acetate succinate – LF; LLQ = Lower Limit of Quantitation; L.M. = Litter Mean; M = Male; mkd = mg/kg/day; N/A = Not applicable; NE = Not Evaluated; PMD = Premating Day; S.D. = Standard Deviation.; [redacted]F = [redacted] Formulation
Mating Index = Mated females/females cohabited.
Fecundity Index = Pregnant females/mated females.
Fertility Index = Pregnant females/females cohabited.
% Peri-implantation loss = [(No. of corpora lutea – no. of implantations)/(no. of corpora lutea)] × 100.
% Postimplantation loss = [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100.

Confidential

Sec. 2.6.7.13A Reproductive and Developmental Toxicity – Oral Developmental Toxicity Study in Rats With Prenatal Evaluation (TT #[redacted]-7040)

Effects on Embryo-Fetal Development

Design Similar to ICH 4.1.3? Yes
Species/Strain: Rat/Crl:WI(Han)
Age on GD 0: ~10 weeks
Study Start Date: [redacted] (staggered start over 4 days)
Special Features: Toxicokinetics, GD 15

Day of Mating: GD 0
Day of Cesarean-Section: GD 21
Method of Administration: Oral gavage
Dosing Volume: 10 mL/kg
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)
Control Article: 1800 mg/kg/day HPMCAS-LF polymer
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water

Test Article: DOR
Study Number: TT #[redacted]-7040
Location in CTD: Vol. Section [Ref. 4.2.3.5.2: TT[redacted]7040FIN]
GLP Compliance: Yes[a]

Treatment Interval: GD 6 through 20 (females scheduled for cesarean-section), GD 6 through 15 (females scheduled for TK blood collection)

No-Observed-Effect Level: ≥450 mg/kg/day (maternal and developmental toxicity)

No-Observed-Adverse-Effect Level: ≥450 mg/kg/day (maternal and developmental toxicity)

Daily dose (mg/kg)	0 (Control)[c]	5	45	450
Maternal Toxicokinetics (GD 15)[b]				
$AUC_{0\text{-}24\ hr}$ (μM•hr)	N/A	61.2	243	345
C_{max} (μM)	N/A	5.08	18.5	26.1
T_{max} (hr)	N/A	1.0	2.0	2.0

Confidential

2.6.7.A.13A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7040 [Ref. 4.2.3.5.2: TT[redacted]7040FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg)	0 (Control)[c]	5	45	450
Number of Animals				
Total No. of Females	24	28	28	28
No. Females Scheduled for Cesarean-Section	21[c]	20	20	20
Noteworthy Findings				
Mortality (No. of Females)	1[d]	0	0	0
Physical Examinations	-	-	-	-
Body Weight Change	-	-	-	-
Food Consumption	-	-	-	-
Gross Examination[e]	-	-	-	-

Confidential

2.6.7.A.13A Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7040 [Ref. 4.2.3.5.2: TT[redacted]7040FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg)	0 (Control)[c]	5	45	450
Number of Animals				
Total No. of Females	24	28	28	28
No. Females Scheduled for Cesarean-Section	21[c]	20	20	20
Noteworthy Findings (continued)				
Reproductive Parameters (mean values)				
No. Litters evaluated	20	18	20	20
No. Corpora lutea/pregnant female	11.3	11.1	11.1	11.0
No. Implantations/pregnant female	9.2	10.1	9.5	9.8
% Resorptions/implantations (L.M.)	4.4	1.6	4.8	4.4
% Dead fetuses/implantations (L.M.)	0	0	0.6	0
No. Live fetuses/pregnant female	8.8	9.9	9.1	9.4
% Peri-implantation loss (L.M.)	18.0	9.7	14.6	12.1
% Postimplantation loss (L.M.)	4.4	1.6	5.3	4.4
Fetal sex ratios	0.50	0.51	0.46	0.53
Live Fetal Weights (g)				
Females	5.01	4.99	5.15	5.40
Males	5.32	5.38	5.39	5.68

C Confidential

2.6.7.A.13A Reproductive and Developmental Toxicity Effects on Embryo-Fetal Development **Study No.:** TT #[redacted]-7040 [Ref. 4.2.3.5.2: TT[redacted]7040FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)[c]	5	45	450
Number of Animals				
Total No. of Females	24	28	28	28
No. Females Scheduled for Cesarean-Section	21[c]	20	20	20
Noteworthy Findings (continued)				
Placental Morphology				
No. abnormal placentas/total examined	0/175	0/178	1/181 (1)[f]	0/188
Fetal Morphology				
External examination	-	-	-	-
Visceral examination	-	-	-	-
Coronal examination	-	-	-	-
Skeletal examination	-	-	-	-

a With the exception of the skeletal evaluation by micro-CT and determination of the physical stability of the formulation. Since physical stability was part of the formulation design activities and definitive chemical stability was performed (GLP), the use of non-GLP conditions for physical stability determinations did not impact the quality and conduct of the study.
b DOR concentrations in plasma from all control group animals at 4 hours postdose were below the lower limit of quantitation (LLQ = 0.029 μM).
c Includes 1 female added to the cesarean section group to replace sacrificed female.
d One control female was sacrificed prior to dosing on GD 8 due to an intubation accident.
e Limited to examination of the thoracic and abdominal viscera.
f Number in parentheses represents a placenta from a dead fetus
– = No noteworthy findings.
#/# = number affected/number examined.
GD = Gestation Day; HPMCAS-LF or LG = Hydroxypropyl methylcellulose acetate succinate – LF or LG; LLQ = Lower Limit of Quantitation; L.M. = Litter Mean; N/A = Not applicable; [redacted]F = [redacted] Formulation; TK = Toxicokinetics.
Fetal sex ratio = [Total no. live female fetuses/(total no. live female fetuses + total no. live male fetuses)].
% Peri-implantation loss = [(No. of corpora lutea – no. of implantations)/(no. of corpora lutea)] × 100;
% Postimplantation loss = [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100.

C Confidential

Sec. 2.6.7.13B Reproductive and Developmental Toxicity – Oral Embryo-fetal Developmental Toxicity Study and Toxicokinetic Study in Rabbits (TT #[redacted]-7050)

Effects on Embryo-Fetal Development

Design Similar to ICH 4.1.3? Yes
Species/Strain: Rabbit/Dutch Belted
Age on GD 0: ~25 weeks
Study Start Date: [redacted]
Special Features: Toxicokinetics, GD 15

Day of Mating: GD 0
Day of Cesarean-Section: GD 28
Method of Administration: Oral gavage
Dosing Volume: 10 mL/kg
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)
Control Article: 1200 mg/kg/day HPMCAS-LF polymer
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water

Test Article: DOR
Study Number: TT #[redacted]-7050
Location in CTD: Vol. Section [Ref. 4.2.3.5.2: TT[redacted]7050FIN]
GLP Compliance: Yes[a]

Treatment Interval: GD 7 through 20 (females scheduled for cesarean-section), GD 7 through 15 (females scheduled for TK blood collection)

No-Observed-Effect Level: 15 mg/kg/day (maternal toxicity); ≥ 300 mg/kg/day (developmental toxicity)

No-Observed-Adverse-Effect Level: 15 mg/kg/day (maternal toxicity); ≥ 300 mg/kg/day (developmental toxicity)

Daily dose (mg/kg)	0 (Control)	2	15	300
Maternal Toxicokinetics (GD 15)[b]				
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	13.8	80.7	315
C_{max} (µM)	N/A	1.06	5.73	20.1
T_{max} (hr)	N/A	2.7	2.3	3.3

Confidential

2.6.7.A.13B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7050
[Ref. 4.2.3.5.2: TT[redacted]7050FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg)	0 (Control)	2	15	300
Number of Animals				
Total No. of Females	22	22	22	22
No. Females Scheduled for Cesarean-Section[c]	18	18	18	18
Noteworthy Findings				
Mortality (No. of Females)	0	0	0	0
Physical Examinations	-	-	-	-
Body Weight Change				
GD 7 to 21	148	161	143	[130]
GD 21 to 28	103	124	125	113
GD 7 to Adj. 28	42.9	61.9	35.8	[16.1]
Food Consumption	-	-	-	-
Gross Examination[d]	-	-	-	-

C Confidential

2.6.7.A.13B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7050
[Ref. 4.2.3.5.2: TT[redacted]7050FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg)	0 (Control)	2	15	300
Number of Animals				
Total No. of Females	22	22	22	22
No. Females Scheduled for Cesarean-Section [c]	18	18	18	18
Noteworthy Findings (continued)				
Reproductive Parameters (mean values)				
No. Litters evaluated	18	18	18	17
No. Corpora lutea/pregnant female	8.0	8.3	8.6	8.5
No. Implantations/pregnant female	7.2	7.2	7.7	7.6
% Resorptions/implantations (L.M.)	3.6	1.5	4.6	3.8
% Dead fetuses/implantations (L.M.)	0	0.7	0	0.6
No. Live fetuses/pregnant female	6.9	7.1	7.4	7.3
% Peri-implantation loss (L.M.)	9.5	12.0	9.8	10.1
% Postimplantation loss (L.M.)	3.6	2.2	4.6	4.4
Fetal sex ratios	0.51	0.54	0.48	0.47
Live Fetal Weights (g)				
Females	30.5	31.2	31.1	29.7
Males	30.6	31.3	32.2	30.9

C Confidential

2.6.7.A.13B Reproductive and Developmental Toxicity

Study No.: TT #[redacted]-7050
[Ref. 4.2.3.5.2: TT[redacted]7050FIN] (Continued)

Effects on Embryo-Fetal Development

Daily Dose (mg/kg)	0 (Control)[c]	2	15	300
Number of Animals				
Total No. of Females	22	22	22	22
No. Females Scheduled for Cesarean-Section[c]	18	18	18	18
Noteworthy Findings (continued)				
Placental Morphology				
No. abnormal placentas/total examined	0/124	0 (0)/127 (1)[e]	1/133	0 (1)/124 (1)[e]
Fetal Morphology				
External examination	-	-	-	-
Visceral examination	-	-	-	-
Coronal examination	-	-	-	-
Skeletal examination	-	-	-	-

a With the exception of the skeletal evaluation by micro-CT, the investigation of pinworms, and determination of the physical stability of the formulation. Since physical stability was part of the formulation design activities and definitive chemical stability was performed (GLP), the use of non-GLP conditions for physical stability determinations did not impact the quality and conduct of the study.
b DOR concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).
c Eighteen rabbits/group were scheduled for cesarean section. Three rabbits/group were scheduled for the toxicokinetic blood collections. The remaining rabbit was included as a potential replacement animal for a female that was not pregnant or otherwise unsuitable for toxicokinetic sample collection.
d Limited to examination of the thoracic and abdominal viscera.
e Number in parentheses represents a placenta from a dead fetus
– = No noteworthy findings.
#/# = number affected/number examined.
[ ] = Test article-related change based on incidence and/or severity.
GD = Gestation Day; HPMCAS-LG or LF = Hydroxypropyl methylcellulose acetate succinate – LG or LF; LLQ = Lower Limit of Quantitation; L.M. = Litter Mean; N/A = Not applicable; [redacted]F = [redacted] Formulation; TK = Toxicokinetics.
Fetal sex ratio = [Total no. live female fetuses/(total no. live female fetuses + total no. live male fetuses)].
% Peri-implantation loss = [(No. of corpora lutea – no. of implantations)/(no. of corpora lutea)] × 100.
% Postimplantation loss = [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100.

C Confidential

Sec. 2.6.7.14 Reproductive and Developmental Toxicity – Oral Pre- and Postnatal Developmental Toxicity Study in Rats (TT #[redacted]-7010)

Effects on Pre- and Postnatal Development, Including Maternal Function

Design Similar to ICH 4.1.2? Yes
Species/Strain: Rat/Crl:WI(Han)
Age on Start of Study: ~10 weeks
Study Start Date: [redacted]
Day of Mating: GD 0
Treatment Interval (F_0 generation): GD 6 through Lactation Day (LD 20)
Special Features: None

Method of Administration: Oral gavage
Dosing Volume: 10 mL/kg
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)
Control Article: 180 mg/mL HPMCAS-LF polymer
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
Litters Culled/Not Culled: Culled to 8 pup/litter on PND 3

Test Article: DOR
Study Number: TT #[redacted]-7010
Location in CTD: Vol. Section [Ref. 4.2.3.5.3: TT[redacted]7010FIN]
GLP Compliance: Yes[a]

No-Observed-Adverse-Effect Level: ≥ 450 mg/kg/day (for both maternal and F_1 generation toxicity)

Daily dose (mg/kg)	0 (Control)	5	45	450
Maternal Toxicokinetics (GD 15)[b,c]				
$AUC_{0\text{-}24\ hr}$ (μM•hr)	N/A	61.2	243	345
C_{max} (μM)	N/A	5.08	18.5	26.1
T_{max} (hr)	N/A	1.0	2.0	2.0

Confidential

Sec. 2.6.7.14 Reproductive and Developmental Toxicity Study No.: TT #[redacted]-7010 [Ref. 4.2.3.5.3: TT[redacted]7010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg)	0 (Control)	5	45	450
Number of Animals				
No. of Mated F_0Females	20	20	20	20
No. of Pregnant F_0Females	19	20	19	20
Noteworthy Findings – F_0 Generation				
Mortality	0	0	0	0
Physical Examinations	-	-	-	-
Body Weight Change	-	-	-	-
Mean Length of Gestation (days)	21.7	21.7	21.7	21.8
Females with Live Pups on PND 21	19	19	19	19
Food Consumption	-	-	-	-
Gross Examination (LD 21)[d]	-	-	-	-

C Confidential

Sec. 2.6.7.14 Reproductive and Developmental Toxicity Study No.: TT #[redacted]-7010 [Ref. 4.2.3.5.3: TT[redacted]7010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg)	0 (Control)	5	45	450
Noteworthy Findings (continued)				
F1 Generation – Preweaning (Mean Values)				
Parental Females	19	20	19	20
Females Failing to Initiate/Complete Parturition	0	1	0	0
Females with Live Pups (PND 0)	19	19	19	20
Number of Implantations/Pregnant Female	10.1	9.5	9.1	9.9
Live Pups/Litter (PND 0)	9.7	9.0	8.7	9.6
Dead Pups (% L.M.)	0	0	2	0
% Postimplantation Survival	96.6	94.6	95.4	97.3
Sex Ratios	0.48	0.57	0.37	0.51
Pup External Morphology (PND 0)	-	-	-	-
Pup Deaths (% L.M.)				
PND 1 to 3	3	2	1	1
PND 4 to 7	2	1	0	0
PND 8 to 14; PND 15 to 21	0	0	0	0
Live Pup Weights (female/male) - grams				
PND 0	5.78/6.16	5.73/6.04	6.03/6.45	6.18/6.52
PND 7	16.0/16.6	16.1/16.3	16.1/16.6	15.5/16.1
PND 14	32.2/33.2	32.6/33.0	32.4/33.3	31.5/32.3
PND 21	50.1/51.7	50.5/51.3	50.5/52.4	49.3/50.5

Confidential

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7010 [Ref. 4.2.3.5.3: TT[redacted]7010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg)	0 (Control)	5	45	450
Noteworthy Findings (continued)				
F1 Generation – Preweaning (Mean Values) (continued)				
Physical Signs	-	-	-	-
F1 Generation – Postweaning (Mean Values)				
Number of Animals (females/males)	36/38	38/36	35/37	38/38
Mortality	0	0	0	0
Physical Signs	-	-	-	-
Body Weight	-	-	-	-
Vaginal Opening	-	-	-	-
Preputial Separation	-	-	-	-
Behavioral Tests				
Passive Avoidance	-	-	-	-
Auditory Startle Habituation	-	-	-	-
Open Field Motor Activity	-	-	-	-

C Confidential

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7010 [Ref. 4.2.3.5.3: TT[redacted]7010FIN] (Continued)

Effects on Pre- and Postnatal Development, Including Maternal Function

Daily Dose (mg/kg)	0 (Control)	5	45	450 F/Control M	450 M/Control F
Noteworthy Findings (continued)					
F_1 Generation - Reproductive Performance					
No. of Females Cohabited	18	19	18	19	18
No. of Males Cohabited	18	19	18	19	18
No. Females Bred	18	19	18	19	17
No. Pregnant Females	17	18	18	17	17
No. Nonpregnant Females	1	1	0	2	0
No. Females Not Bred	0	0	0	0	1
Time to Mating (4-day periods; mean)	1.06	1.11	1.83	1.22	1.13
Reproductive Parameters (Mean Values) (C Section between GD 15-17)					
No. Corpora lutea/pregnant female	13.6	13.2	12.9	13.2	12.5
No. Implantations/pregnant female	10.6	11.9	11.2	11.8	10.7
% Resorptions/implantations (L.M.)	12.7	7.2	6.0	3.3	10.8
% Dead fetuses/implantations (L.M.)	0	0	0	0	0
No. Live fetuses/pregnant female	9.5	11.2	10.6	11.4	9.8
% Peri-implantation loss (L.M.)	23.0	10.4	14.5	11.6	17.1
% Postimplantation loss (L.M.)	12.7	7.2	6.0	3.3	10.8

C Confidential

Sec. 2.6.7.14 Reproductive and Developmental Toxicity **Study No.:** TT #[redacted]-7010 [Ref. 4.2.3.5.3: TT[redacted]7010FIN] (Continued)

a With the exception of the determination of the physical stability of the formulation. Since physical stability was part of the formulation design activities and definitive chemical stability was performed (GLP), the use of non-GLP conditions for physical stability determinations did not impact the quality and conduct of the study.
b Toxicokinetic analysis was not conducted in TT #[redacted]-7010. Data presented are from the rat embryo-fetal development study (TT #[redacted]-7040).
c DOR concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.029 µM).
d Limited to examination of the thoracic and abdominal viscera.
– = No noteworthy findings.
#/# = number affected/number examined.
[ ] = Test article-related change based on incidence and/or severity.
F = Female; GD = Gestation Day; HPMCAS-LF or LG = Hydroxypropyl methylcellulose acetate succinate – LF or LG; LD = Lactation Day; LLQ = Lower Limit of Quantitation; L.M. = Litter Mean; M = Male; N/A = Not applicable; PND = Postnatal Day; [redacted]F = [redacted] Formulation; TK = Toxicokinetics.
Fetal sex ratio = [Total no. live female fetuses/(total no. live female fetuses + total no. live male fetuses)].
% Peri-implantation loss = [(No. of corpora lutea – no. of implantations)/(no. of corpora lutea)] × 100.
% Postimplantation loss = [(No. of resorptions + no. of dead fetuses)/(no. of implantations)] × 100.
% Postimplantation survival = [(No. live pups delivered)/higher of [number of implantations or total pups delivered]) x 100.
Sex ratio = Total no. of live female pups/total no live female and male pups.

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Sec. 2.6.7.15 Studies in Juvenile Animals: Oral Toxicity and Toxicokinetic Study in Juvenile Rats (TT #[redacted]-7140)

Test Article: DOR

Species/Strain: Rats Crl:WI(Han)
Initial Age: 14 days (PND 14)
Date of First Dose: [redacted]
Dose Volume: 10 ml/kg
Method of Administration: Oral gavage
Special Features: Toxicokinetics, PND 55

Duration of Dosing: PND 14 to PND 55
Necropsy: PNW 8/9 (interim); PNW 13 (Postdose)
Duration of Postdose: 4 weeks (PNW 13)
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)
Control Article: 120 mg/mL HPMCAS-LF
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water

Study Number: TT [redacted]-7140
Location in CTD: Vol. Section [Ref. 4.2.3.5.4: TT [redacted]7140FIN]
GLP Compliance: Yes[a]

No-Observed-Adverse-Effect Level: ≥300 mg/kg/day

Daily Dose (mg/kg)	0 (Control)		10		45		300	
Gender	F	M	F	M	F	M	F	M
Toxicokinetics – PND 55[b]								
$AUC_{0\text{-}24\ hr}$ (µM•hr)	N/A	N/A	53.5	43.7	159	109	383	283
C_{max} (µM)	N/A	N/A	5.40	4.36	16.1	11.5	35.3	26.2
T_{max} (hr)	N/A	N/A	1.0	2.0	1.0	2.0	2.0	2.0

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Sec. 2.6.7.15 Studies in Juvenile Animals **Study No.:** TT #[redacted]-7140 [Ref. 4.2.3.5.4: TT[redacted]7140FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		10		45		300	
Number of Animals	F:32	M:32	F:32	M:32	F:32	M:32	F:32	M:32
Noteworthy Findings								
Mortality	0	0	1[c]	0	0	0	0	0
Body Weight Gain	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-
Developmental Landmarks								
Vaginal Opening	-	N/A	-	N/A	-	N/A	-	N/A
Preputial Separation	N/A	-	N/A	-	N/A	-	N/A	-
Open Field Motor Activity	-	-	-	-	-	-	-	-
Hematology (PNW 8)	-	-	-	-	-	-	-	-
Serum Chemistry (PNW 8)	-	-	-	-	-	-	-	-

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Sec. 2.6.7.15 Studies in Juvenile Animals **Study No.:** TT #[redacted]-7140 [Ref. 4.2.3.5.4: TT[redacted]7140FIN] (Continued)

Daily Dose (mg/kg)	0 (Control)		10		45		300	
Noteworthy Findings (continued)								
Urine Examinations								
Number of Animals (PNW 8/PNW 13)	F:20/10	M:20/10	F:20/10	M: 20/10	F: 20/10	M: 20/10	F: 20/10	M: 20/10
Urine Crystals, ex vivo (PNW 8) – Brown, Needle-Like, Appearing in Clusters	0	0	[1]	[1]	[4]	0	[13]	[7]
Urine Crystals , ex vivo (PNW8) – Yellow-Brown, Elongated, Appearing in Small Groups	0	0	0	0	[1]	0	[9]	[7]
Urine Crystals, ex vivo (PNW 13)	-	-	-	-	-	-	-	-
Pathology[d]								
Organ Weights	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Histomorphology	-	-	NE	NE	NE	NE	-	-

a With the exception of the physical stability of the formulation. Since physical stability was part of the formulation design activities and definitive chemical stability was performed (GLP), the use of non-GLP conditions for physical stability determinations did not impact the quality and conduct of the study.
b DOR concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.0291 µM).
c Not test article related; one female (10 mg/kg/day) was sacrificed on PND 15 due to an incorrectly assigned study start date.
d Interim Necropsy (10/sex/group at PNW 9; Final Necropsy 10/sex/group at PNW 13). The remaining 12/sex/group were euthanized and discarded without further examination

DOR = Doravirine; F = Female; HPMCAS-LG or LF = Hydroxypropyl methylcellulose acetate succinate – LG or LF; M = Male; N/A = Not Applicable; NE = Group not examined; PND = Postnatal Day; PNW = Postnatal Week, [redacted]F = [redacted] Formulation
[ ] = Test article-related change based on incidence and/or severity.
- = No noteworthy findings.

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Sec. 2.6.7.16 Local Tolerance

Test Article: DOR

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Isolated Bovine Corneas	In vitro	0.75 mL of a [redacted]% DOR solution	5 corneas	Doravirine was classified as a non-irritant.	TT #[redacted]-7857 [Ref. 4.2.3.6: TT[redacted]7857FIN]
MatTek EpiDerm™	In vitro	100 mg	Each treatment (1, 4, 24 hr) was conducted in duplicate; Positive Control at 4 & 9 hr	Doravirine was classified as a non-irritant.	TT #[redacted]-7858 [Ref. 4.2.3.6: TT[redacted]7858FIN]

DOR = Doravirine

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Sec. 2.6.7.17 Other Toxicity Studies

Test Article: DOR

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	NOAEL (mg/kg/day)	Noteworthy Findings	Study Number
Immunotoxicology							
Mouse (CBA/J)	Topical, ear	3 day	5, 10 and 25% (w/v) DOR in DMF	Main Study: 5 females/group	N/A	Doravirine was not considered a dermal sensitizer	TT #[redacted]-7859 [Ref. 4.2.3.7.2: TT[redacted]7859FIN]
Impurities							
Rats Crl:WI(HAN)	Oral (gavage)	3 Month	0, 115 (Batch Study)		≥ 115	**Test Article-Related Antemortem Findings:** Limited to very slight decreases in mean serum triglyceride levels in both sexes. These isolated decreases in triglycerides were considered of minimal toxicological significance because of the small magnitude of the changes. **Test Article-Related Postmortem Findings:** None. **Mean Plasma MK-1439 Toxicokinetic Parameters[b]:** In females/males, respectively, in Study Week 13: • $AUC0_{-24\ hr}$ (µM•hr): 233/170 • C_{max} (µM): 24.0/18.9 • T_{max} (hr): 1.0/1.0	TT #[redacted]-6035 [Ref. 4.2.3.7.6: TT[redacted]6035FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day) [a]	Gender and No. per Group	NOAEL (mg/kg/day)	Noteworthy Findings	Study Number
Impurities (continued)							
Rats Crl:WI(HAN)	Oral (gavage)	3 Month	30 (0.4% Phenol Degradate)[c]	10/sex/group	≥ 30 mg/kg/day of DOR or 0.12 mg/kg/day of DOR phenol degradate	There were no unscheduled deaths. **Test Article-Related Antemortem and Postmortem Findings**: None **Mean Plasma MK-1439 Toxicokinetic Parameters[d]:** In females/males, respectively, in Study Week 13: • $AUC_{0\text{-}24\ hr}$ (µM/hr): 176/104; • C_{max} (µM): 16.2/12.9; • T_{max} (hr): 1.0/1.0.	TT #[redacted]-6017 [Ref. 4.2.3.7.6: TT[redacted]6017FIN]
Rats Crl:WI(HAN)	Oral (gavage)	3 Month	Group 1: DOR & TDF Degradate G Control Group 2: DOR at 30 mg/kg/day Group 3: TDF Degradate G at 0.3mg/kg/day [fumaric acid ester]	10/sex/group	≥ 30 mg/kg/day of DOR (with impurities of interest) or 0.3 mg/kg/day of TDF degradate [fumaric acid ester]	**Test Article-Related Antemortem Findings:** None **Micronucleus Assay of TDF degradate G**: None **Test Article-Related Postmortem Findings:** None	TT #[redacted]-6010 [Ref. 4.2.3.7.6: TT[redacted]6010FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	NOAEL (mg/kg/day)	Noteworthy Findings	Study Number
Phototoxicity							
Rats Crl:LE (Long-Evans)	Oral (gavage)	3 Day	0, 30, 450	Phototoxicity: 5M; Bioanalysis: 3M	≥450	There were no skin reactions or ocular observations indicative of phototoxicity. A reduction in mean body gain (4.6 g) occurred in the 450 mg/kg/day dose group during the dose period (Days 1-3). The bioanalytical results revealed that concentrations of DOR were below the limit of quantitation in all control rats and that DOR was quantifiable in all plasma samples of test article-dosed rats.	TT #[redacted]-9011 [Ref. 4.2.3.7.7: TT[redacted]9011FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Exploratory Ten-Day Oral-Dose Urine Examination Study in Female Rat

Test Article: **DOR**

Species/Strain: Rats (Female) Crl:WI(Han)
Initial Age: 10 weeks
Date of First Dose: [redacted]
Dose Volume: 10 mL/kg

Duration of Dosing: 10 days
Duration of Postdose: NA
Method of Administration: Oral (gavage)
Vehicle Formulation: 0.5% (w/v) methylcellulose with 5 mM hydrochloric acid in deionized water
DOR Formulation: [redacted]F containing [redacted]% (w/w) of DOR and [redacted]% (w/w) of hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG)

Study Number: TT #[redacted]-1095
Location in CTD: Vol. Section [Ref. 4.2.3.7.7: TT[redacted]1095FIN]
GLP Compliance: No

Special Features: Investigation of urine crystal formation *in vivo* (Days 4 & 10) (samples collected via cystocentesis) and *ex vivo* (Days 3 & 9) (samples collected via metabolism caging). Drug concentrations in plasma, urine supernatant, and urine sediment were measured.

No-Observed-Adverse-Effect Level: Not Applicable

Daily Dose (mg/kg)	450
Number of Animals	F:16
Noteworthy Findings	
Mortality (No. of Animals)	0
Body Weight	-
Gross Examinations (Urinary Bladder, Kidney)	-
Presence of Urine Crystals	
In vivo	0
Ex vivo	
Day 3	[9]*
Day 9	[16]*

* The observation of presence of urine crystal in *ex vivo* overnight urine collection, but not directly in *in vivo* collection (cystocentesis), indicated that urine crystal formation is likely due to changes in external environment (such as temperature decrease from 37°C to ambient temperature, volume decrease by evaporation, protein precipitation, and/or surface contact with urine collection containers).

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Sec. 2.6.7.17 Other Toxicity Studies (Continued) - TT #[redacted]-1095 (continued)

Plasma Concentrations (DOR) – Day 7

Summary Mean (± SE) Plasma DOR Concentrations (µM) in Female Rats Following Dosing of 450 mg/kg/day of DOR: Study Day 7				
Matrix	Day	Dose (mg/kg/day)	Time (hr)	
			4	24
Plasma	7	450	18.7 ± 0.829	5.57 ± 1.25

Urine Sediment Concentrations (DOR) – Days 3 and 9 (Overnight Collection)

Summary Mean (± SE) Urine Sediment DOR Concentrations (µM) in Female Rats Following Dosing of 450 mg/kg/day of DOR: Study Days 3 and 9 (Overnight Urine Collection)			
Matrix	Day	Dose (mg/kg/day)	Time: Overnight Collection
Urine Sediment	3	450	43.1 ± 12.7
	9	450	36.2 ± 9.48
The amount of DOR measured in the sediment was normalized based on the volume of urine from which it was derived.			

Urine Supernatant Concentrations (DOR) - Days 3 and 9 (Overnight Collection)

Summary Mean (± SE) Urine Supernatant DOR Concentrations (µM) in Female Rats Following Dosing of 450 mg/kg/day of DOR: Study Days 3 and 9 (Overnight Urine Collection)			
Matrix	Day	Dose (mg/kg/day)	Time: Overnight Collection
Urine Supernatant	3	450	135 ± 14.9
	9	450	135 ± 11.3

Urine Supernatant Concentrations (DOR) – (Urine Collected by Cystocentesis)

Summary Mean (± SE) Urine Supernatant DOR Concentrations (µM) in Female Rats Following Dosing of 450 mg/kg/day of DOR: Study Day 4 (Urine Collected by Cystocentesis)			
Matrix	Day	Dose (mg/kg/day)	Time (hr)
			4
Urine Supernatant	4	450	95.7 ± 29.6
	10	450	84.8 ± 14.0

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Combination Toxicity with MK-8591 **Test Article: DOR**

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	NOAEL (mg/kg/day)	Noteworthy Findings	Study Number
Rats Crl:WI(HAN)	Oral (gavage)	1 Month	●MK-1439 Control + MK-8591 Control; ●(MK-1439 Control +) 3 mg/kg/day MK-8591; ●30 mg/kg/day MK-1439 (+ MK-8591 Control); ●30 mg/kg/day MK-1439 + 1 mg/kg/day MK-8591; ●30 mg/kg/day MK-1439 + 3 mg/kg/day MK-8591	10F/10M	≥30 mg/kg/day MK-1439 + 3 mg/kg/day MK-8591	There were no unscheduled deaths and no test article-related antemortem findings (clinical signs, or changes in body weight or food consumption). There were no test article-related ophthalmic findings or changes in clinical pathology parameters and no test article-related postmortem findings (gross necropsy, organ weight or histomorphology). The NOEL/NOAEL was ≥30 mg/kg/day DOR & 3 mg/kg/day MK-8591. Mean plasma DOR and MK-8591 TK parameters in SW 5 are presented below	TT #[redacted]-1012 [Ref. 4.2.3.7.7: TT[redacted]1012FIN]

Analyte	Treatment	Sex	$AUC_{0\text{-}24\ hr}$ (µM●hr)	C_{max} (µM)	T_{max} (hr)
MK-1439	30 mg/kg/day MK-1439 + 1 mg/kg/day MK-8591	Female	173 ± 11.8	14.7 ± 0.646	2.0 ± NC
		Male	146 ± 3.97	12.2 ± 0.555	2.0 ± NC
		All	159 ± 6.68	13.5 ± 0.680	2.0 ± NC
MK-1439	30 mg/kg/day MK-1439 + 3 mg/kg/day MK-8591	Female	180 ± 7.54	12.5 ± 0.657	2.0 ± NC
		Male	136 ± 4.94	10.4 ± 0.304	2.0 ± NC
		All	158 ± 7.31	11.4 ± 0.582	2.0 ± NC

NC = Not Calculated
MK-1439 concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.0294 µM) of the bioanalytical method.

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Combination Toxicity with MK-8591 (Continued **Test Article: DOR**

Analyte	Treatment	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
MK-8591	3 mg/kg/day MK-8591	Female	3.06 ± 0.154	1.52 ± 0.405	0.50 ± NC
		Male	3.85 ± 0.334	1.33 ± 0.0887	0.50 ± NC
		All	3.45 ± 0.227	1.42 ± 0.190	0.50 ± NC
MK-8591	1 mg/kg/day MK-8591 + 30 mg/kg/day MK-1439	Female	0.814 ± 0.0589	0.325 ± 0.0258	0.50 ± NC
		Male	1.02 ± 0.142	0.361 ± 0.0393	1.0 ± NC
		All	0.916 ± 0.0771	0.339 ± 0.0236	1.0 ± NC
MK-8591	3 mg/kg/day MK-8591 + 30 mg/kg/day MK-1439	Female	3.28 ± 0.234	1.38 ± 0.170	0.50 ± NC
		Male	3.26 ± 0.308	1.04 ± 0.174	1.0 ± NC
		All	3.27 ± 0.181	1.19 ± 0.116	0.50 ± NC

NC = Not Calculated
MK-8591 concentrations in plasma from all control group animals at 1 hour postdose were below the lower limit of quantitation (LLQ = 0.00170 µM) of the bioanalytical method.

Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Long-Acting Parenteral (LAP) Formulation: The results of these LAP studies have no impact on the oral DOR toxicity profile.

A brief description of each of these studies is presented below.

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	Conclusion	Study Number
Rats (Males) Crl:WI(HAN)	IM	Dosed on Day 1 & 30 Necropsy Day 34	Doses of 2 formulations each administered on SD 1 and SD 30 only Formulation 1: 200 mg of DOR/mL aqueous suspension containing 3% PEG 3350 isotonic Formulation 2: 150 mg of DOR/mL solution in N-methyl pyrrolidone Placebo Control 1: Suspension containing 3% PEG 3350 isotonic Placebo Control 2: N-methyl pyrrolidone	Placebo Control Groups: 2 males/group DOR-Treated Groups: 6 males/group	**No impact on the oral toxicity profile of DOR.** Exploratory DOR LAP formulations dosed IM were generally well-tolerated antemortem. Based on postmortem injection site findings, there was a better local tolerance when DOR was administered IM to male rats with Formulation 1 (200 mg of DOR/mL aqueous suspension containing 3% PEG 3350 isotonic), while the toxicokinetic parameters and the mean estimated SD 34 muscle concentrations were similar for both formulations. The DOR formulation doses consisted of a suspension of DOR milled [redacted] material (particles formed by placebo and test article combination) while the placebo formulations were only suspensions/solutions; as such, local foreign body observations (e.g. granulomatous inflammation) would be expected at injection sites for the test article formulation groups.	TT #[redacted]-6034 [Ref. 4.2.3.7.7: TT[redacted]6034FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Long-Acting Parenteral (LAP) Formulation (continued):

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	Conclusion	Study Number
Rats Crl:WI(HAN)	SC or IM	15 Day (once weekly for a total of 3 doses)	60 mg/kg/dose (8 µm d50 PSD formulation) given as three once weekly doses. Vehicle Control Article = 3.84% PEG 3350, 0.256% Polysorbate 80, 0.9% Sodium Chloride, and 0.176% Sodium Phosphate Monobasic Monohydrate Vehicle Control 1: SC Vehicle Control 2: IM	6/sex/group	**No impact on the oral toxicity profile of DOR.** There were no test article-related antemortem changes including no test article-related changes at the injection sites. The histomorphological changes at the injection site were comparable to those described for the marketed LAP formulation of paliperidone palmitate.	TT #[redacted]-1033 [Ref. 4.2.3.7.7: TT[redacted]1033FIN]
Rats Crl:WI(HAN)	IM	3 Week (once weekly for 3 doses followed by a 1-week treatment free period)	15, 30, 60 mg/kg/dose (2 or 8 µm d50 PSD formulation in Placebo 1 or Placebo 2, respectively) given as three once weekly doses – Groups 4-6 Group 1 = Saline Control Group 2 = Placebo 1: (1% Polysorbate 80) Group 3 = Placebo 2: (0.2% Polysorbate 80)	10/sex/group	**No impact on the oral toxicity profile of DOR.** No adverse antemortem findings and no systemic postmortem findings.	TT #[redacted]-6016 [Ref. 4.2.3.7.7: TT[redacted]6016FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Long-Acting Parenteral Formulation (continued)

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	Conclusion	Study Number
Rats Crl:WI(HAN)	SC	3 Week (once weekly for 3 doses followed by a 1-week treatment free period)	15, 30, 60 mg/kg/dose (2 or 8 µm d50 PSD formulation in Placebo 1 or Placebo 2, respectively) given as three once weekly doses – Groups 4-6 Group 1 = Saline Control Group 2 = Placebo 1: (1% Polysorbate 80) Group 3 = Placebo 2: (0.2% Polysorbate 80)	10/sex/group	**No impact on the oral toxicity profile of DOR**. No adverse antemortem findings and no systemic postmortem findings.	TT #[redacted]-6015 [Ref. 4.2.3.7.7: TT[redacted]6015FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Long-Acting Parenteral Formulation (continued):

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	Conclusion	Study Number
Rats Crl:WI(HAN)	IM	Days 1, 8, 15 with 2-Month Treatment-Free Period	10 or 40 mg/kg/dose (0.25 µm [nano-formulation] d50 PSD) Control: 4% Vitamin E TPGS, 10 mM phosphate buffer, and 0.9% sodium chloride in water for injection	Control: 10 F DOR dose groups: 16 F/group*	**No impact on the oral toxicity profile of DOR.** No adverse antemortem findings and no systemic postmortem findings. Animals in the 10 mg/kg/dose group recovered from the chronic local inflammation at the injection sites at the end of treatment-free period	TT #[redacted]-1065 [Ref. 4.2.3.7.7: TT[redacted]1065FIN]

*Interim Necropsy (~2weeks after completion of the dosing period): 5 rats in the control & 10 rats/DOR group; Final Necropsy (following a 2-month treatment-free period): 5 control rats and 6 rats/DOR group.

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Long-Acting Parenteral Formulation (continued):

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	Conclusion	Study Number
Dogs (Beagle)	IM	1 day (1 or 2 doses) with a 13-week observation period	200 mg/animal Group 2: 2 IM injections (0.5 mL each) of [redacted]% DOR API (d50 PSD of 8.0 µm) in 0.2% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/10 mM sodium phosphate monobasic monohydrate Group 3: Single IM injection (1.0 mL) of [redacted]% DOR API (d50 PSD of 2.0 µm) in 1.0% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/10 mM sodium phosphate monobasic monohydrate Vehicle Control (Group 1): (1.0 mL) 1.0% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/10 mM sodium phosphate monobasic monohydrate	2/sex/group	**No impact on the oral toxicity profile of DOR.** No adverse antemortem findings. (Dogs returned to colony at study termination).	TT #[redacted]-1081 [Ref. 4.2.3.7.7: TT[redacted]1081FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Long-Acting Parenteral Formulation (continued):

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	Conclusion	Study Number
Dogs (Beagle)	IM or SC	1 day (with a 13-week observation period)	Single dose of 200 mg [1.0 mL – SC or 0.66 mL or 1.0 mL – IM] or 300 mg [1.0 mL- IM] (d50 PSD of 8.0 µm) in vehicle Vehicle Control: Day 1 (IM); Day 2 (SC) - 0.2% [w/w] polysorbate 80/3% [w/w] PEG 3350/0.9% sodium chloride/10 mM sodium phosphate monobasic monohydrate)	2/sex/group	**No impact on oral DOR toxicity profile.** IM or SC administration of DOR LAP formulations was tolerated. Clinical observations, changes in body weights, body temperature, and clinical pathology changes were generally transient in duration. (Dogs returned to colony post-study termination).	TT #[redacted]-1061 [Ref. 4.2.3.7.7: TT[redacted]1061FIN]
Dogs (Beagle)	IM	1 day (with a 13-week observation period)	Single dose of 200 mg (1.0 mL/dose) - (d50 PSD of 0.3 µm) in vehicle (4.0% (w/w) TPGS/0.9% sodium chloride/10mM sodium phosphate monobasic monohydrate)	2/sex/group	**No impact on oral DOR toxicity profile.** Administration of an LAP nanosuspension formulation of DOR as a single IM administration to dogs was well tolerated as all animals survived to scheduled termination and there were no test article formulation-related clinical observations or changes in body weights. (Dogs returned to colony post-study termination).	TT #[redacted]-1106 [Ref. 4.2.3.7.7: TT[redacted]1106FIN]

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Sec. 2.6.7.17 Other Toxicity Studies (Continued)

Test Article: DOR

Long-Acting Parenteral Formulation (continued):

Species/ Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)[a]	Gender and No. per Group	Conclusion	Study Number
Dogs (Beagle)	IM	1 day (with ~8.5 month observation period)	Single dose of 200 mg (d50 PSD of 16.0 µm) in 0.2% Polysorbate 80/3.0% PEG 3350/0.9% sodium chloride/0.137% sodium phosphate monobasic	3/sex/group	**No impact on oral DOR toxicity profile.** Administration of a LAP large particle (16.0 µm d50 PSD) suspension formulation of DOR as a single IM administration was well tolerated. All animals survived to scheduled termination, there were no test article formulation-related changes in body weights. Test article formulation-related clinical observations were limited to swollen eyelids (attributed to idiosyncratic dog sensitivity to parenterally-administered polysorbate-based vehicles) seen in one female only on Study Day 1. (Dogs returned to colony at study termination).	TT #[redacted]-1064 [Ref. 4.2.3.7.7: TT[redacted]1064FIN]

API = Active pharmaceutical ingredient; d50 PSD = mass median diameter particle size distribution; DMF = N,NDimethylformamide; DOR = Doravirine; F = Female; HPMCAS-LG = Hydroxypropyl methylcellulose acetate succinate – LG ;IM = Intramuscular; LAP = Long-Acting Parenteral; M= Male; N/A = Not Applicable; NOEL = No-Observed-Effect Level; NOAEL = No-Observed-Adverse-Effect Level; PEG = Polyethylene glycol; SC = Subcutaneous; SD = Study Day; [redacted]F = [redacted] Formulation; SW = Study Week; TDF = Tenofovir Disoproxil Fumarate; TK = toxicokinetic; TPGS = Vitamin E tocopherol polyethylene glycol succinate

a Unless otherwise specified
b DOR concentrations in plasma from all control group animals at 2 hours postdose were below the lower limit of quantitation (LLQ = 0.0287 µM) of the bioanalytical method.
c The purpose of this study was to determine the potential toxicity of a new batch lot of DOR containing 0.4 % of a phenol degradate, and the toxicokinetic profile of DOR when this batch lot is administered orally, once daily, to rats for approximately 3 months.
d DOR concentrations in plasma from all control group animals at 2 hours postdose were below the lower limit of quantitation (LLQ = 0.0284 µM) of the bioanalytical method.

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