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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICE
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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: Omaveloxolone (RTA 408)
Indication: Friedreich's Ataxia
Applicant: Reata Pharmaceuticals, Inc.
Clinical Review Division: DN1
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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	3
1.1	INTRODUCTION	3
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	3
1.3	RECOMMENDATIONS	4
2	DRUG INFORMATION	6
2.1	DRUG	6
2.2	RELEVANT INDs, NDAs, BLAs AND DMFs	7
2.3	DRUG FORMULATION	7
2.4	COMMENTS ON NOVEL EXCIPIENTS	7
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	8
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	8
2.7	REGULATORY BACKGROUND	8
3	STUDIES SUBMITTED	8
3.1	STUDIES REVIEWED / 3.2 STUDIES NOT REVIEWED	8
3.3	PREVIOUS REVIEWS REFERENCED	8
4	PHARMACOLOGY	9
4.1	PRIMARY PHARMACOLOGY	9
4.2	SECONDARY PHARMACOLOGY	9
4.3	SAFETY PHARMACOLOGY	10
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	10
5.1	PK/ADME	10
6	GENERAL TOXICOLOGY	11
6.1	SINGLE-DOSE TOXICITY	11
6.2	REPEAT-DOSE TOXICITY	11
7	GENETIC TOXICOLOGY	16
7.1	<i>IN VITRO</i> REVERSE MUTATION ASSAY IN BACTERIAL CELLS (AMES)	16
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	17
9.1	FERTILITY AND EARLY EMBRYONIC DEVELOPMENT	17
9.2	EMBRYOFETAL DEVELOPMENT	19
9.3	PRENATAL AND POSTNATAL DEVELOPMENT	24
10	SPECIAL TOXICOLOGY STUDIES	27
11	INTEGRATED SUMMARY AND SAFETY EVALUATION	29

1 Executive Summary

1.1 Introduction

Omaveloxolone (RTA 408) has been developed by Reata Pharmaceuticals, Inc. for the treatment of Friedreich's Ataxia in adults and in adolescents at least 16 years of age.

1.2 Brief Discussion of Nonclinical Findings

RTA 408, an activator of the Nrf2 pathway, is for the treatment of Friedreich's Ataxia (FA). The recommended human dose (RHD) is 150 mg/day. There are no safety concerns regarding excipients or impurities.

The ability of RTA 408 to activate Nrf2 has been demonstrated in ARE-luciferase reporter assays and a variety of CNS cell types. RTA 408 restored mitochondrial function in myoblasts under oxidative stress, suppressed IFN γ -induced nitric oxide (NO) production in macrophages, and inhibited proinflammatory gene expression in LPS-stimulated microglial cells. In *in vitro* model of FA, RTA 408 induced Nrf2 target genes in hFXN^{154F} and FA patient-derived cells, as well as increased GSH levels and mitochondrial function in hFXN^{154F} cells. Daily oral administration of RTA 408 in mouse, rat, and monkey increased Nrf2 target gene expression and antioxidant enzyme activity in various tissues including brain. RTA 408 increased the expression of *Fth1* (Ferritin Heavy Chain 1) in mouse myoblasts and dose-dependently increased the expression of *FTH1* in monkey liver after oral dosing.

The major circulating human metabolites are M17 and M22. Following a single oral administration of [¹⁴C]RTA 408, M17 was present in monkeys at higher levels than humans; however, M22 was not observed in monkey plasma. Additional mixed-matrix normalization analyses were used to assess the metabolite profiles for M17 and M22 after repeated oral administration in monkey, rat, Tg.rasH2 mouse, CD1 mouse, and patients with FA. M17 showed adequate safety coverage (>50% peak area ratios in plasma) in all tested species compared with humans; however, M22 was 25.6%, 16.6%, and 5% in monkey, male rat, and female rat, respectively, of levels in FA patients. Therefore, M22 was not adequately tested in the general toxicology studies in rat and monkey or in any reproductive and developmental toxicology studies in rat. M22 showed minimal pharmacological activity and was negative in *in silico* analysis and in a non-GLP Ames assay.

Oral toxicology studies of up to 26 and 39 weeks' duration were conducted in Sprague Dawley (SD) rat and cynomolgus monkey, respectively. The primary toxicities in rats were body weight loss, increased liver weight, panlobular hepatocellular hypertrophy, bile duct hyperplasia, and kidney tubular degeneration/regeneration. Findings in the liver were associated with increases in AST and ALT. Based on the liver (bile duct hyperplasia) and kidney (tubular degeneration/regeneration) findings at all doses (0, 0.3, 1, or 3 mg/kg) in the 26-week study, a NOAEL was not established in rats. The primary toxicity in monkeys consisted of body weight loss, prolongation of

APTT, decreased red cell mass, increased liver weight, kidney tubular degeneration, and bile duct hyperplasia. Based on the APTT prolongation and bile duct hyperplasia at $\geq$ MD, the NOAEL for daily-administration of RTA 408 for 39-week in monkey was 10 mg/kg/day. Additionally, the overall weight of genotoxic evidence indicates that RTA 408 has a low genotoxicity risk to human subjects.

A standard battery of reproductive and development studies of RTA 408 were conducted in SD rat and New Zealand White (NZW) rabbit. A fertility study in rat indicated body weight loss in HDM as well as increased pre- and post-implantation losses and resorptions (early and late), and reduced number of implantation sites and viable embryos in HDF. The NOAEL was the MD of 3 mg/kg. In the rat embryofetal development study (up to 10 mg/kg), there were no RTA 408 related findings. The maternal and embryofetal NOAEL was the HD of 10 mg/kg/day. In the rabbit embryofetal development study (0, 3, 10, or 30 mg/kg/day), abortions at the MD and HD and reduced maternal body weight gain were observed at the HD. Additionally, increases in post-implantation loss, number of late resorptions, resorptions (early and late), incidence of unilateral full rib, as well as reduced fetal body weight were observed at the HD. The maternal NOAEL was the LD of 3 mg/kg/day, and the embryofetal NOAEL was the MD of 10 mg/kg/day. In the prenatal and postnatal development study (0, 1, 3, or 10 mg/kg/day) in rat, drug effects at HD included reduced maternal body weight gain, reduced number of liveborn pups/litter, and increased number of stillborn pups/litter. Additionally, drug effects on F₁ animals included reduced F₁ pup survival at the HD, decreased F₁ mean body weight (pre- and post-weaning) at the MD and HD, changes in sexual maturation (increased age of attaining preputial separation in males and decreased body weights of females at the time of vaginal opening) at the HD, and reduced mean numbers of corpora lutea and impanation sites at the HD. Increased locomotor activity was observed in F₁ animals at all doses. The NOAEL for dams was the MD of 3 mg/kg/day, and the NOAEL for pups was not established.

1.3 Recommendations

1.3.1 Approvability

RTA 408 is approvable from a nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

Carcinogenicity studies (26-week study in Tg.rasH2 mice and 2-year study in SD rats) are to be conducted as post-marketing requirements. Additionally, the reproductive and developmental toxicity studies for M22 are not available. As a post-marketing requirement, the developmental toxicity of M22 should be evaluated in an embryofetal development (EFD) study in one species. Justification should be provided for the species selected.

1.3.3 Labeling

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risks associated with the use of SKYCLARYS in pregnant women. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Oral administration of SKYCLARYS (0, 1, 3, 10 mg/kg/day) to pregnant rat (b) (4)
organogenesis (b) (4)

Oral administration of SKYCLARYS (0, 3, 10, 30 mg/kg/day) to (b) (4)
pregnant rabbits (b) (4) organogenesis resulted in (b) (4)

(b) (4)

8.2 Lactation

There are no data on the presence of SKYCLARYS or its metabolites in human milk. The effects on milk production and the breastfed infant are unknown. (b) (4)

(b) (4) in the milk of lactating rats following (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYCLARYS and any potential adverse effects on the breastfed infant from SKYCLARYS or from the underlying maternal condition.

(b) (4)

12.1 Mechanism of Action

The mechanism by which SKYCLARYS exerts its therapeutic effects in patients with Friedreich's Ataxia is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with SKYCLARYS.

Mutagenesis

SKYCLARYS was negative in (b) (4) (bacterial reverse mutation) and (b) (4) (b) (4) positive in (b) (4) human peripheral blood lymphocyte chromosomal aberration assay.

Impairment of Fertility

Oral administration of SKYCLARYS (0, 1, 3, 10 mg/kg/day) to male (b) (4) female rats prior to and during mating and continuing in females to Gestation Day 7 (b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 1474034-05-3

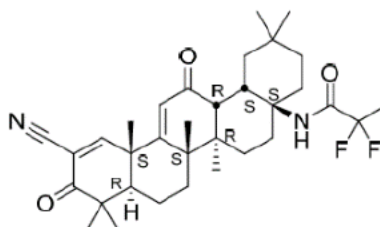
Generic Name: Omaveloxolone (RTA 408)

Code Name: TX63415, FP-190, and A-1402484.0

Chemical Name: N-(2-cyano-3,12-dioxo-28-noroleana-1,9(11)-dien-17-yl)-2,2-difluoropropanamide

Molecular Formula/Molecular Weight: C₃₃H₄₄F₂N₂O₃, 554.70 g/mol

Structure or Biochemical Description:



(Sponsor's Figure)

Pharmacologic Class: Nuclear factor erythroid 2-related factor 2 (Nrf2) activator

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 122349

2.3 Drug Formulation**Table 2: Unit Dose Quantitative Composition of Omaveloxolone Capsules, 50 mg**

Components	Quality Standard Reference	mg/capsule	% w/w	Component Function
Active Component				
Omaveloxolone	In-house	50.0 ^a	(b) (4)	Drug Substance
Inactive Components				
Pregelatinized Starch	NF/Ph.Eur.	(b) (4)		
Silicified Microcrystalline Cellulose ^b	NF/JP			
Croscarmellose Sodium	NF/Ph.Eur./JP			
Magnesium Stearate (b) (4)	NF/Ph.Eur./JP			
Hard HPMC Capsule Shell, Size 0	In-house	1 capsule Table 3	n/a	Capsule Shell
Total Capsule Fill Weight		(b) (4)	100.0%	

Abbreviations: JP=Japanese Pharmacopoeia; NF=National Formulary; Ph.Eur.=Pharmacopoeia Europaea

^a

(b) (4)

^b

(Sponsor's Figure)

2.4 Comments on Novel Excipients

There are no concerns regarding excipients.

2.5 Comments on Impurities/Degradants of Concern

Except for the impurities listed in the table below, all identified drug substance and drug product impurities are controlled in accordance with or below the ICH Q3A (b) (4) and Q3B (b) (4) qualification threshold (QT) limits, respectively. (b) (4) is qualified at (b) (4)% in drug substance and (b) (4)% in drug product based on systemic exposure as a metabolite in humans. (b) (4) and (b) (4) are qualified at (b) (4)% and (b) (4)% in drug substance, respectively, based on the NOAEL (10 mg/kg) from the 9-month monkey study.

Impurities	<i>In silico</i> assessment	Origins	Drug Substance Specification	Drug Product Specification
(b) (4)				

2.6 Proposed Clinical Population and Dosing Regimen

Omaveloxolone is intended to treat Friedreich's ataxia in adults and in adolescents aged 16 years and older. The recommended dosing regimen is 150 mg taken orally once daily.

2.7 Regulatory Background

IND 122349

April 9, 2014, pIND

August 5, 2014, IND submission

April 23, 2021, SPA1 (26-week carcinogenicity study in Tg.rasH2 mice)

September 28, 2021, pNDA

March 3, 2022, SPA2 (2-year carcinogenicity study in Sprague Dawley rats)

3 Studies Submitted

3.1 Studies Reviewed / 3.2 Studies Not Reviewed

All nonclinical studies including pharmacology, PK/ADME, and toxicology were reviewed except for dermal (absorption/TK and toxicity) studies.

3.3 Previous Reviews Referenced

IND (b) (4) Nonclinical review by Jane J. Sohn, Ph.D. (6/29/2012)

IND Nonclinical review by Wei Chen, Ph.D. (9/13/2013)

IND Nonclinical review by Maria I. Rivera, Ph.D. (12/18/2013)

IND Nonclinical review by Jiaqin Yao, Ph.D. (1/17/2014)

IND 122349: Nonclinical review by D. Charles Thompson, Ph.D. (12/21/2015)

IND 122349: Nonclinical review of SPA1, by David L. Carbone, Ph.D. (6/8/2021)

IND 122349: Nonclinical review of SPA2, by Chun-Ting (David) Lee, Ph.D. (2/17/2023)

4 Pharmacology

4.1 Primary Pharmacology

The ability of RTA 408 to activate Nrf2 was demonstrated in two ARE-luciferase reporter assays (human NQO1-ARE and rat GSTA2-ARE), with activity observed at concentrations as low as 3.9 nM. RTA 408 dose-dependently increased mRNA levels of Nrf2 target genes (*NQO1*, *HMOX1*, *GCLC*, or *GCLM*) in CNS cells (neurons, astrocytes, and microglia). RTA 408 restored mitochondrial function (including basal, ATP-linked, and maximal respiration, and spare respiratory capacity) in myoblasts under oxidative stress (treatment with sulfoximine (BSO) and ferric ammonium citrate (FAC)). Additionally, RTA 408 suppressed IFN γ -induced nitric oxide (NO) production in mouse macrophages with an IC₅₀ of 3.8 nM, and concentration-dependently inhibited LPS-induced tumor necrosis factor (*Tnf*), interleukin-6 (*IL-6*), and *Ccl2* gene expression in mouse microglial cells. In *in vitro* model of Friedreich's Ataxia (FA), RTA 408 concentration-dependently increased mRNA levels of Nrf2 target genes in hFXN^{I154F} MEFs (*Nqo1*, *Gclm*, *Gclc*, *Txnrd1*, and *Ho-1*) and in FA patient-derived fibroblasts and lymphoblastoid cells (*NQO1* and *GCLM*). RTA 408 significantly increased GSH levels and mitochondrial function (including basal, ATP-linked, and maximal respiration, and spare respiratory capacity) in hFXN^{I154F} MEFs. Daily oral administration of 10, 30, and/or 100 mg/kg RTA 408 in mouse, rat, and monkey for 14 days resulted in an increased expression of various Nrf2 target genes and activity of the antioxidant enzymes (including NQO1, GST, and/or GSR) in a generally dose-dependent manner in various tissues (mouse and rat: liver; monkey: liver, lung, and brain). RTA 408 was 62 to >1422 times more potent than its metabolites (including M22, M17, M28, M14, M15, and M23) in suppressing IFN γ -induced NO production in mouse macrophages.

4.2 Secondary Pharmacology

RTA 408 was evaluated for off-target binding against an *in vitro* panel of 38 targets comprised of receptors, ion channels, and transporters, as well as 6 enzymes. RTA 408 did not significantly interact with any target.

RTA 408 differentially modulated the expression of aminotransferase genes (including *ALT1*, *ALT2*, *AST1*, and *AST2*) in different cell lines originating from different types of tissues. Among four aminotransferase genes tested, RTA 408 consistently reduced the mRNA levels of *AST2* in all tested cells.

Effect of RTA 408 on aminotransferase gene expression

Cell Lines	Aminotransferase gene expression			
	<i>ALT1</i>	<i>ALT2</i>	<i>AST1</i>	<i>AST2</i>
AML-12 mouse liver cells	↑	–	↑	↓
NRK-52E rat kidney cells	↓	↑	↑	↓
C2C12 mouse myoblast cells	↑	↑	–	↓
RAW 264.7 mouse macrophage cells	↑	↑	↓	↓
HT-29 human colorectal adenocarcinoma cells	↑	↓	↑	↓

“–” no change

RTA 408 significantly increased the expression of *Fth1* (Ferritin Heavy Chain 1) in C2C12 mouse myoblasts. Daily oral administration of 10, 30, and 100 mg/kg RTA 408 in monkey for 14 days resulted in an increased expression of *FTH1* in a dose-dependent manner in liver.

4.3 Safety Pharmacology

Summarized from nonclinical reviews of INDs (b) (4) .

CNS and respiratory safety pharmacology endpoints following single oral doses of RTA 408 up to 30 mg/kg were assessed in SD rats. There were no notable findings. Cardiovascular endpoints were assessed in cynomolgus monkeys administered single oral doses of RTA 408 up to 100 mg/kg. There were no drug effects on body temperature, blood pressure, heart rate, or ECG (PR, RR, QRS, and corrected QT intervals). Additionally, *in vitro* concentrations of up to 1.2 μ M RTA 408 inhibited the hERG current by 21.5%.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Standard PK parameters were assessed following oral administration of RTA 408 in mouse, rat, rabbit, and monkey, with $t_{1/2}$ ranging from 6 to 30 h. Following oral administration to monkeys, [^{14} C]RTA 408 was approximately 3.41% bioavailable and was widely distributed to most tissues, including brain, between 8 and 30 h, with the highest concentrations observed in the gastrointestinal tract. RTA 408 was between 92.7 and 99.6% protein bound in plasma from mouse, rat, dog, rabbit, minipig, and monkey, and was 96.9% protein bound in human plasma. The major circulating human metabolites were M17 and M22 that accounted for 10.9% and 18.6% of total plasma radioactivity, respectively. Following a single oral dose of [^{14} C]RTA 408, M17 was observed at higher plasma levels in monkeys (13.9%) compared to human (10.9%); however, M22 was not observed in monkey plasma. Additional mixed-matrix normalization analytical methodologies were used to assess the metabolite profiles for M17 and M22 after repeated oral administration in monkey, rat, Tg.rasH2 mouse, CD1 mouse, and patients with FA. M17 showed adequate safety coverage (75.1 to 67700% peak area ratios in plasma) in all tested species compared with humans. The ratios for M22 in Tg.rasH2 mouse plasma and CD1 mouse plasma at HD were similar to patients with FA; however, M22 was 25.6%, 16.6%, and 5% in monkey, male rat, and female rat, respectively, of levels in patients. The hepatobiliary route was the primary route of elimination in monkey after oral administration of [^{14} C]RTA 408.

Interspecies comparisons of metabolites (Repeat dose studies)

- Patients with FA: 14-Day oral study of RTA 480 at 150 mg/day
- Male Monkey: 7-Day oral study of RTA 480 at 100 mg/kg/day
- Rat: 7-Day oral study of RTA 480 at 10 mg/kg/day
- Tg.rasH2 mouse: 7-Day oral study of RTA 480 at 100 mg/kg/day
- Male CD1 mouse: 7-Day oral study of RTA 480 at 10, 30, and 100/50* mg/kg/day
(Due to poor tolerability, the HD of 100 mg/kg was lowered to 50 mg/kg on Days 5 to 7)

Cross-Species Matrix-Normalized Peak Area Ratios for RTA 408 and Metabolites

Metabolites	Peak Area Ratios (Animals/Human at 150 mg)							
	Male Monkey	Male Rat	Female Rat	Male Tg Mouse	Female Tg Mouse	Male CD1	Male CD1	Male CD1
	100 mg/kg	10 mg/kg	10 mg/kg	100 mg/kg	100 mg/kg	10 mg/kg	30 mg/kg	100/50 mg
M17	67.7	0.751	0.909	52.3	17.2	2.79	6.60	21.3
M22	0.256	0.166	0.05	1.02	0.883	0.0678	0.117	1.34

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were submitted.

6.2 Repeat-Dose Toxicity

Rat

(28-Day, GLP; RTA408-P-1103; from nonclinical review of 122349 by Chun-Ting (David) Lee):

Male and female SD rats (15/sex/group) were administered doses of 0 (sesame oil), 3, 10, or 30 mg/kg RTA 408 by daily oral gavage for 28 days, with 28 days recovery. A dose-dependent decrease in body weight gain was observed in males at all doses (LD 10%, MD 16%, and HD 44%) with incomplete recovery, which correlated with decreases in food consumption. Increases in AST (up to 2.83-fold) and ALT (up to 6.88-fold) were observed at all doses except the LD, relative to controls, which resolved over the recovery period. Dose-dependent increases in liver weights were observed at all doses, while dose-dependent increases in kidney weights were observed at the MD and HD in females, which did not fully recover during the recovery period. Dose-dependent minimal to severe panlobular hepatocellular hypertrophy was observed at all doses, which was associated with minimal individual hepatocyte necrosis at the MD and HD. Minimal to moderate focal necrosis was observed in all dose groups except LDM. Additionally, minimal to mild bile duct hyperplasia was observed at the MD. All these liver findings showed incomplete recovery. Dose-dependent minimal to mild kidney tubular degeneration/regeneration was observed at the MD and HD with incomplete recovery. TK parameters were evaluated on Days 1 and 28. Increases in C_{max} and AUC were generally dose proportional. The NOAEL of RTA 408 in rats through 28 days could not be defined as the liver findings of focal necrosis and bile duct hyperplasia were observed at the LD at the end of the recovery period.

Toxicokinetics

Study Day	Dose (mg/kg) ^a	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-24hr} (hr*µg/mL)
1	3	74.9	6	1.17
	10	252	8	3.76
	30	820	6	12.5
28	3	120	8	1.87
	10	505	8	7.64
	30	1960	8	28.8

^a Male and female data are combined.

(Sponsor's Table)

(13-Week, non-GLP; RTA408-P-1111; from nonclinical review of 122349 by Chun-Ting (David) Lee):

Male and female SD rats (12/sex/group) were administered doses of 0 (sesame oil), 1, 3, 10, or 30 mg/kg RTA 408 by daily oral gavage for 13 weeks. Five animals including 1 HMDM, 2 HDM, and 2 HDF were found dead or euthanized moribund between Days 54 and 87. COD was considered to be treatment-related multiple organ degeneration/necrosis. Clinical signs at the HD included audible/shallow breathing, white discoloration of the gums, swelling of the lip/nose/nuzzle, red discoloration of the nose/muzzle lacrimation, and salivation. A dose-dependent decrease in body weight gain was observed in males at all doses except the LD (LMD 3%, HMD 42%, and HD 60%). A decrease in body weight gain was also observed in HMDF (42%) but due to the lack of a dose response, the relationship to treatment is not clear. The decrease in body weight gain was not associated with a decrease in food consumption but, rather, increases in food consumption were observed in HDM (13.5%) and HDF (22.7%). Increases in AST (up to 2.9-fold) and ALT (up to 6.7-fold) were observed at all doses except the LD, relative to controls. Dose-dependent increases in liver weights were observed at all doses except the LD. Dose-dependent minimal to severe panlobular hepatocellular hypertrophy was observed at all doses except the LD, which was associated with minimal to moderate individual hepatocyte necrosis in HDM and minimal individual hepatocyte necrosis in HMDF and HDF. Mild to moderate focal to multifocal necrosis was observed in HDM and HDF. Additionally, dose-dependent minimal to moderate bile duct hyperplasia and kidney tubular degeneration/regeneration were observed in males at ≥ HMD and females at ≥ LMD. TK parameters were evaluated on Days 1 and 92. Increases in C_{max} and AUC were generally dose proportional. Based on panlobular hepatocellular hypertrophy with individual hepatocyte necrosis, bile duct hyperplasia, and kidney tubular degeneration/regeneration, the NOAEL of RTA 408 in rats through 13 weeks was determined to be the LD of 1 mg/kg/day in males and females.

Toxicokinetics

Study Day	Dose (mg/kg) ^a	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-24hr} (hr*µg/mL)
1	1	25.7	6	0.375
	3	75.4	9	1.04
	10	218	6	3.41
	30	1050	6	15.9
92	1	57.4	8	0.798
	3	150	8	2.16
	10	528	8	8.20
	30	1070	8	17.4

^a Male and female data are combined.

(Sponsor's Table)

(26-Week, GLP; RTA408-P-1204; from nonclinical review of 122349 by Chun-Ting (David) Lee):

Male and female SD rats (30/sex/group) were administered doses of 0 (sesame oil), 0.3, 1, or 3 mg/kg RTA 408 by daily oral gavage for 26 weeks with 4 weeks recovery; an interim 13-week sacrifice was included. At Week 26, mean body weights relative to controls were reduced in HDM (14%), but increased in LDF (15%), MDF (20%), and HDF (19%), correlating with increases in average food consumption in all female dose groups. At Week 26, increases in AST (1.6-fold in MDF, 1.8-fold in HDM, 2.8-fold in HDF) and ALT (2.4-fold in MDF, 4.4-fold in HDM, 5-fold in HDF) were observed, relative to controls, which resolved over the recovery period. Dose-dependent increases in liver weights were observed at MD and HD at Week 26 with incomplete recovery. Kidney weights were increased in HDF at Week 26, which resolved over the recovery period. Dose-dependent minimal to moderate panlobular hepatocellular hypertrophy was observed in all dose groups except LDM at Week 26, which resolved during the recovery period. Dose-dependent minimal to mild bile duct hyperplasia was observed in all dose groups except LDM at Week 26 with incomplete recovery. Additionally, minimal to mild kidney tubular degeneration/regeneration was observed at HD at Week 26 and was present in all recovery dose groups except MDF. Correlative increases in severity of proteinuria were observed in HDM at Week 26 and in recovery MDM and HDM. TK parameters were evaluated on Days 1, 90, and 180. Increases in C_{max} and AUC were generally dose proportional. Based on adverse bile duct hyperplasia in the liver of males at ≥ MD and of females at ≥ LD and kidney tubular degeneration/regeneration among animals at ≥ LD at Day 211 with correlative increases in severity of proteinuria, the NOAEL of RTA 408 in rats through 26 weeks was < LD in males and females.

Toxicokinetics

Study Day	Dose (mg/kg) ^a	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-24hr} (hr*µg/mL)
1	0.3	7.41	8	0.104
	1	27.8	8	0.419
	3	78.7	6	1.18
90	0.3	15.0	8	0.232
	1	54.0	8	0.800
	3	138	6	2.28
180	0.3	18.4	8	0.285
	1	58.9	8	0.915
	3	142	6	2.41

^a Male and female data are combined.

(Sponsor's Table)

Monkey

(28-Day, GLP; RTA408-P-1104; summarized from nonclinical reviews of INDs (b) (4)

Male and female cynomolgus monkeys (5/sex/group) were administered doses of 0 (sesame oil), 10, 30, or 100 mg/kg RTA 408 by daily oral gavage for 28 days with 28 days recovery. Clinical signs at the HD included watery feces, distended abdomen, inappetence, unkempt appearance, and thin appearance. Mean body weights relative to controls were reduced in HDM (11%) and HDF (7%), with reversal after the recovery period. Increases in reticulocytes (up to 112%) at all doses and APTT (up to 24%) at the MD and HD were observed, relative to controls, which resolved over the recovery period. Dose-dependent increases in liver weights were observed at all doses, which did not fully resolve during the recovery period. Dose-dependent minimal panlobular hepatocellular hypertrophy was observed at MD and HD, which resolved during the recovery period. Minimal kidney vacuolation was observed at MD and HD, which persisted at the recovery phase. Minimal kidney tubular degeneration/necrosis was observed in 1HDM. Additionally, minimal to mild decreased cellularity of bone marrow (femur/rib/sternum) was observed at all doses, which resolved over the recovery period. TK parameters were evaluated on Days 1 and 28. Increases in C_{max} and AUC were generally dose proportional. The NOAEL of RTA 408 in monkeys through 28 days was determined at LD of 10 mg/kg/day due to prolongations in APTT at ≥ MD and kidney vacuolation observed at ≥ MD during the recovery period.

Toxicokinetics

Study Day	Dose (mg/kg)	C _{max} (ng/mL) ^a	T _{max} (hr)	AUC _{0-24hr} (hr*µg/mL)
1	10	44.8 ± 49.7	10	0.502 ± 0.315
	30	105 ± 33.7	12	1.74 ± 0.46
	100	227 ± 177	8	3.16 ± 0.71
28	10	54.8 ± 13.7	4	0.681 ± 0.144
	30	213 ± 44	4	2.76 ± 0.58
	100	358 ± 86	2	5.68 ± 1.29

^aMale and female data are combined. All values represent mean ± SD, except for T_{max} presented as median.

(Sponsor's Table)

(39-Week, GLP; RTA408-P-1205; summarized from nonclinical reviews of IND (b) (4) :

Male and female cynomolgus monkeys (9-10/sex/group) were administered doses of 0 (sesame oil), 10, 30, or 100 mg/kg RTA 408 by daily oral gavage for 39 weeks with 4 weeks recovery; an interim 13-week sacrifice was included. Clinical signs at the MD and HD included decreased activity, inappetence, hunched posture, vomitus, feces watery/discolored, and unkempt appearance. At Week 39, mean body weights relative to controls were reduced in HDM (20%) and HDF (19%), which resolved over the recovery period. At Week 39, increases in leukocytes (1.4-fold) and neutrophils (1.6-fold) were observed in HDF with incomplete recovery, and increases in platelets (up to 1.4-fold) was observed at HD, with reversal after the recovery period. At Weeks 13 and 39, prolongations in APTT (up to 1.8-fold) were observed at MD and HD with incomplete recovery, and decreases in red cell mass (erythrocytes, hemoglobin and hematocrit; up to 17%) were observed in HDF, with reversal after the recovery period. Dose-dependent increases in liver weights were observed at all doses at Week 39 with incomplete recovery. Minimal kidney tubular degeneration/regeneration was observed at HD at Week 39, which resolved during the recovery period. Additionally, minimal to mild bile duct hyperplasia was observed in MDM, HDM, and HDF at Week 39 with incomplete recovery. Increases in C_{max} and AUC were generally dose proportional. The NOAEL of RTA 408 in monkeys through 39 weeks was determined at the LD of 10 mg/kg/day due to prolongations in APTT at ≥ MD and bile duct hyperplasia observed at ≥ MD during the recovery period.

Toxicokinetics

Study Day	Dose (mg/kg) ^a	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-24hr} (hr*µg/mL)
1	10	36.2 ± 19.7	12	0.528 ± 0.191
	30	105 ± 45	10	1.49 ± 0.43
	100	219 ± 128	8	2.92 ± 0.96
90	10	63.1 ± 26.6	4	0.841 ± 0.318
	30	218 ± 93	3	2.69 ± 0.79
	100	443 ± 167	2	6.48 ± 1.99
270	10	54.7 ± 24.1	12	0.856 ± 0.315
	30	138 ± 68	8	1.96 ± 0.771
	100	350 ± 122	4	4.77 ± 1.42

^a Male and female data are combined. All values represent mean ± SD, except for T_{max} presented as median.

(Sponsor's Table)

7 Genetic Toxicology**RTA 408**

(Summarized from nonclinical reviews of

(b) (4)

RTA 408 was negative in an Ames assay. RTA 408 was positive in an *in vitro* chromosomal aberration assay in human lymphocytes but was negative in an *in vivo* rat micronucleus assay and *in vivo* rat liver comet assay. All these studies were conducted in compliance with the OECD guideline.

TX304579 (M22)**7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)****Study title: ADME-TOX - Study of TX304579**

Study no.: RTA-P-20029

Study report location: EDR

Conducting laboratory and location:

(b) (4)

Date of study initiation: October 30, 2020

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: TX304579, Batch #: TX304579_002, and % purity: NA

Methods

Strains: TA98, TA100, TA1535, TA1537
Concentrations in definitive study: 0, 5, 10, 50, and 100 μ M (+/- Aroclor-induced rat liver S9 fraction)
Basis of concentration selection: Preliminary toxicity assay
Negative control: DMSO
Positive control: 2-Aminoanthracene, 9-Aminoacridine, Quercetin, and Streptozotocin (+/- Aroclor-induced rat liver S9 fraction)
Formulation/Vehicle: DMSO
Incubation & sampling time: 96h

Results

TX304579 (M22) was negative for mutagenicity in a non-GLP exploratory Ames assay in the presence or absence of metabolic activation up to 100 μ M (approximately 58 mg/plate). However, only 4 strains were used and the maximum test concentration (approximately 58 mg/plate) and incubation and sampling time (96 h) used in this assay are not consistent with OECD guideline (5 mg/plate and 48-72 hours).

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: RTA 408: Study of Fertility and Early Embryonic Development to Implantation in Rats

Study no.:	RTA-P-18016
Study report location:	EDR
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	September 4, 2018
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RTA 408, Lot G-17-016, 99%

Methods

Doses: 0, 1, 3, 10 mg/kg
Frequency of dosing: Daily
Dose volume: 5 mL/kg
Route of administration: Oral gavage
Formulation/Vehicle: Sesame oil
Species/Strain: SD rat
Number/Sex/Group: 22/sex/group
Satellite groups: None
Study design: Males and females were dosed for 28 and 14 days, respectively, prior to cohabitation, during cohabitation, and in females through Gestation Day (GD) 7.
Deviation from study protocol: No significant deviations

Observations and Results**Mortality and Clinical Signs**

Animals were evaluated twice daily for mortality or signs of morbidity. There were no drug-related deaths or clinical signs.

Body Weight

Body weight was assessed twice weekly. HDM showed reductions in mean body weights relative to controls (7% to 12.3%) from Days 36 to 64.

Food Consumption

Food consumption was recorded weekly. There were no drug effects on food consumption.

Toxicokinetics

Not evaluated.

Dosing Solution Analysis

Dosing solutions were within 15% of their respective target concentrations.

Necropsy

Drug effects in HDF included increases in pre- and post-implantation losses (Con 10.28% vs HD 20.9% and Con 7.37% vs HD 24.77%, respectively) and resorptions (early and late, Con 1 vs HD 2.2), as well as decreases in the number of implantation sites (Con 15.1 vs HD 13.2), the number of viable embryos (Con 14.1 vs HD 10.9), and uterus with cervix weight (37.2%).

Sex: Female		0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Day(s) Relative to Mating (Litter: A)					
Number of Corpora Lutea [g]	Mean	16.8	17.4	18.1	16.2
	SD	2.41	2.52	3.41	2.79
	N	19	19	18	17
No. Implantations/Animal [g1]	Mean	15.1	15.2	15.9	13.2
	SD	2.37	2.85	4.27	5.27
	N	19	19	18	17
% Pre-implantation Loss [g2]	Mean	10.28	13.14	13.02	20.90
	SD	10.340	10.724	18.345	23.159
	N	19	19	18	17
Number of Viable Embryos [g1]	Mean	14.1	13.3	15.4	10.9
	SD	3.54	4.04	4.06	6.53
	N	19	19	18	17
% Post-implantation Loss [g2]	Mean	7.37	13.53	2.83	24.77 b
	SD	15.544	18.399	3.873	26.791
	N	19	19	18	17
Resorptions: Early + Late [g1]	Mean	1.0	1.8 a	0.5	2.2 a
	SD	2.05	2.39	0.71	1.99
	N	19	19	18	17

(Sponsor's Table)

9.2 Embryofetal Development

Dose-ranging studies were conducted in SD rat and NZW rabbit. In rats, daily oral administration of RTA 408 (0, 1, 3, 10 or 30 mg/kg; 5/group) from GDs 6 to 17 resulted in maternal toxicity (increased maternal liver weight) at the HMD and HD, and developmental toxicity (increases in post-implantation loss and the number of early and late resorptions, as well as decreases in the number of viable fetuses, litter size, gravid uterine weight, and fetal body weight) at the HD. The study in rabbits consisted of Phase A (tolerability study) and Phase B (developmental toxicity study). In Phase A, non-pregnant females (2/group) were administered doses of 0, 10, 30 or 100 mg/kg RTA 408 by daily oral gavage for 14 days. Clinical signs included few/absent feces, tan discoloration of the feces, and thin body condition at the HD, as well as body weight loss/reduced body weight gain, and reduced food intake at the MD and HD. Dose levels of 0, 3, 10, 30, and 100 mg/kg/day were used for the Phase B study in pregnant rabbits (6/group) administered RTA 408 from GDs 6 to 18. In Phase B, one HD animal was found dead on GD 20. Maternal toxicity (body weight loss/reduced body weight gain, and reduced food intake), and developmental toxicity (increases in post-implantation loss, number of late resorptions, and resorptions (early and late), as well as decreases in the number of viable fetuses, litter size, gravid uterine weight, and fetal body weights) were observed at the HMD and/or HD.

Study title: RTA 408: Study for Effects on Embryo Fetal Development in Rats with a Toxicokinetic Evaluation

Study no.: RTA-P-18017
Study report location: EDR
Conducting laboratory and location:  (b) (4)
Date of study initiation: October 4, 2018
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: RTA 408, Lot G-17-016, 99%

Key Study Findings**Methods**

Doses: 0, 1, 3, 10 mg/kg
Frequency of dosing: Daily
Dose volume: 5 mL/kg
Route of administration: Oral gavage
Formulation/Vehicle: Sesame oil
Species/Strain: SD rat
Number/Sex/Group: 20/group
Satellite groups: TK (3/group)
Study design: RTA 408 was administered on GDs 6 to 17; cesarean sections were conducted on GD 20.
Deviation from study protocol: No significant deviations

Observations and Results**Mortality and Clinical Signs**

Animals were checked twice daily for mortality or signs of morbidity. There were no drug-related findings.

Body Weight and Food Consumption

Body weights and food consumption were recorded on GDs 0, 6, 9, 12, 15, 18, and 20. There were no drug-related findings.

Toxicokinetics

Increases in C_{max} and AUC were generally dose proportional.

Dose (mg/kg)	GD 6			GD 17		
	T _{max} (hr)	C _{max} (ng/mL)	AUC _{0-24hr} (hr*µg/mL)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{0-24hr} (hr*µg/mL)
1	4	40.0	0.461	4	56.3	0.743
3	4	105	1.73	8	155	2.44
10	4	565	5.71	4	636	7.38

(Sponsor's Table)

Dosing Solution Analysis

Dosing solutions were within 15% of their respective target concentrations.

Necropsy

There were no drug-related findings.

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

There were no drug-related findings.

Offspring (Malformations, Variations, etc.)

There were no drug-related findings.

Study title: RTA 408: A Study for Effects on Embryo Fetal Development in Rabbits with a Toxicokinetic Evaluation

Study no.: RTA-P-18018

Study report location: EDR

Conducting laboratory and location:



Date of study initiation: November 8, 2018

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: RTA 408, Lot G-17-016, 99%

Key Study Findings**Methods**

Doses: 0, 3, 10, 30 mg/kg

Frequency of dosing: Daily

Dose volume: 1 mL/kg

Route of administration: Oral gavage

Formulation/Vehicle: Sesame oil

Species/Strain: NZW rabbits

Number/Sex/Group: 20/group

Satellite groups: TK (4/group)

Study design: RTA 408 was administered on GDs 7 to 19; cesarean sections were conducted on GD 29.

Deviation from study protocol: No significant deviations

Observations and Results

Mortality and Clinical Signs

Animals were evaluated twice daily for mortality or signs of morbidity. Two MDF (#3507 and 3514) aborted and were euthanized on GD 27 and 26, respectively, and three HDF (#4504, 4507, and 4509) aborted and were euthanized on GD 27, 25, and 27, respectively. Drug-related clinical signs at all doses included few/absent/tan discolored feces, thin body condition, and red material in the pan (LD 2, MD 3, HD 5). Early delivery was observed at all doses (LD 1, MD 1, HD 1).

Body Weight and Food Consumption

Body weights and food consumption were recorded on GDs 0, 7, 10, 13, 16, 19, 21, 25, and 29. Body weight loss (-0.0165 kg vs 0.0543 increase in Con) and reduced food consumption (39%) was observed in HDF relative to controls from GDs 7 to 19.

Toxicokinetics

Increases in C_{max} and AUC were generally dose-proportional from the LD to MD but less than dose proportional between the MD and HD.

Dose (mg/kg)	GD 7			GD 19		
	T_{max} (hr)	C_{max} (ng/mL)	AUC _{0-24hr} (hr*µg/mL)	T_{max} (hr)	C_{max} (ng/mL)	AUC _{0-24hr} (hr*µg/mL)
3	8	15.0	0.194	2	18.9	0.314
10	NA	49.0	0.695	8	53.5	0.838
30	NA	63.8	1.03	NA	107	1.50

(Sponsor's Table)

Dosing Solution Analysis

Dosing solutions were within 15% of their respective target concentrations.

Necropsy

There were no drug-related findings.

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

Drug-related adverse effects at the HD included increases in post-implantation loss (Historical Con 4.592% vs HD 11.17%), number of late resorptions (Con 0.1 vs HD 0.7), and resorptions (early and late, Con 0.8 vs HD 1.0). The concurrent control values of post-implantation loss were outside the range identified in historical control animals (concurrent control 11.65 vs historical control 1.04-8.82).

Offspring (Malformations, Variations, etc.)

Drug-related adverse effects at the HD included an increase in the incidence of unilateral full rib (Con 42.1% vs HD 87.5%) and a decrease in fetal body weight (22%).

Sex: Female		0 mg/kg/day	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Day(s) Relative to Mating (Litter: A)					
Number of Corpora Lutea [g]	Mean	10.3	9.5	10.1	10.1
	SD	2.02	1.59	1.59	1.73
	N	19	17	16	16
No. Implantations/Animal [g]	Mean	8.2	8.4	8.6	9.2
	SD	2.51	1.87	1.97	1.38
	N	19	17	16	16
% Pre-implantation Loss [g1]	Mean	20.65	11.43	15.72	7.64 a
	SD	19.117	10.866	12.434	12.019
	N	19	17	16	16
Number of Viable Fetuses [g]	Mean	7.4	8.1	8.1	8.2
	SD	2.67	1.95	2.00	2.07
	N	19	17	16	16
% of Live Male Fts in Litter [g1]	Mean	50.4	48.3	48.5	40.6
	SD	24.83	18.56	12.48	18.01
	N	19	17	16	16
% Post-implantation Loss [g1]	Mean	11.65	4.30	5.02	11.17
	SD	16.356	7.132	7.978	16.818
	N	19	17	16	16
No. Non-Viable Fetuses/Animal	Mean	0.0	0.0	0.0	0.0
	SD	0.00	0.00	0.00	0.00
	N	19	17	16	16
Litter size [g]	Mean	7.4	8.1	8.1	8.2
	SD	2.67	1.95	2.00	2.07
	N	19	17	16	16
Number of Early + Late [g2]	Mean	0.8	0.4	0.4	1.0
	SD	1.13	0.61	0.73	1.51
	N	19	17	16	16
Number of Early Resorptions [g2]	Mean	0.7	0.4	0.4	0.3
	SD	1.15	0.61	0.62	0.60
	N	19	17	16	16
Number of Late Resorptions [g2]	Mean	0.1	0.0	0.1	0.7 b
	SD	0.23	0.00	0.25	1.30
	N	19	17	16	16

(Sponsor's Table)

9.3 Prenatal and Postnatal Development

Study title: RTA 408: Pre and Postnatal Development Toxicity Study Including Maternal Function in Rats

Study no.:	RTA-P-18019
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 8, 2018
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RTA 408, Lot G-17-016, 99%

Key Study Findings

Methods

Doses:	0, 1, 3, 10 mg/kg
Frequency of dosing:	Daily
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Sesame oil
Species/Strain:	SD rats
Number/Sex/Group:	F ₀ : 20/group; F ₁ : 20/sex/group
Satellite groups:	TK (8/group)
Study design:	RTA 408 was administered from GDs 6 to LD 20
Deviation from study protocol:	No significant deviations

Observations and Results

F₀ Dams

Survival/ Clinical signs: There were no drug-related deaths or clinical signs.

Body weight/Food consumption: Body weight gain and food consumption in HDF were reduced by 14.3% and 9.7%, respectively, relative to controls from GDs 6 to 20. Additionally, a decrease in mean food consumption (10.4 to 18.5%) was observed in HDF over the entire period of lactation.

Uterine content: Drug-related adverse effects at the HD included a decrease in the number of liveborn pups/litter at birth (Con 11.8 vs HD 10.75) and on LD 4 prior to culling (Con 11.8 vs HD 9.7), LD 7 (Con 7.9 vs HD 7.2), LD 14 (Con 7.9 vs HD 7.1), LD 21 (Con 7.9 vs HD 7.0), and LD 28 (Con 7.9 vs HD 7.0), as well as increases in the number of stillborn pups/litter at birth (Con 0.0 vs HD 0.5) and stillborn index (Mean %/Litter) (Con 0.0 vs HD 3.61).

Necropsy observation: There was an increase in enlarged livers (5/20) in HDF.

Toxicokinetics: Increases in plasma concentration were generally dose proportional in F₁ pups. Dose-dependent increases in RTA 408 concentration were also observed in milk collected from F₀ females on LD 12.

Analysis ^a	1 mg/kg	3 mg/kg	10 mg/kg
Milk ^b (Lactating Dams, LD 12)	438	1730	6370
Plasma (F ₁ Litter, LD 4)	2.20	6.55	28.3

^a Both milk and plasma samples were collected 6 hours after dosing to dams. Concentrations presented as ng/mL.

^b After milk collection, samples were inadvertently not supplemented with the preservative sodium bisulfite. Further investigation indicated that the impact of this deviation is that the reported omaveloxolone concentrations in milk from lactating rats was decreased approximately 30%.

(Sponsor's Table)

Dosing Solution Analysis: Dosing solutions were within 15% of their respective target concentrations.

Other: N/A

F₁ Generation

- Survival: Drug-related adverse effects at the HD included decreases in F₁ pup survival from LD 0 to LD 4 (viability index; Con 99.58% vs HD 88.96%) and LD 4 to LD 21 (lactation index; Con 99.38% vs HD 92.50%).
- Clinical signs: There were no drug-related deaths or clinical signs.
- Body weight: In the MD group, mean F₁ pup body weight was reduced by 6% on PND 28. In the HD group, mean F₁ pup body weight was reduced by 6 to 23% at birth, through lactation (LD 4, 7, 14, and 21), and post-weaning on PND 28.
- Food consumption: Not evaluated
- Physical development: There were no drug effects on pup reflex, sensory, and developmental indices (static righting reflex, pinna detachment, cliff aversion, eye opening, airdrop righting reflex, and auditory response).
- Neurological assessment: F₁ animals were assessed for motor activity on PND 35 using a Hamilton Kinder Motor Monitor System and for learning and memory on PND 70 to 85 using the step-through passive avoidance test. F₁ males exhibited an increase in the basic movement count (0-5 min: 14.4%; 5-10 min: 17.3%) and total distance (0-5 min: 14.6%; 5-10 min: 15.2%) at HD. F₁ females exhibited an increase in the basic movement count at 0-5 min at all doses (LD 18.9%, MD 20.1%, HD 18.6%) and total distance at 0-5 min at all doses (LD 17.1%, MD 18.1%, HD 17.6%), as well as in the total distance at 5-10 min at LD (19.3%). All these findings were not observed after 10 min. There were no drug effects on learning and memory from the passive avoidance testing.
- Reproduction: Drug-related adverse effects at the HD included increased age of attaining preputial separation in males (Con 41.3 Days vs HD 44.2 Days), decreased body weights of females at the time of vaginal opening (Con 140.4 g vs HD 113.3 g), reduced mean numbers of corpora lutea (Con 19.3 vs HD 16.3) and implantation sites (Con 15.6 vs HD 13.7).
- Other: **F₁ Body Weight (Post-Weaning):** Mean body weight was reduced in MDM (6.9 to 7.3%) from Days 1 to 15, and in HDM (15.4 to 22.0%) and HDF (11.6% to 20.5%) throughout the entire study.

10 Special Toxicology Studies

Dose Range-Finding Studies to Support Planned Carcinogenicity Studies

Dose-ranging studies to support the planned carcinogenicity studies in Tg.rasH2 mice and SD rats were reviewed under SPA by David L. Carbone (June 8, 2021) and Chun-Ting (David) Lee (February 17, 2023), respectively, submitted to IND 122349.

To support the planned 26-week study in Tg.rasH2 mice, the sponsor conducted a 4-week study in CB6F1-TgN (RasH2) mice administered 0 (sesame oil), 30, 100, or 300/150 mg/kg RTA 408 by daily oral gavage. Ulceration of the nonglandular stomach was observed at doses greater than 30 and 100 mg/kg in males and females, respectively. The Executive CAC issued the following recommendations to the sponsor (June 4, 2021):

- The Committee recommended doses of 0 (water or saline), 0 (sesame oil), 5, 10, and 30 mg/kg/day for male mice and 0 (water or saline), 0 (sesame oil), 20, 50, and 100 mg/kg/day for female mice. The high dose for males and females was based on ulceration of the nonglandular stomach at doses >30 mg/kg/day (males) and >100 mg/kg/day (females) in the 4-week dose range-finding study.
- The low and mid doses for male and female mice were selected to provide approximate one-third AUC spacing.
- The Committee recommended the addition of a saline or water control group unless the Sponsor has data for the intended vehicle from prior mouse carcinogenicity studies.
- The Committee noted that the Sponsor included a draft report of the 4-week dose range-finding study. The current recommendations provided by the ECAC are contingent on the results of the final report not being notably different from those in the draft report, such that dose recommendations might have differed.
- The Committee noted that the evaluation of hematology parameters is not required by the FDA.
- If there are survival issues during the study, the Sponsor should contact the Review Division before any changes are made.

To support the planned 2-year study in Sprague Dawley (Hsd:Sprague Dawley SD) rats, the sponsor conducted a 13-week study in which 0 (sesame oil), 1, 3, 10, or 30 mg/kg RTA 408 was administered by daily oral gavage to SD rats. A reduction in body weight gain (42%) relative to controls was observed in HMDF. In addition, a 26-week study was conducted in SD rats administered 0 (sesame oil), 0.3, 1, or 3 mg/kg RTA 408 by daily oral gavage. Mean body weight relative to control was reduced in HDM (14%). The Executive CAC issued the following recommendations to the sponsor (April 14, 2022):

- The Committee recommended doses of 0 (water or saline), 0 (vehicle: sesame oil), 0.1, 0.3, and 1 mg/kg/day for males, with the high dose based on decreased (>10%) body weight (compared to control) at 3 mg/kg/day in the 26-week study.
- The Committee recommended doses of 0 (water or saline), 0 (vehicle: sesame oil), 0.3, 1, and 3 mg/kg/day for females, based on decreased (>10%) body

weight gain at 10 mg/kg/day in the 13-week study.

- The mid- and low- doses for both male and female rats were selected based on adequate AUC spacing.
- The Committee recommended the addition of a saline or water control group unless the Sponsor has data for the intended vehicle from prior rat carcinogenicity studies.
- The Committee noted that the 2-year carcinogenicity study will be performed in a different facility and using a different supplier of rats than the one used for the 13- and 26-week toxicity studies. The carcinogenicity study may not be acceptable if toxicity is significantly different due to these changes such that dose selection would have been altered.
- The Committee discussed the disproportionate M22 metabolite and noted that an ongoing 26-week mouse carcinogenicity study in Tg.rasH2 mice is expected to provide adequate exposure to M22; therefore, M22 does not need to be tested in the 2-year rat study.
- If there are survival issues during the study, the Sponsor should contact the Review Division before any changes are made.

11 Integrated Summary and Safety Evaluation

Introduction

RTA 408 is a Nrf2 activator developed by Reata Pharmaceuticals Inc. for the treatment of Friedreich's Ataxia. The recommended human dose (RHD) is 150 mg/day.

Pharmacology

Primary Pharmacology

The ability of RTA 408 to activate Nrf2 has been demonstrated in ARE-luciferase reporter assays and a variety of CNS cell types including neurons, astrocytes, and microglia, with activity observed at concentrations in the low nM range. RTA 408 restored mitochondrial function in myoblasts under oxidative stress, suppressed IFN γ -induced nitric oxide (NO) production in mouse macrophages, and inhibited proinflammatory gene expression in LPS-stimulated mouse microglial cells. In *in vitro* model of Friedreich's Ataxia (FA), RTA 408 increased mRNA levels of Nrf2 target genes in hFXN^{I154F} MEFs and in FA patient-derived fibroblasts and lymphoblastoid cells. RTA 408 significantly increased GSH levels and mitochondrial function in hFXN^{I154F} MEFs. Daily oral administration of RTA 408 in mouse, rat, and monkey for 14 days increased Nrf2 target gene expression and antioxidant enzyme activity in various tissues including liver, lung, and/or brain. RTA 408 was more potent than its metabolites (including M22, M17, M28, M14, M15, and M23) in suppressing IFN γ -induced NO production in mouse macrophages.

Secondary Pharmacology

RTA 408 was evaluated for off-target binding against an *in vitro* panel of 38 targets as well as 6 enzymes. RTA 408 did not significantly interact with any target.

RTA 408 differently modulated the expression of aminotransferase genes (including *ALT1*, *ALT2*, *AST1*, and *AST2*) in different types of cells, increased the expression of *Fth1* (Ferritin Heavy Chain 1) in mouse myoblasts, and dose-dependently increased the expression of *FTH1* in monkey liver after oral dosing.

Safety Pharmacology

Dedicated single dose oral studies in rat (CNS and respiratory) and monkey (cardiovascular) did not indicate drug effects on safety pharmacology endpoints, and there was no significant effect on QT prolongation in HEK293 cell cultures exposed to up to 1.2 μ M RTA 408.

PK/ADME

Plasma half-life for RTA 408 was approximately 6 to 30 h in mouse, rat, rabbit, and monkey. A single oral dose of [¹⁴C]RTA 408 in monkeys showed that radioactivity was distributed to tissues, including brain, with the highest concentrations observed in the gastrointestinal tract. The major circulating human metabolites were M17 and M22. Following a single oral administration of [¹⁴C]RTA 408, M17 was present in monkeys at higher levels (13.9%) than humans (10.9%); however, M22 was not observed in monkey plasma after a single dose. Additional mixed-matrix normalization analyses were used to assess the metabolite profiles for M17 and M22 after repeated oral administration in

monkey, rat, Tg.rasH2 mouse, CD1 mouse, and patients with FA. M17 showed adequate safety coverage (75.1 to 67700% peak area ratios in plasma) in all tested species compared with humans; therefore, was of less for the toxicities of concern. The ratios for M22 in Tg.rasH2 mouse plasma and CD1 mouse plasma at HD were similar to patients with FA; however, M22 was 25.6%, 16.6%, and 5% in monkey, male rat, and female rat, respectively, of levels in patients. M22 was, therefore, not adequately tested in the general toxicology studies in rat and monkey or in any reproductive and developmental toxicology studies in rat. M22 was >10000 times less potent than RTA 408 in suppressing IFN γ -induced NO production in mouse macrophages; therefore, showed minimal pharmacological activity relative to parent. Additionally, M22 (TX304579) was negative in an ICH M7-compliant *in silico* analysis (Leadscope Genetox Statistical Models and Derek Nexus) and in a non-GLP Ames assay. However, issues in this Ames assay were noted, including only 4 strains used, higher maximum test concentration and longer incubation time than recommended by the OECD guideline, respectively.

Toxicology

General Toxicology

The general toxicology of RTA 408 was assessed in GLP studies in SD rat (28-day and 26-week) and cynomolgus monkey (28-day and 39-week). In rats, drug-related effects included decreases in body weight gain in males (28-day) and absolute body weight in males (39-week), increases in liver weight, panlobular hepatocellular hypertrophy, bile duct hyperplasia, and kidney tubular degeneration/regeneration. Findings in the liver were associated with increases in AST and ALT. Based on the liver (bile duct hyperplasia) and kidney (tubular degeneration/regeneration) findings at all doses in the 26-week study, a NOAEL was not established in rats. In monkeys, drug-related effects included decreases in absolute body weight, prolongations in APTT, decreases in red cell mass (39-week), increases in liver weight, panlobular hepatocellular hypertrophy (28-day), kidney vacuolation (28-day), kidney tubular degeneration, decreased cellularity of bone marrow (28-day), and bile duct hyperplasia (39-week). Based on the prolongations in APTT and bile duct hyperplasia at $\geq$ MD, the NOAEL for daily-administration of RTA 408 for 39-week in monkey was 10 mg/kg/day.

Genetic Toxicology

An OECD-compliant genetic toxicology battery was conducted to support development of RTA 408. RTA 408 was negative in Ames and *in vivo* rat bone marrow micronucleus assays. RTA 408 was positive in an *in vitro* chromosomal aberration assay in human lymphocytes but was negative in an *in vivo* rat liver comet assay. Given the findings of the *in vivo* studies, concern over the positive result in the *in vitro* chromosome aberration assay is reduced.

Reproductive and Developmental Toxicity

A fertility study in SD rats administered 0, 1, 3, or 10 mg/kg/day RTA 408 by oral gavage resulted in a reduction in absolute body weight in HDM relative to controls from Day 36 through the end of the study. Additionally, increases in pre- and post-implantation losses and resorptions (early and late), as well as decreases in the number of implantation sites, the number of viable embryos, and uterus with cervix weight were

observed in HDF. Based on body weight loss in HDM and fertility and embryonic development findings at HD, the NOAEL was the MD of 3 mg/kg.

Embryofetal development was evaluated in SD rats (0, 1, 3, or 10 mg/kg/day) and NZW rabbits (0, 3, 10, or 30 mg/kg/day). In rats, no drug-related findings on maternal and fetal parameters were observed, the maternal and embryofetal NOAEL was the HD of 10 mg/kg/day. In rabbits, 2 MDF and 3 HDF aborted and were euthanized between GD 25 and 27. Drug-related clinical signs at all doses included few/absent/tan discolored feces, thin body condition, and red material in the pan. Early delivery was observed at all doses. Body weight gain and food consumption in HDF were reduced relative to controls from GD 7 to 19. Additionally, drug-related adverse effects at the HD included increases in post-implantation loss, number of late resorptions, resorptions (early and late), and the incidence of unilateral full rib, as well as a decrease in fetal body weight. Based on these findings, the maternal NOAEL was the LD of 3 mg/kg/day, and the embryofetal NOAEL was the MD of 10 mg/kg/day.

Effects on pre- and postnatal development were evaluated in pregnant SD rats administered 0, 1, 3, or 10 mg/kg/day RTA 408 from GD 6 to Lactation Day (LD) 20. The drug effects on F₀ dams at HD included decreases in body weight gain, food intake, and lactation food consumption, as well as an increase in enlarged livers. Additionally, a decrease in the number of liveborn pups/litter at birth and during the lactation periods, as well as increases in the number of stillborn pups/litter at birth and percent of stillborn pups/litter were observed at HD. The drug effects on F₁ animals at HD included decreases in F₁ pup survival to LD 21, decreased mean body weight in F₁ pups (pre-weaning; MD and HD), changes in sexual maturation (increased age of attaining preputial separation in males and decreased body weights of females at the time of vaginal opening), and reduced mean numbers of corpora lutea and impanation sites. Mean F₁ body weight (post-weaning) was reduced in MDM, HDM, and HDF. Additionally, F₁ males exhibited an increase in the basic movement count and total distance at 0-5 min at HD. F₁ females exhibited an increase in the basic movement count and total distance at 0-5 min at all doses, as well as in the total distance at 5-10 min at LD. There were no drug effects on the passive avoidance testing; however, the learning and memory task consisted of passive avoidance which lacks the sensitivity of a more complex learning and memory assessment, such as the Morris or Cincinnati water maze. Based on these findings, the NOAEL for dams was the MD of 3 mg/kg/day, and the NOAEL for pups was not established.

Carcinogenicity

Carcinogenicity studies (26-week study in Tg.rasH2 mice and 2-year study in SD rats) are to be conducted as post-marketing requirements.

Summary and Recommendation

The sponsor's general toxicology studies indicated a risk for drug-related liver and kidney injury based on findings in rats and monkeys, but such effects are likely monitorable in a clinical setting. Carcinogenicity was not evaluated but is to be assessed as a post-marketing requirement.

The nonclinical package provided in the New Drug Application for omaveloxolone (RTA 408) is considered to be adequate to support approval, with one caveat. Since M22 did not show adequate safety coverage in monkey, male rat, and female rat compared with humans, and was formed in the Tg.rasH2 and CD-1 mice at levels similar to those in humans, it is recommended that the sponsor assess the general and developmental toxicity of this metabolite in CD1 mouse and in an embryofetal development study in one species (M22 levels similar to humans), respectively.

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MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 28, 2023

From: Lois M. Freed, Ph.D.
Director, Division of Pharmacology/Toxicology-Neuroscience
Office of Neuroscience

Subject: NDA 216718 (Skyclarys, omaveloxolone)

The sponsor (Reata Pharmaceuticals) submitted NDA 216718 on March 30, 2022, for omaveloxolone for the treatment of Friedreich's ataxia in adults and in adolescents 16 years of age and older. Friedreich's ataxia is a rare neurodegenerative disease caused, in most patients, by a homozygous guanine-adenine-adenine (GAA) trinucleotide repeat expansion in the frataxin (*FXN*) gene, resulting in decreases in frataxin, a protein involved in cellular iron homeostasis.

For the NDA, the sponsor conducted the battery of GLP-compliant nonclinical studies agreed to by the division (Pre-NDA meeting minutes, September 28, 2021), including toxicity studies of up to 6 and 9 months in duration in rat and monkey, respectively, reproductive and developmental toxicology studies, and genetic toxicology studies of omaveloxolone.

The nonclinical studies have been reviewed by Dr. Lee (Review and Evaluation of NDA 216718, Chung-Ting (David) Lee, February 28, 2023) for the NDA. Many of the nonclinical studies were previously reviewed during clinical development; Dr. Lee references these reviews. Based on his review, Dr. Lee has concluded that the nonclinical data support approval of the NDA.

This memo summarizes selected findings from the nonclinical studies.

Pharmacology

The pharmacological activity of omaveloxolone was characterized in a series of in vitro and in vivo assays. In vitro assays in rodent (e.g., mouse myoblasts and microglial) and human (e.g., mesangial, primary astrocytes, RPE) cell lines and

in vivo studies in animals (non-GLP 14-day dose range-finding studies in mouse, rat, and monkey) demonstrated activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which is involved in the cellular response to oxidative stress.

The sponsor conducted no studies of omaveloxolone in an animal model of Friedreich's ataxia, noting that "well-established animal models of FA are not commercially available."

PK/ADME

The PK/ADME of omaveloxolone was assessed in multiple animal species (mouse, rat, rabbit, monkey) and in human.

Oral bioavailability was low (3-12%) in monkey and not assessed in other animal species.

Distribution of omaveloxolone into selected tissues at selected time points post-dose was assessed in 14-day toxicity studies in mouse, rat, and monkey. Brain levels were similar or higher than plasma levels in all three species (brain:plasma ratios: 0.877-1.40, 1.40-1.51, and 3.94-5.27, respectively, at 4 (mouse, rat) or 24 (monkey) hours after the last dose.

In vivo metabolism studies in humans indicated the presence of two major circulating metabolites, M22 (1,2-dihydro-30-COOH omaveloxolone) and M17 (1,2-dihydro-29-OH omaveloxolone), which accounted for 18.6 and 10.9% of total drug-related material in plasma, respectively. Neither of these metabolites was quantitated in the GLP-compliant nonclinical studies; however, the sponsor conducted analyses on pooled plasma samples from 7-day pharmacokinetic studies in Tg.ratH2 mouse (100 mg/kg/day), rat (10 mg/kg/day, the high dose in the embryofetal development study), and monkey (100 mg/kg/day, the high dose in the 39-week oral toxicity study). A mixed-matrix method was used "Because validated bioanalytical methods were not available."

The results of these analyses indicated that plasma levels (relative peak area) of M22 in Tg.rasH2 mouse were 102-88.3% of that in Friedreich's ataxia patients at steady state; however, plasma levels in monkey and rat were only 25.6% and 5-16%, respectively, of that in Friedreich's ataxia patients at steady state, indicating that the safety of M22 was not adequately tested in the completed nonclinical studies. Plasma levels (relative peak area) of M17 in mouse, rat, and monkey were similar or higher than that in patients in all three species (M-F: 530-1720, 75-91, and 6770%, respectively). No metabolite data were provided for rabbit.

Metabolites M17 and M22 were tested for pharmacological activity only in one (IFN γ -induced nitric oxide) assay in RAW264.7 mouse macrophages. Both metabolites were reported to have substantially less activity compared to

omaveloxolone, suggesting that neither metabolite contributes to Nrf2-mediated effects in vivo.

Toxicology

GLP-compliant general oral (gavage) toxicity studies of omaveloxolone were conducted in Sprague Dawley rat and cynomolgus monkey, with durations up to 26 and 39 weeks, respectively. Liver and kidney were target organs in both species, with rat being the more sensitive species.

Rat: in an initial 14-day non-GLP oral toxicity study, omaveloxolone (0, 10, 30, and 100 mg/kg/day) resulted in deaths (by Day 6) at the high dose, with cause of death identified as renal toxicity (tubular degeneration/necrosis and regeneration). Liver findings included panlobular hepatocellular hypertrophy, correlated with increases in GGT, ALT, and AST.

In a GLP-compliant 28-day (+ 28-day recovery) oral toxicity study (0, 3, 10, and 30 mg/kg/day), there were no drug-related deaths; however, kidney toxicity (tubular degeneration/regeneration) was observed at all but the low dose, and liver toxicity (bile duct hyperplasia/hypertrophy, panlobular hepatocyte hypertrophy, focal single cell necrosis) was observed at all doses. Clinical pathology findings included increases in total bilirubin, GGT, AST, ALT, SDH, BUN, and creatinine.

In a non-GLP 13-week oral toxicity study (0, 1, 3, 10, and 30 mg/kg/day), deaths occurred at 10 (Day 54) and 30 (Days 54-87) mg/kg/day, considered the result of multiple organ (liver, kidney, and cardiac myofiber) degeneration/necrosis. Liver findings correlated with increases in total bilirubin, GGT, ALT, and AST.

Additional (non-GLP) studies were conducted in male rat (14-day: 0, 3, and 10 mg/kg/day; 14-day: 0 and 30 mg/kg/day) to further characterize omaveloxolone-induced liver (only up to 10 mg/kg/day) and kidney toxicity. Liver changes (hepatocellular vacuolation, hypertrophy of bile duct epithelium) were correlated with increases in ALT and GLDH and ultrastructural findings (increased glycogen and smooth endoplasmic reticulum but no evidence of peroxisomal proliferation) at 3 and 10 mg/kg/day. Renal tubular degeneration/regeneration correlated with increases in urinary NGAL at 10 mg/kg/day and in urinary Kim-1 and NGAL at 30 mg/kg/day.

In the GLP-compliant 26-week (+ 4-week recovery) oral toxicity study (0, 0.3, 1, and 3 mg/kg/day), there were no drug-related deaths; however, liver (bile duct hyperplasia/hypertrophy) and renal degeneration/regeneration) were observed at all doses. Liver findings were correlated with clinical pathology changes, including increases in total bilirubin, GGT, AST, and ALT. Total, LDL, and HDL cholesterol were increased all doses.

As noted by the sponsor, doses associated with toxicity decreased with increased duration of dosing; in the 26-week study, no NOAEL was identified.

Monkey: in an initial 14-day non-GLP oral toxicity study, omaveloxolone (0, 10, 30, and 100 mg/kg/day) did not cause premature death but was associated with a dose-related decrease in food consumption and watery feces; liver weight was increased at all doses, but no microscopic findings were detected.

In the GLP-compliant 28-day (+ 28-day recovery) oral toxicity study (0, 10, 30, and 100 mg/kg/day), there were no drug-related deaths; however, clinical signs (distended abdomen, inappetence, unkempt and thin appearance) were observed at the high dose, and watery feces were observed in a dose-related manner. (The sponsor attributed fecal changes to omaveloxolone-induced exacerbation of vehicle [sesame oil] effects.) Microscopic findings were observed in liver (panlobular hepatic hypertrophy), gallbladder (hypertrophy/hyperplasia), and kidney (vacuolation), which persisted in recovery.

In the GLP-compliant 39-week (+ 28-day recovery) oral toxicity study (0, 10, 30, and 100 mg/kg/day), there were 8 premature deaths (2 control males, 2 mid-dose males, 3 high-dose males and 1 high-dose female); all (except in the control male) occurred during the first 6 weeks of dosing and were attributed to “dosing injury.” (This suggests some personnel issue.) Clinical signs (hunched posture, unkempt appearance, decreased activity, emesis, watery/discolored feces) were attributed to omaveloxolone-induced exacerbation of vehicle effects. APTT prolongation was observed at all doses. Microscopic changes in kidney (focal tubular epithelial degeneration/regeneration) were observed at the high dose; liver (bile duct hyperplasia) and gallbladder (mucosal epithelial hypertrophy) changes were observed at all doses.

Reproductive and developmental toxicology

A standard battery of reproductive and developmental toxicology studies was conducted for omaveloxolone.

To assess effects on fertility and early embryonic development, omaveloxolone (0, 1, 3, and 10 mg/kg/day) was orally administered to male and female Sprague Dawley rats prior to and during mating and continuing in females to gestation day 7. At the highest dose tested, there was an increase in pre- and post-implantation loss and resorptions, resulting in a decrease in viable embryos at the highest dose tested. The no-effect dose (3 mg/kg/day) for adverse effects on fertility and reproductive function was associated with plasma exposures (AUC) approximately 2 times that in humans (1340-1440 ng*hr/mL) at the recommended human dose of 150 mg/day.

The potential for adverse effects on embryofetal development (EFD) was assessed in embryofetal development studies in pregnant Sprague Dawley rat and New Zealand White rabbit.

Doses for the GLP-compliant EFD study in rat were selected based on a dose range finding study in Sprague Dawley rat at oral doses of 0, 1, 3, 10, and 30 mg/kg/day, administered from gestation days (GD) 6 through GD 17. At 30 mg/kg/day, omaveloxolone produced post-implantation loss and resorptions, resulting in a decrease in viable fetuses, and reduced fetal weight.

In the pivotal study in rat, oral administration of omaveloxolone (0, 1, 3, and 10 mg/kg/day) throughout organogenesis (GDs 6 to 17) resulted in no adverse effects on embryofetal development. At 10 mg/kg/day, plasma exposure (AUC) was approximately 5 times that in humans at the recommended human dose (RHD) of 150 mg/day.

In the GLP-compliant EFD study in rabbit, oral administration of omaveloxolone (0, 3, 10, or 30 mg/kg/day) throughout organogenesis (GDs 7 to 19) resulted in increased embryofetal mortality and skeletal variations and reduced fetal weight at the highest dose tested, which was associated with maternal toxicity. At the no-effect dose for adverse effects on embryofetal development (10 mg/kg/day), plasma exposure was less than that in humans at the RHD.

Potential effects of omaveloxolone on pre- and postnatal development were tested in Sprague Dawley rat; omaveloxolone (0, 1, 3, or 10 mg/kg/day) was orally administered throughout pregnancy and lactation (GD 6 through lactation day 20). Omaveloxolone produced an increase in stillbirths at all doses, reduced body weight in offspring at all but the lowest dose tested, and delayed sexual maturation (males), increased postnatal mortality, and impaired reproductive performance in offspring at the highest dose tested.

The study was notable for the minimal evaluation of potential effects on neurobehavioral function; no complex learning and memory task (e.g., Morris Water maze) or startle reflex with habituation testing was included. However, as assessed, adverse effects on neurobehavioral function were observed in offspring at all doses. Evaluation of locomotor activity (postnatal day [PND] 35) indicated increases in basic movement counts and total distance at the beginning of the monitoring period in males at the high dose and at all doses in females. Effects on learning and memory were evaluated using the step-through passive avoidance test (between PNDs 70 and 85). Latency to step into the dark compartment was decreased in males at all doses on testing days 2 and 3.

A no-effect dose for adverse effects on pre- and postnatal development in rat was not identified. Plasma exposure (AUC) at the lowest dose tested was less than that in humans at the RHD.

Genetic toxicology

A full battery of genetic toxicology studies was conducted for omaveloxolone.

Omaveloxolone was negative in a bacterial reverse mutation (Ames) assay, and positive in a chromosomal aberration assay in human peripheral blood lymphocytes but negative in in vivo (micronucleus and comet in rat) assays.

Carcinogenicity

Carcinogenicity studies of omaveloxolone have not been conducted. The division previously agreed that carcinogenicity studies in mouse and rat may to be submitted post-approval.

The sponsor submitted protocols under SPA for a 26-week carcinogenicity study in Tg.rasH2 mouse and a 2-year carcinogenicity study in Sprague Dawley rat. These were reviewed by the division and the Executive CAC (Executive CAC Minutes, June 4, 2021, and April 14, 2022, respectively) under IND 122349.

Both carcinogenicity studies are ongoing.

Conclusions and Recommendations

The nonclinical studies of omaveloxolone submitted to the NDA have identified clear target organs (primarily liver and kidney) toxicity, as well as adverse effects on reproductive and developmental endpoints, at clinically relevant plasma exposures. Carcinogenicity studies have not been completed, as previously agreed to by the division because of the seriousness of the indication and data from an adequate battery of genetic toxicology studies indicating, overall, a lack of mutagenic or clastogenic potential.

There are two major circulating metabolites in humans, M17 and M22. Quantitation of these metabolites was not included in the GLP-compliant toxicity studies. To estimate metabolite exposures, the sponsor conducted analyses on samples from non-GLP 7-day pharmacokinetic studies using a mixed-matrix approach. These analyses indicated that exposure to M17 was similar or higher at the highest doses tested in the embryofetal development study in rat and the 39-week oral toxicity study in monkey, compared to that in humans at the recommended human dose of 150 mg/day; however, plasma exposures to metabolite M22 were substantially lower at those doses than in humans at the RHD.

Mixed-matrix analysis of samples from a 7-day oral dose range-finding study in Tg.rasH2 mouse indicated similar levels of M22 in male (100%) and females

(88.3%) at 100 mg/kg/day compared to that in humans at the RHD; therefore, it is expected that M22 will be adequately tested in the ongoing 26-week carcinogenicity study in Tg.rasH2 mouse. However, the chronic toxicity and reproductive and developmental effects of M22 have not been assessed in animals. To address these concerns, a post-marketing requirement for a chronic toxicity study and an embryofetal development study of M22, each in one species, is recommended.

From a nonclinical standpoint, there is no objection to the approval of omaveloxolone for the proposed indication, with appropriate labeling and the following post-marketing requirements:

- A 26-week carcinogenicity study of omaveloxolone in Tg.rasH2 mouse
- A 2-year carcinogenicity study of omaveloxolone in rat
- A 26-week toxicity study of metabolite M22 (a major circulating metabolite in humans) in rat, based on the lack of adequate exposure to M22 in the completed 26- and 39-week toxicity studies in rat and monkey, respectively.
- An embryofetal development (EFD) study of metabolite M22 in one species, based on the lack of adequate exposure to M22 in the completed EFD studies of omaveloxolone in rat or rabbit.

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