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APPLICATION NUMBER:

208610Orig1s000

208611Orig1s000

NON-CLINICAL REVIEW(S)

MEMO TO FILE: NDAs 208610 and 208611

DATE: May 23, 2017

TO: File, NDA 208610 / 208611

FROM: Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist, DAIP

THROUGH: Terry Miller, Ph.D.
Pharmacology/Toxicology Supervisor, DAIP

RE: NDA 208610 SDN #45 / 208611 SDN #45, dated 5/19/17, Sponsor's response to labeling revisions

The Applicant raises the following questions regarding their draft labeling.

For section 8.1 Pregnancy, under Animal Data:

1. The Applicant objects to inclusion of information regarding longer gestation length at the high dose in the PPND study.

Discussion:

The highest dose in developmental and reproductive toxicity studies should demonstrate maternal toxicity. In the PPND study, mean body weight on GD 20 in dams treated with 120 mg/kg/day was 5.3% lower than control. This was statistically significant and considered to be test article-related. However, generally a 10% decrease in body weight is considered to be the threshold of maternal toxicity in the absence of any other overt toxicity.

The original reviewer noted that mean gestational length was slightly but statistically significantly longer in the 120 mg/kg/day group than control and that it exceeded the historical control range for mean gestational length. This finding in concert with the minimally decreased body weight was considered sufficient to justify the high dose as being maternally toxic. Interestingly, mean gestation length in the mid-dose group (60 mg/kg/day) was also statistically longer than control, but not greater than the historical control for the laboratory. This appears to be a dose-related trend. The report author did not consider the finding to be treatment-related, stating that gestation length is not a sensitive endpoint.

The Applicant would like to remove information about longer gestation length because they do not consider it to be delafloxacin-related. While the indicator may be relatively insensitive, it was statistically significant, and there appeared to be a dose-related trend. It also supports the presence of maternal toxicity at the high dose and the validity of the study. If this is not a dose-related finding, then the study should be repeated using a high dose that reaches maternal toxicity.

2. The Applicant objects to the description of the separate pharmacokinetics study as not being consistent with the study design of the PPND study. They state that there is no difference in AUC between pregnant and non-pregnant rats, so the stage of gestation should not matter.

Discussion:

The separate non-GLP range-finding pharmacokinetics study evaluated the low (10 mg/kg/day) and high (120 mg/kg/day) doses in a total of 6 pregnant and 6 non-pregnant animals each (3 animals sampled per time point). Dosing was for 7 days (GD 6 through GD 13). Since this is a much shorter dosing interval than in either the fertility or PPND studies, it is not entirely compatible with those study designs. Nonclinical pharmacokinetics studies have demonstrated some degree of accumulation over time that could be missed with an abbreviated period of dosing.

While the AUC was similar at 120 mg/kg/day in pregnant and non-pregnant rats, at 10 mg/kg/day, the value for pregnant rats was approximately twice that for non-pregnant animals.

3. The Applicant objects to the statement (b) (4) (b) (4).

Discussion:

(b) (4)
(b) (4)
The statement was removed following review of that submission, (b) (4)
(b) (4)

4. The Applicant objects to the statement relating the NOAEL dose in the PPND study to a human equivalent dose since there are plasma data.

Discussion:

The plasma data available are limited, not GLP-compliant, and not consistent with the PPND study design. Additionally, the NOAEL dose for maternal toxicity and for pup development was 60 mg/kg/day. There are no pharmacokinetic data provided for that dose, since the referenced dose range-finding study did not include that dose. The statement should remain.

For section 8.2 Lactation, under Animal Data:

1. The Applicant objects to expression of the administered dose in terms of a human equivalent dose. They say there are plasma concentrations available.

Discussion:

The administered dose was 20 mg/kg. Radioactivity levels were measured to determine plasma concentrations at given points in time (4, 8, and 24 hours post-dose), but sampling was likely later than peak plasma concentration and sparse enough to not define a time course of the drug. No AUC was calculated. It is not unreasonable to put the dose in context of a clinical dose, and based on the information derived from this study, the human equivalent dose based on BSA appears to be the best way to do that.

2. The Applicant objects to reporting radioactivity levels in the dams.

Discussion:

Addressing the radioactivity levels in the plasma of the dams seems to be the best way to put the levels secreted in milk and transferred to the pups in context. That comparison should remain in the label.

3. The Applicant objects to statements regarding the drug concentrations in the pups following nursing. They say this only indicates that the pups nursed.

Discussion:

The statement can be modified to indicate that the pups nursed and absorbed drug from the milk without the inclusion of concentration data.

For Section 13.1 (b) (4)

1. The Applicant objects to the description of the separate pharmacokinetics study that was not representative of the study design of the fertility study and suggests alternative wording.

Discussion:

The proposed wording is acceptable after addition of the duration of treatment for males and grammatical correction.

For Section 13.2 Animal Toxicology

1. The Applicant wishes to include more specific information regarding the oral dog study in which articular cartilage degeneration was found.

Discussion:

The Applicant's proposed wording is:

(b) (4)

The following is recommended in order to include more detail requested by the Applicant and to put it in the context of the study, as well as to correct grammar:

In a toxicology study of the formulated tablet in dogs, the femoral head of one of three high dose (480 mg/kg/day) females had minimal focal degeneration of the superficial articular cartilage and a small focal cleft in the articular cartilage. No other joints were examined.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY C NOSTRANDT
05/26/2017

TERRY J MILLER
05/26/2017

MEMO TO FILE: NDAs 208610 and 208611

DATE: May 22, 2017

TO: File, NDA 208610 / 208611

FROM: Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist, DAIP

THROUGH: Terry Miller, Ph.D.
Pharmacology/Toxicology Supervisor, DAIP

RE: NDA 208610 SDN #44 / 208611 SDN #44, receipt date 5/5/2017,
Sponsor's response to nonclinical request

This supporting document is provided in response to the Agency's request for information regarding which GLP-compliant nonclinical toxicology studies were performed using sulfobutylether- β -cyclodextrin (SBECD; Captisol®) and for clarification as to how any of these studies adequately tests the impact of the excipient on both tissue distribution and fetal exposure to delafloxacin in the pregnant rat during the period of organogenesis.

The previous response stated that there are "extensive toxicology data using the Captisol®/delafloxacin combination." The tabulated summary in the current response indicates that the commercial formulation was used in three GLP-compliant studies:

- a 28-day IV toxicology study in dogs (Study no. 0436DM77-001),
- the fertility and early embryonic development study in rats (Study no. WIL-880002), and
- the prenatal and postnatal development (PPND) study in rats (Study no. WIL-880003), as well as the non-GLP pharmacokinetics study in pregnant rats (Study no. WIL-880004).

A Captisol® formulation was used in two in vitro hemolysis studies (Study nos. 8201704 and 8239292, both considered negative for hemolysis). A pre-commercial formulation using 2000 mg/kg Captisol® was used in 2-week comparative studies in rats (Study nos. 1648-09002 and 8235345), and a Captisol® formulation was used in two IV infusion studies that were terminated before completion, one in rats (Study no. 1648-08766) and one in dogs (Study no. 0436DR37-002).

The review of the only GLP toxicology study using the clinical formulation, a 28-day IV toxicology study in dogs (Study no. 0436DM77-001) was unavailable, so the study report is reviewed below:

Study title: A 28-day intravenous infusion toxicity study of RX-3341 in dogs with a 2-week recovery (GLP)

Study no.: 0436DM77-001
Study report location: Electronic submission
Conducting laboratory and location: (b) (4)
Date of study initiation: March 4, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: RX-3341 (delafloxacin meglumine), 310 mg/vial for 300 mg (free acid form) dose/vial, 25 mg/mL after reconstitution; Lot Nos. 12DEL1 and 13DEL1, The appended certificates of analysis indicate that the assay for both lots was approximately (b) (4)% of label claim. The % purity was not provided, but both lots contained approximately (b) (4)% of identified impurities.

Key Study Findings

Male and female beagle dogs were administered RX-3341 once daily intravenously as a continuous 1-hour infusion at dose levels of 0 (placebo control), 10, 25 and 75 mg/kg/day for 28 consecutive days. A two-week drug-free recovery period followed the treatment period for additional control and high dose animals.

Clinical signs consisted of emesis, abnormal feces, salivation, vocalization, aggressive behavior, and decreased activity at the high dose. Emesis and abnormal feces were also recorded at a lower incidence in mid-dose animals. Serum chemistry changes (ALT and ALP increases, total protein and globulin decreases) and increased adrenals weight and kidney weights were reported at the high dose, 75 mg/kg/day. Following a 2-week recovery, ALT increases persisted, but the remaining findings had resolved in high dose animals. The No-Observed-Adverse-Effect-Level (NOAEL) was considered to be 25 mg/kg/day for 28 days in male and female beagle dogs (HED = 12.5 mg/kg/day, or 750 mg/day IV for a 60 kg patient).

The report states that there were no test article-related pathology findings. However, renal lesions, including renal tubule vacuolation, were seen in control and high dose animals at the end of treatment that were attributed to SBECD. Severity appeared to be greater in the high dose animals, leaving it unclear whether or not this may be a result of the combination of these two materials. No histopathology was performed on recovery animals.

Exposure to RX-3341 following a one-hour intravenous infusion at doses of 10, 25 or 75 mg/kg/day was dose-dependent and greater than dose-proportional. Exposure was greater following 28 consecutive days of treatment than following a single dose.

The elimination of RX-3341 was inversely dose-dependent; elimination appeared to decrease as the dose level increased. Elimination was also lower after 28 consecutive days of treatment compared to the elimination following a single dose. There appeared to be a 10 to 20% accumulation of RX-3341 after 28 days of treatment.

Methods

Doses: 0 (placebo), 10, 25 and 75 mg/kg/day
Frequency of dosing: Once daily for 28 consecutive days.
Route of administration: Continuous 1-hour intravenous infusion via a vascular access port (VAP) connected to an indwelling catheter in the right jugular vein. Doses were administered using a calibrated infusion pump set at a constant rate for one hour. The rate of infusion did not exceed 5 mL/minute.
Dose volume: 20 mL/kg
Formulation/Vehicle: The placebo was meglumine/Captisol/EDTA disodium solution; each milliliter of placebo solution contained 4.88 mg of meglumine, 200 mg of Captisol, and 0.28 mg of EDTA disodium.

The stock placebo was diluted in the same manner as the high dose test article formulation (3.75 mg/ml) with 5% Dextrose for Injection, USP (D5W).

The test article was a lyophilized powder which was reconstituted using 5% Dextrose for Injection, USP (D5W). Each vial of test article was reconstituted by adding 10.5 ml of D5W, which provided a stock concentration of 25 mg (free acid form) of test article/ml. Stock solutions were diluted in D5W bags to prepare the 0.5, 1.25 and 3.75 mg/ml RX-3341 dose formulations for the low, mid, and high dose treatments, respectively.

Species/Strain: Beagle dogs
Number/Sex/Group: 3-5 (see table below)
Age: 6-7 months at treatment initiation
Weight: 7.1-10.5 kg on Day 1

Group/Treatment	Dose Level* (mg/kg/day)	Concentration*	Dose Volume	Number of Animals**	
		(mg/ml)	(ml/kg)	Male	Female
1. Placebo Control	0	0	20.0	5	6 ^a
2. RX-3341 Low-dose	10	0.5	20.0	3	3
3. RX-3341 Mid-dose	25	1.25	20.0	3	3
4. RX-3341 High-dose	75	3.75	20.0	5	5

* The dosages and concentrations represented the free acid form of RX-3341 (no correction factor required).

** On Day 29, a targeted 3 animals/sex/group were euthanized. Surviving animals in Groups 1 and 4 remained on study, untreated, for a two-week recovery period.

^a An additional female dog was added to Group 1 to replace one Placebo Control female dog euthanized on Day 5 as a result of a hind leg injury. This additional female dog was dosed for 28 consecutive days. The data for all six Placebo Control females are included in the study report.

Observations and Results

Mortality

Observations for mortality/morbidity were performed twice daily during the treatment and recovery periods.

There was no test article-related mortality. One control female was euthanized on Day 5 following a hind leg injury. On necropsy, a complete tibial fracture of the left hind leg was observed. No abnormal findings for hematology, clinical chemistry or coagulation were reported for blood samples obtained at the time of euthanasia of this animal.

Clinical Signs

During the treatment period, animals were observed prior to dose administration, immediately post-dose, and at 1 to 3 hours post-dose. During the recovery period, animals were observed at least once daily.

Dose-related increased incidence of emesis and abnormal feces (generally characterized as soft or loose feces, on occasion with mucus or red substance, presumably blood, also present) were recorded during the treatment period for mid- and high dose animals. Salivation, vocalization, aggressive behavior, and decreased activity were also observed during the treatment period for animals treated with the high dose, 75 mg/kg/day. Clinical signs appeared to resolve during the recovery period.

Body Weights

Body weights were recorded at randomization and prior to dosing on Days 1, 8, 15 and 22, and post-dose on Day 28. During the recovery period, remaining animals were weighed on Days 35 and 42. Fasted body weights were recorded prior to euthanasia on Day 29 and on Day 43. No test article-related effects were reported on body weights or body weight gains.

Feed Consumption

Food consumption was recorded daily during the treatment and recovery periods. No test article-related effects were reported.

Ophthalmoscopy

Ophthalmology examinations were performed on all study animals during the acclimation period and during the third week of treatment (the Group 1 replacement female; see footnote under the study design table above) and the final week of treatment (all other animals on study). No test article-related effects were reported.

ECG

Electrocardiograms were recorded during the acclimation period and during the final week of the treatment and recovery phases. No test article-related adverse effects on cardiac rhythm or ECG morphology. were reported.

Hematology

Blood samples for evaluation of hematology, coagulation and clinical chemistry were obtained from all study animals during the acclimation period and at the end of the treatment (Day 29) and recovery periods (Day 43). Animals were fasted overnight (approximately 14-18 hours) prior to blood collection.

No test article-related effects were reported.

Clinical Chemistry

Increases in ALT and ALP, and reduced total protein and globulin values, were recorded at the end of the treatment period for males treated with 75 mg/kg/day. A slight increase in ALT was also recorded for females treated with 75 mg/kg/day at the end of the treatment period.

At the end of the recovery period, a slight increase in ALT persisted in the remaining high dose male dogs. All other clinical chemistry changes were reported to have completely reversed.

Urinalysis

Urine samples were collected overnight (approximately 15-17 hours) from all study animals during the acclimation period and at the end of the treatment and recovery periods for urinalysis while fasting.

No test article-related effects were reported.

Gross Pathology

All surviving animals were euthanized by intravenous barbiturate overdose administered by cephalic vein on Day 29 (terminal) or Day 43 (recovery). At the end of the treatment period, on Day 29, three animals per group were euthanized. At the end of the recovery period, on Day 43, the remaining two animals in each of Groups 1 and 4 were euthanized. A fasted terminal body weight was recorded prior to scheduled euthanasia on Day 29 or Day 43. Complete gross necropsies were performed on all animals.

No test article-related findings were reported. Red foci or raised, red or tan areas (occasionally accompanied by white linear striations) in the subcutis covering the vascular access port (VAP) were found in all treatment groups, including controls. Tan discolored areas, sometimes accompanied by white linear striations, remained apparent in the subcutis over the VAP of all remaining control and high dose animals on Day 43. These findings correlated with fibroplasia, granulomatous inflammation, and/or hemorrhage at the injection site. These findings were considered to be secondary to repeated injections into the VAP and not related to the placebo control or the test article.

Organ Weights

The following organs were weighed: adrenals, brain, heart, kidneys, liver, testes, ovaries, spleen, and thyroids/parathyroids. Paired organs were weighed together unless gross abnormalities were present, in which case they were weighed separately.

Test article-related increases in mean absolute and relative adrenal weights were reported at the end of the treatment period (Day 29) for males treated with 75 mg/kg/day, but appeared to have recovered by the end of the recovery period on Day 43.

The mean kidney-to-brain weight ratio for high dose males was statistically significantly increased at the end of the treatment period. This finding was no longer apparent by the end of the recovery period.

Increases in mean absolute thyroids/parathyroids weights for females treated with 10 mg/kg/day, and in mean thyroids/parathyroids-to-body weight and thyroids/parathyroids- to-brain weight ratios for females treated with 10 or 25 mg/kg/day were considered incidental and not related to treatment with RX-3341.

Histopathology

Adequate Battery

A full list of tissues were collected and preserved from all groups. Tissues were sent to (b) (4) where they were processed to paraffin blocks, prepared to slides, and stained with hematoxylin and eosin.

Histopathologic examination was performed on all tissues from Group 1 and 4 animals euthanized on Day 29, and for the Group 1 female euthanized for humane reasons on Day 5. Tissues from recovery animals were not evaluated, so any delayed effects would not have been observed.

Peer Review

No

Histological Findings

No test article-related findings were reported.

Microscopic findings at the injection site (the skin and subcutaneous tissue covering the VAP through which the injections were administered) and at the jugular

vein at the tip of the catheter were similar in control and high dose animals. These were considered to be due to the dosing procedure or consistent with the presence of an indwelling catheter and not due to the test article.

Minimal to mild renal tubule vacuolation was attributed to the Captisol® component of the placebo control vehicle. Kidney findings are presented in the excerpts from the Sponsor's table below:

Males

Kidneys	Number examined:	3	3
	Number unremarkable:	1	1
Dilation, tubules	2>	0	1
	Total Finding Incidence	0	1
Infiltrate, mononuclear cell	1>	0	1
	Total Finding Incidence	0	1
Lipidosis, glomerular	1>	1	0
	Total Finding Incidence	1	0
Vacuolation, tubule epithelium	1>	2	1
	2>	0	1
	Total Finding Incidence	2	2

Females

Kidneys	Number examined:	3	3
	Number unremarkable:	0	1
Infiltrate, mononuclear cell	1>	2	0
	Total Finding Incidence	2	0
Inflammation, mixed cell	1>	1	0
	Total Finding Incidence	1	0
Kidneys	Number examined:	3	3
	Number unremarkable:	0	1
Lipidosis, glomerular	1>	1	0
	Total Finding Incidence	1	0
Vacuolation, tubule epithelium	1>	1	1
	2>	0	1
	Total Finding Incidence	1	2

It is notable that renal tubular dilation was only noted in test article-treated animals and that severity of vacuolation was greater in test article-treated animals. Due to the small number of animals examined, it is unclear whether or not this could represent an interaction between delafloxacin and Captisol. No microscopic examination was performed for low and mid-dose animals at the end of treatment or for control and high dose recovery animals, making it difficult to draw conclusions regarding the effect of the combination of these compounds or regarding reversibility of lesions.

Toxicokinetics

On Day 1 and Day 28, whole blood samples (1.0 ml/sample) were collected for each animal immediately pre-dose (0), at 5 and 30 minutes after the end of the 1-hour infusion, and at 1, 4, 8, and 24 hours post-dose of 1-hr infusion. Plasma was separated and stored frozen at -88.5 to -70.9°C until sent for analysis to (b) (4) using LC-MS/MS.

Exposure to RX-3341 was dose-dependent (C_{max} and AUC), but increases appeared to be greater than dose-proportional on both Days 1 and 28. On Day 1, mean apparent volume of distribution values ranged from 1.7 to 6.2 L, and mean terminal plasma half-life values ranged from 1.1 to 1.8 hours for both sexes across all dose levels. On Day 28, mean apparent volume of distribution values ranged from ~ 1.4 to ~ 4.3 L and mean terminal plasma half-life values ranged from ~ 1 to 1.4 hours for both sexes across all dose levels. Findings were similar for males and females on Day 1 and on Day 28.

Exposure to RX-3341 was slightly greater after multiple RX-3341 dose administrations than the exposure after a single dose administration. Mean apparent body clearance values ranged from ~ 1 to ~ 2.3 L/hr. RX-3341 elimination from plasma and the body appeared to be inversely dose-dependent and RX-3341 elimination on Day 28 was slightly less than that elimination observed on Day 1. Mean accumulation index (AI) values ranged from ~ 1.1 to ~ 1.2 in all but one case (1.48 for Group 3 males), suggesting a possible accumulation of at least RX-3341 of 10-20% after 28 consecutive days of intravenous infusion doses.

Pharmacokinetic parameters are shown in the Applicant's tables below:

Table 1 – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following a Single Intravenous Infusion of RX-3341 (Day 1) to Male and Female Beagle Dogs

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C_{max} (ng/mL)	T_{max} (hr)	C_{last} (ng/mL)	T_{last} (hr)	$\text{AUC}_{0-\text{last}}$ (ng*hr/mL)	$\text{AUC}_{0-\text{inf}}$ (ng*hr/mL)	$T_{1/2,e}$ (hr)	Cl (L/hr)	V_z (L)
2	1	29	F	10	2550	0.083	94.6	8	2997	3207	2.57	3.12	11.6
2	1	32	F	10	3480	0.083	54.5	8	4549	4648	1.59	2.15	4.93
2	1	33	F	10	6760	0.083	32.7	8	7862	7900	1.16	1.27	2.12
				Mean	4263	0.083	60.6	8	5136	5252	1.77	2.18	6.22
				SD	2211.6	0.000	31.4	0.0	2485.1	2404.0	0.723	0.925	4.869
				%RSD	51.9	0.0	51.8	0.0	48.4	45.8	40.8	42.4	78.3
				Min	2550	0.083	32.7	8	2997	3207	1.16	1.27	2.12
				Max	6760	0.083	94.6	8	7862	7900	2.57	3.12	11.6

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C_{max} (ng/mL)	T_{max} (hr)	C_{last} (ng/mL)	T_{last} (hr)	$\text{AUC}_{0-\text{last}}$ (ng*hr/mL)	$\text{AUC}_{0-\text{inf}}$ (ng*hr/mL)	$T_{1/2,e}$ (hr)	Cl (L/hr)	V_z (L)
2	1	5	M	10	3100	0.083	42.1	8	3877	3954	1.56	2.53	5.68
2	1	14	M	10	4420	0.083	40.2	8	5735	5794	1.34	1.73	3.35
2	1	15	M	10	3710	0.083	15.7	8	4003	4023	1.18	2.49	4.24
				Mean	3743	0.083	32.7	8	4538	4590	1.36	2.25	4.42
				SD	660.6	0.000	14.72	0.0	1038.3	1043.0	0.191	0.451	1.176
				%RSD	17.6	0.0	45.1	0.0	22.9	22.7	14.0	20.0	26.6
				Min	3100	0.083	15.7	8	3877	3954	1.18	1.73	3.35
				Max	4420	0.083	42.1	8	5735	5794	1.56	2.53	5.68

Table 1 (continued) – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following a Single Intravenous Infusion of RX-3341 (Day 1) to Male and Female Beagle Dogs

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)
3	1	26	F	25	10300	0.083	81.7	8	14106	14219	1.26	1.76	3.20
3	1	30	F	25	8960	0.5	94.9	8	20063	20192	1.16	1.24	2.07
3	1	34	F	25	20300	0.083	96.8	8	24441	24574	1.14	1.02	1.68
				Mean	13187	0.222	91.1	8	19537	19662	1.19	1.34	2.32
				SD	6196.7	0.241	8.22	0.0	5187.6	5197.8	0.064	0.380	0.789
				%RSD	47.0	108.4	9.0	0.0	26.6	26.4	5.4	28.4	34.1
				Min	8960	0.083	81.7	8	14106	14219	1.14	1.02	1.68
				Max	20300	0.5	96.8	8	24441	24574	1.26	1.76	3.2

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)
3	1	4	M	25	12300	0.083	72.9	8	18219	18310	1.13	1.37	2.22
3	1	6	M	25	10900	0.083	106	8	13536	13708	1.41	1.82	3.71
3	1	10	M	25	7090	0.083	49.0	8	10956	11011	1.16	2.27	3.81
				Mean	10097	0.083	76.0	8	14237	14343	1.23	1.82	3.25
				SD	2696.3	0.000	28.62	0.0	3681.9	3690.7	0.154	0.450	0.891
				%RSD	26.7	0.0	37.7	0.0	25.9	25.7	12.5	24.7	27.4
				Min	7090	0.083	49.0	8	10956	11011	1.13	1.37	2.22
				Max	12300	0.083	106	8	18219	18310	1.41	2.27	3.81

Table 1 (continued) – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following a Single Intravenous Infusion of RX-3341 (Day 1) to Male and Female Beagle Dogs

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)
4	1	19	F	75	27900	0.083	687	8	48801	50152	1.64	1.50	3.55
4	1	27	F	75	45300	0.083	23.4	24	79864	79864	0.96	0.94	1.31
4	1	28	F	75	51000	0.083	72.6	8	70875	70955	0.86	1.06	1.32
4	1	31	F	75	51500	0.083	14.8	24	80670	80670	1.00	0.93	1.35
4	1	35	F	75	33100	0.083	45.3	24	51637	51637	1.15	1.45	2.41
				Mean	41760	0.083	169	17.6	66369	66656	1.12	1.18	1.99
				SD	10722.3	0.000	290.64	8.76	15269.3	14893.6	0.308	0.279	0.991
				%RSD	25.7	0.0	172.4	49.8	23.0	22.3	27.4	23.7	49.9
				Min	27900	0.083	14.8	8	48801	50152	0.86	0.93	1.31
				Max	51500	0.083	687	24	80670	80670	1.64	1.50	3.6

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)
4	1	3	M	75	44000	0.083	154	24	77579	77579	1.18	0.97	1.65
4	1	7	M	75	43800	0.083	1430	8	80487	84005	1.84	0.89	2.37
4	1	11	M	75	41000	0.083	11.1	24	78454	78454	1.14	0.96	1.57
4	1	16	M	75	48100	0.083	373	24	88302	88302	1.02	0.85	1.25
4	1	17	M	75	41400	0.083	102	8	58924	59045	0.95	1.27	1.75
				Mean	43660	0.083	414	17.6	76749	77477	1.23	0.99	1.72
				SD	2829.8	0.000	583.4	8.76	10825.6	11185.9	0.355	0.165	0.410
				%RSD	6.5	0.0	140.9	49.8	14.1	14.4	29.0	16.8	23.9
				Min	41000	0.083	11.1	8	58924	59045	0.95	0.85	1.25
				Max	48100	0.083	1430	24	88302	88302	1.84	1.27	2.37

Table 2 – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following 28 Consecutive Daily Intravenous Infusions of RX-3341 (Day 28) to Male and Female Beagle Dogs

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)	AI
2	28	29	F	10	3900	0.083	39.8	8	4303	4361	1.51	2.29	4.99	1.44
2	28	32	F	10	4670	0.083	20.2	8	5994	6018	1.11	1.66	2.67	1.32
2	28	33	F	10	5490	0.083	14.9	8	6241	6257	1.04	1.60	2.39	0.79
				Mean	4687	0.083	25.0	8	5513	5545	1.22	1.85	3.35	1.18
				SD	795.1	0.000	13.1	0.0	1054.9	1032.6	0.254	0.382	1.427	0.342
				%RSD	17.0	0.0	52.5	0.0	19.1	18.6	20.8	20.7	42.6	28.9
				Min	3900	0.083	14.9	8	4303	4361	1.04	1.60	2.39	0.794
				Max	5490	0.083	39.8	8	6241	6257	1.51	2.29	4.99	1.44

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)	AI
2	28	5	M	10	3270	0.083	17.0	24	3569	3569	1.43	2.80	5.76	0.92
2	28	14	M	10	4790	0.083	28.7	24	7136	7137	1.55	1.40	3.14	1.24
2	28	15	M	10	3800	0.083	12.2	8	3909	3925	1.11	2.55	4.07	0.98
				Mean	3953	0.083	19.3	18.7	4871	4877	1.36	2.25	4.32	1.05
				SD	771.5	0.000	8.5	9.24	1968.6	1965.3	0.227	0.747	1.328	0.173
				%RSD	19.5	0.0	44.0	49.5	40.4	40.3	16.7	33.2	30.7	16.5
				Min	3270	0.083	12.2	8	3569	3569	1.11	1.40	3.14	0.92
				Max	4790	0.083	28.7	24	7136	7137	1.55	2.80	5.76	1.24

Table 2 (continued) – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following 28 Consecutive Daily Intravenous Infusions of RX-3341 (Day 28) to Male and Female Beagle Dogs

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)	AI
3	28	26	F	25	16700	0.083	24.2	24	21808	21808	1.19	1.15	1.98	1.55
3	28	30	F	25	11600	0.083	67.8	24	16894	16894	1.15	1.48	2.45	0.84
3	28	34	F	25	18100	0.083	55.1	8	27039	27098	0.98	0.92	1.30	1.11
				Mean	15467	0.083	49.0	18.7	21914	21933	1.11	1.18	1.91	1.16
				SD	3421.0	0.000	22.4	9.24	5073.3	5103.2	0.113	0.280	0.578	0.356
				%RSD	22.1	0.0	45.7	49.5	23.2	23.3	10.2	23.6	30.3	30.5
				Min	11600	0.083	24.2	8	16894	16894	0.98	0.92	1.30	0.84
				Max	18100	0.083	67.8	24	27039	27098	1.19	1.48	2.45	1.55

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)	AI
3	28	4	M	25	12800	0.083	47.6	8	17238	17294	1.05	1.45	2.18	0.95
3	28	6	M	25	16100	0.083	44.0	24	27314	27314	1.14	0.92	1.50	2.02
3	28	10	M	25	11100	0.083	10.0	24	16183	16183	1.01	1.54	2.25	1.48
				Mean	13333	0.083	33.9	18.7	20245	20264	1.07	1.30	1.98	1.48
				SD	2542.3	0.000	20.7	9.24	6144.6	6131.0	0.067	0.338	0.414	0.536
				%RSD	19.1	0.0	61.3	49.5	30.4	30.3	6.2	26.0	21.0	36.2
				Min	11100	0.083	10.0	8	16183	16183	1.01	0.92	1.50	0.95
				Max	16100	0.083	47.6	24	27314	27314	1.14	1.54	2.25	2.02

Table 2 (continued) – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following 28 Consecutive Daily Intravenous Infusions of RX-3341 (Day 28) to Male and Female Beagle Dogs

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-1st} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)	AI
4	28	19	F	75	44400	0.083	77.1	24	69056	69056	1.09	1.09	1.71	1.42
4	28	27	F	75	46600	0.083	102	24	86393	86393	1.00	0.87	1.26	1.08
4	28	28	F	75	48600	0.083	42.2	24	84277	84277	0.88	0.89	1.13	1.19
4	28	31	F	75	56100	0.083	19.6	24	86438	86438	0.95	0.87	1.19	1.07
4	28	35	F	75	50700	0.083	68.1	24	72307	72307	1.05	1.04	1.57	1.40
				Mean	49280	0.083	61.8	24	79694	79694	0.99	0.95	1.37	1.23
				SD	4471.8	0.000	31.8	0.0	8353.1	8353.1	0.084	0.106	0.254	0.167
				%RSD	9.1	0.0	51.5	0.0	10.5	10.5	8.4	11.1	18.5	13.6
				Min	44400	0.083	19.6	24	69056	69056	0.88	0.87	1.13	1.07
				Max	56100	0.083	102	24	86438	86438	1.09	1.09	1.71	1.42

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	AUC _{0-1st} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	T _{1/2,e} (hr)	Cl (L/hr)	V _z (L)	AI
4	28	3	M	75	48800	0.083	341	24	89749	89749	1.00	0.84	1.20	1.16
4	28	7	M	75	51900	0.083	427	24	129077	129079	1.58	0.58	1.33	1.60
4	28	11	M	75	45800	0.083	92.3	24	76903	76903	1.03	0.98	1.45	0.98
4	28	16	M	75	39000	0.083	43.7	24	79246	79246	1.06	0.95	1.45	0.90
4	28	17	M	75	41100	0.083	13.0	24	53489	53489	0.98	1.40	1.99	0.91
				Mean	45320	0.083	183	24	85693	85693	1.13	0.95	1.48	1.11
				SD	5324.2	0.000	187.8	0.0	27634.0	27634.8	0.254	0.297	0.301	0.295
				%RSD	11.7	0.0	102.4	0.0	32.2	32.2	22.4	31.3	20.3	26.6
				Min	39000	0.083	13.0	24	53489	53489	0.98	0.58	1.20	0.90
				Max	51900	0.083	427	24	129077	129079	1.58	1.40	1.99	1.60

Dosing Solution Analysis

On Day 1 and Day 28, six 1-ml samples were obtained from each dosing formulation, including the placebo control, to determine the concentration and homogeneity of the test article in vehicle. Additionally, on Days 1 and 28, six 1-ml samples were obtained from a vial of reconstituted test article. Samples were stored refrigerated (2.1 – 5.6°C) until sent for analysis. Samples were sent to (b) (4) and were analyzed using LC-MS/MS.

Evaluation of results and acceptance criteria were not provided. The individual sample results for the stock solutions appeared to be in the bioanalytical report for the assay in dog plasma, although there was no discussion in the text of that report of the dosing solution analysis. Delafloxacin concentrations in most samples appeared to be greater than or equal to the nominal concentrations

The fertility and PPND studies that used the clinical IV formulation did not include the same evaluation seen in a general toxicology study and did not evaluate offspring exposed during the period of organogenesis for alterations during that period.

In the fertility study, males and females were administered IV doses of 0, 10, 60, or 120 mg/kg/day during pre-mating and cohabitation periods through gestation day (GD) 7. Clinical signs in this study included unkempt appearance, cool limbs and body, red material around the nose and mouth, drooping eyelids, and yellow staining in the 60 and 120 mg/kg/day dose groups. There were no effects on fertility indices. The NOAEL for maternal toxicity was 10 mg/kg/day, based on clinical signs (however, there were no effects on body weight), and 120 mg/kg/day for reproductive toxicity (HED = 19.4 mg/kg/day 1161 mg/day or 1.9 times the daily IV dose for a 60 kg patient). There was no evaluation of reproductive tissue or embryonic exposure to delafloxacin, and this study was not designed to evaluate alterations to organogenesis.

In the PPND study, rats were administered IV doses of 0, 10, 60, or 120 mg/kg/day from GD 6 through 20 and from lactation Day 5 through 20. Dams at the high dose, 120 mg/kg/day, had slightly lower body weights and slightly longer gestation length than control animals. Effects on pups at that dose included increased mortality during lactation, small stature, and lower body weights, but no changes in learning and memory, sensory function, locomotor activity, developmental landmarks, or reproductive performance were reported. Although the dosing period encompassed the period of organogenesis, no EFD evaluation was performed. The No Adverse Effect Level (NOAEL) for maternal toxicity and pup development in that study was 60 mg/kg/day (HED = 9.7 mg/kg/day, or 580 mg/day for a 60 kg patient, just below the clinical IV dose).

A separate non-GLP pharmacokinetics study was conducted using the same batch of delafloxacin as the fertility and PPND studies, but animals were dosed from GD 6-13, corresponding to the treatment interval in neither study, and failing to cover the entire period of organogenesis that would be treated in an embryo-fetal development study. AUC in pregnant rats treated with 120 mg/kg/day was 226379 ng*hr/mL (compared to 261601 ng*hr/mL in non-pregnant rats) and was 10504 ng*hr/mL in pregnant rats treated with 10 mg/kg/day (compared to 5148 ng*hr/mL in non-pregnant rats). Fetal exposure was not evaluated, and tissue distribution was not assessed. Based on this study, exposure at the 120 mg/kg/day dose in both the fertility and PPND studies was estimated by the Applicant to be approximately 5 times human plasma exposure at the clinical IV dose, based on AUC. Exposure at the NOAEL doses would be considerably lower.

In contrast, in the oral EFD study in rats, pregnant Sprague-Dawley rats were dosed by gavage twice daily (approximately 6 hours between each daily dose) for total daily doses of 200, 600, and 1600 mg/kg/day during the period of organogenesis (GD 6 through 17). Dose-dependent maternal toxicity was reported at 600 and 1600 mg/kg/day, consisting of clinical signs and reduced food consumption at 600 and 1600 mg/kg/day, and reduced body weight gain at 1600 mg/kg/day. The maternal NOAEL was 200 mg/kg/day. All doses were associated with delayed ossification in the fetuses, particularly in the caudal vertebrae and limbs. Fetal body weight was reduced at 1600

mg/kg/day. Toxicokinetic data indicated that AUC_{0-24hr} values were 76, 126, and 222 µg*hr/mL in the 200, 600, and 1600 mg/kg/day groups, respectively, on GD 6 and approximately twice that value on GD 17 (150, 265, and 369, respectively). The Applicant indicated that the AUC at 1600 mg/kg/day on GD 17 was approximately 7 times the estimated human plasma exposure based on AUC). The lowest dose, 200 mg/kg/day (approximately 2.5 times the estimated human plasma exposure based on AUC), was still toxic to the fetus, based on ossification delays.

The first of two 2-week rat studies of experimental formulations containing Captisol® was a bridging study. Study no. 1648-09002 compared delafloxacin in a formulation containing SBEDD to one containing another beta-cyclodextrin, (b) (4) so would not separate out effects attributable to the interaction of delafloxacin with a cyclodextrin from the effects of delafloxacin alone. However, the reviewer concluded that results in rats for the Captisol®-containing formulation “were similar to those resulting from intravenous formulations containing (b) (4) for RX-3341.” (b) (4)

(b) (4) Based on that review, the Captisol® dose in the high dose group was 800 mg/kg (the Applicant claims in this submission that the Captisol® dose was 2000 mg/kg). In Study no. 8235345, formulations containing Captisol® with and without EDTA were compared in non-pregnant animals. Neither of these studies provides a comparison of tissue distribution of delafloxacin with and without SBEDD, nor do they address potential distribution in fetal tissues in pregnant animals during the period of organogenesis.

The submission states that Captisol®-containing concentrations were used in two studies that were terminated early, one in rats (Study no. 1648-08766) and one in dogs (Study no. 0436DR37-002).

In the rat study (Study no. 1648-08766), which was intended to compare formulations containing either Captisol® (SBEDD) or (b) (4), (b) (4), so would not have provided data that would isolate effects of the cyclodextrin. The study plan provided for administration of dosing solutions as a 1-hour intravenous infusion for 14 consecutive days to Sprague Dawley rats, followed by a 7-day recovery period. The study was designed to include five treatment groups as follows: Captisol vehicle alone, RX-3341 formulated in Captisol vehicle (nominal doses of 10, 40, and 80 mg/kg), and RX-3341 formulated in (b) (4) vehicle (nominal dose of 80 mg/kg). However, the test article stock solutions were mistakenly switched so that instead, treatments were: Captisol vehicle alone, RX-3341 formulated in (b) (4) vehicle (calculated actual doses of 15, 60, and 120 mg/kg), or RX-3341 formulated in Captisol vehicle (calculated actual dose of 53 mg/kg). The study was terminated and repeated ((b) (4) Study No. 1648-09002, see above). Insufficient data were reported for this study to be of any utility.

In the dog study (Study no. 0436DR37-002), local vein irritation resulted in early termination of study; this was attributed to daily catheterization procedure, but it is unclear whether or not it could be attributed to the Captisol®-containing vehicle. Only male dogs were dosed and for only 15 consecutive days, followed by a recovery period of 8 days. Doses were 0, 10, 25, and 75 mg/kg/day RX-3341. Clinical signs associated with treatment included emesis, salivation, abnormal stools, and decreased activity. Vocalization and irritability were seen in control and treated groups, and may be related to venous irritation. ALT was increased in the mid-and high dose groups, and cholesterol was increased in the high dose group. At the end of recovery, ALT increases were partially reversed and cholesterol changes were fully reversed. Post mortem findings included macroscopic injection site changes and pale kidneys in control and treated animals, decreased adrenal weight in treated animals (reversible), decreased kidney weights in low and mid-dose animals, vacuolation in renal tubules in control and high dose animals (attributed to Captisol®), and intimal/endothelial proliferation, thrombosis, perivascular fibrosis/fibroplasia, hemorrhage, and mixed or mononuclear cell infiltration associated with the injection sites in all groups. A NOAEL was not established.

The Applicant attempts to extrapolate from the existing data to address potential effects on the developing offspring during the period of organogenesis. They state that pharmacokinetic assessments do not demonstrate differences in plasma exposure to delafloxacin between formulations containing Captisol and formulations using other (b) (4) other cyclodextrins). Plasma exposure was also similar in non-GLP pharmacokinetics studies of 120 mg/kg/day in non-pregnant rats and rats in early pregnancy, but at 10 mg/kg/day, exposure in pregnant rats was approximately twice that in non-pregnant rats. They also state that plasma exposures at a maternally toxic dose in the fertility and PPND studies were 4-5 times clinical exposure (unfortunately the exposure multiples for NOAEL/LOAEL doses were approximately 2.5 in the fertility study and near 1 in the PPND study), and that higher exposures were attained in the embryo-fetal development (EFD) study following oral exposure (because animals were dosed BID with much higher daily doses than in the IV studies), with maternal and fetal effects that were similar to those seen in the fertility and PPND studies. Unfortunately, no direct comparison of fetal effects can be made, since effects of exposure during the period of organogenesis in the oral EFD study was evaluated differently than typically conducted in a PPND study. Additionally, since the Applicant claims exposures that were 7 times clinical exposure at the high dose in the oral EFD study and 5 times the clinical exposure at the high dose in the PPND study; there does not appear to be an advantage in exposure using oral dosing.

The Applicant goes on to state that Captisol® “is not distributed to tissue” and is excreted via the kidney, and would therefore be expected to decrease distribution of delafloxacin to tissues, including fetal tissue. In contrast, a review article (Journal of Pharmaceutical Sciences 99:3291-3301; 2010) of studies conducted with SBECD reports that radiolabeled SBECD in quantitative whole body autoradiography studies

distributed “throughout the body tissues” at levels similar to or less than that in the vascular space, but did not cross the blood-brain barrier. Volume of distribution for SBECD corresponded to that of extracellular water. These findings argue that SBECD is widely distributed and could be distributed to fetal tissue.

The most sensitive indicator cited in this review article of toxicity of SBECD was dose-dependent changes in renal histopathology. Histopathology findings in general IV toxicology studies of SBECD included vacuolation in renal tubules at ≥ 160 mg/kg/day (NOAEL = 80 mg/kg/day for 1 month; HED = 13 mg/kg/day, or 800 mg/day for a 60 kg human¹¹) and in renal pelvis, urinary bladder, hepatocytes at higher doses, foamy macrophages (consistent with phospholipidosis) in lungs, pituitary gland, testis at doses ≥ 300 mg/kg/day (the lowest dose in this study, so a NOAEL was not identified), in liver spleen, and lymph nodes at doses ≥ 1000 mg/kg (mid-dose), and in ovary, uterus, and cardiac valves at the high dose, 3000 mg/kg/day. In the latter study, clinical pathology changes and increases in liver, kidney, and spleen weights were increased at the high dose. In a 6 month IV toxicology study, renal tubular vacuolation, increased kidney weight, epithelial vacuolation of the renal pelvis and bladder, hypertrophic macrophages in the liver, and pulmonary foam cell foci were reported at all doses (200-600 mg/kg/day). In dogs, the NOAEL for renal tubule vacuolation was 30 mg/kg/day (HED = 15 mg/kg/day, or 90 mg/day for a 60 kg human). Captisol® is present in the proposed IV formulation at 2400 mg/dose, or 4800 mg/day (40 mg/kg/dose or 80 mg/kg/day for a 60 kg human). The review article goes on to cite (without details) minimal maternal toxicity and slight perinatal toxicity of SBECD in developmental toxicology studies. The clearance of SBECD is said to be relatively rapid.

The Applicant also states that delafloxacin readily dissociates from Captisol in blood due to high plasma protein binding (mean 83.7% in humans, 91.5% in rats) and that Captisol has been shown not to affect tissue distribution of delafloxacin in a radiolabeled studies in rats (Study nos. RD-01-054 and RBX-01). Following a single oral dose of 20 mg delafloxacin (free acid)/kg (HED = 3.3 mg/kg, or 200 mg for a 60 kg human, approximately 22% of the clinical oral dose) in Study no. RD-01-054, peak mean delafloxacin concentration in uterus appeared to be at one hour (first evaluated time point), and was approximately 8% of the peak kidney concentration and 10% of the peak liver concentration, both seen at the same time point. In Study no. RBX-01, a single IV dose of 10 mg [¹⁴C]-delafloxacin (free acid)/kg (HED = 1.7 mg/kg, or 100 mg for a 60 kg human, approximately 17% of the clinical IV dose) was administered to male rats. The vehicle is not specified in the report, but it appears that this study was cited by the Applicant as containing Captisol®. The first sampling time in this study was at 4 hours post-dose, long after peak exposures following IV administration would be expected. Furthermore, since the test animals were all male, distribution to uterus or female reproductive tract in these animals could not be evaluated.

A placental transfer study (*The Placental Transfer of Total Radioactivity Following a Single Oral Administration of [¹⁴C]Abbott-31492 to the Pregnant Rat. Report no. R&D/02/398; Drug Metabolism Report no. 22*) was submitted in 2002 and reviewed by Dr. Stephen Hundley. In this study, an oral dose of 20 mg/kg ¹⁴C

delafloxacin was administered to pregnant rats on gestation day (GD) 17. Sacrifices were conducted at 1, 2, 4, 8, 24, and 48 hours post-dose. Tissue concentrations and tissue/plasma ratios for the 1, 2, and 4 hour time points are shown in the table from Dr. Hundley's review below:

Tissue	1 Hour Post-Dosing		2 Hours Post-Dosing		4 Hours Post-Dosing	
	µg eq./g	Tissue/Plasma Ratio	µg eq./g	Tissue/Plasma Ratio	µg eq./g	Tissue/Plasma Ratio
Plasma	3.9	---	1.37	---	0.52	---
Liver	11.0	2.8	5.68	3.6	1.79	3.4
Kidney	17.6	4.5	8.79	5.6	3.30	6.3
Amnionic Fluid	0.14	0.04	0.08	0.05	0.05	0.10
Amnion Membrane	0.45	0.11	0.19	0.12	0.10	0.19
Placenta	0.96	0.25	0.57	0.36	0.16	0.31
Ovaries	1.05	0.27	0.46	0.29	0.15	0.29
Uterus	1.48	0.38	0.78	0.50	0.33	0.63
Fetus	0.24	0.06	0.12	0.08	0.04	0.08

These data would be helpful for comparison to tissue distribution studies over the period of organogenesis of delafloxacin in formulations with (IV) and without (oral) SBECD.

Developmental findings related to delafloxacin in the rat oral EFD study included delayed ossification in the fetuses at all doses (≥ 200 mg/kg/day), particularly in the caudal vertebrae and limbs. Fetal body weight was reduced at 1600 mg/kg/day. These findings may be consistent with small stature and reduced pup weights in the PPND study at lower IV doses, but the IV study had the additional finding of early postnatal pup mortality. Without the typical morphological examination performed in an EFD study, it is unclear what the cause of neonatal mortality was. Nevertheless, if Captisol increases tissue distribution of delafloxacin to the fetus at the time of organogenesis, new morphological findings may be apparent, and the findings seen in the oral EFD study might be apparent at lower doses or systemic exposures, decreasing the margin of safety for clinical patients.

Discussion:

Three GLP-compliant toxicology studies used the proposed clinical IV formulation. In Study no. 0436DM77-001, the 28-day IV toxicology study in dogs, accumulation of delafloxacin was demonstrated. Exposure was greater than dose-proportional, and clearance was inversely related to dose. Renal lesions characteristic of SBECD were seen on histopathological examination, the severity of which was greater in high dose animals relative to vehicle control. Evaluation was somewhat limited in this study and did not provide any information that would address tissue concentrations in pregnant animals.

The fertility and PPND studies were performed using the clinical IV formulation, and provided adequate assessment for those evaluations. However, they did not

include the same evaluation seen in a general toxicology study and did not evaluate morphology of offspring exposed during the period of organogenesis for alterations during that period. A separate non-GLP pharmacokinetics study was used to estimate systemic exposure to delafloxacin in both studies, although the treatment period was considerably shorter than that in either the fertility or PPND study and the treatment period did not correlate to the treatment period or pregnancy stages in either study. It did show, however, that exposure in pregnant rats was approximately 2-fold higher than in non-pregnant rats at the 10 mg/kg/day dose.

Two 2-week studies in rats evaluating experimental formulations were not helpful in assessing the potential contribution of SBECD to tissue distribution and toxicity in pregnant animals. One compared a formulation with SBECD to a formulation with (b) (4); both cyclodextrins are likely to have similar effects on tissue distribution. The second study compared formulations with SBECD with and without EDTA.

Terminated studies included a rat study in which the stock test article solutions were mistakenly switched, so the study was terminated without the planned data collection and evaluation. The second terminated study was an intravenous study in dogs in which venous irritation resulted in early termination. Only males were treated, and post mortem findings included vacuolation in renal tubules in control and high dose animals (attributed to Captisol®). Again there were no data derived from these studies to address contribution of SBECD to tissue distribution of delafloxacin or fetal exposure and effects.

The Applicant's argument that Captisol® does not distribute to tissue contradicts published toxicology findings in kidney, liver, lung and other tissues and findings in the Applicant's own studies demonstrating tubular vacuolation in the kidney that was attributed to this excipient. Published articles indicate that Captisol® is distributed "throughout the body tissues" at levels similar to or less than that in the vascular space, with a volume of distribution corresponding to the extracellular fluid compartment. The Applicant also refers to tissue distribution studies of oral and IV (the latter with Captisol®) delafloxacin. The oral study (without Captisol®) demonstrated uterine exposure at 1 hour post-dose. The IV (presumably with Captisol®) whole-body autoradiography study was conducted in male rats, with the first evaluation at 4 hours post-dose; neither uterine exposure nor peak tissue levels could be determined in this study.

Conclusions:

The information provided is not sufficient to define the impact of the excipient, SBECD, on tissue distribution and fetal exposure to delafloxacin in the pregnant rat during the period of organogenesis. An embryo-fetal developmental toxicology (EFD) study ideally would address potential differences in fetal exposure and outcomes with the intravenous formulation of delafloxacin containing SBECD.

A tissue distribution study in pregnant rats treated orally and IV with the respective clinical formulations during the period of organogenesis is recommended. If this study does not demonstrate differences in tissue distribution to the fetus or the

maternal reproductive tract, then an embryo-fetal developmental toxicology (EFD) study may not be needed. However, if the tissue distribution study demonstrates difference, particularly in fetal delafloxacin exposure, that may be attributed to SBECD, then an EFD study of the clinical IV formulation in rats should be performed as originally recommended.

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/s/

AMY C NOSTRANDT
05/25/2017

TERRY J MILLER
05/26/2017

MEMO TO FILE: NDAs 208610 and 208611

DATE: May 2, 2017

TO: File, NDA 208610 / 208611

FROM: Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist, DAIP

THROUGH: Terry Miller, Ph.D.
Pharmacology/Toxicology Supervisor, DAIP

RE: NDA 208610 SDN #41 / 208611 SDN #42, Sponsor's response to nonclinical request for post-marketing study

Due to the apparent lack of information regarding the interactions of delafloxacin and the excipient sulfobutylether- β -cyclodextrin (SBECD; Captisol®) in reproductive toxicology studies, the Applicant was asked to perform an embryo-fetal toxicology study in the rat using the IV to-be-marketed formulation containing SBECD as a post-marketing commitment, should the application be approved. In this submission, the Applicant has indicated that they are not willing to do so.

The submission states that there are extensive toxicology data using the Captisol/delafloxacin combination, including the fertility and embryonic toxicology study and the pre- and post-natal developmental toxicology study. Unfortunately, the only formulation information in those studies and other pivotal toxicology studies are statements regarding the drug substance (e.g. RX-3341) and the vehicle used (e.g. 5% dextrose for injection). It is not stated in the information provided in the study reports whether or not Captisol was present in the test article before reconstitution in 5% dextrose for injection.

The submission goes on to indicate that toxicokinetics evaluation has demonstrated higher exposures following oral dosing relative to IV dosing. Based on the exposure multiples provided by the Applicant for the proposed label, it appears that exposure would be higher for doses administered IV relative to equivalent mg/kg doses administered orally. While higher doses might only be tolerated PO, there is still no information regarding how SBECD might affect tissue distribution and fetal exposure in the pregnant rat during the period of organogenesis.

To be conveyed to the Applicant:

Since toxicology study reports only indicate the drug substance (e.g. RX-3341) and vehicle used (e.g. 5% dextrose for injection), it is unclear which nonclinical studies may have used the to-be-marketed clinical formulation. Please provide a table indicating which GLP-compliant nonclinical studies used the current clinical formulation and which studies did not. Also, provide clarification as to how the repeat-dose toxicity, fertility, and pre-and post-natal toxicity studies conducted with delafloxacin with SBECD

adequately tests the impact of the excipient on both tissue distribution and fetal exposure to delafloxacin in the pregnant rat during the period of organogenesis.

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/s/

AMY C NOSTRANDT
05/02/2017

TERRY J MILLER
05/02/2017

MEMO TO FILE: NDA 208610 / 208611

DATE: April 20, 2017

TO: File, NDA 208610 /208611

FROM: Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist, DAIP

THROUGH: Terry Miller, Ph.D.
Pharmacology/Toxicology Supervisor, DAIP

RE: NDA 208610, SDN #40, Applicant's response to draft nonclinical label revisions

The Applicant provides a counter-proposal to some of the revisions made by the Division to the nonclinical sections of the label.

Their first comments were related to the discussion of fertility data in the rat in Section 13.1. Since there was no TK monitoring in the fertility study, the Division added interspecies comparison based on BSA-normalized doses in addition to comparison of AUC values between clinical trial subjects and data from other rat studies.

Dosing in the fertility study was administered as a single daily IV infusion over one hour. Males were dosed on Study Days 0-58 (a minimum of 28 days prior to cohabitation through one day prior to scheduled euthanasia) for a total of 58-59 doses. Females were dosed on Study Days 14-43 (a minimum of 14 days prior to cohabitation through Gestation Day 7) for a total of 22-30 doses. Doses were 10, 60, or 120 mg/kg/day. The vehicle was 5% dextrose solution for injection, USP.

PK data were derived from other toxicology studies. In Study no. 1648-06247, a 2-week IV toxicology study, delafloxacin was administered in a vehicle made up of mannitol, (b) (4) Meglumine USP, and sterile water (the relative proportions were not provided). It is important to note that this is not the same vehicle used in the fertility study, and pharmacokinetics in this vehicle may be different from what might have been seen in the fertility study. Doses were 10, 60, and 180/120 mg/kg/day delafloxacin. The high dose was reduced to 120 mg/kg after Study Day 1. Doses were administered as a 1-hour infusion. Toxicokinetics samples were collected on Study Days 1 and 14, but only Day 14 high dose data would be for the 120 mg/kg/day dose. For treated males, this would correlate to the first half of the pre-mating dosing period, but would not necessarily capture data at the time of mating or at the time of euthanasia. Data from females in this study would only be relevant for fertility indices, but not for early embryonic development, since pharmacokinetics in pregnant animals might be different, and since the timing of sampling was representative of the pre-mating period only. For males dosed with 120 mg/kg/day, the mean AUC on Day 14 was 211,000 ng*hr/mL (mean AUC_{last} on Day 14 was 210,000 ng*hr/mL). For females dosed with 120 mg/kg/day, the mean AUC on Day 14 was 242,000 ng*hr/mL (mean AUC_{last} on Day 14 was 241,000 ng*hr/mL). The Applicant averaged the exposure in

males and females and compared that value (226 $\mu\text{g}\cdot\text{hr}/\text{mL}$) to clinical data to arrive at a 5-fold greater exposure in rats relative to humans at the 120 mg/kg/day dose.

In Study no. 880004, doses of 10 or 120 mg/kg/day delafloxacin in 5% dextrose for injection were administered as a one-hour daily infusion to 6 non-pregnant and 6 pregnant rats per dose group. For the pregnant rats, dosing was on GD 6-13, which does not correlate with the exposure to pregnant rats from 2 weeks prior to mating through GD 7. Non-pregnant females were similarly dosed over Study Days 0-7. Toxicokinetic sampling was performed on Study Day 7 for non-pregnant females and on Gestation Day 13 for pregnant females. At the 120 mg/kg/day dose, mean AUC_{last} was 261,601 $\text{ng}\cdot\text{hr}/\text{mL}$ for non-pregnant females and 226,379 $\text{ng}\cdot\text{hr}/\text{mL}$ for pregnant females. Since the latter value was similar to the average across males and females in the study described above, the value of 226 $\mu\text{g}\cdot\text{hr}/\text{mL}$ was considered to be applicable to the pregnant females in the fertility study. However, there was no dose solution analysis, so the actual dose administered cannot be verified.

Since duration of dosing and sampling times in these two studies differ from the fertility study design, there is some degree of uncertainty as to whether or not the toxicokinetics values are applicable to the fertility study. However, the dose multiple based on BSA-normalized doses is 1.9, while the exposure multiple based on AUC from the separate studies was approximately 5; these two values are not vastly different. It would be acceptable to use the Applicant's exposure multiple as long as it is clarified that exposure data at this dose came from separate studies in rats, one of which used a different vehicle for delafloxacin, and both of which had dosing periods of shorter duration and sampling times that did not correspond to the gestation or dosing periods examined in the fertility study.

Their next comments are regarding animal toxicology data in Section 13.2. They object to the addition of findings (b) (4) in the description of toxicology study results. However, descriptions of all of these data, both those originally proposed by the Applicant and those added by the Division, have already been removed, as they add nothing over the information from clinical studies.

The only remaining wording in Section 13.2 at this time is the Division's statement, (b) (4)

(b) (4) The Applicant's wording originally stated, (b) (4)

A juvenile animal study was performed, but was only 14 days in duration, and also did not reveal this effect. However, one GLP-compliant 4-week toxicology study, using a formulated tablet, did reveal a single animal with articular cartilage degeneration; the data from this study should be as reliable as those from the pivotal studies of the drug substance that did not employ a clinical formulation. The Applicant states that emesis confounded this study, but emesis was seen in all oral studies in dogs and would lower systemic exposure. They also state that the lesion did not resemble the type of lesion seen in fluoroquinolone-treated dogs. Nevertheless, the following statement was made by the study pathologist in their report, "In the femoral head at Day 29 one Group 4 female (Animal #23) had minimal focal degeneration of the superficial articular cartilage, characterized by shrunken or degenerate

chondrocytes in a disordered or condensed matrix, and a small focal cleft in the articular cartilage. **This is a known toxicity of many fluoroquinolones in juvenile or immature animals**, and is generally considered adverse, even though these subtle lesions likely did not cause any clinical deficits on this study.” The Applicant also states that class labeling includes information regarding arthropathies in the Warnings and Precautions section.

Recommendations:

Since there is little difference between the BSA-normalized dose multiple in the fertility study and the exposure multiples from separate studies, it would be acceptable to use the exposure multiple for interspecies comparison, with the addition of language to specify that the exposure data are from separate IV toxicology studies in rats, one of which used a different vehicle for delafloxacin, and both of which had dosing periods of shorter duration and sampling times that did not correspond to the gestation or dosing periods examined in the fertility study.

It is recommended that all of the content of Section 13.2 be removed, provided that the class effect of arthropathy in animal studies is adequately described in the warning sections.

Addendum – 4/24/17

Information regarding articular cartilage changes in animal studies is not present in the Warnings and Precautions section as indicated by the Applicant. Wording regarding this known effect of fluoroquinolones should remain in Section 13.2:

Fluoroquinolone antibacterials are associated with degenerative changes in articular cartilage and arthropathy in skeletally immature animals. (b) (4)

(b) (4)

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/s/

AMY C NOSTRANDT
04/24/2017

TERRY J MILLER
04/24/2017

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 208610 (450 mg oral tablets)
NDA 208611 (Intravenous)

Supporting document: #001

Applicant's letter date: October 18, 2016

CDER stamp date: October 19, 2016

Product: Baxdela (delafloxacin N-methylglucamine salt)

Indication: 208610—Acute bacterial skin and skin structure infection (ABSSI)

Applicant: Melinta Therapeutics, Inc.

Review Division: Division of Anti-Infective Products

Reviewers: Wendelyn Schmidt with edits and additions where noted by Amy Nostrandt (AN)

Supervisor/Team Leader: Terry Miller

Division Director: Sumathi Nambiar

Project Manager: Fariba Izadi

Template Version: September 1, 2010

Note: The Pharmacology/Toxicology data was contained in NDA 208610.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208610 and 208611 are owned by Melinta or are data for which Melinta has obtained a written right of reference. Any information or data necessary for approval of NDA 208610 and 208611 that Melinta does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved

application is for descriptive purposes only and is not relied upon for approval of NDAs 208610 and 208611.

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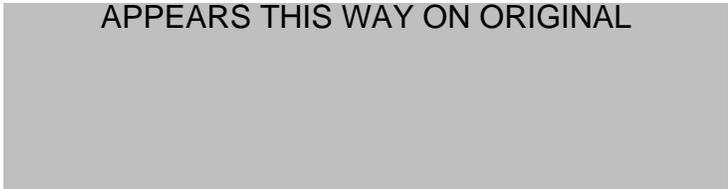


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Executive Summary

1.1 Introduction

Delafloxacin *N*-methylglucamine salt (RX-3341, ABT-492, A-319492^{(b) (4)} and WQ-3034), is a new fluoroquinolone antibiotic that is purported to have a broad spectrum of antibacterial activity. The antibacterial activity of delafloxacin is due to the inhibition of bacterial topoisomerase IV and DNA gyrase (topoisomerase II), enzymes required for bacterial DNA replication, transcription, repair, and recombination.

The application states that delafloxacin is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, ^{(b) (4)} *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group, ^{(b) (4)} *Streptococcus pyogenes*, and *Enterococcus faecalis*, and by the following Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, ^{(b) (4)} *Klebsiella pneumoniae*, ^{(b) (4)} and *Pseudomonas aeruginosa*.

1.2 Brief Discussion of Nonclinical Findings

A battery of safety pharmacology studies examined effects on CNS, cardiovascular, respiratory, and gastrointestinal systems. Effects, when present, appeared to be minimal (e.g. sedation, ptosis, abnormal gait, reduced latency for induced convulsions) and, with the exception of emesis and diarrhea, at higher tested doses.

Repeated dose toxicology studies of delafloxacin were conducted for up to 3 months in rats and dogs. The most prominent effects after both IV and oral dosing were gastrointestinal effects (abnormal stool, dilated cecum, and decreased food intake and/or body weights in rats; and emesis, salivation, and abnormal stool/diarrhea in dogs). Signs of nausea and emesis in dogs after IV administration may be suggestive of a CNS component. Additional findings in the pivotal rat studies included increased cholesterol, noisy respiration and epithelial hyperplasia and interstitial inflammation in the lungs. In pivotal dog studies, red blood cell parameters were decreased and serum ALT and cholesterol were increased; both changes were reversible. Articular cartilage degeneration, a known effect of fluoroquinolones, was noted in one of three high dose females in the only toxicology study of the formulated tablet in dogs.

Several studies were performed to evaluate the effects of delafloxacin formulated with sulfobutylether-beta-cyclodextrin (Captisol®, SBECD). Findings were similar to those in earlier studies, with the exception that vacuolation was seen in the kidney, a finding that has been documented in the literature with this excipient as reversible. Vascular irritation was also noted.

No adverse effects on fertility or early embryonic development were seen in a fertility study of IV delafloxacin in rats at exposures up to 5 times the clinical exposure. In embryo-fetal development studies, oral administration of delafloxacin to pregnant rats during the period of major organogenesis resulted in maternal toxicity and reduced fetal body weights at the highest dose (1600 mg/kg/day) and fetal ossification delays at all

doses. No malformations were reported. The lowest dose in rats, 200 mg/kg/day, would be approximately 2.5 times the estimated human plasma exposure based on AUC. In a study of oral administration in rabbits, doses were too low to be clinically relevant, in order to minimize maternal effects, since this species is particularly susceptible to changes in intestinal flora. In a pre-postnatal development study in rats of IV administered delafloxacin, dams at the highest dose tested (120 mg/kg/day) exhibited slightly lower body weights and slightly longer gestation length than control animals. Exposure at that dose was estimated to be approximately 5 times human plasma exposure based on AUC. Effects on pups at that dose included increased mortality during lactation, small stature, and lower body weights, but no changes to functional or developmental landmarks or reproductive performance were reported. The No Adverse Effect Level (NOAEL) for maternal toxicity and pup development in that study was 60 mg/kg/day, slightly lower than the equivalent clinical IV dose. Radiolabeled studies demonstrated secretion of delafloxacin in milk.

Juvenile (11 week old) beagles (3/sex/dose) were orally administered 0, 80, 160, or 320 mg/kg/day of A-319492 in gel capsules for 2 weeks. An additional 2/sex were administered control or high dose capsules and underwent a 2-week recovery period. One high dose animal died; clinical signs in that animal included respiratory distress. Otherwise clinical signs were limited to vomiting and retching that was dose-related in incidence, but decreased in incidence and frequency after the first week. No hematology changes were reported at the end of treatment, but reticulocytes were decreased by half in high dose recovery animals relative to controls. Based on the death at the high dose, the NOAEL would be the mid-dose, 160 mg/kg/day. It is unclear how much exposure was reduced by emesis, therefore it is most appropriate to make interspecies comparisons using the AUC. At the mid-dose, the AUC was ranged from approximately one-third to two-thirds of the clinical steady state AUC after oral administration. However, the small size and the short duration of this study limit its utility.

Genetic toxicology studies did not reveal any concerns for clinical use. (AN)

1.3 Recommendations

1.3.1 Approvability

The application is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

A GLP-compliant embryofetal development study in rats using the clinical IV formulation, containing SBECD, has been requested to be performed post-approval.

1.3.3 Labeling

Edits below are made to add detail, clarify ambiguities, and conform to PLLR format (AN).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Risk Summary

When delafloxacin was administered orally to rats during the period of organogenesis, no malformations or fetal death were observed at up to 7 times the estimated clinical exposure based on AUC. When rats were dosed intravenously in late pregnancy and through lactation, there were no adverse effects on offspring at exposures approximating the clinical IV exposure based on AUC. (See Data)

Data

Animal Data

In embryo-fetal studies, oral administration of delafloxacin to pregnant rats during the period of major organogenesis resulted in maternal toxicity and reduced fetal body weights at the highest dose (1600 mg/kg/day) and (b) (4) fetal ossification delays at all doses. (b) (4) No (b) (4) malformations were reported up to the highest dose tested (approximately 7 times the estimated human plasma exposure based on AUC). The lowest dose, 200 mg/kg/day (approximately 2.5 times the estimated human plasma exposure based on AUC), was still toxic to the fetus, based on ossification delays. In rabbits, a species known to be extremely sensitive to maternal toxicity of antibacterial drugs, no embryo-fetal developmental toxicity was observed up to the highest dose which induced maternal toxicity (1.6 mg/kg/day, or approximately 0.01 times the estimated human plasma exposure based on AUC). In a pre-postnatal study in rats of IV administered delafloxacin, dams at the highest dose tested (120 mg/kg/day) exhibited slightly lower body weights and slightly longer gestation length than control animals. Exposure at that dose was estimated to be approximately 5 times human plasma exposure based on AUC. Effects on pups at that dose included increased mortality during lactation, small stature, and lower body weights, but (b) (4)

(b) (4)

(b) (4) no changes in learning and memory, sensory function, locomotor activity, developmental landmarks, or reproductive performance were reported. The No Adverse Effect Level (NOAEL) for maternal toxicity and pup development in that study was 60 mg/kg/day (approximately 580 mg/day IV for a 60 kg patient, or just below the clinical IV dose). (b) (4)

8.2 Lactation

Risk Summary

Delafloxacin is excreted in the breast milk of rats (See Data). (b) (4)

Data

Animal Data

After single oral dose of 20 mg/kg (approximately 194 mg for a 60 kg patient) 14C labeled delafloxacin on post-natal day 11, the radioactivity was transferred into the milk of lactating rats. The mean milk/plasma radioactivity concentration ratios in dams at 4 and 8 hours after dosing were 8.5 and 4.0, respectively, and essentially background by 24 hours. The rate of elimination of radioactivity was similar in milk and plasma (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have not been conducted with BAXDELA. Delafloxacin was not mutagenic in a bacterial reverse mutation (Ames) assay, and was not clastogenic in a mouse bone marrow micronucleus test at ≥ 15 times the estimated human plasma exposure based on AUC. In an in vitro clastogenicity assay using isolated human lymphocytes, delafloxacin was negative in short incubations (~3 hours) and, at high cytotoxic concentrations (> 1.0 mM), was positive in a long incubation (~19 hours).

Delafloxacin did not affect the fertility of male and female rats up to the highest IV dose tested (b) (4)

(b) (4) 120 mg/kg/day, or approximately 1161 mg/day or 1.9 times the daily dose for a 60 kg patient). AUC in pregnant rats at 120 mg/kg/day delafloxacin IV was estimated to be approximately 5 times the estimated human plasma exposure based on AUC.

13.2 Animal Toxicology and/or Pharmacology

(b) (4) Articular cartilage degeneration was noted in at least one toxicology study of the formulated tablet in dogs.

2 Drug Information

2.1 Drug

Generic Name: Delafloxacin

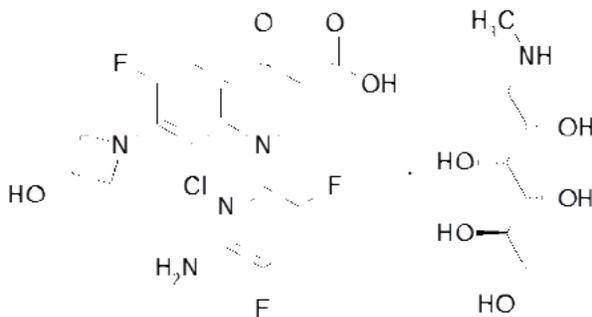
Code Names: RX-3341, ABT-492, A-319492^{(b) (4)}, and WQ-3034

Chemical Name: d-flucitol, 1-deoxy-1-(methylamino)-, 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidiny)-4-oxo-3-quinolinecarboxylate (salt). The salt is N-methylglucamine or meglumine salt.

Molecular Formula/Molecular Weight: salt: 635.977 g/mol; free acid: 440.764 g/mol.

Structure or Biochemical Description:

Figure 1 Delafloxacin Meglumine Salt Chemical Structure



Pharmacologic Class: Fluoroquinolone antibacterial

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 62772 (oral), 76096 (iv)

There is a DMF for the excipient, Captisol®, or sulfobutylether-beta-cyclodextrin (SBECD).

2.3 Drug Formulation

Table 1 Composition of Delafloxacin Tablets, 450 mg

Component	Reference to Quality Standard	Function	mg/tablet	% (wt./wt.)
(b) (4)				
Delafloxacin Meglumine ⁽¹⁾	In-House Standard	Drug substance	649	(b) (4)
Microcrystalline Cellulose ⁽²⁾ (b) (4)	NF	(b) (4)	(b) (4)	(b) (4)
Povidone (b) (4)	USP		33.8	
Crospovidone (b) (4)	NF		(b) (4)	
(b) (4)	(b) (4)			
Sodium Bicarbonate	USP		140.0	
Sodium Phosphate Monobasic Monohydrate	USP		5.5	
Citric Acid, Anhydrous	USP		5.5	
(b) (4)	(b) (4)		(b) (4)	
Magnesium Stearate (b) (4)	NF		10	(b) (4)
(b) (4)				(b) (4)

Table 1 Composition of the Dosage Form

Component and Quality Standard	Function	Strength (label claim)		
		mg/mL prior to lyophilization ^a	mg/dose	mg/vial
Delafloxacin meglumine (amount as free acid) ^b	Active	25.00	300	(b) (4)
Meglumine USP		(b) (4)	58.6	
Betadex Sulfobutyl Ether Sodium (Captisol [®]) NF			2400	
Edetate disodium (EDTA) USP			3.4	
(b) (4)			(b) (4)	
				(b) (4)

2.4 Comments on Novel Excipients

All of the excipients have been used in previously approved drugs at similar or higher levels. Captisol, or sulfobutylether-beta-cyclodextrin (SBECD), seems to be a late addition to the IV formulation and bridging studies have been performed to characterize its safety in the formulation. Those studies are reviewed under General Toxicology Studies below. Reproductive and developmental toxicology studies did not include this excipient in the test article formulation, leaving the potential reproductive and developmental effects of SBECD unknown.

A published review article of SBECD (Journal of Pharmaceutical Sciences 99:3291-3301; 2010) indicates that SBECD may be associated with vacuolation in the kidney; this excipient is rapidly eliminated unchanged in the urine, and is concentrated in the urinary tract. Vacuolation of kidney tubules was seen in at least one toxicology study of delafloxacin formulated with SBECD; the vehicle contained 200 mg Captisol per mL before dilution for infusion. Other findings in animal studies include foamy macrophages in the lungs, which may be consistent with phospholipidosis. The review

article indicates that these findings in animal studies are reversible. The review article also indicates that, in clinical studies, SBECD could be related to pseudo-allergic infusion reactions that are dose-related and quickly resolved.

Captisol® is present in the proposed formulation at 2400 mg/dose, or 4800 mg/day (40 mg/kg/dose or 80 mg/kg/day for a 60 kg human). Findings at equivalent doses in animal studies described in the DMF and in review articles in the literature appear to be limited to renal tubule vacuolation (commonly seen with substituted beta-cyclodextrins), which was reported to not be associated with functional changes and is likely to be reversible.

2.5 Comments on Impurities/Degradants of Concern

Special studies were conducted in dog (1 month oral toxicity of delafloxacin with (b) (4) % of the (b) (4) impurity) to qualify impurities. While there were changes in the articular cartilage in a single female dog, the plasma levels of drug were extremely variable. The variability was blamed on emesis. However, It was determined that a proposed limit of (b) (4) % for (b) (4) and a (b) (4) % limit for (b) (4) were acceptable. Similarly a 2 week study in the rat was conducted to qualify a (b) (4) impurity.

A number of leachable compounds related to the (b) (4) stopper for the IV product were identified by the CMC reviewer. In the absence of toxicology data from the Applicant for these compounds, the Applicant proposed to address this using the ICH M7 maximum daily dose for mutagenic impurities (120 µg/day). (AN)

2.6 Proposed Clinical Population and Dosing Regimen:

The proposed clinical dose for adult patients is 300 mg IV q12h, administered as a 60-minute infusion, or 450 mg PO q12h for 5-14 days.

2.7 Regulatory Background

Not applicable

3 Studies Submitted

3.1 Studies Reviewed

Toxicology:

By Dr. Wendelyn Schmidt:

1. Three month oral toxicity study of Abbott 319492 n-methyl glucamine in rats (with a one-month recovery period). RD-02-763.
2. Three month oral toxicity study of Abbott-319492 n-methyl glucamine in beagle dogs (with one- month recovery period). RD-02-564.
3. Two-week study of the oral toxicity of Abbott-319492 N-methyl glucamine in juvenile beagle dogs (with two-week recovery period). RD/02/792.

By Dr. Amy Nostrandt:

The following studies were performed to characterize formulation effects.

4. Study no. 1648-07836: RX-3341: A 2-Week Intravenous Formulation Bridging Toxicity Study in Sprague Dawley Rats with a 1-Week Recovery Period

5. RX-3341: A Two-Week Intravenous Toxicity Study Comparing (b) (4) and Captisol® Formulations in Sprague Dawley Rats with a One-Week Recovery Period (Bridge Study Number: 1638 - 09002).

(adapted from Dr. Stephen Hundley's earlier review)

6. Study no. 8235345: 2-week intravenous formulation bridging toxicity study with RX-3341 in Sprague Dawley rats with a 1-week recovery phase

7. Study no. 0436DR37.001: A 28-day oral toxicology study of RX-3341 in dogs with a 2-week recovery (GLP)

8. Study no. 0436DR37.002: A 28-day intravenous infusion toxicity study of RX-3341 in dogs with a recovery period of eighteen days

3.2 Studies Not Reviewed

ADME studies:

Absorption

1. Study no. M319492-11: Plasma concentrations of Abbott-319492 (WQ-3034) after oral dosing in mouse TX99-185.
2. Study no. M319492-12: Plasma concentrations of Abbott-319492 (WQ-3034) after iv and oral dosing in mouse.
3. Study no. MWQ3034-2: Preliminary pharmacokinetic evaluation of WQ-3034 after single intravenous or oral doses in rat.
4. Study no. PK-3341-001: RX-3341: Pharmacokinetic evaluation following intravenous administration to rats.
5. Study no. M319492-18: The effect of food on the oral bioavailability of Abbott-319492 in rat.
6. Study no. M319492-16: Plasma concentration of Abbott-319492 after multiple oral dosing in rat.
7. Study no. MWQ3034-3r: Preliminary pharmacokinetic evaluation of WQ-3034 after a single intravenous or oral dose in dog.
8. Study no. M319492-13: Plasma concentrations of Abbott-319492 after escalating oral doses in dog.
9. Study no. M319492-15: Plasma concentrations of Abbott-319492 after multiple oral dosing in dog.
10. Study no. MWQ3034-4: Preliminary pharmacokinetic evaluation of WQ03934 after intravenous or oral dosing in monkey.

Distribution

1. Study no. RBX/01: [¹⁴C]-delafloxacin (RX-3341): tissue distribution and excretion in the rat.

Metabolism

1. Study no. M3034-7: In vitro metabolism of WQ-3034 and WQ-3154.
2. Study no. XT134028: In vitro UDP-glucuronosyltransferase (UGT) reaction phenotyping of delafloxacin (RX-3341).

Excretion:

1. Study no. RBX/01: [¹⁴C]-delafloxacin (RX-3341): Tissue distribution and excretion in the rat.

Formulations Comparison:

1. Study no. M-319492-17: Effect of salt form, formulation and food on the oral bioavailability of Abbott-319492 in dog.
2. Study no. PK-3341-003: RX-3341: comparison of the plasma pharmacokinetics of various formulations of delafloxacin (RX-3441) administered by the oral route to beagle dogs.
3. Study no. PK-3341-004: Comparison of the plasma pharmacokinetics of various oral formulations of delafloxacin (RX-3341) in dogs.

Single Dose Toxicity Studies:

1. Study no. 1648-06484: RX-3341: an acute intravenous infusion toxicity study in Sprague Dawley rats.
2. Study no. TX00-032: Oral escalating-dose toxicity study of Abbott-319492 administered as the n-methyl glucamine salt in dogs.
3. Study no. TB00-052 (RD-01-265): Oral escalating twice daily dose toxicity evaluation study of Abbott-319492 administered as the n-methyl glucamine salt in dogs.
4. Study no. 8254352: Escalating dose range-finding intravenous injection study of RX-3341 in dogs.

Repeat Dose Toxicity Studies:

1. Study no. RD-00-285: Two week oral dosage range-finding toxicity study of Abbott-319492 n-methyl glucamine in rats (exploratory research plan).
2. Study no. 1648-06247: RX-3341: A 14-day intravenous infusion toxicity study in Sprague Dawley rats with a 7-day recovery period.
3. Study no. 1648-06676: RX-3341: A 28-day continuous intravenous infusion toxicity study with a 2-week recovery in Sprague-Dawley rats.
4. Study no. RD-00-503: Two-week oral dosage range-finding toxicity study of Abbott-319492 n-methyl glucamine in beagle dogs (exploratory research report).

Genotoxicity Studies:

1. Study no. TX99-173: Two-dose oral toxicity evaluation study of WQ3034 in male mice. (Study no. TD99-175 is the revised version).

2. Study no. TD99-184 (RD/99/561): Mouse micronucleus assay of WQ-3034.

Reproductive and Developmental Toxicity

1. Study no. RD/03/067: Oral (gavage) dosage-range developmental toxicity study of Abbott-319492 n-methyl glucamine in rats, including a toxicokinetic evaluation.
2. Study no. TX00-181: Five-day oral dosage range-finding study of Abbott-3194922 N-methyl glucamine in female rabbits.
3. Study no. RD/03/068: Oral (stomach tube) dosage-range developmental toxicity study of Abbott 319492 N-methyl glucamine in rabbits, including a toxicokinetic evaluation.
4. Study no. RD/03/069: Oral (stomach tube) dosage-range developmental toxicity study of Abbott-319492 N-methyl glucamine in rabbits.

Special Toxicology:

1. Study no. V0019-100-S: In vitro hemolysis study (Modified ASTM-direct contact method).
2. Study no. 7534-135: Hemolytic potential testing with RX-3341 injectable solution.
3. Study no. 7534-162: Hemolytic potential testing with RX-3341 solution.
4. Study no. 8201704: Hemolytic potential testing with RX-3341 injectable solution.
5. Study no. 8239292: Hemolytic potential testing with RX-3341 solutions.
6. Study no. RD/02/028: Evaluation of Abbott-319492 intravenous formulations for local irritation following subplantar injections in rats.
7. Study no. 0452LM77-01: Perivenous irritation study in rabbits with delafloxacin (RX-3341).

Impurities:

1. Study no. RD/01/178: Bacterial Reverse mutation assay (b) (4) of ABT-492 (Ames Test).
2. Study no. RD/01/179: In vitro micronucleus assay (b) (4) of ABT-492.

Studies to assess antibiotic-induced diarrhea:

1. Study no. 0440LR37-001: A 7-day oral study of RX-3341 in rabbits to assess antibiotic induced diarrhea.
2. Study no. 0443PR37-001: A 3-day oral dose range finding study followed by a 7-day repeat dose oral study of RX-3341 in Gottingen mini-pigs to assess antibiotic-induced diarrhea.

Comparisons with other Fluoroquinolones:

1. Study no. RD/00/008: Hepatic gene expression profiling of quinolone compounds levofloxacin, trovafloxacin and WQ-3034.
2. Study no. RD/01/042: Acute intraperitoneal toxicity evaluation of several quinolones (ciprofloxacin, gatifloxacin, gemifloxacin and Abbott-319492) in mice.
3. Study no. MWQ-3034-5 (VA99-230): One week oral toxicity and pharmacokinetic study of WQ-3034 and trovafloxacin administered to the male rat.

4. Study no. M319492-9 (VA99-759): Oral toxicity and pharmacokinetic study of WQ-3034, levofloxacin and trovafloxacin administered BID to male rats for seven days.
5. Study no. TX99-034: In vitro cytogenetics assay in human lymphocytes of trovafloxacin, sparfloxacin and WQ-3034.

Terminated Studies:

1. Study no. 1648-06090: RX-3341: a 14-day intravenous infusion toxicity study in Sprague Dawley rats with a 7 day recovery period.
2. Study no. 1648-08766: RX-3341: A 14-day intravenous toxicity study comparing (b) (4) and Captisol formulations in Sprague Dawley rats with a 7 day recovery period.

3.3 Previous Reviews Referenced:

Most studies were previously reviewed under either IND 76096 (iv) or 62772 (oral). Those reviewed by Dr. Steve Hundley are marked with an "H", while those reviewed by Dr. Terry Miller are denoted "M". The pharmacodynamics studies were reviewed by the Clinical Microbiology team.

Secondary Pharmacodynamics

1. Study no. RD/01/304: Study of WQ-3034 in various receptor binding assays.
H
2. Study no. RD/01/305: Study of WQ-3034 in various receptor binding assays.
H
3. Study no. RD/01/306: Study of WQ-3034 in various receptor binding assays.
H

Safety Pharmacology:

1. Study no. RD/01/307: WQ-3034: General CNS pharmacology profile in mice and rats after oral administration. H
2. Study no. RD/01/308: WQ-3034 and WQ3154: Evaluation for potential proconvulsant activity after oral administration in the mouse in comparison with levofloxacin, trovafloxacin, enoxacin, and norfloxacin. H
3. Study no. RD/01/309: WQ-3034, enoxacin, and trovafloxacin evaluation for potential proconvulsant activity after oral administration in the mouse (interaction with fenbufen). H.
4. Study no. RD/00/727: Pulmonary safety profile of Abbott-319492 in conscious rats. H
5. Study no. RD/01/647: In vitro effect on hERG current. H
6. Study no. RD/00/294: Abbott-319492: In vitro effects on cardiac Purkinje fiber repolarization. H
7. Study no. RD/99/491: Cardiovascular profile of Abbott-319492 in anesthetized and conscious dogs. H
8. Study no. RD/01/032: Effects of Abbott-319492 on QTc interval, cardiovascular and hemodynamic function in the anesthetized dog. H
9. Study no. RD/00/175: Gastro/emetic characteristics of Abbott-319492. H

ADME studies:

Distribution

1. Study no. RD/00/427: In vitro protein binding of [¹⁴C]-Abbott-319492 in mouse, rat, dog, monkey and human plasma. H
2. Study no. RD/00/428: In vitro binding of [¹⁴C]-Abbott-319492 to human α1-glycoprotein and albumin. H
3. Study no. RD/00/426: In vitro whole blood distribution of [¹⁴C]-Abbott-319492 in humans. H
4. Study no. RD/01/054: The tissue distribution of total radioactivity in the rat following oral administration of [¹⁴C]Abbott-319492. H
5. Study no. RD/02/404: The secretion of total radioactivity in milk of lactating rats following a single oral administration of [¹⁴C] Abbott-319492. H
6. Study no. RD/02/398: The placental transfer of total radioactivity following a single oral administration of [¹⁴C]-Abbott-319492 to the pregnant rat. H

Metabolism

1. Study no. RD/00/534: The metabolism and disposition of [¹⁴C]-Abbott -319492 in rats. H
2. Study no. RD/02/415: The metabolism and disposition of [¹⁴C]-Abbott-319492 in dogs. H
3. Study no. RD/00/552: In vitro metabolism of [¹⁴C]-Abbott-319492 by rat, dog monkey, and human liver microsomes and hepatocytes. H

Single Dose Toxicity Studies:

1. Study no. RD-00-511: Acute oral toxicity evaluation of Abbott-319492 n-methyl glucamine in mice. H
2. Study no. RD-00-510: Acute oral toxicity evaluation of Abbott -319492 n-methyl glucamine in rats. H
3. Study no. RD-02-769: Intravenous escalating-dose range-finding study of Abbott 319492 n-methyl glucamine in dogs. H

Repeat Dose Toxicity Studies:

1. Study no. RD-00-522: One month oral toxicity study of Abbott-319492 n-methyl glucamine in rats (with a two week recovery period). H
2. Study no. RD-02-770: Five day intravenous dosage range-finding study of A319492 n-methyl glucamine in male rats. H
3. Study no. RD-04-050: A-319492: A 14-day intravenous infusion range-finding toxicity study (with toxicokinetics) in Sprague-Dawley rats. H
4. Study no. RD-00-566: One month oral toxicity study of Abbott-319492 n-methyl glucamine in beagle dogs (with two-week recovery period). H
5. Study no. 1648-06250: RX-3341: A 5-day up/down iv infusion dose-range finding toxicity study in beagle dogs. H
6. Study no. 1648-06131: RX-3341: A 14-day repeat dose intravenous infusion toxicity study in beagle dogs with a 7-day recovery period. H

- Study no. 0436DM77-001: A 28-day intravenous infusion toxicity study of RX-3341 in dogs with a 2-week recovery (GLP). M

Genotoxicity Studies:

- Study no. TX00-126, RD/01/293: Salmonella-Escherichia coli/Mammalian – microsome reverse mutation assay with a confirmatory assay with Abbott-319492. H
- Study no. TX00-127, RD/01/294: Chromosomal aberrations in cultured human peripheral blood lymphocytes with Abbott-319492 n-methyl glucamine (Abbott-319492^{(b) (4)}). H
- Study no. TD00-128, RD/01/295: In vivo mouse micronucleus assay with Abbott-319492 n-methyl glucamine (Abbott-31942^{(b) (4)}). H

Reproductive and Developmental Toxicity

- Study no. WIL-880002: An intravenous infusion (1-hour) study of fertility and early embryonic development to implantation of RX-3341 in rats. M
- Study no. WIL-880004: An 8-day intravenous infusion toxicokinetic study of RX-3341 in pregnant and non-pregnant female Sprague-Dawley rats. M
- Study no. RD/02/055: Twelve-day intravenous dosage range-finding study of Abbott 319492 N-methyl glucamine in female rabbits. H
- Study no. RD/01/534: Oral (gavage) developmental toxicity study of Abbott-319492 N-methyl glucamine in rats, including a toxicokinetic evaluation. H
- Study no. RD/01/535: Oral (stomach tube) developmental toxicity study of Abbott-319492 N-methyl glucamine in rabbits, including a toxicokinetic evaluation. H
- Study no. WIL-880003: An intravenous infusion (1-hour) study of the effects of RX-3341 on pre- and postnatal development, including maternal function in rats. M

Special Toxicology:

- Study no. RD/02/029: Vein irritation evaluation of Abbott-319492 intravenous formulations following intravenous administrations for five consecutive days in rats. H

Impurities:

- Study no. RD/01/353: Two-week oral toxicity study of ^{(b) (4)} ^{(b) (4)}
- Study no. 0436RM77.002: A 28-day oral toxicity study ^{(b) (4)} ^{(b) (4)} in male rats with a 2 week recovery. M
- Study no. AD47UW-503-BTL: Bacterial Reverse mutation, ^{(b) (4)} M
- Study no. AD47UW-704ICH-BTL: In vitro mammalian cell gene mutation test ^{(b) (4)} M
- Study no. AD47UW-433MFLOWICH-BTL: In vivo micronucleus and comet assay with flow cytometry analysis ^{(b) (4)} M

6. Study no. AD53DY-503-BTL: Bacterial reverse mutation assay, (b) (4)
M

Studies to assess antibiotic-induced diarrhea:

1. Study no. 040PR37-002: A 7-day repeat dose oral study of RX-3341 in Gottingen mini-pigs to assess antibiotic induced diarrhea. M

Intraperitoneal Administration:

1. Study no. RD-00-513: Acute intraperitoneal toxicity evaluation of Abbott-319492 N-methyl glucamine in mice. H
2. Study no. RD-00-512: Acute intraperitoneal toxicity evaluation of Abbott-319492 N-methyl glucamine in rats. H

Formulation Changes:

1. Study no. 1648-09002: RX-3341: A Two-week intravenous toxicity study comparing (b) (4) and Captisol formulations in Sprague-Dawley rats with a one-week recovery period. H

4 Pharmacology

See Dr. Schmidt's Integrated Summary at the end of this review and the Clinical Microbiology review.

5 Pharmacokinetics/ADME/Toxicokinetics

See Dr. Schmidt's Integrated Summary at the end of this review.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Reviewed by Dr. Wendelyn Schmidt:

1. Study title: Three month oral toxicity study of Abbott 319492 n-methyl glucamine in rats (with a one-month recovery period).

Study no.: RD-02-763.
Study report location: EDR, Abbott Labs
Conducting laboratory and location: Abbott Laboratories, Abbott Park, IL with pathology by PAI, Frederick, MD
Date of study initiation: 3/25/2002
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Abbott-319492 (b) (4) lot # 82174NI00, potency 95.4% "as is," 96.3% "solvent free"

Key Study Findings: The NOAEL for this study was the MD, 600 mg/kg/day, based on body weight losses at the HD, as well as cholesterol increases. There were no specific target organs determined.

Clinical signs included abnormal stool and noisy respiration at the high dose, 1600 mg/kg/day. (AN)

The review below notes decreased body weight gain at the mid-dose and lung lesions (epithelial hyperplasia and interstitial inflammation, dose-related in incidence and persisting after the recovery period) at the mid- and high doses. This would seem to support a NOAEL of 200 mg/kg/day (AUC = 110572.8-116350.2 ng·hr/mL). (AN)

Methods

Doses: 0, 200, 600 or 1600 mg acid/kg/day in 2 divided dose (0, 100, 300, 800 mg acid/dose)
Frequency of dosing: Twice daily for 3 months
Route of administration: Oral
Dose volume: 10 mL/kg
Formulation/Vehicle: 0.2% hydroxypropyl methylcellulose, lot 00-05-11
Species/Strain: Sprague Dawley rats (CRrl:CD@a(SD)IGS BR)
Number/Sex/Group: 10/sex/group
Age: 6 weeks old
Weight: 134-236 g
Satellite groups: 5/sex/dose for TK, 5/sex/control, HD for recovery
Unique study design: Animals were treated by oral gavage twice daily approximately 5-7 hours apart.
Deviation from study protocol: None significant

Observations and Results

Mortality and Clinical Signs (twice daily with detailed observations of behavior on 4 occasions): There were a total of 3 deaths in the main study group which were all attributed to gavage accidents (1 MD male, 2 HD females). The HD male in the recovery group died on Day 61 of undetermined causes. Further details on the deaths of the 2 rats in the satellite groups (1 HD male and 1 MD female) were not provided. Clinical observations were primarily made in the HD group and included abnormal stool (7 males, 3 females), noisy respiration (6 males, 5 females), and matted fur (3 MD males, 10 HD males, 7 HD females). There were no significant observations during the recovery period.

Body Weights (pretreatment, twice weekly during the first month and weekly thereafter): In the HD males, body weight was decreased by approximately 10% as compared to controls beginning on day 17. At the end of the treatment period, body weight gain was decreased by approximately 10% at the MD and 25% in the HD males. There were no remarkable differences in body weight gain during the recovery phase between treated and controls during the study.

Feed Consumption (Weekly): There were no remarkable differences in food consumption in either males or females during the study.

Ophthalmoscopy (pretest, end of treatment, recovery): There were no remarkable observations.

Hematology (6 weeks, end of treatment, recovery): There were no toxicologically relevant changes in hematologic parameters with treatment.

Clinical Chemistry (6 weeks, end of treatment, recovery; standard panel): Cholesterol levels were increased in the HD males and females at Day 37 by between 10 and 30% as compared to controls, but the difference decreased by day 91 and no change was noted at the end of recovery. Sodium levels increased in the HD female rats at day 37 (150 control vs. 161 HD). No other toxicologically relevant changes were noted.

Urinalysis (middle of study, end of treatment, recovery): Changes in urinary parameters were not toxicologically relevant.

Gross Pathology: The main finding was dilation of the cecum, which occurred dose dependently during the treatment phase only.

Organ Weights (end of treatment, recovery): The absolute and relative adrenal weights were increased in both the HD males (absolute increased by 26% as compared to control) and females (absolute increased by 36% as compared to control). HD males showed decreased prostate weight (decrease by 35% as compared to controls). There were no remarkable differences at the end of the recovery period. The toxicologic relevance is unknown as there are no histologic correlates.

Histopathology (control and HD group unless gross lesions found, lung in all doses);

Adequate Battery; Yes

Peer Review: yes

Histological Findings: The major microscopic findings in the rats were confined to the lungs and consisted of epithelial hyperplasia of the bronchioles in males and epithelial hyperplasia in the alveoli, bronchi, and bronchioles in the females in a dose dependent incidence in the MD and HD animals. Additionally, chronic interstitial inflammation was

also noted in the MD and HD rat lungs (up to 50% of the animals in the HD). At the end of the recovery period, the same types of damage were noted in 1-2 of the 5 rats/sex. Severity remained minimal to mild.

Special Evaluation (liver and kidney from 3 rats/sex/ of all doses at end of treatment, recovery): Not conducted.

Reviewer's comment (AN): It is unclear why special evaluation of the liver and kidney was planned in the protocol but not conducted.

Toxicokinetics (Day 0, 87 at 1, 3, 6 (prior to second dose) 7, 9, 12, 24 hours after first dose, samples were analyzed at Abbott Labs after freezing, analysis of parent drug by HPLC with MS/MS detection, LOQ < 10 ng/mL): Two control animals at day 0 and 87 showed drug concentrations > zero at at least 1 time point. The sponsor attributed this to contamination. There were no consistent differences in pharmacokinetics based on gender. Absorption was non-linear with dose. Although there appeared to be some accumulation based on C_{max} between day 0 and day 87, the AUC values did not differ significantly.

Pharmacokinetic Parameters for A-319492

Treatment Group	Day	Dose (mg/kg/day)	C _{max} (ng/mL)	AUC* (ng•hr/mL)	AUC/Do (ng•hr•kg/m)
Tt	0	200	12528.8	110572.8	552.9
	87	200	25129.9	116350.2	581.8
T2	0	600	21647.3	260532.9	434.2
	87	600	38353.4	245557.1	409.3
T3	0	1600	30621.3	341371.9	213.4
	87	1600	41638.7	342772.9	214.2

* AUC_{0-∞} on Day 0, and AUC₀₋₂₄ on Day 87.

Dosing Solution Analysis (day 0, 20, 50): All solutions were within 2% of the nominal dose.

2. Study title: Three month oral toxicity study of Abbott 319492 n-methyl glucamine in dogs (with a one-month recovery period).

Study no.: RD/02/564
 Study report location: Abbott Labs
 Conducting laboratory and location: Abbott Laboratories, Abbott Park, IL
 Date of study initiation: April, 2002
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: A-319492^{(b) (4)} Lot # 82174N100, potency 95.4% "as is," 96.3% "solvent free"

Key Study Findings:

Beagle dogs (4/sex/dose) were administered oral doses of 0, 80, 160, or 320 mg/kg/day of A-319492^{(b) (4)} in capsules for 3 months. Clinical signs were limited to salivation and dose-related incidence and frequency of emesis during the treatment phase. Decreases in erythrocyte parameters in males at all doses and females at the high dose were reported at the end of treatment. Additionally, ALT was increased in high dose animals by up to 20-fold the concurrent control value. These clinical pathology changes appeared to be reversible after the recovery period. At the end of treatment, a dose-dependent decrease in thymus weight was reported in treated males, but thymus weights in high dose recovery animals were greater than controls. Toxicokinetic monitoring appeared to demonstrate accumulation of drug over time.

Although it is unclear how much the dose was reduced by emesis, the NOAEL appears to be 160 mg/kg/day (AUC = 19.6-26.1 µg*hr/mL on Day 1, approximately 52 µg*hr/mL on Day 89), based on reversibility of clinical pathology changes. (AN)

Methods

Doses: 0, 80, 160, 320 mg acid/day
 Frequency of dosing: Once daily for 3 months
 Route of administration: Oral capsules
 Dose volume: n/a
 Formulation/Vehicle: Capsules loaded with A319492, controls administered empty capsules
 Species/Strain: Beagle dogs
 Number/Sex/Group: 4/sex/dose
 Age: 4-6 months
 Weight: M: 6.8 to 7.9 kg; F: 5.6-6.9 kg
 Satellite groups: Control and HD for recovery, 2/sex/dose
 Unique study design: No unique aspects
 Deviation from study protocol: No significant deviations

Observations and Results

Mortality and Clinical Signs (twice daily, detailed observations twice weekly): All dogs survived until scheduled sacrifice. Clinical signs included an increase in number

of animals vomiting frothy or bright green vomitus as well as frequency in emesis with dose which persisted throughout the treatment phase; and increased salivation.

Body Weights (twice weekly during dosing, once weekly in recovery): There were no remarkable differences in body weight or body weight gain between treatment and control dogs.

Feed Consumption (twice weekly during dosing, once weekly in recovery): There were no dose or time dependent differences in food consumption between treatment groups.

Ophthalmoscopy (day 86): There were no remarkable differences between dose groups.

ECG (day -6, 35, 82/83 and 114): There were no noteworthy differences in cardiac parameters with dose.

Hematology (Days 29, 85, and 112): At the end of treatment, all of the delafloxacin treated males showed an approximately 10% decrease in hematocrit, RBC #, and reticulocyte #; however, the control value was higher than at prior timepoints. The HD females also showed a decrement at day 85 in RBC associated parameters. The sponsor deemed this to be toxicologically non-relevant.

Reviewer's note: The RBC associated changes are of questionable significance.

Clinical Chemistry (Day 29, 85, 112): 4/6 HD males at day 85 had increases in ALT (from 2 to 20 fold), but not AST. Similar results were seen in the HD females. In the recovery animals, ALT values did not differ remarkably from controls.

Urinalysis (necropsy): There were no remarkable differences between treated and control dogs values for specific gravity and urinary pH at the end of treatment or recovery.

Gross Pathology: There were no remarkable, dose-dependent findings in the dogs.

Organ Weights: While the males showed a dose dependent decrease in absolute and relative thymus weights of up to approximately 20% as compared to controls, females show no significant changes in weight with treatment. During the recovery period, the thymus weight of the HD animals increased significantly above controls.

Histopathology

Adequate Battery: Yes

Peer Review: yes

Histological Findings: There were no significant microscopic findings.

Special Evaluation (liver, kidney and pancreas for ultrastructural pathology of control, HD groups): There were no remarkable findings with treatment.**Toxicokinetics (day 0, 89; 0.5, 1, 2, 4, 8, 12, 24 hours post-dose):**

		Mean Plasma Concentrations of A-319492 ± SD, JLg/ml		
Collection Interval	Sex	A-319492 dosage, mg acid/kg/day		
		80	160	320
		Mean Plasma AUC (J.Lg•hr/ml) ±SO		
Day0	Males	23.2 ± 12.7	19.6±3.1	25.8 ± 11.1
	Females	26.6 ± 17.1	26.1 ± 11.1	20.5 ± 6.5
Day89	Males	22.3 ± 16.7	51.9 ± 23.6	55.6 ± 36.7
	Females	32.7 ± 8.9	52.1 ± 17.3	95.6 ± 36.8
		Mean Plasma Cmax (J.Lg/ml) ± SD		
Day0	Males	7.7 ± 5.6	6.9 ± 2.6	6.2 ± 1.3
	Females	7.3 ± 3.4	7.4 ± 3.2	6.4 ± 2.3
Day 89	Males	7.5 ± 4.8	15.1 ± 7.1	15.3 ± 9.9
	Females	12.7 ± 3.3	18.7 ± 9.1	21.5 ± 7.5

Dosing Solution Analysis (Study day 0, 27, 56): The amount of drug administered was within 1% of the intended dose at each timepoint.**3. Study title: Two week study of the oral toxicity of Abbott-319492 n-methyl glucamine in juvenile beagle dogs (with 2 week recovery period).**

Study no.: RD/02/792
 Study report location: Abbott Laboratories
 Conducting laboratory and location: (b) (4)
 Date of study initiation: May 27, 2002
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: A-319492, lot # 82174N100, 96.3% pure

Key Study Findings

Juvenile beagles (3/sex/dose) were orally administered 0, 80, 160, or 320 mg/kg/day of A-319492 in gel capsules for 2 weeks. An additional 2/sex were administered control or high dose capsules and underwent a 2-week recovery period. One high dose animal died; clinical signs in that animal included respiratory distress. Otherwise clinical signs were limited to vomiting and retching that was dose-related in incidence, but decreased in incidence and frequency after the first week. No hematology changes were reported at the end of treatment, but reticulocytes were decreased by half in high dose recovery animals relative to controls.

Based on the death at the high dose, the NOAEL would be the mid-dose, 160 mg/kg/day. It is unclear how much exposure was reduced by emesis, therefore it is most appropriate to make interspecies comparisons using the AUC. At the mid-dose, the AUC was 11,250 ng*hr/mL on Day 1 and 22,326 ng*hr/mL on Day 14. (AN)

Methods

Doses:	0, 80, 160, 320 mg/kg/day of the acid form
Frequency of dosing:	Once daily for 14 consecutive days
Route of administration:	Oral in gel capsules
Dose volume:	See above
Formulation/Vehicle:	Control is empty gelatin capsule; bulk drug in capsules
Species/Strain:	Beagle dogs
Number/Sex/Group:	3/sex/dose
Age:	11 weeks
Weight:	M: 2.8 to 4.4 kg; F: 2.3 to 4.0 kg
Satellite groups:	2/sex/control and HD for recovery
Unique study design:	No significant features
Deviation from study protocol:	None significant

Observations and Results

Mortality and Clinical Signs (twice daily):

One HD female died on study day 5 after the administration of the first capsule with respiratory distress, cold to touch, inactivity and recumbency preceding moribund sacrifice. The incidence of vomiting/retching increased with dose. This was usually observed within the first hour of dosing and decreased in frequency and incidence after day 4-5.

Body Weights (pretest, day 1, 4, 7, 10, 14, 18, 21, 24, 28): There were no remarkable differences in the body weights or body weight gains of the treated versus control puppies.

Feed Consumption (daily): In general, there were no remarkable, dose-dependent differences in food consumption between dosing groups.

ECG (pretreatment, end of treatment, end of recovery): There were no noteworthy effects on heart rate, Qt intervals, or QT tracings between treated and control dogs.

Hematology (pretest, day 15, 29): There were no noteworthy differences between treated and control groups; however at the end of the recovery period, the absolute number of reticulocytes were decreased by roughly half in the HD males and females as compared to the controls.

Clinical Chemistry (pretest, day 15, 29): There were no remarkable differences in clinical chemistry values between treated and control dogs at either the end of treatment or recovery. This includes liver enzyme values.

Gross Pathology: There were no remarkable differences between treated and control animals.

Organ Weights; There were no remarkable differences in either relative or absolute organ weights between treated and control puppies at the end of treatment or recovery.

Histopathology

Adequate Battery: yes

Peer Review: Yes

Histological Findings: There were no remarkable differences in the observations between treated and control dogs.

Toxicokinetics:**Pharmacokinetic Parameters for Abbott-319492**

Gender	Treatment	AUC*		AUC/Dose*		C _{max}		T _{max}		T _{1/2}	
		(ng*Hours/mL)		(ng*Hours/ml mg/kg/day)		(ng/mL)		(Hours)		(Hours)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Male	T2	17647.7	10572.6	220.6	132.2	5837.2	3676.1	1.0	1.7	1.7	4.6
	T3	11376.5	24393.6	71.1	152.5	4460.4	8631.7	1.0	1.0	1.4	7.4
	T4	21789.6	15264.5	68.1	47.7	7099.3	5542.5	1.0	1.0	1.3	9.0
Female	T2	13558.7	15415.6	169.5	192.7	4622.3	4594.5	1.0	1.7	1.7	5.3
	T3	11123.7	20257.7	69.6	126.6	3821.1	7311.3	1.0	1.0	1.5	7.8
	T4	20137.1	47074.6	62.9	147.1	7821.0	11191.8	1.0	1.7	1.1	12.2
Overall	T2	15603.2	12994.1	195.1	162.4	5229.8	4135.3	1.0	1.7	1.7	5.0
	T3	11250.1	22325.7	70.3	139.5	4140.8	7971.5	1.0	1.0	1.5	7.6
	T4	20963.4	31169.6	65.5	97.4	7460.2	8367.1	1.0	1.3	1.2	10.6

* AUC and AUC/Dose are extrapolated to infinity on study Day 1, and AUC₀₋₂₄ on Day 14.

Exposure in this study appeared to accumulate over time. (AN)

Dosing Solution Analysis

Capsules were found to contain 97-99% of their intended dose. (AN)

Reviewed by Dr. Amy Nostrandt (studies 4, 6, 7, and 8; study 5 is adapted from Dr. Stephen Hundley's review):

The following studies compared different formulations and evaluated the excipient Captisol® in the experimental formulations.

4. Study title: RX-3341: A 2-Week Intravenous Formulation Bridging Toxicity Study in Sprague Dawley Rats with a 1-Week Recovery Period

Study no.: 1648-07836
 Study report location: Electronic submission
 Conducting laboratory and location: (b) (4)
 Date of study initiation: January 16, 2008
 GLP compliance: Yes, with the exception of some information on excipients, and appended draft specialist reports that do not appear to have ever been finalized.
 QA statement: Yes
 Drug, lot #, and % purity: RX-3341 (N-methylglucamine salt) lot no. A018191-01, purity 99.1%

Key Study Findings

RX-3341 was administered as a 1-hour intravenous infusion for 14 consecutive days to male and female Sprague-Dawley rats at doses of 0, 10, 40, 80, and 120 mg/kg/day. Test article for the first four treatment groups was formulated in Vehicle 1, which contained (b) (4), while the fifth group was administered the highest dose formulated in Vehicle 2, which contained (b) (4). The report indicates that pilot studies had previously demonstrated 50% higher AUC values for the test article administered in vehicle containing (b) (4).

RX-3341 was reasonably well tolerated in this study. Findings were limited to decreases in body weight or body weight gains and food consumption in Groups 4 (80 mg/kg/day in Vehicle 1) and 5 (120 mg/kg/day in Vehicle 2). Slight increases in AST and ALT were reported in Group 5 at Day 15. Pathological findings consisted primarily of inflammation at the injection site and its consequences, such as fibrosis and abscessation. The no-observed-adverse-effect level (NOAEL) was determined to be 80 mg/kg. AUC values at that dose ranged from 126,000 to 221,000 ng*hr/mL on Day 1 and from 73,300 to 133,000 ng*hr/mL on Day 15.

It is unclear what conclusions can be drawn from this study that would be relevant to the proposed drug product. (b) (4) is not included in either formulation of the drug product. (b) (4) is not the cyclodextrin that is included in the proposed IV drug product.

Methods

Doses: 0, 10, 40, 80 (Vehicle 1) and 120 mg/kg/day (Vehicle 2)
 See Sponsor's table below

Frequency of dosing: Once daily for 14 consecutive days

Route of administration: IV infusion over 1 hour into the femoral vein

Dose volume: 10 mL/hr/kg

Formulation/Vehicle: The first stock vehicle (Vehicle 1) consisted of (b) (4), Xylitol NF, Meglumine USP, and Sterile Water for Injection USP.

The second stock vehicle (Vehicle 2) consisted of Mannitol, (b) (4) Meglumine USP, and Sterile Water for Injection USP.

Test article was further diluted in PBS for administration to treated groups.

All formulations were prepared on Study Day -1 and at least once per week thereafter, and were stored at refrigerated temperature (2–8°C) and protected from light, except for Vehicle 1 (Mix 1), which was stored at room temperature.

The report states that, in previous pharmacokinetic studies, following intravenous administration (as a 10 mg/kg bolus), Vehicle 1 provided a 50% increase in exposure (AUC) when compared to similar doses of Vehicle 2.

Species/Strain: Sprague Dawley rats (pre-cannulated)

Number/Sex/Group: 5, plus an additional 5/sex in Groups 1 and 4 for recovery

Age: Approximately 6-9 weeks

Weight: Males – 300.1-371.2 g
 Females – 196.7-247.8 g

Satellite groups: 3 rats/sex (control), and 6 rats/sex (Groups 2-5) per group for toxicokinetics

Deviation from study protocol: The report states that none of the deviations were considered to have affected the outcome of the study.

However, "Test Article RX-3341 (ID #3414H) was stored in the original polypropylene containers without desiccant and without additional protection from exposure to light (as

received)”, and “the pH of each dosing solution was not adjusted to 7.4–7.9.” It is unclear how this might have affected the test article and results.

Technical errors resulted in some clinical pathology tests not being performed and some tissues not being examined. It is unclear whether or not this may have affected study outcome.

Text Table 4: Study Design

Group	Treatment	Test Article Dosage (mg/kg)	Test Article Concentration (mg/mL)	Number of Animals					
				Main Phase		Recovery Phase		Toxicokinetic	
				Males	Females	Males	Females	Males	Females
1	Vehicle ^a	0	0	5	5	5	5	3	3
2	RX-3341 ^b	10	1	5	5	-	-	6	6
3	RX-3341 ^c	40	4	5	5	-	-	6	6
4	RX-3341 ^d	80	8	5	5	5	5	6	6
5	RX-3341 ^e	120	12	5	5	-	-	6	6

^aVehicle 1 (the cyclodextrin-containing formulation) diluted 1:3.75 in 1 X PBS

^bStock 30/mg/mL RX-3341 (prepared by Bridge) formulated with Vehicle 1 and diluted 1:30 in 1 X PBS

^cStock 30/mg/mL RX-3341 (prepared by Bridge) formulated with Vehicle 1 and diluted 1:7.5 in 1 X PBS

^dStock 30/mg/mL RX-3341 (prepared by Bridge) formulated with Vehicle 1 and diluted 1:3.75 in 1 X PBS

^eStock 30 mg/mL RX-3441 (provided by Aptuit) formulated with Vehicle 2 and diluted 1:2.5 in Solutol HS-15

Observations and Results

Mortality

Cageside observations were made at least twice daily. All animals survived until the scheduled termination, except for Animal 16211 (80 mg/kg; 4F), that was found dead on Day 1. This death was not considered to be treatment-related.

On Day 12, animal 16215 (4F) was removed from study due to loss of catheter patency and was euthanized and discarded without necropsy.

Clinical Signs

Clinical observations were recorded daily and prior to scheduled necropsy. No test article-related effects were reported.

Body Weights

Body weights were recorded for main study and recovery animals prior to treatment on Days 1, 8 (all animals), and Day 14 (all unfasted). Fasted body weights were recorded prior to euthanasia on Days 15 and 22.

Mean body weights for Group 5 (120 mg/kg, Vehicle 2) males were generally lower than in other groups. Body weight gains in Group 5 males were lower than in other groups. Statistical analysis was not performed for this group.

Statistically significantly lower total body weight gains were reported for Group 4 (80 mg/kg) females for Days 15-22 and 1-22. These changes were reported to be small in magnitude and most likely due to individual animal variation.

Feed Consumption

Food consumption was recorded weekly. Mean food consumption values for the Group 5 (120 mg/kg) males and females were generally lower than all other groups, correlating with lower body weights and gains in males in that group. Statistical analysis was not performed for this group.

Over the first week of treatment, food consumption was significantly lower for 80 mg/kg males relative to controls, however food consumption over the entire dosing period (Days 1-14) or over the dosing and recovery periods (Days 1-21) in those males was not different from control.

Ophthalmoscopy

Ophthalmologic examinations were conducted using indirect ophthalmoscopy and slit-lamp biomicroscopy (as necessary) following administration of 1% Tropicamide® mydriatic solution. Examinations were performed prior to randomization (all animals) and prior to necropsy (main and recovery phase animals only).

No test article-related findings were reported.

ECG

Not performed

Hematology

Samples were taken for clinical pathology as shown in the Sponsor's table below:

Text Table 8: Blood Sampling Information for Clinical Pathology

Parameter	Chemistry	Hematology	Coagulation	Urinalysis
Collection Day	Prior to necropsy			
Collection Method	Puncture of jugular vein			Metabolism cage
Volume Collected	≥1 mL	≥0.5 mL	≥1.8 mL	Recorded total volume and submitted ≤ 12 mL
Tubes Used	Serum separator tubes	Tubes containing K ₂ EDTA	Tubes containing sodium citrate	Urin-tek tubes

No test article-related findings were reported for hematology and coagulation.

Clinical Chemistry

“Slight” increases in aspartate aminotransferase and alanine aminotransferase on SD 15 were reported in Group 5 male animals treated with RX-3341 at 120 mg/kg.

Urinalysis

No urinalysis data were reported in the main body of the report. In the appended clinical pathology report, it is stated that mean values for urine volume and/or pH were increased in treated Groups 2, 3, and 4 on Day 15, and mean specific gravity was increased for Group 4 males on Day 22. The authors concluded that increased urine pH in Groups 2-4, male and female, was most likely due to bacterial production of urea, but that it was unclear why Groups 1 and 5 did not exhibit a similar change. There is no mention of results of examination of sediment.

Gross Pathology

On Day 15 for the main phase animals (first five animals/sex/group) and on SD 22 for the recovery phase animals, animals were euthanized by carbon dioxide inhalation and exsanguinated. Gross necropsies were performed on all animals.

The report states that the test article had no adverse effect on gross pathology. There were a number of vascular-associated, splenic, or bone marrow lesions that were attributed to the dosing procedure: These occurred in control and treated animals and were thought to be due to injection site infection and inflammation and its consequences.

One 120 mg/kg male had dilation of the right kidney that correlated with locally extensive tubular atrophy. This was considered to be incidental, but this was the highest test article dose group and the only group with (b) (4) in the vehicle formulation, so it is unclear whether or not this lesion was treatment-related.

Organ Weights

Organs weighed were adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes, thymus, and thyroid. Paired organs were weighed together. Bone marrow smears were prepared for all main study and recovery animals but were not evaluated and were discarded.

None of the changes in organ weight were considered to be treatment-related. On Day 15, there was a trend to dose-related decreases in kidney, liver, thymus, and spleen weights in males and lower spleen and thymus weights in treated females, relative to controls, though none were statistically significant. Some of these persisted through recovery. The Sponsor considered these changes to be incidental.

Histopathology

Adequate Battery

A full tissue list was provided in the protocol. The report states that all preserved tissues from animals in Groups 1 (control), 4, and 5 (high dose groups formulated with Vehicles 1 and 2, respectively) were examined, but the protocol indicates that the only tissues processed to slides and examined were the femoral vein (injection site), heart, kidney, liver, spleen, and urinary bladder for those treatment groups. In addition, the report states that all tissues from the found dead animal and gross lesions from all groups were examined. Slides were stained with hematoxylin and eosin and were examined by a board-certified veterinary pathologist.

Peer Review

No

Histological Findings

Inflammatory lesions were noted at the injection sites in animals from all groups as well as in the region of the abdominal aorta and femoral vein, heart, kidneys, and urinary bladder of several animals. The latter were considered to be likely an extension of inflammation from the injection sites. Increased extramedullary hematopoiesis was noted in the liver and spleen of some animals, and was considered likely to be due to increased tissue demand for leukocytes as a result of ongoing inflammation. There was no clear evidence of resolution of the lesions following the 1-week recovery period.

Special Evaluation

None

Toxicokinetics

Text Table 7: Blood Sampling Information for Toxicokinetic Evaluation

Animals/Sex/Group	Group No. 1 (3/sex)	Group No. 2-5 (First 3/sex/group)	Group No. 2-5 (Second 3/sex/group)
Collection Day	SD 1 and 14	SD 1 and 14	SD 1 and 14
Target Collection Time ^a	0 ^b , 24 hours postdose	0 ^b , 1, 4, 12 hours postdose	0.5, 2, 8, and 24 hours postdose
Collection Site	Puncture of jugular vein		
Volume Collected	Approximately 0.4 mL of whole blood per timepoint		
Tubes Used	Tubes containing K ₃ EDTA		

^aAll samples were collected ± 5 minutes for 0.5, 1, 2, 4, and 8-hour postdose; ± 15 minutes for 12 and 24-hour postdose.

^bImmediately (within 2 minutes) following cessation of infusion (See Appendix 16 for deviations).

Plasma was separated and stored frozen at $-75 \pm 15^\circ\text{C}$ and shipped to (b) (4) (b) (4) for analysis using a validated method. On SD 15, the toxicokinetic animals were euthanized by carbon dioxide inhalation and exsanguinated after the last blood collection and discarded without necropsy.

Plasma RX-3341 mean concentration-time profiles on SD 1 and 14 during daily intravenous infusion (1 hour) administration to rats at doses of 10, 40, and 80 mg/kg using Vehicle 1 (Groups 2-4) and at 120 mg/kg using Vehicle 2 (Group 5) were described as being generally characterized by an apparent bi-phasic or multiphasic decline from C_{max} , but with occasional irregularities. C_{max} was observed at the end of the 1-hour infusion (T_{max}) for Groups 2-4 and at 0.5 hours post-infusion for Group 5.

The report states that mean concentrations were measurable through 12 or 24 hours (T_{last}) post-infusion at 10 and 40 mg/kg and through 24 hours post-infusion at 80 and 120 mg/kg. It goes on to state that the terminal phases of the mean concentration-time curves were not always well-characterized, so estimates of half-lives and related data (AUC, V_z , and CL) should be regarded as tentative. Estimates of terminal half-life, volume of distribution, and clearance tended to be somewhat greater on SD 14 than on SD 1, but with exceptions. Trends related to gender and dosage were not well-defined. Nevertheless, the report states that C_{max} for plasma RX-3341 was generally either comparable for males and females or higher for males, and that AUC_{last} was most

frequently higher for males, with the greatest relative difference (approximately 85%) observed at 80 mg/kg on SD 14.

RX-3341 Toxicokinetic Parameters in the Rat

Dose ^a (Group) ^b	Gender	C _{max} (ng/mL)	T _{max} (h) ^c	T _{last} (h) ^c	AUC _{last} (ng·h/mL)	AUC (ng·h/mL)	t _{1/2} (h)	V _z (mL/kg)	CL (mL/h·kg)
Day 1									
10	M	7210	0	12	9990	10200	6.3	8910	983
(2)	F	4580	0	12	5800	5850	3.1 ^d	7690	1710
40	M	33700	0	12	61100	61400	2.4 ^d	2210	652
(3)	F	26300	0	24	39500	40000	7.5	10800	999
80	M	83400	0	24	218000	221000	14.8	7720	362
(4)	F	62500	0	24	126000	126000	4.0	3680	633
120	M	122000	0.5	24	490000	490000	2.8	973	245
(5)	F	121000	0.5	24	430000	430000	3.4	1360	279
Day 14									
10	M	6220	0	24	8680	8830	8.2	13400	1130
(2)	F	5600	0	12	6130	6210	3.9 ^d	9050	1610
40	M	15900	0	24	32300	32900	6.6	11600	1220
(3)	F	22800	0	24	31400	31900	6.4	11500	1250
80	M	67400	0	24	131000	133000	6.7	5780	601
(4)	F	43200	0	24	71000	73300	7.8 ^d	12200	1090
120	M	84400	0.5	24	186000	190000	8.5 ^d	7770	632
(5)	F	57600	0.5	24	112000	119000	7.1 ^d	10300	1010

a: mg/kg; administered daily by intravenous infusion (1 hour).

b: Vehicle 1 was used for Groups 2-4; Vehicle 2 was used for Group 5.

c: Time from the end of the 1-hour infusion.

d: Rsq for the terminal phase regression line was <0.9 when rounded (see Table 3).

Dosing Solution Analysis

Two sets of duplicate samples (2 mL) were taken from top, middle, and bottom of the Groups 2, 4, and 5 dose formulations for homogeneity analysis. Additionally, two sets of duplicate samples (2 mL) were taken from the middle of the Group 3 dose formulation for concentration verification. All samples were stored frozen (-75 ± 15°C) and protected from light. One set of samples was shipped after each formulation day to (b) (4) (on dry ice) for analysis.

Results for the concentration verification formulations indicate that all batch concentrations met the ± 10% criteria with a range of recovery from 93.3 to 101.6%. Homogeneity results also met criteria for acceptance.

A draft report of the following study was reviewed by Dr. Stephen Hundley under IND 76096 SDN #36. Excerpts from his review are reproduced below.

5. RX-3341: A Two-Week Intravenous Toxicity Study Comparing (b) (4) and Captisol® Formulations in Sprague Dawley Rats with a One-Week Recovery Period (Bridge Study Number: 1638 - 09002).

The purpose of this study was to evaluate the toxicological effect, if any, of an intravenous formulation of RX-3341 using Captisol (sulfobutylether-beta-cyclodextrin) (b) (4). A second intravenous formulation using (b) (4) was also examined. RX-3341 was formulated as the N-methylglucamine salt (lot no. 7106AA001) with 99 percent analytical purity. The stock formulations for the intravenous solutions were diluted with 5% dextrose to yield the different dose concentrations. The highest doses were diluted from the stock to yield the following final concentrations: a) Captisol at 80 mg/ml and RX-3341 at 8 mg/ml and b) (b) (4) at 60.3 mg/ml, xylitol at 12.3 mg/ml, and RX-3341 at 8 mg/ml. The RX-3341 dosing routines were zero-level vehicle (Captisol) control, 10 mg/kg in Captisol, 40 mg/kg in Captisol, 80 mg/kg in Captisol, and 80 mg/kg in (b) (4). Intravenous dosing was administered once daily as a one-hour infusion via a femoral vein cannula for 14 consecutive days. Each dose group consisted of five animals of each sex that were sacrificed 24 hours after the terminal dose. Seven-day post dosing recovery animals (five per sex) were added to the zero-level vehicle control and 80 mg/kg dose in Captisol. Toxicokinetic groups consisting of six animals of each sex were also added to each of the RX-3341 dose levels.

Cageside observations were made twice daily and clinical evaluations were conducted once daily during the dose administration phase. Ophthalmological examinations were conducted pre-study and prior to sacrifice on Day 15, with an indirect ophthalmoscope and a slit lamp biomicroscope. Blood samples were drawn for RX-3341 toxicokinetic determinations following the initial and final doses at the following post-infusion time points: 0.5, 1, 2, 4, 8, 12, and 24 hours. Clinical pathology was conducted on blood samples drawn prior to sacrifice. Urinalysis [was conducted presumably on samples collected prior to sacrifice (AN)]. Complete necropsies were conducted on all animals at the terminal dose and post-dosing recovery sacrifices. Histopathology was conducted on the following tissues and organs: injection site, heart, kidney, liver, spleen, urinary bladder, and tissues or organs that exhibited gross lesions. Histopathology was conducted on male and female rats at the terminal dose sacrifice from the zero-level vehicle control, high dose Captisol, and high dose (b) (4) groups and on the males and females at the seven-day post-dosing recovery sacrifice (zero-level vehicle control and high dose Captisol).

Results

No compound or vehicle related effects were observed for the following: clinical observations, clinical pathology (hematology, clinical chemistry, coagulation parameters, and urinalysis), ophthalmology, gross necropsy (pathology), and histopathology. Slight body weight gain depression was observed at the 80 mg/kg dose with the (b) (4) vehicle (10 and 6 percent depression for males and females,

respectively). Infusion site histopathology was observed in the control and RX-3341-dosed animals and is commonly observed in rats with indwelling femoral vein cannulas. The toxicokinetic data generally displayed higher RX-3341 plasma AUC values for males compared to females at the respective dose levels. The plasma RX-3341 AUC values did not increase or change between Day 1 and 14, at the respective dose levels with the two different (b) (4). AUC values increased in proportion to the increase in dose between 40 and 80 mg/kg. The AUC values between the 10 and 40 mg/kg dose levels increased 6- to 7-fold for both male and female rats.

Conclusion

The change in intravenous formulation with Captisol (sulfobutylether-betacyclodextrin) did not result in overt toxicity during the two-week toxicity study at any dose level. No unusual toxicokinetic profiles resulted from the intravenous injection of RX-3341 in the Captisol vehicle on Day 1 and Day 14 of dosing. The results in rats were similar to those resulting from intravenous formulations containing (b) (4) as the (b) (4) for RX-3341.

6. Study title: 2-week intravenous formulation bridging toxicity study with RX-3341 in Sprague Dawley rats with a 1-week recovery phase

Study no.: 8235345
Study report location: Electronic submission
Conducting laboratory and location: (b) (4)
Date of study initiation: October 14, 2010
GLP compliance: Yes, with the exceptions that the test article "was not characterized under GLP regulations" and documentation of centrifuge, harvesting, and freezer time information for Group 5 TK blood collection on Day 14 is missing.
QA statement: Yes
Drug, lot #, and % purity: RX-3341, lot no. L0106833, purity 99.2%

Key Study Findings

RX-3341, when given for 1 hour/day by intravenous infusion for 15 days at a dose level of 0, 10, 40, or 80 mg/kg/day in Vehicle 1 (containing EDTA) or 80 mg/kg/day in Vehicle 2 (without EDTA) to male and female rats was considered to be well tolerated. In animals given 80 mg/kg/day with either vehicle, differences when compared with control animals (body weight change, decreased in food consumption, and incidence and/or severity of microscopic changes at the infusion site) were generally less pronounced when the vehicle contained EDTA (Vehicle 1), but none were considered to be toxicologically significant. Administration of RX-3341 at 80 mg/kg/day in Vehicle 1 for 15 days resulted in a C_{max} and AUC_{0-25hr} of 63.4 µg/mL and 127 µg*hr/mL, respectively, for males and 52.5 µg/mL and 85.8 µg*hr/mL, respectively, for females on Day 14. Dose administration at 80 mg/kg/day in Vehicle 2 for 15 days

resulted in comparable exposures (C_{max} and AUC_{0-25hr} of 49.3 µg/mL and 130 µg*hr/mL, respectively, for males and 54.7 µg/mL and 94.2 µg*hr/mL, respectively for females).

Methods

Doses: See Sponsor's Study Design table below
Frequency of dosing: Once daily
Route of administration: IV infusion for approximately 1 hour
Dose volume: 10 mL/kg/day
Formulation/Vehicle: Vehicle 1: Captisol®, EDTA USP, Meglumine USP, and Sterile Water for Injection, USP.
EDTA was present in Vehicle 1 at 0.22 mg/mL.

Vehicle 2: Captisol®, Meglumine USP, and Sterile Water for Injection, USP

(Captisol® = Beta-cyclodextrin sulfobutyl ether sodium)
Species/Strain: Sprague Dawley rats
Number/Sex/Group: See Sponsor's table below
Age: 8-9 weeks at the start of dosing
Weight: Males – 284-369 g
Females – 194-253 g
Satellite groups: Toxicokinetics animals are noted in the Sponsor's study design table below.
Deviation from study protocol: None that were considered to have affected the integrity of the study.

Study design:

Group ^{a,b,c}	Subgroup ^{d,e}	No. of Animals		Dose Level (mg/kg/day)	Dose Concentration ^f (mg/mL)
		Male	Female		
1 (Control - Vehicle 1)	1 (Toxicity)	10	10	0	0
	2 (Toxicokinetic)	3	3	0	0
2 (Low - Vehicle 1)	1 (Toxicity)	5	5	10	1
	2 (Toxicokinetic)	6	6	10	1
3 (Mid - Vehicle 1)	1 (Toxicity)	5	5	40	4
	2 (Toxicokinetic)	6	6	40	4
4 (High - Vehicle 1)	1 (Toxicity)	10	10	80	8
	2 (Toxicokinetic)	6	6	80	8
5 (High - Vehicle 2)	1 (Toxicity)	5	5	80	8
	2 (Toxicokinetic)	6	6	80	8

a Group 1: Vehicle 1 diluted using 1x phosphate buffered saline (PBS) only at the same ratio as Group 4 with 1x PBS.

b Groups 2 through 4: Stock 25 mg/mL RX-3341 (free acid) was formulated with Vehicle 1 and diluted using 1x PBS to achieve the desired dosing concentrations.

c Group 5: Stock 20 mg/mL RX-3341 (free acid) was formulated using Vehicle 2 and diluted using 1x PBS to achieve the desired dosing concentrations.

d Terminal sacrifice after at least 14 days of dosing. Animals designated for recovery sacrifice (last five animals/sex from Groups 1 and 4) underwent at least 1 week of recovery following dose administration.

e Toxicokinetic animals were included for blood collection only; animals were sacrificed and discarded after final blood collection.

f Concentrations were corrected for *as is* salt content (correction factor 1.44) and for water and lot specific purity using an overall correction factor of 1.482.

Observations and Results

Mortality

No test article-related mortality was reported. Three toxicokinetic animals died, but these deaths were considered to be procedure-related or related to catheterization.

Clinical Signs

Animals were checked twice daily (AM and PM) for mortality, abnormalities, and signs of pain or distress. Detailed observations were made pre-treatment, prior to dosing on Day 1, weekly throughout dosing and recovery, and on the day of scheduled sacrifice. No test article-related findings were reported.

Body Weights

Body weights were recorded before dosing on Day 1 and weekly thereafter. At the end of the dosing phase, group mean body weights in males given 80 mg/kg/day (Vehicle 2) were lower than in control males, although not statistically different. Males given 80 mg/kg/day (Vehicle 1 or 2) had statistically significantly lower body weight gains when compared with control males, and these differences were more pronounced in males given Vehicle 2 than in males given Vehicle 1. Females given 40 (Vehicle 1) or 80 mg/kg/day (either vehicle) had a decreased body weight gain during the second week of dosing. This finding persisted in recovery in females given 80 mg/kg/day (Vehicle 1).

Feed Consumption

Food consumption was recorded weekly. Test article-related, statistically significantly lower food consumption was reported in males given 80 mg/kg/day (Vehicle 2) during Week 1 of the dosing phase relative to control males. A similar but lower magnitude trend occurred in males given 80 mg/kg/day (Vehicle 1), but this difference was not statistically significant when compared with control animals. Food consumption remained lower for males given 80 mg/kg/day (Vehicle 2) during Week 2 of the dosing phase relative to controls, but was not statistically significant. In females, food consumption was slightly lower in all groups given RX-3341 (either vehicle) when compared with control females during Week 1 of the dosing phase, but these differences were not statistically significant. Food consumption in females in Week 2 was comparable among groups. During the recovery phase, food consumption for males and females given 80 mg/kg/day (Vehicle 1) was slightly increased relative to controls.

Ophthalmoscopy

Examinations, by indirect ophthalmoscopy following treatment with a mydriatic agent, were performed on all animals prior to dosing, and on recovery animals on Day 15 of the dosing phase, and on Day 7 of the recovery phase.

Reviewer's comment: Main study animals should have been examined at the end of treatment. The numbers of recovery animals alone may have been too small to be sensitive enough to detect any effects.

No test article-related findings were reported.

ECG

Not performed

Hematology

Blood samples were collected on the day of scheduled sacrifices for hematology, coagulation, and clinical chemistry from fasted main study animals via the jugular vein.

Hematology effects were limited to minimal to mild decreases in absolute neutrophil count for males and females at all dose levels.

Clinical Chemistry

Total protein and albumin were decreased in females at all dose levels. Cholesterol was increased in males at 80 mg/kg/day. Chloride was decreased in females at 80 mg/kg/day. All of these changes were described as minimal or mild. Effects at 80 mg/kg/day were similar in magnitude regardless of the vehicle.

The change in total protein and albumin were not reversed following recovery.

Urinalysis

Urine samples were collected chilled during the overnight period before blood collection from fasted main study animals.

No data were reported for urinalysis.

Gross Pathology

After at least 14 days of dosing, five animals/sex/group were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. After at least 14 days of dosing followed by at least 1 week of recovery, all remaining toxicity animals were anesthetized with sodium pentobarbital, exsanguinated, and necropsied.

The only test article-related macroscopic observation reported was large cecum, present in several RX-3341-treated animals at the terminal sacrifice and at the recovery necropsy in one female given 80 mg/kg/day. This finding correlated microscopically with dilatation in the cecum and is not an uncommon finding following antibiotic treatment in this species.

Catheter or infusion sites were thickened, correlating with microscopic findings of vessel wall inflammation and/or thrombosis. It is unclear whether this was secondary to the catheter or if an irritant effect of the dosing solution contributed to this finding.

Organ Weights

The following organs were weighed: adrenal (2), brain, epididymis (2), heart, kidney (2), liver, ovary (2), spleen, testis (2), thymus, thyroid (2 lobes) with parathyroid. Paired organs were weighed together.

No test article-related organ weight changes were reported at the terminal or recovery sacrifice.

Histopathology

Adequate Battery

Bone marrow smears were prepared from the femur of each toxicity animal at each scheduled sacrifice. Evaluation was not performed.

A set of tissues were collected from toxicity animals and preserved in 10% neutral-buffered formalin, with the exception of the eyes, Harderian gland, optic nerves, and testes, which were preserved in modified Davidson's fixative.

A limited set of tissues were examined: From toxicity animals in Groups 1, 4, and 5 (control and high dose) sacrificed at the end of the dosing phase and from toxicity animals in Groups 1 and 4 (control and high dose) sacrificed at the recovery sacrifice (recovery phase), the infusion site, catheterization site, heart, kidney, liver, spleen, and urinary bladder were embedded in paraffin, sectioned, stained, and examined microscopically by a board-certified veterinary pathologist.

Additionally, the infusion site from toxicity animals in Groups 2 and 3 sacrificed at the terminal sacrifice (dosing phase) were embedded in paraffin, sectioned, stained, and examined microscopically by a board-certified veterinary pathologist. Macroscopic lesions collected from toxicity animals in Groups 1 through 5 were processed and examined microscopically.

Peer Review

No

Histological Findings

The marginal increase in incidence of inflammation and/or thrombosis at the infusion site in males given 80 mg/kg/day (Vehicle 1 or 2) compared with controls at the terminal sacrifice and the higher incidence and/or severity of these findings at the recovery sacrifice in males given 80 mg/kg/day (Vehicle 1) were considered to be potential test article-related effects. No test article-related microscopic findings were reported at the terminal or recovery sacrifice in other tissues examined.

Special Evaluation

None

Toxicokinetics

Blood samples were collected by jugular venipuncture on Days 1 and 14 of the dosing phase within 2 minutes of the end of infusion and 24 hours post end of infusion from three animals/sex from Group 1. Blood samples were taken within 2 minutes of the end of infusion and approximately 0.5, 1, 2, 4, 8, 12, and 24 hours post end of infusion from two animals/sex from Groups 2 through 5 on those same days. Plasma was separated and frozen at -60 to -80°C and shipped ^{(b) (4)} for analysis.

Exposure to RX-3341 increased with dose from 10 to 80 mg/kg/day in Vehicle 1. The report states that exposure after administration of 80 mg/kg/day in Vehicle 2 was generally similar to the exposure after administration in Vehicle 1. The increases in C_{max} and AUC₀₋₂₅ with dose were greater than dose proportional. Gender differences in RX-3341 C_{max} and AUC₀₋₂₅ values were reported to have been less than 2-fold. The report states that no accumulation of RX-3341 was observed after multiple dosing of RX-3341 in rats. Values for C_{max} and AUC₀₋₂₅ were reported to be similar for RX-3341 administered in Vehicle 1 or Vehicle 2.

Table 1
Toxicokinetic Parameters for RX-3341 in Rat Plasma

Day	Dose Group	Dose Level (mg/kg/day)	Sex	DN C _{max}		T _{max} (hr)	AUC ₀₋₄ (μg hr/mL)	AUC ₀₋₂₄ (μg hr/mL)	DN AUC ₀₋₂₄		t _{1/2} (hr)	CL (mL/hr/kg)	V _d (mL/kg)	
				C _{max} (μg/mL)	[(μg/mL)/ (mg/kg/day)]				[(μg hr/mL)/ (mg/kg/day)]	AUC ₀₋₂₄ (μg hr/mL)				
1	2	10	M	7.16	0.716	1.00	8.74	8.81	0.881	NC	NC	NC	NC	
			F	4.69	0.469	1.00	5.38	5.38	0.538	5.44	7.35	1838	3415	
	3	40	M	37.1	0.926	1.00	55.0	55.0	1.37	55.2	6.25	725	1101	
			F	21.7	0.543	1.00	31.2	31.2	0.781	NC	NC	NC	NC	
	4	80	M	80.7	1.01	1.00	169	169	2.12	170	6.71	472	724	
			F	72.5	0.906	1.00	117	117	1.46	NC	NC	NC	NC	
	5	80	M	78.2	0.977	1.00	196	196	2.45	197	8.45	406	776	
			F	82.7	1.03	1.00	122	122	1.52	NC	NC	NC	NC	
	14	2	10	M	5.39	0.539	1.00	7.70	7.70	0.770	7.75	4.82	1298	2444
				F	2.79	0.279	1.00	4.37	4.37	0.437	NC	NC	2290	NC
3		40	M	38.9	0.973	1.00	58.5	58.5	1.46	58.8	6.43	684	1178	
			F	16.9	0.421	1.00	23.6	23.6	0.590	24.6	11.8	1695	5237	
4		80	M	63.4	0.792	1.00	127	127	1.59	128	9.02	631	1314	
			F	52.5	0.656	1.00	85.8	85.8	1.07	87.5	9.41	933	2277	
5		80	M	49.3	0.616	1.00	130	130	1.63	NC	NC	614	NC	
			F	54.7	0.683	1.00	94.2	94.2	1.18	NC	NC	850	NC	

NA Not calculated.

Note: Groups 1, 2, 3, and 4 received RX-3341 in Vehicle 1. Group 5 received RX-3341 in Vehicle 2.

Dosing Solution Analysis

Samples were taken from the vehicle and test article preparations on Days 1 and 8 for analysis for concentration. The Day 1 samples ranged between 100.1 to 101.2% of the nominal concentration, and the Day 8 samples ranged between 99.1 to 103.1% of the nominal concentration. Analyses of homogeneity and stability do not appear to have been included in this study.

7. Study title: A 28-day oral toxicology study of RX-3341 in dogs with a 2-week recovery (GLP)

Study no.:	0436DR37.001
Study report location:	Electronic submission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	
GLP compliance:	Yes, with the exception of test article manufacture and characterization and plasma bioanalysis
QA statement:	Yes
Drug, lot #, and % purity:	RX-3341 (delafloxacin meglumine tablets, 450 mg), lot nos. NB1083-120, NB1083-125, NB1083-128, NB1083135, NB1083-137, NB1083-137S, NB1083-137L, NB1083-138, NB1083-155, NB1083-156, NB1083-165, and NB1083-166 Potency (as % of label) ranged from 94.2% to 101.4%

Key Study Findings

Following once daily oral administration of the formulated tablet at doses of 160, 320, and 480 mg/kg/day for 28 days, emesis and salivation were seen at all doses. Serum potassium was low in females at all doses. Articular cartilage degeneration was seen at the high dose and is a known effect of this drug class. The NOAEL was considered to be the mid-dose, 320 mg/kg/day for 28 days, but the actual dose to which the animals were exposed was likely lower due to emesis. The mean AUC_{last} at that dose ranged from 19451-25419 ng*hr/mL in males and females on Day 1 and from 30093-36530 ng*hr/mL in males and females on Day 28.

Methods

Doses:	0 (empty gelatin capsules), 160, 320, and 480 mg/kg/day (Doses were rounded to the nearest half tablet)
Frequency of dosing:	Once daily for 28 days
Route of administration:	Oral
Dose volume:	N/A; Tap water was administered as needed to administer the capsules or tablets.
Formulation/Vehicle:	Clinical tablet formulation (450 mg delafloxacin)
Species/Strain:	Beagle dogs
Number/Sex/Group:	3/sex/group plus an additional 2/sex in the control and high dose groups for recovery
Age:	5-6 months at the start of dosing
Weight:	5.8-10.1 kg on Day -1
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None that appeared to affect the outcome of the study

Observations and Results

Mortality

Observations for mortality and morbidity were performed at least twice daily (prior to dosing and at 1-3 hours post-dose) during the dosing period and at least once daily on non-dosing days and on the day of euthanasia.

No unscheduled deaths were reported.

Clinical Signs

Emesis and salivation were observed at all doses; the incidence and frequency of those signs were dose-dependent. Often the vomitus contained the partially dissolved tablet. At the low dose, the incidence and frequency of these signs were significantly lower than in the two higher dose groups, and appeared to decrease as the study progressed. A few animals were noted to have yellow mucous in the feces.

Body Weights

Body weights were recorded at the time of randomization, prior to dosing on Days -1, 7, 14, 21, and 27, and on Days 34 and 41 of recovery.

No test article-related effects were reported.

Feed Consumption

Food consumption was recorded daily. No test article-related effects were reported.

Ophthalmoscopy

Examinations performed once before treatment initiation and once during the final week of dosing.

No test article-related effects were reported.

ECG

ECGs were recorded for all animals prior to treatment initiation, during the final week of dosing, and during the final 3 days of recovery.

No test article-related effects were reported for rhythm or morphology. No interval measurements were taken.

Hematology

Blood was collected from overnight-fasted animals for hematology, clinical chemistry, and coagulation prior to treatment initiation, and on Days 29 and 43.

No test article-related effects were reported.

Clinical Chemistry

Females in all dose groups had statistically significant decreases in potassium relative to controls. Most of the individual values from treated females and some of the individual values from treated males were below the range of historical controls.

Urinalysis

Urine was collected overnight (12-18 hours) prior to treatment initiation, and on Days 29 and 43.

No test article-related effects were reported.

Gross Pathology

Animals were sacrificed on Day 29 or on Day 43 by IV barbiturate overdose, and a complete gross necropsy was performed. Fasted terminal body weights were recorded prior to sacrifice.

No test article-related effects were reported.

Organ Weights

The following organs were weighed: adrenals, brain, heart, kidneys, liver, testes, ovaries, spleen, thyroids/parathyroids. Paired organs were weighed together unless gross abnormalities were present.

No test article-related effects were reported.

Histopathology**Adequate Battery**

A full list of tissues was collected and preserved in fixative. Slides were prepared and examined for all tissues collected on Day 29 from control and high dose animals. The liver and femur with articular cartilage were also processed to slides for low and mid-dose animals and examined. For animals euthanized on Day 43, only the liver and femur with articular cartilage were processed to slides and examined.

Peer Review

No

Histological Findings

On Day 29, the femoral head of one high dose female had minimal focal degeneration of the superficial articular cartilage, characterized by shrunken or

degenerate chondrocytes in a disordered or condensed matrix, and a small focal cleft in the articular cartilage. The report acknowledges that this is a known toxicity of fluoroquinolones in juvenile or immature animals. No cartilage findings were reported on Day 43.

Glycogen-type vacuolation of hepatocytes was noted in treated animals at the Day 29 necropsy and in all four control animals at the recovery necropsy. It was considered to be an incidental finding.

Special Evaluation

None

Toxicokinetics

Blood was collected immediately pre-dose, and at 1, 2, 4, 8, and 24 hours post-dose on Days 1 and 28. Plasma was separated and frozen at -70°C until analysis by LC-MS/MS.

Systemic exposure was dose-dependent and slightly less than dose-proportional. In addition, it was greater after 28 days of dosing than following a single dose, possibly indicating accumulation of drug with repeated dosing. Exposure may have been affected by emesis in 19 of 22 animals on Day 1 and 14 of 22 animals on Day 28. The contribution of emesis to the variability in toxicokinetic parameters is likely, but no trend was recognized between individual animal emesis events and plasma concentration-time profiles, and no individual animal data were excluded.

Dosing Solution Analysis

N/A

8. Study title: A 28-day intravenous infusion toxicity study of RX-3341 in dogs with a recovery period of eighteen days

Study no.:	0436DR37.002
Study report location:	Electronic submission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	17 October 2013
GLP compliance:	No (The tabulated summary indicates yes, but the protocol was amended to be non-GLP compliant when the study was aborted.)
QA statement:	No
Drug, lot #, and % purity:	RX-3341 (delafloxacin meglumine, 310 mg/vial for 300 mg (free acid form) dose/vial, yielding 25 mg/mL per vial after reconstitution; assay was (b) (4) % of label claim; lot no. 12DEL1

Key Study Findings

Local vein irritation resulted in early termination of study – attributed to daily catheterization procedure, but it is unclear whether or not it could be attributed to the Captisol®-containing vehicle. Only male dogs were dosed and for only 15 consecutive days, followed by a recovery period of 8 days. Doses were 0, 10, 25, and 75 mg/kg/day RX-3341. Clinical signs associated with treatment included emesis, salivation, abnormal stools, and decreased activity. Vocalization and irritability were seen in control and treated groups, and may be related to venous irritation. ALT was increased in the mid-and high dose groups, and cholesterol was increased in the high dose group. At the end of recovery, ALT increases were partially reversed and cholesterol changes were fully reversed. Post mortem findings included macroscopic injection site changes and pale kidneys in control and treated animals, decreased adrenal weight in treated animals (reversible), decreased kidney weights in low and mid-dose animals, vacuolation in renal tubules in control and high dose animals (attributed to Captisol®), and intimal/endothelial proliferation, thrombosis, perivascular fibrosis/fibroplasia, hemorrhage, and mixed or mononuclear cell infiltration associated with the injection sites in all groups. A NOAEL was not established.

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Methods

Doses:	0 (placebo), 10, 25, and 75 mg/kg/day
Frequency of dosing:	Once daily for 15 consecutive days
Route of administration:	Continuous IV infusion over 1 hour
Dose volume:	20 mL/kg
Formulation/Vehicle:	Placebo: Meglumine/Captisol/EDTA disodium solution in sterile water for injection; each mL contained 4.88 mg meglumine, 200 mg Captisol, and 0.28 mg of EDTA disodium. The dilution, if any, for the placebo infusion was not specified. The test article (lyophilized powder) was reconstituted in 5% Dextrose for Injection, USP (D5W) for 25 mg/mL stock solutions. Stock solutions were added to D5W bags for infusion in amounts to provide 0.5, 1.25, and 3.75 mg/mL, but the amount of placebo stock solution added to D5W for the control group is not specified.
Species/Strain:	Beagle dogs
Number/Sex/Group:	Male dogs only 5 in each of the control and high dose groups 3 in each of the low and mid-dose groups (One mid-dose male was replaced with a spare animal after Day 2 dosing)
Age:	6.75-7.25 months
Weight:	8.2-9.7 kg
Satellite groups:	None
Unique study design:	The dogs were catheterized daily prior to infusion; administration generally alternated between legs using the cephalic and possibly saphenous veins.
Deviation from study protocol:	Most deviations were secondary to the early study termination

Observations and Results**Mortality**

Animals were checked for mortality and morbidity at least twice daily (AM and PM). No unscheduled deaths were reported.

Clinical Signs

During the dosing period, observations were made pre-dose, immediately post-dose, and 1-3 hours post dose. Observations were made once daily during recovery

Vein irritation was first observed on Day 4 and was generally mild to moderate in severity. It was attributed to the daily catheterization procedure (it is unclear why indwelling catheters were not used) and was found in all groups, including control.

It should be noted that the control solutions also contained Captisol, and this excipient may have contributed to irritation in all groups. The report states that vein irritation persisted for at least three days in control and high dose recovery animals after cessation of treatment.

Treatment related clinical signs included emesis salivation, decreased activity, vocalization, irritability and abnormal stools. All but vocalization and irritability were observed in treated animals only. Emesis and salivation were observed in most treated animals and were dose-related in incidence. Decreased activity was noted only in all 5 high dose animals, and soft or loose stools were noted in most high dose animals.

Body Weights

Body weights were recorded on Days -1, 7, 14, and 21. No test article-related effects were reported.

Feed Consumption

Food consumption was recorded daily. No test article-related effects were reported.

Ophthalmoscopy

Ophthalmic examinations were performed once prior to treatment initiation. No test article-related effects were reported, but there were no post-treatment examinations due to the lack of availability of the veterinary ophthalmologist when the study was aborted.

ECG

ECGs were recorded prior to treatment initiation, on Day 15 during the final week of treatment and during the recovery phase on Day 22. No test article-related effects were reported.

Hematology

Blood was collected prior to treatment initiation and at the end of the treatment and recovery periods (Days 16 and 23, respectively) from overnight-fasted animals for hematology, serum chemistry, and coagulation evaluations.

No test article-related effects were reported.

Clinical Chemistry

ALT was statistically significantly increased in the mid-and high dose groups, and cholesterol was statistically significantly increased in the high dose group. At the end of recovery, ALT increases were partially reversed and cholesterol changes were fully reversed.

Urinalysis

No test article-related effects were reported.

Gross Pathology

On Day 16, 3 males per group, and on Day 23, 2 males from each of the control and high dose groups were euthanized by IV barbiturate overdose. A fasted terminal

body weight was recorded for each animal. Complete gross necropsies were performed.

Gross lesions included swollen, discolored, or thickened injections sites for all dogs, including controls, which persisted through the recovery period in all four recovery animals. Pale kidneys were apparent in two control males and one high dose male at the end of treatment and in one high dose male at the end of recovery.

Organ Weights

Organs weighed were: adrenals, brain, heart, kidneys, liver, spleen, testes, and thyroids/parathyroids. Paired organs were weighed together unless gross abnormalities were present.

Absolute and relative adrenal weights were decreased in all treated groups at the end of treatment, but appeared to have recovered in high dose males at the end of the recovery period.

Absolute and relative kidney weights were decreased at the end of treatment in low and mid-dose animals, but recovery was not assessed in those groups.

Histopathology

Adequate Battery

A complete tissue list was collected from all animals and placed in the appropriate fixative. Microscopic examination was performed on all tissues from male dogs in the control and high dose groups euthanized on Day 16 and on the injection sites of males from low and mid-dose groups euthanized on Day 16. There is no mention of examination of any tissues from animals euthanized at the end of the recovery period.

Peer Review

Not performed

Histological Findings

No test article-related findings were reported. However, vacuolation in the renal tubules in examined males (control and high dose) at the end of treatment was attributed to Captisol® in the vehicle formulation (*Reviewer's comment: Captisol® is in the clinical formulation*). Recovery was not assessed. Severity was moderate in placebo males and mild in high dose males. The report states that since the treatment formulas were diluted in D5W, the Captisol® concentration was higher in the placebo dosing solutions, which may account for the higher severity in the placebo group.

Microscopic findings at the injection sites in all groups at the end of treatment included intimal/endothelial proliferation, thrombosis, perivascular fibrosis/fibroplasia (correlating with gross findings of thickening), hemorrhage (correlating with gross findings of red discoloration/swelling) and mixed or mononuclear cell infiltration. Recovery was not assessed.

Reviewer's comment: It is unclear whether the vascular irritation is due to the daily catheterization procedure (it is also unclear why an indwelling catheter was not used) or due to the vehicle formulation.

Special Evaluation

None

Toxicokinetics

Blood samples were collected on Days 1 and 15 at the following time points: immediately pre-dose, at 5 and 30 minutes post-infusion, and at 1, 4, 8, and 24 hours post-infusion. Plasma was separated and sent to (b) (4) for analysis.

Exposure to RX-3341 after a single dose was dose-dependent and slightly greater than dose-proportional. Exposure was greater after 15 days of dosing, indicating accumulation over time. Systemic clearance was lower after repeated dosing than after a single dose. Half-life was 1.3-2.7 hours after a single dose and 4-6.5 hours after 15 days of treatment.

Table 1 – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following a One Hour Intravenous Infusion to Male Beagle Dogs (Day 1)

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	T _{1/2α} (hr)	AUC _{last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	C _{max} Dose	AUC _{0-inf} Dose	Cl (L/hr/kg)	V _Z (L/kg)
2	1	1	M	10	4830	0.083	48.8	8	1.45	5625	5703	483	570	1.75	3.66
2	1	11	M	10	5360	0.083	17.9	8	1.08	6188	6209	536	621	1.61	2.52
2	1	17	M	10	4460	0.083	68.7	8	1.45	7239	7360	446	736	1.36	2.84
				Mean	4883	0.083	45.1	8	1.33	6351	6424	488	642	1.57	3.01
				SD	452.4	0.0000	25.60	0.0	0.214	819.2	849.2	45.2	85.0	0.198	0.588
				%RSD	9.3	0.0	56.7	0.0	16.1	12.9	13.2	9.3	13.2	12.6	19.6
				Min	4460	0.083	17.9	8	1.08	5625	5703	446	570	1.36	2.52
				Max	5360	0.083	68.7	8	1.45	7239	7360	536	736	1.75	3.66
3	1	2	M	25	13600	0.083	143	8	1.30	21260	21489	544	860	1.16	2.19
3	1	5	M	25	14100	0.083	44.7	24	4.65	25343	25610	564	1024	0.976	6.54
3	1	6	M	25	12200	0.083	119	8	1.33	17039	17213	488	689	1.45	2.79
				Mean	13300	0.083	102	13.3	2.43	21214	21437	532	858	1.20	3.84
				SD	984.9	0.0000	51.3	9.24	1.926	4152.2	4198.7	39.4	167.5	0.239	2.357
				%RSD	7.4	0.0	50.1	69.3	79.3	19.6	19.6	7.4	19.5	20.0	61.4
				Min	12200	0.083	44.7	8	1.3	17039	17213	488	689	0.976	2.19
				Max	14100	0.083	143	24	4.65	25343	25610	564	1024	1.45	6.54
4	1	3	M	75	45900	0.083	457	8	1.26	77141	77928	612	1039	0.962	1.74
4	1	8	M	75	61000	0.083	43.5	24	2.62	148052	148211	813	1976	0.506	1.92
4	1	9	M	75	54500	0.083	56.9	24	3.70	98165	98436	727	1312	0.762	4.07
4	1	10	M	75	43000	0.083	16.2	24	2.89	75774	75834	573	1011	0.989	4.12
4	1	16	M	75	41500	0.083	17.9	24	2.98	54642	54721	533	730	1.37	5.88
				Mean	49180	0.083	118	20.8	2.69	90755	91026	652	1214	0.918	3.55
				SD	8305.8	0.0000	190.1	7.16	0.894	35537.9	35515.6	115.7	473.4	0.3183	1.729
				%RSD	16.9	0.0	160.7	34.4	33.2	39.2	39.0	17.8	39.0	34.7	48.8
				Min	41500	0.083	16.2	8	1.26	54642	54721	533	730	0.506	1.74
				Max	61000	0.083	457	24	3.7	148052	148211	813	1976	1.37	5.88

Table 2 – Individual and Mean Toxicokinetic Parameters for RX-3341 in Dog Plasma Following 15 Consecutive Daily One Hour Intravenous Infusions to Male Beagle Dogs (Day 15)

Group #	Day	Dog #	Sex	RX-3341 (mg/kg/day)	C _{max} (ng/mL)	T _{max} (hr)	C _{last} (ng/mL)	T _{last} (hr)	T _{1/2,α} (hr)	AUC _{last} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	C _{max} Dose	AUC _{0-inf} Dose	Cl (L/hr/kg)	V _z (L/kg)	AI
2	15	1	M	10	5850	0.083	14.7	24	5.21	8795	8893	585	889	1.12	8.46	1.6
2	15	11	M	10	6180	0.083	14.3	24	7.50	8716	8849	618	885	1.13	12.2	1.4
2	15	17	M	10	4750	0.083	26.6	24	6.71	8158	8385	475	839	1.19	11.5	1.1
				Mean	5593	0.083	18.5	24	6.47	8556	8709	559	871	1.15	10.7	1.4
				SD	748.8	0.0000	6.99	0.0	1.163	347.2	281.5	74.9	27.8	0.0379	1.99	0.21
				%RSD	13.4	0.0	37.7	0.0	18.0	4.1	3.2	13.4	3.2	3.3	18.5	15.6
				Min	4750	0.083	14.3	24	5.21	8158	8385	475	839	1.12	8.46	1.1
				Max	6180	0.083	26.6	24	7.5	8795	8893	618	889	1.19	12.2	1.6
3	15	14	M	25	11800	0.083	34.5	24	5.21	22130	22364	472	895	1.12	8.40	1.0
3	15	5	M	25	15000	0.083	61.3	24	7.14	27567	28138	600	1126	0.888	9.15	1.1
3	15	6	M	25	15800	0.083	27.7	24	4.61	25883	26049	632	1042	0.960	6.38	1.5
				Mean	14200	0.083	41.2	24	5.65	25193	25517	568	1021	0.989	7.98	1.2
				SD	2116.6	0.0000	17.76	0.0	1.322	2783.3	2923.5	84.7	116.9	0.1187	1.433	0.26
				%RSD	14.9	0.0	43.2	0.0	23.4	11.0	11.5	14.9	11.5	12.0	18.0	21.2
				Min	11800	0.083	27.7	24	4.61	22130	22364	472	895	0.888	6.38	1.0
				Max	15800	0.083	61.3	24	7.14	27567	28138	632	1126	1.12	9.15	1.5
4	15	3	M	75	51000	0.083	136	24	4.25	113545	114305	660	1524	0.656	4.02	1.5
4	15	8	M	75	65000	0.083	199	24	3.55	183458	184457	867	2459	0.407	2.08	1.2
4	15	9	M	75	61900	0.083	89.3	24	4.30	104607	105067	825	1401	0.714	4.43	1.1
4	15	10	M	75	56400	0.083	32.9	24	3.19	89722	89842	752	1198	0.835	3.84	1.2
4	15	16	M	75	45200	0.083	77.7	24	4.54	58790	59233	603	790	1.27	8.30	1.1
				Mean	55900	0.083	107	24	3.97	110024	110581	745	1474	0.776	4.53	1.2
				SD	8024.3	0.0000	63.2	0.0	0.569	46020.1	46283.5	106.9	616.9	0.3170	2.289	0.16
				%RSD	14.4	0.0	59.1	0.0	14.4	41.8	41.9	14.3	41.8	40.8	50.5	13.4
				Min	45200	0.083	32.9	24	3.19	58790	59233	603	790	0.407	2.08	1.1
				Max	65000	0.083	199	24	4.54	183458	184457	867	2459	1.27	8.3	1.5

Dosing Solution Analysis

Samples obtained on Day 1 were evaluated for concentration; formulations were 102-106% of nominal concentrations. Dose solutions were reported to be homogeneous, and the placebo solution was negative for RX-3341 on Day 1.

7 Genetic Toxicology

See Dr. Schmidt's Integrated Summary (Section 11)

8 Carcinogenicity

Carcinogenicity studies were not performed and generally are not needed for a therapeutic drug administered for the proposed duration.

9 Reproductive and Developmental Toxicology

See Dr. Schmidt's Integrated Summary (Section 11)

10 Special Toxicology Studies

See Dr. Schmidt's Integrated Summary (Section 11)

11 Integrated Summary and Safety Evaluation

Delafloxacin is a fluoroquinolone antibacterial that targets bacterial DNA gyrase and topoisomerase IV enzymes to form irreversible DNA strand breaks. The microbiological and efficacy studies were reviewed separately by the microbiologist, Dr. Jalal Sheikh. Both oral (tablet) and intravenous forms of the drug are discussed in the following summary

Safety Pharmacology:

Binding to a screening panel of receptors from the central nervous, cardiovascular, gastrointestinal and pulmonary systems was negligible.

At doses of 300 and 1000 mg/kg/in mice or rats, some sedation, ptosis and abnormal gait were noted. No effects on analgesia or body temperature were noted. With electroconvulsive shock in mice, delafloxacin exhibited a slight anticonvulsant effect at 10 mg/kg but not doses of 30 or 100 mg/kg. The latency to clonic convulsion with pentylenetetrazole was reduced at low doses of delafloxacin, but not at 300 mg/kg. Taken together, there is a minimal convulsant effect.

ECGs were followed in the unconscious dog after dosing intravenously with 3, 10, and 30 mg/kg delafloxacin and in conscious dogs, with oral doses at 10, 30, and 100 mg/kg. There were no effects on ECG. Effects on cardiac contractility were mixed. In anesthetized dogs with intravenous dosing at 70 mg/kg, a reduction in blood pressure was also noted, but a similar reduction was not seen with conscious dogs. Emesis and diarrhea were noted in ferrets at oral doses of 3, 10, and 30 mg/kg. No effects on pulmonary functions in rats were noted at oral doses up to 600 mg/kg. A hERG study was negative at up to 185 uM delafloxacin.

ADME:

The protein binding of delafloxacin ranged from > 90% in the mouse and rat, roughly 75% in the dog, 78-80% in the monkey and 83 to 85% in the human. Twenty to 30% of the delafloxacin radioactivity in whole blood was associated with the cellular fraction (erythrocytes, leukocytes and platelets). Radiolabeled delafloxacin was excreted primarily via the feces (86% of the dose in males, 78% in females) following oral administration at 20 mg/kg/ in the rat. An additional 9.5% of the total radioactivity was excreted in urine in males (17.4% in females). More than 90% of the total radioactivity was recovered by 48 hours. The highest amounts of radioactivity were seen in the liver and kidneys at 1 and 2 hours post-dose. Levels equivalent to or exceeding those in plasma were seen in bone mineral at 2, 4, and 8 hours post-dose. With intravenous dosing, roughly twice as much radioactivity was seen in the urine, with similar amounts to that seen with oral doses in the feces. Biliary excretion accounted from 55% of the

total radioactivity in orally dosed males and 28% in intravenously dosed males over the first 24 hours post-dose. The half-life in rat was less than 1 hour by either route. Parent drug only was found in rat plasma, while parent drug and 5 metabolites (including 2 glucuronides) in the feces, and a single glucuronide metabolite and parent drug in urine. The metabolism following microsomal incubation from hepatocyte preparations from different species are shown in the table below. Both rat and dog produced the same metabolites as humans, and so are appropriate model species.

In the dog, fecal excretion of radioactivity after an intravenous dose accounted for 84% of the dose while urinary excretions was 4.3%; with oral dosing, it was 88% and 4.9% respectively.

	24-Hour Incubations – 25 µM [¹⁴ C]ABT-492								
	Relative Percent of Total Radioactivity								
	M1	M2	M3	M5	M6	M7	M8	M11	ABT
Human	---	---	0.9	1.0	---	---	---	---	98
Rat	0.6	0.7	3.2	2.2	---	0.6	---	---	93
Monkey	4.4	---	13.9	9.4	---	---	1.7	---	71
Dog	6.1	---	24.9	15.6	0.9	---	---	0.9	52

The Applicant's nonclinical pharmacokinetics summary states that oral bioavailability was 28% in the rat and > 50% in dogs following a dose of 5 mg/kg. Plasma half-lives were 2.0-4.6 hours in rats and 3.4-4.0 hours in dogs. In comparison, the clinical overview states that mean absolute oral bioavailability in humans was 58.8%. It also states that the mean terminal half-life of delafloxacin, calculated by noncompartmental analysis, ranged from 8.21 to 10.9 hours after single IV (300 mg) administration and was 14.1 hours after single oral (450-mg to-be-marketed tablet) administration, respectively.

General Toxicity:

Toxicology studies have been conducted both genders of mice, rats, and dogs. They are summarized in the following table.

Toxicology studies with delafloxacin					
Species	Schedule	Route	Total Daily Dose mg/kg	LLD* mg/kg	Observations
Mouse	X	IP	26, 52, 104, 208, 416,	416	Decreased activity, ataxia etc; at death one rat with

			832		hepatocellular necrosis and degeneration
	X	PO	208, 416, 832, 1664, 3328	1664	Increased salivation, decreased activity, ataxia
Rat	X	IP	52, 104, 208, 418, 832	416	Decreased activity, ataxia, lacrimation; no gross pathology
	X	PO	208, 416, 832, 1664, 3328	1664	Increased salivation, decreased activity, no gross pathology
	DX5	IV (tail vein)	0, 37.5, 75, 150, 300, 600	300	Severe tail vein irritation at all doses terminated study at day 3
	DX14	IV, femoral vein cannula over 1 hr	0, 10, 60, 180/120	180	NOAEL = 10 mg/kg; clinical signs of prostration, tremors, rapid respiration. No remarkable hematology, clinical chemistry, or gross/histopathology.
	DX28 bid	PO	0, 200, 600, 1200	>1200	Increased cholesterol, increased cecum weights
	DX3 mos	PO	0, 200, 600, 1600	>1600	Decreased body weight, increased cholesterol at 1600; no target organs of toxicity determined
Dog	Single dose escalating study	IV	0, 19, 38, 75, 150, 300	300	Washout period of 48 hrs between doses. Clinical effects at 300 mg/kg: ptosis, ataxia, emesis and contracting nictitating membranes. Emesis at 75, 150 mg/kg. At 150 mg/kg DX4, had elevated AST/ALT, GGT and ALP.

	DX14	IV	0, 10, 25, 75	>75	Emesis at 25, 75 mg/kg; mild infusion site reactions. No gross or histopathology changes
	DX28	PO	0, 80, 160, 320	>320	Emesis at all doses, increasing in # animals/frequency with increasing dose
	DX3 mos	PO	0, 80, 160, 320	>320	Salivation and dose-related emesis during treatment, decreases in erythrocyte parameters in males at all doses and females at the high dose, increased ALT at high dose

*Lowest lethal dose

In summary, the major toxicity by both intravenous and oral routes in the dog was emesis. At near lethal doses, CNS toxicity was noted in both the rats and dogs. Toxicity to organs was negligible, and no significant histopathologic damage was seen at any dose in either species. No remarkable changes with drug administration were noted in the cardiovascular, pulmonary or renal systems. While joint damage is a hallmark of most fluoroquinolones, articular changes were only noted in one animal.

Modest irritation was noted with subplantar injections of delafloxacin in saline, and to a lesser extent, when (b) (4) was used for formulation. Tail vein irritation (swelling and necrosis) was also noted when delafloxacin was injected for 5 consecutive days in the rat. (b) (4) slightly mitigated the effects.

Fertility and Reproductive Toxicity

Intravenous fertility studies were conducted in the rats at doses of 0, 10, 60 and 120 mg/kg for up to 4 weeks prior to mating the males and 2 weeks prior to mating in the females. There were no significant effects on a complete battery of fertility effects (e.g. corpora lutea, copulation index etc) at 120 mg/kg (approximately 1161 mg/day or 1.9 times the daily dose for a 60 kg patient). In a separate study, AUC in pregnant rats at 120 mg/kg/day delafloxacin IV was estimated to be approximately 5 times the estimated human plasma exposure based on AUC.

Embryo-fetal development studies (Segment II) were conducted in rat and rabbit. The doses in the rabbit were low so that the animals could survive the gastrointestinal

effects. Rabbits were dosed on gestation days 6 through 18 at 0, 0.1, 0.4, and 1.6 mg/kg/day via stomach tube. Maternal toxicity consisted of scant/absent fecal elimination, alopecia, abortion (1 at day GD 26), and weight loss at the high dose. There were no effects on the offspring (no significant differences in variations, malformations or body weight). The NOAEL for the offspring was the top dose of 1.6 mg/kg which had an AUC of 440 ng·hr/mL, approximately 0.01 times the estimated human plasma exposure based on AUC.

The rats were dosed by oral gavage bid with a total daily dose of 0, 200, 600, and 1600mg/kg on gestation days 6 through 17. A decrease in body weight gain was seen at the highest dose in the dams. In the offspring there were no changes in resorptions, deaths, or variations/malformations between treated and control litters/individual offspring. At the HD, fetal body weights were decreased. Ossification of the caudal vertebrae and other sites were reduced at all doses. The delayed ossification limited the fetal NOAEL to less than 200 mg/kg. The AUC at Day 17 at 200 mg/kg was 150 ug·hr/mL, approximately 2.5 times the estimated human plasma exposure based on AUC.

A tissue distribution study with ¹⁴C–delafloxacin showed ratios of 0.06 to 0.08 when comparing fetal levels of radioactivity to plasma levels over 4 hours post-dose. Ratios of radioactivity between placenta and maternal plasma ranged from 0.25 to 0.36 over the same period. In dams dosed orally with radiolabelled delafloxacin, radiolabel in milk was seen at 8 fold higher levels than in the plasma at 4 hours post-dose. Radioactive levels from the pup stomach were approximately 10 fold higher than the plasma of the dams.

In the peri- and post natal study in rats at intravenous doses of 0, 10, 60 and 120 mg/kg, the maternal and F1 general NOAEL was considered to be 60 mg/kg/day. Gestation was slightly prolonged in the F0 dams. The F1 offspring showed a slightly higher incidence of mortality as well as lower body weights than the control offspring. There were no significant differences in treated and control rat pups for developmental milestones or variations/malformations/fertility indices. The NOAEL was roughly equivalent to the human clinical dose on an exposure basis.

A 2-week study was conducted in juvenile beagles (3/sex/dose) at oral doses of 0, 80, 160, or 320 mg/kg/day in gel capsules. An additional 2/sex were administered control or high dose capsules and underwent a 2-week recovery period. One high dose animal died; clinical signs in that animal included respiratory distress. Otherwise clinical signs were limited to vomiting and retching that was dose-related in incidence, but decreased in incidence and frequency after the first week. No hematology changes were reported at the end of treatment, but reticulocytes were decreased by half in high dose recovery animals relative to controls. Based on the death at the high dose, the NOAEL would be

the mid-dose, 160 mg/kg/day. AUC at that dose was 11,250 ng*hr/mL on Day 1 and 22,326 ng*hr/mL on Day 14, or 0.36-0.72 times the steady state clinical AUC. The duration of this study may not have been adequate for this species. (AN)

Genetic Toxicology:

No carcinogenicity studies were conducted with delafloxacin, nor were they expected based on duration of use. Delafloxacin was negative for mutagenicity or clastogenicity in the Ames, the human peripheral blood lymphocyte chromosomal aberration, and oral mouse micronucleus assays. [While there was a positive finding in the in vitro chromosomal aberration assay, it was seen at the highest concentrations under cytotoxic conditions. It was consistent with findings with other fluoroquinolones and was thought to be due to inhibitory effects on eukaryotic topoisomerase. (AN)]

Special Toxicology:

Phototoxicity is a characteristic finding with fluoroquinolones. The application states that this molecule was designed to minimize the potential of this drug for phototoxicity. No nonclinical phototoxicity testing was performed. (AN)

APPEARS THIS WAY ON
ORIGINAL

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/s/

AMY C NOSTRANDT
04/24/2017

TERRY J MILLER
04/24/2017

Comments from A. Jacobs, AD

April 13, 2017

For NDA 208610 delafloxacin

1. I concur that there are no nonclinical approval issues.
2. I concur that the embryofetal risk of the entire clinical formulation could be assessed postmarketing
3. I have discussed a few other issues with the reviewer and supervisor, and they have been addressed as appropriate.

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/s/

ABIGAIL C JACOBS
04/25/2017

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:

Applicant:

Stamp Date:

Drug Name:

NDA/BLA Type:

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no comments or requests from the sponsor at this time.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WENDELYN J SCHMIDT
11/16/2016

TERRY J MILLER
11/16/2016