2.6.6.6 Reproductive and developmental toxicology

Reviewer's Note:
The Sponsor was informed during the Pre-IND Meeting of 28 FEB 2002 for IND 68,436 that a Segment II study in rabbits would suffice to evaluate the potential for additive or synergistic effects of the combination of SS and NAP on reproduction and development, since the components are currently marketed in the U.S. for chronic or chronic/intermittent use. Hence, the only studies submitted and reviewed below are a definitive embryo-fetal development study in pregnant rabbits, and dose-ranging embryo-fetal development studies in rabbit and rat.

Embryofetal development

Oral (Stomach Tube) Developmental Toxicity Study of Sumatriptan Succinate Combined with Naproxen Sodium in Rabbits

Key study findings:

- The maternal and developmental NOAELs were less than 9/5 mg/kg/day NAP/SS, due to significant reductions in maternal and fetal weights observed at 9/5 mg/kg/day NAP/SS and all other treated groups.
- Groups 90/50 and 90/0 showed roughly equivalent significant reductions in litter size, and increases in total resorptions per litter, early resorptions per litter, percent of dead or resorbed conceptuses per litter, and in the number of does with any resorptions.
- Groups 9/5, 45/25, and 0/50 showed non-significant increases in numbers of early or late resorptions, average number of total resorptions, and percent dead or resorbed conceptuses per litter.
- The highest percentage of fetal alterations was observed in groups 90/50 and 90/0, with increases in the incidences of specific malformations (interventricular septal defect in group 90/50, and fused caudal vertebrae in both 90/50 and 90/0 groups) and variations (absent intermediate lobe of the lung, irregular ossification of the skull, and incompletely ossified sternal centra in both groups).
- Except for the finding of isolated interventricular septal defects described above in group 90/50, the toxicities reported for groups 90/50 and 90/0 are quite similar in this study, suggesting that the combination of SS and NAP is not likely to induce greater reproductive and developmental toxicity than NAP alone.
- The safety margin between the NOEL for teratogenicity in rabbits given the combination of NAP and SS and the expected plasma exposures in humans given one oral tablet of Trexima® are 20-28-fold for SS, and 1-2-fold for NAP. However, teratogenicity was only observed at doses well above those that were maternally toxic.

Study no.: POZEN Study #MT400-T12, [redacted] Study # 2216-010
Volume #, and page #: eNDA 21-926, Module 4, Section 4.2, Page 6948
Conducting laboratory and location: [redacted]
Date of study initiation: 18 MAY 2002
GLP compliance: Yes, statement signed 25 SEP 2003 by the Study Director

QA reports: yes (X) no ( ), statement signed 25 SEP 2003 by the QA Principle Auditor
Drug, lot #, and % purity: Sumatriptan Succinate (SS) Lot # QT0 1004, Purity 99.5%
Naproxen Sodium (NAP) Lot #NPXNAM-127, Purity 99.3%

Methods

Doses:

Group	Dosage[a] (mg/kg/day)	Concentration[a] (mg/mL)	Volume (mL/kg)	Number of Rabbits	Assigned Rabbit Numbers	
					Main Study	Satellite Study
I	0/0	0/0	10	20 + 2[b]	201 - 220	321 - 322
II	9/5	0.9/0.5	10	20 + 4[b]	221 - 240	323 - 326
III	45/25	4.5/2.5	10	20 + 4[b]	241 - 260	327 - 330
IV	90/50	9.0/5.0	10	20 + 4[b]	261 - 280	331 - 334
V	90/0	9.0/0	10	20 + 4[b]	281 - 300	335 - 338
VI	0/50	0/5.0	10	20 + 4[b]	301 - 320	339 - 342

a. Expressed as naproxen sodium/sumatriptan base (NAP/SB).
b. Rabbits assigned to toxicokinetic study.
The test article was considered 100% pure for the purpose of dosage calculations.

(reproduced directly from eNDA 21-926, Module 4, Section 4.2, Page 6965)

Species/strain: New Zealand White [Hra:(NZW)SPF] pregnant female rabbits, 5-6 month old, 2.8-4.3 kg, from [redacted]

Number/sex/group: 20 F/group Main Study

Route, formulation, volume, and infusion rate: oral (stomach tube) solution in reverse osmosis membrane processed deionized water; dosage volume was adjusted daily on the basis of individual body weight

Satellite groups used for toxicokinetics: 4 F/group treated, 2 F control

Study design: dosing occurred once daily from DGs 6-18 in main study, and DGs 6-20 in the TK satellite study; main study rabbits were sacrificed by IV Beuthanasia®-D on DG 29, and fetuses were removed by C-section.

Parameters and endpoints evaluated: observations (0-60 min postdose, daily); body weight (BW, daily); food consumption (FC, daily); TK (DG 6 & 19; 0.5, 1, 2, 4, 8, 12, 16, and 24 hrs postdose; DG 20 ~1 hr postdose maternal & fetal); gross lesions were examined upon sacrifice and C-section for main study rabbits DG 29; number and distribution of corpora lutea; pregnancy status; number and distribution of implantation sites; number of early and late resorptions; number of live and dead fetuses; size, color, and shape of placenta; fetus weights; gross external alterations on fetus; fetus sex; fetal brain examination in situ after cross-section between parietal and frontal bones; examination for skeletal alterations after staining with alizarin red S; examination of rabbits found dead or sacrificed moribund or aborted; gross lesions were recorded and retained in fixative.

Results

Mortality (dams):
45/25 NAP/SS: 1/20 found dead (FD) DG 24; 1/20 aborted DG 26

90/50 NAP/SS: 1/20 aborted DG 21

90/0 NAP/SS: 1/20 FD DG19; 1/20 aborted DG 21

0/50 NAP/SS: 2/20 FD DG 12 & 18; 2/20 sacrificed moribund (SM) D18 & 28; 1/20 aborted DG 26; (1/20 FD DG 14 due to gavage error)

Clinical signs (dams):
Treatment-related increases were observed in the following signs:

- scant/soft/liquid feces (9/5, 45/25/ 90/50, 90/0, and 0/50 groups)
- dehydration, emaciation, ↓motor activity, clear perinasal substance, lateral recumbency (0/50 group only in does that were FD, SM, or aborted)

Body weight (dams):
Significant decreases in BW were observed in the following groups: 45/25 (↓8-11% DG 13-29), 90/50 (↓9-14% DG 11-29), 90/0 (↓8-10% DG 16-28), and 0/50 (8-9% DG 15-17).

Significant decrease in body weight gain (BWG) was observed in group 9/5 (DG 16-19), and significant BW losses were observed in the following groups: 45/25 (DG 9-12), 90/50 (DG 6-12), 90/0 (DG 8-12, 15-19), and 0/50 (DG 9-12).

Mean BWG (DG 0-29) was reduced significantly in a dosage-related manner in 9/5 (↓24%), 45/25 (↓69%), 90/50 (↓56%), and 90/0 (↓53%) groups compared to the 0/0 control group.

Mean changes in BW from DG 6 to DG 19 (the dosing period) were:
0/0 (↑6.8%), 9/5 (↑3.7%), 45/25 (↓0.3%), 90/50 (↓4.8%), 90/0 (↓2.2%), 0/50 (↑4.0%).

Examination of the graph of maternal body weight changes below suggests that BW reductions induced during the dosing period by HD NAP (90 mg/kg/day) and by HD SS (50 mg/kg/day) were additive. Mean maternal BW in the combined HD NAP/SS group (90/50) was clearly below those of both HD NAP and HD SS groups during the entire dosing period.

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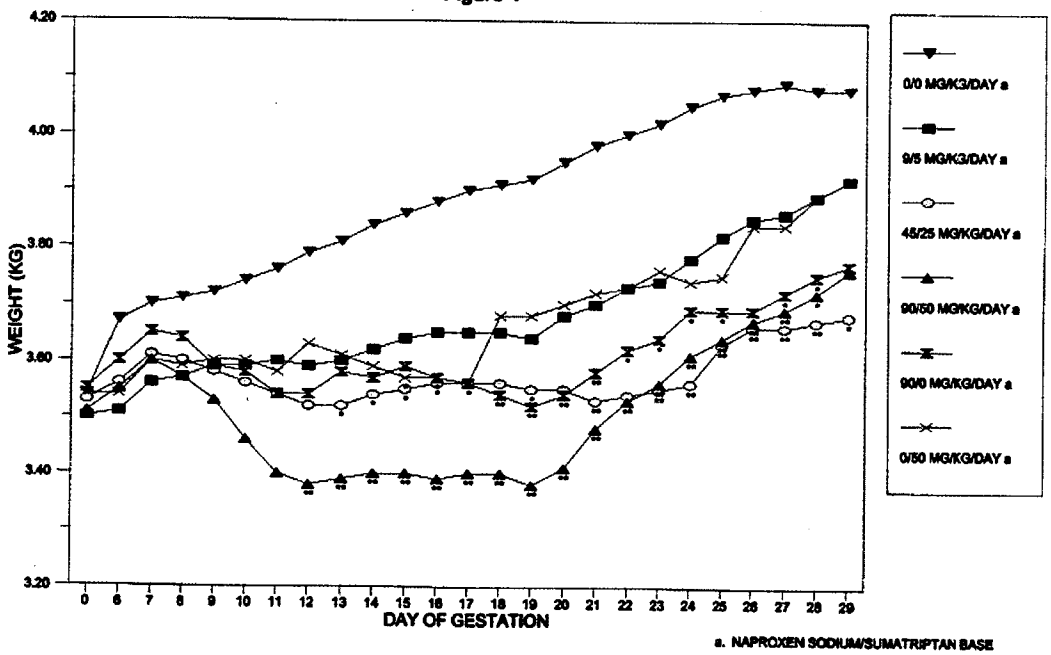
MATERNAL BODY WEIGHTS

Figure 1



a. NAPROXEN SODIUM/SUMATRIPTAN BASE

(reproduced directly from eNDA 21-926, Module 4, Section 4.2, Page 6995)

Food consumption (dams):
Mean daily FC was significantly reduced DG 6-19 compared to group 0/0 in groups: 9/5 (↓14%), 45/25 (↓31%), 90/50 (↓52%), 90/0 (↓38%)

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On Original

Toxicokinetics:

Table 2. Sumatriptan Toxicokinetic Parameters on Days 6 and 19 of Presumed Gestation for New Zealand White Rabbits

Group	Rabbit ID #	Dose (mg/kg) NAP/SS	Day 6 C_{max} ng/mL	t_{max} hr	AUC_{0-t} hr-ng/mL	t½ hr	AUC_{0-Inf} hr-ng/mL	Day 19 C_{max} ng/mL	t_{max} hr	AUC_{0-24} hr-ng/mL	t½ hr	AUC_{0-Inf} hr-ng/mL
II	323	9/5	93	0.5	120	1.2	193	128	0.5	127	1.0	187
	324	9/5	83	0.5	184	2.5	279	92	1.0	147	5.6	724
	325	9/5	65	0.5	92	1.9	199	134	1.0	196	2.0	405
	326	9/5	67	0.5	93	1.6	173	162	0.5	179	0.7	214
	Mean		77.0	0.5	122.2	1.8	216.7	129.0	0.8	162.3	2.3	382.5
	(SD)		(13.3)	(0.0)	(43.4)	(0.6)	(46.6)	(28.7)	(0.3)	(31.8)	(2.3)	(247.6)
III	327	45/25	731	0.5	1471	1.8	1936	6694*	1.0*	30674*	6.5*	50430*
	328	45/25	732	0.5	2207	1.7	2279	1475	0.5	3158	2.7	3321
	329	45/25	425	0.5	1224	1.8	1296	541	0.5	2514	2.9	2653
	330	45/25	478	1.0	1876	2.6	2114	1335	1.0	5434	3.0	5555
	Mean		591.4	0.6	1694.7	2.0	1906.3	1117.1	0.7	3761.3	2.9	3843.2
	(SD)		(162.9)	(0.3)	(434.7)	(0.4)	(436.4)	(583.5)	(0.3)	(1534.3)	(0.1)	(1519.6)
IV	331	90/50	1749	1.0	7239	2.8	7410	NA	NA	NA	NA	NA
	332	90/50	639	0.5	4339	3.4	4519	1328	2.0	7760	3.2	7911
	333	90/50	1957	0.5	6552	1.5	6731	5274	0.5	9566	2.0	9664
	334	90/50	2699	0.5	10286	2.2	10528	NA	NA	NA	NA	NA
	Mean		1761.8	0.6	7163.8	2.5	7296.8	3301.0	1.3	8663.0	2.6	8787.3
	(SD)		(651.6)	(0.3)	(2456.6)	(0.8)	(2483.2)	(2798.1)	(1.1)	(1276.4)	(0.8)	(1238.8)
VI	339	0/50	1538	0.5	4667	1.6	4824	2778	0.5	7479	2.6	7632
	340	0/50	433	1.0	2285	2.4	2468	2398	0.5	5034	1.9	5311
	341	0/50	1754	0.5	4476	1.8	4668	NA	NA	NA	NA	NA
	342	0/50	1392	1.0	8434	2.0	8624	3849	0.5	14994	2.3	15104
	Mean		1279.2	0.8	4465.5	1.9	4626.2	3008.5	0.5	9169.3	2.3	9415.7
	(SD)		(563.2)	(0.3)	(1699.9)	(0.3)	(1654.7)	(752.4)	(0.0)	(5190.7)	(0.4)	(5085.0)

*Rabbit 327 Day 19 data was excluded as an outlier.

(reproduced directly from eNDA 21-926, Module 4, Section 4.2, Page 7284)

Table 3. Naproxen Toxicokinetic Parameters on Days 6 and 19 of Presumed Gestations for New Zealand White Rabbits

Group	Rabbit ID #	Dose (mg/kg) NAP/SS	Day 6 C_{max} µg/mL	t_{max} hr	AUC_{0-t} hr-µg/mL	t½ hr	AUC_{0-Inf} hr-µg/mL	Day 19 C_{max} µg/mL	t_{max} hr	AUC_{0-24} hr-µg/mL	t½ hr	AUC_{0-Inf} hr-µg/mL
II	323	9/5	17.2	1.0	141.0	3.7	152.4	23.6	0.5	169.7	3.0	183.0
	324	9/5	24.3	4.0	212.7	2.9	219.0	24.4	4.0	225.0	2.4	230.6
	325	9/5	20.3	2.0	138.7	12.3	399.3	25.5	4.0	241.3	2.3	246.7
	326	9/5	27.2	0.5	175.6	1.8	178.5	37.5	1.0	207.1	2.3	213.9
	Mean		22.3	1.9	167.8	5.2	237.3	27.8	2.4	210.8	2.5	218.5
	(SD)		(4.4)	(1.5)	(34.8)	(4.8)	(11.4)	(6.5)	(1.9)	(30.7)	(0.3)	(27.2)
III	327	45/25	92.8	1.0	816.9	2.8	821.5	96.3	0.5	557.6	14.8	1871.9
	328	45/25	95.6	8.0	983.2	2.5	987.4	114.8	4.0	926.2	3.2	933.0
	329	45/25	72.7	0.5	657.8	2.6	663.9	96.7	0.5	958.4	7.6	1074.7
	330	45/25	74.4	4.0	927.6	3.3	939.7	NA	NA	NA	NA	NA
	Mean		83.9	3.4	846.4	2.8	868.1	102.3	1.7	814.1	8.5	1289.2
	(SD)		(12.9)	(3.4)	(143.5)	(0.3)	(135.5)	(16.9)	(2.0)	(222.7)	(5.9)	(596.1)
IV	331	90/50	220.7	2.0	2178.7	3.2	2195.2	108.7	4.0	1126.9	3.4	1143.2
	332	90/50	119.5	12.0	1907.9	6.2	2204.2	155.0	4.0	1614.7	2.8	1628.8
	333	90/50	123.3	1.0	1344.5	2.5	1348.5	208.3	0.5	1258.8	1.6	1265.1
	334	90/50	139.1	0.5	1455.1	3.0	1467.5	NA	NA	NA	NA	NA
	Mean		150.6	3.9	1721.8	3.7	1803.9	157.4	2.8	1333.5	2.8	1361.7
	(SD)		(47.5)	(5.5)	(99.5)	(1.7)	(99.7)	(49.8)	(2.0)	(252.3)	(2.0)	(248.6)
V	335	90/0	170.6	2.0	1361.7	5.1	1428.7	186.6	1.0	1354.4	1.7	1363.4
	336	90/0	179.0	0.5	1326.0	3.7	1339.9	NA	NA	NA	NA	NA
	337	90/0	183.6	0.5	1226.0	3.8	1244.2	NA	NA	NA	NA	NA
	338	90/0	101.9	4.0	1016.1	3.9	1036.4	155.0	2.0	1115.9	1.9	1124.6
	Mean		158.9	1.8	1232.5	4.1	1262.3	176.8	1.5	1236.1	1.8	1244.0
	(SD)		(38.3)	(1.7)	(156.2)	(0.7)	(166.4)	(22.4)	(0.7)	(168.6)	(0.1)	(166.9)

(reproduced directly from eNDA 21-926, Module 4, Section 4.2, Page 7285)

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

Treatment-related findings included the following:

- Groups 90/50 and 90/0 showed ↓litter size, ↑resorptions/litter, ↑early resorptions/litter, ↑resorbed conceptuses/litter, and ↑# does with resorptions. These effects were slightly greater for the 90/0 group than the 90/50 group.
- Groups 9/5, 45/25, and 0/50 showed ↑early or late resorptions/litter, ↑total resorption, and ↑ % dead or resorbed conceptuses/litter; however, none of these increases were statistically significant compared to the 0/0 group.
- Fetal BW/litter was reduced at 9/5 (↓14%), 45/25 (↓11%), and 0/50 (↓12%) (lack of significant reductions in 90/50 and 90/0 groups was thought to be due to the smaller litter sizes in these two groups).

No treatment-related changes were observed in fetal sex ratios, # of dead fetuses, or placentae.

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TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP		I	II	III	IV	V	VI
DOSAGE (MG/KG/DAY)a		0/0	9/5	45/25	90/50	90/0	0/50
RABBITS TESTED	N	20	20	20	20	20	20
PREGNANT	N(%)	20(100.0)	19(95.0)	20(100.0)	18(90.0)	18(90.0)	19(95.0)
FOUND DEAD	N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)	0(0.0)	3(15.8)
MORIBUND SACRIFICED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(10.5)
ABORTED AND SACRIFICED	N(%)	0(0.0)	1(5.3)	1(5.0)	1(5.6)	1(5.6)	1(5.3)
DELIVERED AND SACRIFICED	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	19	18	18	17	17	19
CORPORA LUTEA	MEAN±S.D.	10.5 ± 2.1	10.9 ± 1.7	10.3 ± 1.7	9.9 ± 2.2	10.1 ± 1.4	11.7 ± 2.4
IMPLANTATIONS	MEAN±S.D.	9.0 ± 2.6	10.3 ± 1.6	9.2 ± 2.5	8.2 ± 2.2	9.4 ± 1.6	10.5 ± 2.2
LITTER SIZES	MEAN±S.D.	8.3 ± 2.5	8.6 ± 2.2	7.0 ± 2.6	5.2 ± 2.3**	5.3 ± 3.4*	8.8 ± 3.0
LIVE FETUSES	N	155	148	127	88	90	111
	MEAN±S.D.	8.2 ± 2.5	8.2 ± 2.7	7.0 ± 2.6	5.2 ± 2.4**	5.3 ± 3.4	8.5 ± 3.4
DEAD FETUSES	N	2	7	0	1	0	1
	MEAN±S.D.	0.1 ± 0.4	0.4 ± 0.8	0.0 ± 0.0	0.0 ± 0.2	0.0 ± 0.0	0.2 ± 0.8
RESORPTIONS	MEAN±S.D.	0.8 ± 1.3	1.7 ± 2.4	2.2 ± 2.5	2.9 ± 2.2**	4.1 ± 3.2**	1.7 ± 2.5
EARLY RESORPTIONS	N	8	6	32	37	48	12
	MEAN±S.D.	0.4 ± 0.8	0.3 ± 0.7	1.8 ± 2.4	2.2 ± 2.0**	2.8 ± 2.8**	0.9 ± 1.9
LATE RESORPTIONS	N	7	24	7	13	22	10
	MEAN±S.D.	0.4 ± 1.0	1.3 ± 2.2	0.4 ± 0.8	0.8 ± 0.9	1.3 ± 2.1	0.8 ± 2.0
DOES WITH ANY RESORPTIONS	N(%)	7(36.8)	9(50.0)	12(66.7)	15(88.2)	15(88.2)	6(46.2)

a. Dosage occurred on days 6 through 18 of gestation. Dosage is expressed as naproxen sodium/sumatriptan base.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

(reproduced directly from eNDA 21-926, Module 4, Section 4.2, Page 7010)

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TABLE 8 (PAGE 2): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0/0	II 9/5	III 45/25	IV 90/50	V 90/0	VI 0/50
RABBITS TESTED	N	20	20	20	20	20	20
PREGNANT	N(%)	20(100.0)	19(95.0)	20(100.0)	18(90.0)	18(90.0)	19(95.0)
FOUND DEAD	N(%)	0(0.0)	0(0.0)	1(5.0)	0(0.0)	0(0.0)	3(15.8)
MORIBUND SACRIFICED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(10.5)
ABORTED AND SACRIFICED	N(%)	0(0.0)	1(5.3)	1(5.0)	1(5.6)	1(5.6)	1(5.3)
DELIVERED AND SACRIFICED	N(%)	1(5.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	19	18	18	17	17	13
DOES WITH ALL CONCEPTUSES DEAD OR RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	1(5.9)	2(11.8)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	19(100.0)	18(100.0)	18(100.0)	16(94.1)	15(88.2)	13(100.0)
PLACENTAE APPEARED NORMAL b	N(%)	19(100.0)	18(100.0)	18(100.0)	17(100.0)	16(100.0)	13(100.0)

a. Dosage occurred on days 6 through 18 of gestation. Dosage is expressed as naproxen sodium/sumatriptan base.
b. Excludes does with all early resorptions.

(reproduced directly from eNDA 21-926, Module 4, Section 4.2, Page 7011)

Offspring (malformations, variations, etc.):

Treatment-related changes observed:

- ↑# litters with fetuses with any alterations (9/5, 45/25, 90/50, and 90/0)
- ↑# fetuses with any alterations (9/5, 45/25, 90/50, and 90/0)
- ↑% fetuses with any alterations/litter (90/50 and 90/0)

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TABLE 10 (PAGE 1): FETAL ALTERATIONS - SUMMARY

DOSAGE GROUP DOSAGE (MG/KG/DAY)a		I 0/0	II 9/5	III 45/25	IV 90/50	V 90/0	VI 0/50
LITTERS EVALUATED	N	19	18	18	17	15	13
LITTERS INCLUDED IN ANALYSES	N	19	18	18	16b	15	13
FETUSES EVALUATED	N	157	155	127	89	90	114
LIVE	N	155	148	127	88	90	111
DEAD	N	2c	7c	0	1c	0	3c
LITTERS WITH FETUSES WITH ANY ALTERATION OBSERVED	N(%)	6(31.6)	11(61.1)**	11(61.1)**	13(81.2)**	14(93.3)**	5(38.5)
FETUSES WITH ANY ALTERATION OBSERVED	N(%)	11(7.1)	32(21.6)**	26(20.5)**	28(31.8)**	23(25.6)**	9(8.1)
% FETUSES WITH ANY ALTERATION/LITTER	MEAN±S.D.	10.2 ± 23.6	23.0 ± 30.3	18.2 ± 20.8	33.2 ± 26.5*	32.0 ± 27.5*	6.7 ± 10.5

a. Dosage occurred on days 6 through 18 of gestation. Dosage is expressed as naproxen sodium/sumatriptan base.
b. Excludes litter 273, which consisted of eight resorptions and one dead fetus.
c. Dead fetuses were excluded from group averages and statistical analyses; observations for those conceptuses are cited on Table 22.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

(reproduced directly from eNDA 21-926, Module 4, Section 4.2, Page 7013)

Specific malformations increased: (% of fetuses)

- fused caudal vertebrae (3.4% 90/50, 2.2% 90/0, 0% 0/0)
- interventricular septal defect (3.4% 90/50, 0% 0/0)

Specific variations increased: (% of fetuses)

- absent intermediate lobe of the lung (9.1% 90/50, 4.4% 90/0, 1.3% 0/0)
- irregular ossification of the skull (6.8% 90/50, 5.6% 90/0, 1.3% 0/0)
- incompletely ossified sternal centra (3.4% 90/50, 4.4% 90/0, 0% 0/0)

Sponsor's Conclusions:
The maternal NOAEL was less than 9/5 mg/kg/day NAP/SS, due to reduced maternal body weight gain and food consumption in the 9/5 group during the dosing period compared to control group values. Cmax of SS at 9/5 was ~2.5-fold greater than human exposure to SS after a single dose of 100 mg SS, and Cmax of NAP was 0.3-fold of the human exposure after a single dose of 500 mg NAP.

The developmental NOAEL was also less than 9/5 mg/kg/day NAP/SS, due to significant reduction in fetal weight in this group.

Groups 90/50 and 90/0 showed significant reductions in litter size, and increases in total resorptions per litter, early resorptions per litter, percent of dead or resorbed conceptuses per litter, and in the number of does with any resorptions.

Groups 9/5, 45/25, and 0/50 showed non-significant increases in numbers of early or late resorptions, average number of total resorptions, and percent dead or resorbed conceptuses per litter.

The highest percentage of fetal alterations was observed in groups 90/50 and 90/0, with increases in the incidences of specific malformations (interventricular septal defect in group 90/50, and fused caudal vertebrae in both 90/50 and 90/0 groups) and variations (absent intermediate lobe of the lung, irregular ossification of the skull, and incompletely ossified sternal centra in both groups).

The finding of two fetuses with isolated interventricular septal defects at 90/50 (and none in any other group) was thought to be possibly related to the increased exposures to NAP (AUC ↑43%) and SS (AUC ↑58%) compared to exposures in groups 90/0 and 0/50, respectively. *(Reviewer's Note: these AUC differences are based on Day 6 $AUC_{0-\infty}$ values; however, on Day 19, $AUC_{0-\infty}$ values in the 90/50 group were ↓6.7% SS and ↑8.7% NAP compared to those in groups 0/50 and 90/0, respectively.*

Reviewer's Comments:
Except for the finding of isolated interventricular septal defects described above in group 90/50, the toxicities reported for groups 90/50 and 90/0 are quite similar in this study, suggesting that the combination of SS and NAP is not likely to induce greater reproductive and developmental toxicity than NAP alone.

It is not clear why treatment with SS alone (0/50) induced greater mortality, since, otherwise, it appeared to be less toxic than treatment with NAP or NAP/SS.

No-effect levels for maternal and fetal toxicity (decreased body weight) were not established in this study. The lowest dose that induced maternal and fetal toxicity (9/5 mg/kg NAP/SS) was associated with mean plasma exposures ($AUC_{0-\infty}$) that were 0.14 and 1.4 times the exposures to NAP and SS, respectively, observed in humans at the recommended dose of TREXIMA®. However, this study did demonstrate that significant teratogenic effects only occurred at doses that were maternally toxic.

The Sponsor's conclusions omitted the findings that the number of litters with fetuses with any alterations, the number of fetuses with any alterations and the percentage of fetuses per litter with any alterations was increased with the dose of NAP ± SS.

Based on the pharmacokinetic information presented in the table below, the highest no-effect level for teratogenicity in rabbits given the NAP/SS (45/25 mg/kg) was associated with mean plasma exposures ($AUC_{0-\infty}$) that were 0.84 and 14 times the exposures to NAP and SS, respectively, observed in humans at the recommended dose of TREXIMA®.

Sumatriptan Exposure Ratios

Species	Dose	Cmax (ng/mL)	Cmax Ratio	$AUC_{0-\infty}$ (ng*hr/mL)	$AUC_{0-\infty}$ Ratio
Humans (Study MT400-101*)	1 tablet	74.9	--	270	--
Rabbit Maternal BW LOEL	9 mg/kg NAP 5 mg/kg SS	129	1.7	382	1.4
Rabbit Fetal BW LOEL	9 mg/kg NAP 5 mg/kg SS	129	1.7	382	1.4
Rabbit NOEL Teratogenicity	45 mg/kg NAP 25 mg/kg SS	1117	15	3843	14
Rabbit NOEL Teratogenicity	0 mg/kg NAP 50 mg/kg SS	3008	40	9416	35
Rabbit Teratogenicity	90 mg/kg NAP 50 mg/kg SS	3301	44	8787	33

Naproxen Exposure Ratios

Species	Dose	Cmax (ug/mL)	Cmax Ratio	$AUC_{0-\infty}$ (ug*hr/mL)	$AUC_{0-\infty}$ Ratio
Humans (Study MT400-101*)	1 tablet	69.7	--	1548	--
Rabbit Maternal BW LOEL	9 mg/kg NAP 5 mg/kg SS	27.8	0.40	218	0.14
Rabbit Fetal BW LOEL	9 mg/kg NAP 5 mg/kg SS	27.8	0.40	218	0.14
Rabbit NOEL Teratogenicity	45 mg/kg NAP 25 mg/kg SS	102	1.5	1293	0.84
Rabbit Teratogenicity	90 mg/kg NAP 50 mg/kg SS	157	2.25	1352	0.87
Rabbit Teratogenicity	90 mg/kg NAP 0 mg/kg SS	171	2.45	1244	0.80

(*Human Values are Geometric Means (N=8) from Clinical Study Report MT400-101)
(Rabbit values are from Day 19; Reviewer's Tables)

Additional details on does found dead, sacrificed early, or aborting:
45/25 NAP/SS: 1/20 found dead (FD) DG 24; 1/20 aborted DG 26

(Doe 259: FD DG 24; soft/liquid feces DG 20-24; scant feces DG 23-24; head tilt DG 24; BW loss DG 17-24; ↓FC DG 18-24; black regions in all areas of stomach; 2 cm perforation in cardiac region of stomach, with thin surrounding tissue; litter consisted of 3 early and 4 late resorptions)

(Doe 257: aborted & sacrificed DG 26; soft/liquid feces DG 13-18, 22-25; scant feces Dg 19-21, 23-25; red substance in cage pan DG 26; BW loss DG 9-26, ↓FC DG 10-26; red substance in stomach; 2 early resorptions, 2 implantation sites assumed cannibalized, 3 fetuses (partly cannibalized) and one placenta found in cage pan; 2 fetuses had unossified pubic bones, 3 appeared normal)

90/50 NAP/SS: 1/20 aborted DG 21

(Doe 276 aborted & sacrificed DG 21; scant feces DG 10-15, 19-21; no feces DG 16-18; soft/liquid feces DG 20-21; red substance in cage pan DG 21; BW loss, ↓FC DG7-21; 9 implantation sites and 8 placentas found in cage pan)

90/0 NAP/SS: 1/20 FD DG19; 1/20 aborted DG 21

(Doe 300: FD DG 19; soft/liquid feces DG 12-18; scant feces DG 14-18; dehydration and red substance found in cage pan DG 18; BW loss DG 7-18; ↓FC DG 6-19; not pregnant)

(Doe 296 aborted & sacrificed DG 21; soft/liquid feces DG 18-21; scant feces DG 10, 20-21; red substance in cage pan DG 21; 1 conceptus, 1 early resorption, 1 late resorption found in utero, and 1 conceptus and 1 placenta found in cage pan; remaining 4 conceptuses presumed cannibalized)

0/50 NAP/SS: 2/20 FD DG 12 & 18; 2/20 sacrificed moribund (SM) D18 & 28; 1/20 FD DG 14 (Doe 313: dosing accident); 1/20 aborted DG 26

(Doe 314: SM DG 28; soft/liquid feces DG 15, 23-26; scant feces DG 27; tan gelatinous substance in cage pan DG 28; BW loss and ↓FC DG 22-28; tan areas on all lobes of liver; black areas in stomach; tan caseous material adhered to lining of uterus; rough mottled placenta; pale spleen; litter consisted of 7 apparently normal live fetuses and 4 late resorptions)

(Doe 317: FD DG 18; soft/liquid feces DG 12-15, 17; scant feces DG 16; dehydration, salivation DG 17; BW loss and ↓FC DG 11-18; 9 fetuses in litter)

(Doe 319: SM DG 18; soft/liquid feces DG 12-13, 15-17; scant feces DG 12-14, 16-18; ↓motor activity, clear perinasal substance, lateral recumbency, labored breathing DG 18; BW loss and ↓FC DG 10-18; thin area in mucosal lining within cardiac region of stomach; 3 dead fetuses and five late resorptions in litter)

(Doe 320: FD DG 12; soft/liquid feces DG 6-11; ↓motor activity DG 10; dehydration, emaciation, scant feces DG 10-11; BW loss and ↓FC DG 6-12; 12 early resorptions in litter)

(Doe 316 aborted & sacrificed DG 26; soft/liquid feces DG 13-19, 22-24; scant feces DG 16-24; dehydration, emaciation DG 25-26; red substance in cage pan DG 26; BW loss and ↓FC DG 9-21; red substance in stomach; dark firm areas in lungs; 6 late resorptions found in cage pan; 1 more late resorption aborted prior to sacrifice)

Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of MT 400 in Rabbits
(POZEN Study #MT400-T10; [redacted] Protocol #2216-010P; Completed 10 OCT 2003; GLP; QA; Naproxen Sodium (NAP) Lot #NPXNAM-126, Purity 99.5%; Sumatriptan Succinate (SS) Lot QT0 1002, Purity 99.4%, dosed calculated as base; eNDA 21-996, Module 4, Page 6794)

Methods:
Five presumed pregnant F New Zealand White [Hra:(NZW)SPF] rabbits were assigned to each of the following groups: 0/50, 90/1, 90/5, 90/15, 90/50, and 90/0 mg/kg/day NAP/SS, and treated via gavage at 10 mL/kg once daily on DG 6-18 (days of gestation). Observations included viability checks (2X/day), clinical signs (for ~1 hr postdose), body weight (BW, daily), and food consumption (FC, daily). All surviving rabbits were sacrificed on DG 29 and examined for the number and distribution of corpora lutea, implantation sites, and uterine contents. Gross necropsy of the thoracic, abdominal, and pelvic viscera was performed. Fetuses were weighed and examined for gross external alterations and sex.

Results:
No mortality or abortions were observed, except for one at 90/15, which aborted and was sacrificed DG 24, with soft/liquid feces DG17-20 and 22-24, fluctuating BW, and reduced FC during the dosing period. Necropsy of this doe showed firmness and discolorations (dark red, tan, green) in right cardiac and distal end of left apical lobes of lung. The litter consisted of two dead fetuses (appearing normal) and three late resorptions in utero (too much autolysis for examination).

Treatment-related clinical signs included soft/liquid/scant feces in 1-3 does/group at 90/5, 90/15, and 90/50, and ungroomed coat in 1/5 at 90/50. Maternal BWG was dose-dependently reduced in combination groups during the dosing period (+0.13, +0.14, +0.07, and -0.12 kg in groups 90/1, 90/5, 90/15, and 90/50, respectively, compared to +0.25 and +0.23 kg in groups 0/50 and 90/0, respectively). No significant differences in final BW were observed. Food consumption was reduced in groups 90/1, 90/15, and 90/50 vs. comparators, but only during the dosing period.

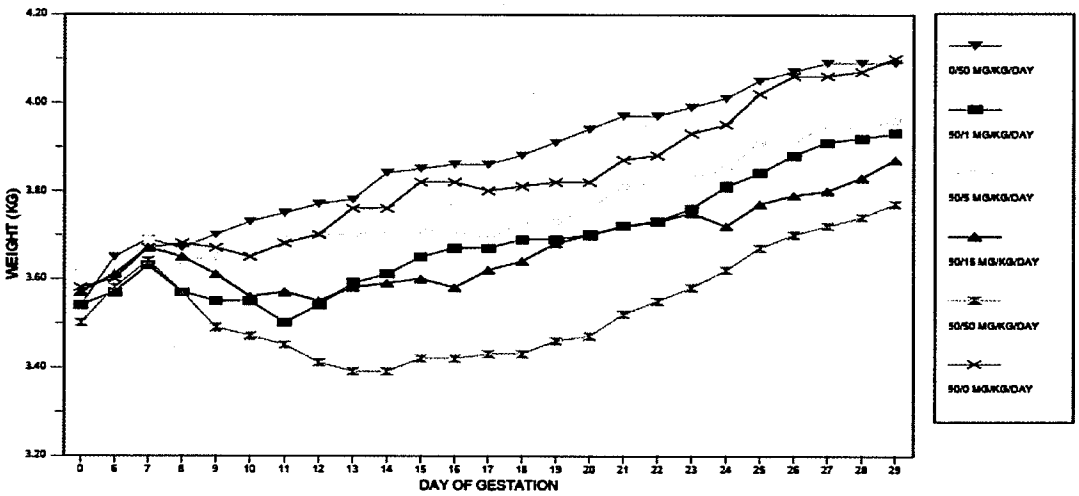
Increases in numbers of early resorptions, numbers of litters with resorptions, and percentage of resorbed conceptuses per litter were observed in groups 90/1, 90/5, 90/15, 90/50, and 90/0 compared to group 0/50. These parameters showed greater increases in the 90/50 group compared to the 90/0 group. Mean fetal BW was reduced only at 90/50 (based on only 14 fetuses). Gross external malformations were observed in two fetuses at 90/1 (one with gastroschisis and one with a short tail), and in two fetuses (one with gastroschisis and one with a short tail) and two late resorptions (one with acrania, gastroschisis, medial rotation of right hindlimb, short tail, and fused forepaw digits; and one with gastroschisis, downward flexed forepaws, absent tail, no anal opening, and no external urogenital area) at 90/50.

Conclusions:
The proposed high dose of 90/50 mg/kg/day NAP/SS is expected to produce tolerable maternal and fetal toxicity in the definitive developmental toxicity study in rabbits (reduced maternal BWG during treatment at 90/1, 90/5, 90/15, and 90/50; reduced fetal BW in at 90/50 mg/kg/day NAP/SS; and increased malformations at 90 mg/kg/day NAP ± SS).

PROTOCOL 2216-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF MT 400 IN RABBITS
(SPONSOR'S STUDY NUMBER: MT 400-T10)

MATERNAL BODY WEIGHTS

Figure 1



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PROTOCOL 2216-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF MT 400 IN RABBITS
(SPONSOR'S STUDY NUMBER: MT 400-T10)

TABLE 8 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY

GROUP DOSAGE (MG/KG/DAY)a		I 0/50	II 90/1	III 90/5	IV 90/15	V 90/50	VI 90/0
RABBITS TESTED	N	5	5	5	5	5	5
PREGNANT	N(%)	5(100.0)	5(100.0)	4(80.0)	5(100.0)	5(100.0)	5(100.0)
ABORTED	N(%)	0(0.0)	0(0.0)	0(0.0)	1(20.0)	0(0.0)	0(0.0)
RABBITS PREGNANT AND CAESAREAN-SECTIONED ON DAY 29 OF GESTATION	N	5	5	4	4	5	5
CORPORA LUTEA	MEAN±S.D.	10.0 ± 1.9	9.4 ± 1.8	10.0 ± 0.8	8.5 ± 1.3	8.2 ± 2.3	10.8 ± 2.9
IMPLANTATIONS	MEAN±S.D.	9.6 ± 1.7	9.2 ± 1.9	8.8 ± 1.0	8.5 ± 1.3	7.8 ± 2.8	10.6 ± 2.6
LITTER SIZES	MEAN±S.D.	9.4 ± 1.7	6.6 ± 3.0	3.2 ± 3.6	6.5 ± 2.9	4.6 ± 3.0	8.6 ± 2.1
LIVE FETUSES	N	47	33	13	26	23	43
	MEAN±S.D.	9.4 ± 1.7	6.6 ± 3.0	3.2 ± 3.6	6.5 ± 2.9	4.6 ± 3.0	8.6 ± 2.1
DEAD FETUSES	N	0	0	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.2 ± 0.4	2.6 ± 1.9	5.5 ± 4.4	2.0 ± 1.6	3.2 ± 1.3	2.0 ± 2.5
EARLY RESORPTIONS	N	0	11	22	6	12	6
	MEAN±S.D.	0.0 ± 0.0	2.2 ± 1.8	5.5 ± 4.4	1.5 ± 1.9	2.4 ± 1.8	1.2 ± 1.3
LATE RESORPTIONS	N	1	2	0	2	4	4
	MEAN±S.D.	0.2 ± 0.4	0.4 ± 0.5	0.0 ± 0.0	0.5 ± 1.0	0.8 ± 0.8	0.8 ± 1.3
DOES WITH ANY RESORPTIONS	N(%)	1(20.0)	4(80.0)	3(75.0)	3(75.0)	5(100.0)	3(60.0)
DOES WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	0(0.0)	0(0.0)
DOES WITH VIABLE FETUSES	N(%)	5(100.0)	5(100.0)	3(75.0)	4(100.0)	5(100.0)	5(100.0)
PLACENTAE APPEARED NORMAL	N(%)	5(100.0)	5(100.0)	3(100.0)	4(100.0)	5(100.0)	5(100.0)

a. Dosage occurred on days 6 through 18 of gestation. Dosage is expressed as naproxen sodium/sumatriptan base.

(reproduced directly from eNDA 21-996, Module 4, Page 6812)

PROTOCOL 2216-010P: ORAL (STOMACH TUBE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF MT 400 IN RABBITS
(SPONSOR'S STUDY NUMBER: MT 400-T10)

TABLE 9 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

GROUP DOSAGE (MG/KG/DAY)a		I 0/50	II 90/1	III 90/5	IV 90/15	V 90/50	VI 90/0
LITTERS WITH ONE OR MORE LIVE FETUSES	N	5	5	3	4	5	5
IMPLANTATIONS	MEAN±S.D.	9.6 ± 1.7	9.2 ± 1.9	8.3 ± 0.6	8.5 ± 1.3	7.8 ± 2.8	10.6 ± 2.6
LIVE FETUSES	N	47	33	13	26	23	43
	MEAN±S.D.	9.4 ± 1.7	6.6 ± 3.0	4.3 ± 3.5	6.5 ± 2.9	4.6 ± 3.0	8.6 ± 2.1
LIVE MALE FETUSES	N	21	19	8	13	14	22
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	44.2 ± 8.1	56.4 ± 10.8	70.8 ± 26.0	47.2 ± 19.0	71.6 ± 29.4	50.1 ± 15.4
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	47.14 ± 4.04	46.61 ± 3.35	49.74 ± 7.64	46.46 ± 7.20	43.49 ± 9.78	46.30 ± 3.88
MALE FETUSES	MEAN±S.D.	47.88 ± 4.67	47.65 ± 2.49	49.71 ± 8.07	46.04 ± 7.30	42.74 ± 11.39	45.39 ± 4.83
FEMALE FETUSES	MEAN±S.D.	46.32 ± 3.99	45.40 ± 4.82	45.34 ± 2.10 [2]b	46.86 ± 7.03	40.78 ± 3.83 [3]c	47.80 ± 1.98
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	2.0 ± 4.5	30.1 ± 27.2	46.3 ± 44.6	26.1 ± 23.5	45.4 ± 24.1	16.2 ± 20.1

[ ] - NUMBER OF VALUES AVERAGED
a. Dosage occurred on days 6 through 18 of gestation. Dosage is expressed as naproxen sodium/sumatriptan base.
b. Litter 8461 had no female fetuses.
c. Litters 8471 and 8473 had no female fetuses.

(reproduced directly from eNDA 21-996, Module 4, Page 6812)

Oral (Gavage) Dosage-Range Developmental Toxicity Study of MT 400 in Rats

(POZEN Study #MT400-T09; [redacted] Protocol #2216-009P; Completed 10 OCT 2003; GLP; QA; Naproxen Sodium (NAP) Lot #NPXNAM-126, Purity 99.5%; Sumatriptan Succinate (SS) Lot QT0 1002, Purity 99.4%, dosed calculated as base; eNDA 21-996, Module 4, Page 6647)

Methods:
Five presumed pregnant F[redacted]:CD®(SD)IGS BR VAF/Plus® rats were assigned to each of the following groups: 0/1000, 25/50, 25/250, 25/500, 25/1000, and 25/0 mg/kg/day NAP/SS, and treated via gavage at 10 mL/kg once daily on DG 7-17 (days of gestation). Observations included viability checks (2X/day), clinical signs (for ~1 hr postdose), body weight (BW, daily), and food consumption (DG 0, 7, 10, 12, 15, 18, and 21). All surviving rats were sacrificed on DG 21 and examined for the number and distribution of corpora lutea, implantation sites, and uterine contents. Gross necropsy of the thoracic, abdominal, and pelvic viscera was performed. Fetuses were weighed and examined for gross external alterations and sex.

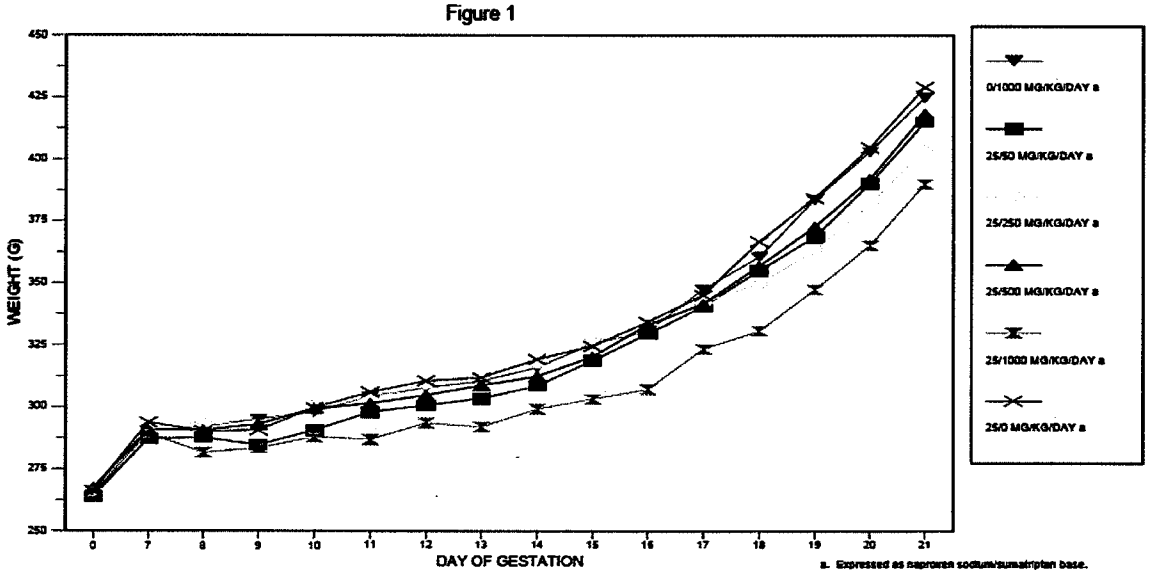
Results:
No treatment-related mortality or clinical signs were observed. Maternal body weight gains were reduced during the dosage treatment period (DG 7-18) in combination dosage groups (68.0, 57.4, 66.2, and 41.6 g at 25/50, 25/250, 25/500, and 25/1000 mg/kg/day NAP/SS, respectively) compared to NAP alone (73.0 g at 25/0) and SS alone (70.4 g at 0/1000) groups. No significant differences in final BW were observed *(note the lack of a vehicle control group).* Food consumption was reduced in the 25/1000 groups compared to all other groups, but only during the dosing period. No dead fetuses were observed. All C-section and litter parameters examined were comparable among groups, except that fetal body weights were dose-dependently reduced in the 25/250, 25/500, and 25/1000 mg/kg/day groups compared to groups 0/1000 and 25/0. No treatment-related fetal gross external malformations or variations were observed. One fetus with a cleft palate from a dam treated at 25/500 mg/kg/day was not considered treatment-related.

Conclusions:
Based on these results, dosages of up to 25/1000 mg/kg/day NAP/SS are expected to produce tolerable maternal and fetal toxicity in rats (reduced maternal BWG during treatment, and reduced fetal BW at $\geq$ 25/250 mg/kg/day NAP/SS).

PROTOCOL 2216-009P: ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF MT 400 IN RATS
(SPONSOR'S STUDY NUMBER: MT 400-T09)

MATERNAL BODY WEIGHTS

Figure 1



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PROTOCOL 2216-009P: ORAL (GAVAGE) DOSAGE-RANGE DEVELOPMENTAL TOXICITY STUDY OF MT 400 IN RATS
(SPONSOR'S STUDY NUMBER: MT 400-T09)

TABLE 8 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY

GROUP DOSAGE (MG/KG/DAY)a,b		I 0/1000	II 25/50	III 25/250	IV 25/500	V 25/1000	VI 25/0
LITTERS WITH ONE OR MORE LIVE FETUSES	N	5	5	4	4	5	5
IMPLANTATIONS	MEAN±S.D.	16.6 ± 1.3	14.8 ± 2.6	16.2 ± 2.2	17.5 ± 3.3	15.6 ± 1.1	17.6 ± 2.6
LIVE FETUSES	N	78	73	60	68	72	85
	MEAN±S.D.	15.6 ± 0.9	14.6 ± 2.7	15.0 ± 1.8	17.0 ± 2.9	14.4 ± 1.1	17.0 ± 2.1
LIVE MALE FETUSES	N	44	35	29	35	43	39
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	56.7 ± 12.4	48.1 ± 12.6	48.9 ± 18.7	50.5 ± 15.5	60.1 ± 20.8	45.5 ± 5.6
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	5.11 ± 0.33	5.46 ± 0.10	4.95 ± 0.64	4.88 ± 0.20	4.86 ± 0.42	5.23 ± 0.23
MALE FETUSES	MEAN±S.D.	5.21 ± 0.31	5.59 ± 0.20	5.08 ± 0.52	5.04 ± 0.15	4.92 ± 0.45	5.34 ± 0.21
FEMALE FETUSES	MEAN±S.D.	5.02 ± 0.37	5.33 ± 0.12	4.85 ± 0.66	4.72 ± 0.20	4.81 ± 0.42	5.14 ± 0.25
% RESORBED CONCEPTUSES/LITTER	MEAN±S.D.	5.8 ± 3.9	1.4 ± 3.2	7.6 ± 2.0	2.6 ± 3.0	7.3 ± 9.6	3.1 ± 4.4
		NO FETAL ALTERATIONS WERE IDENTIFIED AT GROSS EXTERNAL EXAMINATION					

a. Dosage occurred on days 7 through 17 of gestation.
b. Expressed as naproxen sodium/sumatriptan base.

(reproduced directly from eNDA 21-996, Module 4, Page 6665)

2.6.6.7 Local tolerance

No local tolerance studies were submitted.

2.6.6.8 Special toxicology studies

No special toxicology studies were submitted.

2.6.6.9 Discussion and Conclusions

Repeat-Dose Toxicology Studies

In the pivotal 90-day repeat-dose toxicology study in mice (MT400-T19), high dose naproxen sodium (NAP) induced gastrointestinal toxicity characteristic of NSAIDs: ulcer, erosion, and inflammation of the glandular stomach. In female mice, the GI toxicity induced by NAP (50 mg/kg/day) was observed in the presence or absence of high dose sumatriptan sodium (SS, 320 mg/kg/day reduced to 210 mg/kg/day in Wk 4), but was increased in incidence and severity in the presence of SS, despite a 31% **lower** Day 90 NAP AUC in the presence of SS. In the absence of other explanations, the exacerbation of NAP-induced GI toxicity by SS must be considered as a real possibility.

Male mice in study MT400-T19 treated with HD NAP (100 mg/kg/day) alone showed no GI toxicity, while those given the HD combination (320/100 mg/kg/day SS/NAP) characteristic NAP-related toxicity. The difference in toxicity between these two groups could be related to the 37.5% higher NAP exposure in the SS/NAP group (Day 90 AUC). Also, it is not clear why females in the HD SS/NAP group showed greater toxicity than the males, since their NAP exposures appeared to be similar (Day 90 $AUC_{0-\infty}$ = 381 ug*hr/mL F, 363 ug*hr/mL M).

Other treatment-related findings in study MT400-T19 were consistent with compensatory changes secondary to the GI toxicity induced by NAP: mild increases in WBC count, neutrophils, reticulocytes and platelets; increased absolute and relative spleen weights (correlated with increased erythroid extramedullary hematopoiesis); mild reductions in RBC count, HGB, and HCT; and decreased serum total protein and albumin.

HD recovery groups (4-wks off drug) showed decreased incidence and severity of the NAP-related GI toxicity, suggesting at least partial reversibility.

A 28-day study of SS and NAP alone and in combination was conducted in female minipigs, but the sponsor considered this study to be compromised by findings that the dosing solutions were for NAP and SS were ~15.5% greater and ~26% lower than targeted concentrations. Moderate to marked gastric ulcers/erosions (and associated secondary changes similar to those mentioned above) were observed in 3/3 animals in groups 0/125, 0/100, and 150/100 mg/kg/day SS/NAP, but lower incidence and severity were seen at 100/100, 50/100, and 10/100. The reasons for these differences are not clear, and TK data was not analyzed because the sponsor was informed that a non-rodent study would not be required.

Two 28-day rat studies with SS and/or NAP demonstrated NAP-dependent changes in hematology and clinical chemistry consistent with findings of regenerative anemia associated with gastrointestinal toxicity (inflammation, erosion, and ulceration) and renal toxicity (tubular dilatation and/or regeneration) observed in prior rodent studies. No increase in these NAP-related toxicities was seen in the presence of SS, but no histopathological evaluations were conducted.

A 28-day mouse study (MT400-T02) demonstrated NAP-related GI toxicity (and mortality in F) and kidney toxicity in the presence and absence of SS. NAP-related lesions observed included inflammation, erosion, and ulceration of the glandular stomach, trace erosions in duodenum and jejunum, and renal tubular dilatation and/or regeneration. Other changes observed were considered secondary to the GI toxicity induced by NAP, and included regenerative macrocytic hypochromic anemia, increased white blood cell and neutrophils counts, decreased serum albumin, peritonitis, increased total bone marrow erythroid and granulocytic cells, enlarged mesenteric lymph nodes and spleens, increased liver and spleen weights, and extramedullary hematopoiesis of liver and spleen. NAP-related toxicity was not exacerbated by coadministration of SS in this study in males or females, even though NAP exposures (AUC) were consistently increased with SS in F mice.

Similar primary and secondary NAP-related toxicities were observed in the original 90-day study with SS and NAP in mice (MT400-T05). In this study, primary changes included GI inflammation, erosion, ulceration, and hyperplasia (mostly in the glandular stomach); and mild renal tubular dilatation. Secondary changes included regenerative macrocytic hypochromic anemia, decreased serum albumin and total protein, myeloid hyperplasia, extramedullary hematopoiesis of liver and spleen, and thymic atrophy/necrosis. Recovery groups demonstrated reversibility of almost all changes, with only trace to mild inflammation and/or hyperplasia of glandular stomach observed. Mortality rates and GI toxicity were increased in M and decreased in F HD SS/NAP groups compared to the corresponding HD NAP alone groups at the same NAP dosage. However, these differences could be at least partially explained by the differences in NAP exposure in HD NAP groups, which was increased 51% in M with HD SS and decreased 37% in F with HD SS coadministration (based on NAP $AUC_{0-\infty}$ Day 90). The conclusions reached in this study must be interpreted cautiously due to failure to achieve consistent accuracy and homogeneity of the dosing solutions.

In examining the question of whether or not SS can exacerbate the known GI toxicity of NAP, the evidence from the three mouse studies summarized above is mixed. In the pivotal 90-day study (MT400-T19), the HDF SS/NAP group showed greater GI toxicity than the corresponding HDF NAP alone group, despite 31% lower NAP AUC in the SS/NAP group. In the same study HDM SS/NAP mice showed greater GI toxicity than HDM NAP alone mice, but this could be because NAP exposure was 37.5% higher in the SS/NAP group. In the original 90-day mouse study (MT400-T05), greater GI toxicity in HDM SS/NAP correlated with increased NAP exposure, and lower toxicity in HDF SS/NAP correlated with lower NAP exposure when compared with their corresponding HD NAP alone groups. Finally, in the 28-day mouse study (MT400-T02), NAP-related GI toxicity was similarly extensive in the presence or absence of SS in both M and F, even though NAP exposures were higher in F with SS.

Taken together, the mouse data are equivocal: SS/NAP groups showed greater GI toxicity than NAP alone groups in F (MT400-T19), M (MT400-T19), and M (MT400-T05) (with the latter two possibly being explained away by NAP exposure differences), but not in F (MT400-T05), M (MT400-T02), or F (MT400-T02). Of the three studies, this reviewer considers study MT400-T02 to be the most reliable. Technical problems associated with study MT400-T19 included abnormally high early deaths due to gavage trauma and lower urinary tract obstruction and lowering of the HDF SS dose from 320 to 210 after 4 weeks, and some other unusual procedures. Technical problems associated with study MT400-T05 included unacceptable variation in the concentration of the dosing formulations in 14-25% of samples, unacceptable inhomogeneity of dosing formulations of some samples, and unexplained detection of drug in plasma from control animals. Study MT400-T02 appeared to be free of technical problems, and allowed comparison of a toxic concentration of NAP alone and in combination with three different concentrations of SS in both M and F. Examination of the frequency of erosions/ulcers in this experiment (see table below) clearly demonstrates that coadministration of the highest dose of SS (500 mg/kg/day) with 75 mg/kg/day did not exacerbate the GI toxicity induced by 75 mg/kg/day NAP in M or F. The occurrence of one or two ulcers/erosions in M at 160/75 and 320/75 and not in M at 0/75 mg/kg/day SS/NAP seems likely to be due to variation at this threshold toxic dose of NAP in M rather than to the presence of SS, since no ulcers/erosions were seen in M given 500 mg/kg/day SS with 75 mg/kg/day NAP.

Animals with Ulcers/Erosions in 28-Day Mouse Study (N=10/sex/group)					
SS/NAP mg/kg/day	0/0	0/75	160/75	320/75	500/75
Male mice	0	0	1E	2E	0
Female mice	0	5U, 2E	2U, 1E	1U, 2E	1E

(Reviewer's Table; U=Ulcer, E=Erosion; U and E were mutually exclusive in this experiment)

The 28-day minipig and the two 28-day rat studies did not show increased NAP-related toxicity in the presence of SS, but the value of these studies is limited by the inaccuracy of the dosing solutions of the minipig study and the lack of histopathology data in the rat studies.

All toxicities observed in the general toxicology studies were attributed to NAP rather than to SS.

Below is a table of Cmax and AUC values to allow comparison of exposures between mice at the effect and no-effect doses and expected human exposures at the maximum recommended dose:

Sumatriptan Exposure Ratios

Species	Dose	Cmax (ng/mL)	Cmax Ratio	$AUC_{0-\infty}$ (ng*hr/mL)	$AUC_{0-\infty}$ Ratio	Treatment-Related GI Toxicity?
Humans (Study MT400-101*)	1 tablet	74.9	--	270	--	--
HDF SS/NAP 90-Day Mouse	320(210)/ 50 mg/kg	6860	92	21093	78	Ulcer/erosion (4/10, 1/10 rec)
NOEL SS/NAP 90-Day Mouse	100/30 mg/kg	2001	27	9380	35	No
HDF SS 90-Day Mouse	320(210) mg/kg	7451	99	22591	84	No
HDM SS/NAP 90-Day Mouse	320/100 mg/kg	9657	129	39730	193	Ulcer/atrophy/ hyperplasia (3/10)
NOEL SS/NAP 90-Day Mouse	100/30 mg/kg	2515	34	8217	30	No
HDM SS 90-Day Mouse	320 mg/kg	10415	139	29423	109	No

Naproxen Exposure Ratios

Species	Dose	Cmax (ug/mL)	Cmax Ratio	$AUC_{0-\infty}$ (ug*hr/mL)	$AUC_{0-\infty}$ Ratio	Treatment-Related GI Toxicity?
Humans (Study MT400-101*)	1 tablet	69.7	--	1548	--	--
HDF SS/NAP 90-Day Mouse	320(210)/ 50 mg/kg	99.7	1.4	381	0.25	Ulcer/erosion (4/10, 1/10 rec)
NOEL SS/NAP 90-Day Mouse	100/30 mg/kg	74.3	1.1	369	0.24	No
HDF NAP 90-Day Mouse	50 mg/kg	123	1.8	553	0.36	Erosion (1/10)
HDM SS/NAP 90-Day Mouse	320/100 mg/kg	103	1.5	363	0.23	Ulcer/atrophy/ hyperplasia (3/10)
NOEL SS/NAP 90-Day Mouse	100/30 mg/kg	52	0.75	154	0.10	No
HDM NAP 90-Day Mouse	100 mg/kg	108	1.5	264	0.17	No

(*Human Values are Geometric Means (N=8) from Clinical Study Report MT400-101)
(Mouse values are from Day 90; "rec" = 4 week recovery group; Reviewer's Tables)

Mean NAP plasma exposures ($AUC_{0-\infty}$) at the combined SS/NAP dose NOEL were 0.10-0.24 times those in humans at the maximum recommended dose of TREXIMA. However, it is generally recognized that rodents are more sensitive than humans to the GI toxicity of NSAIDs, and NSAID-related GI toxicity in humans is well described in the labels for all marketed NSAIDs and in the proposed label for Trexima. Mean SS plasma exposures ($AUC_{0-\infty}$) at the combined SS/NAP dose NOEL were 30-35 times those in humans at the maximum recommended dose of TREXIMA. Sumatriptan succinate alone was not toxic in this study at 320/(210) mg/kg/day in F, and at 320 mg/kg/day in M, yielding wide margins of safety: 84-fold and 109-fold in F and M, respectively, above expected human exposures, based on AUC.

Despite the wide margins of safety for SS described above, the lack of a MTD for SS in all mouse studies submitted to this NDA is an issue that remains to be addressed. In the 28-day mouse dose-ranging study with SS and NAP (MT400-T02), 500 mg/kg/day was chosen as the highest dose of SS based largely on the acute oral LD_{50} in mice of ~1.2 g/kg reported in the FDA supervisory overview of pharmacology and toxicology for SS in NDA 20-132 (IMITREX® Tablets). However, no toxicity was attributed to SS in the group given 500/75 mg/kg/day SS/NAP or the group given 160 mg/kg/day SS alone in Study MT400-T02. Similarly, in the first 90-day mouse study (Study MT400-T05), no SS-related toxicities were observed up to the highest doses studied (320 [M] or 210 [F] mg/kg/day SS alone and 320 mg/kg/day SS in combination with NAP). Likewise, no SS-related toxicity was reported in the second 90-day mouse study at the highest doses used (320 [M] and 320 lowered to 210 Wk 4 [F] mg/kg/day SS). Finally, in the in vivo mouse micronucleus study (MT400-T08), single oral doses of SS up to 1500 mg/kg (M) and 1625 mg/kg (F) induced no observable changes in mortality, clinical signs, or body weight when given in combination with 500 mg/kg (M) or 375 mg/kg (F) NAP.

Genotoxicity

The genotoxic potential of SS and NAP, alone and in combination, was assessed in an *in vitro* bacterial mutagenicity assay, an *in vivo* mouse micronucleus assay, and two *in vitro* chromosomal aberrations assays in mammalian cells.

In the bacterial mutagenicity assay, SS and NAP alone up to 5000 ug/plate, or in combination 1:1 at up to 2500/2500 ug/plate were negative for induction of reverse mutations in all bacterial strains tested.

In the *in vivo* mouse micronucleus assay, SS and NAP, given via oral gavage alone and in combination at up to maximum tolerated doses (1500 mg/kg SS and 500 mg/kg NAP in males and 1625 mg/kg SS and 375 mg/kg NAP in females), were negative for induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells.

In the initial CHO cell chromosome aberrations assay, cultures treated with the highest doses of NAP showed increased frequency of chromosomal aberrations in the presence or absence of SS in the presence or absence of S9 metabolic activation. The frequency of chromosome aberrations was increased more in cultures treated with SS/NAP (10% at **2500/2500 ug/mL –S9; 11% at 2000/2000 ug/mL +S9**) than with NAP alone (4.5% at **5000 ug/mL –S9; 4.0% at 2500 ug/mL +S9), in spite of the much lower NAP** concentration in the SS/NAP cultures. The levels of cytotoxicity in the groups considered positive for increased frequency of chromosomal aberrations were well within the acceptable range for this type study (Relative Mitotic Index [RMI] ranged from 37% to 20% of control values, and Relative Cell Growth [RCG] ranged from 76% to 41%)

A follow-up non-GLP chromosomal aberrations assay in CHO BWL cells was conducted to test the hypothesis that the positive clastogenic results obtained in the initial CHO cell chromosome aberrations assay with high concentrations of NAP and SS/NAP might have occurred because direct addition of the test articles to the culture media covering the cells produced transient locally high concentrations of test article. The results demonstrated that mixing the drugs with fresh medium before addition to the cells (indirect addition) made no difference, as clastogenicity was comparable to the positive control in both cultures treated with SS/NAP at 2500/2500 ug/mL **–S9 (25% cells with aberrations via** direct addition of drugs; 28% via indirect addition; 26% w/positive control). Again, cytotoxicity levels were moderate, but well within the acceptable range for this assay (RMI = 24% and 33%; RCG = 44% and 47%, in cultures with direct vs. indirect addition, respectively).

The sponsor considered the positive results at only the highest doses of NAP in the **chromosomal aberrations assays above to be a "threshold effect" "most likely associated** with NAP-induced alterations in cell division and increased apoptosis, which have been reported in the literature for other drugs of this **class" rather than a** direct genotoxic effect (eNDA 210926, Module 2, Section 2.6, Page 20). However, the Relative Cell Growth (RCG) values associated with positive clastogenicity findings were 76-41%, approximately equal to the desired level of toxicity of >50% reduction in cell number for this assay. These RCG values are not indicative **of conditions of "very low survival" at which non-direct genotoxic mechanisms can lead to "positive" results related to** cytotoxicity *(see ICH S2A [1996] "Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals").* Therefore, these data suggest that naproxen may have a direct genotoxic effect on mammalian cells at high concentrations.

SS was not genotoxic alone, but there was some evidence to suggest that SS might exacerbate the genotoxicity of NAP.

Carcinogenicity

No carcinogenicity studies were submitted for Trexima, and none were required, since the components are currently marketed in the U.S. for chronic or chronic/intermittent use, and since the new non-clinical studies conducted with SS/NAP did not yield any findings suggesting increased carcinogenic potential for SS/NAP in combination compared to SS or NAP alone.

The labeling for Imitrex describes a 104-week rat carcinogenicity study at up to 160 mg/kg/day SS (~15 times the maximum recommended single human oral dose [MRHD] of 100 mg on a mg/m^2 basis dose); and a 78-week mouse carcinogenicity study at up to 160 mg/kg/day SS via drinking water (average exposures were ~40X those at the MRHD). Neither study showed a treatment-related increase in tumors.

The labeling for Anaprox describes a 2-year rat carcinogenicity study at up to 24 mg/kg/day NAP in which no evidence of tumorigenicity was found. Maximum exposures in rat plasma were 0.28 times the systemic exposure at the MRHD.

In addition, the sponsor of the current NDA conducted a 2-year rat carcinogenicity study in which a comparator group was treated with a maximum tolerated oral dose of NAP. Plasma exposures in males and females averaged 0.1-0.3 times the systemic exposure to NAP in humans given one Trexima tablet [redacted].

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies with SS and NAP included a definitive embryo-fetal development study in pregnant rabbits, and dose-ranging embryo-fetal development studies in rabbit and rat. The normal requirements for a definitive embryo-fetal development study in rats, a fertility study in rats, and a peri-/post-natal developmental toxicity study in rats were waived because the components of TREXIMA® are currently marketed in the U.S. for chronic or chronic/intermittent use.

In the definitive embryo-fetal development study in rabbits, significant reductions in maternal and fetal weights were observed even at the lowest combination dose tested, 9/5 mg/kg/day NAP/SS, so a NOAEL was not established. This dose was associated with mean plasma exposures ($AUC_{0-\infty}$) that were 0.14 and 1.4 times the exposures to NAP and SS, respectively, attained in humans at the recommended dose of TREXIMA®.
Effects of NAP and SS on maternal BW appeared to be additive, as reductions in the 90/50 group were greater than those in the 90/0 or 0/50 group. Mean fetal BW/litter was reduced 11-14% in groups 9/5, 45/25, and 0/50, but reductions in groups 90/50 and 90/0 did not reach significance, perhaps due to decreases in numbers of litters and litter size.

High dose NAP alone (90/0) and NAP/SS (90/50) groups showed significant reductions in litter size, and increases in total resorptions per litter, early resorptions per litter, percent of dead or resorbed conceptuses per litter, and in the number of does with any resorptions. These parameters showed slightly greater increases in the 90/0 group compared to the 90/50 group. Low dose (9/5) and mid-dose (45/25) SS/NAP groups, and the HD SS alone (0/50) group showed non-significant increases in numbers of early or late resorptions, average number of total resorptions, and percent dead or resorbed conceptuses per litter. The highest no-effect dose for these toxicities was 25/45 mg/kg/day sumatriptan/naproxen, which was associated with plasma exposures ($AUC_{0-\infty}$) to naproxen that were 0.84 times those attained at the maximum recommended single human oral dose of one tablet of TREXIMA.

The highest percentage of fetal alterations was observed in groups 90/50 and 90/0, with increases in the incidences of specific malformations (interventricular septal defect in group 90/50, and fused caudal vertebrae in both 90/50 and 90/0 groups) and variations (absent intermediate lobe of the lung, irregular ossification of the skull, and incompletely ossified sternal centra in both groups). Except for the finding of isolated interventricular septal defects described above in group 90/50, the toxicities reported for groups 90/50 and 90/0 are quite similar in this study, suggesting that the combination of SS and NAP is not likely to induce greater reproductive and developmental toxicity than NAP alone. The highest no-effect level for teratogenicity in rabbits given the NAP/SS (45/25 mg/kg) was associated with mean plasma exposures ($AUC_{0-\infty}$) that were 0.84 and 14 times the exposures to NAP and SS, respectively, observed in humans at the recommended dose of TREXIMA®.

In the rabbit dose-ranging study, maternal body weight gain was reduced with increasing dose of SS in combination with the high dose of NAP (groups 90/1, 90/5, 90/15, and 90/50 mg/kg/day NAP/SS), compared to groups with NAP alone (90/0) and SS alone (0/50) but only during the dosing period. Increases in numbers of early resorptions, numbers of litters with resorptions, and percentage of resorbed conceptuses per litter were observed in groups 90/1, 90/5, 90/15, 90/50, and 90/0 compared to group 0/50. In contrast to the findings in the definitive rabbit study described above, these parameters showed greater increases in the 90/50 group compared to the 90/0 group. Average fetal BW was reduced only at 90/50 (based on only 14 fetuses). Gross external malformations were observed in two fetuses at 90/1 (one with gastroschisis and one with a short tail), and in two fetuses (one with gastroschisis and one with a short tail) and two late resorptions (one with acrania, gastroschisis, medial rotation of right hindlimb, short tail, and fused forepaw digits; and one with gastroschisis, downward flexed forepaws, absent tail, no anal opening, and no external urogenital area) at 90/50. Thus, while SS and NAP toxicities appeared to be additive with respect to maternal and fetal body weight changes, other measures of reproductive and developmental toxicity were attributed to the high dose of NAP.

In the rat dose-ranging study, maternal body weight gain was reduced during the dosing period in all NAP/SS combination groups (25/50, 25/250, 25/500, and 25/1000 mg/kg/day NAP/SS) compared to the NAP alone group (25/0) and the SS alone group (0/1000), with the largest reduction occurring in the group with the highest dose of NAP. Thus, the maternal toxicity of NAP and SS appeared to be additive in rats as well as in rabbits. Mean fetal BW/litter were also reduced in the 25/250, 25/500, and 25/1000 mg/kg/day groups compared to the 25/0 and 0/1000 groups, suggesting that fetal toxicity was additive as well. No treatment-related changes in C-section or litter parameters, or in fetal gross external malformations or variations were observed.

Taken together, the three embryo-fetal toxicity studies demonstrated that NAP and SS toxicities resulting in reduction maternal and fetal body weights appeared to be additive. In contrast, increases in resorption parameters and incidence of malformations and variations observed in animals treated with HD NAP were not consistently exacerbated by coadministration of HD SS. Also, the teratogenic effects attributed to NAP were only observed at doses well above those that were maternally toxic.

Impurities in the Drug Substance

Sumatriptan succinate drug substance batch #K034010, used for the pivotal clinical trials with TREXIMA, contained two identified single impurities, and possible unidentified single impurities, at levels exceeding the qualification threshold [redacted]. These values also exceeded those in sumatriptan succinate batches used in the nonclinical studies (K026882, QT01002, and QT01004). However, qualification by conducting additional nonclinical studies is not necessary in this case, because the sponsor has a right of reference to the approved NDAs for IMITREX® products, and can therefore adopt a drug substance specification based on the limits for the approved products. The sumatriptan succinate in TREXIMA is manufactured by Glaxo Wellcome Manufacturing Pte Ltd, and the synthesis is described in NDA 20-080 for IMITREX® Injection.

The level of the largest single impurity in all clinical and non-clinical batches of naproxen sodium drug substance was < 0.1%, which is below the thresholds for identification (> 0.10%) and qualification (> 0.15%).

2.6.6.10 Tables and Figures

Tables and Figures were included within the text.

2.6.7 TOXICOLOGY TABULATED SUMMARY

[see eNDA 21-996, Module 2, Section 2.6.7, Pages 73-163]

OVERALL CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

The nonclinical package submitted in support of the NDA for Trexima was designed to address four key questions:

1. Does naproxen sodium have the potential to exacerbate the known vasoconstrictive properties of sumatriptan?
2. Does the combination of naproxen sodium and sumatriptan succinate have the potential to induce new toxicities, or to exacerbate the known target organ toxicities of either agent alone?
3. Does the combination of naproxen sodium and sumatriptan succinate, or either agent alone, have the potential to be genotoxic?
4. Does the combination of naproxen sodium and sumatriptan succinate, or either agent alone, have the potential for embryofetal toxicity or teratogenicity?

Does naproxen sodium have the potential to exacerbate the known capacity of sumatriptan to induce coronary artery vasoconstriction?
This question was addressed by conducting a cardiovascular safety pharmacology study in 6 female beagles surgically implanted with tiny electronic devices and probes to collect information on coronary artery diameter, carotid artery diameter, blood pressure and several other parameters at baseline and after IV injection of SS in the presence or absence of NAP, infused for 1 minute just prior to the SS injection. Unfortunately, no reliable conclusions can be drawn from this study due to wide inter-individual and intra-individual variation observed in most parameters measured and serious design flaws. The most serious design flaw was the omission of a vehicle control injection for SS. Without this control (or a low, ineffective dose of SS) it is not clear whether the minimal or maximal changes from baseline parameters recorded in the one hr after SS injection are due to the injection procedure, the vehicle, natural variation, or the SS. Hence, it is not clear that any SS-induced changes were measured here, so the meaning of any effects (or lack of effects) of NAP on these changes is questionable. Other design flaws included insufficient numbers of dogs per group and insufficient numbers of repetitions of treatments to detect a significant NAP-induced change in the predicted SS-induced ~5% reduction in the coronary artery diameter (and similarly small changes in other parameters).

Does the combination of naproxen sodium and sumatriptan succinate have the potential to induce new toxicities, or to exacerbate the known target organ toxicities of either agent alone?

This question was addressed in general toxicology studies conducted in mice (two 90-day studies and one 28-day dose-ranging study), rats (two 28-day dose-ranging studies), and minipigs (one 28-day dose-ranging study). In these studies, high dose NAP induced occasional renal toxicity (tubular dilatation and/or regeneration) and consistent gastrointestinal toxicity characteristic of NSAIDs (ulcer, erosion, and inflammation of the glandular stomach). Coadministration of SS did not consistently exacerbate these NAP-related toxicities. High dose SS alone was not toxic in these studies, and the combination of SS and NAP did not induce any new toxicities compared to SS or NAP alone.

On the other hand, the pivotal 90-day mouse study failed to adequately address this issue. The doses of SS used did not induce any SS-related toxicity, so it was impossible to assess the potential for NAP to exacerbate any SS-mediated toxicity. While it is true that the safety margins based on SS AUC comparisons of HD mouse groups with expected human exposures after one tablet of TREXIMA are ≥ 78-fold, it is still important to characterize the clinical signs and target tissue toxicities at a maximum tolerated dose of SS and of the combination of SS and NAP. No mouse studies submitted or cited by the sponsor describe any toxicity attributed to SS, except an acute oral LD_{50} in mice of ~1.2 g/kg reported in the FDA supervisory overview of pharmacology and toxicology for SS in NDA 20-132 (IMITREX® Tablets). The LD_{50} value of 1.2 g/kg is contradicted by the **results from the sponsor's in vivo mouse** micronucleus study (MT400-T08), in which single oral doses of SS up to 1500 mg/kg (M) and 1625 mg/kg (F) induced no observable changes in mortality, clinical signs, or body weight when given in combination with 500 mg/kg (M) or 375 mg/kg (F) NAP.

The pivotal 90-day mouse study also failed to use an appropriately high dose of NAP to adequately assess the potential for SS to exacerbate the known GI and kidney toxicity of NAP. No treatment-related kidney changes were observed in this study, and gastric lesions were described by the sponsor as **"very subtle," as evidenced by their low** incidence and minimal severity. No treatment-related mortality was observed in this study, and main study mice given the highest dose of NAP (± SS) showed only 2/40 ulcers and 3/40 erosions.

Finally, the results of the pivotal 90-day mouse study must be considered questionable considering certain unexpected complications and unusual procedures. High rates of early death triggered a reduction in the HD of SS from 320 to 210 mg/g/day in F at the beginning of Wk 4, even though the deaths turned out to be due to high rates of gavage error and fatal urinary tract obstruction (UTO, in M; 24 times higher than reported rates of spontaneous UTO in this strain). Some replacement animals were started two and a half weeks after the initiation of treatment. Also, the protocol was unusual in assigning the first 20 surviving mice per sex per group to the main study, and in specifying necropsy of the first 10 surviving mice per sex per group (in addition to mice found dead or sacrificed moribund).

Does the combination of naproxen sodium and sumatriptan succinate, or either agent alone, have the potential to be genotoxic?

The genotoxic potential of SS and NAP, alone and in combination, was assessed in an *in vitro* bacterial mutagenicity assay, an *in vivo* mouse micronucleus assay, and two *in vitro* chromosomal aberrations assays in mammalian cells. The results of the *in vitro* bacterial mutagenicity assay and *in vivo* mouse micronucleus assay were clearly negative in valid studies. In contrast, high dose NAP ± high dose SS was positive in the initial CHO cell chromosomal aberrations assay, in the presence or absence of metabolic activation, in association with moderate, but not excessive, cytotoxicity. This positive result was confirmed in a non-GLP follow-up study testing only HD NAP + HD SS in the absence of metabolic activation. In the original study, SS was not genotoxic alone, but there was some evidence to suggest that SS might exacerbate the genotoxicity of NAP: the frequency of chromosomal aberrations was increased more than 2-fold in HD NAP + HD SS cultures vs. HD NAP alone cultures with and without metabolic activation, despite 50% lower NAP concentrations in the NAP + SS cultures. Cytotoxicity was also increased in HD NAP + HD SS cultures vs. HD NAP alone cultures, but did not reach levels considered excessive.

Does the combination of naproxen sodium and sumatriptan succinate, or either agent alone, have the potential for embryofetal toxicity or teratogenicity?

This question was addressed by conducting a definitive embryo-fetal development study in pregnant rabbits, and dose-ranging embryo-fetal development studies in rabbit and rat. In the definitive embryo-fetal development study in rabbits, significant reductions in maternal and fetal weights were observed even at the lowest combination dose tested, but significant increases in resorption parameters and specific malformations and variations were only observed in HD NAP groups ± SS. The slight increases in specific malformations and variations attributed to HD NAP included interventricular septal defects, fused caudal vertebrae, absent intermediate lobe of the lung, irregular ossification of the skull, and incompletely ossified sternal centra.

The rabbit dose-ranging study showed reductions in maternal body weight gain (BWG) with increasing dose of SS in combination with the high dose of NAP, reduction of fetal BW at HD SS/NAP, increased resorption parameters at HD NAP ± SS, and increased gross external malformations at HD NAP + LD and HD SS. The rat dose-ranging study showed reduced maternal BWG and fetal BW with increasing SS dose in the presence of HD NAP, but no treatment-related changes in resorption parameters or fetal gross external malformations or variations. While there are no teratogenic effects described in the current labeling for ANAPROX®, there is evidence in the published literature that interventricular septal defects are increased after oral administration of other NSAIDs (ibuprofen, ketorolac, meloxicam, diflunisal, and aspirin; *see Cappon 2003, Cook 2003, and Moore 1998*).

Taken together, the three embryo-fetal toxicity studies demonstrated that NAP and SS toxicities resulting in reduction maternal and fetal body weights appeared to be additive. In contrast, increases in resorption parameters and incidence of malformations and variations observed in animals treated with HD NAP were not consistently increased further by coadministration of HD SS. Also, the teratogenic effects attributed to NAP were only observed at doses well above those that were maternally toxic.

Significant reductions in maternal and fetal weights were observed even at the lowest combination dose tested, 9/5 mg/kg/day NAP/SS, which was associated with mean plasma exposures ($AUC_{0-\infty}$) that were 0.14 and 1.4 times the exposures to NAP and SS, respectively, observed in humans at the recommended dose of TREXIMA®. The highest no-effect level for teratogenicity in rabbits given the NAP/SS (45/25 mg/kg) was associated with mean plasma exposures ($AUC_{0-\infty}$) that were 0.84 and 14 times the exposures to NAP and SS, respectively, observed in humans at the recommended dose of TREXIMA®.

The positive findings of embryofetal toxicity and teratogenicity described above warrant inclusion in the labeling for TREXIMA, and maintenance of the Pregnancy Category C rating.

Unresolved toxicology issues:

Does naproxen exacerbate the vasoconstrictive effects and/or the risk of coronary artery vasospasm of sumatriptan?

The potential for naproxen to exacerbate the known capacity of sumatriptan to induce coronary artery vasoconstriction remains unknown, due to the lack of a valid nonclinical study addressing this issue. It is not clear whether the wide intra-individual and inter-individual variation observed in the coronary artery diameter measurements in the completed study arose from inherent variability in this parameter, inappropriate experimental design (e.g., lack of a vehicle control for the SS injection), or technical problems associated with the implantation and/or performance of the ultrasonic dimension transducers in the left circumflex coronary artery. If technically feasible, a valid nonclinical study addressing this issue would require much higher numbers of animals, repeated measurements under identical conditions, inclusion of appropriate controls, and sufficient washout periods between treatments to allow for complete clearance of the drugs.

It is also not clear what should constitute a positive finding in such a study, or how such a finding should be interpreted with respect to the clinical risk of coronary artery vasospasm in humans given TREXIMA vs IMITREX. Carel et al. (2001, *Br J Pharmacol* 132:1071-1083) reported that IV sumatriptan induced a complex biphasic response (transient increase, followed by a sustained decrease) in coronary artery diameter in conscious dogs, while small coronary arteries showed increased blood flow and decreased resistance. Should the vasodilation phase be measured in addition to the vasoconstriction phase? Do significant changes in one or both of these parameters necessarily predict increased risk of coronary vasospasm with TREXIMA vs IMITREX? Would lack of significant changes in one or both of these parameters necessarily rule out increased risk of coronary vasospasm with TREXIMA vs IMITREX?

This reviewer believes that questions concerning the technical feasibility, as well as the interpretability, of a new cardiovascular safety pharmacology study in dogs to address this issue argue against requiring such a study as a condition for approval of TREXIMA.

Does the combination of naproxen sodium and sumatriptan succinate have the potential to induce new toxicities, or to exacerbate the known target organ toxicities of either agent alone?

This issue remains unresolved because the pivotal 90-day mouse study failed to include a Maximum Tolerated Dose of SS, failed to include doses of NAP that induced moderate GI and kidney toxicity, and was complicated by high rates of early death due to gavage errors and fatal urinary obstruction and unusual procedures.

A new 90-day repeated dose general toxicity study should be conducted with SS and NAP, including Maximum Tolerated or Maximum Feasible Doses of each drug for each sex, alone and in combination.

Does sumatriptan potentiate the clastogenicity of naproxen?

The potential for sumatriptan to potentiate the clastogenicity of naproxen in mammalian cell culture systems under conditions of moderate, but not excessive, cytotoxicity remains unresolved. This could be sorted out by conducting additional experiments with multiple concentrations of NAP ± SS near those found to be positive in the initial CHO cell chromosomal aberration assays. However, the clinical importance of this question is not clear, since carcinogenicity studies in rats have demonstrated that NAP is not tumorigenic at maximum tolerated doses in rats (though the plasma exposures to NAP in those studies was ≤ 0.28 times that in humans at the maximum recommended oral dose of NAP).

This reviewer believes that additional genotoxicity studies to address this issue should not be required as a condition for approval of TREXIMA.

Recommendations:

The nonclinical package is adequate to support an approvable action for NDA 21-926 TREXIMA (sumatriptan succinate/naproxen sodium) Tablets for the acute treatment of migraine.

To investigate the potential of the combination of sumatriptan succinate and naproxen sodium to induce new toxicities, or to exacerbate the known target organ toxicities of either agent alone, the sponsor should be required to conduct a new 90-day repeated dose general toxicity study with SS and NAP, including Maximum Tolerated or Maximum Feasible Doses for each sex, of each drug, alone and in combination.

Post-marketing adverse event reports should be monitored carefully for signals indicative of increased risk of events related to vasospasm or vasoconstriction with TREXIMA vs. IMITREX, based on possible pharmacodynamic interactions between naproxen and sumatriptan.

Draft Language for Letter to Sponsor:

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/s/

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Please see separate memo for comments.