Clinical Pharmacology Review

PRODUCT (Generic Name):	Sumatriptan & Naproxen Sodium
PRODUCT (Brand Name):	TREXIMET®
sNDA:	21-926/s-012
DOSAGE FORM:	Tablet
DOSAGE STRENGTHS:	10 mg sumatriptan and 60 mg naproxen sodium
INDICATION:	Migraine with or without aura in pediatrics 12 yr and above
SUBMISSION DATE:	11/14/2014
SPONSOR:	Pernix Therapeutics Inc.
Clin Pharm REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I

Executive Summary and Recommendation:

TREXIMET® is a fixed-dose combination product of sumatriptan (a $5HT_{1B/1D}$ agonist) and naproxen sodium (a non-steroidal anti-inflammatory drug, NSAID). It was approved on April 15, 2008, for the acute treatment of migraine with or without aura in adults. The currently marketed formulation is a bilayer tablet containing 85 mg sumatriptan (as sumatriptan succinate) and 500 mg naproxen sodium. The information provided in this supplement NDA, including a placebo-controlled efficacy trial (TXA107979), a pharmacokinetic (PK) study (TXA108504) and a long-term safety study (TXA107977), aims to support extending the current indication to adolescents 12 to 17 years old. The recommended dose for adolescents is a single tablet of TREXIMET® 10/60 mg (sumatriptan 10 mg and naproxen sodium 60 mg) per 24-hour period.

This sNDA is acceptable from a Clinical Pharmacology perspective provided agreement is reached for the Labeling with the sponsor. With this sNDA, the sponsor has fulfilled the requirements described in the Pediatric Written Request letter.

Summary of Efficacy trial and PK study:

- Efficacy Trial:

Sumatriptan oral tablets were ever evaluated in a clinical study of adolescent migraineurs with a range of doses (25, 50, and 100 mg) (Winter P, et al. *J Neurol Sci* 1997;150 Suppl:S172). For the pain-free endpoint, although all sumatriptan doses were numerically higher than placebo, the differences were not statistically significant at 2 hours, nor was there a clear separation between the sumatriptan doses. Due to the relatively flat dose-response curve observed in that trial (SUMA2002), a wider dose range of sumatriptan was evaluated in the current efficacy trial for TREXIMET® (TXA107979) to improve the ability to define a dose response. A typical pharmacological approach for dose selection and evaluation was taken, i.e., a three-fold increment between doses. The currently approved dose for TREXIMET® in adults is 85 mg sumatriptan and was chosen as the highest dose tested in the efficacy trial in adolescents. With a three-fold increment, the

other two doses selected were 10 mg and 30 mg of sumatriptan. The naproxen doses were changed accordingly in proportional to sumatriptan.

This efficacy trial (TXA107979) contained a placebo run-in phase and only non-responders to placebo were further randomized to drug treatments (three dose levels) or placebo groups. Single doses of 10/60 mg, 30/180 mg and 85/500 mg (sumatriptan/naproxen sodium) were shown to be effective as measured by the primary endpoint (the percentage of subjects who are pain-free at two hours post treatment). However, the higher doses did not provide a greater response than that of the 10/60 mg dose. Thus, the recommended dose proposed by the applicant for adolescents aged 12 to 17 years is a single tablet of TREXIMET® 10/60 mg (sumatriptan/naproxen sodium) per 24-hour period. The maximum single dose in adolescents is 85/500 mg per 24-hour period. The efficacy and safety of taking a second dose of TREXIMET® within a 24-hour period have not been established in adolescents. The 30/180 mg tablet is not intended to be marketed. There were no PK samples collected from the efficacy trial (TXA107979).

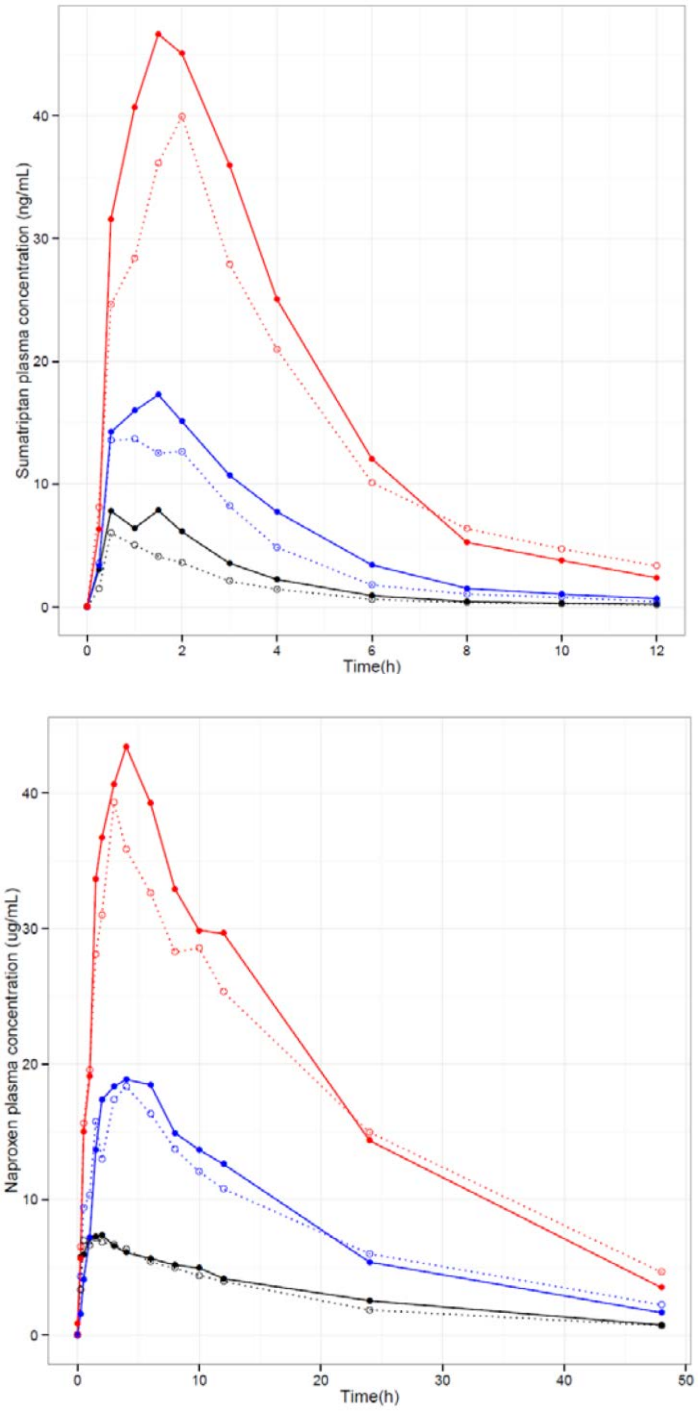
- PK Study:

The PK study was an open-label, randomized, parallel group study conducted in 24 adolescents migraineurs (outside a migraine attack) and in 26 healthy adults to compare exposure of sumatriptan and naproxen following single-dose administration of TREXIMET® tablets at three doses used in the clinical trials (10/60 mg, 30/180 mg and 85/500 mg). The bioanalytical methods used to determine sumatriptan and naproxen concentrations are the same as those described in the original NDA for adults.

Comparison of PK between adolescents and adults:

- Naproxen: Adolescents were shown to have similar or slightly higher plasma concentrations with adults at all the three doses (Table 7. the point estimates of geometric mean ratio (adolescents/adults) for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, or C_{max} were up to 1.16).
- Sumatriptan: At 85/500 mg dose, adolescents had slightly greater plasma concentrations than adults (up to 19% higher for $AUC_{0\text{-}2hr}$). The difference was larger at 10/60 mg dose, with adolescents having 50 – 60% higher $AUC_{0\text{-}2hr}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of sumatriptan than adults (Table 5).

Figure 1. Mean Plasma Concentration-Time Profiles for Sumatriptan (upper panel) and Naproxen (lower panel) across the Three Dosage Strengths



Solid lines = adolescents and dotted lines = adults
● 10/60 mg adolescents (n=7), ● 30/180 mg adolescents (n=8), ● 85/500 mg adolescents (n=9),
○ 10/60 mg adults (n=7), ○ 30/180 mg adults (n=8), ○ 85/500 mg adults (n=9)

Dose Proportionality:
Sumatriptan AUC increased in a dose proportional manner and its C_{max} increased just slightly less than dose proportional (Table 8). Naproxen AUC and C_{max} increased less than dose proportionally and this trend was more pronounced for C_{max} (Table 9) It is speculated that the less-than-dose-proportional increase of naproxen exposure is related

to the difference in formulations for different strengths and resulted different dissolution profiles of naproxen. The formulations of the three dosage strengths are of the same design (bilayer tablets) and contain the same excipients (except (b) (4)). (b) (4)

(b) (4)

(b) (4). All three strengths are manufactured using the same manufacturing process.

Table 1. Formulations and Product Batches Used in Clinical Studies of Efficacy, Safety and Pharmacokinetics

Dose Strength	TREXIMET Tablets 10/60 mg		TREXIMET Tablets 30/180 mg		TREXIMET Tablets 85/500 mg		Function[1]	Reference to Standard[1]
GSK R&D Tablet Batch Number GSK Commercial Manufacturing Site Tablet Batch Number	081166993 –	091214298 –	081161614 –	091214333 –	041015799 B916681	071140802 R303658	–	–
Clinical Studies Pivotal Efficacy Long Term Extension Safety Pharmacokinetics	TXA107979 – TXA108504		TXA107979 – TXA108504		– TXA107977 –	TXA107979 TXA107977 TXA108504	–	–
Component	Quantity per Tablet (mg)						–	–
Sumatriptan Layer								
(b) (4)								
Sumatriptan succinate[2]	14.0		(b) (4)		119.0		Active	GlaxoSmithKline
(b) (4) dibasic calcium phosphate							(b) (4)	USP/USNF
Microcrystalline cellulose								USNF
(b) (4)								USP
Total (b) (4)								–
(b) (4)								
								–
Sodium bicarbonate								USNF
(b) (4)								USP/USNF
								USNF
								USNF
								–
(b) (4)								
(b) (4)								
Naproxen sodium	60.0		(b) (4)		500.0		Active	USP
(b) (4)								
Film-coating								
(b) (4) Blue (b) (4)							(b) (4)	Supplier
(b) (4)								USP
Total (film-coated tablet)	**1004.25**		**1107.25**		**1107.25**		–	–

Note:
1. Applicable for all strengths.

(b) (4)

In vitro dissolution tests at pH of 6.8 demonstrated superimposed release profiles of sumatriptan from the three strengths. The comparable profiles of naproxen between 10/60 mg and 30/180 mg strengths were shown in Figure 3. A slower dissolution profile of naproxen was observed for the 85/500 mg strengths. Accordingly, in clinical setting, the T_{max} of naproxen plasma concentrations after a 10/60 mg dose was observed to be earlier (median: 1 hr, range: 0.25 – 4 hr) than the ones for 30/180 mg dose (median: 3 hr, range: 1.5 – 6 hr) and 85/500 mg (median: 3 or 4 hr, range: 1 – 9 hr or 2 – 9 hr). The pairwise comparison of AUC and C_{max} also showed that the less-than-dose-proportional increase of naproxen exposure is more obvious between the 85/500 mg and 30/180 mg strengths, while the increase of naproxen concentrations between the 10/60 mg and 30/180 mg strengths is closer to linearity (Table 2).

Figure 2. Comparison of Dissolution Profiles of Sumatriptan from 3 Dosage Strengths of TREXIMET® Tablets

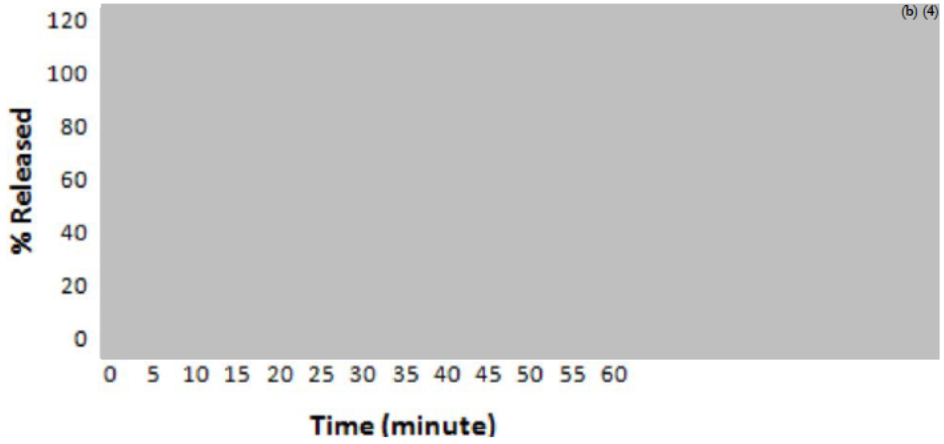
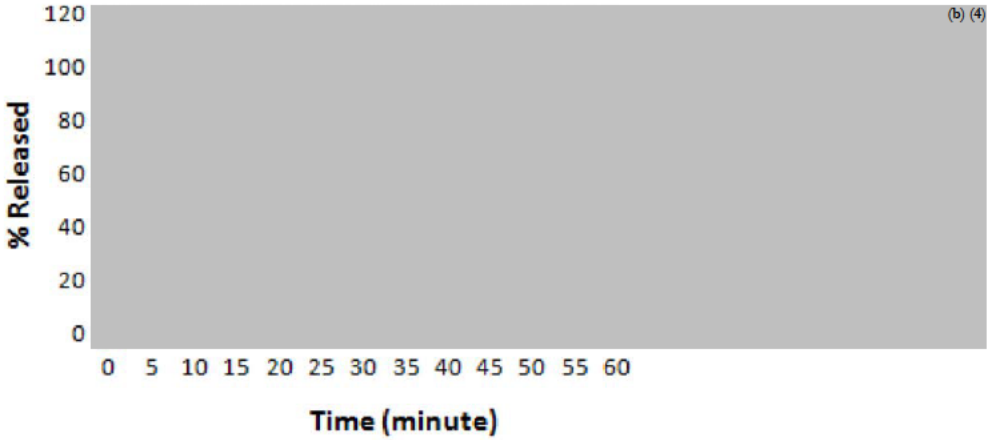


Figure 3. Comparison of Dissolution Profiles of Naproxen from 3 Dosage Strengths of TREXIMET® Tablets



Batch 081166993 was used in TXA107979 (Safety & efficacy) and TXA108504 (PK),
Batch 081161614 was used in TXA107979 (Safety & efficacy) and TXA108504 (PK), and
Batch 041015799 was used in TXA107977 (long term safety, open label)

Dissolution method: US Pharmacopeial (USP) Apparatus 1 (rotating basket at 75 rpm) with a dissolution medium of pH 6.8 phosphate buffer

Table 2. ANCOVA Results of Dose Proportionality for Sumatriptan and Naproxen in Adolescent Subjects

Sumatriptan AUC(0–t); hour.ng/mL			Naproxen AUC(0–t); hour.ug/mL		
Comparison	Ratio	90% CI for Ratio	Comparison	Ratio	90% CI for Ratio
30 mg : 10 mg	0.926	(0.657, 1.307)	180 mg : 60 mg	0.949	(0.697, 1.293)
85 mg : 10 mg	0.993	(0.711, 1.388)	500 mg : 60 mg	0.732	(0.542, 0.989)
85 mg : 30 mg	1.072	(0.776, 1.481)	500 mg : 180 mg	0.771	(0.577, 1.030)
Sumatriptan Cmax; ng/mL			Naproxen Cmax; ug/mL		
Comparison	Ratio	90% CI for Ratio	Comparison	Ratio	90% CI for Ratio
30 mg : 10 mg	0.740	(0.501, 1.091)	180 mg : 60 mg	0.851	(0.637, 1.137)
85 mg : 10 mg	0.686	(0.470, 1.002)	500 mg : 60 mg	0.638	(0.481, 0.846)
85 mg : 30 mg	0.928	(0.644, 1.337)	500 mg : 180 mg	0.749	(0.571, 0.984)

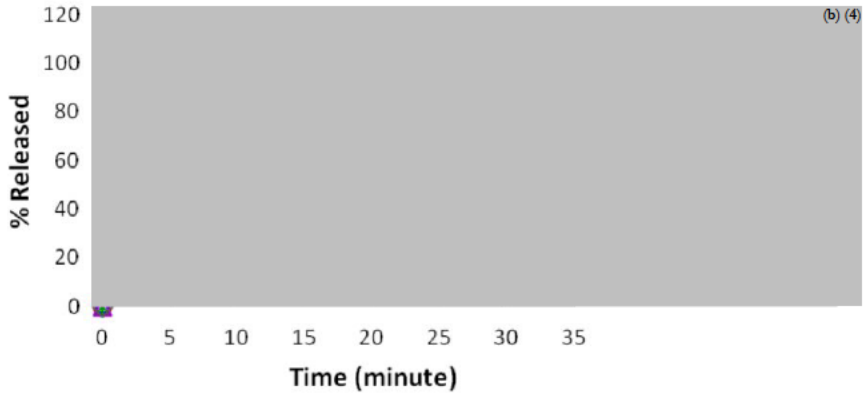
- Food Effect:

No food effect study was conducted for the newer strengths. In the efficacy trial (TXA107979), investigational products can be taken with or without food. The effect of food on the bioavailability of a TREXIMET® 85/500 mg tablet was evaluated in healthy adults as part of the initial NDA submission. In that study, food had no effect on the rate or extent of absorption of naproxen or sumatriptan, though food intake caused a slight delay in the T_{max} of sumatriptan by 0.6 hours. Per the current labeling, TREXIMET® 85/500 mg can be administered without regard to food. For sumatriptan, it is reasonable to extrapolate the food-effect findings for 85/500 strength to the lower strength 10/60 mg, since the *in vitro* dissolution profiles superimposed and *in vivo* data showed roughly linear PK. As to naproxen, considering that the 85/500 strength has slower dissolution, its absorption may be more susceptible to biopharmaceutics related changes (e.g., food intake) than lower strengths. Since no significant food effect was observed for this higher strength, it can be reasonably assumed that there is no significant food effect for the 10/60 mg strength, either. Thus, for the 10/60 mg dose proposed for pediatric of 12-17 years old, it can be taken with or without food.

- To-be-marketed formulation vs. Clinical formulation

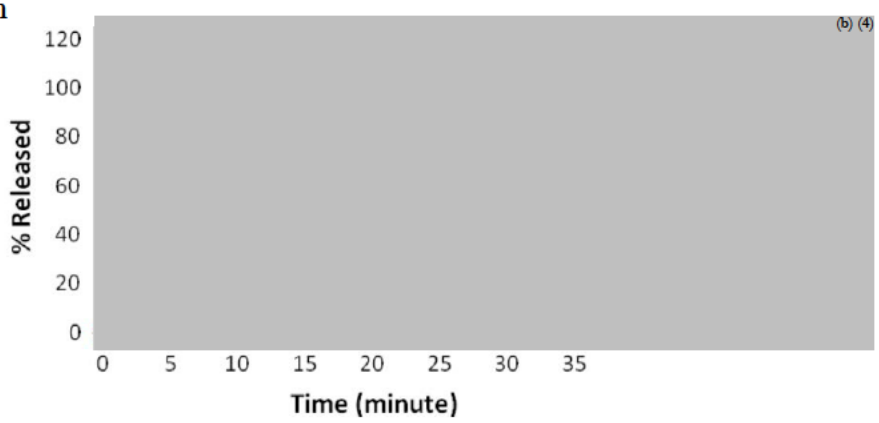
The 85/500 mg tablet tested in the clinical studies is the currently marketed formulation approved for use in adults. Some changes were introduced between the clinical trial tablet of the 10/60 mg strength and the commercial formulation. The naproxen layer remains identical. The overall composition of the sumatriptan layer is also identical between the two formulations; however, a slight change was made (b) (4) to improve the manufacturability at commercial scale. In addition, the (b) (4) used for the clinical tablet was switched (b) (4) for the commercial formulation in order to provide differentiation from the 85/500 mg tablet. As the total amount (b) (4) in the sumatriptan formulation is unchanged and the (b) (4) is for cosmetic purposes only, these changes were considered as minor modifications and did not affect the disintegration characteristics of the tablets, which was confirmed by *in vitro* dissolution tests (Figure 4 and 5).

Figure 4. Comparison of Sumatriptan Dissolution from Batches of Treximet 10/60 mg Tablets Used in Clinical Studies and in Stability Studies for the Proposed Commercial Formulation



* manufactured using the proposed commercial formulation

Figure 5. Comparison of Naproxen Dissolution from Batches of Treximet 10/60 mg Tablets Used in Clinical Studies and in Stability Studies for the Proposed Commercial Formulation



Xinning Yang, Ph.D.
Division of Clinical Pharmacology I

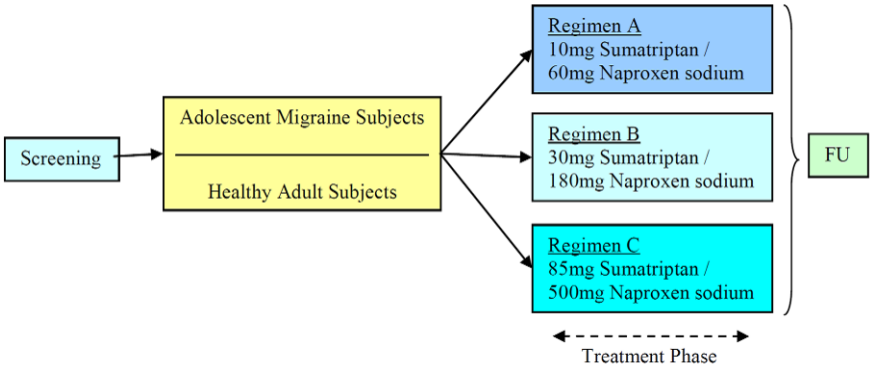
Team Leader: Angela Men, M.D. Ph.D._____

Individual Study Review:

Study TXA108504**:** An open label, single dose, randomized, parallel group pharmacokinetic study to evaluate a combination product containing naproxen sodium and sumatriptan in adolescent subjects with migraine and healthy adult subjects administered at three doses. (November 4, 2008 – September 10, 2009)

Objectives:

- Primary: to compare the pharmacokinetics (PK) of naproxen sodium and sumatriptan following the administration of the combination tablet at three doses (sumatriptan/naproxen sodium 10 mg/60 mg, 30 mg/180 mg, 85 mg/500 mg) in adolescent migraine subjects who are outside an attack, and healthy adult subjects.
- Secondary: To investigate the safety and tolerability of the combination tablet at three doses in adolescent migraine subjects and healthy adult subjects

<table>
<tr><td>Study Design</td><td>After a screening visit within 28 days prior to the first dose of study medication, each eligible subject participated in one dosing session with one of the three dose regimens of sumatriptan/naproxen sodium. Follow-up (FU) was performed 7–14 days after the dose.
 
</td></tr>
<tr><td>Study Population</td><td>Approximately 27 adolescent and 27 adult subjects were planned to be enrolled. The actual numbers dosed were 24 adolescent and 26 adult subjects.
<table>
<tr><th>Demographics</th><th>Adolescent subjects</th><th>Healthy adult subjects</th></tr>
<tr><td>Age in Years, Mean [Range]</td><td>14.8 [12–17]</td><td>29.8 [18–54]</td></tr>
<tr><td>Number of subjects in each age band</td><td></td><td></td></tr>
<tr><td>12–14 years, inclusive</td><td>13</td><td>Not applicable</td></tr>
<tr><td>15–17 years, inclusive</td><td>11</td><td>Not applicable</td></tr>
<tr><td>Sex, n (%)</td><td></td><td></td></tr>
<tr><td>Female:</td><td>16 (67)</td><td>15 (58)</td></tr>
<tr><td>Male:</td><td>8 (33)</td><td>11 (42)</td></tr>
<tr><td>Body Mass Index in kg/m², Mean [Range] [1]</td><td>22.16 [17.1–30.1]</td><td>25.30 [20.1–31.8]</td></tr>
<tr><td>Height in cm, Mean [Range]</td><td>164.8 [153–184]</td><td>173.8 [155–196]</td></tr>
<tr><td>Weight in kg, Mean [Range]</td><td>60.09 [47.7–80.0]</td><td>76.55 [56.1–113.6]</td></tr>
<tr><td>Ethnicity, n (%)</td><td></td><td></td></tr>
<tr><td>Hispanic or Latino:</td><td>1 (4)</td><td>0</td></tr>
<tr><td>Not Hispanic or Latino:</td><td>23 (96)</td><td>26 (100)</td></tr>
<tr><td>Race, n (%)</td><td></td><td></td></tr>
<tr><td>White – White/Caucasian/European Heritage</td><td>21 (88)</td><td>24 (92)</td></tr>
<tr><td>African American/African Heritage</td><td>1 (4)</td><td>2 (8)</td></tr>
<tr><td>Mixed Race</td><td>1 (4)</td><td>0</td></tr>
<tr><td>White – Arabic/North African Heritage</td><td>1 (4)</td><td>0</td></tr>
</table>
1. Rounded from source data.</td></tr>
<tr><td>Dosage and Administration</td><td>A single dose of combination tablet was administered with 240 mL water. Subjects were strongly recommended to have a light breakfast/snack on the morning of the study day, but food and water should not be taken</td></tr>
</table>

<table>
<tr><td></td><td>from 30 minutes before dosing until 1 hour after dosing (apart from the water taken with the dose).
Healthy adult subjects should fast overnight (from 10 pm) prior to clinical laboratory test.
Meals were provided on each day the subject is confined to the clinical research unit. Light snacks may be provided from 1 hour post-dose and a meal should not be given for at least 3 hours after dosing.</td></tr>
<tr><td>Sampling</td><td>To determine plasma concentrations of sumatriptan and naproxen, blood samples were collected at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours post-dose (24 and 48 hour procedures only apply for naproxen).</td></tr>
<tr><td>Bioanalysis</td><td>The same assays were used for the previous PK studies and have been reviewed in the original NDA.
<table>
<tr><td>Analyte</td><td>Sumatriptan (ng/ml)</td><td>Naproxen (µg/ml)</td></tr>
<tr><td>Method</td><td>LC-MS/MS</td><td>LC-MS/MS</td></tr>
<tr><td>Internal Standard</td><td>[$^{2}H_3$]-sumatriptan</td><td>[$^{2}H_3$, ^{13}C]-naproxen</td></tr>
<tr><td>LLOQ</td><td>0.1</td><td>0.1</td></tr>
<tr><td>Calibration Curve Range</td><td>0.1, 0.2, 0.4, 1, 4, 10, 80, 100</td><td>0.1, 0.2, 0.4, 1, 4, 10, 80, 100</td></tr>
<tr><td>QC</td><td>0.4, 4, 80</td><td>0.4, 5, 80</td></tr>
<tr><td>Accuracy (%Bias)</td><td>2.1 – 14.2%</td><td>-6.1 – 11.4%</td></tr>
<tr><td>Precision (%CV)</td><td>3.1 – 5.9%</td><td>27% (at 0.4 µg/ml), 6.7% (at 5 and 80 µg/ml)</td></tr>
</table></td></tr>
<tr><td>PK Assessment</td><td>AUC_{0-2}, $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, T_{max}, $t_{1/2}$, and CL/F for sumatriptan
$AUC_{0-\infty}$, AUC_{0-t}, C_{max}, T_{max}, $t_{1/2}$, and CL/F for naproxen</td></tr>
<tr><td>Safety Assessment</td><td>Adverse events, blood pressure, heart rate, 12-Lead ECG and clinical laboratory evaluations</td></tr>
</table>

Pharmacokinetic Results:

1. The PK parameters and profiles of sumatriptan and naproxen are shown in the following tables and figures.

Table 3. Summary [Geometric Mean (Between-Subject Coefficient of Variation)] of Pharmacokinetic Parameters for Plasma Sumatriptan

Regimen	Group	N	AUC(0-2) ng.h/mL (CVb%)	AUC(0-t) ng.h/mL (CVb%)	AUC(0-∞) ng.h/mL (CVb%)	Cmax ng/mL (CVb%)	tmax[1] h (range)	t½ h (CVb%)
A	MA	7	11.3 (62.0)	22.8 (56.7)	23.3 (56.0)	8.6 (56.7)	1.1 (0.5–2)	1.7 (12.0)
	HA	8	6.9 (71.3)	14.9 (40.4)	15.5 (37.6)	5.7 (61.3)	0.5 (0.5–2)	1.9 (23.6)
B	MA	8	24.8 (38.3)	63.4 (33.4)	65.1 (33.3)	19.1 (40.7)	0.75 (0.5–2)	1.9 (7.2)
	HA	9	21.0 (35.1)	46.8 (43.9)	47.9 (43.8)	17.1 (31.9)	1.0 (0.5–2)	1.9 (15.3)
C	MA	9	62.8 (44.4)	193.7 (30.7)	199.3 (30.9)	50.2 (41.3)	1.5 (0.5–3)	1.9 (15.6)
	HA	9	50.2 (32.1)	162.8 (33.5)	174.7 (37.2)	45.0 (26.7)	2.0 (0.5–4)	2.4 (25.9)

1. Median (range).

Regimen A = sumatriptan/naproxen sodium 10 mg/60 mg; Regimen B = sumatriptan/naproxen sodium 30 mg/180 mg; Regimen C = sumatriptan/naproxen sodium 85 mg/500 mg tablet; MA = migraine adolescents; HA = healthy adults;

Figure 6. Mean (+ SD) Sumatriptan Plasma Concentrations – Time Profiles (Top left panel: 10 mg sumatriptan/60 mg naproxen sodium; Tope right panel: 30 mg sumatriptan/180 naproxen sodium; Bottom: 85 mg sumatriptan/500 mg naproxen sodium. The upper curves in each panel represented PK profiles obtained in adolescents, while the lower curves were from adults.)

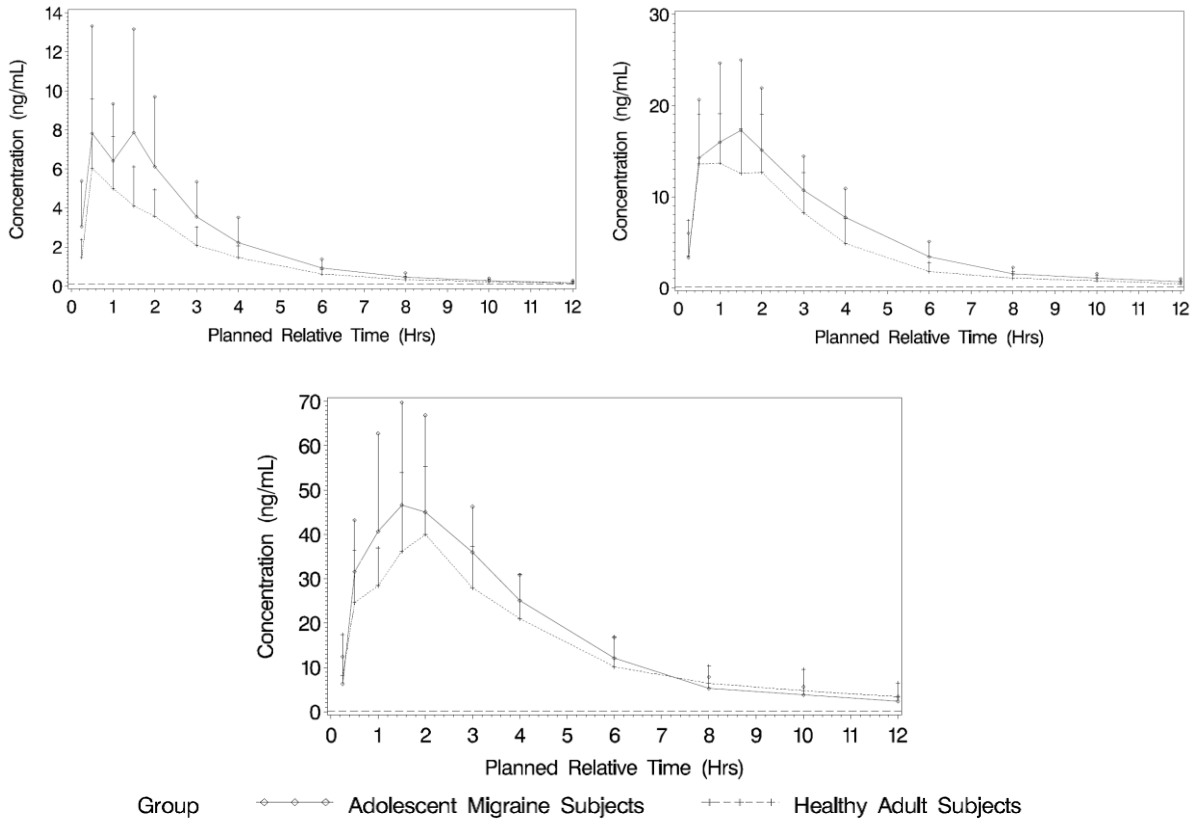


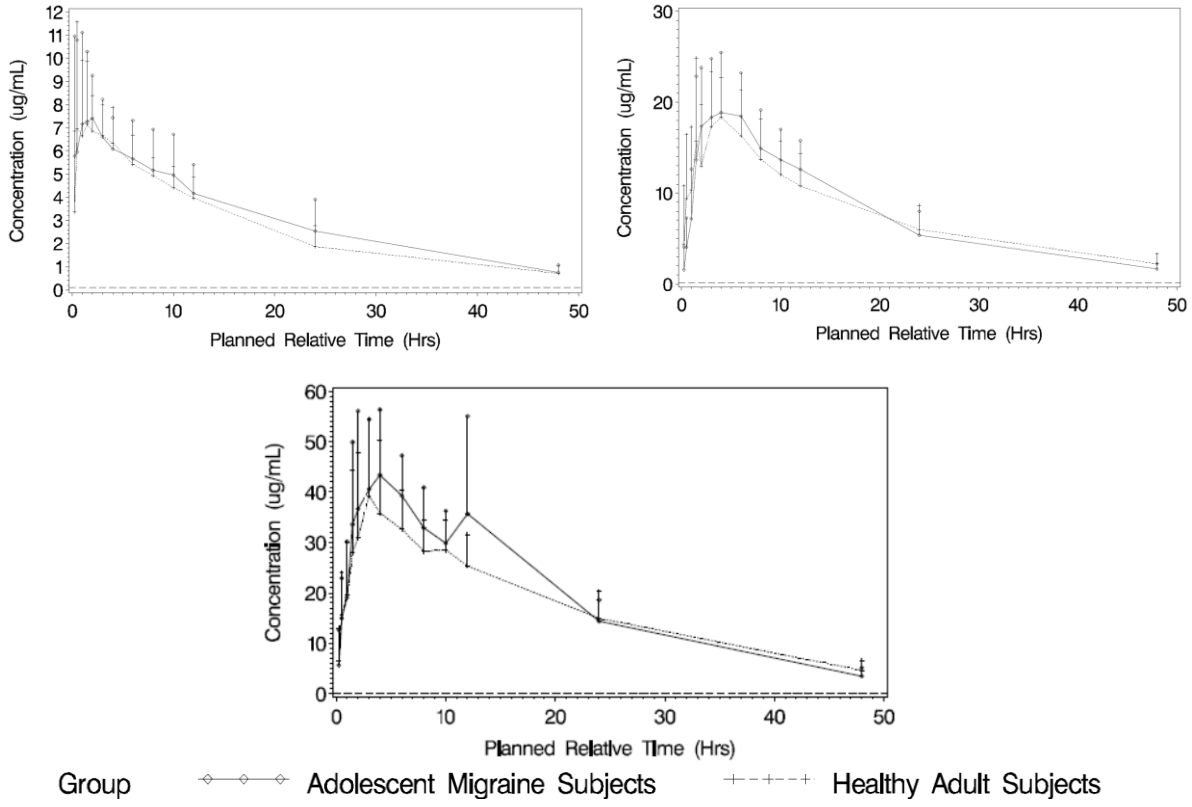
Table 4. Summary of Pharmacokinetic Parameters for Plasma Naproxen

Regimen	Group	N	AUC(0-t) µg.h/mL (CVb%)	AUC(0-∞) µg.h/mL (CVb%)	Cmax µg/mL (CVb%)	tmax[2] h (range)	t½ h (CVb%)
A	MA	7	139.1 (36.7)	156.3 (39.4)	9.1 (26.5)	1.0 (0.25-4)	16.3 (23.5)
	HA	8	121.8 (30.2)	136.0 (34.2)	9.2 (26.1)	1.0 (0.5–4)	14.3 (22.0)
B	MA	7	355.6 (35.9)	396.7 (33.7)	21.2 (33.0)	3.0 (1.5–6)	14.4 (22.4)
	HA	9	346.5 (36.7)	397.3 (39.0)	22.2 (14.4)	3.0 (1.5–6)	16.6 (13.0)
C	MA	9	848.4 (22.0)	917.6 (23.1)	48.4 (28.4)	4.0 (2–9)	13.4 (16.7)
	HA	9	781.3 (24.6)	882.8 (27.1)	42.9 (26.9)	3.0 (1–9)	15.4 (16.5)

1. Subject 910 was excluded due to an anomalous pharmacokinetic profile.
2. Median (range).

Regimen A = sumatriptan/naproxen sodium 10 mg/60 mg; Regimen B = sumatriptan/naproxen sodium 30 mg/180 mg; Regimen C = sumatriptan/naproxen sodium 85 mg/500 mg tablet; MA = migraine adolescents; HA = healthy adults;

Figure 7. Mean (+ SD) Naproxen Plasma Concentrations – Time Profiles (Top left panel: 10 mg sumatriptan/60 mg naproxen sodium; Tope right panel: 30 mg sumatriptan/180 naproxen sodium; Bottom: 85 mg sumatriptan/500 mg naproxen sodium.)



2. Comparison of Sumatriptan PK between adolescents and adults

Sumatriptan plasma concentrations in adolescent patients were higher than those in healthy adults at all the three dose levels (Table 5); this was most evident at the lowest dose studied (50 – 60% higher AUC and C_{max} in adolescents receiving 10 mg sumatriptan, regimen A). It remains unclear why the difference between adolescents and adults was bigger at the low dose level compared to the middle (12 – 26% higher AUC and 8% higher C_{max}, 30 mg sumatriptan, regimen B) and high dose levels (11 – 19% higher AUC and 6% higher C_{max}, 85 mg sumatriptan, regimen C).

In general, subjects with lower body weight have lower drug clearance and thus higher AUC. However, this cannot fully explain the observed difference in sumatriptan AUC between adolescents and adults across the three dose groups. The average body weight of the adolescents receiving 10/60 mg dose was closer to that of the adults administered with 10/60 mg, compared to the adolescents vs. adults getting 30/180 mg or 85/500 mg doses (Table 6). Yet, the difference in sumatriptan AUC between adolescents and adults was largest in the 10/60 mg dose group.

Table 5. Summary of Mixed Model Analyses of Plasma Sumatriptan PK Parameters

Parameter	Regimen	Geometric LS Mean Migraine Adolescents	Geometric LS Mean Healthy Adults	Geometric Mean Ratio	90% CI	CVb
AUC(0-2) (ng.h/mL)	A	11.47	7.16	1.60	(0.905, 2.839)	68.34
	B	23.10	20.66	1.12	(0.834, 1.498)	34.45
	C	58.06	48.92	1.19	(0.930, 1.515)	30.02
AUC(0-∞) (h.ng/mL)	A	23.44	15.66	1.50	(0.977, 2.291)	48.67
	B	59.22	46.87	1.26	(0.940, 1.698)	34.78
	C	192.30	172.64	1.11	(0.851, 1.459)	33.30
AUC(0-t) (h.ng/mL)	A	22.93	15.06	1.52	(0.981, 2.363)	50.42
	B	57.60	45.80	1.26	(0.936, 1.690)	34.80
	C	184.85	160.61	1.15	(0.900. 1.472)	30.24
Cmax (ng/mL)	A	8.67	5.78	1.50	(0.887, 2.533)	61.71
	B	18.29	16.97	1.08	(0.792, 1.467)	36.40
	C	46.47	43.83	1.06	(0.864, 1.302)	25.03

Regimen A = sumatriptan/naproxen sodium 10 mg/60 mg; Regimen B = sumatriptan/naproxen sodium 30 mg/180 mg; Regimen C = sumatriptan/naproxen sodium 85 mg/500 mg tablet. Note: geometric mean ratio is the ratio of migraine adolescents over healthy adults.

Table 6. Demographic Characteristics of Adolescent Migraine Subjects and Healthy Adult Subjects

Demographics	10 mg/ 60 mg	30 mg/ 180 mg	85 mg/ 500 mg	Total
Age in Years, Mean [Range]	14.3 [12–17]	15.0 [13–17]	15.0 [14–17]	14.8 [12–17]
Number of subjects in each age band				
12–14 years, inclusive	4	4	5	13
15–17 years, inclusive	3	4	4	11
Sex, n (%)				
Female:	4 (57)	6 (75)	6 (67)	16 (67)
Male:	3 (43)	2 (25)	3 (33)	8 (33)
Body Mass Index in kg/m^2, Mean [Range] [1]	22.65 [18.7–26.0]	21.74 [17.9–25.1]	22.15 [17.1–30.1]	22.16 [17.1–30.1]
Height in cm, Mean [Range]	162.1 [154–177]	166.6 [157–184]	165.1 [153–182]	164.8 [153–184]
Weight in kg, Mean [Range]	59.66 [47.8–67.1]	60.15 [48.6–68.9]	60.38 [47.7–80.0]	60.09 [47.7–80.0]

Demographics	10 mg/ 60 mg	30 mg/ 180 mg	85 mg/ 500 mg	Total
Age in Years, Mean [Range]	29.1 [18–54]	29.9 [19–46]	30.3 [18–52]	29.8 [18–54]
Sex, n (%)				
Female:	5 (63)	5 (56)	5 (56)	15 (58)
Male:	3 (38)	4 (44)	4 (44)	11 (42)
Body Mass Index in kg/m^2, Mean [Range] [1]	24.13 [20.1–29.4]	25.35 [21.5–31.8]	26.29 [20.1–31.7]	25.30 [20.1–31.8]
Height in cm, Mean [Range]	171.6 [155–185]	176.2 [162–189]	173.2 [158–196]	173.8 [155–196]
Weight in kg, Mean [Range]	71.00 [56.1–86.8]	79.41 [56.3–113.6]	78.61 [64.0–98.2]	76.55 [56.1–113.6]

3. Comparison of Naproxen PK between adolescents and adults

Naproxen PK parameters in adolescents were similar or just slightly higher than those in adults.

Table 7. Summary of Mixed Model Analyses of Plasma Naproxen PK Parameters (CVb: between-subject variability)

Parameter	Regimen	Geometric LS Mean Migraine Adolescents	Geometric LS Mean Healthy Adults	Geometric Mean Ratio	90% CI	CVb
AUC(0-∞) (h.µg/mL)	A	154.19	132.74	1.16	(0.837, 1.611)	36.58
	B	425.24	393.11	1.08	(0.753, 1.554)	43.28
	B[1]	385.83	394.43	0.98	(0.705, 1.358)	37.49
	C	921.27	884.02	1.04	(0.842, 1.289)	25.99
AUC(0-t) (h.µg/mL)	A	137.27	119.00	1.15	(0.857, 1.554)	33.08
	B	377.05	342.80	1.10	(0.775, 1.561)	41.73
	B[1]	344.90	343.85	1.00	(0.726, 1.387)	36.97
	C	854.85	783.28	1.09	(0.896, 1.329)	24.04
Cmax (µg/mL)	A	9.10	9.21	0.99	(0.770, 1.266)	27.40
	B	23.26	22.23	1.05	(0.797, 1.373)	31.89
	B[1]	21.27	22.30	0.95	(0.765, 1.189)	24.75
	C	47.13	42.54	1.11	(0.887, 1.384)	27.20

1. Mixed model analysis excluding Subject 910.

Regimen A = sumatriptan/naproxen sodium 10 mg/60 mg; Regimen B = sumatriptan/naproxen sodium 30 mg/180 mg; Regimen C = sumatriptan/naproxen sodium 85 mg/500 mg tablet. Note: geometric mean ratio is the ratio of migraine adolescents over healthy adults.

4. Dose Proportionality Evaluation for Sumatriptan PK

Sumatriptan AUC increased dose proportionally, while its C_{max} increased slightly less than dose proportionally.

Table 8. Dose Proportionality Assessment for Sumatriptan by Groups (using a power model)

Analyte	Parameter	Group	Adjusted Mean Slope	Standard Error	90% CI for Slope
Sumatriptan	AUC(0-t) (h.ng/mL)	Adolescent Migraine Subjects	0.999	0.089	(0.846, 1.152)
		Healthy Adult Subjects	1.117	0.085	(0.972, 1.263)
		All Subjects (i.e., combined groups)	1.065	0.065	(0.955, 1.175)
	Cmax (ng/mL)	Adolescent Migraine Subjects	0.827	0.101	(0.654, 1.001)
		Healthy Adult Subjects	0.964	0.088	(0.814, 1.114)
		All Subjects (i.e., combined groups)	0.901	0.068	(0.787, 1.015)

5. Dose Proportionality Evaluation for Naproxen PK
Naproxen AUC and C_{max} increased less than dose proportionally. This was more obvious for C_{max}.

Table 9. Dose Proportionality Assessment for Naproxen by Groups (using a power model)

Analyte	Parameter	Group	Adjusted Mean Slope	Standard Error	90% CI for Slope
Naproxen	AUC(0-t) (h.µg/mL)	Adolescent Migraine Subjects	0.850	0.081	(0.710, 0.989)
		Healthy Adult Subjects	0.876	0.068	(0.759, 0.993)
		All Subjects (i.e., combined groups)	0.865	0.053	(0.777, 0.953)
	Cmax (µg/mL)	Adolescent Migraine Subjects	0.786	0.076	(0.656, 0.916)
		Healthy Adult Subjects	0.724	0.052	(0.635, 0.813)
		All Subjects (i.e., combined groups)	0.755	0.045	(0.680, 0.830)

Safety:
All dose levels of sumatriptan/naproxen were generally well tolerated by both adolescent and adult subjects. In adolescent migraine subjects, migraine was the most frequently reported AE, occurring in three subjects (13%), one with each dosing regimen. In healthy adult subjects, the most frequently reported AE was dizziness, which occurred in two subjects (8%), one randomized to sumatriptan/naproxen 10 mg/60 mg and the other randomized to 85 mg/500 mg.

Conclusion:
1. Exposures to sumatriptan in adolescent migraine patients were higher compared with those in healthy adults at all three dose levels. The most evident was shown at the lowest dose (50–60% higher AUC and C_{max} in adolescents at 10 mg sumatriptan). Naproxen PK was generally similar between adolescents and adults.

2. Naproxen AUC and C_{max} increased less than dose proportionally. This was more obvious for C_{max}. Sumatriptan AUC increased in a dose proportional manner with C_{max} increasing just slightly less than dose proportional.

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/s/

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04/15/2015

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