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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	21926
Drug Name:	TREXIMET
Indication(s):	Acute Treatment of Migraine with or without Aura
Applicant:	GlaxoSmithKline
Date(s):	11/14/2014
Review Priority:	Priority
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1 EXECUTIVE SUMMARY

The study, TXA107979, in adolescent migraineurs was undertaken to assess the efficacy of sumatriptan/naproxen sodium since the marketed dose (sumatriptan 85 mg/naproxen sodium 500 mg) effectively treats migraine in adults, and clinical studies with the combination tablet had demonstrated superior efficacy than either component alone. The current study is part of an adolescent program for the combination tablet. In this study, all dose groups showed statistically significant efficacy compared with placebo for the primary endpoint of pain-free at 2 hours. In addition to the statistically significant efficacy seen for all three dose groups for the primary endpoint, statistical significance for sustained pain-free 2-24 hours post-dose, photophobia-free at 2 hours, and phonophobia-free at 2 hours was also demonstrated for the high dose group versus placebo.

2 INTRODUCTION

TREXIMET is currently available as a single tablet containing sumatriptan 85 mg (as sumatriptan succinate) and naproxen sodium 500 mg. The New Drug Application (NDA) for TREXIMET (NDA 021926) was approved by the Food and Drug Administration (FDA) on April 15, 2008, for the acute treatment of migraine with or without aura in adults 18 years of age and older. In adults with migraine attacks with or without aura, TREXIMET has demonstrated superior efficacy, similar tolerability, and medication satisfaction to its components. In adults, TREXIMET has similarly demonstrated benefits in the early intervention paradigm and in migraine subpopulations. With this evidence and because migraine in adults and adolescents has the same underlying pathogenic mechanism, it was thought that TREXIMET might be efficacious in adolescents with migraine attacks with or without aura.

Pursuant to the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), GlaxoSmithKline (GSK) was required to conduct the following studies as a Postmarketing Requirement:

1. A controlled effectiveness study of TREXIMET for the acute treatment of migraine attacks with or without aura in pediatric subjects 12 to 17 years of age
2. A long-term open label safety study in pediatric subjects with migraine 12 to 17 years of age.

In order to fulfill this requirement, GSK conducted studies TXA107979 (pivotal efficacy and safety study in adolescents) and TXA107977 (open-label long-term safety study in adolescents). In correspondence dated November 22, 2013, the Agency agreed with GSK's proposals and confirmed the content and format of the sNDA to fulfill the PREA requirements and the Written Request for Pediatric Studies for TREXIMET.

The information provided in the current application supports extending the current TREXIMET indication described above for acute treatment of migraine to adolescents 12 to 17 years of age. This application is based on a single placebo-controlled clinical study (TXA107979).

2.1 Overview

Study TXA107979 was a multicenter (US only), outpatient, double-blind, randomized, placebo-controlled, parallel group study of non-responders to placebo planned in adolescent migraineurs

12 to 17 years of age. Eligible subjects entered a 12-week, single-blind Run-In Phase during which they were to treat one moderate-to-severe migraine attack with single-blind placebo. Those subjects who reported pain 2 hours after dosing (placebo non-responders) were eligible to be randomized into the next 12-week phase of the study to receive one of four designated treatment options: 1) sumatriptan and naproxen sodium 10/60 mg; 2) sumatriptan and naproxen sodium 30/180 mg; 3) sumatriptan and naproxen sodium 85/500 mg; or 4) placebo.

The study was initiated on December 01, 2008 and completed on June 10, 2010. The protocol was amended one time prior to the completion of enrollment and applied to all centers. Amendment 01, dated 18 November 2009, was submitted to the FDA on 09 December 2009. This amendment corrected the sample size assumptions and the apportionment of alpha for the control of Type I error. The power calculations for the high, middle, and low doses were also revised.

The primary efficacy endpoint in study TXA107979 was the percentage of subjects who were pain-free at 2 hours post-treatment for migraine attack 2. Pain-free was defined as the absence of headache pain post-treatment from moderate or severe pain at baseline, without prior use of rescue medication. All three dose groups of TREXIMET demonstrated superior efficacy compared with placebo with respect to the percentage of subjects who were pain-free at two hours post-dose.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\CDSESUB1\evsprod\NDA021926\0079.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are no statistical issues with the data and analysis quality.

3.2 Evaluation of Efficacy

3.2.1 STUDY DESIGN AND ENDPOINTS

TXA107979 was a multicenter, outpatient, double-blind, randomized, placebo-controlled, parallel group, approximately 25-week, two-attack migraine study with a single-blind placebo Run-In Phase. Subjects were required to meet International Headache Society (IHS) International Classification of Headache Disorders-II (ICHD-II) criteria for migraine, with or without aura. A total of 77 US sites entered 976 subjects into the Screening Phase of which 865 subjects were enrolled into the single-blind placebo Run-In Phase (Enrolled Population).

Study Objectives
The primary objective of this study was to evaluate the efficacy of a range of doses of a combination product containing sumatriptan and naproxen sodium for the acute treatment of migraine in adolescent migraineurs ages 12 through 17 years.

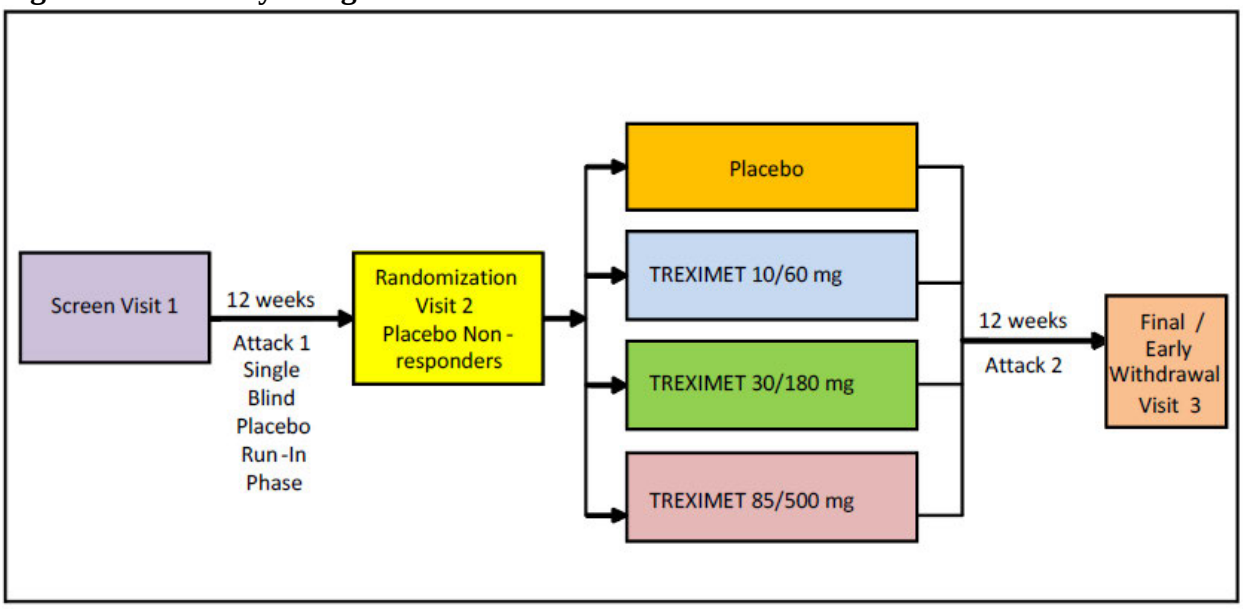
Secondary objectives include the following:

- To evaluate the safety and tolerability of a range of doses of sumatriptan and naproxen sodium for the acute treatment of migraine in adolescent migraineurs.
- To investigate the dose-response of a range of doses of sumatriptan and naproxen sodium for the acute treatment of migraine in adolescent migraineurs.

Treatment

Eligible subjects entered a 12-week, single-blind Run-in Phase during which they treated one moderate-to-severe migraine attack with single-blind placebo. Those subjects who reported pain 2 hours after dosing (placebo non-responders) and who continued to meet all other eligibility criteria were eligible to be randomized into the next 12-week phase of the study to receive one of four designated treatment options, see Figure 3-1. The subjects were randomized in a 3:2:2:3 ratio to placebo and the 3 active dose groups.

Figure 3-1 Study Design



[Source: Sponsor's Study Report Figure 1]

Efficacy Endpoints

All endpoints/assessments listed are for the evaluation of second migraine attack, first attack required before the randomization.

Primary Endpoint

- The percentage of subjects who are pain-free at two hours post-treatment.

Secondary efficacy endpoints

- Percentage of subjects who achieve a sustained pain-free period from 2-24 hours (pain-free at 2 hours and maintained through 24 hours)
- Percentage of subjects who are free of photophobia at two hours post-treatment
- Percentage of subjects who are free of phonophobia at two hours post-treatment
- Percentage of subjects who are pain-free at one hour post-treatment

- Percentage of subjects experiencing sustained freedom of photophobia from 2 to 24 hours
- Percentage of subjects experiencing sustained freedom of phonophobia from 2 to 24 hours
- Percentage of subjects with sustained freedom of nausea from 2 to 24 hours
- Proportion of subjects who used rescue medication between 2 to 24 hours post-treatment
- Time to first dose of rescue medication
- Percentage of subjects who are free of nausea at two hours post-treatment

3.2.2 STATISTICAL METHODOLOGIES

The initial protocol was written on August 07, 2008. Amendment 1 corrected sample size assumptions and the apportionment of alpha for the control of type I error on November 18, 2009. TXA107979 had only one version of the Reporting and Analysis Plan, which was finalized prior to unblinding of the study on June 18, 2010.

Sample Size Assumptions
Sample size assumptions were based on historical data, assuming that the 2 hour pain-free rates for the high dose versus placebo are 29% and 15%, respectively, n=153 subjects per treatment group are required to treat a migraine headache to detect this difference at alpha=0.05 and power=80%. Given the randomization ratio to treatment groups is 3:2:2:3, n=102 subjects will be randomized to each of the middle and low dose groups. For the middle and low dose groups that treat a migraine versus placebo, the corresponding power will be approximately 67%. Thus, the total number of subjects who will treat a migraine headache will be N=510. Finally, the randomization will be stratified by age-group (12-14 and 15-17 years old). It is estimated that 15% of randomized subjects will not have an opportunity to treat a migraine during the study period; thus, approximately 600 subjects are required for randomization. Further, the subject attrition during the Screening Phase and Run-in Phase is expected to be 15% and 20%, respectively. Thus approximately 904 subjects will be screened to enroll approximately 765 subjects to achieve approximately 510 subjects who treat a migraine with randomized Investigational Product.

Analysis Populations
The Safety Population (Safety) will consist of subjects who take at least one dose of Product.

The Modified-Safety Population (Modified-Safety) will consist of subjects in the Safety Population who takes a dose of double-blind, randomized treatment.

The Intent-to-Treat (ITT) population will consist of subjects in the Modified-Safety Population who provided any post-treatment efficacy assessment. Specifically, subjects must have provided some assessment of their migraine pain or associated symptoms for migraine attack 2 to be included in the ITT Population; The ITT Population will be used to assess all efficacy endpoints, as well as the health outcomes endpoints.

Efficacy Analysis Methods
The comparisons of each dose group of the combination product versus the placebo group described below. The primary null hypothesis is to be tested at a two-sided alpha level of 0.05.

H_{1h}: % of subjects pain-free at 2 hours post-treatment is equal for the high dose vs. placebo.

A Cochran-Mantel-Haenszel (CMH) test was used to test the primary null hypothesis of no difference between the high dose group and placebo for the percentage of subjects who are pain-free at two hours post-treatment versus the alternative hypothesis that there is a difference. The CMH test controlled for baseline migraine headache pain severity and age group.

The secondary null hypotheses involving the primary endpoint are:

H_{1m}: % of subjects pain-free at 2 hours post-treatment is equal for the middle dose vs. placebo.
H_{1l}: % of subjects pain-free at 2 hours post-treatment is equal for the low dose vs. placebo.

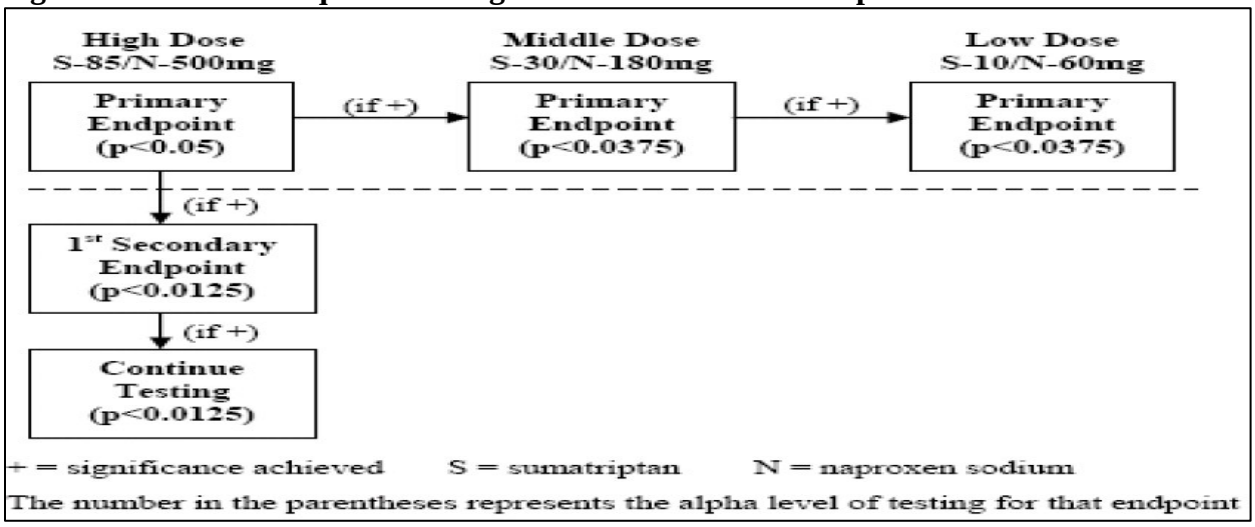
There are also following additional secondary null hypotheses for the high dose of sumatriptan and naproxen sodium versus placebo:

H_{2h}: % of subjects who achieve a sustained pain-free period from 2-24 hours is equal.
H_{3h}: % of subjects who are free of photophobia at two hours post-treatment is equal.
H_{4h}: % of subjects who are free of phonophobia at two hours post-treatment is equal.
H_{5h}: % of subjects who are pain-free at one hour post-treatment is equal.
H_{6h}: % of subjects experiencing sustained freedom of photophobia from 2 to 24 hours is equal.

All other efficacy endpoints (including health outcomes) in this study were binary endpoints, except for the time to rescue medication. All binary endpoints were analyzed similarly to the primary endpoint.

Multiplicity
A fixed sequence testing methodology was used to control inflation in the Type I error rate due to multiple testing, see Figure 3-2.

Figure 3-2 Fixed Sequence testing to maintain the overall alpha level of 0.05



[Source: Sponsor's RAP Figure 2]

First, the high dose group was compared with the placebo group. If this comparison was statistically significant at an alpha level of 0.05, the middle dose group was compared with the placebo group at an alpha level of 0.0375. Finally if both previous comparisons were statistically significant, the low dose group and the placebo group were compared at an alpha level of 0.0375.

If the high dose versus placebo comparison of the primary endpoint was statistically significant, the secondary endpoints were also to be tested sequentially at an alpha level of 0.0125 in the order in which they are listed in the secondary endpoints for the high dose versus placebo until non-significance was reached.

Examination of Subgroups
The primary endpoint (the percentage of subjects who are pain-free at 2 hours post-treatment) will be summarized by the following subgroups:

- Age (12-14, 15-17 years of age)
- Gender (male, female)
- Race (white, non-white)
- Baseline migraine pain severity (moderate, severe)
- Baseline presence of nausea (yes, no)
- Time to treatment (<=30 min, > 30 min)
- Awoke with migraine pain (yes, no)
- Migraine with aura (yes, no)
- Average number of migraine attacks per month (< 4 attacks, >= 4 attacks);
- Years since onset of migraine (< 5 years, >= 5 years).

No formal statistical between treatment group comparisons will be made.

3.2.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A total of 77 sites entered 976 subjects into the Screening Phase of which 865 subjects were enrolled into the single-blind placebo Run-In Phase (Enrolled Population). A total of 683 (79%) of enrolled subjects took at least one dose of single-blind placebo during the Run-In Phase or double-blind phase. Of the subjects enrolled, 589 (68%) completed the Run-In Phase, were subsequently randomized, and entered the Double-Blind Treatment Phase (Randomized Population). Four hundred ninety (490) subjects took a dose of randomized treatment (Modified Safety Population), and all 490 provided post-treatment efficacy assessment(s) (Intent-to-Treat Population).

Subject disposition in the Double-Blind Treatment Phase (Table 3-1) and the proportion of subjects for each premature discontinuation reason were similar across treatments and were similar across both age groups. More subjects in the older age group (15-17 years) compared with the younger age group (12-14 years) were randomized (268:321 subjects) and exposed to double-blind treatment (Modified-Safety/ITT Population: 225:265 subjects). Within each age group, the proportion of subjects for each premature discontinuation reason was generally similar across treatments. Majority of premature discontinuation were due to subjects did not have opportunity to treat migraine (57 subjects or 10% of randomized population). Twenty subjects (3% of randomized population) were lost to follow-up.

Table 3-1 Subject Disposition (Double-Blind Treatment Phase)

Subject Status & Analysis Populations	Placebo n (%)	Suma 10mg/Nap 60mg n (%)	Suma 30mg/Nap 180mg n (%)	Suma 85mg/Nap 500mg n (%)	12-14 yr n (%)	15-17 yr n (%)	Total n (%)
Randomized Population	**176**	**119**	**117**	**177**	**268**	**321**	**589**
Completed the Study	145 (82)	96 (81)	97 (83)	152 (86)	225 (84)	265 (83)	490 (83)
Prematurely Discontinued	31 (18)	23 (19)	20 (17)	25 (14)	43 (16)	56 (17)	99 (17)
Subject did not have opportunity to treat migraine	20 (11)	10 (8)	13 (11)	14 (8)	28 (10)	29 (9)	57 (10)
Lost to follow-up	8 (5)	4 (3)	4 (3)	4 (2)	7 (3)	13 (4)	20 (3)
Withdrew consent	0	6 (5)	0	2 (1)	3 (1)	5 (2)	8 (1)
Protocol deviation	3 (2)	0	0	3 (2)	2 (<1)	4 (1)	6 (1)
Investigator discretion	0	3 (3)	1 (<1)	1 (<1)	2 (<1)	3 (<1)	5 (<1)
Adverse event	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Lack of efficacy	0	0	1 (<1)	0	0	1 (<1)	1 (<1)

[Source: Sponsor's Study Report Table 4]

Demographic characteristics for the 490 subjects in the ITT Populations are summarized in Table 3-2. The average age was 15 years (range 12 to 18 years). The majority of subjects were female (59%) and White (81%). Demographic characteristics were generally similar across treatment groups, although subjects in the high dose group were slightly heavier than others. Mean weights (kg) were 63.8, 64.2, 62.8, and 66.8 for the placebo, low, middle, and high dose groups, respectively.

Table 3-2 Demographics (ITT)

	Placebo N=145	Suma 10mg/Nap 60mg N=96	Suma 30mg/Nap 180mg N=97	Suma 85mg/Nap 500mg N=152	12-14 yr N=225	15-17 yr N=265	Total N=490
Age, years							
Mean (SD)	14.7 (1.76)	14.8 (1.81)	14.7 (1.65)	14.8 (1.69)	13.1 (0.79)	16.1 (0.84)	14.7 (1.72)
Median	15.0	15.0	15.0	15.0	13.0	16.0	15.0
Min, Max	12, 18	12, 18	12, 18	12, 18	12, 14	15, 18	12, 18
Sex, n (%)							
Female	85 (59)	52 (54)	56 (58)	94 (62)	114 (51)	173 (65)	287 (59)
Male	60 (41)	44 (46)	41 (42)	58 (38)	111 (49)	92 (35)	203 (41)
Ethnicity, n (%)							
Hispanic or Latino	13 (9)	6 (6)	13 (13)	24 (16)	24 (11)	32 (12)	56 (11)
Race, n (%)							
White	108 (76)	75 (78)	84 (87)	130 (86)	181 (81)	216 (82)	397 (81)
African American	25 (17)	17 (18)	9 (9)	12 (8)	31 (14)	32 (12)	63 (13)
Weight, kg							
Mean (SD)	63.8 (16.67)	64.2 (19.29)	62.8 (14.49)	66.8 (19.13)	58.7 (15.55)	69.6 (17.78)	64.6 (17.63)
Median	63.6	61.5	60.7	63.6	56.8	65.9	62.0
Min, Max	34, 134	34, 119	35, 98	34, 127	34, 105	38, 134	34, 134
BMI, kg/m²							
Mean (SD)	23.5 (5.28)	23.3 (5.62)	22.9 (4.53)	24.6 (5.68)	22.6 (5.06)	24.6 (5.44)	23.7 (5.36)
Median	22.6	22.3	22.0	23.2	21.6	23.4	22.7
Min, Max	14, 43	14, 41	15, 36	14, 44	14, 39	17, 44	14, 44

[Source: Sponsor's Study Report Table 8, verified by reviewer]

3.2.4 RESULTS AND EXPLORATORY ANALYSES

All efficacy and health outcome results reported are for the randomized, double-blind treated migraine attack (attack 2) for the ITT Population.

3.2.4.1 Primary Efficacy Results

The primary efficacy endpoint, pain-free status at 2 hours post-dose, is summarized in Table 3-3. The percentages of subjects pain-free at 2 hours post-dose for all three doses of combination product of Sumatriptan and Naproxen Sodium versus placebo were statistically significant. Differences for active dose groups versus the placebo group ranged within 14.1% to 19.3%. Three Placebo and two high dose patients do not have pain-free status at 2 hours due to either took prohibited medications or treated migraine attack when severity was none or mild and were excluded from randomized population.

Table 3-3 Subjects Pain-Free at 2 hours post-dose (ITT)

	Placebo N=145 n (%)	Suma 10mg/ Nap 60 mg N=96 n(%)	Suma 30mg/ Nap 180 mg N=97 n(%)	Suma 85mg/ Nap 500 mg N=152 n(%)
Pain Free (2 hours) n/N (%)	14/142* (9.9%)	28/96 (29.2%)	26/97 (26.8%)	36/150* (24.0%)
Treatment Diff (95% CI)		19.3% (9.0%, 29.6%)	16.9% (6.9%, 27.0%)	14.1% (5.7%, 22.6%)
p-value		0.0001	0.0006	0.0014

[Source: Reviewer's Results.
* Three Placebo and Two Suma 85mg/Nap 500mg subjects missed pain free status at 2 hours]

3.2.4.2 Secondary Efficacy Analysis

Per the fixed sequence testing methodology to control the overall Type I error rate for this study at 0.05 (Section 3.2.2), because the primary efficacy endpoint was statistically significant, comparison of the high dose versus placebo group for the secondary endpoints at alpha=0.0125 was to occur sequentially in the order listed in Section 3.2.2.

Statistically significant differences in the high dose group vs. placebo were found for sustained pain-free 2-24 hours post-dose, photophobia-free at 2 hours post-dose, and phonophobia-free at 2 hours post-dose, see Table 3-4. The next endpoint in the fixed sequence testing, pain-free at 1 hour post-dose, was not statistically significant, and thus all endpoints after this endpoint could not be tested according to the testing methodology.

Table 3-4 Secondary Efficacy Endpoints for the High dose vs. Placebo (ITT)

	Suma 85mg/ Nap 500mg		Placebo		Treatment Difference (95% CI)	P-value
	n/N	%	n/N	%		
Sustained Pain-Free (2-24 hours)	13/142	9.2	35/150	23.3	14.2% (2.9%, 22.4%)	0.001
Photophobia-Free (2 hours)	59/144	41.0	89/151	58.9	18.0% (6.7%, 29.2%)	0.002
Phonophobia-Free (2 hours)	60/144	41.7	90/151	59.6	17.9% (6.7%, 29.2%)	0.002
Pain-Free (1 hour)	6/142	4.2	11/150	7.3	3.1% (-2.2%, 8.4%)	**0.321**

[Source: Reviewer's results]

In adult migraineurs, whether patients experienced nausea or not is an important secondary measure. In the current study, there is no difference at the percentage of subjects reported no nausea at 2 hours post-dose between high dose and placebo. However, the high dose reported statistically significant higher percentage nausea-free cases between 2 and 24 hours post dose than placebo group, see Table 3-5.

Table 3-5 Nausea-free Endpoints for the High dose vs. Placebo (ITT)

	Suma 85mg/ Nap 500mg		Placebo		Treatment Difference (95% CI)	P-value
	n/N	%	n/N	%		
Nausea-Free (2 hours)	101/142	70	106/150	70	1% (-10%, 11%)	0.907
Nausea-Free (2-24 hours)	47/144	33	94/151	62	16% (4%, 27%)	0.007

[Source: Reviewer's results]

3.2.4.3 Reviewer's Analyses

The main reason for a subject to prematurely discontinue the double blind treatment phase is "Subject did not have opportunity to treat migraine." There are 57 (10%) of randomized subjects excluded from ITT (Table 3-1) because of this reason. A slightly more in the Placebo compared with the High dose (20:14 subjects).

The next main reason of premature discontinuation is "Loss to follow-up." There are 20 (3%) of subjects lost to follow-up in this study. Once again, a slightly more in the Placebo compared with the High dose (8:4 subjects)

Suppose all 77 of above subjects had the second migraine attack and, hence, included into the ITT population. The reviewer performed the following sensitive analyses to assess the robustness of the primary finding.

A. Assume all 77 subjects did not have pain-relief at 2 hours post-dose with having exhibited their assigned treatments.
B. Assume all subjects did not have opportunity to treatment migraine did not have pain-relief at 2 hours post-dose with having exhibited their assigned treatments.
C. Assume all subjects lost to follow-up did not have pain-relief at 2 hours post-dose with having exhibited their assigned treatments.
D. Assume all Placebo subjects did not have opportunity to treatment migraine are pain free at 2 hours pose-dose.
E. Assume all Placebo subjects Lost to follow-up are pain free at 2 hours pose-dose.

Table 3-6 Sensitivity Analyses on Pain-Free at 2 Hours Post-Dose

Sensitivity Analyses	Placebo n/N (%)	Suma 85mg/ Nap 500 mg n/N(%)	Treatment Diff (95% CI)	P-value
A	14/170 (8.2)	36/168 (21.4)	13.2% (5.7%, 20.7%	0.0006
B	14/162 (8.6)	36/164 (22.0)	13.3% (5.6%, 21.0%)	0.0009
C	14/150 (9.3)	36/154 (23.4)	14.0% (5.9%, 22.2%)	0.001
D	34/162 (21.0)	36/164 (22.0)	1% (-8%, 10%)	0.8322
E	22/150 (14.7)	36/154 (23.4)	8.7% (-0.05%, 17.5%)	0.053

[Source: Reviewer's Results]

Based on the finding of Table 3-6, the primary efficacy endpoint finding is very robust despite of the consider amount of premature discontinuations. Note, the Analyses D and E are extremely unlikely events. However, the High dose still has numerical higher proportion of pain-free at 2 hours when compared with Placebo.

3.3 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, and Race group

The following subsections present the summary pain-free at hours post-treatment and the estimate of treatment effect in the subgroups of the age, gender, and race.

4.1.1 AGE

There are two age groups in this study: 12-14 and 15-17 year old age groups. In both age groups, all three dose groups increased the proportion of subjects pain-free at 2 hours from

placebo. Within the 12-14 year old group, a numerically higher response was seen from the low dose group than other two higher dose groups, see Table 4-1.

Table 4-1 Summary of Pain-Free at 2 Hours by Age group

Age Group	Pain Free (2 hours)	Placebo	Suma 10mg/ Nap 60 mg	Suma 30mg/ Nap 180 mg	Suma 85mg/ Nap 500 mg
12-14	n/N (%)	10/70 (14%)	18/43 (42%)	13/46 (28%)	17/65 (26%)
15-17	n/N (%)	4/72 (6%)	10/53 (19%)	13/51 (25%)	19/85 (22%)

[Source: Reviewer's results]

4.1.2 GENDER

The consistent findings as the primary efficacy results are observed within both gender group. Within male and female subjects, all three active dose groups experienced higher proportion of subjects pain-free at 2 hours than placebo group, see Table 4-2.

Table 4-2 Summary of Pain-Free at 2 Hours by Sex group

Gender	Pain Free (2 hours)	Placebo	Suma 10mg/ Nap 60 mg	Suma 30mg/ Nap 180 mg	Suma 85mg/ Nap 500 mg
Male	n/N (%)	6/58 (10%)	16/44 (36%)	10/41 (24%)	15/57 (26%)
Female	n/N (%)	8/84 (10%)	12/52 (23%)	16/56 (29%)	21/93 (23%)

[Source: Reviewer's results]

4.1.3 RACE

The majority of subjects are Whites (81%). Each of other race group consist very few subjects and even fewer or no pain-free status at 2 hours, so this review combined them all into Non-white group. Within White subjects, all three active dose groups observed higher proportions of subjects with Pain-free at 2 hours than placebo. However, placebo group had numerically favorable results than both middle and high dose groups in the Non-white subjects, see Table 4-3.

Table 4-3 Summary of Pain-Free at 2 Hours by Race group

Gender	Pain Free (2 hours)	Placebo	Suma 10mg/ Nap 60 mg	Suma 30mg/ Nap 180 mg	Suma 85mg/ Nap 500 mg
White	n/N (%)	7/107 (7%)	22/75 (29%)	24/84 (29%)	34/130 (26%)
Non-white	n/N (%)	7/33 (21%)	6/21 (29%)	2/13 (15%)	2/20 (10%)

[Source: Reviewer's results]

4.2 Other Subgroup Populations

The proportion of subjects pain-free at 2 hours was also summarized by other seven different subject characteristic subgroups as described in the Examination of Subgroups. The results in Table 4-4 were consistent with the primary analysis results. Within each level of each subgroup, all three active dose groups experienced higher proportion of subjects pain-free at 2 hours than placebo group.

Table 4-4 Summary of Pain-Free at 2 Hours by Subgroups

Subgroup	Placebo	Suma 10mg/ Nap 60 mg	Suma 30mg/ Nap 180 mg	Suma 85mg/ Nap 500 mg
Baseline migraine pain severity				
Moderate	7/66 (11%)	17/48 (35%)	19/52 (37%)	28/86 (33%)
Severe	7/76 (9%)	11/48 (23%)	7/45 (16%)	8/64 (13%)
Time to Treatment				
<= 30 min	9/69 (13%)	13/43 (30%)	15/53 (28%)	16/69 (23%)
>30 min	5/73 (7%)	15/53 (28%)	11/44 (25%)	20/81 (25%)
Awoke with migraine pain				
Yes	2/49 (4%)	7/28 (25%)	7/32 (22%)	7/39 (18%)
No	12/93 (13%)	21/68 (31%)	19/65 (29%)	29/111(26%)
Migraine with aura				
Yes	8/57 (14%)	8/41 (20%)	12/50 (24%)	7/48 (15%)
No	6/85 (7%)	20/55 (36%)	14/47 (30%)	29/102 (28%)
Average # of migraine attacks				
< 4 months	6/64 (9%)	12/39 (31%)	14/46 (30%)	15/53 (28%)
>= 4 months	8/78 (7%)	16/57 (28%)	12/51 (24%)	21/97 (22%)
Years since onset of migraine				
< 5 years	4/54 (7%)	11/41 (27%)	10/42 (24%)	14/62 (23%)
>= 5 years	10/88(11%)	17/55 (31%)	16/55 (29%)	22/88 (25%)
Presence of baseline nausea				
Yes	3/62 (5%)	7/42 (17%)	10/45 (22%)	11/63 (17%)
No	11/80 (14%)	21/53 (40%)	16/52 (31%)	25/87 (29%)

[Source: Reviewer's results]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The study TXA107979 demonstrated the following efficacy findings.

1. All 3 dose groups, 10/60 mg, 30/180 mg, and 85/500 mg, were superior to placebo with respect to the primary endpoint, the proportion of subjects pain-free at 2 hours post-dose.
2. In the prospectively defined fixed sequence hierarchical analysis for secondary endpoints, the 85/500 mg dose group demonstrated superior efficacy compared to placebo for the following secondary endpoints: percentage of subjects who were sustained pain-free 2 to 24 hours post-dose, photophobia-free at 2 hours, and phonophobia-free at 2 hours.

5.2 Conclusions and Recommendations

The efficacy results from study TXA107979 support the use of TREXIMET in adolescents 12 to 17 years of age for the acute treatment of pain and associated symptoms of migraine with or without aura. All dose groups showed statistically significant efficacy compared with placebo for the primary endpoint of pain-free at 2 hours. In addition to the statistically significant efficacy seen for all three dose groups for the primary endpoint, statistical significance for sustained pain-free 2-24 hours post-dose, photophobia-free at 2 hours, and phonophobia-free at 2 hours was also demonstrated for the high dose group versus placebo.

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/s/

STEVE G BAI
03/27/2015

KUN JIN
03/27/2015
I concur with the review.

KOOROS MAHJOOB
03/27/2015
I concur with the review.