CLINICAL REVIEW

Application Type	505 (b) (2)
Application Number(s)	21926
Priority or Standard	Priority
Submit Date(s)	Nov 14, 2014
Received Date(s)	Nov 14, 2014
PDUFA Goal Date	May 14, 2015
Division / Office	DNP / OND
Reviewer Name(s)	Ramesh Raman, MD, FACP
Review Completion Date	April 15, 2015
Established Name	Sumatriptan & Naproxen sodium
(Proposed) Trade Name	Treximet
Therapeutic Class	Triptan + NSAID
Applicant	Pernix Therapeutics
Formulation(s)	Oral Tablets 10/60 mg
Dosing Regimen	Single tablet
Indication(s)	Acute treatment of Migraine with and without aura
Intended Population(s)	Adolescent population (12 to 17 years)

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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1.1 Recommendation on Regulatory Action

Approval with label changes.

1.2 Risk Benefit Assessment

Executive Summary

Introduction

Treximet® was approved on April 15, 2008 under NDA 021926 for treatment of migraine with and without aura in *adults*. Treximet® is a combination drug that contains sumatriptan (a triptan) and naproxen sodium (a NSAID). The recommended dosage and strength for the adult indication is a single tablet of Treximet® (85/500 mg) containing 85mg of sumatriptan and 500mg of naproxen sodium. The sought indication (from the proposed label) is - "TREXIMET, which contains a serotonin (5-HT1B/1D) receptor agonist (triptan) and an NSAID, is indicated for the acute treatment of migraine with or without aura in adults and in adolescents aged 12 to 17 years." The sought dosage and strength is a single tablet of Treximet® containing 10 mg of sumatriptan (as sumatriptan succinate) and 60 mg of naproxen sodium. As a 505 (b) (2) application, Treximet® relies on data from NDA 020132 (Imitrex) and NDA 018164 (Anaprox DS Tablets).

This sNDA was submitted to fulfill the requirement for pediatric studies under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c; issued April 15 2008) and the Written Request (WR) for Pediatric studies (originally issued Jun 29 2007and updated/amended August 2014). Per Approval Letter of April 15, 2008, pediatric studies in the 0-6 year age group was waived (as it was thought that such studies were highly impossible or impractical to conduct) and studies in the 6-17 year age group were deferred (until the older 12-17 years safety and efficacy data has been collected). Based on the likelihood that there was general comparability between the adolescent and adult population, the findings in adults that demonstrated sufficient safety served as the basis for studies to be initiated in the adolescent age group without the need for other data.

Therefore, pursuant to PREA and WR, the Sponsor was required to conduct the following studies as a Postmarketing Requirement for the acute treatment of migraine in adolescents 12 to 17 years of age with a history of migraine headaches:

- Study 1: Adolescent Pharmacokinetic Study- To evaluate the pharmacokinetics of Treximet (MT 400) in adolescents 12 to 17 years of age with a history of migraine and to evaluate the pharmacokinetics compared to adults (historical controls).
- Study 2: (Pivotal) Adolescent Efficacy (and Safety) Study- To evaluate the efficacy and safety of Treximet (MT 400) in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.
- Study 3: Adolescent Long-Term Safety Study- To evaluate the long-term safety of Treximet (MT 400) in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.

For reasons discussed in section 2.5, the date that these studies were required to be completed changed from Nov 30, 2010 to Nov 30, 2014. The study reports for each of the required aforementioned studies were submitted on Nov 14, 2014.

The Studies & Results

The following three studies that were completed were:

- Study 1: Adolescent Pharmacokinetic Study
- Study 2: Adolescent Efficacy Study
- Study 3: Adolescent Long-Term Safety Study

PK

Study 1 (TXA108504): Adolescent Pharmacokinetic Study (compared to Healthy Adults)

This PK study was reviewed in detail by the Agency reviewer, Dr. Xinning Yang. This study is discussed in more detail in Section 5.3.

Study 1 was an open-label, randomized, parallel group PK study conducted in *24 adolescents* migraineurs (outside an attack) and in *26 healthy adults* to compare exposure of sumatriptan and naproxen following single-dose administration of TREXIMET® tablets at three doses (10/60 mg, 30/180 mg and 85/500 mg). According to Dr. Yang, the bioanalytical methods used to determine sumatriptan and naproxen concentrations were the same as those described in the original NDA for adults. Dr. Yang concluded that exposures to sumatriptan in adolescent migraine patients were higher compared with those in healthy adults, at all three dose levels. This was most evident at the lowest dose (50–60% higher AUC and Cmax in adolescents at 10 mg sumatriptan). Naproxen PK was generally similar between adolescents and adults. Overall, the Sponsor's conclusions were in agreement with Dr. Yang's conclusions.

As required, this PK study was successfully completed establishing the PK profile of Treximet in the adolescent population with results that were overall acceptable.

Overall, as noted in section 5.3 of this review, the clinical safety data from the PK study did not raise any clinically worrisome signals or findings of concern. In concurrence with the Sponsor, the adolescent subjects exposed to Treximet in this PK study tolerated Treximet reasonably well.

Efficacy

Study 2 (TXA107979): Pivotal Adolescent Efficacy (and Safety) Study

This pivotal efficacy study was reviewed by the Agency statistical reviewer, Dr. Steve Bai. The results from this study served as the prime basis for the regulatory recommendation in the efficacy (and safety) determinations of Treximet in the adolescent population. This study is discussed in more detail in Section 5.3.

Study TXA107979 was a multicenter (US only), outpatient, double-blind, randomized, placebo-controlled, parallel group study of non-responders to placebo 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 treatment options: 1) placebo; 2) sumatriptan and naproxen sodium 10/60 mg; 3) sumatriptan and naproxen sodium 30/180 mg; or 4) sumatriptan and naproxen sodium 85/500 mg. The rationale for the selected doses is discussed in section 5.3.

The *primary efficacy endpoint* was the percentage of subjects who were *pain-free* at two hours post-treatment. 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. The basis for and the appropriateness of selecting a pain free endpoint is discussed in section 5.3. The primary efficacy endpoint in study TXA107979 was further summarized by 9 subgroups.

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, randomized treatment (Safety Population). 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). For the Modified-Safety/Intent-to-Treat (ITT) Populations, 145 subjects received placebo, 96 received sumatriptan and naproxen sodium 10/60 mg, 97 received sumatriptan and naproxen sodium 30/180 mg, and 152 received sumatriptan and naproxen sodium 85/500 mg (randomization ratio of 3:2:2:3).

The modified-safety population (MSP; defined as subjects in the Safety Population who took a dose of double-blind, randomized treatment) and the intent-to-treat (ITT) population (defined as subjects in the Modified-Safety Population who provided any post-treatment efficacy assessment) served as the main population for safety and efficacy determinations respectively.

Barring some differences (as noted on section 5.3), the demographic characteristics of subjects in the Modified-Safety and ITT Populations were generally similar across treatment groups. A similar distribution of subjects was observed for the Safety Population of this study and the Safety Population of the TREXIMET long-term safety study (study TXA107977- see section 5.3).

The majority of subjects in each treatment group were White, females, with a median age of 15 years (range 12 to 18 years). Within each age group, similar proportions were enrolled, provided data, and completed the study. However, a greater percentage of subjects were female within the 15 to 17 versus 12 to 14 year age group (65% vs. 51%).

The efficacy results from study TXA107979 that support the use of TREXIMET in adolescents for the sought indication can be summarized as follows:

- As shown in Table 6.4.1a and discussed in section 6.1.4, all 3 dose groups, namely, 10/60 mg, 30/180 mg, and 85/500 mg, were superior to placebo with respect to the primary endpoint. The 10/60 mg dose group compared to the 85/500 mg group had numerically greater efficacy at the earlier time points, 1 hour and 2 hours post dose. Whereas, the 85/500 mg group compared to the 10/60 mg group had numerically greater efficacy at later time points, 4 and 4 to 24 hours post dose.
- As shown in Table 6.1.4b and discussed in section 6.1.4, barring some differences in results within some subgroups (e.g., age and race), the results of the subgroup analyses (2 hours pain free post-dose) indicated that all three dose groups had a higher proportion of subjects who were pain free at 2 hours compared to the placebo group.
- As shown in Table 6.1.5 and discussed in section 6.1.5, based on a prospectively defined fixed sequence hierarchical analysis for secondary endpoints, 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. According to Dr. Bai, 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. With respect to nausea-free endpoint, there was no difference between the placebo group and the high dose Treximet group at 2 hours post-dose. However, in the high dose Treximet group a higher percentage of subjects reported a sustained nausea free effect between 2-24 hours that was statistically significant compared to placebo.

Study 3: Adolescent Long-Term Safety Study

See below.

Safety

The overall exposure and the long term exposure of adolescents to Treximet as discussed in sections 5.3 and 7.2.1 and shown in Tables 7.2.1 and 5.3-3c, were adequate enough in numbers and duration for the tested doses that enabled a clinically meaningful review of the safety data. Likewise the demographic and other characteristics of the study population as discussed in section 5.3 were acceptable and largely representative of the intended target population. The categorization of the analyses populations that were exposed upon which safety results were reported were clinically meaningful and the results interpretable.

There were no deaths reported in any of the studies.

As shown in Table 7.3.2, a total of 6 SAEs were reported in 5 subjects following TREXIMET treatment (incidence rate of 0.5%). As discussed in section 7.3.2, there were 2 subjects who experienced SAEs from the pivotal study TXA107979 and these were not discussed further because these events occurred during the single-blind placebo treatment period. Overall, in concurrence with the Sponsor, attribution of the event to Treximet as a cause was either remote or unlikely or unrelated or was attributable to other underlying conditions.

There were no withdrawals due to AEs in the double-blind treatment group from the pivotal study or the PK study. In the long-term safety study, 7% of subjects in the Safety Population prematurely discontinued the study due to an AE; 40 of 41 subjects discontinued within the first 6 months of the study. Nausea was the most common AE leading to withdrawal (n=7; 1%). All other AEs leading to withdrawal occurred in <1% of subjects.

As shown in Table 7.4.1 and discussed in section 7.4.1, the incidence of the most common AE during the double-blind treatment-emergent AEs from the pivotal study was low with only nasopharyngitis, hot flush (subject verbatim text: “hot flash” or “hot flashes”), and muscle tightness having incidence ≥2% in any treatment group. All of the AEs of hot flush and muscle tightness emerged within 72 hours after double-blind treatment dosing, whereas, only one of the five subjects with nasopharyngitis experienced this AE within 72 hours after double-blind treatment dosing. Nausea (reported as the most common AE leading to withdrawal in the long-term safety study), was reported as a double-blind treatment-emergent AE in the pivotal study by a low number of subjects (0, 0, 0, and 1% of subjects in the placebo, low, middle, and high dose groups, respectively).

In concurrence with the Sponsor, overall, there were no new safety signals that were identified from adult post-marketing reports; postmarketing data regarding GI events to date (as of the report date) are consistent with the known safety profile of TREXIMET and are as reflected in the USPI.

Risk vs Benefits

Although there are many drugs that are used in clinical practice (Table 2.2) to treat pediatric migraine patients, only 2 drugs (Almotriptan for use in children older than age 12 years, and rizatriptan for children older than age 6 years) are FDA approved justifying a relative unmet medical need compared to the adult population. TREXIMET is the only single fixed combination tablet(s) of a triptan and an NSAID.

The benefit that Treximet can offer is evidenced via the acceptable results stemming from the prospectively conducted clinical trials that establish its PK properties and effectiveness in the target population.

The short term and long term risks associated with the administration of Treximet in the adolescent population has been adequately evaluated via three prospectively conducted clinical trials. There were no safety signals that were worrisome or reports of signals contained in the boxed warning for the adults (package insert). There were no additional safety signals that were identified in the post market data that were outside of the known safety profile of the combination tablet.

In summary, with a demonstrated benefit and an acceptable safety profile, approval of Treximet as an effective treatment option for the acute treatment of migraine with and without aura is adolescents is therefore justified.

Concurrence of approval from all disciplines and concurrence from the Sponsor for the proposed label changes will be required prior to approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

It is recommended that the Sponsor collect data via controlled clinical study (s) that can establish the safety and efficacy of Treximet in the 6-11 year age group for the acute treatment of migraine with or without aura.

Reviewer comments

As it was noted in the Aug 2008 NDA approval letter, under PREA, pediatric studies for the ages 6 years to 17 years were deferred and studies in the 6 to 11 year age group was allowed to be delayed until safety and effectiveness data in the 12 -17 year age group had been collected. The data in this submission has established the safety and effectiveness of Treximet in the adolescent age group (12-17 years). Therefore studies in the 6-11 year group as a post-marketing requirement is still outstanding.

The recommendation for pediatric studies in the 6-11 year age group is justified for the following reasons.

- Rizatriptan (Maxalt) carries an approved indication in the ≥ 6 to17 year age group for the treatment of migraine. Although during its pediatric drug development there were study feasibility issues related to the age group of 6-11 years that led to a regulatory amendment to the Written Request (August 2009), Maxalt was also approved in the 6-11 year age group based on clinical data that was subsequently generated. Of note, the amendment to the WR involved a change in the date by which the studies were to be submitted to the Agency. Specifically, the date requirement of March 31, 2011 for submitting non-clinical data and clinical data in the 6-11 year age group was removed from the WR and the original date of March 31, 2011 remained for submitting data in the adolescent population (12-17 years).
- Because of the aforementioned impact of study feasibility on the pediatric drug development of Maxalt in the 6-11 year age group, as part of PREA assessments, DNP recently revisited the study feasibility issue for another drug (also a triptan) intended to treat migraine in the 6-11 year age group. In summary, the determination that studies in the 6-11 year age group are feasible (and therefore required) were driven by these two recent assessments- a) the literature suggesting that there are between 4-11% pediatric patients in age group 6-11 years based on epidemiological estimates using varied diagnostic criteria (indicating at least 50,000 pediatric patients in age group 6-11 years using the lower estimate of 4%); and b) outpatient drug utilization data (consultation provided by OSE/DEPI-II) indicating a 21% increase (from approximately 185,000 patients in 2011 to 224,000 patients in 2014) in the use of all triptan products in the pediatric population aged 0-17 years from years 2011 through 2014.

2 Introduction and Regulatory Background

2.1 Product Information

Treximet®, under NDA 021926, was approved on April 15, 2008 for treatment of migraine with and without aura in *adults*. Treximet® is a combination drug that contains sumatriptan (a triptan) and naproxen sodium (a NSAID). The recommended dosage and strength for the adult indication is a single tablet of Treximet® (85/500 mg) containing 85mg of sumatriptan and 500mg of naproxen sodium. The sought dosage

and strength for the *adolescent* population (10/60 mg) is a single tablet of Treximet® containing 10 mg of sumatriptan (as sumatriptan succinate) and 60 mg of naproxen sodium. As a 505 (b) (2) application, Treximet® relies on data from NDA 020132 (Imitrex) and NDA 018164 (Anaprox DS Tablets).

Treximet® Tablets 10/60 mg are bilayer, immediate release tablets for oral administration. The tablets are modified capsule-shaped, (b) (4) blue film-coated and debossed with "*TREXIMET*" on one side and "*10-60*" on the other. They have approximate dimensions of (b) (4).

According to the Sponsor, the formulation selection for Treximet® Tablets 10/60 mg was based on prior knowledge of the approved Treximet® Tablets 85/500 mg. Three dosage strengths of Treximet Tablets, 10/60 mg, 30/180 mg and 85/500 mg, were evaluated in these clinical studies. The Sponsor states that the composition of the clinical Treximet Tablets 85/500 mg is identical to the approved Treximet® Tablets 85/500 mg. The formulations of Treximet Tablets 10/60 mg and Treximet Tablets 30/180 mg were based on the approved Treximet® Tablets 85/500 mg. The same conventional excipients as that used in the 85/500 mg tablets were used in the 10/60 mg and the 30/180 mg tablets except for talc.

Reviewer comments

Reference is made to the Agency CMC review for further details and comments.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.2 Currently Available Treatments for Proposed Indications

Ref: Copied from Continuum; Headaches in Children; Neurology 2012; 18(4):853-868

The medications that are used to treat acute migraine in the pediatric population are shown in the table. Almotriptan is FDA approved for use in children older than age 12 years, and rizatriptan for children older than age 6 years.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The regulatory milestones and related activities are summarized in Table 2.5.

This sNDA is intended to fulfill the requirement for pediatric studies under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) and the Written Request (WR) for Pediatric studies (August 2014).

On August 20, 2014, GlaxoSmithKline (GSK) transferred ownership to Pernix Ireland Limited (formerly known as Worrigan Limited).

The NDA for Treximet® Tablets for acute treatment of migraine with or without aura in adults was approved on April 15, 2008. Pursuant to PREA (issued April 15 2008) and WR (issued Jun 29 2007), the Sponsor was required to conduct the following studies as a Postmarketing Requirement for the acute treatment of migraine in adolescents 12 to 17 years of age with a history of migraine headaches (the indication):

- Study 1: Adolescent Pharmacokinetic Study- To evaluate the pharmacokinetics of Treximet (MT 400) in adolescents 12 to 17 years of age with a history of migraine and to evaluate the pharmacokinetics compared to adults (historical controls).
- Study 2: Adolescent Efficacy Study- To evaluate the efficacy and safety of Treximet (MT 400) in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.
- Study 3: Adolescent Long-Term Safety Study- To evaluate the long-term safety of Treximet (MT 400) in the treatment of adolescents 12 to 17 years of age with a history of migraine headaches.

Reports of these studies were to be submitted to the Agency within 3 years of the NDA approval (April 15, 2011 per PREA and Dec 1 2010 per WR).

In order to fulfill these post marketing PREA and WR requirements, the Sponsor conducted three studies (study TXA107979- pivotal efficacy and safety study in adolescents [identified as study 2 above]; study TXA107977- open-label long-term safety study in adolescents [identified as study 3 above]; and study TXA108504- single-dose PK study in adolescent migraineurs and healthy adult subjects [identified as study 1 above).

Reports of these 3 studies were submitted to NDA 021926 and to IND 068436 on November 30, 2010 under general correspondence. These were subsequently withdrawn (April 8, 2011) as study reports to fulfill PREA obligations were not submitted

in the form of a sNDA. In addition, stability data for the Treximet 10/60mg tablets were yet to be generated. The Sponsor (on April 11, 2011) committed to submitting the study reports by Dec 2012.

In correspondence dated July 31, 2012, Sponsor informed the Agency that they would be unable to submit the sNDA in December 2012 as committed due to unanticipated manufacturing delays of the pivotal stability batches for the TREXIMET Tablets 10/60 mg. This CMC related reason coupled with an ongoing Agency review of Sponsor's response to the Agency's April 13, 2012 Complete Response letter for NDA 021926/S-0009 (subsequently approved on Oct 24, 2012) which sought approval of Dr. Reddy's Laboratory as an alternate source of naproxen, served as the reasons for further delay in submitting the pediatric study reports. On December 12, 2012, Sponsor formally requested an extension in the submission date to November 30, 2014 for the sNDA submission which was granted (on Jun 4, 2013) by the Agency. Sponsor submitted a new Written Request to NDA 021926 on July 19, 2013, which was essentially identical to the original Written Request issued on June 29, 2007. The Written Request was reissued to the Sponsor on August 18, 2014.

Table 2.5 Regulatory Overview: NDA 21926

Regulatory Milestone		**Date**
Treximet® for Adult Acute Migraine Indication	Approval	April 15 2008
PREA required pediatric studies* (2*,3*)	Trigger	Apr 15 2008
	Study reports due[1]	Apr 15 2011[1,B]
	Study Reports (2*,3*) submitted (under GC to NDA seq. 0044) and Study Report (1*) submitted (under seq. 0048)	Nov 30 2010
	Study reports Withdrawn[A]	April 8 2011
	Study Reports due[B]	Dec 2012
	Request for Revised Timeline[2]	Dec 12 2012
	Deferral Extension Granted[2]	Jun 4 2013
	Study Reports due[2]	Nov 30 2014
	Study Reports Submitted (this submission)	Nov 14 2014
Written Request pediatric studies* (1*,2*,3*)	WR #1 (Sponsor request)	Aug 1 2006
	WR #1 Trigger (to IND 068436)	Jun 29 2007
	WR #1 Study reports due	Dec 1 2010
	Study Reports (1*,2*,3*) submitted (under GC to NDA seq. 0044 & seq. 0048)	Nov 30 2010
	Study reports Withdrawn[A]	April 8 2011
	WR #2 (Sponsor request)	Jul 19 2013
	WR #2 trigger	Aug 18 2014

	WR #2 Study reports due[3]	Nov 30 2014
	Study Reports Submitted (this submission)	Nov 14 2014

*Study 1 = Adolescent PK Study (study TXA108504)
*Study 2 (1277-1) = Adolescent Efficacy Study (study # TXA107979)
*Study 3 (1277-2) = Adolescent Long-term Safety Study (study # TXA107977)
A= Per Sponsor's letter of April 8, 2011. Reason for withdrawal- Study reports should be re-submitted as part of a supplemental NDA. Stability data yet to be generated.
B= Per Sponsor's letter of April 11, 2011. A) Commit to submit sNDA by end of Dec 2012. B) Justification for missing Apr 15, 2011 PREA date.
1= Per Approval Letter of April 15, 2008 (Waive 0-6 years [highly imposs ble or impractical]; Defer 6-17 years [approved adult but no pediatric studies]; May proceed with 12-17 years [findings in adults demonstrate sufficient safety to proceed in this age group]; Delay studies in 6-12 years until the older 12-17 years safety and efficacy data has been collected]). Studies 2 and 3 required.
2= Per Sponsor's letter dated Dec 12, 2012: A) Reason for Extension- due to problems associated with target potency issues pertaining to sumatriptan component and due to delay in manufacturing delays of the stability batches. B) New date of Nov 2014 proposed. C) Granted new date of Nov 2014- per Jun 4 2013 Agency letter.
3= Per Jun 4 2013 and Aug 18 2014 Agency letters

In addition to the aforementioned PREA and WR related pre-NDA submission regulatory activities, there were activities related to SPA and the NDA submission (pre-NDA meeting). Reference is made to these respective meeting minutes.

Reviewer comments

As a requirement to fulfill an internal procedural policy, the Division presented the necessary information on the pediatric drug development program of this NDA to the Agency Pediatric Exclusivity and PeRC committees. It is the understanding of this reviewer that both the committees concurred with the Division's assessment and recommendation. This regulatory concurrence that was required influenced the final recommendation.

Although there were multiple interactions between the Agency and the Sponsor with respect to the SPA under which the pivotal study TXA107979 was successfully conducted, it should be noted that there was no formal final agreement on record for the SPA. However, agreement on some of the critical trail design elements such as on the primary and secondary end-points were reached (see minutes 7/23/2008) although the discussions on other issues continued subsequently.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

These are acceptable.

3.2 Compliance with Good Clinical Practices

The Sponsor states that all studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with

the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

3.3 Financial Disclosures

The submitted (under section m1) information is noted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Reference is made to the respective reviews.

4.1 Chemistry Manufacturing and Controls

None. See CMC review.

4.2 Clinical Microbiology

None.

4.3 Preclinical Pharmacology/Toxicology

None.

4.4 Clinical Pharmacology

Reviewer comments

The clinical pharmacology of Treximet as it relates to the adolescent pediatric population that was evaluated via the clinical PK study is discussed in section 5.3 and was reviewed in detail by the Agency reviewer, Dr. Xinning Yang. Reference is made to Dr. Dr. Yang's review.

5 Sources of Clinical Data

All data were generated by the Sponsor conducted clinical trials as shown in Table 5.1.

5.1 Tables of Studies/Clinical Trials

Table 5.1 Studies/Clinical Trials*

*Copied from Sponsor; Clinical Summary Section. Edited for format only.

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)/Location of Report
Pharmacokinetic Studies						
TXA108504	Single dose PK	R, OL, PG, multicenter	Adolescent migraine subjects (12 to 17 years) and healthy adult subjects (18 to 55 years)	TREXIMET Tablets 10/60 mg, 30/180 mg, and 85/500 mg; Oral; Single dose	Adolescent migraine subjects: 24 randomized 24 completed: • 10/60 mg: 7 • 30/180 mg: 8 • 85/500 mg: 9 Healthy adult subjects: 26 randomized 26 completed: • 10/60 mg: 8 • 30/180 mg: 9 • 85/500 mg: 9	Completed (Full CPSR)/ Module 5.3.3.2

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)/Location of Report
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
TXA107979	Pivotal efficacy and safety	R, DB, PC, PG, two-attack study with a SB P run-in phase, multicenter	Adolescent migraine subjects (12 to 17 years)	TREXIMET Tablets 10/60 mg, 30/180 mg, and 85/500 mg or placebo; Oral; 12-week SB phase followed by 12-week DB phase	Placebo: 176 randomized 145 completed 10/60 mg: 119 randomized 96 completed 30/180 mg: 117 randomized 97 completed 85/500 mg: 177 randomized 152 completed	Completed (Full CSR)/ Module 5.3.5.1
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
TXA107977	Long-term safety	OL, single-arm, multicenter	Adolescent migraine subjects (12 to 17 years)	TREXIMET Tablets 85/500 mg; Oral; up to twelve months	656 enrolled 622 treated 435 completed six months 363 completed twelve months	Completed (Full CSR)/ Module 5.3.5.2

CPSR = Clinical Pharmacology Study Report
CSR = Clinical Study Report
DB = Double-blind
OL = Open label
P = Placebo
PC = Placebo-controlled
PG = Parallel Group
PK = Pharmacokinetics
R = Randomized
SB = Single-blind

Table 5.1 Studies/Clinical Trials*

*Copied from Sponsor; Clinical Summary Section. Edited for format only.

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)/Location of Report
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
TXA107979	Pivotal efficacy and safety	R, DB, PC, PG, two-attack study with a SB P run-in phase, multicenter	Adolescent migraine subjects (12 to 17 years)	TREXIMET Tablets 10/60 mg, 30/180 mg, and 85/500 mg or placebo; Oral; 12-week SB phase followed by 12-week DB phase	Placebo: 176 randomized 145 completed 10/60 mg: 119 randomized 96 completed 30/180 mg: 117 randomized 97 completed 85/500 mg: 177 randomized 152 completed	Completed (Full CSR)/ Module 5.3.5.1
Efficacy and Safety Studies: Uncontrolled Clinical Studies						
TXA107977	Long-term safety	OL, single-arm, multicenter	Adolescent migraine subjects (12 to 17 years)	TREXIMET Tablets 85/500 mg; Oral; up to twelve months	656 enrolled 622 treated 435 completed six months 363 completed twelve months	Completed (Full CSR)/ Module 5.3.5.2

CPSR = Clinical Pharmacology Study Report
CSR = Clinical Study Report
DB = Double-blind
OL = Open label
P = Placebo
PC = Placebo-controlled
PG = Parallel Group
PK = Pharmacokinetics
R = Randomized
SB = Single-blind

5.2 Review Strategy

The focus of this review was on the pivotal safety and efficacy study TXA107979. The long-term safety study (TXA107977) was an open-label study that primarily evaluated safety and tolerability without statistical testing on the efficacy endpoints. Therefore, the focus of the long term study was on the safety findings. The PK study (TXA108504) was reviewed by the Agency PK reviewer and therefore the focus of this review was on the safety findings of the PK study. To avoid redundancy, the safety findings of the long-term safety study and the PK study are discussed under section 5.3 below and additionally, relevant safety findings was integrated in section 7 along with the pivotal study. Because study TXA107979 was the pivotal controlled efficacy and safety and study, the efficacy findings is discussed under section 6 and safety findings under section 7. Relevant details of the study design for study TXA107979 that were critical in the safety and efficacy determinations such as the definition of the double-blind treatment phase, the relevant population for analyses and definitions, subject disposition during the double-blind treatment phase, etc., are discussed in section 5.3.

The names “Treximet®”, “Treximet” and “combination tablet” are used synonymously in this review.

5.3 Discussion of Individual Studies/Clinical Trials

PK STUDY (TXA108504)

Study Period: Nov 4 2008 to Sep 10 2009
Study Centers: Three US centers

Study TXA108504 was an open label, single dose, randomized, parallel group pharmacokinetic study that evaluated three doses of Treximet in adolescent subjects with migraine and healthy adult subjects. The primary objective was to compare the PK profile of Treximet between adolescents and adults and the secondary objective was to investigate the safety and tolerability of Treximet.

Adolescent subjects with a diagnosis of migraine according to International Classification of Headache Disorders, 2nd edition (ICHD-II) criteria were enrolled. They had at least a 6-month history of moderate to severe migraine and were 12–17 years old at screening and ≤18 years at dosing, with body weight ≥33.4 kg, and a healthy weight using age-based body mass index (BMI). They showed QTc (Bazett) or QTc (Fridericia) <450 msec without bundle branch block. Healthy adult subjects aged 18–55 years and BMI 18–32 kg/m2 were also recruited. They showed QTcB or QTcF <450 msec; or QTc <480 msec in those with bundle branch block. Any subject with hypertension, cardiovascular disease, ischemic vascular disease or gastrointestinal ulceration was specifically excluded from study participation.

24 adolescents and 26 adults were dosed under three treatment regimens-

- Regimen A: (Adolescents N= 7; Healthy Adults N= 8) sumatriptan/naproxen sodium 10 mg/60 mg immediate release oral tablet (batch number 081166993).
- Regimen B: (Adolescents N= 8; Healthy Adults N= 9) sumatriptan/naproxen sodium 30 mg/180 mg immediate release oral tablet (batch number 081161614).
- Regimen C: (Adolescents N= 9; Healthy Adults N= 9) sumatriptan/naproxen sodium 85 mg/500 mg (TREXIMET™) immediate release oral tablet (batch number R303658).

After a screening visit within 28 days prior to the first dose of the study medication, each subject participated in one dosing session with one of the three dose regimens of sumatriptan/naproxen sodium. Sequential pharmacokinetic samples were collected through 48 h after dosing. Follow-up was performed 7–14 days after the dose and the total duration of the study period was 2–6 weeks for each subject.

Reviewer comments

Reference is made to the agency PK reviewer for further comments on the study design, methodology and PK results.

RESULTS

Study Population

The demographics and subject disposition is summarized as shown in the Table 5.3-1.

Table 5.3-1 Demographics & Subject Disposition: Study TXA108504*

Number of Subjects	Adolescents	Healthy Adults
Number of subjects planned, N:	27	27
Number of subjects randomised, N:	24	26
All Subjects (Safety) Population, n (%):	24 (100)	26 (100)
Pharmacokinetic Population, n (%):	24 (100)	26 (100)
Number completed as planned, n (%):	24 (100)	26 (100)
Number withdrawn (any reason), n (%):	0	0
Demographics	**Adolescent subjects**	**Healthy Adults**
Age in Years, Mean [Range]	14.8 [12–17]	29.8 [18–54]
Number of subjects in each age band		
12–14 years, inclusive	13	Not applicable
15–17 years, inclusive	11	Not applicable
Sex, n (%)		
Female:	16 (67)	15
Male:	8 (33)	11
Body Mass Index in kg/m^2, Mean [Range]	22.16 [17.1–30.1]	25.30 [20.1–31.8]
Height in cm, Mean [Range]	164.8 [153–184]	173.8 [155–196]
Weight in kg, Mean [Range]	60.09 [47.7–80.0]	76.55 [56.1–113.6]
Ethnicity, n (%)		
Hispanic or Latino:	1 (4)	0
Not Hispanic or Latino:	23 (96)	26
Race, n (%)		
White – White/Caucasian/European Heritage	21 (88)	24
African American/African Heritage	1 (4)	2
Mixed Race	1 (4)	0
White – Arabic/North African Heritage	1 (4)	0

*Copied Sponsor's Synopsis, p 2. Edited for format only
1= Rounded from source data.

PK Results (summary)

Per Sponsor-

1. Exposure to *sumatriptan* in adolescent migraine sufferers was higher compared with healthy adults at all three dose levels; this was most evident at the lowest dose studied (50–60% higher AUC and Cmax in adolescents at 10 mg) which would be expected to be a sub-therapeutic dose. The difference in exposure between adolescents and adults was not statistically significant following any of the three dose regimens.

2. There was no significant difference between the two groups in *naproxen* pharmacokinetic parameters following dosing with any of the three dose regimens.

Reviewer comments

The Agency reviewer, Dr. Xinning Yang, also reached a similar conclusion. Reference is made to Dr. Dr. Yang's review for further comments.

Safety Results

Deaths

There were no deaths reported in this study.

Non-fatal Serious Adverse Events

There was one SAE that was reported. See below under 7.3.2 for details.

AE & Withdrawal

There were no AEs that led to withdrawal or premature discontinuation from the study.

Frequent Adverse Events

Treatment-emergent AEs irrespective of causality were reported by 18 of 50 subjects in the study (36%): seven adolescent subjects and 11 healthy adult subjects. In adolescent subjects, migraine was the most frequently reported AE, occurring in three subjects (13%), one with each dose regimen. In healthy adult subjects, the most frequent AE was dizziness, which occurred in two subjects (8%).

One adult subject (subject 903), a 26 year old male, randomized to sumatriptan/naproxen 30 mg/180 mg had mild nondrug- related AEs of increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT). This subject had ALT values of 41 IU/L at Screening and 229 IU/L at Follow-up (normal range: 0–48 IU/L); AST was 21 IU/L at Screening and 523 IU/L at Follow-up (normal range: 0–42 IU/L). Total bilirubin, GGT and alkaline phosphatase values were normal. At an unscheduled visit 23 days later, values had returned to the normal range. There were no other changes in clinical laboratory values which were considered clinically important by the Investigator.

There were no clinically important changes reported in 12-lead ECG recordings.

There were no clear trends in vital signs post dose in either adolescent or adult groups. However, two AEs were recorded relating to vital signs. An increase in blood pressure was reported as an AE post dose in one adult subject who had been randomized to

sumatriptan/naproxen 85mg/500mg. This was judged to be mild in severity by the Investigator and resolved spontaneously after approximately 30 minutes. An AE of bradycardia was recorded in one adult subject who had been randomized to sumatriptan/naproxen 10mg/60mg but was judged to be mild by the Investigator and had resolved within approximately 1 h.

Pregnancy during Study

No pregnancies were reported in female subjects enrolled in this PK study.

PIVOTAL STUDY (STUDY TXA107979)

Title: A Randomized, Multicenter, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of a Combination Product Containing Sumatriptan and Naproxen Sodium for the Acute Treatment of Migraine in Adolescents

Study center(s): Multicenter study; 77 centers in the United States

Study Period: 01 Dec 2008 – 10 Jun 2010

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.

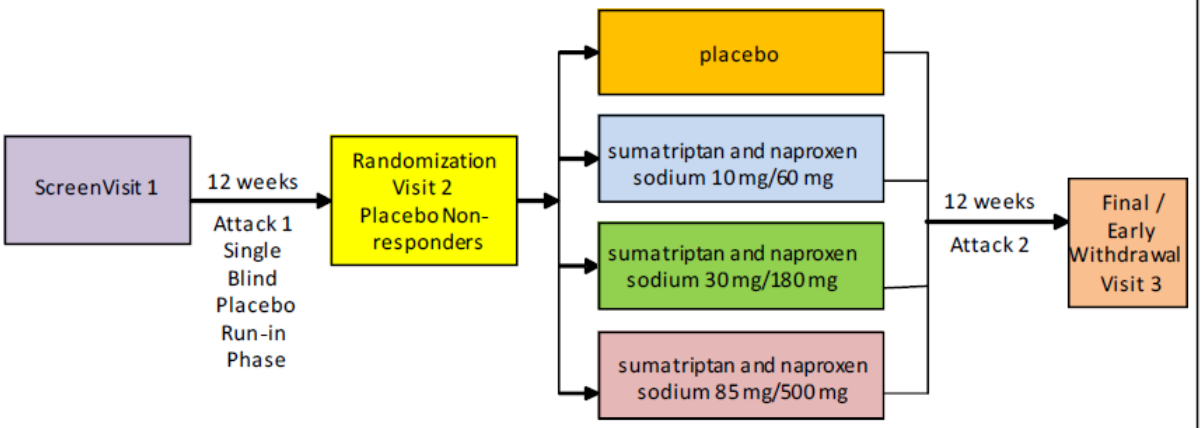
The secondary objectives of this study were the evaluation of safety, tolerability, and dose response of a range of doses of sumatriptan and naproxen sodium for the acute treatment of migraine in adolescent migraineurs.

Methodology & Study Design*:

*See Figure 5.3-2a

Figure 5.3-2a Study Design: Study TXA107979*

*Copied from Sponsor; Study Report TXA107979; p. 32. Edited for format only.



This was a multicenter, outpatient, double-blind, randomized, placebo-controlled, parallel group study of non-responders to placebo.

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 treatment options: 1) placebo; 2) sumatriptan and naproxen sodium 10/60 mg; 3) sumatriptan and naproxen sodium 30/180 mg; or 4) sumatriptan and naproxen sodium 85/500 mg.

The study included up to three visits over approximately 25 weeks for eligible subjects: V1) a Screening Visit; V2) a Randomization Visit; and V3) a Final/Early Withdrawal Visit. The Randomization Visit occurred within approximately two weeks of treatment of migraine attack 1. The Final/Early Withdrawal Visit occurred either: A) if the subject was no longer eligible due to placebo response experienced during treatment of migraine attack 1; B) after treatment of two migraine attacks within the study period; C) upon early withdrawal; or D) if the subject failed to treat two migraine attacks within the study period. In all cases, the Final/Early Withdrawal Visit was to occur within four to seven days following the dose of double-blind Investigational Product (IP).

Study medication was administered as soon as possible after the development of a migraine associated with moderate-to-severe headache pain. The baseline for each migraine attack was the time when subjects took study medication: either single-blind IP for migraine attack 1 or double-blind IP for migraine attack 2. A 24-hour pain-free period prior to the onset of headache pain was required to establish that each migraine represented a new headache, rather than a recurrence of a previous headache.

Diagnosis and main criteria for inclusion:

Per Agency PREA requirements, subjects enrolled in the study were to be adolescent males or females aged 12 to 17 years old at screening. Age stratification (12-14 years or 15-17 years of age) was used to fulfil this regulatory requirement that randomization was not to exceed 60% nor drop below 40% in either age group. Subjects had to have migraine with or without aura (International Classification of Headache Disorders-II [ICHD-II] criteria, 1.2.1 or 1.1) and be able to distinguish migraine from other types of headaches (i.e., tension-type headaches).

A history of at least two, but no more than eight, attacks per month for the six months prior to the Screening Visit was required to increase the likelihood that subjects would experience an attack during the study period and to minimize the likelihood of having chronic forms of headache. Subjects were required to have migraine attacks that typically lasted a minimum of three hours and were associated with moderate-to-severe headache pain. Subjects were required to have less than 15 headache days per month in total. Subjects were excluded from participation if they had significant risk factors for cardiovascular or cerebrovascular disease, a history of, or current, seizure, bleeding disorder, or cardiovascular, cerebrovascular, or gastrointestinal medical condition, or met any of the other specified exclusion criteria.

Rationale for Dose Selection:

The doses studied were TREXIMET 10/60 mg, 30/180 mg, and 85/500 mg. According to the Sponsor; considered an established pharmacological approach, a 3-fold increment between doses was selected.

Dose selection was primarily based on results of previous studies of sumatriptan alone in adolescents as well as results of clinical trials of TREXIMET (85/500 mg) in adults. Experience with the individual components of TREXIMET supported the expectation that the TREXIMET 85/500 mg dose was safe for adolescents. The 100 mg sumatriptan dose was well-tolerated by adolescents [Sponsor's reference Winner, 1997]. Naproxen sodium tablets have been available over-the-counter as Aleve since 1994 and are approved for use in children ≥12 years, with labeling that allows up to a total daily dose of 660 mg (lower than the 500 mg highest dose used in study TXA107979).

Since the pharmacokinetic profiles of drugs were similar between adolescents and adults, the approved adult dose, 85/500 mg, was included in study TXA107979 with the expectation that it would also be efficacious and safe for adolescents. A relatively flat dose response curve with little difference in response between doses was observed in sumatriptan study SUMA2002 [Sponsor's reference Winner, 1997]. Therefore, a wider dose range was evaluated to improve chances of identifying a dose response. Specifically, a lower sumatriptan dose (10 mg in combination with naproxen) was included as an anticipated no-effect dose.

Treatment administration:

Each subject was expected to take only one tablet of IP per migraine attack. Subjects in the Screening/Run-In Phase were to treat a migraine attack (attack 1) with single-blind placebo IP (batch R303662). Subjects in the randomized Double-Blind Treatment Phase were to treat a migraine attack (attack 2) with one of the following bilayer tablets in a randomization ratio of 3:2:2:3:

- matching placebo (batch R303662)
- sumatriptan 10 mg/naproxen sodium 60 mg (low dose) (batches 081166993 and 091214298)
- sumatriptan 30 mg/naproxen sodium 180 mg (middle dose) (batches 081161614 and 091214333)
- sumatriptan 85 mg/naproxen sodium 500 mg (high dose) (batch R303658)

In the event that subjects needed a rescue medication, they were to be advised to use one of the following: one oral dose of naproxen sodium at the dose recommended by their study physician (not to exceed a maximum of 15 mg/kg per 24 hours), one oral dose of an over-the-counter pain reliever not to exceed the maximum recommended single dose, or an antiemetic drug.

Study Assessments and Procedures*

*See Table 5.3-2a. Copied from Submission Study Report TXA 107979 pp. 41-42. Edited for format only.

Table 5.3-2a Study Assessments and Procedures StudyTXA107979

	Screening Visit	Run-In Phase 12-weeks attack 1	Randomization Visit	Double-Blind Treatment Phase[1] 12-weeks attack 2	Final/Early Withdrawal Visit
Visits	**V1**		**V2**		**V3**
Procedures					
Eligibility					
Informed Consent (& Assent if required)	X				
Subject Demography	X		X		
Inclusion/Exclusion	X		X		
Medical History	X		X		
IHS Diagnosis	X		X		
Migraine History	X		X		
Medication History	X		X		
Efficacy Assessments					
Pain Intensity (1, 2, 4-24 hr)		X		X	
Associated Symptoms (1, 2, 4, 4-24 hr) (Nausea, Photophobia, Phonophobia, Vomiting)		X		X	
Global Satisfaction Questions/PPMQ-R (BL, SCR and Post-Treatment at 2 & 24 hr)	X			X	
Return to Normal Function Question (0,1, 2, & 4 hr)		X		X	
Safety Assessments					
Adverse Events[2]	X	X	X	X	X
Physical Exam	X				
Concomitant Medication(s)	X	X	X	X	X
Vital Signs (HR, BP)	X		X		
12-lead ECG	X				
Lab Assessments					
Hematology/Chemistry/ Urinalysis[3]	X				
Urine Pregnancy Test[3]	X	X	X	X	X
Urine Toxicology Screen[4]	X		X		
Pharmacogenetics (PGx) Sample	X				
Investigational Product (IP)					
Dispense IP and Diary	X		X		
Randomization			X		
Review Diary	X		X		X
Review unused IP			X		X
Review Study Procedures	X		X		
Return Unused IP & Diary			X		X

1. With sponsor approval, subject may have been granted > 12 weeks to treat with randomized treatment.
2. Serious adverse events related to study participation were reported from the initial Screening visit throughout the study. All other adverse events (AEs) were collected from the start of treatment with IP until the follow-up contact.
3. Female subjects of childbearing potential were tested for pregnancy at the Screening Visit, Randomization Visit, and at the Final Visit. Additionally, a urine pregnancy test was performed at home, or in the clinic if preferred, every four weeks (at weeks 4, 8, 12, 16, 20, and 24), unless performed at a clinic visit within a week of the scheduled pregnancy test. Premenarcheal subjects were tested for pregnancy at each clinic visit. Premenarcheal subjects who became menarcheal and were still eligible for the study were subject to the same pregnancy testing requirements as mandated above. For those subjects that were granted > 12 weeks post-randomization to treat migraine attack 2, pregnancy testing was required at the scheduled visits as described above, at 4-week intervals, at 24-weeks post-enrollment in the study, and at the Final/Early Withdrawal Visit.
4. Sites called a parent/legal guardian following receipt of lab results to confirm eligibility and start IP or to return IP.

Endpoints:

The following endpoints were evaluated (for migraine attack 2):

Primary efficacy endpoint was the percentage of subjects who were pain-free at two hours post-treatment. 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.

Reviewer comments

The basis for selecting a pain free endpoint that was "qualitative" (and not quantitative) intrinsically rendered it less sensitive to placebo effect alleviating concerns of potential failed results that were seen in previous single-agent sumatriptan oral and nasal spray studies in adolescents which evaluated degrees of pain (quantitative). Further, as noted in 2012, the IHS recommended that 2 hour pain-free response be the primary measure of efficacy in clinical trials and that headache relief should not be used as a primary endpoint because of its poor alignment with patient treatment goals [Silberstein, 2013]. Further, although there was no SPA agreement for this study that was reviewed under the SPA, the Division did not diasgree with chosen end-point. "The primary efficacy endpoint of no headache pain at 2 hours after treatment" was the primary effiacy end-point that was evaluated in the Rizatriptan drug development program for children and adolescents (age 6-17 years) which was approved in 2012 for the treatment of migraine.

Secondary efficacy endpoints were the percentages of subjects who were sustained pain-free from 2-24 hours, photophobia-free at 2 hours, phonophobia-free at 2 hours, pain-free at 1 hour, sustained photophobia-free from 2-24 hours, sustained phonophobia-free from 2-24 hours, sustained nausea-free from 2-24 hours, the percentage of subjects who used rescue medication, the time to dose of rescue medication, and the percentage of subjects who were nausea-free at 2 hours.

Other endpoints were the percentages of subjects who were satisfied with current migraine treatment (at Screening), were satisfied with IP, returned to normal functioning post-treatment, had pain-relief post-treatment, and were free of photophobia, phonophobia, and nausea at specific times post-treatment.

Analysis Populations and Definitions*
*See Table below under Subject Disposition

The following populations were used for safety and effiacy analysis:

- Screened Population
  All subjects screened for this study, i.e., all subjects in the InForm database.
- Enrolled Population
  Screened subjects who were not identified as screen failures.

- Safety Population
  Subjects who took at least one dose of IP (i.e., single-blind placebo during the Run-In Phase or double-blind, randomized treatment).
- Placebo Responders Population
  Subjects in the Safety Population who were noted as run-in failures by the site, with "pain-free at two hours post-dose" of single-blind placebo cited as the reason for run-in failure, and are thus ineligible to be randomized.
- Randomized Population
  Subjects who were randomized to double-blind treatment.
- Modified-Safety Population
  Subjects in the Safety Population who took a dose of double-blind, randomized treatment.
- Intent-to-Treat (ITT) population
  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.
- Per Protocol (PP) Population
  All ITT subjects who did not violate any major protocol requirements. Major protocol violations included: subjects who did not have migraine with or without aura, subjects with migraines typically <3 hours in duration, subjects with ≥15 headache days per month, subjects taking ergot or unstabilized migraine prophylaxis medications, subjects who had a recent history of using opioids or barbiturates or illicit substances, subjects who used prohibited medications, subjects who rescued in ≤2 hours post-dose of IP, subjects who treated while pain was "mild" or "none", subjects who received treatment other than what they were randomized to receive, subjects who were placebo responders during the single-blind placebo Run-In Phase.

Reviewer Comments

In conjunction with the study design, the modified-safety population (MSP) and the intent-to-treat (ITT) population served as the main population for safety and efficacy determinations respectively.

RESULTS

Study Population

Subject Disposition (Double-blind Treatment Phase)*
*See Table 5.3-2b

Table 5.3-2b Subject Disposition (Double-blind Treatment Phase) & Subject (n) Analysis Population: Study TXA107979*

Subject Status & Analysis Populations	Placebo n (%)	10/60 n (%)	30/180 n (%)	85/500 n (%)	12-14 yr n (%)	15-17 yr n (%)	Total n (%)
Screened Population	NA	NA	NA	NA	444	532	976
Enrolled Population	NA	NA	NA	NA	408	457	865
Safety Population	NA	NA	NA	NA	317 (78)	366 (80)	683 (79)
Placebo Responders Population	NA	NA	NA	NA	33 (8)	28 (6)	61 (7)
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)
Modified-Safety Population	145 (82)	96 (81)	97 (83)	152 (86)	225 (84)	265 (83)	490 (83)
Intent-to-Treat Population	145 (82)	96 (81)	97 (83)	152 (86)	225 (84)	265 (83)	490 (83)
Per Protocol Population	127 (72)	92 (77)	89 (76)	141 (80)	211 (79)	238 (74)	449 (76)

*Copied & combined Sponsor's Tables 4 & 6, Study Report TXA107979, p. 58, 61. Modified format & minor content (deleted prefix Suma and Nap in each dose group)
Source: Table 1.4, Table 1.5, Table 1.9, Table 1.53, Table 1.54, Table 1.55, and Table 1.56

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, randomized treatment (Safety Population). 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). Forty-one subjects had a major protocol violation; thus, there were 449 subjects in the Per Protocol Population.

For the Modified-Safety/Intent-to-Treat (ITT) Populations, 145 subjects received placebo, 96 received sumatriptan and naproxen sodium 10/60 mg, 97 received sumatriptan and naproxen sodium 30/180 mg, and 152 received sumatriptan and naproxen sodium 85/500 mg (randomization ratio of 3:2:2:3).

Fewer subjects were enrolled (408:457) and randomized (268:321) in the younger age group (12-14 years) compared with the older age group (15-17 years). This trend continued for the number of subjects taking each treatment (single-blind or double-blind IP). The Safety Population consisted of 317 subjects who were 12-14 years and 366 subjects who were 15-17 years. The Modified-Safety/ITT Population consisted of 225 subjects (46%) who were 12-14 years and 265 (54%) who were 15-17 years.

Reviewer comments

Premature Discontinuation

As noted in the table above (subject disposition), a total of 99 subjects discontinued prematurely from the study. For the two categories with the most number of subjects who discontinued prematurely, namely, “Subject did not have opportunity to treat migraine” and “Lost to follow-up”, the Agency statistical reviewer performed additional sensitive analyses to assess its impact on the robustness of the primary finding and concluded that the primary efficacy results were robust despite these premature discontinuations (see Dr. Steven Bai’s review for additional details.)

Subject Demographics (Modified-Safety & ITT Populations)*
*See Table 5.3-2c

Demographic characteristics for the 490 subjects in the Modified-Safety and ITT Populations that are summarized in the table below were similar to the overall demographics for the Safety Population. 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.

The demographics for each *age group* were also similar for the Modified-Safety/ITT Populations compared with the Safety Population. Within each age group, demographic characteristics were generally similar across treatments for the Modified-Safety Population and the identical ITT Populations with subjects in the high dose group being slightly heavier than others as seen in the overall populations.

Migraine history at baseline was evaluated using the ITT Population. The mean age at onset for migraine in these subjects was 10 years. The median number of migraine attacks per month was 4, and the median number of days per month with headache was 7. The average duration of migraine attacks ranged from 3 to 24 hours for 69% of subjects and from 24 to 48 hours for 24% of subjects. Seventy-six percent reported that they typically do not experience recurrence of their migraine within 24 hours. Most (67%) subjects reported that they experience migraines without aura only. Within the ITT Population, migraine diagnostic classification and migraine history results were generally similar for both age groups and across the treatment groups. Over 99% of ITT subjects treated a migraine with randomized double-blind IP at moderate or severe pain severity. The mean time between the onset of the headache and the use of randomized IP dose was 2.25 hours. Prevalence of migraine symptoms at time of dosing was as follows: photophobia, 85%; phonophobia, 78%; nausea, 44%, and vomiting, 5%. Migraine pain, associated symptoms, and characteristics for the attack treated with randomized IP were reported to be generally similar for both age groups and across the treatment groups.

Table 5.3-2c Demographics (Modified-Safety & ITT Populations): Study TXA107979

	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

*Copied Sponsor's Table 8, Study Report TXA107979, p. 64. Modified format & minor content (deleted prefix Suma and Nap in each dose group)
Source: Table 1.17, Table 1.18, Table 1.21, Table 1.22, Table 1.63, Table 1.64, Table 1.65, Table 1.66, Table 1.67, Table 1.68, Table 1.69, Table 1.70

Efficacy and Safety Results

See sections 6 and 7 below.

LONG TERM SAFETY STUDY (TXA107977)

This was a Phase IIIB long-term safety study of TREXIMET® for the Treatment of Migraine in Adolescents conducted in the US across 70 centers between 13-Jul-2007 – 20-Aug-2009.

The primary objective of this study was to evaluate the safety and tolerability of the combination tablet containing sumatriptan succinate and naproxen sodium for the acute treatment of migraine for up to 12 months (long-term) in adolescents 12 to 17 years of age. The secondary objectives were to: (1) evaluate the efficacy of the Treximet tablet, (2) obtain data related to migraine symptoms, and (3) assess the quality of life and satisfaction with treatment in adolescents, before and after using the Treximet tablet as an acute migraine treatment, over a period of up to 12 months.

This study was a prospective, open-label, single-arm, multicenter, outpatient investigation in which adolescent migraineurs (aged 12 to 17 years) were asked to treat each of their migraine attacks with the Treximet for a period of up to 12 months. A minimum of 200 subjects for at least 6 months, and a minimum of 75 subjects for 12 months were required to be evaluated. Subjects returned to the clinic at 3 month intervals for interim safety evaluations.

Male and female adolescents 12 to 17 years of age with migraine with or without aura were the study population. Subjects were eligible to participate in the study if they had a 6 month history of moderate to severe migraine attacks, lasting at least 2 hours, on average 2 to 8 migraines per month, with less than 15 headache days per month and no known contraindications to triptans or non-steroidal anti-inflammatory drug (NSAIDs).

Subjects were excluded from participation in the study if they: had significant risk factors of cardiovascular or cerebrovascular disease; had a history of/or current seizure or bleeding disorder or cardiovascular, cerebrovascular, or gastrointestinal medical condition; had a hypersensitivity, allergy or intolerance to either triptans or NSAIDs; or were currently taking a medication which may interact with either a triptan or NSAID.

Treximet tablets containing 85 mg sumatriptan and 500 mg naproxen sodium (Batch number B916681 and R303658), was administered. A single Treximet tablet was supplied for each migraine attack that could not exceed one tablet in 24 hours. In the event that subjects needed a rescue medication, they were to be advised to use an alternative, non-triptan, non-ergot, non-narcotic medication recommended by their physician.

The primary endpoints in this study were the evaluation of safety data (adverse events, laboratory changes, electrocardiogram (ECG) changes, and vital signs) after acute treatment of migraine with Treximet for up to 12 months, in adolescents aged 12 to 17 years.

Per protocol, safety assessments were required to be evaluated at 3, 6, 9, and 12 months, as well as across all attacks, and for the first 6 months compared to the second 6 months. Investigators were to monitor the safety of the subjects throughout the study. In addition, clinical and medical monitoring (Sponsor's [GSK] staff or designee) assisted the investigators and site personnel, as appropriate.

Reviewer Comments

The following was reported by the Sponsor- "During the conduct of the study, Sponsor (GSK) determined that two investigators (and site personnel) were not adequately monitoring the safety of their subjects (Site 039898 and Site 040534). Data from these two sites were excluded from an additional analysis of safety to ensure their data did not affect the overall results of this multi-center study (Other Analyses)".

Site 039898 enrolled 9 subjects (3% of total n of 300) who were 12-14 years of age and 7 subjects (2% of total n of 356) in the 15-17 years age group. Site 040534 enrolled 4 subjects (1% of total n of 300) who were 12-14 years of age and 3 subjects (<1% of total n of 356) in the 15-17 years age group (ref: Sponsor's Table 1.1; page 145/7765 study report TXA107977). Given these small numbers, its exclusion, in the opinion of this reviewer, did not impact the overall safety findings.

Per protocol, adverse events were assessed at each visit, monitored throughout the study and recorded in the electronic data collection system. All adverse events occurring from the first dose of the combination tablet to the Final Visit were to be recorded. SAEs were to be recorded from the start of the study. All AEs and SAEs were to be followed until resolution, until the condition stabilized, until the event was otherwise explained, or until the subject was lost to follow-up. SAEs were to be reported to Sponsor [GSK] within 24 hours. Adverse events (AEs) were to be coded using the MedDRA coding dictionary to collapse similar investigator terms for the adverse events. The various coded (preferred) terms were to be grouped into body system categories.

RESULTS

Study Population

The analysis populations were defined as follows:

- Safety Population: % subjects in the Enrolled Population who took at least one dose of Treximet.

- ITT Population: % subjects in the Enrolled Population who took at least one dose of Treximet and had at least one post-treatment migraine assessment.
- 6 Month Completer Population: % of the subjects in the Enrolled Population who were treated with at least dose of the Treximet Tablet, completed at least one study visit (3 or 6 month visit), provided data for at least 6 migraines, and who continued in the study for at least 166 days.
- 12 Month Completer Population: % of the subjects in the Enrolled Population who were treated with at least one dose of study drug, completed at least 1 study visit in the 2nd six month period, provided data for at least 12 migraines, and who continued in the study for at least 346 days.

The number of subjects enrolled and in each of the analysis populations is summarized in the subject disposition Table 5.3-3a.

Table 5.3-3a Subject Disposition: Study TXA107977*

Subject Status & Analysis Populations	12-14 yr n (%)	15-17 yr n (%)	Total n (%)
Planned Enrollment	325	325	650
Enrolled Population	300	356	656
Safety Population	285 (95)	337 (95)	622 (95)
Intent-to-Treat (ITT) Population	273 (91)	318 (89)	591 (90)
3 Month Visit	244 (81)	267 (75)	511 (78)
6 Month Visit	208 (69)	227 (64)	435 (66)
6 Month Completer Population	152 (51)	181 (51)	333 (51)
9 Month Visit	184 (61)	206 (58)	390 (59)
12 Month Visit	171 (57)	192 (54)	363 (55)
12 Month Completer Population	81 (27)	100 (28)	181 (28)
Prematurely Discontinued (Safety Population)	114 (40)	145 (43)	259 (42)
Completed the Study (Safety Population)	171 (60)	192 (57)	363 (58)

*Copied Sponsor's Table Study Report, p 49. Edited for format only.

As shown in the table above, of the subjects in the Safety Population, a total of 58% completed the study and 42% discontinued prematurely. The reasons for subjects not completing the study were: 14% decided to withdraw from the study; 7% were lost to follow-up; 7% withdrew due to an adverse event (see below); 5% violated the protocol; 5% withdrew due to lack of efficacy; 3% did not meet treatment eligibility criteria; and 1% withdrew for other reasons.

The demographics of the safety population are shown in the Table 5.3-3b. The average age for the Safety Population was 15 years (range 12 to 17 years). The majority of

subjects were female (59%) and Caucasian (85%). The demographic characteristics for the 6 and 12 Month Completer Populations were similar to that of the Safety Population.

Table 5.3-3b Demographics Safety Population: Study TXA107977*

Safety Population	12-14 yr N=285	15-17 yr N=337	Total N=622
Age (years)			
Mean (SD)	13.1 (0.85)	16.1 (0.80)	14.7 (1.68)
Median	13.0	16.0	15.0
Min, Max	12, 14	15, 17	12, 17
Sex, n (%)			
Female	134 (47)	233 (69)	367 (59)
Male	151 (53)	104 (31)	255 (41)
Ethnicity, n (%)			
Hispanic or Latino	24 (8)	19 (6)	43 (7)
Race n (%)			
Caucasian	240 (84)	287 (85)	527 (85)
Body Mass Index (kg/m2)			
Mean (SD)	22.01 (4.611)	23.77 (5.249)	22.97 (5.040)
Median	20.77	22.41	21.66
Min, Max	14.4, 38.9	16.3, 47.9	14.4, 47.9

*Copied Sponsor's Table Study Report, p 52. Edited for format only.

Exposure*
*See Table below

The drug exposure is shown in the Table 5.3-3c.

Table 5.3-3c Drug Exposure: Study TXA107977*

Safety Population	12-14 yr N=285	15-17 yr N=337	Total N=622
Total Number of Tablets Taken	6202	6725	12927
Total Number of Tablets Taken per Subject			
Mean (SD) tablets per subject	21.8 (21.30)	20.0 (17.27)	20.8 (19.23)
Median tablets per subject	15.0	15.0	15.0
Days from 1st up to and including the last dose			
Mean (SD)	222.7 (129.49)	216.9 (127.96)	219.5 (128.60)
Median	284.5	275.5	279.0
Number of Tablets Taken per Month			
Mean (SD)	2.3 (2.06)	2.6 (3.88)	2.5 (3.17)

Median	1.8	1.9	1.9
*Copied Sponsor's Table Study Report, p 58. Edited for format only.			

Overall, 622 subjects treated any type of headache attack with the combination tablet. Within the Safety Population, subjects took 12,927 combination tablets to treat their migraine or non-migraine headaches. Overall, the number of tablets taken in the 12 to 14 age group (n=6202) was similar to that taken by the 15 to 17 age group (n=6725). On average, subjects took 20.8 tablets during the study; the average number of days between the first and up to and including the last dose was 219.5 days. Subjects took an average number of 2.5 combination tablets per month.

During the first six months of the study, subjects took more tablets (n=8275) in comparison to the second six months of the study (n=4652); however, per subject, the average number of tablets was similar (first six months: 13.4 tablets; second six months: 12.2 tablets).

In the 6 Month Completer Population, a total of 333 (n) subjects (12-14 years= 152 [n], 15-17 years= 181 [n]) took 10,378 combination tablets to treat their migraine and non-migraine headaches over their time in the study. The average number of tablets taken per month was slightly higher in the 6 Month Completer Population in comparison to the Safety Population.

Within the 12 Month Completer Population, a total of 181 (n) subjects (12-14 years= 81 [n], 15-17 years= 100 [n]) took 6,858 combination tablets to treat their migraine and non-migraine headaches. The average number of tablets taken per subject was higher than that reported in the Safety Population. The average number of tablets taken per month (3.1) was higher in comparison to the Safety Population.

Safety Results

Deaths

There were no deaths reported in this study.

Non-fatal Serious Adverse Events

See below under 7.3.2

All Adverse Events

Overall Summary*
*See Table 5.3-3d

The following trends were observed:

- In the Safety Population, the most common body system in which any adverse event was reported in at least one subject was infections and infestations (32%), followed by musculoskeletal and connective tissue disorders (18%), gastrointestinal disorders (18%), nervous systems disorders (16%), respiratory, thoracic and mediastinal disorders (11%), injury, poisoning and procedural complications (11%), general disorders and administration site conditions (10%), psychiatric disorders (5%), reproductive system and breast disorders (4%), skin and subcutaneous tissue disorders (4%); immune system disorders (3%); ear and labyrinth disorders (2%) and vascular disorders (2%) (Sponsor's Table 3.88; Study Report TXA107977).
- In the Safety Population, the most common adverse events were: nausea, upper respiratory tract infection, nasopharyngitis, sinusitis, dizziness, and neck pain. These events were also commonly reported in the 6 and 12 Month Completer Populations; however, additional events were also commonly reported in these populations. Generally, more subjects reported at least one adverse event in the first six months of the study in comparison to the second six months of the study across populations.
- Age: The proportion of subjects who reported at least one adverse event was higher in the older subjects in comparison to the younger subjects across populations. In the Safety Population, 65% of the 15 to 17 year old subjects reported at least one adverse event in comparison to 61% of the 12 to 14 year old subjects. A similar trend existed in subjects who reported at least one moderate or severe adverse event (12 to 14 years: 40%; 15 to 17 years: 45%) and across populations.
- Gender: In the Safety Population, the proportion of female subjects who reported any type of adverse event was slightly higher than in the male subjects (females= 65%; males= 61%), with the exception of "serious" adverse events which were reported in <1% of each gender. The largest difference between females and males was in reporting drug-related adverse events (females: 31%; males: 23%).
- Race: In the Safety Population, the proportion of Caucasians who reported any type of adverse event was higher in comparison to the other race groups, with the exception of "serious" adverse events which were reported in <1% of subjects of each race group. Sixty-five percent of Caucasians reported at least one adverse event in comparison to 58% of the race group Other and 49% of African Americans.
- Drug-related Adverse Events: Based on the investigator's judgment as being drug related, 27% of subjects within the Safety Population were considered to have experienced at least one adverse event after treatment with the combination tablet. Nervous system disorders and gastrointestinal disorders were considered the most common body systems to be affected. The most commonly reported adverse events across the Safety, 6 and 12 Month Completer Populations were nausea, dizziness, chest discomfort, muscle tightness, neck pain, paresthesia and somnolence. These adverse events were similarly reported across all three populations. Generally, the proportion of subjects reporting drug-related adverse events was higher in the first six months of the study in comparison to the second six months of the study across populations.

Table 5.3-3d Overview of AE Across Populations: Study TXA107977*

All Populations	Safety Population N=622 n (%)	6 Month Completer Population N=333 n (%)	12 Month Completer Population N=181 n (%)
Subjects with any adverse events	393 (63)	239 (72)	130 (72)
Subjects with any moderate or severe adverse event	264 (42)	164 (49)	86 (48)
Subjects with any drug-related adverse event	170 (27)	93 (28)	46 (25)
Subjects with any serious adverse event	4 (<1)	3 (<1)	1 (<1)
Subjects discontinued due to an adverse event	41 (7)	6 (2)	0

*Copied Sponsor's Table Study Report, p 70. Edited for format only

- Subjects who withdrew due to AE: 7% of subjects (7% of 622) in the Safety population prematurely discontinued the study due to an adverse event. 40 of 41 subjects discontinued within the first 6 months of the study. Nausea was the most common adverse event leading to withdrawal (n=7; 1%). All other adverse events leading to withdrawal occurred in <1% of subjects (Sponsor's Table 3.120*).*
- Clinical Laboratory Evaluations: With evaluations every three months, in general, there were no clinically important findings of concern in the summaries of chemistry analytes, hematology, or urinalysis in any of the populations (Safety, 6 Month or 12 Month Completer) or subgroups (age, gender, or race).

  Reviewer comments

  There were higher proportions of subjects than expected with values below the lower limit of normal for all time points for both hematocrit and hemoglobin. In concurrence with the Sponsor, there was no clear explanation for this finding and the normal range used by the central lab may have been set higher for adolescent females. There was no clear trend suggesting an effect of the combination tablet.

  There were 5 subjects (Subject 210, Subject 1563, Subject 2017, Subject 2926, and Subject 2804) who were reported with values considered of potential clinical importance - one subject with increase in potassium (defined as 1.2 x upper limit of normal- at 7.1mmol/L [normal range 3.5-5.3]) and four subjects with increases in liver enzymes (defined as 2 x upper limit of normal for both ALT and AST). With the exception of one subject who was diagnosed with lipid storage disorder (Subject 210) during the study, all these elevations were transient and were considered related to other medical conditions such as due to medication effects, infection (infectious mononucleosis, other viral infections, etc.) or lab processing error (elevated potassium- which upon repeat was reported normal).

Pregnancy during study

Five subjects became pregnant during the study; four of the subjects were withdrawn prematurely due to "protocol violation". The other subject was found to be pregnant at her 12 Month Visit. Two subjects had normal deliveries (Site 0039891/Subject 001726- reported as live birth; Site 040476/Subject 002250- reported as live birth) and, two had elective abortions (Subject 001003/ Site 0039825 - the gestational age and fetal sex at termination was reported as unknown; Subject 002003/Site 039923- gestational age was reported as under 10 weeks and the sex was reported as unknown) and one had a spontaneous abortion (Site 040493/Subject 002483- reported as spontaneous abortion).

Reviewer comments

The presented case narratives (section 12.4 of the submission) for these subjects who became pregnant during the study are noted.

6 Review of Efficacy

Reviewer comments

Please see section 5.2 (review strategy).

Efficacy Summary

6.1 Indication

The sought indication (from the proposed label)-

"TREXIMET, which contains a serotonin (5-HT1B/1D) receptor agonist (triptan) and an NSAID, is indicated for the acute treatment of migraine with or without aura in adults and in adolescents aged 12 to 17 years."

6.1.1 Methods

Reviewer comments

In order to simultaneously analyze dose response with respect to the primary endpoint and compare the 85/500 mg dose group to placebo with respect to the secondary endpoints, a fixed sequence hierarchical testing methodology was used by the Sponsor. 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 for the high dose versus placebo until non-significance was reached. This methodology was proposed to control inflation in the Type I error rate due to multiplicity of testing. These Sponsor proposed methodologies were found to be acceptable by the Agency statistical reviewer. Reference is made to Dr. Steve Bai's review for further details.

6.1.2 Demographics

See section 5.3.

6.1.3 Subject Disposition

See section 5.3.

6.1.4 Analysis of Primary Endpoint(s)

As noted previously, the primary efficacy endpoint was the percentage of subjects who were pain-free at two hours post-treatment. The primary results addtionally included analyses of the following subgroups who were pain-free at two hours post-treatment-

- 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).

Results*

*See Tables 6.1.4a & 6.1.4b

Table 6.1.4a Primary Efficacy Results Proportion of Subjects Pain-Free at 2 Hours Post-Dose (ITT population): Study TXA107979*

	Placebo N=145 n (%)	TREXIMET 10/60mg N=96 n (%)	TREXIMET 30/180mg N=97 n (%)	TREXIMET 85/500mg N=152 n (%)
Pain-free (2 hours): n/N (%)	14/142 (10%)	28/96 (29%)	26/97 (27%)	36/150 (24%)
Treatment Difference (95% CI)	NA	20% (9%, 30%)	16% (7%, 26%)	13% (5%, 22%)
Unadjusted p-value[1]	NA	<0.001	<0.001	0.003
Adjusted p-value[2]	NA	0.003	0.003	0.003

*Copied Sponsor's Table 7, Clinical Overview, p. 39. Modified for format only.
Data Source: CSR TXA107979, Table 2.1, Table 2.2, Table 2.5
NOTE: Differences in percentages, confidence intervals, and p-values for active vs. placebo treatment groups are based on Cochran-Mantel-Haenszel methods, with adjustment for age and baseline pain severity.
1. Not adjusted for multiplicity.
2. Adjusted for multiplicity according to the fixed-sequence testing strategy.

The proportion of subjects pain-free at 2 hours post-dose is summarized by treatment group and compared to the placebo group in the table above. All 3 TREXIMET dose groups were significantly more effective than placebo 2 hours post-dose (multiplicity adjusted p=0.003). Results were similar for the ITT and PP Populations.

Reviewer comments

It is noted in the Agency statistical review (Table 3.3) that the values under Treatment Diff (95% CI) and the p-values that were calculated independently by Dr. Steve Bai are different than what is shown in the table above. These values calculated by Dr. Bai are shown below:

For Treximet 10/60: Treatment Diff = 19.3% (CI 9%, 29.6%; p-value= 0.0001
For Treximet 30/180: Treatment Diff= 16.9% (CI 6.9%, 27%); p-value= 0.0006
For Treximet 85/500: Treatment Diff = 14.1 % (CI 5.7%, 22.6%); p-value= 0.0014.

Dr. Bai further noted that 3 placebo subjects and 2 Treximet 85/500 subjects did not have pain free status at 2 hours (Treated migraine attack when severity was none or mild and or Took prohibited medication) and were excluded from the randomized population.

The Sponsor stated the following with respect these exclusions-

"A re-analysis of this primary endpoint was done, excluding the five ITT subjects from the two sites with compliance violations (Site 055575 and Site 055760), to evaluate the robustness of the study findings (Table 2.66 and Table 2.67). The results of this

analysis were consistent with the conclusions of the analysis done for all subjects (i.e., including these five subjects) and did not impact the study outcome".

"GSK assessment of sites 055575 and 055760 resulted in significant findings of GCP noncompliance regarding inadequate monitoring of subject safety, and identified irregularities that could invalidate efficacy data. In total, 12 subjects were randomized at sites 055575 and 055760. Five of these subjects (2 placebo and 3 sumatriptan 85 mg/naproxen sodium 500 mg) received a dose of double-blind treatment and were in the ITT Population. A subset of the ITT Population excluding data from these two sites was created and used to repeat the primary efficacy analysis. This decision was made before the unblinding of study data. The analysis that excludes data from these two sites is provided to demonstrate robustness of the study findings (Table 2.66 and Table 2.67). Primary efficacy results were consistent whether the data from the two sites were included or excluded, and there was no difference in the overall efficacy conclusions of the study. Findings were reported to the FDA Department of Scientific Investigation."

The subgroup analyses and results (pain free at 2 hours):*

*See Table 6.1.4b

Table 6.1.4b Primary Efficacy Results Summary of Pain-Free at 2 Hours Post-Dose by Sub Groups: Study TXA107979*

	Placebo	Treximet 10/60 mg	Treximet 30/180 mg	Treximet 85/500mg
Age				
12-14	10/70 (14%)	18/43 (42%)	13/46 (28%)	17/65 (26%)
15-17	4/72 (6%)	10/53 (19%)	13/51 (25%)	19/85 (22%)
Gender				
Male	6/58 (10%)	16/44 (36%)	10/41 (24%)	15/57 (26%)
Female	8/84 (10%)	12/52 (23%)	16/56 (29%)	21/93 (23%)
Race				
White	7/107 (7%)	22/75 (29%)	24/84 (29%)	34/130 (26%)
Non-white	7/33 (21%)	6/21 (29%)	2/13 (15%)	2/20 (10%)
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%)

*Copied and Combined Tables 4-1 to 4-4 from Dr. Steven Bai's Review. Modified for format with corrections for minor typographical errors only.

The summary of the results of the subgroup analyses (2 hours pain free post-dose) shown in the table are:

- Age: In both age groups (12-14 and 15-17 years), all three dose groups had higher proportion of subjects who were pain-free at 2 hours compared to placebo group. Within the 12-14 year old group, a numerically higher response was seen in the low dose group than other two higher dose groups.
- Gender: The consistent findings as the primary efficacy results were observed within both gender groups. Within male and female subjects, in all three active dose

groups, a higher proportion of subjects were pain-free at 2 hours compared to placebo group.

- Race: The majority of subjects were Whites (81%). Since each of the other race group consisted of very few subjects, these were combined by Dr. Steven Bai into a single group called Nonwhite group. Within White subjects, all three active dose groups had a higher proportion of subjects who were pain-free at 2 hours compared to placebo. However, in the Non-white group, the placebo subjects had numerically favorable results than both middle and high dose groups.
- Other Subgroups: The results were consistent with the primary analysis results. Within each level of each subgroup, in all three active dose groups there were higher proportions of subjects indicating favorable results compared to the placebo group.

6.1.5 Analysis of Secondary Endpoints(s)

As noted in section 6.1.1 under methodology and by Dr. Steven Bai in his review, the secondary efficacy analysis for the high dose versus placebo was adjusted for multiplicity according to the fixed sequence testing strategy for the following 10 secondary efficacy endpoints that were evaluated sequentially for migraine attack 2 and the results summarized in Table 6.1.5-

- Percentage of subjects who were sustained pain-free from 2 to 24 hours
- Percentage of subjects who were photophobia-free at 2 hours
- Percentage of subjects who were phonophobia-free at 2 hours
- Percentage of subjects who were pain-free at 1 hour
- Percentage of subjects who were sustained photophobia-free from 2 to 24 hours
- Percentage of subjects who were sustained phonophobia-free from 2 to 24 hours
- Percentage of subjects who were sustained nausea-free from 2 to 24 hours
- Percentage of subjects who used rescue medication from 2 to 24 hours
- Time to dose of rescue medication
- Percentage of subjects who were nausea-free at 2 hours

Reviewer comments

It is noted in the Agency statistical review (Table 3.4) that the values under Treatment Diff (95% CI) and the p-values that were calculated independently by Dr. Steve Bai are different than what is shown in the table below. Reference is made to Dr. Bai's review. As with some of the differences that were noted above in the primary efficacy results between the Sponsor's values and Dr. Bai's recalculated vales, these differences in the secondary analyses were not major and if any the values were comparable.

The results of the secondary endpoints (fixed sequence testing) shown in the table below can be summarized as follows:

- 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. According to Dr. Bai, 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.
- With respect to nausea-free endpoint, there was no difference between the placebo group and the high dose Treximet group at 2 hours post-dose. However, in the high dose Treximet group a higher percentage of subjects reported a sustained nausea free effect between 2-24 hours that was statistically significant (see hatched areas in the table below) compared to placebo.

Results of secondary efficacy endpoints (All doses vs. Placebo)

Analyses of secondary endpoints for the middle Treximet dose vs. placebo and the low Treximet dose vs. placebo had similar results to the analyses of the high Treximet dose vs. placebo. One exception was nausea-free at 2 hours post-dose, for which the response varied by dose and appeared better than placebo at the low dose only. The percentage of subjects who used rescue medication within 24 hours post-dose was similar across the active dose groups, and was numerically lower for the active dose groups than placebo (32%, 15%, 16%, and 14% for the placebo, low, middle, and high dose groups, respectively). At all time points 2-24 hours post-dose, a numerically lower percentage of subjects in all active dose groups had used rescue medication than in the placebo group.

Table 6.1.5 Secondary Efficacy Endpoints for the High Dose versus Placebo (ITT Population): Study TXA107979*

	Placebo N=145 n/N (%)	Suma 85mg/Nap 500mg N=152 n/N (%)	Treatment Difference (95% CI) % (%, %)	Unadjusted p-value[1]	Adjusted p-value[2]
Sustained Pain-Free (2-24 hours)	13/142 (9%)	35/150 (23%)	13% (5%,	0.002	0.008
Photophobia-Free (2 hours)	59/144 (41%)	89/151 (59%)	19% (7%,	0.002	0.008
Phonophobia-Free (2 hours)	60/144 (42%)	90/151 (60%)	19% (7%,	0.002	0.008
Pain-Free (1 hour)	6/142 (4%)	11/150 (7%)	3% (-3%,	0.322	1.000
Sustained Photophobia-Free (2-24 hours)	44/144 (31%)	75/151 (50%)	20% (9%,	<0.001	1.000
Sustained Phonophobia-Free (2-24 hours)	47/144 (33%)	79/151 (52%)	20% (9%,	<0.001	1.000
Sustained Nausea-Free (2-24 hours)	68/144 (47%)	94/151 (62%)	16% (4%,	0.007	1.000
Used Rescue Medication (2-24 hours)[3]	47/145 (32%)	21/152 (14%)	- 19%	<0.001	1.000
Time to first Rescue Medication (in hours)	N/A	N/A	N/	<0.001	1.000
Nausea-Free (2 hours)	101/144 (70%)	106/151 (70%)	1% (-10%,	0.907	1.000

*Copied Sponsor's table 16, Study Report TXA107979, p. 79 of 814. Modified for format only.
Source: Table 2.3
NOTE: Differences in percentages, confidence intervals, and p-values for active vs. placebo treatment groups are based on Cochran-Mantel-Haenszel methods, adjusted for age, and for pain related endpoints, adjusted for baseline pain severity as well.
NOTE: For definition of endpoints, see Section 4.8.3.1.
1. Not adjusted for multiplicity.
2. Adjusted for multiplicity according to the fixed-sequence testing strategy.
3. Protocol violators who rescued in ≤2 hours post-treatment were also included.

6.1.6 Other Endpoints

Other efficacy endpoints summarized at the specified time points after dosing with double-blind IP that were reported by the Sponsor were: the percentage of subjects with pain-relief (1, 2, and 4 hours), the percentage of subjects pain-free (4 and 4-24 hours), the percentage of subjects free of photophobia or phonophobia (1, 4, and 4-24 hours), and the percentage of subjects free of nausea (1 and 4 hours). Other than for pain-relief at 1 hour and nausea-free at 1 hour post-dose, the Sponsor reported that a general trend was observed for the active dose groups to respond better than the placebo group across all of these endpoints.

In addition, Health Outcome Assessments were assessed and the following data was summarized at specified time points after dosing with the double-blind IP: 1) the percentage of subjects satisfied with current migraine treatment (at Screening) and at 2 and 24 hours post-treatment, and 2) the percentage of subjects who reported "normal" functioning at 0, 1, 2, and 4 hours post-treatment. Sponsor reported the following health outcome assessments related results-

Satisfaction with medication efficacy, side effects, and overall satisfaction:

The overall trend at both 2 hours and 24 hours post-dose was that there were more subjects satisfied ("satisfied" or "very satisfied") with each of the active doses vs. placebo for each of the global satisfaction questions, except for satisfaction with side effects for the high dose group vs. placebo for which satisfaction with side effects was only comparable. At 2 hours post-dose, the percentage of subjects satisfied with overall efficacy was 39%, 54%, 70%, and 56%, satisfied with overall medication was 41%, 64%, 68%, and 57%, and satisfied with side effects was 54%, 72%, 73%, and 56% for the placebo, low, middle, and high dose groups, respectively. At 24 hours post-dose, the percentage of subjects satisfied with overall efficacy was 41%, 71%, 74%, and 62%, satisfied with overall medication was 45%, 68%, 72%, and 64%, and satisfied with side effects was 58%, 78%, 77%, and 63% for the placebo, low, middle, and high dose groups, respectively.

Ability to Function:

The percent of subjects reporting normal functioning at 2 and 4 hours post-dose for all active dose groups was similar and showed a trend for improvement over placebo. The percentage of subjects reporting normal functioning at the time of dosing and at 2 and 4 hours post-dose was 5%, 19%, and 43% for the placebo group, 2%, 35%, and 59% for the low dose group, 2%, 31%, and 60% for the middle dose group, and 3%, 30%, and 60% for the high dose group.

6.1.7 Subpopulations

See 6.1.4

7 Review of Safety

Safety Summary

7.1 Methods

See section 5.2 Review Strategy. Of the three studies submitted, because Study TXA107979 was the pivotal randomized placebo controlled trial, it's safety data served as the main reference in safety evaluations and therefore discussed under section 7. Relevant safety data from the PK study and the uncontrolled open-label long term safety study was also included in this section although these were discussed under section 5.3. In particular, data stemming from the Modified-Safety population (defined as subjects in the safety population who took a dose of double-blind, randomized treatment) was considered more relevant in the adverse events assessments.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 5.1.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 7.2.1 Overall Exposure All Studies*

Study Drug	Exposure Count (Study)
TREXIMET 85 mg/500 mg	622 (TXA107977)
	152 (TXA107979)
	9 (TXA108504)
	TOTAL = 783
TREXIMET 30/180 mg	97 (TXA107979)
	8 (TXA108504)
	TOTAL = 105
TREXIMET 10/60 mg	96 (TXA107979) 7 (TXA108504) **TOTAL = 103**
OVERALL TOTAL	**991**

*Copied Sponsor's Table 11 Clinical Overview p.50. Edited for format only. Data Source: CSR TXA107979, Table 1.4; CSR TXA107977, Table 1.8; CSR TXA108504, Table 9.01

The demographics of the study population for all the studies including the pivotal study TXA 107979 is discussed in section 5.3.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in any of the studies.

7.3.2 Nonfatal Serious Adverse Events

A total of 6 SAEs were reported in 5 subjects following TREXIMET treatment (incidence rate of 0.5%). See Table 7.3.2. The 2 subjects who experienced SAEs from the pivotal study TXA107979 are not discussed further because these events occurred during the single-blind placebo treatment period.

Table 7.3.2 SAE All Studies*

Subject	Age/Sex/Race	SAE Preferred Term	Withdrawn Y/N	Resolved Y/N
Study TXA107979; Single-Blind Placebo				
1953	14yrs/Male/White	Testicular torsion	N	Y
1360	17yrs/Male/White	Concussion, Clavicle fracture, Jaw fracture	Y Y	Y Y
Study TXA107977; TREXIMET 85/500 mg				
749	17yrs/Female/White	Suicide attempt	Y	Y
929	12yrs/Male/White	Syncope Hemolytic anemia	N	Y
978	15yrs/Male/White	Suicidal ideation	N	Y
2483	16yrs/Female/African American	Spontaneous abortion	N	Y
Study TXA108504; TREXIMET 30/180 mg				
726	16yrs/Female/White	Suicide attempt	N	Y

*Copied Sponsor's Table 16, Clinical Overview Section, p. 57. Edited for format only

Pivotal Study (study TXA107979)

Two (<1%) subjects reported a total of 4 SAEs. There were no SAEs on subjects receiving TREXIMET; all the SAEs were single-blind, placebo-emergent events. One

subject was withdrawn due to SAEs (concussion, clavicle fracture, jaw fracture). All events resolved.

Reviewer Comments

In concurrence with the investigator and the Sponsor, all these placebo-emergent events can be considered as being unrelated to Treximet.

Long term Safety Study (study TXA107977)

Overall, 4 (<1%) subjects in the Safety Population reported a total of 5 SAEs. None were considered by the investigator to be related to study drug, and all resolved. One SAE (suicide attempt) led to premature withdrawal from the study.

Subject 749 (site 039820)- Suicide Attempt

This was a 17 year old CF who was screened in April of 2008 with no other significant past medical history. During the study period, the subject had experienced 8 migraine attacks all of which was treated with one Treximet tablet (85/500). The last dose of Treximet was on Sep 19, 2008. On (b) (6) days after the start of the study), the subject attempted suicide by taking an intentional overdose of hydrocodone and exedrin. Subject was hospitalized and subsequently discontinued from the study on (b) (6) (b) (6) after resolution.

Reviewer Comments

Although the exact cause for the suicide attempt has not been provided, attribution of the suicide attempt to Treximet as a cause is remote and unlikely.

Subject 929 (site 039824)- Syncope, Hemolytic Anemia

This was 12 year old CM who was screened on May 2, 2008 with a history of asthma, seasonal allergies and ADHD. Concomitant medications included Adderall XR, Advair, melatonin, and Singulair. From June 02, 2008 until June 08, 2008, the subject received Bactrim DS for the treatment of a toe infection. During the study, this subject experienced a total of 9 migraines, 8 of them were treated with Treximet. The last dose of the Treximet was taken on June 11, 2008.

The following is the Sponsor's narrative:

"On June 10, 2008, this subject reported experiencing shortness of breath, chest heaviness, tingling hands feet, and decreased energy. On (b) (6), the subject continued to feel unwell (b) (6), complaining of dizziness and tingling along with some shortness of breath. Later that day, at 2:03 pm, the subject took a dose

of the Combination Tablet for a migraine that began at 1:03pm; the migraine was reported resolved at 3:03 pm. His complaints continued and he was taken to a walk-in medical clinic and evaluated. At the clinic the subject generally appeared well, but was reported to be not eating and to be intermittently taking Tums for ongoing nausea. The subject was further noted to have lost 5lbs since May 30, 2008. A chest x-ray, CBC, and electrolytes were normal; EBV testing was indicative of an ongoing infection and the subject was discharged with a presumptive diagnosis of a viral syndrome.

On (b) (6)*, the subject experienced grade 3 (severe) vasovagal syncope. The subject's mother, a registered nurse, reported that the subject collapsed on exiting from the bathroom and appeared cyanotic; earlier, the subject had been noted to be pale and experiencing nausea and vomiting. The mother believed the subject to be "pulseless" and attempted a chest compression, at which point the subject "awoke" and pushed her away. The subject later reported that he had gone to the bathroom because of the nausea and had become light-headed and passed out as he left.*

The subject was taken to the hospital and evaluated. Chest x-ray, ECG, eGFR, and urinalysis were within normal limits. Troponin I, d-dimer, total CK, and stool guiac were negative. Screens for mono and influenza antigens A and B were negative; a strep A screen was positive, as was an antistreptolysin O titer. Chemistries were normal except for slight decreases in sodium, creatinine, alkaline phosphatase, albumin, and total protein; BUN was slightly elevated. Hematology revealed a WBC of 9.66 k/cm3 (3.6-9.0); hematocrit of 27.24% (44.9-51.1); hemoglobin of 9.49 g/dl (14.9-17.1); and MCV of 80.7 (86-96); platelets were normal. Venous thromboembolism and cardiac arrest were ruled out. IV fluids were administered. The subject was determined to have vasovagal syncope, anemia, and strep pharyngitis, and was discharged to home on Zithromax to follow-up with his physician.

On (b) (6)*, repeat labs were obtained. Relevant laboratory values were: hemoglobin 8.3 g/dl (12.0-16.0); hematocrit of 24% (36-49); and platelet count 272 per mm3 (130-400). The subject was admitted to the hospital on* (b) (6)*, and treated with packed red blood cells and iron supplements. Relevant laboratory data prior to discharge were: hematocrit 36.2% and hemoglobin 12.7 g/dl. This event resolved on* (b) (6)

In summary, this twelve year old had hemolytic anemia presumed to be secondary to a viral etiology, vasovagal syncope, and strep pharyngitis. The vaso-vagal syncope and hemolytic anemia was, in the opinion of the investigator, a serious adverse event, "not related" to the use of the Combination Tablet.

The subject returned to the clinic for a Final Visit on May 20, 2009. Vital signs at this Final Visit were: height 146 cm; weight 35.2 kg; BMI 16.51 kg/m2; blood pressures of 104/58 mmHg, 100/58 mmHg, and 98/58 mmHg; and heart rate of 90 bpm. An ECG performed at this visit was reported as normal. In addition, there were no clinically significant laboratory findings reported for this subject during the study."

Reviewer Comments

There were multiple active medical problems that this subject was experiencing and the subject was receiving multiple medications. There was no confirmed etiology for the anemia that required transfusion. Therefore the designation of the anemia as a hemolytic anemia is not substantiated. As vasovagal etiology as cause for the event of syncope is plausible.

Subject 978 (site 039987)- Suicidal Ideation

This 15-year-old Caucasian male with past medical history of psychiatric disorders, mood disorder, respiratory, thoracic and mediastinal disorders, metabolism and nutrition disorders and eye disorders was screened for participation on July 2, 2008. During the study, this subject experienced a total of 14 migraines, 12 of them were treated with Treximet. On (b) (6) days after this subject's first dose of Treximet and (b) (6) days after the last dose, the subject developed suicidal ideation and was hospitalized. The subject's mother stated that she believed the event was triggered by difficulties being experienced by a friend of the subject. This subject was treated with bupropion hydrochloride and Abilify. This event was reported as resolved on (b) (6). The subject returned to the clinic for a final Visit on June 29, 2009. An ECG performed at this visit was reported as normal. There were no clinically significant laboratory findings reported for this subject during the study.

The discharge summary (b) (6) stated the subject's discharge diagnosis was Impulse control disorder NOS, mood disorder NOS. Upon discharge, this subject's condition was noted as improved.

Reviewer Comments

In concurrence with the investigator and the Sponsor, attribution of the suicidal ideation to Treximet that occurred (b) (6) days after the last dose of Treximet, as a cause, is unlikely in this subject with underlying psychiatric history.

Subject 002483 (site 040493)- Abortion spontaneous

This 17-year-old African American female was screened for participation on January 10, 2008. During the study, this subject experienced a total of 8 migraines of which she treated each of them with Treximet. Concomitant medications included loratadine, BC powder and Yazmin. This subject returned for a Final Visit on (b) (6) at which time the subject's urine pregnancy test came back positive. The subject's last menstrual period was (b) (6). Her estimated date of delivery was (b) (6)

Follow up information on September 22, 2009- the subject's mother was contacted who stated that the subject had a spontaneous abortion (b) (6) weeks gestation) which was (b) (6) days after starting Treximet. Her last dose of Treximet was on November 23, 2008.

PK Study (study TXA108504)

Subject 726 (site 56824)- Suicide attempt

This 16-year-old female subject with a history of sexual abuse (undergoing counseling) was enrolled in an open-label study for the treatment of migraine. The subject received TREXIMET (30/180 mg tab) single dose on 11 January 2009. Concomitant medications included paracetamol, ibuprofen, diphenhydramine hydrochloride and Robitussin with codeine. On (b) (6) days after the start of TREXIMET, the subject had attempted suicide by overdosing paracetamol (Tylenol), ibuprofen (Advil) and diphenhydramine hydrochloride (Benadryl) and Robitussin with codeine. The subject was hospitalized in the intensive care unit for (b) (6) and then transferred to a psychiatric hospital. The subject was treated with activated charcoal. The event was considered resolved on (b) (6).

There was 1 SAE, a suicide attempt (an overdose of Tylenol, Advil and Benadryl) in a subject who received a single dose of TREXIMET 30/180 mg in the study. The SAE occurred (b) (6) days after dosing, and was judged by the Investigator not to be related to study drug. The subject was hospitalized and the event was reported as resolved after (b) (6).

7.3.3 Dropouts and/or Discontinuations

Table 7.3.3 Subject Disposition All Studies*

	TXA107979		TXA107977	TXA108504
	Placebo	TREXIMET (any dose)	TREXIMET (85/500 mg)	TREXIMET (any dose)
Adolescents Enrolled	**865**		**656**	**24**
TOTAL Adolescents Randomized[1] / Exposed[2]	**176[1]**	**413[1]**	**622[2]**	**24[2]**
Completed, n (%)	**145 (82)**	**345 (84)**	**363 (58)**	**24 (100)**
Prematurely Discontinued (Total)	**31 (18)**	**68 (16)**	**259 (42)**	**0**
Subject did not have opportunity to treat migraine	20 (11)	37 (9)	0	0
Lost to follow-up	8 (5)	12 (3)	43 (7)	0
Withdrew consent	0	8 (2)	90 (14)	0

Protocol deviation	3 (2)	3 (<1)	30 (5)	0
Investigator discretion	0	5 (1)	0	0
Adverse event	0	2 (<1)	41 (7)	0
Lack of efficacy	0	1 (<1)	28 (5)	0
Did not meet treatment eligibility criteria	0	0	18 (3)	0
Other reasons	0	0	9 (1)	0

*Copied Sponsor's Table 10, Clinical Overview, p. 49
Data Source: CSR TXA107979, Table 1.4; CSR TXA107977, Table 1.8; CSR TXA108504, Table 9.01
1=Number of subjects randomized; 2=Number of subjects exposed to TREXIMET

Withdrawal from Study due to an Adverse Event

Pivotal Study (studyTXA107979)

Three (<1%) subjects in the single blind placebo group reported 5 AEs which resulted in withdrawal. These consisted of rectal hemorrhage, increased blood pressure, and clavicle fracture/concussion/jaw fracture (reported as a SAE). There were no withdrawals due to AEs in the double-blind treatment group.

Long term Safety Study (studyTXA107977)

Overall 7% of subjects in the Safety Population prematurely discontinued the study due to an AE; 40 of 41 subjects discontinued within the first 6 months of the study. *Nausea was the most common AE leading to withdrawal* (n=7; 1%). All other AEs leading to withdrawal occurred in <1% of subjects (see CSR TXA107977, Table 3.120). There was 1 SAE (suicide attempt) which resulted in withdrawal (see 7.3.2).

PK Study (study TXA108504)

There were no AEs leading to withdrawal.

7.4 Supportive Safety Results

Pivotal Study TXA107979: Overview of Treatment-Emergent Adverse Events By Double-Blind Treatment (Modified-Safety Population)*

*See Table 7.4

Table 7.4 Overview of Treatment-Emergent Adverse Events By Double-Blind Treatment (Modified-Safety Population): Pivotal Study TXA107979*

	Placebo N=145 n (%)	Suma 10mg/Nap 60mg N=96 n (%)	Suma 30mg/Nap 180mg N=97 n (%)	Suma 85mg/Nap 500mg N=152 n (%)	Total N=490 n (%)
Subjects with any AE	12 (8)	12 (13)	9 (9)	19 (13)	52 (11)
Subjects with any AE occurring within 72 hours of dosing	7 (5)	6 (6)	7 (7)	17 (11)	37 (8)
Subjects with any drug-related AE	3 (2)	2 (2)	4 (4)	16 (11)	25 (5)
Subjects with any moderate or severe AE	5 (3)	6 (6)	3 (3)	9 (6)	23 (5)
Subjects with AE leading to withdrawal	0	0	0	0	0
Subjects with any SAE	0	0	0	0	0

*Copied from Sponsor. Study Report TXA107979. Table 27, p. 97 of 814. Modified for format only.
Source: Table 3.5, Table 3.11

Summary of observations of Treatment Emergent AE: Pivotal Study TXA107979

- Sponsor reported that the incidence of AEs was generally similar across treatment groups. However, AEs occurring within 72 hours after dosing and drug-related AEs both showed a dose response effect, with incidence of events increasing with increasing dose.
- Age: The proportion of subjects who reported at least one AE was generally similar in the younger (12-14 years) and older (15-17 years) subjects across the Enrolled, Safety, and Modified-Safety Populations (Sponsor's Tables 3.2, 3.3, 3.6, 3.64, 3.65). In the Modified-Safety Population, the proportion of subjects reporting at least one double-blind treatment-emergent AE was slightly higher in the older versus younger age group (12-14 years: 9%; 15-17 years: 12%). Between the two age groups, there was some variability in AE incidence by treatment group. In the 12-14 years age group, only the high dose group had incidence of AEs that was numerically higher than placebo (incidence of AEs: 8%, 5%, 7%, and 14% for placebo, low, middle and high dose groups, respectively). In the 15-17 years age group, all active dose groups had an incidence of AEs that was numerically higher than placebo, but the incidence of AEs was highest for the low dose group (incidence of AEs: 8%, 19%, 12%, and 11% for placebo, low, middle and high dose groups, respectively) (Sponsor's Table 3.64, 3.65).
- Gender: In the Modified-Safety Population, the proportion of subjects reporting at least one double-blind treatment-emergent AE was similar in females and males (females: 10%; males: 11%) (Sponsor's Tables 3.38, 3.39).
- Race: In the Modified-Safety Population, the proportion of subjects reporting at least one double-blind treatment-emergent AE was similar in whites and non-whites (whites: 10%; non-whites: 12%) (Table 3.50, Table 3.51).

- Organ System: In the Modified-Safety Population, among all double-blind treatment-emergent AEs, there was a greater incidence of nervous system AEs reported by all active dose groups compared with placebo, and a greater incidence of musculoskeletal AEs reported by the high dose group versus all others (nervous system: 0%, 4%, 3%, 4%; musculoskeletal: 1%, 1%, 0%, 5% for placebo, low, middle, and high dose groups, respectively).
- AE Occurring within 72 hours of dosing: A dose response was seen with 5% of subjects experiencing an AE within 72 hours after treatment with double-blind placebo compared with 6%, 7%, and 11% for the low, middle, and high dose groups, respectively. The only AEs occurring within 72 hours of double-blind treatment with an incidence of ≥2% per treatment group were muscle tightness and hot flush (i.e., hot flash[es]). Two percent (2%) of subjects in the high dose group reported muscle tightness within 72 hours after treatment compared with 0%, 0%, and 0% for the placebo, low, and middle dose groups, respectively. Two percent (2%) of subjects in the middle dose group reported hot flush within 72 hours after treatment compared to 0%, 0%, and <1% for the placebo, low, and high dose groups, respectively. (Sponsor's Table 3.11).
- AE Assessed as Drug-Related:
    - Assessed as drug related by the investigator, in the Modified-Safety Population, a dose response was seen with 2% of subjects experiencing a drug-related AE in the placebo group compared with 2%, 4%, and 11% for the low, middle, and high dose groups, respectively (Sponsor's Table 3.12).
    - The incidence of drug-related events emerging within 72 hours after double-blind treatment was 2% in the placebo group and 2%, 4%, and 10% for the low, middle, and high dose groups, respectively (Sponsor's Table 3.13). The only drug-related AE with an incidence of ≥2% and the only drug-related event emerging within 72 hours after double-blind treatment dosing with an incidence of ≥2% was muscle tightness in 3 (2%) subjects in the high dose group (Sponsor's Tables 3.12 and 3.13).
    - By age group, 6% of 15-17 year old subjects compared with 2% of 12-14 year old subjects in the middle dose group reported a drug-related double-blind treatment emergent AE, otherwise the incidence of AEs in each treatment group was similar across the two age groups (Sponsor's Tables 3.74 and 3.75). Six percent of 15-17 year old subjects compared to 2% of 12-14 year old subjects in the middle dose group reported a drug related AE emerging within 72 hours after double-blind treatment dosing, otherwise the incidence of AEs emerging within 72 hours of dosing in each treatment group was similar across the two age groups (Sponsor's Tables 3.76 and 3.77).

7.4.1 Common Adverse Events

Pivotal Study TXA107979: Most Common Double-Blind Treatment-Emergent Adverse Events (Modified-Safety Population)*

*See Table 7.4.1

Table 7.4.1 Most Common[1] Treatment-Emergent Adverse Events By Double-Blind Treatment (Modified-Safety Population): Pivotal Study TXA107979*

	Placebo N=14 5 n (%)	Suma 10mg/Nap 60mg N=96 n (%)	Suma 30mg/Nap 180mg N=97 n (%)	Suma 85mg/Nap 500mg N=152 n (%)
Subjects with any AE	**12 (8)**	**12 (13)**	**9 (9)**	**19 (13)**
Nasopharyngitis	3 (2)	0	1 (1)	1 (<1)
Hot flush (i.e., hot flash[es])	0	0	2 (2)	1 (<1)
Muscle tightness	0	0	0	3 (2)

*Copied from Sponsor. Study Report TXA107979. Table 29, p. 98/814. Modified for format only. Source: Table 3.14
1=Defined as ≥2% of subjects in any double-blind treatment group

The incidence of double-blind treatment-emergent AEs was low with only nasopharyngitis, hot flush (subject verbatim text: "hot flash" or "hot flashes"), and muscle tightness having incidence ≥2% in any treatment group. All of the AEs of hot flush and muscle tightness emerged within 72 hours after double-blind treatment dosing (Sponsor's Table 3.15), whereas, only one of the five subjects with nasopharyngitis experienced this AE within 72 hours after double-blind treatment dosing (Sponsor's Table 3.11).

Nausea (reported as the most common AE in the long-term safety study as noted above), was reported as a double-blind treatment-emergent AE by a low number of subjects (0, 0, 0, and 1% of subjects in the placebo, low, middle, and high dose groups, respectively) (Sponsor's Table 3.8).

7.4.2 Laboratory Findings

According to the Sponsor, labs were performed only at screening and no labs were collected post-treatment.

7.4.3 Vital Signs

According to the Sponsor, vitals were performed only at screening and no vitals were collected post-treatment.

7.4.4 Electrocardiograms (ECGs)

According to the Sponsor, ECGs were performed only at screening and no ECGs were collected post-treatment.

7.4.5 Special Safety Studies/Clinical Trials

NA

7.4.6 Immunogenicity

NA

8 Postmarket Experience

The report of post marketing experience was submitted under module 5.3.6.

SPONTANEOUS ADVERSE EVENT REPORTING

TREXIMET was approved in April 2008 in the USA for acute treatment of migraine attacks with or without aura in adults.

Cumulative post-marketing experience to the end of December 2013 was estimated to be (b) (4) prescriptions sold (Source: Intercontinental Medical Statistics (IMS), US National Disease and Therapeutic Index). This was estimated to be equivalent to approximately 1,291,175 patients (assuming (b) (4) prescriptions per patient) or alternatively, equivalent of 17.76 million treated migraine attacks treated (this assumes (b) (4) per prescription and (b) (4) to treat each migraine). Information on post marketing safety data provided in this section was derived from the Sponsor's (GSK) worldwide safety database, clinical studies performed since the initial marketing authorization application (MAA) was approved and published reviews and case reports.

The objective of this post market report was to provide the currently available information describing the use of TREXIMET in patients of all ages for the acute treatment of migraine attacks with or without aura. Where applicable, ages were split into adults (over 18 years old), adolescents (12-17 years old) and children (under 12 years old).

Database Search Strategy

Sponsor used the following criteria to search the worldwide safety database:

- Data lock points: 28th February 2014
- Report types: Spontaneous and post-marketing surveillance (PMS) reports
- Age: All
- MedDRA version: 17.0

Search Results

Overall, the search retrieved 613 individual reports; 602 described TREXIMET use in adult patients, 10 described TREXIMET use in adolescent patients and one case described TREXIMET exposure in an infant who was breastfed.

Four hundred and sixty three cases (75%) described females, 91 cases (15%) described males, and gender was unknown / unspecified in 59 cases (10%). Where specified, age ranged from 13 years to 80 years, with a median age of 43 years. The age and gender distribution from spontaneous reports is similar to the profile of migraineurs; therefore no sub-group at a particular risk of AEs was identified.
A total of 11 cases in the 10-19 year age group were identified.

Breakdown of the 613 spontaneous reports by the System Organ Class (SOC) of the primary event (usually the most medically serious) was provided in Figure 2 of the report. The most commonly reported (top 5) adverse events (AEs) were within General disorders and administration site conditions (173 cases, 28.2%), Nervous system disorders (107 cases, 17.5%), Gastrointestinal disorders (102 cases, 16.6%), Cardiac disorders (37 cases, 6%) and Musculoskeletal and Connective Tissue disorders (33 cases, 5.4%). The top 3 reported events within each of these SOCs were as follows: General disorders and administration site conditions: drug ineffective (n=99); chest discomfort (n=30), feeling abnormal (n=30); Nervous system disorders: dizziness (n=44), headache (n=27), paraesthesia (n=27); Gastrointestinal disorders: nausea (n=66), vomiting (n=38), diarrhea/abdominal discomfort/abdominal pain upper (n=13 each); Cardiac Disorders: palpitations (n=21), myocardial infarction (n=13), cardiac disorder/tachycardia (n=3 each); Musculoskeletal and connective tissue disorders: neck pain (n=12), muscle tightness (n=12), myalgia/pain in jaw (n=10 each).

The majority of the most frequently reported events were events labeled in the USPI, with the exception of drug ineffective, headache and feeling abnormal.

Cases with a fatal outcome

Patients < 18 years old: There were no cases with a fatal outcome.

Adults: There were six reports describing death or a fatal outcome, four of which were received from consumers and were not medically verified.

Three of the six reports consisted of “death” as the only event and no cause of death was provided. Of the remaining reports, there was a report of somnolence and asthenia in a female patient (age unspecified) with a seriousness criteria of “patient died” – no further details were provided; a poorly documented report of a female patient (age unspecified) who was hospitalized for a cerebral hemorrhage and subsequently died – cause of death was not provided. The final report was a consumer report describing death in a female patient who had used TREXIMET for several years and had been hospitalized previously for migraine; TREXIMET and other unspecified medications

were reported to be ineffective and led the patient to be in pain and to cry. The events leading up to the patient's death and cause of death were not specified.

Serious Adverse Events

Patients < 18 years old: 3 of the 11 reports were considered serious. The cases were – paralysis in a 14 year old female requiring hospitalization with no additional information; palpitations and chest pain in a female aged between 10-19 years with no additional information; and deafness in a neonate who was exposed to Treximet via breast milk.

Adults: There were 114 cases which described a serious adverse event in adults who had received TREXIMET. The SOC distribution of these cases was provided in Figure 3 of the report. The top 3 reported events within the 3 most common SOCs were as follows: Nervous System Disorders SOC; dizziness (n=11), serotonin syndrome / paraesthesia / somnolence (n=6 each); Cardiac Disorders: myocardial infarction (n=13) and arteriospasm coronary / palpitation (n=3 each); General disorders and Administration site conditions: drug ineffective (n=10), chest discomfort (n=8), chest pain (n=8).

Adverse Events of Special Interest:

- Cardiovascular
  - In patients < 18 years old, other than a non-serious report of chest pain and a serious report of palpitations and chest pain (see above), there were no reports describing cardiovascular events consistent with those described in the boxed warning of the USPI in this patient population.
  - In Adult patients, there were 13 reports of myocardial infarction, 3 reports of coronary arteriospasm and 3 reports of cardiac disorder within the Cardiac disorders SOC. Within the Nervous system disorders, there were 2 reports each of cerebral hemorrhage and cerebrovascular accident and a single report of a transient ischemic attack. Within the Vascular disorders SOC, 2 reports each of hemorrhage and vasospasm and a single report of aortic aneurysm.
- Gastrointestinal
  - In patients < 18 years old, there were no reports indicative of GI toxicity.
  - In Adult patients, there were 8 reports of gastric disorder; only one report was medically verified and all 8 reports consisted of non-specific events such as gastric problems/stomach issues/stomach distress/stomach trouble/stomach complaints. 2 of the 8 reports of gastric disorder were serious, and the serious criteria were due to events in other SOCs both cases. One patient experienced a hemiparesis and one patient experienced a myocardial infarction which resulted in the cases being serious. In addition to the 8 reports of gastric disorder, there were 11 individual cases which described the following gastrointestinal events, some of which were serious- gastrointestinal disorder, haematemesis and ulcer hemorrhage; 2 reports each of gastric

hemorrhage and gastrointestinal hemorrhage and single reports of gastric ulcer, colitis ischemic and haematochezia.

Reviewer comments

Serious cardiovascular events including myocardial infarction and stroke are known class effects of non-steroidal anti-inflammatory drugs (NSAIDs). Serious cardiac events, including myocardial infarction resulting from coronary artery vasoconstriction are known class effects of triptans. The combination product therefore has a potentially increased risk of cardiovascular events and these have been closely monitored. Boxed warning statements are included in the TREXIMET United States Prescribing Information (USPI) and patient labeling to warn of the risk of these events.

In summary, in concurrence with the Sponsor, no new safety signals relating to cardiovascular events were identified from adult post-marketing reports; postmarketing data to date (as of the report date) are consistent with the known safety profile of TREXIMET and are comparable to those described in the USPI.

Like wise, serious gastrointestinal (GI) events including inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine are reported class effects of NSAIDs. Risks of GI toxicity associated with TREXIMET use are contained within a boxed warning in the USPI and is included in the medication guide. Because of the potential for GI toxicity resulting from the non-steroidal anti-inflammatory (NSAID) component of TREXIMET, GI events have been closely monitored.

In summary, in concurrence with the Sponsor, overall, there were no new safety signals that were identified from adult post-marketing reports; postmarketing data regarding GI events to date (as of the report date) are consistent with the known safety profile of TREXIMET and are as reflected in the USPI.

PUBLISHED LITERATURE REVIEW

A comprehensive review of the published literature was performed. The aim of this was to summarize the published data relating to the use of TREXIMET for the treatment of migraine.

Search Strategy

A search for published biomedical/scientific articles reporting the safety of TREXIMET was conducted in Embase.com (covers Embase and Medline) for literature citations and abstracts, and SearchLight for conference literature and abstracts.

The search strategy utilized the following parameters:

Search period:	Embase: 01 January 2004 (International Birth Date) to 28 February 2014 Searchlight: 01 January 2004 to 28 February 2014
Population:	All ages
Indications:	All indications
Search terms:	Toxicity and intoxication, fertility, drug safety, device safety, toxicology, toxicity testing, carcinogenesis, mutagenicity, morbidity, mortality, reproduction, pregnancy disorder, lactation, pregnancy disorders of endocrine origin, obstetric care, breast feeding, prenatal drug exposure, drug milk level, breast milk, prenatal disorder, embryonic and fetal functions, parameters concerning the fetus, newborn and pregnancy, drug abuse, addiction, kidney dysfunction, liver dysfunction, drug withdrawal, treatment failure, drug resistance, drug efficacy
Language:	English language only

According to the Sponsor, the searches described above yielded several hundred reports for Embase and Searchlight. These were reviewed to retrieve relevant articles for further discussion. Key references were identified as articles in which the safety of TREXIMET in all ages was a primary focus or significant information on the safety of TREXIMET in this population was provided. These articles were summarized and full abstracts (where available) were provided. The Sponsor concluded that no new safety information was identified following the published literature review.

Reviewer comments

In the absence of any specific safety concern that was identified, and with a safety data base in the adolescent population that stems from the Sponsor conducted controlled clinical trials that primarily served as the basis on which the safety profile of Treximet was assessed in the adolescent population, these articles were not reviewed in detail and no further comments will be made.

9 Appendices

None.

9.1 Literature Review/References

See section 8.

9.2 Labeling Recommendations

See attached PLR with suggested changes.

9.3 Advisory Committee Meeting

Not applicable.

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

/s/

RAMESH RAMAN
05/12/2015

ERIC P BASTINGS
05/13/2015