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RESEARCH**

APPLICATION NUMBER:
22-430

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

SECONDARY REVIEW FOR NDA 22430

Date: October 26, 2009

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Drug: Lysteda (tranexamic acid)

NDA: 22430

Subject: Quantitative Safety Review of NDA 22-430

Overview

The purpose of this secondary review is to address the questions raised by the medical division, the Division of Reproductive and Urological Products (DRUP), regarding the primary statistical safety review written by Dr. Olivia Lau for NDA 22-430, dated July 30, 2009. The primary statistical safety review should be interpreted in light of the following points:

- The scope of the primary statistical safety review was limited to the data from the clinical trials submitted by the sponsor.
- The clinical trials conducted by the sponsor were powered for efficacy rather than safety endpoints.
- Since the sponsor did not pre-specify safety endpoints, all analyses of safety endpoints should be regarded as exploratory in nature.
- All p values, risk ratios and confidence intervals should be interpreted as exploratory and hypothesis generating rather than as inferential values corresponding to hypothesis tests.
- Missing data and the use of non-comparative, open-label studies pose significant problems for meaningful statistical analysis of most of the safety data.
- Since all conclusions in the primary review are exploratory in nature, we defer to the review division for the clinical relevance and significance of any observed outcomes or imbalances.
- It has come to our attention that the review division has access to other data outside of the scope of the submitted clinical trials data. Since the primary statistical safety review considered only the submitted clinical trials data, the conclusions and caveats in the primary review are limited to data submitted by the sponsor. We cannot comment on whether the totality of the other existing data together with the submitted clinical trials data is adequate to establish the long term safety and risk/benefit profile for Lysteda, but will defer to the judgment of the review division in this matter.

Objective

This secondary review has been written to address the clarifications sought by of the review division, DRUP, regarding the primary review of NDA 22-430, conducted by Dr. Olivia Lau, dated July 30, 2009.

DRUP Points of Concern

DRUP Point 1: The overall conclusions of the review notes that “the randomized studies are insufficiently powered to detect safety outcomes” and “insufficient data to adequately

assess the long term safety implications of chronic exposure to tranexamic acid” (p 5). On p 24, the review states that “insufficient data to perform statistical inference” The review frequently characterizes exposure as “only” (e.g., p 8 - “only 607 have at least 12 menstrual cycles of safety data.”) In Section 6.1 (p 22), the review describes abnormalities observed on ocular, renal and VTE parameters among tranexamic acid subjects, without providing a balanced discussion of the same parameters in placebo subjects. The Summary and Conclusion section (p 24) states that “VTE adverse events, other adverse events, ophthalmologic changes (decreased visual acuity, abnormal color vision, and abnormal retinal examination), and decreased renal function were observed to some extent in the randomized studies, but the relatively small sample sizes mean that the confidence intervals for the relative risk were extremely wide.”

1a. DRUP: We acknowledge that the Applicant was never requested to power the studies for safety outcomes.

1a. DBVII Response: Agreed, the studies were powered for efficacy endpoints rather than quantitative safety endpoints.

1b. DRUP: Regarding the adequacy of exposure, the Applicant provided more than DRUP had requested (i.e., 10,000 cycles of use, and 200 women completing one year of treatment requested; while the Applicant provided over 12,000 cycles, 387 subjects completing one year and 227 women completing two years of treatment). This exposure also exceeds that recommended in the ICH E1 guidance for safety assessment of drugs intended for long-term treatment of non-life-threatening conditions. The ICH guidance notes that “safety evaluation during clinical drug development is not intended to characterize rare adverse events occurring in less than 1 in 1000 patients.”

1b. DBVII Response: The majority of the long term safety data comes from open-label trials or open-label extensions of randomized placebo controlled trials. This poses significant problems for meaningful statistical analysis. Additionally, the use of an aggregated number cycles to infer safety presupposes that the instantaneous risk of occurrence of adverse events stays constant irrespective of multiple or successive exposure. The validity of such a presupposition for this product is unknown.

1c. DRUP: We feel there should be some discussion of the basis for the concerns about long-term safety, given that this drug is administered intermittently, only during menses (no more than 5 [sequential] days/month), and has an elimination half-life of about 11 hours.

1c. DBVII Response: We defer to the review division in this matter. Statistically, we can only say that the data are indeterminate, no safety signals for serious adverse events were observed, but the studies were neither designed nor powered to rule out potential long term safety issues. As noted in 1b, any statistical interpretation of the long term safety data with the noted deficiencies is problematic.

1d. DRUP: The Summary and Conclusion statement implies that the listed events are of concern. However, as detailed in the following sections, there were no clear signals of increased risk in Lysteda-exposed subjects.

1d. DBVII Response: No implication was meant to be imputed from the listed events.

DRUP Point 2. In the review, possible venous thromboembolic events (VTEs) were assessed using a Standardized MedDRA Query. The review states that 2 VTEs occurred in subjects randomized to tranexamic acid, and one to an open-label subject.

2a. DRUP: All three of these events were reviewed by the clinical reviewers in DRUP, and are not considered VTEs. The single event judged to be a true VTE (a DVT) occurred in a placebo subject.

2a. DBVII Response: We defer to the clinical judgment of the review division in this matter.

DRUP Point 3. Regarding the data assessing visual effects of the drug, the review characterizes exposure as “only” (e.g., p 8, “only 357 have any ophthalmologic data from cycle 12 or later.”). The review notes slightly higher rates of decreased visual acuity among tranexamic acid subjects (although the CI around the OR included 1). Change in color vision was more prominent among placebo subjects (again, non-significant CI). Retinal status did not differ between randomized treatment groups. For all three parameters, the review reports shifts from normal to abnormal, but provides no information on shifts from abnormal to normal.

3a. DRUP: Although DRUP requested ocular examinations as part of the phase 3 safety program, we did not specify any minimum number of subjects to be evaluated.

3a. DBVII Response: Ophthalmology examinations were specified for all subjects as part of the protocols. The sponsor provided ophthalmology data for 570 subjects, out of a safety population of 1,204 subjects.

3b. DRUP: Table 10 (p 18) shows a lower risk of adverse events under the Eye Disorders SOC for tranexamic acid subjects as compared to placebo (OR 0.66, 0.45-0.96). We concur with this in our review; visual AEs generally occurred with greater frequency in placebo arm of the placebo-controlled studies, and the rate in the open-label studies was similar to that reported by the placebo subjects, even though the placebo-controlled studies were of shorter duration.

3b. DBVII Response: No response appears to be necessary.

3c. DRUP: We note the consultative review by Dr. Wiley Chambers, DAIOP concluded that “with the exception of conjunctivitis, venous stasis retinopathy and potential thromboembolic events, no significant ophthalmologic findings were clearly identified in the clinical trials. Most of the ophthalmic findings in the clinical trials are considered incidental findings typically found in the population of patients studied.”

3c. DBVII Response: We defer to the clinical judgment of the review division regarding the interpretation of the consultative review.

DRUP 4. With respect to overall adverse events, the review pooled data from both dose levels (1.95 g/day and 3.9 g/day) in the safety analysis after testing for a dose-response trend. The review identifies seven adverse event preferred terms that are reported to demonstrate statistically significantly increased risk in tranexamic subjects vs. placebo subjects.

4a. **DRUP:** It does not appear that adjustments for multiple comparisons were made in evaluating the multiple adverse event preferred terms. We question the reporting of statistical hypothesis testing of safety outcomes, given that this was not a planned evaluation, and given the apparent lack of adjustment for multiple comparisons.

4a. **DBVII Response:** No hypothesis tests were conducted in the primary review. Since all analyses in the primary review were exploratory in nature, multiplicity adjustments are not appropriate. Furthermore, under ascertainment problems are a recognized issue with safety analyses.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22430

ORIG-1

XANODYNE
PHARMACEUTICS
INC

Lysteda

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/s/

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10/27/2009

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10/27/2009



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number	22-430
Drug Name	tranexamic acid (LYSTEDA)
Indication(s)	Treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of associated symptoms
Applicant	Xanodyne Pharmaceuticals, Inc.
Date(s)	Submission Date: January 30, 2009 PDUFA Date: July 30, 2009
Review Priority	Priority
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1 Executive Summary

The sponsor seeks approval to market tranexamic acid for the treatment of heavy menstrual bleeding associated with menorrhagia. This report is a statistical evaluation of ophthalmologic, renal, venous thromboembolic (VTE), and other adverse events associated with exposure to tranexamic acid. Data were obtained from 481 randomized and 1,015 open-label, non-comparative Phase 3 subjects. Since one of the four Phase 3 studies was an open-label extension of a randomized study, there are 292 subjects who were enrolled in both the randomized and open-label studies. Given the limited amount of data available from randomized studies and the infrequency of the safety endpoints, it is not possible to estimate the increase or decrease in relative risk with statistical significance at the 5% level for the ophthalmologic, renal, or VTE adverse events.

The ophthalmologic data included visual acuity, color vision, and retinal examinations for both randomized and open-label subjects. Data from ophthalmologic examinations were only available for about one half of the randomized placebo subjects, approximately two thirds of the randomized tranexamic acid subjects, and less than one third of the open-label tranexamic acid subjects. In the randomized studies, there was no statistically significant increase in relative risk between the tranexamic acid and placebo groups: for decreased visual acuity, the relative risk (RR) was 1.21 with a 95% confidence interval (CI) of (0.83, 1.76); for changes in color vision among subjects with baseline normal color vision, RR = 0.61 with a 95% CI of (0.03, 11.24); and for changes in retinal status among subjects with baseline normal retinal status, RR = 0.96 with a 95% CI of (0.01, 173.08). In addition, 17.1% of the open-label subjects experienced a decrease in visual acuity; 2.1% experienced a change in color vision; and 3.2% experienced a change in retinal status. Adverse events of the eye disorders system organ class were also observed.

Decreases in renal function were assessed by calculating the change in estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) study method and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method. A decrease in renal function was defined as a 33% decrease in eGFR or eGFR below 60. Using the MDRD method in subjects with baseline normal renal function (eGFR > 80), the relative risk of a decrease in renal function was 0.40 with a 95% confidence interval of (0.11, 1.44). Similarly, using CKD-EPI, the relative risk is 0.42 with a 95% confidence interval of (0.06, 2.90).

VTEs were identified by comparing the MedDRA-coded adverse event preferred terms to from the embolic and thrombotic events Standardized MedDRA Query. In the randomized studies, one VTE-related adverse event was identified in each of the the placebo and tranexamic acid groups. The relative risk is 0.41 with a 95% CI of (0.01, 20.08). Two VTE-related adverse events occurred in the open-label studies.

An analysis of other adverse events reveals that tranexamic acid subjects from the randomized studies are at an increased risk of adverse events from the following MedDRA system

organ classes: blood and lymphatic system disorders (RR = 1.63, 95% CI = (1.02, 2.60)); respiratory, thoracic and mediastinal disorders (RR = 1.41, 95% CI = (1.21, 1.63)); infections and infestations (RR = 1.18, 95% CI = (1.10, 1.26)); musculoskeletal and connective tissue disorders (RR = 1.17, 95% CI = (1.12, 1.22)); and nervous system disorders (RR = 1.04, 95% CI = (1.02, 1.06)). At the preferred term-level, seven terms were more likely to be observed in the tranexamic acid group: musculoskeletal pain (RR = 2.34, 95% CI = (1.34, 4.07)); nasal congestion (RR = 2.17, 95% CI = (1.02, 4.62)); anemia (RR = 1.93, CI = 1.09, 3.43); arthralgia (RR = 1.79, 95% CI = (1.13, 2.84)); fatigue (RR = 1.76, 95% CI = (1.20, 2.58)); back pain (RR = 1.35, 95% CI = (1.22, 1.50)); and headache (RR = 1.07, 95% CI = (1.04, 1.09)). These increases in relative risk are statistically significant at the 5% level.

The report concludes by discussing the limitations of the safety analysis. The randomized studies are insufficiently powered to detect safety outcomes. The varying duration of treatment in the Phase 3 study protocols combined with a high early termination rate in the long-term studies resulted in insufficient data to adequately assess the long term safety implications of chronic exposure to tranexamic acid. In addition, the subjects for whom lab and ophthalmic data were collected constitute a convenience sample.

2 Introduction

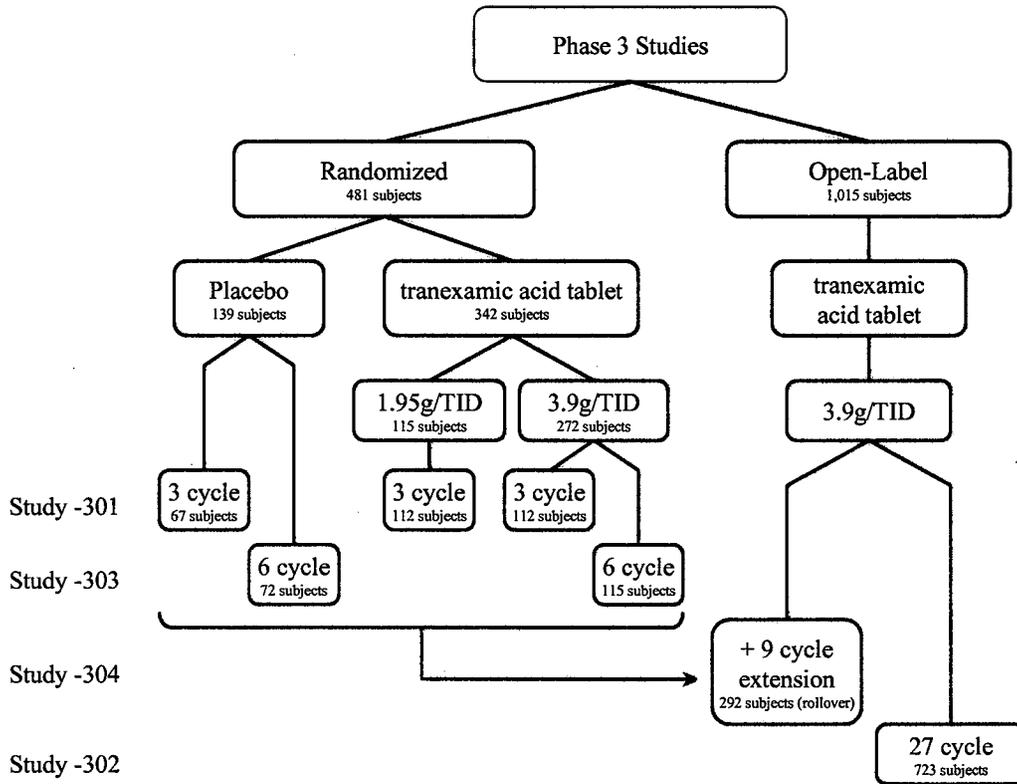
The FDA has previously approved tranexamic acid under the trade name Cyklokapron. In 1986, Cyklokapron was approved in an IV and immediate-release oral tablet formulation for short term use (2 to 8 days) in hemophiliacs during and following tooth extraction. The sponsor seeks approval to market tranexamic acid as a 650 mg tablet for the treatment of heavy menstrual bleeding (menorrhagia). The suggested dosing regimen for this indication is 2 tablets taken 3 times a day (total daily dose of 3.9g/day) for up to 5 consecutive days during the menstrual period. The intended patient population for this new indication are women of child-bearing age with history of menorrhagia.

This report provides a statistical summary of the safety outcomes observed in the four Phase 3 trials for tranexamic acid for the treatment of menorrhagia. In addition to adverse events and VTE adverse events in particular, the safety outcomes of interest in this report include deterioration of renal function, and changes in ophthalmic indicators, particularly visual acuity, retinal status, or color vision.

3 Data Sources

The sponsor submitted four Phase 3 studies under NDA 22-430 to support the new indication. The data considered in this report were drawn from the demographics, drug usage, adverse events, laboratory, and ophthalmic data sets of the Integrated Summary of Safety (ISS)

Figure 1: Phase 3 Trial Design



submitted in the safety update dated April 30, 2009.¹ All subjects enrolled in the randomized studies (-301 and -303) had completed or withdrawn, and 96% of the subjects enrolled in study -302 and 94% of the subjects enrolled in study -304 had completed or withdrawn.

The design of these trials is summarized in Figure 1. Studies XP12B-MR-301 and XP12B-MR-303 were randomized, placebo-controlled, double-blinded studies for three and six menstrual cycles, respectively. The study drug for a particular menstrual cycle was dispensed in the form of a blister pack during subject visits between menstrual cycles. Subjects who completed the scheduled evaluations in the randomized studies (with no major protocol violations and no study events that, in the opinion of the investigator, would preclude enrollment) were rolled-over into study XP12B-MR-304, an open-label, active-treatment only extension study, which followed subjects for an additional 9 menstrual cycles. Of the 420

¹These data are located in directory /Cdsesub1/evsprod/NDA022430/0009/m5/datasets/iss/analysis/ in the CDER EDR.

Table 1: Treatment assignment by study for safety population

	Placebo	tranexamic acid	
		1.95g/TID	3.9g/TID
Study -301	67	115	112
Study -303	72	–	115
Study -302	–	–	723
Study -304	–	–	292
Total	139	115	950

Table 2: Original treatment assignment for subjects enrolled in study -304

	Placebo	tranexamic acid	
		1.95g/TID	3.9g/TID
Study -301	43	79	73
Study -303	30	–	67

subjects who completed studies -301 and -303, 292 rolled-over into study -304. Table 2 shows the original treatment assignment in studies -301 and -303 for subjects who were enrolled in study -304. The 73 placebo subjects who rolled-over into study -304 received their first exposure to tranexamic acid in study -304. In addition, study XP12B-MR-302 was an open-label, active-treatment only study that followed subjects for up to 27 menstrual cycles. In the open-label studies, the study drug was dispensed in a bottle with a multi-cycle supply.

There are three doses of tranexamic acid in the Phase 3 studies. Subjects were assigned to the recommended therapeutic dose of 3.9g/TID tranexamic acid, a reduced dose of 1.95g/TID tranexamic acid, or 0g of tranexamic acid in the placebo group. Only subjects in Study -301 were randomized to all three arms.

The safety population in this submission consists of 1,204 unique subjects who were enrolled, received at least one dose of the study drug, and had at least one follow-up visit during the four Phase 3 trials. In the four Phase 3 studies, 139 subjects received at least one dose of the placebo, and 1,138 subjects received at least one dose of tranexamic acid (including the 73 placebo subjects who rolled-over into study -304). Table 1 shows the number of subjects assigned to each treatment arm by study.

Table 3 describes the number of subjects who completed at least 3, 6, 12, 15, 21, and 27 menstrual cycles from the time of their first dose of the study drug according to the ISS drug usage data. Although study -302 enrolled the majority of subjects, the high drop out

Table 3: Available data

Treatment Assignment	Menstrual cycles since 1st exposure					
	3	6	12	15	21	27
<u>Placebo</u>						
Study -301	64					
Study -303	65	55				
Total	129	55				
<u>Any tranexamic acid dose</u>						
Study -301 / -304	241	179	122			
Study -302	643	563	422	346	286	231
Study -303 / -304	134	123	63	57		
Total	1,018	865	607	403	287	231

rate in study -302 combined with the limited duration of the other Phase 3 studies means that only 607 (60% of) subjects in the any tranexamic acid group have at least 12 menstrual cycles of safety data. Of these subjects, only 395 have serum creatinine labs data from cycle 12 or later, and only 357 have any ophthalmologic data from cycle 12 or later.

Adverse events reports are contained in the ISS adverse events (AE) data set. The preferred term (PREFTERM) variable was coded using MedDRA version 7.0. Adverse events were collected from subject diaries at each visit and study termination.

The laboratory data were contained in the ISS laboratory (LAB) data set. In the case of studies -301 and -303, subject visits were scheduled 1-7 days after the completion of the previous menstrual cycle. Per protocol, subjects were to fast for 12 hours prior to the collection of labs data.

The ophthalmologic data are contained in the ISS ophthalmic exam (OPTHEXAM) data set submitted with the safety update on April 30, 2009. The ophthalmology examination protocol for each of the Phase 3 studies was substantively similar: the ophthalmology examination was to have been performed at baseline and at one or more visits during the course of treatment and at study termination. All four study protocols required assessment of left visual acuity, right visual acuity, the HRR test for color blindness, intraocular pressure, and a retinal exam (conducted using a dilated fundus examination with binocular indirect view of the retinal periphery). All of the Phase 3 protocols state that the exams could have been conducted by an ophthalmologist or an optometrist, and that the site investigator was responsible for ensuring that the subject eye examinations were completed as scheduled and the reports reported on the CRF. Since ophthalmologic data are only available for approximately 570 subjects of the 1,204 in the safety population, a request was submitted to the sponsor on March 27, 2009 for any additional ophthalmologic data.

4 Statistical Methodology

This section discusses the statistical methodology employed in this report, including any statistical assumptions.

4.1 Assumptions

4.1.1 Unit of analysis

The unit of analysis in this report is the subject, rather than the subject-cycle. If an adverse event occurs at any time after the first dose of the study medication, the subject is considered to have experienced an adverse event. The number of instances and the duration of exposure were not considered. The number of subjects for whom data are available are reported in Table 4, and in the case of the renal and ophthalmologic data, are smaller than the overall population due to missing data. Using the subject as the unit of analysis may be appropriate for assessing change from baseline with intermittent observation periods, such as with the renal and ophthalmologic analysis. Since the majority of the tranexamic acid group was enrolled in the 27 cycle study (-302), the probability of detecting a rare adverse event may be higher in the open-label subjects than in the randomized subjects.

4.1.2 Dose response

Pooling subjects across doses may be appropriate if there is no dose-response effect. To test for a dose-response, a Cochran-Armitage trend test was performed for subjects in study -301. For each of the 320 adverse event preferred terms reported in study -301, the number of subjects (who reported at least one instance of the adverse event) were tabulated by treatment. For 316 of 320 preferred terms, the p -value was greater than 0.05, which indicates that we cannot reject the null hypothesis that there is no trend between dosing categories. For lichenification, muscular weakness, palpitations, and toothache, the p -value was less than 0.05, but in each case, the lowest event rate was observed in the 3.9g/day group and the highest rate event was observed in the placebo group. Since there is no statistical evidence of increasing adverse event rates in response to increasing tranexamic acid daily dose, the 3.9g/day and 1.95g/day dose groups are pooled into one treatment category for the purposes of this report.

4.1.3 Randomized versus open-label studies

The analyses presented separate the randomized and open-label studies as two groups, even though the Phase 3 studies targeted similar patient populations with almost identical inclusion-exclusion criteria. Differences in the mechanism for distributing the study drug (single-cycle blister pack versus multi-cycle canister), differences in study design (blinded,

placebo randomized versus open-label, single arm), and differences in the frequency of study visits (every cycle versus after multiple cycles) affect the collection of adverse event data. Even if the open-label and randomized studies targeted the same patient population, these differences in the study protocols mean that adverse event data may be systematically over- or under-reported due to differences in the study design. Hence, it would be inappropriate to pool subjects across the randomized and open-label studies.

4.2 Comparative risk assessment

In addition to adverse events generally, this report examines three specific potential adverse events: ophthalmic events, decreases in renal function, and adverse events related to VTEs. In each case, the risk of an event in the treatment group is compared to the risk of an event in the placebo group using the risk ratio and associated 95% confidence interval. The confidence interval is calculated using asymptotic approximation. A relative risk greater than 1 indicates a higher risk in the the tranexamic acid group compared to placebo.

In cases where there are events observed in the tranexamic acid group, but no events in the placebo group, the relative risk is mathematically undefined. Continuity correction assumptions allow the calculation of a finite risk ratio, but the estimate depends on the choice of the continuity correction factor (the standard 0.5 was employed in this report). In cases where continuity correction was employed in the calculation of the relative risk, the risk difference and associated 95% confidence interval (calculated by inverting a two-sided test) is also provided for reference.

Since a baseline measurement and at least one post-baseline measurement are required to assess treatment emergent changes, including subjects for whom no post-baseline data are available would artificially deflate the proportion of subjects experiencing adverse events. Table 4 shows the number of unique subjects who were randomized, received at least one dose of tranexamic acid, and received at least one follow-up observation during which lab or ophthalmic data were recorded.

4.3 Ophthalmic events

For the purposes of this report, an adverse ophthalmic event is defined as:

1. A decrease in visual acuity in either the left or right eye;
2. A change in retinal status from baseline normal to abnormal at a later visit; or
3. A change in color vision from baseline normal to abnormal at a later visit.

In addition, the adverse events data were examined for preferred terms that mapped to the eye disorders SOC.

Table 4: Number of subjects with post-baseline safety data

	Randomized		Open-label
	Placebo	tranexamic acid	tranexamic acid
Adverse events ¹	139	342	1,015
Serum creatinine labs	114	271	716
Ophthalmic data ²			
Visual acuity ³	75	248	293
Color vision ⁴	75	244	281
Retinal exam ⁴	71	222	278

¹Includes all subjects in safety population.

²Given that only 47% of the 1,204 Phase 3 safety subjects have any sort of ophthalmic data, a request was sent to the sponsor for any additional ophthalmic data on March 27, 2009. This report reflects the ophthalmic data provided by the sponsor through the safety update (submitted April 30, 2009).

³Either left or right visual acuity.

⁴Among subjects with baseline normal exam.

4.4 Changes in estimated glomerular filtration rate

Estimated creatinine clearance was calculated using two equations. Since subject weight is not available at post-baseline visits, the Modification of Diet in Renal Disease (MDRD) study method of Levey et al (1999), which does not require weight, is preferred to the Cockcroft-Gault formula, which does require weight. If S_{cr} is serum creatinine in mg/dL, the MDRD equation for females is

$$eGFR_{MDRD} = 186 \times S_{cr}^{-1.154} \times Age^{-0.203} \times 0.742 \times [1.201 \text{ if black}].$$

Similarly, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method of Levey et al (2009) does not require subject weight. Levey et al (2009) argue that MDRD underestimates eGFR for subjects with higher GFR, and that CKD-EPI is more accurate than MDRD for subjects in the normal reference range. The CKD-EPI equation for females is

$$eGFR_{CPK-EPI} = 141 \times \min(S_{cr}/0.7, 1)^{-0.329} \times \max(S_{cr}/0.7, 1)^{-1.209} \\ \times 0.993^{Age} \times 1.018 \times [1.159 \text{ if black}].$$

In both equations above, estimated GFR is given in units of mL / min / 1.73m². According to the FDA guidance on renal impairment, individuals with eGFR greater than 80 units are considered to have normal renal function. Table 5 shows the number of subjects with baseline normal renal function using the eGFR calculated from the MDRD and CKD-EPI

Table 5: Number of subjects with normal baseline renal function (eGFR \geq 80)

	Placebo			tranexamic acid		
	MDRD \geq 80 ¹	CKD-EPI \geq 80 ²	Any labs	MDRD \geq 80	CKD-EPI \geq 80	Any labs
Randomized						
Study -301	38	46	51	150	156	208
Study -303	49	51	63	66	75	111
Total	87	97	114	216	231	319
Open-label						
Study -302				310	370	523
Study -304				151	161	193
Total				461	531	716

¹The Modification of Diet in Renal Disease study method of Levey et al (1999).

²The Chronic Kidney Disease Epidemiology Collaboration method of Levey et al (2009).

methods. There are 1,166 subjects with baseline serum creatinine data and at least one post-baseline measurement. Since MDRD underestimates eGFR for subjects with higher GFR, it is not surprising that more subjects seem to have baseline renal impairment when using the MDRD equation.

After consultation with the medical officer, the following criteria were selected to define a decrease in renal function:

1. A 33% decrease from baseline eGFR; or
2. A post-baseline eGFR of 60 or lower.

Using the CREAT variable to estimate creatinine clearance may be problematic for two reasons. First, the timing of the last dose of tranexamic acid relative to the collection of lab samples varied. Subjects were instructed to take the study drug during their menstrual period. Available lab data were collected at study visits which were scheduled per protocol 1 to 7 days after the conclusion of the preceding menstrual period. Since the sponsor's Clinical Overview, Section 3.1, reports that the mean terminal half life of the proposed formulation is 10-13 hours, labs taken 1-7 days after the end of the menstrual period may not capture the full extent of renal impairment. Second, repeated renal measurements are rarely available. Among randomized subjects, only 53 subjects in the 6-cycle study have two post-baseline lab assessments; no subjects in the 3-cycle study have more than one lab assessment. Among the open-label subjects in study -302, only 127 subjects have two lab assessments, 158 have three, and 91 have four. In other words, only 52.5% of the open-label subjects have repeated post-baseline lab data. Without repeated measurements, it is not possible to ascertain if renal function returned to the normal reference range after an observed decrease.

4.5 Adverse events

Adverse events with MedDRA preferred terms related to venous thromboembolisms (VTEs) were identified using the embolic and thrombotic events Standardized MedDRA Query (SMQ) from MedDRA version 11.0. This SMQ includes preferred terms from three related SMQs: embolic and thrombotic events, arterial; embolic and thrombotic events, venous; and embolic and thrombotic events, vessel type unspecified and mixed arterial and venous. Because the sponsor's data are coded in MedDRA version 7.0 and preferred terms were added from version 7.0 to 11.0, only preferred terms from the embolic and thrombotic events SMQ that are in MedDRA version 7.0 are included in the definition. These terms are listed in Appendix A.

5 Findings

5.1 Ophthalmic Events

Ophthalmic events were observed in both the treatment and control groups. These findings are summarized in Table 6. A total of 95 subjects reported at least one of the following events: a decrease in visual acuity in either eye, a change from baseline normal color vision to post-baseline abnormal color vision, or a change from baseline normal retinal status to post-baseline abnormal status.

5.1.1 Visual acuity

Decreased visual acuity was the most common ophthalmic reaction. In the randomized studies, 6 (8%) placebo subjects and 24 (9.7%) tranexamic acid subjects experienced a decrease in visual acuity in either the left or right eye. The relative risk was 1.21 with a 95% confidence interval of (0.83, 1.76). In the open label studies, 79 instances of decreased visual acuity were observed in either the left or right eye among 50 (17.1%) subjects.

5.1.2 Color Vision

Among subjects with baseline normal color vision, changes in color vision were observed in both the randomized and open-label studies. In the randomized studies, 1 (1.3%) placebo subject and 2 (0.8%) tranexamic acid subjects experienced a change from normal to abnormal color vision. The relative risk was 0.61 with an associated 95% confidence interval of (0.03, 11.24). In the open-label studies, 6 (2.1%) subjects experienced a change from normal color vision to abnormal color vision at a later examination.

Table 6: (Number of subjects) / (total subjects with safety data) for ophthalmologic adverse events in 3-6 cycle randomized studies

	Tranexamic acid	Placebo	Relative Risk	
			RR	95% CI
Decreased visual acuity	24/248	6/75	1.21	(0.83, 1.76)
Normal → abnormal color vision	2/244	1/75	0.61	(0.03, 11.24)
Normal → abnormal retinal status	1/222	0/71	0.96	(0.01, 173.08)

5.1.3 Retinal Status

Among subjects with baseline normal retinal status, changes in retinal status were only observed in tranexamic acid subjects. In the randomized studies, none of the placebo subjects and 1 (0.4%) of tranexamic acid subjects were observed to have a change from baseline normal to post-baseline abnormal retinal status. With continuity correction, the relative risk is 0.96 with a 95% confidence interval of (0.01, 173.08). The risk difference is 0.003 with an exact 95% confidence interval of (-0.022, 0.018). In the open-label studies, 9 (3.2%) subjects were observed to have a change from normal to abnormal retinal status.

5.1.4 Eye-related adverse events

In addition to the ophthalmic examination, data on adverse events related to the eye disorders SOC may also be relevant. In the randomized studies, cases of blepharospasm, cataract nuclear, color vision test abnormal blue-yellow, conjunctival haemorrhage, conjunctivitis, eye irritation, eye pruritus, lenticular opacities, ocular discomfort, retinal degeneration, vision blurred, and visual disturbance were reported in the tranexamic acid subjects. In the open-label studies, 180 instances of eye disorder adverse events were reported in 33 patients. Within the eye disorders SOC, there were 66 preferred terms with at least one report among the open-label subjects. These terms, and the frequency with which they were observed, are listed in Appendix B.

5.2 Changes in estimated glomerular filtration rate

Glomerular filtration rate was estimated using both the MDRD and CKD-EPI equations to assess identify instances of decreased renal function. Tables 7 and 8 summarize the decreases in renal function observed in the randomized and open-label studies. Using CKD-EPI generally produced one fewer instance of decreased renal function than the MDRD method. This is not surprising since Levey et al (2009) argue that MDRD tends to underestimate renal function in the normal reference range. Irrespective of the method employed to estimate

GFR, subjects in both the treated and placebo group were observed to have experienced decreases in renal function. Due to the relatively small sample in the randomized studies, however, it is not possible to detect the direction or magnitude of the change in risk between the treatment and placebo groups.

In the randomized studies, 87 placebo subjects had baseline normal renal function using the MDRD method to calculate eGFR, and 97 subjects had baseline normal renal function using the CKD-EPI method. Of the tranexamic acid subjects in the randomized studies, 216 had baseline normal renal function using the MDRD equation and 231 using the CKD-EPI equation. Among these subjects, three placebo subjects and three tranexamic acid subjects experienced decreases in renal function using the eGFR given by the MDRD equation. The relative risk using MDRD is 0.40 with a 95% confidence interval of (0.11, 1.44). Using the CKD-EPI equation to estimate eGFR identifies two placebo subjects and two tranexamic acid subjects who experienced decreases in renal function during the randomized studies. The relative risk using CKD-EPI is 0.42 with a 95% confidence interval of (0.06, 2.90). In the randomized studies, using the MDRD equation identified one additional patient who experienced a decrease in renal function in each of the placebo and tranexamic acid groups.

In the open-label studies, there were 716 subjects with any renal labs data, of whom 416 had baseline normal renal function using the MDRD equation, and 531 had baseline normal renal function according to the CKD-EPI equation. Among subjects with baseline normal renal function, 9 subjects (2.8%) experienced a decrease in renal function using the MDRD equation, while 8 subjects (1.5%) experienced a decrease using the CKD-EPI equation. 7 subjects experienced a decrease in renal function according to both methods.

5.3 Venous thromboembolism-related adverse events

Six subjects experienced VTE-related adverse events, which are summarized in Table 9. Two instances of “ultrasound doppler abnormal” occurred during the screening cycles prior to drug administration. In the randomized studies, one placebo subject and one tranexamic acid subject experienced a VTE-related adverse event. The relative risk is 0.41 with a 95% confidence interval of (0.01, 20.08). With 139 placebo subjects and 342 tranexamic acid subjects enrolled for a maximum of six menstrual cycles, the probability of observing a VTE-related adverse event is small. This limitation is further discussed in Section 6.2.1.

5.4 Other adverse events

In addition to VTE and eye disorder adverse events, relative risks and associated 95% confidence intervals were calculated for all MedDRA system organ classes (SOCs) and preferred terms. For the subject-level analysis, subjects who experienced more than one occurrence of the same adverse event were only counted once.

Table 7: Using MDRD to estimate decreases in estimated glomerular filtration rate among subjects with baseline normal renal function, by (#decreases / # measurements) per cycle

Menstrual Cycle	Randomized		Open-label	
	Placebo	tranexamic acid	tranexamic acid	
3	3/87 (3.4%)	2/215 (0.9%)		
6	0/22 (0%)	1/60 (1.7%)	6/343	(1.7%)
9			2/313	(1.5%)
12			0/38	(0%)
15			1/199	(0.5%)
27			0/113	(0%)

Table 8: Using CKD-EPI to estimate decreases in estimated glomerular filtration rate among subjects with baseline normal renal function, by (#decreases / # measurements) per cycle

Menstrual Cycle	Randomized		Open-label	
	Placebo	tranexamic acid	tranexamic acid	
3	2/97 (2.0%)	1/229 (0.4%)		
6	0/24 (0%)	1/69 (1.4%)	6/403	(1.5%)
9			1/371	(0.3%)
12			0/39	(0%)
15			1/241	(0.4%)
27			0/133	(0%)

Table 9: Summary of VTE adverse events

Study	Subject ID	Treatment	Preferred Term	SAE	Severity
-301	301-721-1002	Screening phase	Ultrasound doppler abnormal	N	Mild
-303	303-633-3010	Screening phase	Ultrasound doppler abnormal	N	Mild
-303	303-622-3009	Randomized tranexamic acid	Ultrasound doppler abnormal	N	Mild
-303	303-626-3010	Randomized placebo	Deep vein thrombosis	Y	Moderate
-302	302-511-2023	Open-label tranexamic acid	Blindness transient	N	Moderate
-304	301-774-1004	Open-label tranexamic acid	Brain stem infarction	Y	Life-threatening

For the randomized studies, Table 10 displays this information by MedDRA SOC and Table 11 by MedDRA preferred term. Table 10 shows that events in the following SOCs were more likely to occur among tranexamic acid subjects than among the placebo subjects in the 3 and 6 cycle studies: blood and lymphatic system disorders (RR = 1.63, 95% CI = (1.02, 2.60)); respiratory, thoracic and mediastinal disorders (RR = 1.41, 95% CI = (1.21, 1.63)); infections and infestations (RR = 1.18, 95% CI = (1.10, 1.26)); musculoskeletal and connective tissue disorders (RR = 1.17, 95% CI = (1.12, 1.22)); and nervous system disorders (RR = 1.04, 95% CI = (1.02, 1.06)). These increased relative risks are statistically significant at the 5% level.

Disaggregating adverse events into preferred terms in Table 11 reveals seven terms that occur more commonly among tranexamic acid subjects than placebo subjects in the randomized 3 and 6 cycle studies. These are: musculoskeletal pain (RR = 2.34, 95% CI = (1.34, 4.07)); nasal congestion (RR = 2.17, 95% CI = (1.02, 4.62)); anemia (RR = 1.93, CI = 1.09, 3.43); arthralgia (RR = 1.79, 95% CI = (1.13, 2.84)); fatigue (RR = 1.76, 95% CI = (1.20, 2.58)); back pain (RR = 1.35, 95% CI = (1.22, 1.50)); and headache (RR = 1.07, 95% CI = (1.04, 1.09)). These increases in relative risk are statistically significant at the 5% level, and the increased relative risk of musculoskeletal pain and nasal congestion is over twice as high on average in the tranexamic acid subjects than the placebo subjects.

Data from more than six cycles of exposure to tranexamic acid are available only from the open-label studies. Table 12 shows the number of instances and the number of subjects reporting at least one instance of an adverse event by SOC.

Table 10: Number of randomized subjects out of 139 placebo subjects and 342 tranexamic acid subjects reporting adverse events by MedDRA system organ class (primary axis).

	tranexamic acid		Placebo		RR ¹	95% CI
	Instances	Subjects	Instances	Subjects		
Metabolism and nutrition disorders	5	3 (1%)	0	0 (0%)	2.85	(0.03, 246.62)
Surgical and medical procedures	5	5 (1%)	1	1 (1%)	2.03	(0.20, 20.93)
Blood and lymphatic system disorders	21	20 (6%)	5	5 (4%)	1.63	(1.02, 2.60)
Respiratory, thoracic and mediastinal disorders	112	52 (15%)	25	15 (11%)	1.41	(1.21, 1.63)
Congenital, familial and genetic disorders	1	1 (0.3%)	0	0 (0%)	1.22	(0.01, 223.01)
Renal and urinary disorders	3	3 (1%)	1	1 (1%)	1.22	(0.09, 16.31)
Infections and infestations	119	84 (25%)	39	29 (21%)	1.18	(1.10, 1.26)
Musculoskeletal and connective tissue disorders	337	121 (35%)	96	42 (30%)	1.17	(1.12, 1.22)
General disorders	54	47 (14%)	34	17 (12%)	1.12	(0.98, 1.29)
Psychiatric disorders	61	35 (10%)	23	13 (9%)	1.09	(0.91, 1.32)
Immune system disorders	63	24 (7%)	16	9 (6%)	1.08	(0.82, 1.43)
Ear and labyrinth disorders	15	8 (2%)	3	3 (2%)	1.08	(0.45, 2.61)
Nervous system disorders	525	184 (54%)	267	72 (52%)	1.04	(1.02, 1.06)
Gastrointestinal disorders	250	112 (33%)	110	48 (35%)	0.95	(0.91, 0.99)
Reproductive system and breast disorders	472	187 (55%)	229	81 (58%)	0.94	(0.92, 0.95)
Skin and subcutaneous tissue disorders	25	19 (6%)	10	9 (6%)	0.86	(0.63, 1.16)
Investigations	56	39 (11%)	34	19 (14%)	0.83	(0.73, 0.95)
Endocrine disorders	2	2 (1%)	1	1 (1%)	0.81	(0.04, 15.07)
Injury, poisoning and procedural complications	13	9 (3%)	5	5 (4%)	0.73	(0.41, 1.32)
Vascular disorders	7	7 (2%)	4	4 (3%)	0.71	(0.34, 1.51)
Eye disorders	17	13 (4%)	10	8 (6%)	0.66	(0.45, 0.96)
Cardiac disorders	3	3 (1%)	2	2 (1%)	0.61	(0.12, 3.06)
Hepatobiliary disorders	0	0 (0%)	3	2 (1%)	0.08	(0.00, 8.82)

No adverse events were observed in the randomized studies in either the tranexamic acid or placebo arms in the following SOCs: Neoplasms benign, malignant and unspecified; Pregnancy, puerperium and perinatal conditions; and social circumstances.

¹Relative risk calculated as (proportion of treated subjects) / (proportion of placebo subjects).

Table 11: Number of randomized subjects out of 139 placebo subjects and 342 tranexamic acid subjects reporting adverse events by MedDRA preferred term, including all preferred terms with statistically-significant increases, and the next 20 most common preferred terms.

	tranexamic acid		Placebo		RR ¹	95% CI
	Instances	Subjects	Instances	Subjects		
Musculoskeletal pain	38	23 (7%)	5	4 (3%)	2.34	(1.34, 4.07)
Nasal congestion	36	16 (5%)	3	3 (2%)	2.17	(1.02, 4.62)
Anemia	20	19 (6%)	4	4 (3%)	1.93	(1.09, 3.43)
Arthralgia	34	22 (6%)	7	5 (4%)	1.79	(1.13, 2.84)
Fatigue	29	26 (8%)	12	6 (4%)	1.76	(1.20, 2.58)
Back pain	152	70 (20%)	39	21 (15%)	1.35	(1.22, 1.50)
Headache	402	160 (47%)	195	61 (44%)	1.07	(1.04, 1.09)
Menstrual discomfort	398	163 (48%)	182	71 (51%)	0.93	(0.91, 0.95)
Abdominal discomfort	58	33 (10%)	23	13 (9%)	1.03	(0.85, 1.25)
Nausea	39	30 (9%)	19	16 (12%)	0.76	(0.64, 0.90)
Viral upper respiratory tract infection	32	29 (8%)	11	10 (7%)	1.18	(0.92, 1.50)
Diarrhoea	38	28 (8%)	13	9 (6%)	1.26	(0.97, 1.65)
Migraine	58	21 (6%)	45	8 (6%)	1.07	(0.78, 1.47)
Multiple allergies	44	19 (6%)	12	5 (4%)	1.54	(0.96, 2.48)
Abdominal pain	23	19 (6%)	9	8 (6%)	0.97	(0.70, 1.34)
Pain in extremity	39	18 (5%)	13	5 (4%)	1.46	(0.90, 2.37)
Abdominal pain upper	18	17 (5%)	5	5 (4%)	1.38	(0.85, 2.25)
Muscle cramps	29	17 (5%)	16	7 (5%)	0.99	(0.68, 1.44)
Sinusitis	18	15 (4%)	7	6 (4%)	1.02	(0.66, 1.57)
Myalgia	18	14 (4%)	0	0 (0%)	11.81	(0.21, 668.08)
Cough	15	14 (4%)	7	7 (5%)	0.81	(0.54, 1.21)
Dyspepsia	15	13 (4%)	13	8 (6%)	0.66	(0.45, 0.96)
Sinus headache	16	12 (4%)	4	3 (2%)	1.63	(0.73, 3.61)
Sinus congestion	18	11 (3%)	2	2 (1%)	2.24	(0.72, 6.98)
Depression	12	10 (3%)	3	2 (1%)	2.03	(0.64, 6.46)
Influenza	10	10 (3%)	2	2 (1%)	2.03	(0.64, 6.46)
Seasonal allergy	19	10 (3%)	4	4 (3%)	1.02	(0.52, 1.98)

¹Relative risk calculated as (proportion of treated subjects) / (proportion of placebo subjects).

Table 12: Open-label tranexamic acid subjects ($n = 1,015$) reporting adverse events by MedDRA system organ class (primary axis)

MedDRA System Organ Class	Instances	Subjects
Reproductive system and breast disorders	4,646	627 (62%)
Nervous system disorders	5,576	613 (60%)
Infections and infestations	1,042	455 (45%)
Musculoskeletal and connective tissue disorders	2,958	452 (45%)
Gastrointestinal disorders	1,968	419 (41%)
Respiratory, thoracic and mediastinal disorders	1,019	290 (29%)
General disorders and administration site conditions	489	196 (19%)
Investigations	276	173 (17%)
Psychiatric disorders	611	155 (15%)
Injury, poisoning and procedural complications	189	121 (12%)
Immune system disorders	416	118 (12%)
Skin and subcutaneous tissue disorders	186	108 (11%)
Eye disorders	130	99 (10%)
Ear and labyrinth disorders	65	51 (5%)
Blood and lymphatic system disorders	50	46 (5%)
Vascular disorders	61	33 (3%)
Renal and urinary disorders	40	28 (3%)
Metabolism and nutrition disorders	29	25 (2%)
Cardiac disorders	31	22 (2%)
Neoplasms benign, malignant and unspecified	12	11 (1%)
Surgical and medical procedures	12	11 (1%)
Hepatobiliary disorders	7	7 (0.7%)
Pregnancy, puerperium and perinatal conditions	6	6 (0.6%)
Endocrine disorders	4	4 (0.4%)
Social circumstances	2	2 (0.2%)
Congenital, familial and genetic disorders	1	1 (0.1%)

Table 13: 25 most-common adverse events for open-label tranexamic acid subjects ($n = 1,015$), by MedDRA preferred term

MedDRA Preferred Term	Instances	Subjects
Headache	4,436	553 (54%)
Menstrual discomfort	3,308	489 (48%)
Back pain	1,312	289 (28%)
Viral upper respiratory tract infection	257	169 (17%)
Pain in extremity	250	120 (12%)
Arthralgia	456	118 (12%)
Nausea	269	118 (12%)
Sinusitis	205	115 (11%)
Musculoskeletal pain	234	113 (11%)
Diarrhoea	292	107 (11%)
Throat irritation	182	106 (10%)
Abdominal discomfort	255	104 (10%)
Migraine	598	95 (9%)
Cough	122	92 (9%)
Sinus congestion	238	84 (8%)
Dysmenorrhoea	708	83 (8%)
Insomnia	374	83 (8%)
Sinus headache	330	83 (8%)
Abdominal pain upper	196	79 (8%)
Seasonal allergy	204	77 (8%)
Upper respiratory tract infection	114	74 (7%)
Fatigue	251	72 (7%)
Neck pain	157	72 (7%)
Dyspepsia	254	69 (7%)
Nasal congestion	172	68 (7%)

6 Discussion

This section includes a discussion of the results and the limitations posed by the study design.

6.1 Results

Decreased visual acuity, abnormal color vision (among subjects with baseline normal color vision), abnormal retinal status (among subjects with baseline normal retinal status), decreased renal function (among subjects with baseline normal renal function), and VTE-related adverse events were observed in the subjects exposed to tranexamic acid in the randomized clinical trials conducted to support the indication evaluated in this report. Given the limited amount of data available from randomized studies and the infrequency of the safety endpoints, however, it is not possible to estimate the increase or decrease in relative risk with statistical significance at the 5% level for these adverse events.

The ophthalmologic data included visual acuity, color vision, and retinal examinations for both randomized and open-label subjects. Data from ophthalmologic examinations were only available for about one half of the randomized placebo subjects, approximately two thirds of the randomized tranexamic acid subjects, and less than one third of the open-label tranexamic acid subjects. In the randomized studies, there was no statistically significant increase in relative risk between the tranexamic acid and placebo groups for decreased visual acuity, abnormal color vision among subjects with baseline color vision, and abnormal retinal status among subjects with baseline normal retinal status.

The ophthalmologic events occurred at a higher rate in the long-term, open-label studies than in the shorter, randomized studies. Decreased visual acuity was observed among 17.1% of the open-label subjects, compared to 9.7% of the randomized tranexamic acid subjects. Abnormal color vision among subjects with baseline normal color vision was observed among 2.1% of the open-label subjects, compared to 0.8% of the randomized tranexamic acid subjects. Abnormal retinal status was observed among 3.2% of the open-label subjects compared to 0.4% of the randomized tranexamic acid subjects. Since all of the long-term data are from the open-label studies, it is difficult to determine if these differences are the result of longer or chronic exposure to tranexamic acid, or due to differences in study design.

An analysis of other adverse events reveals that tranexamic acid subjects from the randomized studies are at an increased risk of certain types of adverse events. The increases in relative risk are statistically significant at the 5% level. These include events from the following MedDRA system organ classes: blood and lymphatic system disorders; respiratory, thoracic and mediastinal disorders; infections and infestations; musculoskeletal and connective tissue disorders; and nervous system disorders. At the preferred term-level, seven terms were more likely to be observed in the tranexamic acid group: musculoskeletal pain; nasal congestion; anemia; arthralgia; fatigue; back pain; and headache.

Table 14: Study completion

	Planned Study Duration	Enrolled Subjects	Completed Subjects	Completion Percentage
Study -301	3 cycles	304	272	89%
Study -303	6 cycles	196	148	76%
Study -304	9 cycles ¹	292	186	64%
Study -302	27 cycles	784	215	27%

¹Open-label extension for studies -301 and -303. Placebo subjects from prior studies switched to active treatment.

6.2 Limitations in the study design

Subjects who were enrolled in long-term, open-label studies without placebo control, cannot be pooled with subjects from shorter, randomized, placebo-controlled trials, because differences in study design create differences in the data collected from the two groups of subjects. Since most of the subjects on tranexamic acid were enrolled in the long-term, open-label studies, this means that most of the data on exposure to tranexamic acid and all of the long-term exposure data cannot be included in the comparative analysis. The following sub-sections discuss this problem in more detail.

6.2.1 Long-term safety data

Table 14 shows the completion rates reported in the TERM (study termination) analysis datasets provided with each study report. Per protocol, none of the placebo subjects have data from more than six cycles of exposure; given that the adverse events examined in this report are rare but potentially very serious, the limited size and duration of the placebo-exposed group is insufficient to assess the baseline risk of renal impairment, ophthalmologic changes, and VTE adverse events in the intended patient population. Only 215 subjects completed study -302, the 27 cycle safety study.

In the case of rare, but potentially serious adverse events, observing zero events among the placebo group indicates that the number and exposure of placebo treated subjects was insufficient to observe an event. With 139 placebo subjects, the probability of not observing an adverse reaction that has an event rate of 1/1,000 in the population is $0.999^{139} = 0.87$. For an adverse reaction with an event rate of 1/500 in the population, the probability of observing no events in the placebo group is 0.76. Without observing events in the placebo group, it is not possible to assess the baseline risk of adverse events in the intended patient population; without the baseline risk, it is not possible to assess the change in risk posed by exposure to the treatment.

6.2.2 Ophthalmic exam data not randomized

Despite study protocols that specified the collection of ophthalmic data from all subjects, only 47% of the 1,204 safety subjects had a baseline ophthalmologic exam and at least one follow up exam. Because over half of subjects are missing ophthalmic data, these data can no longer be considered a randomized sample. In particular, if ophthalmic data were collected only when an ophthalmologist or optometrist was available at the site, then these data constitute a convenience sample.

7 Summary and Conclusions

This report contains a statistical evaluation of the Phase 3 safety data for NDA 22-430 related to VTE adverse events, other adverse events, ophthalmologic changes (decreased visual acuity, abnormal color vision, and abnormal retinal examination), and decreased renal function. All of these events were observed to some extent in the randomized studies, but the relatively small sample sizes mean that the confidence intervals for the relative risk were extremely wide. Thus, while decreased visual acuity, abnormal color vision, abnormal retinal status, VTE adverse events, and decreases in renal function were all observed in the randomized tranexamic acid group, the 95% confidence interval for the relative risks includes 1, such that no statistical inference can be drawn at a 5% level.

Events that were significantly more likely in the tranexamic acid group had a lower bound for the 95% confidence interval for the relative risk that was greater than 1. In the randomized studies, seven preferred terms satisfy this condition; tranexamic acid subjects were more likely to experience headache, back pain, anemia, arthralgia, musculoskeletal pain, fatigue, and nasal congestion, and adverse events coded to the blood and lymphatic system disorders, respiratory, thoracic and mediastinal disorders, infections and infestations, musculoskeletal and connective tissue disorders, and nervous system disorders system organ classes.

Due to low study completion rates, intermittent collection of ophthalmic and labs data, and the division of subjects between the open-label and randomized studies, there is insufficient data to perform statistical inference at the conventional 5% level of significance.

Appendix A: MedDRA VTE Preferred Terms

Table 15: MedDRA VTE preferred terms

Acute myocardial infarction
Amaurosis

Continued on next page

Table 15 – continued from previous page

Amaurosis fugax
Angiogram abnormal
Angiogram cerebral abnormal
Angiogram peripheral abnormal
Angioplasty
Aortic bypass
Aortic embolus
Aortic surgery
Aortic thrombosis
Aortogram abnormal
Arterectomy with graft replacement
Arterial bypass operation
Arterial graft
Arterial occlusive disease
Arterial stent insertion
Arterial therapeutic procedure
Arterial thrombosis
Arterial thrombosis limb
Arteriogram abnormal
Arteriogram carotid abnormal
Arteriovenous fistula occlusion
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Atherectomy
Atrial thrombosis
Axillary vein thrombosis
Basilar artery occlusion
Basilar artery thrombosis
Blindness transient
Bone infarction
Brain stem infarction
Brain stem thrombosis
Budd-chiari syndrome
Carotid arterial embolus
Carotid artery occlusion
Carotid artery thrombosis
Carotid endarterectomy
Catheter related complication

Continued on next page

Table 15 – continued from previous page

Catheterisation venous
Cavernous sinus thrombosis
Central venous catheterisation
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral ischaemia
Cerebral thrombosis
Cerebral venous thrombosis
Cerebrospinal thrombotic tamponade
Cerebrovascular accident
Cerebrovascular accident prophylaxis
Cerebrovascular disorder
Cerebrovascular insufficiency
Cerebrovascular operation
Cerebrovascular stenosis
Choroidal infarction
Compression stockings application
Coronary angioplasty
Coronary arterial stent insertion
Coronary artery embolism
Coronary artery reocclusion
Coronary artery thrombosis
Coronary bypass thrombosis
Coronary endarterectomy
Coronary revascularisation
Deep vein thrombosis
Diplegia
Disseminated intravascular coagulation
Disseminated intravascular coagulation in newborn
Embolia cutis medicamentosa
Embolic cerebral infarction
Embolic stroke
Embolism
Endarterectomy
Femoral artery occlusion
Graft thrombosis

Continued on next page

Table 15 – continued from previous page

Haemorrhagic cerebral infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Hemiparesis
Hemiplegia
Hepatic artery embolism
Hepatic vein occlusion
Hepatic vein thrombosis
Iliac artery embolism
Iliac artery thrombosis
Iliac vein occlusion
Infarction
Inferior vena caval occlusion
Injection site thrombosis
Intestinal infarction
Intra-aortic balloon placement
Intracardiac thrombus
Intracranial venous sinus thrombosis
Intraoperative cerebral artery occlusion
Intravenous catheter management
Ischaemic cerebral infarction
Ischaemic stroke
Jugular vein thrombosis
Lacunar infarction
Mesenteric artery embolism
Mesenteric artery stenosis
Mesenteric vascular insufficiency
Mesenteric vein thrombosis
Optic nerve infarction
Paget-schroetter syndrome
Papillary muscle infarction
Paraparesis
Paraplegia
Paresis
Pelvic venous thrombosis
Penile vein thrombosis
Peripheral artery angioplasty
Peripheral embolism

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Table 15 – continued from previous page

Phlebectomy
Phleboplasty
Pituitary infarction
Pneumatic compression therapy
Portal shunt
Portal vein occlusion
Portal vein thrombosis
Post thrombotic syndrome
Postoperative thrombosis
Postpartum venous thrombosis
Precerebral artery occlusion
Pulmonary artery thrombosis
Pulmonary embolism
Pulmonary infarction
Pulmonary microemboli
Pulmonary thrombosis
Pulmonary veno-occlusive disease
Pulmonary venous thrombosis
Quadripareisis
Quadriplegia
Renal artery occlusion
Renal artery thrombosis
Renal infarct
Renal vein embolism
Renal vein occlusion
Renal vein thrombosis
Retinal artery embolism
Retinal artery occlusion
Retinal artery thrombosis
Retinal infarction
Retinal vascular thrombosis
Retinal vein occlusion
Retinal vein thrombosis
Shunt occlusion
Shunt thrombosis
Silent myocardial infarction
Spinal artery embolism
Spinal cord infarction

Continued on next page

Table 15 – continued from previous page

Splenic infarction
Splenic vein thrombosis
Stent occlusion
Stroke in evolution
Subclavian artery embolism
Subclavian artery thrombosis
Subclavian vein thrombosis
Superior mesenteric artery syndrome
Superior sagittal sinus thrombosis
Superior vena caval occlusion
Surgical vascular shunt
Testicular infarction
Thrombectomy
Thromboangiitis obliterans
Thrombolysis
Thrombophlebitis
Thrombophlebitis migrans
Thrombophlebitis neonatal
Thrombosed varicose vein
Thrombosis
Thrombosis prophylaxis
Thrombotic microangiopathy
Thrombotic stroke
Thrombotic thrombocytopenic purpura
Thyroid infarction
Transient ischaemic attack
Transverse sinus thrombosis
Truncus coeliacus thrombosis
Tumour embolism
Ultrasonic angiogram abnormal
Ultrasound doppler abnormal
Vascular operation
Vasodilation procedure
Vena cava embolism
Vena cava filter insertion
Vena cava thrombosis
Venogram abnormal
Venoocclusive disease

Continued on next page

Table 15 – continued from previous page

Venooclusive liver disease
Venous occlusion
Venous operation
Venous thrombosis limb
Vertebral artery occlusion
Vertebral artery thrombosis
Visual acuity reduced transiently

Appendix B: Eye disorder adverse events

Table 16: Adverse events in the open-label studies with “Eye disorder” as the primary system organ class

Preferred term	Instances	Subjects
Abnormal sensation in eye	1	1
Amblyopia	2	2
Angle closure glaucoma	1	1
Astigmatism	1	1
Blepharospasm	3	2
Blindness transient	1	1
Borderline glaucoma	1	1
Cataract	3	3
Cataract cortical	2	2
Cataract subcapsular	3	2
Chalazion	3	2
Chorioretinal scar	1	1
Ciliary muscle spasm	1	1
Colour vision tests abnormal blue-yellow	4	3
Colour vision tests abnormal red-green	2	2
Conjunctival haemorrhage	1	1
Conjunctivitis	13	13
Conjunctivitis allergic	1	1
Corneal abrasion	2	2
Corneal bleeding	3	3
Corneal pigmentation	1	1

Continued on next page

Table 16 – continued from previous page

Preferred term	Instances	Subjects
Corneal scar	2	2
Dermatitis	1	1
Dry eye	10	8
Eye allergy	5	4
Eye discharge	5	4
Eye haemorrhage	1	1
Eye infection	3	3
Eye infection staphylococcal	1	1
Eye irritation	9	7
Eye pain	7	7
Eye pruritus	13	10
Eye redness	4	4
Eye swelling	5	5
Eyelid oedema	1	1
Halo vision	1	1
Headache	6	4
Iritis	5	2
Lacrimal gland enlargement	1	1
Lenticular opacities	2	2
Macular hole	1	1
Macular pseudohole	1	1
Migraine	2	1
Miosis	1	1
Myofascial spasm	1	1
Myopia	2	2
Ocular hypertension	1	1
Optic disc disorder	1	1
Optic disc drusen	2	2
Optic nerve cup/disc ratio	1	1
Optic nerve cup/disc ratio increased	1	1
Papilloedema	2	1
Photophobia	1	1
Post procedural pain	3	2
Rash	1	1
Retinal artery stenosis	1	1
Retinal degeneration	3	3
Retinal naevus	2	2

Continued on next page

Table 16 – continued from previous page

Preferred term	Instances	Subjects
Retinal pigmentation	4	4
Seasonal allergy	1	1
Sinus pain	1	1
Viral upper respiratory tract infection	1	1
Vision blurred	10	9
Visual acuity reduced	1	1
Vitreous detachment	2	2
Vitreous disorder	1	1

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Signatures

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22430	ORIG 1	XANODYNE PHARMACEUTICS INC	TRANEXAMIC ACID 650MG MODIFIED RELEASE T

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

/s/

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07/30/2009

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07/30/2009

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07/30/2009



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-430/N000

Drug Name: Tranexamic acid (Modified Release Tablets)

Indication(s): Treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of associated symptoms

Applicant: Xanodyne Pharmaceuticals, Inc.

Date(s): Submission Date: 01/30/2009
PDUFA Date: July/30/2009
Completion Date: 06/15/2009

Review Priority: Priority

Biometrics Division: Division of Biometrics 3

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Keywords: NDA review, Clinical studies, ANCOVA, Multi-center

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results support the efficacy of 3.9 g/day (1.3 g TID) dose level of tranexamic acid, a modified-release formulation, in reducing the Menstrual Blood Loss (MBL) compared with placebo in women with evidence of heavy menstrual bleeding (HMB).

From a statistical perspective, this application provided adequate data to support the efficacy of tranexamic acid in the treatment of HMB.

1.2 Brief Overview of Clinical Studies

The sponsor, Xanodyne Pharmaceuticals Inc., submitted safety and efficacy data from two Phase 3 studies in supporting tranexamic acid in the treatment of HMB and amelioration of associated symptoms. Study XP12B-MR-301, entitled “A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study to Evaluate Efficacy and Safety of 0.65 g and 1.3 g Oral Doses of XP12B-MR TID Administered During Menstruation for the Treatment of Menorrhagia”, was conducted in 63 US sites.

Study XP12B-MR-303, entitled “A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study to Evaluate Efficacy and Safety of a 1.3 gram Oral Dose of XP12B-MR TID Administered During Menstruation for the Treatment of Menorrhagia”, was conducted in 40 US sites. In study XP12B-MR-301, eligible healthy women of 18 to 49 years of age with cyclic HMB associated with menorrhagia were randomized to receive either 1.95 g/day or 3.9 g/day or placebo, whereas, in Study XP12B-MR-303, eligible subjects were randomized to receive only 3.9 g/day of tranexamic acid or placebo.

The primary endpoint was the mean change from pre-treatment to post-treatment alkaline hematin MBL values in both studies. The key secondary endpoints were Limitation of Social or Leisure Activities (LSLA), Limitation in Physical Activities (LPA) and total number of large stains. There were 11 other secondary endpoints which were considered exploratory.

1.3 Statistical Issues and Findings

There were no major statistical issues with regards to analysis of primary and secondary endpoints. However, three pre-specified endpoints were based on subjective patient reported outcome questionnaire, the validity and reliability of which has not been documented. In this review, we report the least square mean (ANCOVA model based) change in MBL as opposed to sponsor’s reported sample mean. In both studies, other secondary endpoints were considered exploratory. Although two key secondary endpoints were statistically significant, but lack of clinically meaningful justification and the validity issues inherent in PRO based endpoints, the inclusion of such secondary endpoints in the label should be exercised with caution.

2. INTRODUCTION

2.1 Overview

The sponsor, Xanodyne Pharmaceuticals, Inc., is seeking approval of tranexamic acid for the treatment of HMB (menorrhagia) and the amelioration of associated symptoms. Tranexamic acid has been used in UK for the treatment of menorrhagia and prevention of bleeding such as in dental extraction in hemophilia. Oral tranexamic acid therapy typically starts at 1-1.5 g, 3 or 4 times daily, for the first 5 menstrual cycle days of HMB.

To support the efficacy and safety of tranexamic acid, the sponsor submitted two Phase 3 clinical studies (XP12B-MR-301 and XP12B-MR-303). For safety evaluation, a thorough QT study (XP12B-104) was submitted as well as two ongoing open-label safety extension studies (27-cycle study XP12B-MR-302 and 9-cycle study XP12B-MR-304). This review will focus only on the efficacy data from these two Phase 3 trials, which was summarized in Table 2.1.

Table 2.1 Summary of Pivotal Studies				
Study	Study site (number)	Study Design	Study Regimen/Number of Subjects	Duration of Treatment
XP12B-MR-301	US (63)	Multi-center, Randomized, Double-blind, Placebo controlled.	Total Screened: 1224 Total Randomized: 304 Placebo: 69 Tranexamic acid (1.95 g/day): 117 Tranexamic acid (3.9 g/day): 118	12 weeks
XP12B-MR-303	US (40)	Multi-center, Randomized, Double-blind, Placebo controlled.	Total Screened: 711 Total Randomized: 196 Placebo: 73 Tranexamic acid (3.9 g/day): 123	24 weeks

Sources: Tables 9.1-1 and 10.1-1

2.2 Data Sources

All pertinent study information was submitted electronically. The data quality of the submission was within acceptable limits. The analysis datasets and associated definition files were listed in Table 2.2.

Table 2.2 Data Sources		
Study	File	Location
XP12B-MR-301	Datasets	\\CDSESUB1\EVSPROD\NDA022430\0000\m5\datasets\xp12b-mr-301\analysis
	Definition	\\CDSESUB1\EVSPROD\NDA022430\0000\m5\datasets\xp12b-mr-301\analysis\define.xml
XP12B-MR-303	Datasets	\\CDSESUB1\EVSPROD\NDA022430\0000\m5\datasets\xp12b-mr-303\analysis
	Definition	\\CDSESUB1\EVSPROD\NDA022430\0000\m5\datasets\xp12b-mr-303\analysis\define.xml

3. STATISTICAL EVALUATION

3.1 Overview of Studies XP12B-MR-301 and XP12B-MR-303

3.1.1 Designs and Objectives

Study XP12B-MR-301 consisted of three arms: 1.95 g/day, 3.9 g/day of tranexamic acid and placebo with three-cycles of treatment. Study XP12B-MR-303 consisted of two arms: 3.9 g/day of tranexamic acid and placebo with six-cycles of treatment. Both studies were conducted in the US.

Design: Both studies were randomized, double-blind, placebo-controlled, multi-center, parallel-group. The primary objective of the studies was to determine the efficacy of tranexamic acid TID dose administered during menstruation for up to 5 days to reduce MBL compared with placebo in women with objective evidence of HMB. The secondary objectives were to determine (1) the subjective improvement in LSLA and LPA scores from the Menorrhagia Impact Questionnaire (MIQ) (2) the reduction in the number of large stains exceeding the capacity of sanitary protection reported during the menstrual period from daily diaries; and (3) to determine the safety of a tranexamic acid TID dose administered during menstruation in women with HMB.

Both studies consisted of a screening phase of 2 menstrual periods for eligibility determination. Following the screening phase, subjects were randomized to receive either tranexamic acid dose or placebo.

The planned durations of the trials were 6-8 months in Study XP12B-MR-301 and 9-11 months in Study XP12B-MR-303. Treatment compliance was assessed by the number of returned tablets. Although the amount of medication was designed for up to 5 days per menstrual cycle, the study subjects were not required to take all tablets in each menstrual cycle. The primary efficacy variable was assessed for pre-treatment menstrual cycles 1 and 2 (Visits 1B and 1C) in both studies and for post-treatment cycles 1 (Visit 3), 2 (Visit 4), and 3 (Visit 5) in Study XP12B-MR-301 and for post-treatment cycles 1 (Visit 3), 2 (Visit 4), 3 (Visit 5), and 6 (Visit 8) in Study XP12B-MR-303.

Primary Efficacy Endpoint: The primary efficacy endpoint is the change from baseline to study endpoint, computed by subtracting the average post-treatment MBL from the average pre-treatment MBL.

Secondary Efficacy Endpoints: There were 14 secondary endpoints, of which the three were pre-specified as key secondary efficacy endpoints, while the rest were considered exploratory.

Pre-specified secondary endpoints:

- Limitation of Social and Leisure Activities (LSLA) score (MIQ Question 4)

- Limitation of Physical Activities (LPA) score (MIQ Question 3)
- Total number of large stains reported during the menstrual period on patient diaries

Other secondary efficacy variables are:

- Hemoglobin – clinical laboratory value
- Ferritin – clinical laboratory value
- Blood loss score from the MIQ
- Limitation in Work Outside or Inside the Home (LWH) from the MIQ
- Patient assessment of clinical meaningfulness from the MIQ
- Total number of times sleep is interrupted during the menstrual period from patient diaries
- Total number of large clots reported during the menstrual period from patient diaries
- Total number of small clots reported during the menstrual period from patient diaries
- Total number of small stains reported during the menstrual period from patient diaries
- The total number of large stains reported during the menstrual period from patient diaries.
- Total number of sanitary products used during the menstrual period (as reported by the testing laboratory)

Determination of Sample Size: The sample size was calculated in order to have a 90% power of detecting a 50 ml difference between the mean change from baseline MBL in the active treatment and placebo group. Assuming a 65 mL reduction in MBL in the active group and a 15 mL reduction in MBL in the placebo group, with a common SD of 85 mL and allocation ratio of 2:1, the study was planned to randomize 92 subjects in the active and 46 subjects in the placebo group.

Definition of Analysis Sets (Population): For efficacy evaluation, four analyses datasets were used: intent-to-treat (ITT), modified ITT, modified ITT with baseline observation carry forward (BOCF), and per-protocol (PP).

- ITT dataset included all randomized subjects who took the study medication
- mITT dataset included ITT subjects who had baseline and at least one post-baseline primary efficacy evaluation
- mITT with BOCF datasets included ITT subjects who had baseline primary efficacy evaluation. For subjects whose all post-baseline primary efficacy evaluations were missing, their baseline values were imputed.
- PP dataset included all ITT subjects who had a baseline primary efficacy evaluation and had completed all study visits and had no major protocol violations.

Handling of Missing Data: Only MBL data was imputed as follows. When there was a missing collection day, the missing value code was examined. When the missing value code was a zero code, a zero was imputed. When the missing value code was a non-zero code then the bleeding

diary was consulted. If in the bleeding diary the subject indicated she had either spotting or no bleeding on that day then a zero was imputed. Otherwise the pre-treatment or post-treatment mean for the subject's given collection day was imputed.

If there was only one sample for a day and the sample was missing, then the day was treated as a missing collection day.

For missing periods (i.e. no sanitary product collection on any day during bleeding for a period), they were treated as missing in the analyses.

Pool of Sites: Sites were not pooled.

Statistical Methods: The statistical methods of analysis included analysis of covariance (ANCOVA) model to analyze the between-treatment group comparison of the mean change from pre-treatment to post-treatment alkaline hematin MBL values. The ANCOVA model included fixed effect of treatment and the baseline as a covariate. The primary efficacy analysis was conducted using mITT datasets. Analyses on mITT with BOCF and PP datasets were considered as sensitivity analyses. A point estimate of the MBL mean change from baseline was calculated for each treatment group. In order to claim efficacy, the primary efficacy variable had to satisfy the following three conditions:

- The comparison between tranexamic acid group and placebo group is statistically significant.
- A point estimate in tranexamic acid group has to be greater than or equal to 50 mL (reduction).
- A point estimate in tranexamic acid group has to be greater than or equal to a clinically meaningful reduction from baseline in MBL of 36 mL, which was identified through a Receiver Operating Characteristic (ROC) analysis in Study XP12B-MR-301.

ANCOVA was also used to analyze key secondary endpoints, and Fisher's exact test was used to perform responder analysis based on the proportion of patients who experienced a reduction from baseline.

All other secondary analysis was considered supportive analysis to the primary analysis.

ROC analysis was performed to determine a cutoff point in reduction of MBL that was meaningful to subjects. A subject was considered to have meaningful improvement if at last visit she had answered "YES" to both MIQ Questions 6 and 6c. The Question 6 was "Compared to your previous menstrual period, would you say your blood loss during this period was better?" The Question 6c was "Was this a meaningful or important change for you?" Using this as true improvement, the ROC curve was graphed for the entire observed value range of the primary efficacy variable with an increment of 1 mL. In the ROC graph, the sensitivity is the y-axis and the false negative rate (100-specificity) is the x-axis. A reduction of 36 mL was considered as the clinically meaningful cutoff point. At this point, the sensitivity was 65% and specificity was 66%. This means that by using 36 mL as clinical cutoff point, 65% of all the true positive responses and 66% of all the true negative responses can be correctly determined.

Multiple Comparisons/Multiplicities: In Study XP12B-MR-301, the primary hypothesis for the comparison of 3.9 g/day and placebo group was tested first. If the test was statistically significant, then the three pre-specified secondary efficacy endpoints were tested sequentially in the following order: (1) LSLA (3.9 g/day versus placebo group); (2) LSA (3.9 g/day versus placebo group); (3) Large Stains responder (3.9 g/day versus placebo group). The test would be stopped if at any point in the testing sequence, a hypothesis for a prespecified secondary endpoint was accepted. If all three hypotheses were rejected for 3.9 g/day dose, then the same sequential test would be performed for 1.95 g/day dose.

In Study XP12B-MR-303, the testing procedure was the same except that the comparison was only between 3.9 g/day group and placebo group.

Interim Analysis: Both studies had an interim analysis plan after 50% of the subjects had completed the MBL efficacy assessment in order to re-adjust the sample size based on the two secondary endpoints: LSLA and LSA. It was performed by Data Monitoring committee (DMC) using conditional power method (Chen et al. 2004). The DMC reports indicated that the committee for Xanodyne Study XP12B-MR-303 recommended the sponsor to increase the sample size by 28 in the treatment group and by 18 in the placebo group.

3.1.2 Reviewer's Comments on the Design

In both studies, sample sizes were adequate to test the primary hypothesis with 90% power. The interim analysis to re-adjust the sample sizes was also appropriately planned. Use of ANCOVA was acceptable provided the normality assumptions are not violated. The protocol did not have any pre-specified alternative methods of analysis.

The ROC analysis was considered only exploratory. Multiplicity was addressed by sequential gate-keeping approach, where, the primary null hypothesis must be rejected in order to test for the key secondary endpoints and the low dose would not be tested until the high dose rejected all the three key secondary endpoints. Therefore, no alpha adjustment for the multiplicity was necessary.

3.2 Results: Study XP12B-MR-301

3.2.1 Subject disposition

At 63 US sites, a total of 304 subjects were randomized with a ratio of 2:1 in treatment group versus placebo group. The number of enrollment among the sites ranges from 1 to 27. The dispositions of the subjects are shown in Table 3.2.1.

Subjects	Treatment Group			Overall N
	Tranexamic Acid (1.95 g/day) N	Tranexamic Acid (3.9 g/day) N	Placebo N	
Total Randomized	118	117	69	304
Completed Study	103	106	63	272
Discontinued (%):	15 (12.71)	11 (9.40)	6 (8.70)	32 (10.53)
Adverse Event	1 (6.67)	3 (27.27)	1 (16.67)	5 (15.63)
Lack of Efficacy	0	0	0	0
Withdrawn Consent	2 (13.33)	0	1 (16.67)	3 (9.38)
Protocol deviation	3 (20.00)	1 (9.09)	1 (16.67)	5 (15.63)
Failed to return	6 (40.00)	5 (45.45)	1 (16.67)	12 (37.50)
Death	0	0	0	0
Other Reasons	3 (20.00)	2 (18.18)	2 (33.33)	7 (21.88)
Analysis Population:				
Intent to Treat	115	115	67	297
modified Intent to Treat	112	115	67	294
mITT with LOCF	115	115	67	297
Per Protocol	68	71	36	175

Sources: Tables 10.1-1 and 11.1-1

3.2.2 Patient demographics and baseline characteristics

Most important baseline characteristics were balanced across treatment groups as shown in Table 3.2.2. The baseline alcoholic and tobacco usages were also similar among three treatment groups. The distribution of the duration of HMB was similar between the active and placebo groups.

Demographic Variable	Tranexamic Acid (1.95 g/day) N=115	Tranexamic Acid (3.9 g/day) N=115	Placebo N=67
Mean Age (SD)	39.19 (6.248)	40.18 (6.296)	38.93 (6.056)
Mean year of HMB (SD)	11.94 (8.892)	12.13 (9.401)	9.98 (8.438)
Race: n (%):			
White	77 (66.96)	76 (66.09)	43 (64.18)
Black	34 (29.57)	31 (26.96)	22 (32.84)
Asian	0	3 (2.61)	0
Native American	1 (0.87)	0	0
Pacific Islander	0	1 (0.87)	0

Demographic Variable	Tranexamic Acid (1.95 g/day) N=115	Tranexamic Acid (3.9 g/day) N=115	Placebo N=67
Other	3 (2.61)	4 (3.48)	2 (2.99)
Mean Baseline Menstrual Blood Loss (mL) (SD)	168.90 (82.253)	178.03 (112.159)	153.58 (67.881)

Sources: Table 11.2-1 and reviewer's analysis

3.2.3 Primary Efficacy

As noted earlier, the primary efficacy endpoint was the change from baseline to post-treatment in MBL. To claim efficacy, the following three conditions had to be satisfied:

- (1) the MBL mean change from baseline compared with placebo had to be statistically significant;
- (2) the point estimate of the MBL mean change from baseline for a treatment group must be greater or equal to 50 mL; and
- (3) the point estimate of the MBL mean change from baseline for a give treatment group was greater than or equal to 36 mL in the MBL reduction identified by an ROC analysis in this trial.

Results of our analysis are shown in Table 3.2.3. Mean reduction in MBL was statistically significantly greater for 3.9 g/day dose of tranexamic acid compared with placebo. This dose did meet the above clinical criteria of demonstrating efficacy. Note that the cutoff point of 36 mL based on ROC analysis was exploratory in nature.

By using 36 mL as clinical significant cutoff point, 65% of all true positive women (experiencing reduction of MBL) will be correctly identified and 66% of all true negative women will be correctly identified. This means 35% of women still experiencing heavy MBL will be wrongly classified as women having clinically meaningful reduction in MBL. Using 50 mL as cutoff point, 25% of women would still be experiencing heavy MBL and were wrongly classified as women having clinically meaningful reduction in MBL.

Treatment	N	Baseline Mean (SD)	Change (SD)	Least Squares Mean	P-value
Tranexamic Acid (3.9 g/day)	112	168.99 (82.992)	65.31 (51.136)	65.32	<0.0001
Tranexamic Acid (1.95 g/day)	115	178.03 (112.159)	46.45 (57.142)	44.07	<0.0001
Placebo	67	153.58 (67.881)	2.98 (45.947)	7.06	

Source: Table 11.4-1 and reviewer's analysis

3.2.4 Secondary Efficacy

The results of pre-specified secondary endpoints are shown in Tables 3.2.4.1, 3.2.4.2 and 3.2.4.3. Analyses on other secondary endpoints are considered exploratory, and therefore, not reported in this review. Based on the sponsor's multiple testing procedures, only 3.9 g/day doses demonstrate statistically significant improvement in two secondary endpoints: LSLA and LPA compared with placebo. No significant improvement was noted for the third endpoint, reduction in the number of larger stains.

Table 3.2.4.1 Mean Reduction From Baseline for MIQ Question 4 (LSLA) (ANCOVA) – mITT Population				
Treatment	N	Baseline Mean (SD)	Least Square Mean Change	P-value
Tranexamic Acid (3.9 g/day)	112	3.00 (1.079)	0.98	<0.0001
Tranexamic Acid (1.95 g/day)	115	2.93 (0.996)	0.74	0.0055
Placebo	66	2.85 (0.973)	0.39	

Source: Table 11.4-2 and reviewer's analysis

Table 3.2.4.2 Mean Reduction From Baseline for MIQ Question 3 (LPA) (ANCOVA) – mITT Population				
Treatment	N	Baseline Mean (SD)	Least Square Mean Change	P-value
Tranexamic Acid (3.9 g/day)	112	3.07 (1.039)	0.94	<0.0001
Tranexamic Acid (1.95 g/day)	115	2.97 (0.977)	0.70	0.0030
Placebo	66	2.96 (0.865)	0.34	

Source: Table 11.4-2 and reviewer's analysis

Table 3.2.4.3 Large Stain Responder Analysis – mITT Population			
Treatment	N	Number (%) of Responder (experiencing reduction)	P-value
Tranexamic Acid (3.9 g/day)	111	71 (63.96)	0.1560
Tranexamic Acid (1.95 g/day)	114	70 (61.40)	0.2753
Placebo	67	35 (52.24)	

Source: Table 11.4-3

3.2.5 Reviewer's Comment on the Efficacy Results

Results of our analysis confirmed the sponsor's results that both doses of tranexamic acid was statistically significant in reducing the menstrual blood loss compared with placebo. However, as per sponsor's winning criteria only 3.9 g/day could be considered efficacious. Results for two secondary endpoints: LSLA and LPA were also statistically significant compared with placebo. Results from corresponding nonparametric analysis confirmed the findings.

3.3 Results: Study XP12B-MR-303

3.3.1 Subject disposition

At 40 US sites, a total of 196 subjects were randomized with a ratio of 2:1 in treatment group versus placebo group. The number of enrollment among the sites ranges from 1 to 18. Other important details are shown in Table 3.3.1.

Table 3.3.1 Disposition of Subjects: Study XP12B-MR-303			
Subjects	Treatment Group		
	Tranexamic Acid (3.9 g/day) N	Placebo N	Overall n
Total Randomized	123	73	196
Completed Study	94	54	148
Discontinued (%):	29 (23.58)	19 (26.03)	48 (24.49)
Adverse Event	3 (10.34)	3 (15.79)	6 (12.50)
Lack of Efficacy	0	2 (10.53)	2 (4.17)
Withdrawn Consent	6 (20.69)	2 (10.53)	8 (16.67)
Protocol deviation	2 (6.90)	5 (26.32)	7 (14.58)
Failed to return	10 (34.48)	6 (31.58)	16 (33.33)
Death	0	0	0
Other Reasons	8 (27.59)	1 (5.26)	9 (18.75)
Analysis Population:			
Intent to Treat	117	72	189 (96.43)
modified Intent to Treat	115	72	187 (95.41)
mITT with LOCF	117	72	189 (96.43)
Per Protocol	56	29	85 (43.37)
<i>Sources: Tables 10.1-1 and 11.1-1</i>			

3.3.2 Patient demographics and baseline characteristics

Most important baseline characteristics were similar across treatment groups as shown in Table 3.3.2. The baseline alcoholic and tobacco usages were also similar among two treatment groups. The duration distribution of HMB was nearly identical between active group and placebo group.

Demographic Variable	Tranexamic Acid (3.9 g/day) N=117	Placebo N=72
Mean Age (SD)	38.74 (6.324)	38.85 (6.837)
Mean year of HMB (SD)	10.08 (9.354)	10.08 (8.629)
Race: n (%):		
White	86 (73.50)	51 (70.83)
Black	23 (19.66)	18 (25.00)
Asian	1 (0.85)	1 (1.39)
Native American	0	0
Pacific Islander	0	0
Other	7 (5.98)	2 (2.78)
Mean Baseline Menstrual Blood Loss (mL) (SD)	177.82 (108.804)	152.98 (66.583)

Sources: Table 11.2-1 and reviewer's analysis

3.3.3 Primary Efficacy

The primary endpoint for 3.9 g/day dose met the efficacy requirements specified in the protocol, which were the same as those in Study XP12B-MR-301. Table 3.3.3 showed that 3.9 g/day dose appeared both statistically and clinically significant in the reduction of MBL.

Treatment	N	Baseline Mean (SD)	Least Squares Mean Change	P-value
Tranexamic Acid (3.9 g/day)	115	172.29 (95.552)	66.30	<0.0001
Placebo	72	152.98 (66.583)	17.82	

Source: Table 11.4-1

3.3.4 Secondary Efficacy

Prespecified secondary endpoints were focused in this section. Analyses on other secondary endpoints are considered as exploratory investigation. Based on the sponsor's multiple testing procedure, 3.9 g/day dose appeared effective in the improvement of LSLA and LPA. However, this dose failed to demonstrate efficacy in reducing total number of large stains. The details were shown in Tables 3.3.4.1, 3.3.4.2 and 3.3.4.3.

Table 3.3.4.1 Mean Reduction From Baseline for MIQ Question 4 (LSLA) (ANCOVA) – mITT Population				
Treatment	N	Baseline Mean (SD)	Least Square Mean Change	P-value
Tranexamic Acid (3.9 g/day)	115	2.92 (1.021)	0.85	<0.0001
Placebo	72	2.74 (0.979)	0.44	
<i>Source: Table 11.4-2 and reviewer's analysis</i>				

Table 3.2.4.2 Mean Reduction From Baseline for MIQ Question 3 (LPA) (ANCOVA) – mITT Population				
Treatment	N	Baseline Mean (SD)	Least Square Mean Change	P-value
Tranexamic Acid (3.9 g/day)	115	3.05 (0.953)	0.87	<0.0001
Placebo	72	2.90 (0.953)	0.40	
<i>Source: Table 11.4-2 and reviewer's analysis</i>				

Table 3.2.4.3 Large Stain Responder Analysis – mITT Population			
Treatment	N	Number (%) of Responder (experiencing reduction)	P-value
Tranexamic Acid (3.9 g/day)	115	66 (57.39)	0.4525
Placebo	72	37 (51.39)	
<i>Source: Table 11.4-3</i>			

3.3.5 Reviewer's Comment on the Efficacy Results

The 3.9 g/day dose, compared with placebo, is statistically significant in reducing MBL, improving LSLA and LPA during the 24-week study period. Results from corresponding nonparametric analysis confirmed the findings.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

There is no subgroup analysis.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

We have reviewed the two Phase 3 clinical studies in supporting tranexamic acid for the treatment of HMB. There were no statistical issues with regards to the method of analysis.

5.2 Conclusions and Recommendations

The results support the efficacy of 3.9 g/day tranexamic acid in reducing the MBL. The 3.9 g/day dose was considered both clinically and statistically effective. The improvements in two secondary endpoints, namely, LSLA and LPA were also statistically significantly superior to placebo.

From a statistical perspective, the efficacy data provided in this application do support the efficacy of 3.9 g/day tranexamic acid in the treatment of HMB and associated LSLA and LPA.

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/s/

Xin Fang
6/15/2009 04:19:11 PM
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Mahboob Sobhan
6/15/2009 04:30:14 PM
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STATISTICS FILING MEMORANDUM FOR A NEW NDA

NDA: 22-430
Drug Name: Lysteda™ (Tranexamic Acid Modified-Release Tablets)
Sponsor: Xanodyne Pharmaceuticals, Inc.
Indications: Treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of associated symptoms
Medical Officer: Daniel Davis, M.D., HFD-580
Statistician: Xin Fang, Ph.D., HFD-725
Project Manager: Jennifer Mercier
Submission Date: 01/30/2009
45 day Meeting Date: 03/02/2009

A: Summary of Clinical Studies

The objective of this filing review is to determine whether this NDA is sufficiently complete for substantive statistical review. As part of the determination, we looked at the format and contents of the safety and efficacy data sets that will allow us to perform pertinent statistical analysis as per study protocol. Data from two randomized, placebo-controlled, double-blind, multicenter, Phase-3 studies (XP12B-MR-301, XP12B-MR-303) were submitted to support the safety and efficacy of tranexamic acid modified-released tablets in the treatment of heavy menstrual bleeding and the amelioration of associated symptoms. Study XP12B-MR-301 was a three-arm study with 3-cycle of treatments and Study XP12B-MR-303 was a two-arm study with 6-cycle of treatments. In both studies, the primary efficacy endpoint was the menstrual blood loss during the entire menstrual period as assessed by the Alkaline Hematin Method (AHT). The prespecified secondary endpoints were the Limitation of Social or Leisure Activities (LSLS) score from the Menorrhagia Impact Questionnaire (MIQ) (Question 4), the Limitation in Physical Activities (LPA) score from the MIQ (Question 3), and the total number of large stains reported during the menstrual period on patient diaries. There were 11 secondary endpoints were not prespecified.

Based on the data from two studies, the sponsor concluded that tranexamic acid modified-released tablets (two 650mg TID) are effective in the treatment of heavy menstrual bleeding and amelioration of associated symptoms.

B: Conclusion

After the preliminary review of the submission for the following items in the checklist, we have determined that this NDA is fileable. All data sets are accessible and statistical analysis can be performed. The sponsor provided all other required information to perform statistical evaluation except for the data of interim analyses. From statistical perspective, this NDA is fileable.

STATISTICS FILING MEMORANDUM FOR A NEW NDA

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		√		Only female (Age is 18-49.)
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.		√		Interim analysis datasets are not available.
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

<u>Xin Fang</u>	<u>02/24/2009</u>
Reviewing Statistician	Date
 <u>Mahboob Sobhan</u>	 <u>02/24/2009</u>
Supervisor/Team Leader	Date

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this page is the manifestation of the electronic signature.**

/s/

Xin Fang
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Mahboob Sobhan
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