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APPLICATION NUMBER:

22-430

MEDICAL REVIEW(S)

Clinical Memo to NDA 22-430 Lysteda

Date: November 10, 2009

Reviewer: Daniel Davis, MD

Lysteda label changes:

On November 10, 2009, minor changes were made to the clinical sections of the Lysteda label. These changes were sent to the Applicant for final review and acceptance. By COB on November 10th, the Applicant accepted the changes, and returned a clean, agreed-to electronic copy of the final label via the gateway.

No other disciplines were involved with the minor changes to the final label; therefore, no additional reviews were required or entered into DARRTS for NDA 22-430.

Daniel Davis, MD
Primary Clinical Reviewer
Division of Reproductive and Urologic products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22430	ORIG-1	XANODYNE PHARMACEUTICS INC	Lysteda
NDA-22430	TRIAGE-1	XANODYNE PHARMACEUTICS INC	Lysteda

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/s/

DANIEL DAVIS
11/10/2009

Clinical Review
Daniel Davis, MD
NDA 22-430
Lysteda- tranexamic acid

CLINICAL REVIEW

Application Type NDA
Application Number(s) 22-430
Priority or Standard Priority

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Division / Office Division of Reproductive and Urologic
Products / ODE III

Reviewer Name(s) Daniel Davis, MD, MPH
Review Completion Date November 06, 2009

Established Name Tranexamic acid tablet, 650 mg
(Proposed) Trade Name **Lysteda™**
Therapeutic Class Antifibrinolytic drug
Applicant Xanodyne Pharmaceuticals, Inc.

Formulation(s) Immediate release tablet
Dosing Regimen Two 650 mg tablets three times daily
Indication(s) **"Treatment of cyclic heavy menstrual
bleeding" (typically defined as menstrual
blood loss > 80 mL)**
Intended Population(s) Women of reproductive age

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AHT	Alkaline hematin test
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMI	Body-mass index
CFB	Change from baseline
CPMP	Committee for Proprietary Medicinal Products
DSMB	Data Safety Monitoring Board
GI	Gastrointestinal
HMB	Heavy menstrual bleeding (menorrhagia)
HRQoL	Health-Related Quality of life
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
ITT	Intent-to-treat
IUCD	Intrauterine contraceptive device
LPA	Limitation in Physical Activity
LSLA	Limitation in Social and Leisure Activities
LWH	Limitation in Work Outside and Inside the Home
MBL	Menstrual blood loss
mITT	Modified intent-to-treat
MIQ	Menorrhagia Impact Questionnaire
NSAID	Nonsteroidal anti-inflammatory drug
PRO	Patient-reported outcome
REMS	Risk Evaluation and Mitigation Strategy
RMQ	Ruta Menorrhagia Questionnaire
ROC	Receiver operating characteristic
SAP	Statistical analysis plan
SD	Standard deviation
TBM	To-be-marketed
TXA	Tranexamic acid
VWD	von Willebrand disease
WLS	Weighted least squares
XP12B-MR	Modified-release tranexamic acid

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend the approval of tranexamic acid 650 mg administered as two tablets three times a day (3.9 grams/day) for up to five days during monthly menstruation for the following indication: for the treatment of cyclic heavy menstrual bleeding.

1.2 Risk Benefit Assessment

The overall risk benefit assessment shows that the safety profile of tranexamic acid at the recommended dose is acceptable. The common but non-serious side effects and the rare serious adverse events are discussed in the final label. It is of note that the lower dose of 1.95 grams/day also shows improvement for the treatment of heavy menstrual bleeding (HMB), although the treatment effect is not as large as seen with the higher dose. If women do not tolerate the common adverse events associated with the higher dose, then it is reasonable to try the lower dose (one 650 mg tablet three times a day) for up to five days.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I do not recommend a Postmarketing Risk Evaluation and Mitigation Strategy (REMS) for this product. Tranexamic acid is approved at the same or higher doses and has been used for the treatment of HMB in several countries since at least 1986. The overall postmarketing safety experience with tranexamic acid globally is acceptable and does not suggest the need for a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarketing Requirement:

The Applicant Xanodyne had proposed to conduct a pediatric pharmacokinetic (PK) study in children aged 12 to 17 years as a Phase 4 commitment. A synopsis of this proposed study was provided with the NDA and was discussed with the PeRC (Pediatric Review Committee) on May 27, 2009. The committee questioned the following items, but did grant a partial waiver and deferral for this product:

1. The occurrence of HMB in the adolescent age group
2. Need to study the very young adolescents (ages 12-14)
3. Inclusion and exclusion criteria

On June 18th, the Applicant submitted information to the NDA showing that the prevalence of HMB in the adolescent population is approximately 4% for girls 13 to 17

years of age. Data for girls at 12 years of age was not found in their literature search, and data from the US Physicians Drug and Diagnosis Audit showed that of all physician visits specifically for excessive menstruation, 0.5% of the women were 13 year olds and 0.2% of 14 year olds. While data are sparse regarding the prevalence of HMB in adolescents, I recommend that a pediatric PK study in young adolescents be required as a postmarketing requirement, to evaluate an adolescent age group that can be reasonably enrolled [enrollment for age 12 to 14 may be very difficult]. Otherwise, I do not recommend any additional specific postmarketing requirements for the same reasons as stated in section 1.3.

The Applicant provided agreement on September 15, 2009 to conduct the adolescent PK study following approval, and agreed to the following milestones:

Protocol Submission Date:	February 2010
Study Start Date:	September 2010
Final Report Submission Date:	March 2012

Postmarketing Commitment:

There are limited data on the risk of thromboembolic events associated with the concomitant use of tranexamic acid and hormonal contraception. From the medical literature, there are no clinical or epidemiology studies or reviews that look primarily at this risk. Given that both products are indicated for women of reproductive age, and that hormonal contraceptives are often used off-label to manage heavy menstrual bleeding, it is unknown to what extent the two products will be used concomitantly. Because women using hormonal contraceptives were excluded from the clinical trials supporting the approval of Lysteda, it is not known whether the population of women using both products concomitantly is large enough to study, should further study be warranted. Therefore, a postmarketing commitment (PMC) has been requested by the Division to conduct a pharmacoepidemiologic study based on drug use information to assess the patterns of concomitant use of Lysteda and hormonal contraception. The study should assess the ages of women using both products as compared to women using Lysteda alone. The Applicant agreed to the PMC on October 21, 2009.

2 Introduction and Regulatory Background

2.1 Product Information

Tranexamic acid [trans-4-(aminomethyl) cyclohexanecarboxylic acid] is an antifibrinolytic drug which inhibits breakdown of fibrin in clotted blood by blocking the activation of plasminogen. This helps in the slowing or cessation of further bleeding. Tranexamic acid was first introduced into clinical medicine in the late 1960s and has subsequently been in widespread use in more than 80 countries for the treatment and prophylaxis of hemorrhage associated with excessive fibrinolysis (as with conization of the cervix, dental procedures, nosebleeds, and anterior eye chamber bleeding) and prophylaxis of hereditary angioedema. For the treatment of heavy menstrual bleeding

(i.e., menorrhagia), tranexamic acid was first marketed in 1966 and has been marketed for more than 3 decades in Japan, Australia, Europe, and Canada for the treatment of hemorrhage or risk of hemorrhage in conditions of increased fibrinolysis or fibrinogenolysis (including thrombolytic overdose). The approved oral dosage is between 1000 mg BID (2 grams/day) and 1500 mg QID (6 grams/day). **The Applicant's** proposed total dose is 3.9 grams/day for a maximum of five days during menses.

In Sweden, tranexamic acid has been approved for over the counter (OTC) availability since January 1997. Multistate European approval of tranexamic acid to treat menorrhagia was granted in July 2000 by **the European Union's Committee for Proprietary Medicinal Products (CPMP, 2000)**. Tranexamic acid is approved in Canada and Australia for the treatment of menorrhagia. In the US, oral and intravenous (IV) tranexamic acid was approved in 1986 to treat patients with hemophilia for short-term use (2 to 8 days) to reduce or prevent hemorrhage, and to reduce the need for replacement therapy during and following tooth extraction. Currently in the US, Cyklokapron® (tranexamic acid) is available only as an IV injection. This current NDA submission is the first time that US marketing approval has been sought for tranexamic acid for the treatment of HMB (menorrhagia).

2.2 Currently Available Treatments for Proposed Indications

The medical term for heavy menstrual bleeding (HMB) is menorrhagia. Menorrhagia is defined as prolonged or excessive uterine bleeding that occurs at regular intervals, or more strictly, 1) the loss of 80 mL or more of blood per menstrual cycle, or 2) bleeding that lasts for more than 7 days. The term is sometimes confused with metrorrhagia, defined as irregular menstrual bleeding or bleeding between periods, and menometrorrhagia, defined as frequent menstrual bleeding that is excessive and irregular in amount and duration.

Currently used medical therapies for HMB include the following:

- combination hormonal contraceptives
- oral progestins administered during the luteal phase
- progesterone-containing intrauterine device (IUD)
- nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid (Ponstel)
- desmopressin
- ethamsylate

In the U.S., only the oral progestins and (since September 30, 2009) the progesterone IUD are approved for the treatment of HMB. The other products are used off-label. In countries where it is approved, oral tranexamic acid is considered a first-line treatment for the management of HMB, especially for women in whom hormonal treatment is either contraindicated or not preferred.

2.3 Availability of Proposed Active Ingredient in the United States

In the United States, tranexamic acid (Cyklokapron®) is approved for short-term use (2 to 8 days) by intravenous administration to reduce or prevent hemorrhage and the need for replacement fluid or blood therapy during and after tooth extraction. For business reasons, but not for safety concerns, marketing of the same product for oral administration (at doses up to 6 g/day) has been discontinued by its Sponsor.

2.4 Important Safety Issues with Consideration to Related Drugs

There are three anti-fibrinolytic drugs that are commonly used in the U.S. at the time of major surgery to reduce bleeding and hence the need for transfusions and the need for repeat surgery because of bleeding. They are aprotinin and the two lysine analogues tranexamic acid (TXA) and epsilon aminocaproic acid (EACA). The safety areas of concern when used for major surgery have been vascular occlusion, renal dysfunction, and death. The July 2007 Cochrane review of these three products, especially when used for cardiac surgery, concluded that **“aprotinin did not increase the risk of myocardial infarction, stroke, renal dysfunction, or overall mortality..... Similar trends were seen with the lysine analogues but data were sparse....In most circumstances the lysine analogues are probably as effective as aprotinin and are cheaper; the evidence is stronger for tranexamic acid than for EACA.”**¹ A recent article in the NEJM (1-26-06)² reporting on a large (N= 4,374) placebo-controlled observational study of the three same anti-fibrinolytic drugs used in cardiac surgery patients concluded:

The association between aprotinin and serious end-organ damage indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

The BART study from Canada, a randomized comparison of aprotinin, tranexamic acid and EACA in coronary artery bypass surgery in 3,000 patients at increased risk for blood loss and transfusion, was planned to evaluate the relative efficacy, safety, and tolerability of the 3 antifibrinolytics.³ This trial was halted in October 2007 following results of a planned periodic analysis that showed an increased incidence of all-cause mortality with aprotinin versus tranexamic acid or ECAC. As a result, world-wide marketing of aprotinin has been withdrawn until the results of the trial could be more thoroughly analyzed and the benefit-risk profile of aprotinin clarified.

Reviewer's comment:

These three articles are reassuring concerning the safe use of tranexamic acid for major surgery and cardiac surgery. The patients in these cases were at high risk of

¹ The Cochrane Collaboration: Henry DA, et al. “Anti-fibrinolytic use for minimizing perioperative allogenic blood transfusion (Review), *The Cochrane Library* 2009, Issue 2.

² Mangano DT, et al. The risk associated with aprotinin in cardiac surgery, *NEJM* 2006 Jan 26; 354 (4):353-65.

³ Fergusson DA, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *NEJM* 2008 May 29; 358 (22):2319-31.

thromboembolic events and other complications, but tranexamic acid was found to be relatively safe, especially compared to aprotinin.

Cyklokapron (intravenous tranexamic acid) was approved in December 1986 under NDA 19-281 for limited use in patients with **hemophilia, for 2-8 days' use, to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.** The U.S. label for Cyklokapron has labeled contraindications in patients with (1) acquired defective color vision, (2) subarachnoid hemorrhage, and (3) active intravascular clotting. The Precautions section notes that venous and arterial thrombosis or thromboembolism has been reported with the use of Cyklokapron.

Reviewer's comment:

George Shashaty, MD, is the FDA hematology reviewer for the IV tranexamic acid (Cyklokapron) product, approved in hemophilia patients during and following tooth extractions. He did a review of the Cyklokapron label in December 2008 and is the primary reviewer of adverse events for the product. He is aware of no new safety concerns with the use of the intravenous tranexamic acid product as used in the United States.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On 12-16-03, IND 68,096 was submitted to the Division of Reproductive and Urologic Products (DRUP) for the clinical development of tranexamic acid for the treatment of menorrhagia. At a pre-IND meeting in November 2003, it was recommended that Xanodyne conduct a chronic and repeat-dose toxicology study in the most sensitive species and a combined embryo-fetal development/pre- and postnatal development study (Segment II/III) prior to initiation of Phase 3 clinical trials. These additional nonclinical studies would be required to support a chronic indication defined as a total of at least 6 months exposure over a 10-year period. In addition, the Division recommended two adequate and well controlled clinical trials to evaluate safety and efficacy. In regards to safety data, the Division recommended that the Phase 3 trials(s) continue for at least 1 year and that safety data would be needed from at least 300 women at 6 months and at least 100 women at 1 year at doses as great as or greater than the to-be-marketed dose. At least six months of efficacy data would be needed to demonstrate durability of effect. With respect to endpoints, a validated measure of an objective endpoint would be needed for Phase 3, and a health-related quality of life endpoint might be studied as an acceptable secondary endpoint. Xanodyne was advised also to address the QT prolongation potential of tranexamic acid.

At the 8-25-04 guidance meeting, the Division recommended that the safety database include (1) 200 women completing one year of exposure and (2) a total of 10,000 cycles of exposure. Quality of Life instruments should be validated and stated as part of the statistical analysis plan (SAP) if Xanodyne intended to use the results to support labeling claims.

At the 9-20-04 End-of-Phase 2 meeting, the Division concurred that no drug-drug interaction (DDI) studies are required between tranexamic acid and other drugs that are primarily renally eliminated. The Phase 3 protocol designs were discussed, including the trial endpoints, inclusion/exclusion criteria, and data analysis. The Division requested that Xanodyne determine what women with menorrhagia view as a clinically significant change or improvement in their HMB and incorporate this change into the primary endpoints.

On 5-11-05 and 5-20-05, the Applicant submitted a request for a Special Protocol Assessment for Study MR-301 (placebo controlled with two doses of tranexamic acid) and Study MR-303, respectively. In the 6-24 and 6-30-05 Special Protocol Assessment correspondence, the Division provided comments on the MR-301 and MR-303 studies, respectively, in the areas of efficacy assessments and endpoints, safety assessment, data collection instruments, inclusion/exclusion criteria, and statistical comments. The Division suggested that the primary analysis for efficacy outcomes use the change from baseline in menstrual blood loss (MBL) averaged over the 3 cycles for which alkaline hematin measurements were obtained.

At the 10-14-05 Type A meeting, the Phase 3 protocol designs were discussed, including the trial endpoints, inclusion/exclusion criteria, methodology for measuring MBL, and data analysis. The Division agreed that the trials exclude women on hormonal contraceptives because of concern about an increased risk of thrombosis in these women. Xanodyne was encouraged to include a global question at the end of the first on-treatment menstrual cycle to document any patient-perceived change in menstrual bleeding during the initial menstrual period. Such a question could be used to provide an anchor for analyses to evaluate how much change in MBL is meaningful to patients.

In the DRUP correspondence dated 9-28-06, the plan to use the patient-reported outcome (PRO) Menstrual Impact Questionnaire (MIQ) Question 6 only in Study MR-301 to establish what subjects consider a meaningful reduction in MBL was deemed acceptable. The Division recommended that the protocol describe the methodology and procedures used to determine the MBL cut point found to be meaningful. The Division stated that success on the primary efficacy endpoint should fulfill the following two requirements: 1) at least a 50 mL difference between the treatment groups in the reduction of MBL from baseline to on-treatment cycles, and 2) the point estimate of the reduction in MBL must be greater than or equal to the reduction in MBL identified as meaningful to women through the receiver operator characteristic (ROC) analysis. Testing the slope of MBL across treatment periods 1, 2, 3, and 6 to assess durability of response in Study MR-303 was acceptable. The Division agreed that improvement in limitation of physical and social/leisure activities and a reduction in large stains were important to women and were appropriate pre-specified secondary endpoints. The Division agreed that it was acceptable to validate MIQ Questions 1-6 in the 9-month MR-302 extension safety study, but noted that validating the questions during the Phase 3 program would be at **the Applicant's risk should issues** with the MIQ be identified.

At the 2-21-07 Type A meeting, the sample-size re-estimation and method of data imputation were discussed. The Division accepted the primary efficacy population, defined as all randomized patients who have at least one efficacy data point (mean blood loss from one menstrual period). The Division stated that if the Applicant sought a labeling claim for the three important secondary endpoints, then each randomized study would need independently to show statistical significance for each of the three secondary endpoints. According to the meeting minutes, the final Statistical Analysis Plan would be submitted to DRUP as soon as possible.

In a 2-20-08 letter, the Division stated that because the primary objective in study MR-301 was to determine the efficacy of tranexamic acid 3.9 g/day and tranexamic acid 1.95 g/day compared to placebo, the primary efficacy analysis should be tested by dose in a step-down manner to determine the lowest effective dose; then the three key secondary endpoints should be tested in a step-down manner for the dose(s) that are statistically significant based on the primary efficacy analysis.

On 10-31-08 a pre-NDA meeting was held. Regarding exposure, the Division wanted to see the average number of days of exposure to tranexamic acid per cycle. Xanodyne asked if the analyses outlined in the pivotal trials supported the language for the proposed indication and dosing regimen. The Division responded that the approved indication and dosing regimen are determined by the actual NDA review and not determined beforehand. The Division did not make a commitment that the data **appeared to support the broad statement “the amelioration of symptoms associated with heavy menstrual bleeding.”**

Other key issues discussed at the pre-NDA meeting included the following:

1. Regarding efficacy, the Division indicated that the results should also be presented for each study individually (the Applicant proposed a pooled analysis), as this would constitute the primary review of efficacy data by the Division.
2. Regarding the safety analysis plan, the Division agreed with the plan to integrate the safety data from all four Phase 3 studies. For the racial subgroup analyses, it was recommended that Xanodyne split the groups into more than the two groups proposed (Caucasian and non-Caucasian). The Division also requested a brief synopsis of the safety events of special interest (e.g., thrombotic events) and the data available to assess such events of interest.
3. Regarding post-marketing plans, the Division indicated that the plan would be a review issue and recommended that Xanodyne proactively plan for risk mitigation if a safety issue were identified. The Division suggested that it might request an adequately powered postmarketing epidemiologic safety study to assess thrombotic risks and other safety signals that may be detected over the course of the review.
4. Regarding pediatric deferral, the Division recommended submitting a proposal for a **“comprehensive pediatric study in adolescents” as part of the pediatric deferral request.**

5. Regarding case report forms (CRFs) for subjects who died or discontinued due to an adverse event, the submission plan was found to be acceptable. The Division also requested CRFs for subjects who were evaluated for thrombotic events during the studies, and CRFs and subject narratives for subjects who had serious adverse events. The Division agreed with the plan not to submit patient profiles (individual subject data listings) for these four studies.
6. ECGs and waveform data should be submitted through the Mortara ECG Warehouse in XML format.
7. Regarding the plans for the Safety Update, the Division felt that the timing and contents of the update would depend on the type of review designated for the submission. If the submission was designated for standard review, Xanodyne would provide the Safety Update four months after the initial NDA submission. If the final study reports for these safety studies were not complete at the time of the Safety Update, submission of CRFs and narratives along with line listing of adverse events, summary tables of deaths, discontinuations due to adverse events and serious adverse events, and supportive datasets would constitute an acceptable Safety Update from the safety studies.
8. Regarding the need for an Advisory Committee meeting, the Division said that this would be determined after submission of the NDA.
9. Regarding clinical pharmacology, dosing requirements for the proposed tranexamic acid modified release formulation in the presence of renal impairment need to be adequately addressed. A pharmacokinetic (PK) study of the proposed formulation in subjects with various degrees of renal impairment could be conducted in order to optimize dosing regimens in such patients. Alternatively, if such a study is not conducted and Xanodyne believes that adequate data are available in this regard, the Division would like to see this information along with adequate justification that addresses how this information would be applicable to the proposed oral formulation. Xanodyne indicated that since the application is a 505(b)(2), the plan was to rely on the same labeling as the reference drug product regarding the effect of renal impairment.

2.6 Other Relevant Background Information

During the review process the following submissions (Amendments) pertaining to the clinical review were received from the Applicant:

1. 3-20-09: Applicant response to DRUP Statistical Safety Information Request #1 (3-06-09) and QT/IRT Information Request #2 (3-18-09)
2. 3-25-09: Applicant response to DRUP Clinical Information Request #1 for clinical sites (3-20-09) and QT/IRT Information Request #1 for ECG raw data (3-20-09)
3. 3-31-09: Applicant response to DRUP Statistical Safety Information Request #2 (3-27-09)
4. 4-30-09: 90-day Safety Update (Amendment 0009)

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5. 5-18-09: Foreign labeling (Clinical information request # 2)
6. 6-18-09: Adolescent menorrhagia prevalence data
7. 6-30-09: Major chemistry amendment in response to the request for data concerning the "modified-release" formulation
8. 9-4-09 and 9-11-09: Label submissions
9. 9-28-09 and 9-30-09: Responses to Information Request # 6, regarding further safety updates for Studies 302 and 304

In addition, the Applicant submitted in October 2009 amendments for labeling and two safety updates (as requested by the Division).

Reviewer's comment:

The submission received on 6-30-09 constituted a major amendment. Because the receipt date was within three months of the user fee goal date, the goal date was extended by three months to provide time for a full review of the submission. The extended user fee goal date is October 30, 2009.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There are no issues with the quality and integrity of the NDA submission. The Applicant has responded promptly and completely to information requests from the Division.

On 4-03-09 the Division requested that Division of Scientific Investigation (DSI) inspect the three sites listed in the table below. There was no specific safety or efficacy concern at any of the sites. Sites 602 and 524 enrolled a relatively large number of women. At site _____, the investigator's financial disclosure stated that _____ received _____ in consulting fees from the Applicant, which is the primary reason why this site was inspected.

b(6)

Table 1: Sites for DSI Inspections

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #746 Andrea Lukes Women's Wellness Center 249 E Highway 54, Suite 330 Durham, NC 27713	Trial MR-301 and 304	Enrolled 15 women in a 3-month trial & 7 women continued in a 9-month extension trial	Heavy Menstrual Bleeding
Site #602, Jeffrey Baker 2327 Coronado St. Idaho Falls, ID 83404	Trial MR-303 and 304	Enrolled 18 women in a 6-month trial and 15 women continued in the 9-month extension trial.	Heavy Menstrual Bleeding
Site #524 R Garn Mabey, Jr. 2881 N. Tenaya Way Las Vegas, NV 89128	Trial MR-302	Enrolled 44 women in the 27-month open label extension trial.	Heavy Menstrual Bleeding

The Lukes site inspection found no regulatory violations. The DSI report for the Baker site noted some minor regulatory violations that were isolated in occurrence and are not expected to impact study outcome. The Mabey site inspection found that three subjects in Study MR-302 took tranexamic acid in excess of protocol requirements; otherwise, the study appears to have been conducted adequately.

Reviewer's comment:

The DSI inspections at the three sites are acceptable. The three subjects at the Mabey site were not part of the primary efficacy dataset and should be included in the overall safety data, so data from these subjects should not be excluded. The inspection results from the other two sites are satisfactory and no data from these sites needs to be excluded.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in compliance with the guidelines for Good Clinical Practices and ICH guidelines.

3.3 Financial Disclosures

One investigator, _____ reported that _____ had received _____ from _____ for consulting services during the course of the _____ clinical trial. _____ was a principal investigator (PI) in this trial and randomized _____ subjects at _____ site, which represented ~5% of the total subjects for the trial. _____ was not involved in database cleaning activities nor was _____ involved in the analysis of the study results. The FDA's DSI inspection of _____ facility and data did not show any problems or irregularities.

b(6)

b(6)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were three significant CMC issues. One was the use of the term “modified release.” Another was the inspection of the manufacturing site in ———. A third was stability data for the product to be marketed. Information requests (IRs) were sent to the Applicant and seven amendments were submitted to the Division containing adequate information to resolve the CMC issues. The ——— drug substance manufacturing site was inspected and found to be acceptable as of September 21, 2009. The release testing sites for the drug substance and the finished drug were found to be acceptable based on profile. b(4)

The final recommendation of the chemistry reviewer, Gene W. Holbert, PhD, on September 24, 2009 was the following:

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for “Approval”.

Reviewer's comment:

The Applicant had originally designated the product as a modified release (MR) tablet claiming that it would be better tolerated than an immediate release (IR) tablet. The biopharmaceutics review by Patrick Marroum, PhD, in the Office of New Drug Quality Assessment, did not agree. After further review of the plasma concentration profile, he made the final determination that the tablets were immediate release (very similar to the already approved Cyklokapron immediate release formulation) and should not be labeled as modified release. From a clinical point of view, the designation is not important because the efficacy and safety was established in the four clinical trials based on the to-be-marketed tranexamic acid 650 mg tablet.

4.2 Clinical Microbiology

There was no clinical microbiology issue, as the product is an oral tablet, and therefore no microbiology review was warranted for this NDA.

4.3 Preclinical Pharmacology/Toxicology

In addition to relying on the findings of safety for Cyklokapron as reflected in the approved labeling for that product, the Applicant conducted and submitted three nonclinical studies:

- A 39 week repeat dose toxicity study in dogs
- An embryo-fetal-developmental toxicity study in rats
- A perinatal developmental toxicity study in rats

Clinical Review
Daniel Davis, MD
NDA 22-430
Lysteda- tranexamic acid

In her review dated June 22, 2009, the primary Toxicology Reviewer, Kim Hatfield, PhD, found no major issues in her thorough review of the non-clinical data. She recommended no additional non-clinical studies and made some minor changes to the **Applicant's proposed label, which were acceptable to the Applicant.**

Reviewer's comment:

The CDTL review has a more detailed discussion of the nonclinical pharmacology/toxicology review by Dr. Hatfield and agrees with her final conclusions.

4.4 Clinical Pharmacology

In the early stage of the development program for the tranexamic acid tablets, prototypes with 3 different drug release profiles were used for proof of concept purposes, all of which were developed and manufactured by Xanodyne Pharmaceuticals, Inc. These were:

- Immediate-release (IR) tablets
- Delayed-release (DR) tablets
- Modified-immediate release (MR) tablets.

The biopharmaceutical properties of three tranexamic acid formulations were studied in a series of three Phase 1 studies in healthy female volunteers. In all three studies, tranexamic acid in plasma was measured using a validated bioanalytical method (gas chromatography/ mass spectroscopy). A systemic bioavailability study (12B-101), a fed vs. fasting bioavailability study (12B-102), and a steady-state pharmacokinetic performance study (12P12B-103) were all performed. In summary, the Agency clinical pharmacology reviewer, Hyunjin Kim, Pharm.D., concluded that these three biopharmaceutical/pharmacokinetic Phase 1 studies were acceptable and correctly performed. Food does not significantly impact the absorption of tranexamic acid from the to-be-marketed formulation, so in the Phase 3 clinical trials, patients were instructed to take Lysteda without regard to meals. The delayed-release product formulation, however, did not achieve the desired biopharmaceutical and pharmacokinetic properties and was not used in any additional clinical studies. In his October 16, 2009 review, Dr. Kim agreed with the final labeling. The initial recommendation from Dr. Kim follows:

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 22-430 acceptable provided that agreement is reached between the sponsor and the Division regarding the language in the package insert.

Dr. Kim further stated in a memorandum dated October 27, 2009:

The original Clinical Pharmacology review of NDA 22-430...stated that the clinical pharmacology information submitted in NDA 22-430 was acceptable provided that agreement is reached between the sponsor and the Division regarding the language in the package insert. The agreement on language in the package insert was reached on 10/27/09. The final agreed upon label is included in section 1.3 of this review.

Reviewer's comment:

During the NDA review cycle, the Applicant's proposed modified-release formulation was found by the FDA chemist, Dr. Patrick Marroum, not to exhibit the characteristics of a modified-release product. The medical team and the reviewers from the Division of Clinical Pharmacology 3 agreed with Dr. Marroum's conclusions. After a thorough FDA review and discussions with the Applicant, it was decided that the to-be-marketed product had the characteristics of an immediate-release product and will not be labeled as modified release.

4.4.1 Mechanism of Action

Tranexamic acid is a synthetic lysine amino acid derivative, which diminishes the dissolution of hemostatic fibrin by blocking the activation of plasmin. In the presence of **tranexamic acid, plasminogen's lysine receptor** binding sites for fibrin are occupied, preventing binding of plasminogen to fibrin monomers, thus preserving and stabilizing **the hemostatic fibrin's matrix structure.**

The antifibrinolytic effects of tranexamic acid are mediated by competitive (immediate) inhibition, rapidly reversible dose-related binding interactions at multiple distinguishable binding sites within plasminogen. Native human plasminogen contain 4 to 5 lysine binding sites with low affinity for tranexamic acid ($K_d = 750 \mu\text{mol/L}$) and 1 with high affinity ($K_d = 1.1 \mu\text{mol/L}$). The high affinity lysine site of plasminogen is involved in its binding to fibrin. Saturation of the high affinity binding site with tranexamic acid displaces plasminogen from the surface of fibrin. Although, plasmin may be rapidly formed by conformational changes in plasminogen, its binding to and dissolution of the fibrin matrix is inhibited and thereby, less active bleeding occurs.

4.4.2 Pharmacodynamics

The pharmacodynamics of tranexamic acid is thoroughly discussed in the primary clinical pharmacology review by Hyunjin Kim, Pharm.D., M.S. Sections 2.2.5.2 through 2.2.5.5 of his review cover the absorption, distribution, metabolism, and excretion of tranexamic acid. The review also covers the intrinsic factors (section 2.3) and extrinsic factors (section 2.4) affecting tranexamic acid.

4.4.3 Pharmacokinetics

Highlights of the pharmacokinetics (PK) of tranexamic acid are summarized in the final review (10-16-09) by Hyunjin Kim, the primary clinical pharmacology reviewer:

- *Tranexamic acid was absorbed with a median (range) t_{max} of 3 (2 - 4) hours following a single administration of two Lysteda 650 mg tablets under fasting state.*
- *The absolute bioavailability (F) of Lysteda was 43.9%.*
- *A single and multiple dose trial was conducted to assess the PK linearity of Lysteda following a single oral dose (Day 1) and multiple dose administration (2 x 650 mg*

every 8 hours, Days 2 to 7) under fasting state. Steady state was reached within 32 hours after the first dose. Drug accumulation ratios at steady state were 1.19 for C_{max} .

- *The PK linearity of Lysteda was calculated by comparing the ratio of least square means of AUC_r (Day 7) to AUC_{inf} (Day 1). The ratio of least square means of AUC_r (Day 7) to AUC_{inf} (Day 1) was 0.973 with 90% Confidence Interval (CI) between 86.5 and 109.5.*
- *Lysteda exhibited linear PK independent of time following repeated administration (three times daily) of a 1,300 mg (2 x 650 mg) dose under fasting state. The ratio of AUC_r (Day 7) to AUC_{inf} (Day 1) was close to 1.*
- *The plasma binding of tranexamic acid is about 3% and is mostly accounted for by its binding to plasminogen⁴.*
- *Urinary excretion via glomerular filtration is the main route of elimination. More than 95% of the dose is excreted in the urine as the unchanged drug, which suggests that there is less than 5% of metabolism⁵.*
- *The mean (coefficient of variation, CV) terminal half-life of tranexamic acid following a single dose administration of Lysteda was 11.4 hours (17.6%). Following an IV injection of Cyklokapron, the mean terminal half-life was 10.2 (13.0%) hours. Most elimination occurred in 10 hours for both Lysteda and Cyklokapron IV.*

4.4.4 Drug-drug Interactions

No clinically significant drug-drug interactions between tranexamic acid and concomitantly administered drugs have been reported in the published literature. Because metabolism of tranexamic acid is minimal, there is low potential for other drugs to interfere with its metabolism. Furthermore, tranexamic acid is eliminated by glomerular filtration, which is not a saturable process, and it is unlikely that any drug interactions will occur with other drugs that are eliminated primarily through the kidney. Per agreements with the Division during the End-of-Phase 2 meeting, no drug-drug interactions were performed as part of the tranexamic acid program.

Although no clinical studies were performed to examine the effects of alcohol on the PK of tranexamic acid, the impact of different ratios of alcohol in the dissolution media on the release profile was explored. Results from this study showed that the dissolution profiles in 5%, 10%, and 20% alcohol were similar to the dissolution profile in de-ionized water, but the dissolution profile in 40% alcohol was dissimilar. There was also a trend showing a reduction in the dissolution rate as the amount of alcohol in the dissolution medium increases, with dissolution in 40% alcohol being the slowest. These results show that the tablets are not expected to show dose dumping in the presence of alcohol.

⁴ Prescribing information of Cyklokapron IV (NDA 19-281)

⁵ *Id.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A brief description of all clinical studies is found in the Applicant's two tables that follow.

Table 2: Listing of all Bioanalytical and Pharmacology Studies

Study Number/ Identifier	Study Title
Study Number VXAN07900B1 Alkaline Hematin Methods Validation Report	The Measurement of Human Menstrual Blood Volume on Feminine Hygiene Products Using the Alkaline Hematin Spectrophotometric Quantification Method, Study Number VXAN07900B1
BXANO7903B1	Bioanalytical Study Report for the Measurement of Human Menstrual Blood Loss on Feminine Hygiene Products Using the Alkaline Hematin Spectrophotometric Quantification Method
BXANO7902B1	Bioanalytical Study Report for the Measurement of Human Menstrual Blood Loss on Feminine Hygiene Products Using the Alkaline Hematin Spectrophotometric Quantification Method
XP12B-101	Comparative, Randomized, Single-Dose, 4-Way Crossover Absolute Bioavailability and Bioequivalence Study of Xanodyne Tranexamic Acid Tablet Formulations in Healthy Adult Women Volunteers under Fasting Conditions
XP12B-102	Comparative, Randomized, Single-Dose, 4-Way Crossover Relative Bioavailability Study of Xanodyne Tranexamic Acid Formulations in Healthy Adult Women Volunteers under Fed to Fasting Conditions
XP12B-103	Comparative, Randomized, Parallel, Single Dose and Steady-State Pharmacokinetic Assessment Study of Xanodyne Tranexamic Acid Tablet Formulations in Healthy Adult Women Volunteers under Fasting Conditions

Source: Applicant Table 1-1: Location of synopses for all Clinical studies.

Reviewer's comment:

The above table lists the three studies (VXAN and BXAN codes) that tested the measurement of human menstrual blood volume on feminine hygiene products using the alkaline hematin spectrophotometric (AHSQ) quantification method. This method was used by the Applicant because the Division wanted the change in menstrual blood loss

to be measured as accurately as possible for the final approval of this drug. Other less accurate methods that have been used in clinical studies include 1) pictographs (entirely visual in nature), 2) weighing of tampons and sanitary pads, and 3) a subject's general impressions (the least accurate method).

Table 3: Listing of all Clinical Studies

XP12B-104	A Randomized, Single-Dose, Double-Blind, Placebo- and Positive-Controlled 4-Way Crossover Study of the Electrocardiographic QT Interval Prolongation Effect of (XP12B-MR) Tranexamic Acid in Healthy Fasting Adult Female Subjects
XP12B-MR-301	A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study to Evaluate Efficacy and Safety of 0.65 gram and 1.3 gram Oral Doses of XP12B-MR TID Administered During Menstruation for the Treatment of Menorrhagia
XP12B-MR-303	A Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study To Evaluate Efficacy And Safety Of A 1.3 G Oral Dose Of XP12B-MR TID Administered During Menstruation For The Treatment Of Menorrhagia
XP12B-MR-302	A Long Term, Open Label, Multicenter Study to Evaluate the Safety of a 1.3 gram Oral Dose of a New Modified Release Tranexamic Acid Formulation Administered Three Times Daily for up to 5 Days During the Menstrual Cycle in Women with Heavy Menstrual Bleeding Associated with Menorrhagia
XP12B-MR-304	A MultiCenter, Open Label Extension Study to Evaluate the Safety of a 1.3 gram Oral Dose of XP12B-MR TID Administered During Menstruation for the Treatment of Menorrhagia
PRO MIQ Validation Report	Menorrhagia PRO Item Questionnaire (MIQ) Validation in Women with Heavy Menstrual Blood Loss

Source: Applicant Table 1-1: Location of synopses for all Clinical studies.

5.2 Review Strategy

The regulatory history, proposed label, and integrated summaries of safety and efficacy were read first. Studies MR-301 and MR-303 were the primary studies analyzed for efficacy data, while the four studies MR-301, 302, 303, and 304 were analyzed collectively for safety data. The MIQ Validation Report was reviewed by the Clinical Team Leader (Dr. Soule). The MIQ was an important instrument used for the secondary endpoints in the Applicant's **overall development plan**.

Efficacy was reviewed by the clinical (medical) and biometrics (statistical) reviewers, whereas there were several components of the safety review:

1. Clinical (medical) - Daniel Davis and Lisa Soule
2. Safety team - Olivia Lau and George Schuette
3. Pharmacovigilance team - Mark Miller and Melissa Truffa
4. Cardio-renal consult for the QT study
5. Ophthalmological consult for the subset of women with extensive eye/visual examinations

5.3 Discussion of Individual Studies/Clinical Trials

Studies MR-301, -302, -303, and -304 are discussed in detail in Section 6, Review of Efficacy.

Reviewer's comment:

Throughout this review, the four Phase 3 clinical trials are referred to using the nomenclature MR-301 or simply -301, respectively, for each study.

6 Review of Efficacy

Efficacy Summary

The two efficacy studies MR-301 and -303 with tranexamic acid 650 mg tablets (2 tablets taken three times a day) demonstrated the efficacy of the 3.9 g/day dose compared with placebo. Average reductions in MBL of approximately 40% were observed at the 3.9 g/day dose in both studies. Using the 3.9 g/day dose, but not the lower 1.95 g/day dose, these reductions met the following three criteria for being statistically significant and clinically meaningful to women who participated in the trials:

- Statistically significant reduction from baseline in MBL in the 3.9 g/day and 1.95 g/day active treatment groups compared to placebo
- Change in MBL from baseline measured as > 50 ml
- Change from baseline of MBL for both studies must be > the reduction of 36 ml identified as meaningful to women through the agreed upon analysis from Study MR-301

Sustained efficacy was demonstrated in changes in MBL through 6 menstrual cycles. Treatment-related MBL changes were associated with statistically significant improvements in two of the three prespecified key secondary endpoints (health-related quality of life parameters), namely, limitations in social and leisure activities (LSLA) and limitations in physical activities (LPA). There was not a significant reduction in the third secondary endpoint, large stains due to HMB, based on responses in the daily subject diaries.

In both studies, 44% of subjects returned to normal MBL after treatment (i.e., achieved a mean treatment MBL of less than 80 mL) with the 3.9 g/day tranexamic acid dose. Active treatment was used, on average, for 3-3.4 days per menstrual period, but is

approved for up to 5 consecutive days of use. The tranexamic acid 650 mg tablets had no effect on the duration of menstrual cycles.

In Study 301, the raw mean reduction of 46.45 mL in menstrual blood loss with the lower 1.95 g/day dose is still impressive and came close to meeting the predetermined criterion of attaining at least 50 ml in the reduction of MBL compared to placebo. Granted, it is not as large a reduction as the raw mean value of 65.3 mL seen with the 3.9 g/day dose. I believe, however, this statistically significant clinical finding should be noted in the clinical trial section of the label so that consumers and healthcare providers will know that a dose reduction may be acceptable, especially for women who do not tolerate some of the common side effects when taking tranexamic acid.

6.1 Indication

The indication is for the treatment of cyclic heavy menstrual bleeding (HMB) by reducing menstrual blood loss (MBL) in the target population of women of child-bearing age with regular menstrual periods.

6.1.1 Methods

Two Phase 3, double-blind, placebo-controlled studies were conducted: Study MR-301, in which subjects were treated for 3 menstrual cycles, and Study MR-303, in which subjects were treated for 6 menstrual cycles. Both studies consisted of a screening phase of two menstrual periods (no treatment) to determine eligibility. Study MR-301 evaluated the efficacy and safety of both 0.65 and 1.3 gram oral doses (1.95 g/day and 3.9 g/day, respectively) of tranexamic acid administered three times a day (TID) compared to placebo, while Study MR-303 studied only the 1.3 gram TID dose. The quantitative alkaline hematin method was used on all the sanitary protection products collected during baseline and designated menstrual periods throughout the two trials. MBL during Cycles 1-3 and 1-3 plus Cycle 6 were quantified in studies MR-301 and MR-303, respectively. The sanitary products were then sent to a central laboratory for the quantitative measurements. This method is believed to be one of the most accurate ones available for objectively measuring actual MBL. Analysis of bleeding and spotting between expected menstrual periods was not performed.

Each subject received study drug in blister packs and was instructed to take 2 tablets orally 3 times daily with liquids for up to 5 consecutive days (not to exceed 3 doses in 1 day or 15 doses during the menstrual period) beginning when HMB was first experienced. Subjects were instructed to swallow the tablets whole and never to chew, divide, or crush them and to take the doses at least 6 hours apart. Study drug could be taken with food or liquid, but dosing did not have to be timed with respect to meals.

Enrolled subjects had to have a MBL \geq 60 ml during the first pretreatment menstrual period and an average MBL \geq 80 ml over the two pretreatment menstrual periods. A normal pelvic exam, Pap smear, and transvaginal ultrasound (TVU) were also required for enrollment. At the conclusion of a subject's participation in the study, a follow-up phone call was made 30 days (+/- 5 days) after the last day of study drug.

The overall objective was to assess the efficacy and safety of the to-be-marketed (TBM) tranexamic acid to reduce menstrual blood loss in women with HMB when administered for up to five days during menstruation compared to placebo.

Menstrual Impact Questionnaire (MIQ) and ROC Analysis

During the development program, the Applicant introduced the Menorrhagia Impact Questionnaire (MIQ), a patient-reported outcome (PRO) instrument developed by the Applicant based on interviews with subjects in Study 302. The three most important concerns identified were:

- Number of changes of sanitary pads
- Limitations of activity
- Problems with soiling

The Applicant proposed to use the MIQ to evaluate limitations of activity, and to validate the instrument in a subset of women in Study 302. In addition, a question from the MIQ would be used as a global item to assess the reduction in MBL that is clinically meaningful to women with menorrhagia; this would be done in Study 301. Revised study protocols were submitted to the Division and comments were provided to the Applicant in September 2006.

During the drug development process, the Division indicated that an important endpoint for the assessment of the efficacy of tranexamic acid should measure a change that women with HMB themselves would perceive as clinically significant. A validated global satisfaction question (MIQ Question 6) was asked at the end of the first on-treatment menstrual cycle in Study MR-301 to document **each subject's perceived change in menstrual bleeding**. A blinded evaluation of the responses provided the data for construction and analysis of the ROC curve. Using this analysis, the minimum MBL change (cut point) that subjects found meaningful was 36 ml. In other words, an MBL reduction of at least 36 ml provided the best sensitivity and specificity for defining those who experienced a meaningful improvement in their condition

Four patient-reported outcome (PRO) measures were developed for use in the Phase 3 studies. These PRO measures, found in the MIQ, were developed based on the 2006 FDA guidance for PRO instruments. A menstrual cycle bleeding diary was also developed as part of the PRO initiative. The MIQ was then validated in a substudy of MR-302, as discussed with the Division, and this supported the use of the MIQ to measure responses in the patient population targeted for Studies MR-301 and MR-303. The MIQ was also used to measure several exploratory secondary endpoints. The three pre-specified secondary efficacy variables are 1) the Limitation in Social or Leisure Activities (LSLA) score from the MIQ, 2) the Limitation in Physical Activities (LPA) score from the MIQ, and 3) the total number of Large Stains during the menstrual period as recorded on the patient daily diaries. Other secondary endpoints included the assessment of hemoglobin and ferritin per laboratory analysis, menstrual blood loss score from the MIQ, Limitation in Work Outside or Inside the Home (LWH) score and

the patient assessment of meaningfulness score from the MIQ, total number of times sleep is interrupted and total number of large clots reported on the Blood Diary Card.

Reviewer's comment:

The design and endpoints in the two placebo-controlled studies were agreed to between the Applicant and the Division during the series of meetings held throughout the development plan for Lysteda (see Section 2.5). The Applicant's use of the meta-analysis approach for evaluating efficacy for tranexamic acid is also acceptable to this reviewer as a secondary analysis, but each study individually needed to meet the agreed upon efficacy endpoints.

Inclusion Criteria:

The criteria were identical for both short-term studies:

1. **Generally healthy women, 18 to 49 years of age, with cyclic HMB** associated with menorrhagia, and a history of 3 or more consecutive days of HMB in at least 4 of the last 6 menstrual periods.
2. Menstrual blood loss of greater than or equal to 60 mL collected on feminine hygiene protection during the first pretreatment menstrual period, and an **average MBL of greater than or equal to 80 mL over 2 pretreatment menstrual periods** (as assessed by the AHT assay method).
3. **Normal pelvic examination, cervical cytology (Papanicolaou [Pap] test), and transvaginal ultrasonography (TVU)** conducted within the first 12 days of the menstrual cycle. If a Pap test had been done within 6 months of screening Visit 1A, or a TVU within 3 months of Visit 1A, they did not have to be repeated as long as the reports were available and the results were normal. The TVU was considered abnormal if (1) the endometrial thickness was 5 to 12 mm and there was a clinical history that suggested long-term unopposed estrogen exposure (≥ 1 year) or (2) if the endometrial thickness was greater than 12 mm. **Presence of fibroids was not considered an abnormal finding for the purpose of this study unless determined by the Investigator to be of a significant number and size to warrant surgical management.** If the TVU was abnormal, a normal endometrial biopsy was required. If an endometrial biopsy had been done within 3 months of the TVU, it did not have to be repeated as long as the report was available and the results were not exclusionary.
4. Regularly occurring menstrual periods of less than or equal to 10 days duration with 21 to 35 days from the start of one period until the start of the next menstrual period (for at least the last 6 months).
5. Negative urine pregnancy test at Visit 1C (first treatment visit).
6. For contraception, females of childbearing potential must have been:
 - a) Surgically sterile (6 months post bilateral tubal ligation); or

- b) In a monogamous relationship with a sterile partner (at least 6 months post vasectomy) or with a partner of the same sex; or
- c) Using an acceptable barrier method (e.g., condom or diaphragm) with spermicide for the duration of the study; or
- d) Using a copper intrauterine device (IUD).

7. In the opinion of the Investigator, the subject must have been able to understand the study, cooperate with all study procedures, able to return to the study site for visits within the required visit windows, and likely to complete the study.

8. Subjects provided voluntary, written consent to participate in the study by signing and dating an IRB-approved ICF before any screening procedures were performed.

Exclusion Criteria:

The criteria were identical for both studies [bolding is by the clinical reviewer]:

1. History or presence of **clinically significant hepatic or renal disease or other medical disease** that might have confounded the study or been detrimental to the subject (e.g., clinically significant cardiac arrhythmia, uncontrolled diabetes, or uncontrolled hypertension), as determined by the Investigator.
2. Clinically **significant abnormalities on screening physical examination** that might have confounded the study or been detrimental to the subject, as assessed by the Investigator. Abnormal clinically significant ECG as determined by the centralized cardiologist, or laboratory tests suggestive of a potential pituitary-prolactin stimulating tumor (prolactin ≥ 30 $\mu\text{g/L}$), thrombocytopenia (platelet count $<100,000/\text{mm}^3$), uncontrolled hypothyroidism (thyroid-stimulating hormone [TSH] ≥ 10 mU/L), or severe anemia (hemoglobin <8 g/dL).
3. Anovulatory dysfunctional uterine bleeding, metrorrhagia (irregular or frequent noncyclic flow), menometrorrhagia (irregular or frequent excessive noncyclic flow), or polymenorrhea (frequent flow, cycles of less than 21 days).
4. History or presence of endometrial polyps, endometrial hyperplasia, endometrial carcinoma, or cervical carcinoma (included cervical carcinoma in situ).
5. History of bilateral oophorectomy or hysterectomy.
6. **Women who were pregnant, breastfeeding, planning to become pregnant during the study, or became pregnant during the study.**
7. History or active presence of myocardial infarction or ischemic disease. History or active presence of cerebrovascular accident, stroke, or transient ischemic attack.
8. History or presence of thrombosis, thromboembolic disease, or coagulopathy, including, but not limited to, pulmonary embolism, deep venous thrombosis, phlebitis, and any intravascular clotting disorder.

9. History or known presence of acquired or inherited thrombophilia, including, but not limited to, antithrombin deficiency, Protein C and/or S deficiency, antiphospholipid syndrome, Factor V Leiden mutation, prothrombin mutation, thalassemia, or sickle cell disease (sickle cell trait individuals were not excluded).

10. History or presence of subarachnoid hemorrhage.

11. Use of medications taken to relieve HMB prior to screening, including the use of vaginal (rings, creams, and gels) and transdermal hormone products; use of oral estrogen-, progestin-, or selective estrogen receptor modulator (SERM)-containing hormone products, or intrauterine progestins containing drug products within 8 weeks prior to screening unless the subject agreed to the required washout period of 8 weeks. Use of Lupron 3-month depot injection, estrogen pellet, or long-acting progestin injectables within 6 months prior to screening.

12. Use of meclufenamate sodium, mefenamic acid, danazol, desmopressin acetate, or herbal remedies within 8 weeks prior to screening. Herbal remedies including, but not limited to: **Capsella bursa pastoris (shepherd's purse)**, **Vitex agnus castus (Chasteberry or Vitex)**, **Cimicifuga racemosa (black cohosh)**, **Symphytum officinale (comfrey)**, and/or **Angelica sinensis (Dong quai)**.

13. Use of or anticipated use of the following drugs: oral, transdermal, injectable, and vaginal (NuvaRing®) hormonal contraceptives; anticoagulants (warfarin [Coumadin®], heparin, etc), aminocaproic acid, or hydroxychloroquine (Plaquenil®).

14. Current use of an IUD other than copper IUDs.

15. History or presence of hypersensitivity or idiosyncratic reaction to antifibrinolytics (tranexamic acid or aminocaproic acid).

16. Use of any investigational drug within the past 30 days.

17. Presence of untreated malabsorption disorder or malnutrition, including, but not limited to, chronic diarrhea, celiac disease, short bowel syndrome, **Whipple's disease**, or history of gastric bypass procedure.

18. Presence of defective color vision as determined by the optometrist or ophthalmologist. Inability of the subject to correctly identify symbols on Plate 7 of the Hardy Rand Rittlers (HRR) eye test was not considered defective color vision provided the subject correctly identified the symbols on Plates 11 to 20.

19. History or presence of glaucoma, ocular hypertension, macular degeneration, and retinopathies.

20. History or presence of alcoholism or drug abuse within the past year.

21. Malignancy or treatment for malignancy within the previous 2 years, with the exception of basal cell carcinomas of the skin or squamous cell carcinoma of the skin.

22. Did not read or understand English.

Reviewer's comment:

The bolding in the text is mine. The inclusion and exclusion criteria are extensive. It is apparent that the population of women studied in the two short-term efficacy and safety trials were generally healthy women, age 18-49, with laboratory-proven menorrhagia measuring on average at least 80 mL of blood loss per untreated baseline menstrual period. Pelvic pathology (especially uterine), other than fibroids, was generally ruled out since all enrolled subjects had a baseline transvaginal ultrasound performed. Of particular note are the following:

- (1) Women with uterine fibroids were allowed in the trials unless the clinician determined them to need surgical management.
- (2) Most significant is that hormonal contraception was not allowed immediately before or at any time during the trials. Contraception was mandatory throughout the trials with abstinence, sterilization, barrier methods, or a copper IUD being acceptable.
- (3) Menorrhagia was clearly documented by history and an accurate quantitative laboratory analytic method (the AHT).

6.1.2 Demographics

In the ITT population (all randomized subjects who ingested at least one dose of study medication) of Study MR-301, there were no statistically significant differences between the three groups in any demographic variable or baseline characteristics. Subjects ranged in age from 19 to 50 years old. Caucasians were 66% of the total ITT population, Blacks were 29%, and all other groups were 5%. The range of median duration of HMB was 8 to 10 years, whereas the range was from 0.5 to 37 years. Across the three groups, 40% had fibroids that the examining clinician judged to not require surgery. History of alcohol and tobacco use is noted in Table 4.

In the ITT population of Study MR-303, there were no statistically significant differences between the two groups in any demographic variable or baseline characteristics. Subjects ranged in age from 20 to 49 years old. Caucasians were 72.5% of the total ITT population, Blacks were 22%, and all other groups were ~6%. The range of median duration of HMB was 7 to 7.1 years, whereas the range was from 0.4 to 36 years. Across the two treatment groups, 37% had fibroids. History of alcohol and tobacco use is noted in Table 4 and Table 5.

Table 4: Study MR-301 Baseline Characteristics- ITT Population

Demographic Variable	XP12B-MR 3.9 g/day N = 115	XP12B-MR 1.95 g/day N = 115	Placebo N = 67	F	ANOVA F P-value
Age – years (a)					
n	115	115	67		
Mean (SD)	39.19 (6.248)	40.18 (6.296)	38.93 (6.056)	1.1	0.3284
Median	39.00	41.00	39.00		
Range (min – max)	20.00 – 50.00	20.00 – 49.00	19.00 – 48.00		
Heavy menstrual bleeding duration – years					
n	115	114	67		
Mean (SD)	11.94 (8.892)	12.13 (9.401)	9.98 (8.438)	1.4	0.2562
Median	10.00	10.00	8.00		
Range (min – max)	0.50 – 33.83	0.75 – 37.00	0.50 – 31.00		
Presence of Fibroids (b)					Chi-square P-value
Present	51 (44.35)	44 (38.26)	24 (35.82)	NA	NA
Absent	64 (55.65)	71 (61.74)	43 (64.18)		
Race, n (%)					
White	77 (66.96)	76 (66.09)	43 (64.18)	NA	0.5694
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		
Other	3 (2.61)	4 (3.48)	2 (2.99)		
History of Alcohol Use, n (%)					
Yes	67 (58.26)	60 (52.17)	44 (65.67)	NA	0.2025
No	48 (41.74)	55 (47.83)	23 (34.33)		
Alcohol (number of years), n (%)					
<1 year	3 (4.48)	0	2 (4.88)	NA	0.5571
1-5 years	10 (14.93)	9 (14.52)	6 (14.63)		
>5 years	54 (80.60)	53 (85.48)	33 (80.49)		
Total	67 (100.00)	62 (100.00)	41 (100.00)		
History of Tobacco Use, n (%)					
Yes	48 (41.74)	41 (35.65)	29 (43.28)	NA	0.5102
No	67 (58.26)	74 (64.35)	38 (56.72)		
Tobacco (number of years), n (%)					
<1 year	3 (6.25)	1 (2.44)	0	NA	0.3639
1-5 years	13 (27.08)	9 (21.95)	11 (37.93)		
>5 years	32 (66.67)	31 (75.61)	18 (62.07)		
Total	48 (100.00)	41 (100.00)	29 (100.00)		

Source: Applicant Table 4.1-2, ISE page 30 of 93.

Table 5: Study MR-303 Baseline Characteristics- ITT Population

Demographic Variable	XP12B-MR 3.9 g/day N = 117	Placebo N = 72	F	ANOVA F P-value
Age – years (a)				
n	117	72		
Mean (SD)	38.74 (6.324)	38.85 (6.837)	0.00	0.9087
Median	39.00	41.00		
Range (min – max)	21.00 – 49.00	20.00 – 48.00		
Heavy menstrual bleeding duration – years				
n	117	71		
Mean (SD)	10.08 (9.354)	10.08 (8.629)	0.00	0.9965
Median	7.00	7.08		
Range (min – max)	0.58 – 35.00	0.42 – 36.00		
Presence of Fibroids (b)				
Yes	44 (37.61)	27 (36.49)	NA	NA
No	73 (62.39)	47 (63.51)		
Race, n (%)				
White	86 (73.50)	51 (70.83)	NA	0.6343
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)		
History of Alcohol Use, n (%)				
Yes	55 (47.01)	38 (52.78)	NA	0.4410
No	62 (52.99)	34 (47.22)		
Alcohol (number of years), n (%)				
<1 Year	1 (1.89)	1 (2.86)	-	0.8891
1-5 Years	9 (16.98)	7 (20.00)		
>5 Years	43 (81.13)	27 (77.14)		
Total	53 (100.00)	35 (100.00)		
History of Tobacco Use, n (%)				
Yes	42 (35.90)	27 (37.50)	NA	0.8241
No	75 (64.10)	45 (62.50)		
Tobacco (number of years), n (%)				
<1 Year	1 (2.44)	1 (3.70)	-	0.9086
1-5 Years	9 (21.95)	5 (18.52)		
>5 Years	31 (75.61)	21 (77.78)		
Total	41 (100.00)	27 (100.00)		

Source: Applicant Table 4.2-2, ISE page 41 Of 93.

Reviewer's comment:

Both trials were blinded and randomized. The overall percentage of African-Americans (26%) is impressive while there were very few Asians (1%). The 38-40% incidence of fibroids is also important, as many of these women would traditionally have a hysterectomy because of their fibroids and HMB. If the product proves to be an effective, safe, and satisfactory alternative to surgical options (e.g., hysterectomy, myomectomy, endometrial ablation) for treating HMB, it will be helpful for a large number of American

women over a wide range of age. According to the Center of Disease Control and Prevention (CDC), 3 million women of reproductive age in the U.S. report HMB yearly.

6.1.3 Subject Disposition

Subject disposition by treatment group for the two randomized Phase 3 efficacy studies is summarized individually and then combined in the following three tables.

Table 6: Subject Disposition Study MR-301 (3-month treatment)

	3.9 g/day n (%)	1.95 g/day n (%)	Placebo n (%)	Overall n (%)
Screening (n= 1,224)				
Not enrolled				920 (75.2)
Enrolled/Randomized	118 (38.8)	117 (38.5)	69 (22.7)	304 (24.8)
Study Execution				
Completed	103 (87.3)	106 (90.6)	63 (91.3)	272 (89.5)
Withdrawal	15 (12.7)	11 (9.4)	6 (8.7)	32 (10.5)
Withdrawal Reason	n (% of 15)	n (% of 11)	n (% of 6)	n (% of 32)
Other event	3 (20.0)	2 (18.2)	2 (33.3)	7 (21.9)
Subject request	2 (13.3)	0	1 (16.7)	3 (9.4)
Protocol violation	3 (20.0)	1 (9.1)	1 (16.7)	5 (15.6)
Death	0	0	0	0
Poor efficacy	0	0	0	0
Failed to return	6 (40.0)	5 (45.5)	1 (16.7)	12 (37.5)
Adverse event	1 (6.7)	3 (27.3)	1 (16.7)	5 (15.6)

Source: Modified by reviewer from the final MR-301 Study Report

Table 7: Subject Disposition Study MR-303 (6-month treatment)

	3.9 g/day n (%)	Placebo n (%)	Overall n (%)
Screening (n= 711)			
Not enrolled			515 (72.4)
Enrolled/Randomized	123 (62.8)	73 (37.2)	196 (27.6)
Study Execution			
Completed	94 (76.4)	54 (74.0)	148 (75.5)
Withdrawal	29 (23.6)	19 (26.0)	48 (24.5)
Withdrawal Reason	n (% of 29)	n (% of 19)	n (% of 48)
Other event	8 (28.6)	1 (5.7)	9 (18.8)
Subject request	6 (20.7)	2 (10.5)	8 (16.7)
Protocol violation	2 (6.9)	5 (26.3)	7 (14.6)
Death	0	0	0
Poor efficacy	0	2 (10.5)	2 (4.2)
Failed to return	10 (34.5)	6 (31.6)	16 (33.3)
Adverse event	3 (10.3)	3 (15.8)	6 (12.5)

Source: Modified by reviewer from the MR-303 Study Report.

Reviewer's comment:

There do not appear to be any major differences in the subject disposition in the two clinical studies except to note that the overall completion percentage for active and placebo treatment was higher in the shorter 3-month trial (89.5%) compared to the longer 6-month trial (75.5%). This finding is what would normally be expected over time. The Applicant's pooled data from the two studies is shown in the next table.

Table 8: Subject Disposition and Interim Status (Pooled over MR-301 and 303)

Study Phase	Outcome	3.9 g/day XP12B-MR n (%) (a,b,c)	1.95 g/day XP12B-MR n (%) (a,b,c)	Placebo n (%) (a,b,c)	Overall n (%) (a,b,c)
Screening	Screen Failure				1435 (74.16)
	Enrolled	241 (48.20)	117 (23.40)	142 (28.40)	500 (25.84)
Study Execution	Completed	197 (81.74)	106 (90.60)	117 (82.39)	420 (84.00)
	Withdrawn	44 (18.26)	11 (9.40)	25 (17.61)	80 (16.00)
	Primary Reasons for Withdrawal				
	- Other Event	11 (25.00)	2 (18.18)	3 (12.00)	16 (20.00)
	- Subject Request Unrelated to the Study	8 (18.18)	0	3 (12.00)	11 (13.75)
	- Protocol Violation	6 (13.64) (d)	1 (9.09)	6 (24.00)	13 (16.25)
	- Death	0	0	0	0
	- Unsatisfactory Response - Efficacy	0	0	2 (8.00)	2 (2.50)
	- Failed to Return	16 (36.36)	5 (45.45)	7 (28.00)	28 (35.00)
	- Adverse Event	3 (6.82) (d)	3 (27.27)	4 (16.00)	10 (12.50)

Source: Applicant's ISE, pg 49 of 93 (Table 4.3-1).

a: The number of subjects is used for the denominator for calculated percentages for the screening phase percentages.

b: The enrolled number of subjects is used as the denominator for calculated percentages for the study execution phase percentages.

c: The number of subjects withdrawn is used as the denominator for calculated percentages for the reason for withdrawal.

Of the 500 subjects randomly assigned to a treatment group, 241 (48.2%) were assigned to receive tranexamic acid 3.9 g/day; 117 (23.4%) were assigned to receive tranexamic acid 1.95 g/day; and 142 (28.4%) were assigned to receive placebo.

A total of 420 (84.0%) of the 500 subjects completed their study, with 197 (81.7%) completing in the 3.9 g/day active treatment group, 106 (90.6%) completing in the 1.95 g/day active treatment group, and 117 (82.4%) completing in the placebo group. Eighty subjects (16.0%) discontinued early from the studies, most from the active treatment groups (44 subjects [18.3%] in 3.9 g/day group, 11 subjects [9.4%] in the 1.95 g/day group). The most frequent reason for withdrawal was subject failure to return (28 subjects [35.0% of 80]). At the time of the original submission, ten subjects (12.5%) withdrew from the studies due to AEs. Of these 10 subjects, 3 each were in the 3.9 g/day treatment and 1.95 g/day treatment groups and 4 were in the smaller placebo group. The final safety update showed one more subject receiving 3.9 g/day tranexamic acid as withdrawing due to an adverse event.

Reviewer's comment:

The “other events” leading to study withdrawal included amenorrhea, pregnancy, cycle irregularity, scheduling problems, and moving away from the study site. None of these “other events” included adverse events. “Failure to return” was sometimes documented as moving away from the site, domestic problems, and scheduling problems; otherwise, the subject simply failed to return, attempts to make contact were not successful, and no further information was recorded.

In Study MR-301, five subjects experienced a total of five AEs leading to withdrawal from the study [1 at the 3.9 gram dose, 3 at the 1.95 gram dose, and 1 on placebo]. Four of the AEs had resolved by the time of the subjects' follow-up visit, except for the AE of severe anemia, which was ongoing at that visit. In Study MR-303, three subjects (632-3011, 632-3044, 658-3001) receiving tranexamic acid withdrew from the study. Further discussion of AEs, whether resulting in discontinuation or not, is found in review Sections 7.3.2 and 7.3.3.

6.1.4 Analysis of Primary Endpoint(s)

Sample Size:

The Applicant calculated the sample size in order to have a 90% power to detect a 50 ml difference between the mean change from baseline menstrual blood loss (MBL) in the active treatment and placebo groups. 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 arm and 46 subjects in the placebo group.

Populations: All efficacy analyses were conducted on the ITT and mITT populations. The mITT population was the primary population for efficacy analyses. The analysis populations are defined as follows:

- ITT Population: included all randomized subjects who ingested at least 1 dose of study drug.
- mITT Population: included all randomized subjects who received at least 1 dose of study drug, had a baseline primary efficacy evaluation and had sufficient primary efficacy data to construct one menstrual period of data after the first dose of study drug.
- 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 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. Missing periods (i.e. no sanitary product collection on any day during bleeding for a period) were treated as missing in the analyses.

Primary Endpoint: The menstrual blood loss (MBL) during the entire menstrual period, as measured by the alkaline hematin test (AHT) was assessed for each subject at each of the baseline and prespecified treatment cycles. In order to claim efficacy, the primary efficacy variable (the mean change from the baseline pre-treatment values to post-treatment alkaline hematin MBL values) had to satisfy the following three conditions in each of the two efficacy studies:

- Statistically significantly greater reduction from baseline in MBL in the active treatment group(s) compared to placebo
- Change in MBL from baseline measured as > 50 ml
- Change from baseline in MBL for both studies must be > the reduction of 36 ml identified as meaningful to women through the agreed upon ROC analysis from Study MR-301

After the primary efficacy analysis was calculated for the 1.95 g/day, 3.9 g/day, and placebo groups in the 3-month Study MR-301, the analysis of the three pre-specified secondary endpoints for each dose level proceeded via a sequential gate method for the dose or doses that were statistically significant based on the primary efficacy analysis. Each hypothesis test was conducted at the $\alpha = 0.05$ level of significance. If the primary hypothesis concerning the comparison of the 3.9 g/day active treatment and placebo groups was rejected (i.e., the active treatment met the primary endpoint), then the prespecified secondary efficacy variables were to be tested sequentially in the following order: (1) LSLA (3.9 g/day active treatment versus placebo group), (2) LPA (3.9 g/day active treatment versus placebo group), and (3) total number of large stains responder analysis (3.9 g/day active treatment versus placebo group). If, at any point in the testing sequence, a hypothesis for a prespecified secondary variable was not rejected, then the analyses on that variable and the remaining pre-specified secondary variables were to be exploratory in nature. For LSLA and LPA, the between-treatment test was conducted using an ANCOVA. The model included a factor for the treatment group, and the baseline value from the prespecified secondary variable was included as a covariate. The within-treatment test was conducted using a paired difference t-test. For the total number of large stains reported **from the subjects'** bleeding diary, the intrasubject differences were calculated (average number of bleeding events recorded during treatment minus the baseline average). The proportion of subjects who experienced a reduction from baseline in the number of large stains was compared between treatment groups using a **two-tailed Fisher's Exact test**.

For the 1.95 g/day dose, the null hypothesis concerning the comparison of the 1.95 g/day active treatment and placebo groups was not rejected. Therefore, the prespecified secondary efficacy variables were not tested sequentially and the Applicant did not pursue any further testing of this lower dose.

Reviewer's comment:

Although it is not crystal clear whether the Division's requested success criterion was for change in MBL from baseline of > 50 ml for the active treatment alone or as compared to the change for placebo treatment, the higher 3.9 g/day dose met either criteria for the primary efficacy endpoint and the lower 1.95 g/day dose did not. The sequential testing of the three prespecified secondary efficacy variables was then followed per protocol for the 3.9 g/day dose.

Study 301 and 303 Primary Efficacy Results:

Results of the analysis by the statistical reviewer, Xin Fang, Ph.D., are shown in Table 9 and Table 10, respectively. He reported results on changes in MBL in terms of the least square means (based on the ANCOVA model), rather than the Applicant's reported sample mean. Mean reduction in MBL was statistically significantly greater for the 3.9 g/day dose of tranexamic acid compared with placebo. This dose did meet the above clinical criteria of demonstrating efficacy. He noted that the cutoff point of 36 mL based on ROC analysis was exploratory in nature.

Table 9: Study 301 - Mean Reduction in MBL (mL)

Mean Reduction From Baseline in Menstrual Blood Loss (mL) Using the Alkaline Hematin Method – mITT Population					
Treatment	N	Baseline Mean (SD)	Change (SD)	Least Squares Mean	P-value
Tranexamic Acid (3.9 g/day)	112	169.0 (83.0)	65.3 (51.1)	65.3	<0.0001
Tranexamic Acid (1.95 g/day)	115	178.0 (112.2)	46.45* (57.1)	44.1*	<0.0001
Placebo	67	153.6 (67.9)	3.0 (46.07)	7.1	

Source: Modified from Table 3.2.3, Statistical review of Dr. Fang, dated June 15, 2009. Numbers are rounded off to the nearest decimal point. T

* The change for the 1.95 g/day dose did not meet the > 50 mL criteria for success.

Table 10: Study 303 - Mean Reduction in MBL (mL)

Mean Reduction From Baseline Menstrual Blood Loss (mL) Using the Alkaline Hematin Method – mITT Population				
Treatment	N	Baseline Mean (SD)	Least Squares Mean Change	P-value
Tranexamic Acid (3.9 g/day)	115	172.3 (95.6)	66.3	<0.0001
Placebo	72	153.0 (66.6)	17.8	

Source: Modified from Table 3.3.3, Statistical review of Dr. Fang, dated June 15, 2009. Numbers are rounded off to the nearest decimal point.

Dr. Fang made the following recommendation in his final review dated June 15, 2009:

The results support the efficacy of 3.9 g/day (1.3 g TID) dose level of tranexamic acid... 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.

Reviewer's comment:

I concur with both the Applicant's and Dr. Fang's conclusion that the 3.9 g/day dose meets all the criteria for the primary efficacy endpoint and that the lower 1.95 g/day dose does not. Because the 1.95 g/day dose in Study MR-301 did not achieve the predetermined condition of at least a 50 mL difference in the reduction of MBL from baseline to on-treatment cycles for the primary endpoint, this dose was not developed further by the Applicant. Study MR-301 established the 3.9 g/day active treatment dose as the lowest effective dose (LED) using criteria established by the Division in agreement with the Applicant.

In Study 301, the raw mean reduction of 46.45 mL in menstrual blood loss with the lower 1.95 g/day dose is still impressive and came close to meeting the predetermined criterion of attaining at least 50 ml in the reduction of MBL compared to placebo. Granted, it is not as large a reduction as the raw mean value of 65.3 mL seen with the higher 3.9 g/day dose. I believe, however, this statistically significant clinical finding should be noted in the clinical trial section of the label so that consumers and healthcare providers will know that a dose reduction may be acceptable, especially for women who do not tolerate some of the common side effects when taking tranexamic acid.

6.1.5 Analysis of Secondary Endpoints(s)

The prespecified secondary efficacy variables in sequential order of statistical analysis were:

- Limitation in Social and Leisure Activities (LSLA) score from the MIQ (Question 4)
- Limitation in Physical Activities (LPA) score from the MIQ (Question 3), and

- **Total number of large stains during the menstrual period** reported in subject diaries for the specified cycles

The MIQ key questions are listed here (see Section 9.4 Extra Materials for the entire MIQ):

- Question 4: During your most recent menstrual period, how much did your bleeding limit your **social and leisure activities**? (*Please circle the number of your answer*)- 1. Not at all; 2. Slightly; 3. Moderately; 4. Quite a bit; 5. Extremely.
- Question 3: During your most recent menstrual period, how much did your bleeding limit your **physical activities**? (*Please circle the number of your answer*)- 1. Not at all; 2. Slightly; 3. Moderately; 4. Quite a bit; 5. Extremely.

The same data analysis techniques were employed as for the MBL data. The statistical analyses for these variables was conducted using the difference in the average value on treatment (Periods 1 to 3 in Study 301; periods 1-3 and 6 in Study 303) compared to the average value at baseline (pretreatment menstrual Periods 1 and 2) for the treatment and placebo groups. The averages were taken over non-missing values. For LSLA and LPA, the statistical analyses were conducted on the change from baseline values directly, while for the total number of large stains, the proportion of subjects who experienced a reduction in large stains from baseline was statistically analyzed.

For LSLA and LPA, a between-treatment group comparison of the mean change from pretreatment to treatment for each efficacy study (MR-301 and -303) was conducted (3.9 g active treatment group vs. placebo and 1.95 g active treatment group vs. placebo for Study MR-301 study; only 3.9 g active treatment group vs. placebo group for Study MR-303). In addition, a meta-analysis across both efficacy studies was performed by the Applicant to compare treatment-group change from baseline means for the 3.9 gram active treatment group vs. placebo. The analysis of variance (ANOVA) model for the meta-analysis contained terms for study and treatment group.

The total number of large stain responder values was analyzed using a 2-sample binomial test within each efficacy study (3.9 g active treatment group vs. placebo and 1.95 g active treatment group vs. placebo for Study MR-301; only 3.9 g active treatment group vs. placebo group for Study MR-303).

An exploratory meta-analysis across efficacy studies of the 3.9 g active treatment and **placebo groups' data was performed using a generalized linear model for binomial data** with a logit link function and using weighted least squares (WLS) on the probability differences. The generalized linear model contained terms for study and treatment group. All analyses of the prespecified secondary efficacy variables were conducted on the ITT and mITT population data.

LSLA Endpoint:

Table 11 and Table 12 represent a summary of the change from baseline for the MIQ Question 4 regarding the limitations of social and leisure activities (LSLA).

Table 11: LSLA Mean Change from Baseline to Treatment – mITT Population

Study	3.9 g/day				1.95 g/day				Placebo			
	N	Raw Mean	SD	LS Mean CFB	N	Raw Mean	SD	LS Mean CFB	N	Raw Mean	SD	LS Mean CFB
MR-301	112	3.00	1.08	0.98	115	2.93	1.00	0.74	66	2.85	0.97	0.39
MR-303	115	2.92	1.02	0.85					72	2.74	0.98	0.44
Meta-analysis	227	2.95	0.88	0.88					138	2.79	0.86	0.37

Source: the values for Studies 301 and 303 are from the FDA statistical review by Xin Fang. The values for the meta-analysis are modified from the Applicant's ISE, pg 55 of 93 (Table 4.3-5). Values for MR-303 reflect only the first three menstrual cycles. LSLA = Limitation of Social and Leisure Activities; CFB = change from baseline; LS = least squares; mITT = modified intent-to-treat; SD = standard deviation

Reviewer's comment:

As is shown in Table 12 that follows, the mean change treatment effect (least square mean change from baseline for the 3.9 g/day active treatment group minus that for the placebo group) of 0.59 and 0.41 in the two studies is statistically significant. The meta-analysis by the Applicant is considered only as a secondary analysis and not the primary analysis.

Table 12: Statistical Significance for LSLA Endpoint Change from Baseline

Study	3.9 g/day vs. Placebo		1.9 g/day vs. Placebo	
	Treatment Effect	P-value	Treatment Effect	P-value
MR-301 ^A	0.59	< .0001	0.35	< .0055
MR-303 ^A	0.41	< .0001		
Meta-analysis ^B	0.51	< .0001		

^ASource: the values for Studies 301 and 303 are from the FDA statistical review by Xin Fang.

^BThe values for the meta-analysis are modified from the Applicant's ISE, pg 55 of 93 (Table 4.3-5).

Reviewer's comments:

The treatment effect of the 3.9 g/day dose vs. placebo was statistically significant for both individual studies MR-301 and -303. Using the Applicant's meta-analysis, the treatment effect of the 3.9 g/day dose vs. placebo was also statistically significant (p <0.0001).

In addition, both the Applicant's and the FDA statistician's exploratory analysis of the 1.95 g/day dose vs. placebo demonstrated a treatment effect of 0.35 that was statistically significant (p=0.0055), but approval of this lower dose is not recommended because the lower dose did not meet all three of the conditions for success for the primary endpoint.

LPA Endpoint:

Table 13 and Table 14 represent a summary of the change from baseline for the MIQ Question 3 regarding the limitations of physical activities (LPA).

Table 13: LPA Mean Change from Baseline to Treatment – mITT Population

Study	3.9 g/day				1.95 g/day				Placebo			
	N	Raw Mean	SD	LS CFB Mean	N	Raw Mean	SD	LS CFB Mean	N	Raw Mean	SD	LS CFB Mean
MR-301	112	3.07	1.04	0.94	115	2.97	0.98	0.70	66	2.96	0.87	0.34
MR-303	115	3.05	0.95	0.87					72	2.90	0.95	0.40
Meta-analysis	227	3.06	0.98	0.88					138	2.92	0.91	0.34

Source: the values for Studies 301 and 303 are from the FDA statistical review by Xin Fang.

The values for the meta-analysis are modified from the ISE, pg 57 of 93 (Table 4.3-6).

Values for MR-303 reflect only the first three menstrual cycles.

LPA = Limitation of Physical Activities; CFB = change from baseline; LS = least squares; mITT = modified intent-to-treat; SD = standard deviation

Reviewer's comment:

As is shown in Table 14 that follows, the mean change treatment effect (least square mean change from baseline for the 3.9 g/day active treatment group minus that for the placebo group) of 0.60 and 0.47 in Studies 301 and 303, respectively, is statistically significant. The meta-analysis by the Applicant is considered only as a secondary analysis and not the primary analysis.

Table 14: Statistical Significance for LPA Endpoint Change from Baseline

Study	3.9 g/day vs. Placebo		1.9 g/day vs. Placebo	
	Treatment Effect*	P-value	Treatment Effect	P-value
MR-301 ^A	0.60	< .0001	0.36	0.0030
MR-303 ^A	0.47	< .0001		
Meta-analysis ^B	0.54	< .0001		

^ASource: the values for Studies 301 and 303 are from the FDA statistical review by Xin Fang.

^BThe values for the meta-analysis are modified from the Applicant's ISE, pg 57 of 93 (Table 4.3-6).

*Treatment Effect = least square means change from baseline for the 3.9 gram arm minus that for the placebo arm.

Reviewer's comments:

The treatment effect of the 3.9 g/day dose vs. placebo (least squares mean change from baseline for the 3.9 g/day active treatment group minus that for the placebo group) was statistically significant for both individual studies MR-301 and -303. Using a meta-analysis, the treatment effect of the 3.9 g/day dose vs. placebo was also statistically significant (p <0.0001).

In addition, the exploratory analysis of the 1.95 g/day dose vs. placebo determined that the treatment effect was 0.36 and statistically significant (p=0.0030), but approval of this lower dose is not recommended because the lower dose did not meet all three of the conditions for success on the primary endpoint.

Large Stains Endpoint:

Table 15 and Table 16 present the summary of the large stain responder analysis for the 3.9 g/day and 1.95 g/day active treatment and placebo groups.

The percentage of treatment success in Studies MR-301 and -303 was 64.0% and 56.1%, respectively, for the 3.9 g/day active treatment group, compared with 52.2% and 44.4%, respectively, in the placebo group. The treatment effect for the 3.9 g/day dose vs. placebo (percentage success for the 3.9 g/day active treatment group minus that for the placebo group) was ~11.7 for both Studies -301 and -303 and was not statistically significant.

The exploratory analysis of the treatment effect for the 1.95 g/day MR dose vs. placebo (percentage success for the 1.95 g/day active treatment group minus that for the placebo group) was not statistically significant.

Table 15: Summary of Large Stain Responder Analysis – mITT Population

Study or Analysis	3.9 g/day			1.95 g/day			Placebo		
	N	# of Treatment Success	% Success	N	# of Treatment Success	% Success	N	# of Treatment Success	% Success
MR-301	111	71	64.0	114	70	61.4	67	35	52.2
MR-303	114	64	56.1				72	32	44.4
Meta-analysis Log Odds Ratios	225	135	60.0				139	67	48.2
Meta-analysis WLS	225	135	60.0				139	67	48.2

Source: modified from the ISE, pg 59 of 93 (Table 4.3-7).
 Values for MR-303 reflect only the first three menstrual cycles.
 WLS = weighted least squares; mITT = modified intent-to-treat

Reviewer's comments:

In his analysis, the FDA statistician used slightly different values for the percentage of treatment success (positive responders) and calculated higher p-values for each trial. He did not comment on the two exploratory meta-analyses that were performed by the Applicant. As shown in Table 16 below, none of the analyses show that there is a significant difference between tranexamic acid and placebo treatment on reduction of large stains.

What is surprising is the high placebo response in light of the difference in menstrual blood loss due to tranexamic acid compared to placebo. This prespecified secondary endpoint is not critical to the approval of the product, but the negative results should be included in the label, especially because the positive results for LSLA and LPA are included in the final label. The Applicant was informed during early discussions that pre-specified secondary endpoints intended to support labeling claims would be described in labeling whether or not they were successful.

Table 16: Statistical Significance for Large Stain Responder Analysis

Study	3.9 g/day vs. Placebo		1.9 g/day vs. Placebo	
	Treatment Effect	P-value	Treatment Effect	P-value
MR-301	11.73	0.156	9.16	0.275
MR-303	11.70	0.134		
Meta-analysis Log Odds Ratios	8.71	0.029		
Meta-analysis WLS	11.71	0.028		

Source: modified from the ISE, pg 59 of 93 (table 4.3-7).
 WLS = weighted least squares; mITT = modified intent-to-treat

Reviewer's comment:

The data here shows that there was not a statistically significant difference between active treatment and placebo. This prespecified secondary endpoint is not critical to the approval of the product. However, since the positive results for LSLA and LPA are included in the final label, the results for the Large Stain Responder Analysis will also be included in the label to give a full and balanced report of the clinical trial results.

6.1.6 Other Endpoints

The secondary efficacy variables are as follows:

- Blood loss score from the MIQ (Question 1);
- Limitations in Work (LWH) from the MIQ (Question 2);
- Subject assessment of clinical meaningfulness from the MIQ (Question 6);
- Total number of times sleep was interrupted during the menstrual period from subject diaries;
- Total number of small clots reported during the menstrual period from subject diaries;
- Total number of large clots reported during the menstrual period from subject diaries;
- Total number of small stains reported during the menstrual period from subject diaries;
- Total number of large stains reported during the menstrual period on subject diaries (ANOVA analysis);
- Hemoglobin – clinical laboratory value;
- Ferritin – clinical laboratory value; and
- Total number of sanitary products used during the menstrual period (as reported by the testing laboratory).

The statistical analyses for subject diary response variables and MIQ response variables was conducted on the difference in the average value on treatment (menstrual periods 1 to 3) compared to the average value at baseline (pretreatment menstrual periods 1 and 2) for the treatment and placebo groups. The averages were taken over non-missing values.

For all secondary variables, except the subject assessment of clinical meaningfulness from the MIQ, a between-treatment group comparison of the mean change from pretreatment to treatment for each efficacy study (MR-301 and -303) was conducted (3.9 g/day treatment group versus placebo group and 1.95 g/day treatment group versus placebo group for Study MR-301; 3.9 g/day active treatment group versus placebo group only for Study MR-303) along with a meta-analysis across efficacy studies to compare treatment group change from baseline means for the 3.9 g/day active treatment group versus placebo group. The ANOVA model for the meta-analysis contained terms for study and treatment group.

Concerning the raw data for the total number of large stains response variable, a table of summary statistics (n, mean, SD, minimum, maximum, median, count and percentage of subjects with at least 1 large stain) was computed for each treatment group for each period for Study -301 and -303).

Reviewer's comments:

These secondary efficacy variables are intended to be exploratory and should not be used for labeling claims. Looking only at the data for the 3.9 g/day dose from the meta-analysis for the mITT population in Study -301 and -303, the tranexamic acid treatment effect for the following secondary endpoints was statistically significant compared to placebo treatment:

- 1. Blood loss (MIQ Question 1)**
- 2. Score for Limitations of Work inside and outside the home (MIQ Question 2)**
- 3. Small stains and large stains**
- 4. Sleep interruptions during time of the menstrual period**
- 5. Hemoglobin**
- 6. Sanitary products used**

The treatment effect was not statistically significant for the following secondary endpoints:

- 1. Small clots and large clots**
- 2. Ferritin**

Clinical Meaningfulness of Treatment:

A responder analysis using the subjects' assessment of meaningfulness from the MIQ was conducted for the MBL response. A receiver operating characteristic (ROC) analysis was conducted to assess the reduction of MBL that was meaningful to subjects. A responder was defined as a subject who had an MBL decrease from pretreatment to treatment and reported a meaningful improvement on the MIQ at Visit 3.

Question 6 was: “Compared to your previous menstrual period, would you say your blood loss during this period was better?” Question 6c was: “Was this a meaningful or important change for you?” A subject was considered to have reported a meaningful improvement on the MIQ if Question 6 was marked 1 (better) and Question 6c was marked 1 (yes).

Using this as meaningful 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. In his review, Xin Fang, the FDA statistical reviewer, notes that “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.”

Treatment “success” was defined by the Applicant as responding “Yes” to Question 6c on the MIQ. According to the Applicant’s analysis, the percentage of treatment success in MR-301 and -303 was 72.0% and 67.3%, respectively, for the 3.9 g/day active treatment group, compared with 37.5% and 44.4%, respectively, in the placebo group. As shown in Table 17, the treatment effect for the 3.9 g/day dose vs. placebo (percentage success for the 3.9 g/day active treatment group minus that for the placebo group) was statistically significant for both MR-301 and -303. The exploratory treatment effect for the 1.95 g/day dose vs. placebo (percentage success for the 1.95 g/day active treatment group minus that for the placebo group) was 28.24 and also statistically significant (p=0.0005).

Table 17: Summary of “Yes” Responses on MIQ Question 6c and Responder Analysis

Study (mITT population)	3.9 g/day vs. Placebo		1.9 g/day vs. Placebo	
	Treatment Effect*	P-value	Treatment Effect	P-value
MR-301	34.50	< 0.0001	28.24	0.0005
MR-303	22.85	0.0039		
Meta-analysis Log Odds Ratios	25.19	< 0.0001		
Meta-analysis WLS	28.82	< 0.0001		

Source: modified from the ISE, pg 66 of 93 (table 4.3-9).

*Treatment effect = % success for active treatment minus % success for placebo treatment.

Success was defined as a positive response on Question 6c on the MIQ.

MIQ = Menorrhagia Impact Questionnaire WLS = weighted least squares; mITT = modified intent-to-treat population

Reviewer's comment:

The subjects' own assessment of the clinical meaningfulness of the treatment benefit they experienced is shown in the table above and is statistically significant when comparing the two active treatment groups with the placebo groups. It is of note that the response for the lower 1.95 g/day dose is also statistically significant (p-value 0.0005). As stated earlier in this review, I believe that this finding is noteworthy and should potentially be included in the approved label as it may be of value for women who do not tolerate the common side effects of the higher 3.9 g/day dose, but want to try a lower dose to treat their menorrhagia.

6.1.7 Subpopulations

Subgroup analyses of change from baseline MBL were conducted for the following variables: age, body-mass index, race, and tobacco status. For these analyses, tables of summary statistics (n, change from baseline mean, change from baseline SD) were calculated for each treatment group and for each subgroup variable classification for MR-301 and MR-303 and combined over both studies. The Applicant concluded that no clinically meaningful differences were observed in the mITT population for the primary efficacy endpoint when the subjects were stratified by race, BMI, or current tobacco use. The numbers of subjects per age group were too small to provide meaningful conclusions about differences among the age groups. The subgroup analyses were strictly exploratory in nature.

Reviewer's comment:

I agree with the Applicant's choice of the subgroups within each variable. I reviewed the tables of summary statistics (pg 68-71 of the ISE) for the four variables and conclude that it is difficult to detect clinically meaningful differences. Two trends are noted, however:

- 1. Older women (especially > age 45) had a greater change in MBL from baseline compared to younger women**
- 2. Women with a lower body mass index (< 25) had a greater change in MBL from baseline compared to women with a higher BMI**

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy of tranexamic acid in the treatment of HMB was demonstrated in Studies -301 and -303. Menstrual blood loss was significantly reduced in subjects in Study -301 treated with 3.9 g/day tranexamic acid vs. placebo (65.1 mL [38.6% reduction] vs. 3.0 mL [1.9%]; p<0.0001. For Study -303, the findings were 69.6 mL [40.2% reduction] vs. 12.5 mL [8.2%]; p<0.0001. This reduction met the criterion for being meaningful according to the prescribed criteria (MBL cut point >50 mL) as well as meaningful to women who participated in the studies (MBL cut point =36 mL). These values are discussed in Section 6.1.6, the subsection Clinical Meaningfulness of Treatment.

In Studies 301 and 303, each subject received study drug in blister packs and was instructed to take 2 tablets orally 3 times daily with liquids for up to 5 consecutive days (not to exceed 3 doses in 1 day or 15 doses during the menstrual period) beginning

when HMB was first experienced. Subjects were instructed to swallow the tablets whole and never to chew, divide, or crush them and to take the doses at least 6 hours apart. Study drug could be taken with food or liquid.

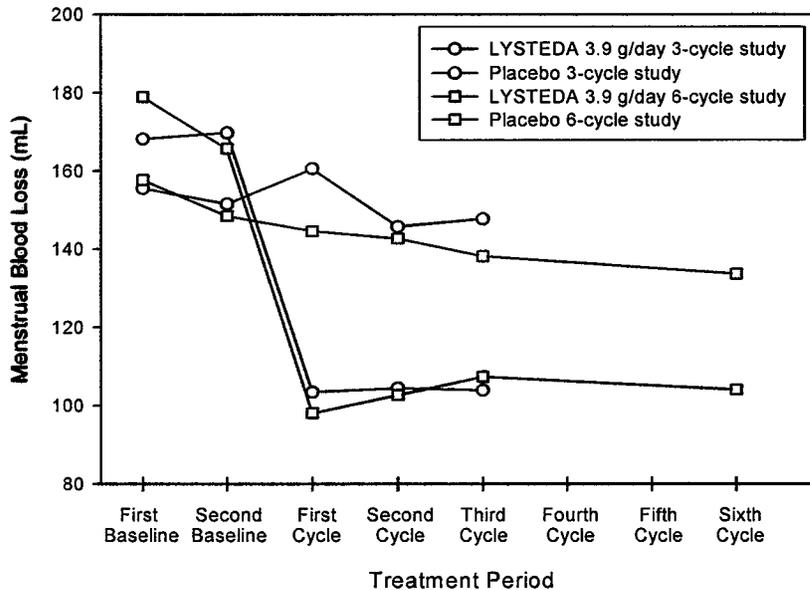
Since tranexamic acid is primarily eliminated via the kidneys by glomerular filtration, dosage adjustment is recommended for patients with reduced renal function and the recommended algorithm will be included in labeling.

Tranexamic acid is indicated for the chronic treatment of cyclic HMB that will take place monthly during reproductive or child bearing age. In order to simulate the various plasma concentrations expected for different oral dosage regimens of tranexamic acid, the average plasma concentration-time data from the to-be-marketed formulation were used to derive compartmental pharmacokinetic parameters. Simulations performed with these compartmental parameters supported the selected dosage regimen of the **Applicant's 650-mg formulation**, both as a total 3.9 g/day dose, but more specifically as a 1.3 g (two 650-mg tablets) oral dose administered 3 times daily. Acceptable and desirable steady-state simulated peak, trough, and average plasma concentrations were achieved with this regimen and it was therefore used as the preferred regimen for **the Applicant's clinical efficacy and safety studies**.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No specific studies were performed to evaluate the persistence of efficacy after active treatment was stopped. There was no direct evidence of tolerance developing to the use of tranexamic acid (3.9 g/day) over 3 menstrual cycles and over 6 menstrual cycles versus placebo in the double-blind, placebo-controlled efficacy studies (see Figure 1). The change in MBL from baseline was similar across all post-baseline treatment cycles.

Figure 1: MBL Levels over Duration of Therapy



Source: Section 14.3 Summary of MBL Results- Lysteda label

6.1.10 Additional Efficacy Issues/Analyses (Meta-Analysis)

Meta-Analysis across MR-301 and MR-303:

The following are supportive efficacy analyses. For the efficacy meta-analysis, a baseline average MBL and a post-treatment average MBL was computed for each subject based on the baseline and Periods 1 to 3 of the treatment period. Use of only Periods 1 to 3 of post-treatment MBL data from the 6-month Study MR-303 facilitated endpoint data that was computed in a consistent manner across efficacy studies. The MBL endpoint was the change from baseline computed by subtracting the average post-treatment MBL (Periods 1 to 3) from the average pretreatment (baseline) MBL.

The meta-analysis of MBL consisted of the a between-treatment group comparison (3.9 g vs. placebo) of the mean change from pretreatment to treatment alkaline hematin MBL values using a meta-analysis of the combined data from Studies -301 and 303. Table 18 presents the summary of change from baseline MBL levels using the AHT method for the 3.9 g/day and 1.95 g/day active treatment and placebo groups in the meta-analysis; the individual study results are repeated for comparison.

Table 18: Change from Baseline MBL (mL) – mITT Population

Study	3.9 g/day				1.95 g/day				Placebo			
	N	Raw CFB Mean	SD	LS CBF Mean	N	Raw CFB Mean	SD	LS CBF Mean	N	Raw CFB Mean	SD	LS CBF Mean
MR-301	112	65.3	51.1	65.3	115	46.5	57.1	44.1	67	3.0	45.9	7.1
MR-303	115	69.8	64.8	66.4					71	11.2	36.6	16.1
Meta-analysis	227	67.6	58.4	64.9					138	7.2	41.4	11.2

Source: modified from the Applicant's ISE, pg 53 of 93 (Table 4.3-4).
 Values for MR-303 reflect only the first three menstrual cycles.
 MBL = menstrual blood loss; CFB = change from baseline; LS = least squares;
 mITT = modified intent-to-treat; SD = standard deviation

Reviewer's comments:

Looking at the combined meta-analysis data, the raw mean change (reduction) from baseline in MBL, using a meta-analysis, was 67.6 mL for the 3.9 g/day active treatment, compared to 7.2 mL for the placebo group. For this dose, the treatment effect (change from baseline for the 3.9 gram arm minus that for the placebo arm) exceeded the agreed-upon 50 ml criterion for study success. It is important to note that the data here demonstrates that both Studies -301 and -303 had similar treatment effects, so the meta-analysis results are not driven by the results from primarily one study.

Table 19: Statistical Significance for Efficacy Endpoint Change from Baseline

Study	3.9 g/day vs. Placebo		1.9 g/day vs. Placebo	
	Treatment Effect*	P-value	Treatment Effect	P-value
MR-301	58.26	< .0001	37.01	< .0001
MR-303	50.25	< .0001		
Meta-analysis	53.75	< .0001		

Source: modified from the ISE, pg 53 of 93 (table 4.3-4).
 *Treatment effect = least square means change from baseline for the 3.9 gram arm minus that for the placebo arm.

Reviewer's comments:

For Studies MR-301 and -303, the treatment effect of the 3.9 g/day tranexamic acid dose vs. placebo (least squares mean change from baseline for the 3.9 g/day active treatment group minus that for the placebo group) was statistically significant (58.3 mL [p <0.0001])

and 50.3 mL [$p < 0.0001$], respectively). Using a meta-analysis, the treatment effect of the 3.9 g/day tranexamic acid dose vs. placebo was also statistically significant (53.8 mL [$p < 0.0001$]).

The treatment effect of the 1.95 g/day XP12B-MR dose vs. placebo (least squares mean change from baseline for the 1.95 g/day active treatment group [only in Study MR-301] minus that for the placebo group) was 37.0 mL and statistically significant ($p < 0.0001$). Although this effect does not meet all the criteria required for success, I believe this information would be helpful if it is included in the approved product label.

Study MR-302:

Study MR-302 was a separate, on-going, long-term (27-cycle), open-label, nonrandomized, multicenter, safety study of a 3.9 g/day dose of tranexamic acid administered for up to 5 days (maximum of 15 doses) for the reduction of blood loss in generally healthy women (age 18 to 50 years) with HMB. The study had a screening phase of one baseline menstrual period to determine eligibility, followed by a treatment phase of up to 27 menstrual cycles. This study was also designed to provide supportive evidence of efficacy and used the SF-36 and Ruta Menorrhagia Questionnaire (RMQ) to determine the effect of treatment on overall health-related quality of life (QoL). In addition, because HMB can lead to iron-deficiency anemia, hemoglobin and ferritin levels were evaluated as secondary efficacy endpoints to determine whether treatment with tranexamic acid reduced the incidence and extent of iron-deficiency anemia. A tertiary objective of this study was to establish the reliability, validity, ability to detect change, and interpretability of the MIQ™ patient reported outcome (PRO) questions that were used in the pivotal efficacy studies MR-301 and -303. The MIQ™ questions and the Menstrual Cycle Bleeding Diary to be utilized in the pivotal efficacy studies were evaluated for responsiveness (discussed in the MIQ PRO Validation Report).

In Study -302, the demographic and baseline characteristics were similar to those in the pivotal Phase 3 efficacy studies. The median age of subjects was 39 years. The median duration of HMB was 6.3 years. The majority of subjects were either Caucasian (75.7%) or black (20.5%), and 5.7% were self-reported as Hispanic or Latino. Approximately 17% of subjects were taking multivitamins and 8% of subjects were taking iron supplements.

Reviewer's comment:

Across the Applicant's Phase 3 program different methods were used to determine subject eligibility. In MR-301 and -303, subjects who had an average MBL =80 mL per period over the two pretreatment menstrual periods (as assessed by the AHT method) were eligible to participate. In contrast, the diagnosis of HMB in MR-302 was based on the medical judgment of the investigator after review of the subject's medical history. Additional screening parameters included the following: physical and gynecological examinations; clinical laboratory evaluation using blood chemistry, hematology, and urinalysis results; impact of menstrual bleeding on subject's ability to engage in normal activities; and menstrual period evaluation during screening. Despite the different criteria for enrollment, the demographic characteristics across all four Phase 3 studies

were very similar, so this reviewer concludes that the study populations are definitely comparable.

For the following SF-36 Health Survey component/concept scores, improvement (mean increase) from pretreatment was statistically significant at all time points (Cycles 1 through 15) for the following measures: mental component, vitality concept, social functioning, role-emotional concept, and mental health scores. The scores for the physical component, physical functioning, role-physical concept, and bodily pain, improvement (mean increase) from pretreatment was statistically significant at all but one of the time points. For the general health concept scores, improvement (mean increase) from pretreatment was statistically significant for treatment cycle 1, 2, and 3, but not for the later visits. The findings and the p-values for all the categories/domains of the SF-36 Health Survey are shown in Table 20 below based on the Applicant's analysis.

Table 20: SF-36 Health Survey Analyses (Study MR-302)

Category/Domain	Baseline (Visit 2) Mean	Change From Baseline on Treatment						
		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Physical Component Scores	51.06	-1.02 (<0.0001)	-0.80 (0.0028)	-1.26 (<0.0001)	-1.14 (0.0002)	-1.00 (0.0020)	-0.40 (0.2359)	-0.83 (0.0433)
Mental Component Scores	47.09	-2.42 (<0.0001)	-2.63 (<0.0001)	-2.56 (<0.0001)	-2.81 (<0.0001)	-2.54 (<0.0001)	-2.47 (<0.0001)	-2.56 (<0.0001)
Physical Functioning Component Scores	88.79	-1.88 (0.0026)	-2.14 (0.0012)	-2.47 (0.0004)	-2.57 (0.0010)	-2.43 (0.0038)	-2.26 (0.0121)	-1.48 (0.1637)
Role-Physical Concept Scores	79.86	-4.98 (<0.0001)	-4.23 (<0.0001)	-5.35 (<0.0001)	-5.25 (<0.0001)	-5.13 (<0.0001)	-2.26 (0.0610)	-4.33 (0.0021)
Bodily Pain Concept Scores	66.14	-4.00 (<0.0001)	-2.75 (0.0048)	-4.60 (<0.0001)	-4.93 (<0.0001)	-3.12 (0.0065)	-2.47 (0.0507)	-4.67 (0.0013)
General Health Concept Scores	77.96	-1.16 (0.0022)	-1.14 (0.0084)	-1.00 (0.0182)	-0.76 (0.1385)	-0.66 (0.2467)	0.04 (0.9455)	0.22 (0.7529)
Vitality Concept Scores	52.56	-6.15 (<0.0001)	-7.22 (<0.0001)	-7.83 (<0.0001)	-8.07 (<0.0001)	-7.68 (<0.0001)	-7.11 (<0.0001)	-7.22 (<0.0001)
Social Functioning Concept Scores	79.06	-6.11 (<0.0001)	-5.80 (<0.0001)	-6.50 (<0.0001)	-6.56 (<0.0001)	-6.29 (<0.0001)	-4.91 (<0.0001)	-6.92 (<0.0001)
Role-Emotional Concept Scores	83.96	-3.44 (<0.0001)	-3.67 (<0.0001)	-3.29 (0.0004)	-4.17 (<0.0001)	-3.47 (0.0024)	-2.81 (0.0148)	-3.77 (0.0082)
Mental Health Concept Scores	73.31	-3.24 (<0.0001)	-3.37 (<0.0001)	-3.51 (<0.0001)	-3.66 (<0.0001)	-3.23 (0.0002)	-3.50 (<0.0001)	-2.67 (0.0075)

Source: modified from the ISE, pg 75 of 93 (Table 4.3-3).

Visit 3 = Treatment cycle 1; Visit 4 = cycle 2; Visit 5 = cycle 3; Visit 6 = cycle 6; Visit 7 = cycle 9; Visit 8 = cycle 12; Visit 9 = cycle 15.

Note: The analyses were performed on the absolute change from baseline, which was defined as the value at baseline minus the value on treatment. A decrease from baseline is reflected in a positive numeric value, and an increase from baseline is reflected in a negative numeric value.

Reviewer's comment:

The SF-36 Health Survey and its analysis was a secondary endpoint and not essential for the approval of the NDA. Furthermore, the results will not be included in the approved label because they were considered to be only exploratory in nature in the extended trial. The overall result here is that the subjects had a positive response during the extended 27-month MR-302 trial for the mental and physical scores. There was a positive response (statistically significant) on the general health concept score, but only for the first three treatment cycles.

Improvement (mean reduction) from pretreatment for all Ruta Menorrhagia Instrument scores (global score, physical function score, and social function score) was statistically significant at all time points (Visits 3 through 9) as shown in Table 21 taken from the Applicant's ISE.

Table 21: Ruta Menorrhagia Instrument Analyses (Study MR-302)

Category/Domain	Baseline (Visit 2) Mean	Change From Baseline on Treatment					
		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit
Global Score	39.81	13.53 (<0.0001)	14.75 (<0.0001)	14.85 (<0.0001)	14.90 (<0.0001)	15.23 (<0.0001)	12.6 (<0.00)
Physical Function Score	29.24	15.62 (<0.0001)	17.86 (<0.0001)	16.61 (<0.0001)	17.77 (<0.0001)	17.63 (<0.0001)	15.9 (<0.00)
Social Function Score	51.00	27.65 (<0.0001)	30.77 (<0.0001)	31.27 (<0.0001)	31.80 (<0.0001)	32.57 (<0.0001)	28.5 (<0.00)

Source: modified from the ISE, pg 77 of 93 (Table 4.3-4).

Visit 3 = Treatment cycle 1; Visit 4 = cycle 2; Visit 5 = cycle 3; Visit 6 = cycle 6; Visit 7 = cycle 9; Visit 8 = cycle 12; Visit 9 = cycle 15.

Note: The analyses were performed on the absolute change from baseline, which was defined as the value at baseline minus the value on treatment. A decrease from baseline is reflected in a positive numeric value, and an increase from baseline is reflected in a negative numeric value.

Reviewer's comment:

The Ruta instrument and its analysis was a secondary endpoint and not essential for the approval of the NDA. Furthermore, the results will not be included in the approved label because they were considered to be only exploratory in nature in the extended trial. The statistically significant improvement in the three scores for the Ruta instrument provides further support for the clinical meaningfulness of the treatment effect seen with tranexamic acid. Both physical and social functioning are shown to be improved using the analysis of two key MIQ questions and will be labeled as such.

Study MR-304:

This was a multicenter, open-label extension study for subjects completing either MR-301 or MR-303. The study consisted of a treatment phase of nine menstrual periods to assess the safety of tranexamic acid at the daily oral dose of 3.9 g/day for up to five days during menstruation. Data from 221 subjects from 75 sites were included in the ITT analysis for the interim database freeze. There were no efficacy analyses in this study.

7 Review of Safety

Safety Summary:

The combined safety results from the eight clinical studies included in the Applicant's safety evaluation show an acceptable adverse event (AE) profile for tranexamic acid 650 mg tablets. The frequencies of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), gastrointestinal (GI) AEs, and ophthalmic AEs were similar between placebo and the two tranexamic acid treatment groups. No venous thrombotic or thromboembolic events were observed in subjects treated with tranexamic acid tablets. No systematic or clinically meaningful changes in clinical laboratory parameters were apparent, nor did tranexamic acid prolong the QT interval. Menorrhagia in subjects was diagnosed by physician criteria in Study MR-302, while in the randomized, controlled efficacy studies, measurement of menstrual blood loss (MBL), as determined by the quantitative alkaline hematin method, exceeding an 80 mL threshold was an additional eligibility requirement. The percentage of subjects experiencing AEs in the active treatment groups among the two short-term exposure efficacy studies and two long-term exposure safety studies was similar. The safety data for the tranexamic acid tablet formulation used in the clinical studies for this NDA provide sufficient evidence for the short-term and long-term safety of Lysteda and that the benefit-risk ratio is acceptable in women age 18 to 50 with heavy menstrual bleeding (HMB) studied for up to 27 menstrual cycles. The findings that have been reported in the medical literature and postmarketing databases are supportive of a daily dose of 3.9 grams tranexamic acid for the treatment of menorrhagia, but are not critical for the approval of Lysteda's overall safety..

7.1 Methods

The integrated safety data were organized by the Applicant in short-term and long-term exposure groups. The short-term exposure group includes randomized subjects (1.95 g/day or 3.9 g/day tranexamic acid or placebo) from the 2 placebo-controlled studies (MR-301 and MR-303). The long-term exposure group includes all subjects who were exposed to 3.9 g/day tranexamic acid in any of the four Phase 3 studies. Within-group changes over time were analyzed for each safety parameter using the given group of subjects. Subjects who participated in the 3.9 g/day dose group during either Study MR-301 or -303 and then participated in the 3.9 g/day dose group during Study MR-304 have their exposure marked as a consecutive set of cycles across both studies and are not double counted.

Reviewer's comment:

Data from the two safety report updates that were submitted on 4-30-09 and 9-28-09 were analyzed by the Cross-Discipline Team Leader (CDTL) Dr. Soule and did not change the safety data or the conclusion that the 3.9 g/day dose is safe.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety database is from the four Phase 3 studies. Safety data from all four Phase 3 tranexamic acid studies (MR-301, -302, -303, -304) were integrated into a single pooled database. Safety data from the four Phase 1 studies were not included in the integrated summary of safety (ISS) database, but are individually summarized and **discussed in the Applicant's NDA submission.**

7.1.2. Categorization of Adverse Events

Short-term Exposure:

All AEs for the Phase 3 studies included in the integrated database were coded using a Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary, version 7.1. The effect of short-term exposure to tranexamic acid on the frequency of AEs was summarized using counts and percentages of subjects who experienced an AE during the Treatment Period, by dose group and overall, using MedDRA System Organ Class (SOC) and Preferred Term (PT). Three additional tables were constructed for the following sets of AEs:

- **Treatment-emergent adverse events (TEAEs) that occurred during dosing**
- **TEAEs that occurred during a subject's menstrual period**
- **TEAEs that did not occur during dosing or during a subject's menstrual period**

The same three short-term exposure AE tables were repeated for summaries by severity (mild, moderate, or severe) and causality (possibly, probably, or definitely related; probably not, or definitely not related). Subgroup analyses were also conducted by age and race.

Long-term Exposure:

The effect of long-term exposure to tranexamic acid on AEs was summarized by the count and percentage of subjects with a first report of a TEAE during 1 of the 4 treatment cycle epochs or intervals (e.g., cycles 1-6, 7-12, 13-18, or 19-27), when using the MedDRA SOC and PT system for analysis of AEs.

Reviewer's comment:

It is important to note that clinical Studies MR-302 and -304 were ongoing at the time of the NDA submission. For these studies, the initial NDA submission includes all case report form (CRF) data for subject visits occurring through approximately 30 May 2008. An initial interim database freeze occurred on 28 July 2008 for both of these ongoing studies. Between 30 May 2008 and 28 July 2008, the interim databases were cleaned. Discrepancies from these interim data are present between CRFs, databases, and clinical study reports for Studies MR-302 and -304. As a result, in some cases, the narratives for subjects who experienced an SAE or who were withdrawn from the study due to an AE are more complete and contain current information that is not reflected in the CRFs, databases, tables, and listings in the Applicant's ISS at the time of the original submission (1-30-09). Also, because of the timing of the data loads with respect to the database locks for Studies MR-302 and -304, data for the electrocardiogram (ECG) and

clinical laboratory parameters were, at the original submission time, more complete (up-to-date) than the data for the AEs recorded on the CRFs.

The Applicant submitted two safety updates. The first was the required Safety Update received on 4-30-09, and the second was requested by the Division to include the final data from Studies 302 and 304 and was received on 9-28-09.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

As noted in Section 7.1.1 above, safety data from all four Phase 3 tranexamic acid studies (MR-301, -302, -303, -304) were integrated into a single pooled database. This was agreed to at one of the pre-NDA meetings with the Division.

7.2 Adequacy of Safety Assessments

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

Analyses for both safety population groups were performed on the intent-to-treat (ITT) population only. The ITT population included all randomized subjects who ingested at least one dose of study medication. In the four Phase 3 studies, 1,205 ITT subjects treated for 11,704 cycles were eligible for inclusion in the original ISS analyses. Of these 1,205 ITT subjects, 486 were included in the short-term exposure group and 1101 were included in the long-term exposure group. A small number of subjects (approximately 18) experienced AEs that started in either Study MR-301 or 303 and continued into extension Study MR-304; these AEs were not counted twice.

Table 22: Exposure Groups in Phase 3 Clinical Studies

Final Exposure Data

Exposure Group	Study MR-301	Study MR-302 (up to 27 cycles)	Study MR-303	Study MR-304
Short-term N = 486 (all subjects)	297		189	
Long-term N = 1,310 (3.9 g/day use)	118	723	123	260

Source: from the Applicant's Final Safety Update 9-28-09.

Table 23: Extent of Exposure Days to Tranexamic Acid 3.9 g/day

Summary Statistic	Study MR-301 (3 cycles)	Study MR-303 (6 cycles)	Long-term studies (up to 27 cycles)
		N = 115	N = 116
Total exposure days	1,094	2,135	35,304 ^B
Average # of exposure days/subject	9.51	18.41	33.21
Average # of exposure days/cycle	3.39	3.42	3.02
Average dose taken per day during exposure	3.72 g/day	3.76 g/day	3.80 g/day

Source: modified from the Applicant's Summary of Clinical Safety, pg 9 of 23 (Table 2.2-1).

^A N = 1,101 ITT subjects in this category, but 38 subjects took tablets and no dates were recorded so the N is corrected to 1,063.

^B This exposure is rounded to the nearest 1/3 of a day for each subject.

Reviewer's comment:

The final exposure data are discussed in the CDTL review. The total exposure presented here (based on the original NDA submission) in the long-term studies represents approximately 11,690 menstrual cycles or 900 women-years of use (assuming 13 cycles per year). This exceeded what was requested by the Division (10,000 cycles and as least 200 women completing one year of treatment). The exposure also approximated ICH guidelines for drugs to be used on a chronic basis (1,500 subjects total, 600 for six months and 100 for 12 months).

It is interesting to note that for all of the groups listed in the table, the average number of exposure days per menstrual cycle ranged from 3 to 3.4 days, although the treatment may be taken for up to 5 consecutive days. This demonstrates to me that the subjects did not arbitrarily use tranexamic acid for the allowable 5 days, but used their judgment for when to stop the medication. In the long-term studies, the average use of tranexamic acid was 11 menstrual cycles which is acceptable for long-term (chronic) use of a medication that is not taken every day continuously, but is taken on average for 3-3.4 days every 28 days.

In the Statistical Safety Review by Olivia Lau, PhD, from the Division of Biometrics VII, she concluded that "the randomized studies are insufficiently powered to detect safety outcomes" and that the long term studies resulted in "insufficient data to adequately assess the long term safety implications of chronic exposure to tranexamic acid." The Division (DRUP) and I definitely do not agree with this conclusion. The Division requested 10,000 cycles of use, 200 women completing one year of treatment, while the Applicant provided over 12,000 cycles of use, 387 subjects completing one year, and 227

women completing two years of treatment. The studies were adequately powered for efficacy and were not intended to be powered for quantitative safety endpoints. In addition to the clinical trials performed for this NDA submission, the Division will use and evaluate safety data from postmarketing experience and the medical literature. In his 10-27-09 secondary review (memo) concerning Dr. Lau's review, her Team Leader Paul Schuette, PhD, wrote "we defer to the review Division in this matter" referring to the adequacy of the data for long term safety. I believe that there is ample data from the clinical trials and other sources to perform an overall review of the safety for this product.

Demographics:

Across the Phase 3 clinical program, the mean age of subjects was similar in all 3 groups; 38.5, 40.2, and 38.9 years in the 3.9 g/day active treatment group, 1.95 g/day active treatment group, and placebo group, respectively. Subjects in the double-blind, placebo-controlled studies had a mean body mass index (BMI) of approximately 32 kg/m². Mean duration of HMB was 10.1, 12.1, and 10.0 years in the 3.9 g/day treatment group, 1.95 g/day treatment group, and placebo group, respectively. Across all groups, approximately 66% to 74% of subjects were white and approximately 21% to 29% of subjects were black. Asian, Native American, Pacific Islander, and Other were represented by <4% of subjects. Tobacco and alcohol use were similar among the treatment groups. Although 36% of subjects overall had a history of tobacco use, 78% of subjects were not currently using tobacco. Current use of alcohol was reported by 53% of subjects. Fibroids were present in 41%, 38%, and 36% of subjects in the 3.9 g/day active treatment group, 1.95 g/day active treatment group, and placebo group, respectively.

Reviewer's comment:

Several factors are reassuring concerning the demographics:

1. The mean age (~39 years) represents women who might not want or need hormonal contraception, but who clearly have a need for a medical treatment for their menorrhagia.
2. The mean BMI (~32 kg/m²) demonstrates that heavier women were included in the trials.
3. Fibroids were relatively common in the women, so the medical treatment will be an option for women with fibroids who experience HMB.
4. A significant number of African-American women were enrolled which is often not the case in clinical trials. Fibroids are more common in African-American women compared to Caucasians, so it is important that this population was included.
5. The 10+ years mean duration of HMB demonstrates that the women in the trials were being treated for a chronic condition and presumably will take the tranexamic acid for chronic use unless other medical or surgical measures are taken.
6. Alcohol and tobacco use were allowed during the trials.

7.2.2 Explorations for Dose Response

As noted earlier, Study MR-301 explored the safety and efficacy of 1.95 and 3.9 g/day (administered as 0.65 gram and 1.3 grams tranexamic acid three times a day) for menorrhagia. Both doses were safe in the short study, but the lower dose failed to meet the three pre-specified primary endpoints, so the Applicant is seeking approval of the 1.3 gram dose taken three times a day for up to five days (i.e., 3.9 g/day).

7.2.3 Special Animal and/or In Vitro Testing

See the pharmacology-toxicology review by Kim Hatfield, PhD. Adequate pre-clinical testing was performed and there were no safety signals except for the ophthalmology signals in dogs. Further ophthalmological studies were performed in the clinical trials to assess the ophthalmological safety of tranexamic acid.

7.2.4 Routine Clinical Testing

Clinical Laboratory Evaluations:

From the Applicant's original Summary of Clinical Safety (pg 20 of 23), in the short-term exposure group, greater percentages of subjects with hemoglobin values below the normal range at baseline shifted to normal at the end of study visit for both MR-301 and MR-303 in the 3.9 g/day active treatment group compared with the placebo group. In the long-term exposure group, of hematology values below normal range, low hemoglobin was most commonly seen over the cycles analyzed (0, 6, 9, 15, and 27). The percentage of subjects with hemoglobin values below the normal range decreased over time, from 30.5% of subjects (329 of 1080) at cycle 0 to 21.4% of subjects (15 of 70) at cycle 27. The numbers of subjects with improvements in hemoglobin were greater in the long-term exposure group compared with the short-term exposure group, regardless of iron supplementation or multivitamin use; overall, the numbers were too small to determine if tranexamic acid had an indirect effect on improvements in hemoglobin levels. Although findings were mixed across the Phase 3 program regarding improvements in iron deficiency anemia, this is not entirely unexpected due to the design of the Phase 3 studies: Iron supplementation could have been initiated at the Investigators' discretion if the subjects' hemoglobin was <12 g/dL at enrollment or if subjects' hemoglobin declined <11 g/dL while on study. Furthermore, diet was not controlled in the Phase 3 program and few women were anemic at study entry in the Phase 3 clinical trials.

In the short-term exposure group, greater percentages of subjects with ferritin values below the normal range at baseline shifted to normal at the end of study visit for both MR-301 and MR-303 in the 3.9 g/day active treatment group compared with the placebo group. Furthermore, in the long-term exposure group (on 3.9 g/day active treatment), for subjects with ferritin values below the normal range at baseline, the majority (58%) shifted to within normal range at the study termination visit. Changes in urinalysis and chemistry parameters were small and not clinically significant in the short-term or long-term exposure groups.

Reviewer's comments:

The general trend was that hemoglobin values stayed the same or improved over the duration of treatment with tranexamic acid. Obviously dietary factors and iron supplementation are significant confounding factors.

No clinically relevant shifts were observed from normal to abnormal across the studies between treatments for hematology or serum chemistry parameters. Two subjects on tranexamic acid had hypoglycemia that was reported as a serious adverse event, but the AE did not result in study withdrawal.

Vital Signs and ECG Evaluations:

No clinically significant changes in vital signs were noted among the treatment groups. There were no clinically significant ECG abnormalities noted. In addition, a formal QT prolongation study was performed and reviewed by the special QT review team at FDA. The study design was acceptable and the results showed no significant QT prolongation at both therapeutic and supra-therapeutic doses of tranexamic acid.

Reviewer's comment:

There are no safety signals here and no evidence that tranexamic acid has an adverse effect on vital signs or ECG results.

7.2.5 Metabolic, Clearance, and Interaction Workup

No special studies were performed for these categories. The data on lower dosing for women with renal impairment is based on previous data from the literature and other approved labels for tranexamic acid. The Division clinical pharmacology reviewer agrees with the dosing regimen as written in the approved Lysteda label.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following ADR report for tranexamic acid use in the UK from 1963 to January 2009 was reviewed and is shown in Table 24. The single active constituent is tranexamic acid and no concomitant medications were recorded here. So, the number of the total unique reports is the same as the single active constituent numbers.

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Table 24: United Kingdom Adverse Drug Reaction Data 1963-2009

Drug name:	TRANEXAMIC ACID	Report type:	Spontaneous
Report run date:	16-Jan-2009	Report origin:	UNITED KINGDOM
Data lock date:	15-Jan-2009 07:59:43 PM	Route of admin:	ALL
Period covered:	01-Jul-1963 to 15-Jan-2009	Reporter type:	ALL
Earliest reaction date:	01-Nov-1972	Reaction:	ALL
MedDRA version:	MedDRA 11.1	Age group:	ALL

System Organ Class	Single active constituent		Multiple active constituent		Total unique reports*	
	All	Fatal	All	Fatal	All	Fatal
Blood disorders	3	0	0	0	3	0
Cardiac disorders	17	1	0	0	17	1
Congenital disorders	2	0	0	0	2	0
Ear disorders	4	0	0	0	4	0
Eye disorders	48	0	0	0	48	0
Gastrointestinal disorders	53	2	0	0	53	2
General disorders	39	0	0	0	39	0
Hepatic disorders	3	0	0	0	3	0
Immune system disorders	1	0	0	0	1	0
Infections	3	1	0	0	3	1
Injuries	3	0	0	0	3	0
Investigations	8	0	0	0	8	0
Metabolic disorders	3	0	0	0	3	0
Muscle & tissue disorders	16	0	0	0	16	0
Neoplasms	2	0	0	0	2	0
Nervous system disorders	134	3	0	0	134	3
Psychiatric disorders	24	0	0	0	24	0
Renal & urinary disorders	6	1	0	0	6	1
Reproductive & breast disorders	5	0	0	0	5	0
Respiratory disorders	27	5	0	0	27	5
Skin disorders	48	0	0	0	48	0
Surgical & medical procedures	1	0	0	0	1	0
Vascular disorders	35	1	0	0	35	1

TOTAL NUMBER OF REACTIONS	485	14	0	0	485	14
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TOTAL NUMBER OF FATAL ADR REPORTS*		14		0		14*
TOTAL NUMBER OF ADR REPORTS*	293		0		293*	

Source: found by the medical officer on an EMEA website for tranexamic acid citing the UK experience.

Reviewer's comment:

Although there are 14 fatalities listed above, this report covers all uses of tranexamic acid in all age groups, men and women, with the first ADR report received in 1972 (37 years ago). The intravenous product in the UK is approved for short term use in prophylaxis and treatment in patients at high risk of peri- and post-operative hemorrhage and for treatment of hemorrhagic complications in association with thrombolytic therapy. The oral product is approved for short term use for hemorrhage or risk of hemorrhage in

conditions such as menorrhagia, prostate and bladder surgery, epistaxis, cervical conization, and dental extractions in hemophiliacs. From the data above there is no way of telling if 1) any of the fatalities were in women being treated for HMB (menorrhagia), 2) concomitant medications were in fact involved, and 3) there was causal relationship between the use of tranexamic acid and the death. Given the fact that tranexamic acid has been in use in the UK since 1963 and both the tablet and intravenous (IV) formulations are still on the market this reviewer considers the above data to be reassuring. The UK labels have been amended as recently as October 2007 and January 2008, respectively for the IV and oral products reflecting minor changes with postmarketing data.

Directly from the Australian label, last revised in March 2008:

Gastrointestinal discomfort occurs in more than 30% of patients after oral administration of 6 g/day. The discomfort disappears when the dose is reduced.

Common side effects (> 1/100) GI: Nausea, vomiting, diarrhea.

Less common side effects Skin: Allergic skin reactions

Rare side effects (< 1/1000): Thromboembolic events, impaired color vision and other visual disturbances. Exceptional cases of giddiness have been reported.

Reviewer's comment:

The Australian dose of 6 grams/day is higher than the US dose of 3.9 grams/day for the treatment of HMB. This reviewer does not agree with the statement that the common GI side effects will "disappear" when the dose is reduced, but does believe that the GI side effects will be less common or prominent when the dose is reduced.

7.3 Major Safety Results

7.3.1 Deaths

Three deaths occurred, 1 each during the screening period in studies MR-301 and -302, and 1 during Study MR-302 (subject 525-2005). Detailed narratives of the three deaths are included in the individual clinical study reports. No study drug was taken by the two subjects who died between screening and dosing. No additional deaths were reported in the 90-day Safety Update (4-30-09) and the second Safety Update (9-28-09).

Reviewer's comment:

The narrative and CRF for subject 525-2005 was thoroughly reviewed. The 32 year old woman had no significant medical history or ongoing medical conditions. She took tranexamic acid for 3 days for 3 menstrual cycles. She was admitted to the hospital with severe community-acquired pneumonia and overwhelming sepsis in _____; in the hospital she had a cardiac arrest followed by multi-system failures over the course of the next two weeks. **It is the Applicant's opinion and this reviewer's opinion that the death was not related to taking tranexamic acid. There was no evidence of a thromboembolic event (appropriate studies were negative). The subject was anticoagulated and did have**

b(6)

a venous filter inserted, but these procedures were prophylactic in light of her prolonged illness/immobilization and not in response to a documented thromboembolism.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

In the short-term 3-6 month exposure group (N = 486), eight subjects experienced eleven SAEs overall (4, 1, and 3 subjects in the 3.9 g/day, 1.95 g/day, and placebo groups, respectively).

In the long-term exposure group (exposure > 6 months), thirty seven (3.36%) of the 1,101 subjects experienced 53 SAEs, most of which were experienced by only a single subject per preferred term (PT). The most frequently reported SAEs occurred in the **system organ classes (SOCs) "infections and infestations" (n=7; 0.6%), "reproductive system and breast disorders" (n=10; 0.9%), and "nervous system disorders" (n=6; 0.5%).** The most frequently reported SAEs by PT were migraine and menorrhagia, reported by 3 and 6 subjects, respectively in the final safety update (9-28-09).

Reviewer's comment:

The SAEs were reviewed and the two most common (migraine and menorrhagia) were considered serious because the subjects visited an Emergency Room or were hospitalized. See section 7.3.4 for further discussion of potential clinically significant serious adverse events (SAEs).

Table 25: SAEs over all 4 Studies

Study #, Subject #	SAE (Bold = led to study discontinuation)	Study Drug	Severity	Reviewer Assessment of Association
Study 301				
301 752-1002	Dyspepsia	3.9 g/day	Hospitalization	Unlikely
	Gastritis	3.9 g/day	Hospitalization	Unlikely
	Chest pain	3.9 g/day	Severe	Unlikely
301 721-1008	Ovarian torsion	1.95 g/day	Hospitalization	Unlikely
Study 303				
303 619-3002	Tachycardia (SVT)	3.9 g/day	Hospitalization	Unlikely
303 633-3003	Blood sugar decreased	3.9 g/day	Life-threatening	Unlikely
303 653-3010	Menorrhagia	3.9 g/day	Hospitalization	Probable – lack of efficacy only 1 treatment cycle
303 616-3009	Acute bronchitis	Placebo	Hospitalization	Unlikely
	PTSD	Placebo	Hospitalization	Unlikely
303 626-3010	DVT	Placebo	Moderate	Unlikely
303 654-3003	Urticaria	Placebo	(omitted)	Unlikely
Study 302				
302 504-2002	Malaria	3.9 g/day	Hospitalization	Unlikely
302 504-2005	Ectopic pregnancy	3.9 g/day	Severe	Unlikely

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Study #, Subject #	SAE (Bold = led to study discontinuation)	Study Drug	Severity	Reviewer Assessment of Association
302 505-2001	Menorrhagia	3.9 g/day	Severe	Possible- poor efficacy (11 cycles of use)
	Anemia	3.9 g/day	Severe	
302 507-2005	Menorrhagia	3.9 g/day	Hospitalization	Probable – lack of efficacy
302 516-2005	Adenomyosis	3.9 g/day	Hospitalization	Unlikely
302 519 2006	Cholecystitis	3.9 g/day	Moderate	Unlikely
302 519-2040	Renal cell carcinoma	3.9 g/day	Hospitalization	Unlikely
302 519-2052	Migraine	3.9 g/day	Severe	
302 524-2022	Aseptic meningitis	3.9 g/day	Hospitalization	Unlikely
	Typical migraine	3.9 g/day	Hospitalization	Unlikely
302 524-2041	Colitis	3.9 g/day	Hospitalization	Unlikely
302 525-2005	Pneumococcal sepsis	3.9 g/day	Death	Unlikely
	Bilateral pneumonia	3.9 g/day	Death	Unlikely
	Cardiac arrest	3.9 g/day	Life-threatening	Unlikely
302 526-2018	Suicide attempt	3.9 g/day	Life threatening	Unlikely
302 529-2005	Dysmenorrhea*	3.9 g/day	Severe	Unlikely
302 530-2022	Seizure	3.9 g/day	Moderate	Possible
302 532-2017	Appendicitis	3.9 g/day	Hospitalization	Unlikely
302 532-2042	Migraine	3.9 g/day	Hospitalization	
302 536-2001	Depression	3.9 g/day	Hospitalization	Unlikely
302 536-2051	Ventral hernia	3.9 g/day	Hospitalization	Unlikely
	Abdominal wall abscess	3.9 g/day	Hospitalization	Unlikely
	Abdominal seroma	3.9 g/day	Hospitalization	Unlikely
	Abdominal wall abscess	3.9 g/day	Hospitalization	Unlikely
	Abdominal wall hematoma	3.9 g/day	Hospitalization	Unlikely
	Abdominal wall abscess	3.9 g/day	Hospitalization	Unlikely
302 536-2066	Enlarging uterine fibroids	3.9 g/day	Hospitalization	Unlikely
	Postoperative ileus	3.9 g/day	Hospitalization	Unlikely
302 543-2002	Fibroid uterus	3.9 g/day	Hospitalization	Unlikely
302 543-2005	Facial cellulitis	3.9 g/day	Hospitalization	Unlikely
302 547-2016	Syncopal episode	3.9 g/day	Severe	
302 552-2004	Finger cellulitis	3.9 g/day	Hospitalization	Unlikely
	Abscess	3.9 g/day	Hospitalization	Unlikely
302 555-2005	Asthma	3.9 g/day	Hospitalization	Unlikely
302 555-2011	Menorrhagia	3.9 g/day	Life-threatening	Possible – lack of efficacy (after 19

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Study #, Subject #	SAE (Bold = led to study discontinuation)	Study Drug	Severity	Reviewer Assessment of Association
				cycles of use)
302 560-2033	Depression exacerbation	3.9 g/day	Hospitalization	Unlikely
302 563-2040	Enlarging uterine fibroids	3.9 g/day	Hospitalization	Unlikely
302 563-2063	MRSA of clavicle	3.9 g/day	Hospitalization	Unlikely
302 565-2014	Ankle fracture	3.9 g/day	Hospitalization	Unlikely
302 565-2024	Astrocytoma	3.9 g/day	Severe	Unlikely
	Seizure	3.9 g/day	Severe	Unlikely
302 567-2010	Menorrhagia	3.9 g/day	Hospitalization	Possible – lack of efficacy (after 14 cycles of use)
302 571-2023	Intractable migraine	3.9 g/day	Moderate	Unlikely
	Brachial neuritis	3.9 g/day	Moderate	Unlikely
	Headache	3.9 g/day	Severe	Unlikely
Study 304				
304 633-3003	Hypoglycemia	3.9 g/day	Life-threatening	Unlikely
304 716-1007	Menorrhagia	3.9 g/day	Hospitalization	Possible – lack of efficacy (after 4 cycles of use)
304 755-1003	Menorrhagia	3.9 g/day	Hospitalization	Unlikely – occurred 12 days following first Rx cycle; underwent hysteroscopic polypectomy then hysterectomy
304 762-1001	Stomach cancer (carcinoid)	3.9 g/day	Severe	Unlikely
304 774-1004	Right pontine ischemic infarct	3.9 g/day	Life-threatening	Unlikely
	Calcified mid-basilar fusiform aneurysm	3.9 g/day	Life-threatening	Unlikely
	Trigeminal neuralgia	3.9 g/day	Moderate	Unlikely

Source: From the CDTL review- based on Table 12.3-2, p 66, Final Study report of Study 301, Table 12.3-2, p 63, Final Study report of Study 303, **Data Listing 26, pp 108 – 115 [Study 302]** and Data Listing 20, p 144 [Study 304], Applicant's submission of **September 28, 2009**.

Reviewer's comment:

The SAEs listed as the reason for withdrawal covered a wide range of conditions, including but not limited to: prolonged or dysfunctional or heavy menstrual bleeding, uterine pain, migraine headache, malaria, depression, staph infection, renal cell carcinoma, and pontine infarct.

Of the 42 women taking tranexamic acid and reporting at least one SAE, it appears that two subjects are probably related to study medication. Subject 303 653-3010 underwent an elective hysterectomy for menorrhagia after taking one cycle of treatment. This SAE

reflects a possible lack of efficacy rather than a safety concern; the pathology report revealed multiple uterine fibroids, the largest 3 cm. Subject 302 507-2005 underwent a vaginal hysterectomy secondary to menorrhagia following one cycle of treatment; she had been considering a hysterectomy prior to enrolling in the study. Both of these SAEs are considered likely attributable to lack of efficacy of Lysteda.

Subjects 302 505-2001, 302 555-2011, 302 567-2010 and 304 716-1007 are considered possibly related to lack of efficacy, although all took Lysteda for a number of cycles. It is unclear why Subject 302 555-2011 is considered to have experienced a “life-threatening” SAE, as she underwent an elective hysterectomy for long-standing menorrhagia.

Subject 302 530-2022 experienced a seizure five hours after taking her third day of dosing in her second cycle on treatment. She was evaluated by a neurologist who noted concomitant use of Welbutrin, which can lower the seizure threshold. She was further evaluated by a cardiologist, who diagnosed “convulsive syncope” on the basis of a positive tilt table test.

The most commonly reported SAEs include menorrhagia (7), migraine (4) and enlarging fibroids (3). Menorrhagia and fibroids would be expected in a population with HMB, particularly where fibroids were not an exclusion criterion. Migraine is relatively common in the population of reproductive-aged women, and is included in labeling, as it was also a common AE noted more often in Lysteda-treated women than placebo subjects (see Section 7.4.1 and Table 36).

In many cases the adverse events were not serious except for the fact that the subject was hospitalized. The other interesting observation is that only 19 of the 42 subjects (45%) actually discontinued from their trial due to the SAE.

7.3.3 Dropouts and/or Discontinuations

Subject Disposition:

Final disposition data for Study 301 and 303 are shown earlier in this review in Table 6 and Table 7.

Final disposition data for the much larger open-label and uncontrolled Study 302 and 304 are shown here in Table 26 and Table 27.

Table 26: Subject Disposition- Study 302

Outcome	N	%
Enrolled	781	100
Completed	239	30.6
Withdrawn	542	69.4
Failed to Return	156	20.0% of 781
Subject Request	116	14.9
Other	112	14.3
Adverse Event	97	12.4
Unsatisfactory Efficacy	30	3.8
Protocol Violation	30	3.8
Death	1	0.1

Source: Based on Table 16, p 3 of 16, Applicant's Submission of September 30, 2009

Table 27: Subject Disposition- Study 304

Outcome	N	%
Enrolled	288	100
Completed	196	68.1
Withdrawn	92	31.9
Failed to Return	45	15.6% of 288
Other	15	5.2
Unsatisfactory Efficacy	13	4.5
Subject Request	11	3.8
Adverse Event	6	2.1
Protocol Violation	2	0.7
Death	0	0.0

Source: Based on Table 1, p 13 of 16, Applicant's Submission of September 30, 2009

Reviewer's comment:

As would be expected, the withdrawal rate is much higher in the 27-month study than the 9-month extension study. The overall patterns are similar, with vague descriptions such as "failure to return" being the most common reason listed for early withdrawal, with "subject request" and "other" also being frequent. The occurrence of AEs leading to discontinuation was greater in the longer study. This is expected because more AEs would be expected with longer use, and because the shorter study was an extension study, so many of the subjects susceptible to drug-related AEs likely did not opt to continue into the trial.

The number of subjects enrolled, completed, and withdrawn (in descending order) in the four Phase 3 studies is presented in Table 28. Of a total 1,310 enrolled subjects, 48.2% completed the study in the 3.9 g/day active treatment group. The overall completion rate in the 3.9 g/day active treatment group reflects the greater number of subjects that discontinued from the 27-month Study MR-302 compared with the other Phase 3 studies. The number and percentage of subjects who withdrew from the four studies for any reason increased relative to the overall time commitment per protocol. For example, Study MR-301 (3 cycles) had the lowest attrition (12.7%), followed by Study MR-303 (23.6 % over 6 cycles), Study MR-304 (31.9% over 9 cycles), and Study MR-302 (69.4% over 27 cycles). Overall, for the 3.9 g/day treatment group with a total on 1,310 women enrolled and 678 withdrawals, the most frequently reported primary

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reason for withdrawal from the studies was “failure to return” (reasons listed included noncompliance, schedule conflicts, moving, too busy, lost to follow-up) .

Table 28: Subject Disposition in ITT Population on 3.9 g/day dose- all four studies

Outcome	N	%
Enrolled	1,310	100
Completed	632	48.2
Withdrawn	678	51.8
Failed to Return	217	32.0% of 678
Other	138	20.4
Subject Request	135	19.9
Adverse Event	107	15.8
Unsatisfactory Efficacy	43	6.3
Protocol Violation	37	5.5
Death	1	0.1

Source: reviewer’s composite table from Table 6, Table 7, Table 26, and Table 27 in this review.

Reviewer’s comment:

The data in the table here reflect a composite of the final data for the four Phase 3 trials. The data are hard to interpret, primarily because all the women who were exposed to the 3.9 g/day are lumped together whether they were exposed for 3, 6, 9, or up to 27 months. For the 1.95 g/day women, exposure was for only 3 months, and for the placebo group, exposure was for either 3 or 6 months. With the considerably longer exposure time to the 3.9 g/day dose, it is obvious that the expected number of adverse events (whether related to drug exposure or not), failure to return, and protocol violations will be larger. Thus, the low 48.2% completion rate for the women receiving 3.9 g/day tranexamic acid does not necessarily reflect a safety or efficacy concern. See Table 29 and Table 30 for a further breakdown of premature withdrawals by three-month intervals in the two long-term safety studies.

Table 29: Premature Withdrawals by 3-month Intervals (Study 302)

Reason for Withdrawal	Months 1-3		Months 4-6		Months 7-9		Months 10-12		Months 13-15		Months 16-18		Months 19-21		Months 22-24		Month 25-2
	N	%*	N	%*	N	%*	N	%*	N	%*	N	%*	N	%*	N	%*	N
N at start of interval (% of total N)	781	100	615	78.7	541	69.3	461	59.0	382	48.9	332	42.5	300	38.4	277	35.5	258
# Withdrawn	166	21.3	74	12.0	80	14.8	79	17.1	50	13.1	32	9.6	23	7.7	19	6.9	19
Failed to Return	64	8.2	25	4.1	20	3.7	14	3.0	12	3.1	6	1.8	4	1.3	5	1.8	6
Subject Request	31	4.0	14	2.3	16	3.0	25	5.4	16	4.2	5	1.5	2	0.7	4	1.4	3
Other	32	4.1	14	2.3	15	2.8	19	4.1	6	1.6	8	2.4	10	3.3	3	1.1	5
Adverse Event	26	3.3	11	1.8	18	3.3	13	2.8	10	2.6	6	1.8	5	1.7	5	1.8	3
Unsatisfactory Efficacy	3	0.4	5	0.8	4	0.7	7	1.5	4	1.0	4	1.2	1	0.3	1	0.4	1
Protocol Violation	10	1.3	4	0.7	7	1.3	1	0.2	2	0.5	3	0.9	1	0.3	1	0.4	1
Death	0		1	0.2	0		0		0		0		0		0		0

*% is based on N at start of interval

Source: CDTL review, based on Tables 16.1 – 16.9, pp 4- 12 of 16, Applicant's Submission of September 30, 2009

Table 30: Premature Withdrawals by 3-month Intervals (Study 304)

Reason for Withdrawal	Month 1-3		Month 4-6		Month 7-9	
	N	%*	N	%*	N	%*
N at start of interval (% of total N)	288	100	247	85.8	215	74.7
# Withdrawn	41	14.2	32	13.0	19	8.8
Failed to Return	23	8.0	14	5.7	8	3.7
Subject Request	5	1.7	5	2.0	1	0.5
Other	6	2.1	7	2.8	2	0.9
Adverse Event	1	0.3	2	0.8	3	1.4
Unsatisfactory Efficacy	6	2.1	4	1.6	3	1.4
Protocol Violation	0		0		2	0.9

*% is based on N at start of interval

Source: CDTL review, based on Tables 1.1 – 1.3, pp 14 -16 of 16, Applicant's Submission of September 30, 2009

Reviewer's comment:

Withdrawal patterns in the first 9 months of treatment showed a cumulative range of 25-31% withdrawals at 6 months and 31-41% at 9 months. Although the data here are difficult to interpret, relatively few discontinuations were recorded as due to AEs.

A general trend is seen with the proportion of withdrawals decreasing over time. Withdrawal due to unsatisfactory efficacy did not increase with time, which provides indirect evidence of the durability of treatment benefit. The predominant reasons for withdrawal were 1) failed to return, 2) subject request, and 3) other. Although these three reasons sometimes were also noted to be due to moving away, scheduling problems,

amenorrhea or irregular cycles, or pregnancy, it is possible that additional withdrawals were associated with adverse events.

Withdrawals due to Adverse Events:

The number of subjects who withdrew due to an adverse event is shown in Table 31 through Table 34.

Table 31: Adverse Events Leading to Withdrawal – Study 301

Preferred Term Total N= 297	1.95 g/day # Subjects withdrawing (Total 3 of 115 or 2.6%)	3.9 g/day # Subjects withdrawing (Total 1 of 115 or 0.9%)	Placebo # Subjects withdrawing (Total 1 of 67 or 1.5%)
Anemia (1)	1		
Headache			1
Myalgia		1	
Prolonged menstrual bleeding	1		
Worsening anemia	1		

Source: Section 14.2.2, pp 494-98, Final Study report of Study 301

Table 32: Adverse Events Leading to Withdrawal – Study 303

Preferred Term Total N= 189	3.9 g/day # Subjects withdrawing (Total 3 of 117 or 2.6%)	Placebo # Subjects withdrawing (Total 3 of 72 or 4.2%)
Abnormal uterine bleeding		1
Anemia		1
Elevated FSH	1	
Heart pounding	1	
Nausea		1
Rash	1	

Source: Section 14.2.2, pp 476-81, Final Study report of Study 303

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Table 33: Adverse Events Leading to Withdrawal – Study 302 (3.9 g/day)

Preferred Term [Bolded terms = SAE (# of reports)]	# Subjects withdrawing (Total 97 of 781 or 12.4%)
Headache (1)	9
Menorrhagia (3)	8
Menstrual disorder	5
Uterine leiomyoma (2)	5
Amenorrhea	3
Depression (1)	3
Migraine	3
Pregnancy	3
Rash	3
Diarrhea	2
Dizziness	2
Dysfunctional uterine bleeding	2
Dysmenorrhea (1)	2
Hemoglobin decreased	2
Hypertension	2
Irregular menstruation	2
Menstrual discomfort	2
Palpitations	2
Uterine polyp	2
Adverse events with only one report (in alphabetical order) Bolded terms were counted as SAEs	
Abdominal discomfort	1
Abnormal sensation in eye	1
Alopecia	1
Angle closure glaucoma	1
Astrocytoma	1
Benign intracranial hypertension	1
Cataract	1
Cervix smear abnormal	1
CVA	1
Dermal cyst	1
Dyspnea	1
Ectopic pregnancy	1
Esophageal discomfort	1
Fatigue	1
Gastritis	1
GGT increased	1
HPV positive	1
Irritable bowel syndrome	1
Macular hole	1
Malaria	1
Menopause	1
Nausea	1
Optic disc drusen	1

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Preferred Term [Bolded terms = SAE (# of reports)]	# Subjects withdrawing (Total 97 of 781 or 12.4%)
Partial seizures	1
Pelvic pain	1
Peripheral edema	1
Premenstrual syndrome	1
Renal cell carcinoma	1
Rheumatoid arthritis	1
R bundle branch block	1
Subcutaneous hemorrhage	1
Uterine pain	1
Vision blurred	1
Visual acuity reduced	1
Visual field defect	1

Source: From CDTL review- data listing 4.1, pp 53 to 62, Applicant's Submission of September 30, 2009

Table 34: Adverse Events Leading to Withdrawal – Study 304 (3.9 g/day)

Preferred Term [Bolded terms = SAE]	# Subjects withdrawing (Total 6 of 288 or 2.1%)
Brain stem infarction	1
Carcinoid tumor of stomach	1
Dyspnea/throat tightness	1
Hemoglobin decreased	1
Menometrorrhagia	1
Menorrhagia	1

Source: From CDTL review- data listing 2.1, p 130, Applicant's Submission of September 30, 2009

Reviewer's comment:

The case in Study 304 of dyspnea/throat tightness occurred in subject 724-1009, a 45 year old white subject who developed severe shortness of breath, facial flushing, and throat tightening on Day 4 of taking tranexamic acid. She was treated in the Emergency Room with oral lorazepam, and IV diphenhydramine and methylprednisone. After 6 hours of observation, she was sent home on prednisone 50 mg oral tablets x 5 days. This may represent a case of serious allergic reaction. One other case report of anaphylaxis associated with bolus intravenous administration of tranexamic acid was reported in the French medical literature (Ann Fr Anesth Reanim. 23: 607-09, 2004) in a 72 year old man undergoing cardiac surgery. .

Considering all the AEs that were recorded as the primary reason for withdrawal from the placebo-controlled and open-label studies, there do not appear to be any signals of concern except the case of dyspnea/throat tightness that occurred in Study 304. The approved label notes the potential concern for a severe allergic reaction, VTE, and visual and ocular events. The most common AEs occurring more frequently in Lysteda-treated subjects compared to placebo treatment are listed in the comparative Table 2 in the final label and are addressed in Table 36 of this review.

7.3.4 Significant Adverse Events:

Below are listed potentially significant adverse events considered by this reviewer to be possibly related to taking tranexamic acid during the four clinical trials. In the review by the statistical safety reviewer, Dr Olivia Lau, Ph.D., three possible venous thromboembolic events (VTEs) were assessed using only a Standardized MedDRA Query. Dr. Lau states that one VTE occurred in a subject randomized to tranexamic acid, and two in open-label subjects. She did not, however, review the actual CRFs or narrative summaries for these subjects. The Applicant reported that there were no venous thrombotic or thromboembolic events during the clinical trials, but there were two events that could be considered as possible vascular events, so further discussion is important for this category of serious adverse events.

Possible vascular events:

1. Right pontine ischemic infarct (Subject 304-774-1004) in a 32 year old with a documented calcified mid basilar artery **fusiform aneurysm (with three "daughter aneurysms") leading to the infarct and possible** trigeminal neuralgia. Extensive testing was performed; follow-up visits and information were reported to the study site. In the opinion of the investigator, **the DSMB, and the Applicant's medical officer**, this event was not a thromboembolic event and probably not related to tranexamic acid.
2. Blindness, transient (Subject 302-511-2023): the adverse event on Day 46 of the **study was described as "one second loss of vision."** This subject did not discontinue from the clinical trial, so her adverse event must not have been considered to be a significant clinical event or drug-related; otherwise, she would have been discontinued from the trial.
3. Abnormal Doppler: In Study 303, Subject 622-3009 was identified in Dr. Lau's review as a possible case of VTE, **due to a Preferred Term AE of "Ultrasound Doppler Abnormal."** Further investigation indicates that the verbatim term on the **Case Report Form was "uterus: axial 10-12 wks size; soft, slightly irregular contour."** This subject experienced a twin pregnancy on study, and her narrative makes no mention of any concern about a VTE. The ultrasound study was performed on the same day as her early termination visit due to the pregnancy. Thus, this does not appear to be a report of a venous Doppler study indicative of a possible DVT.

Reviewer's comment:

I disagree with Dr. Lau's statement that there were three VTEs in tranexamic acid subjects in the trials. I do not consider any of the events to be thromboembolic events or clearly related to the use of tranexamic acid. My assessment is that 1) the pontine infarct was directly related to the pre-existing calcified aneurysm, 2) the blindness was transient (lasting one second) and of undetermined etiology with the subject continuing in the trial, and 3) the abnormal Doppler ultrasound considered in the Lau review as a VTE was an abdominal ultrasound that did not demonstrate a thromboembolic finding, but did diagnose a twin pregnancy.

Cancer events:

1. Stomach carcinoid tumor (Subject 304-762-1001) in a 43 year old black woman after 6 treatment cycles. The subject was not taking any concomitant medications at the time of the diagnosis and was withdrawn from the study.
2. Renal cell carcinoma (Subject 302-519-2040) in a 38 year old woman after 24 treatment cycles. A right nephrectomy was performed in _____ and the subject was terminated from the study.
3. Glioma (astrocytoma) (Subject 302-565-2024) in a 40 year old after 18 treatment cycles. She had a seizure and an MRI and CT scan were performed; a biopsy showed an inoperable Stage II glioma and the subject was scheduled for treatment with radiation therapy and chemotherapy. She was terminated from the clinical trial.

b(6)

Infections:

1. Abdominal wall abscess (Subject 302-536-2051) in a 43 year old black woman two weeks after a hernia repair revision in _____. She was hospitalized again for the same abdominal abscess in _____. After 14 treatment cycles the subject remained enrolled in the study.
2. Aseptic meningitis (Subject 302-524-2022) in a 43 year old black woman after 19 treatment cycles. Spinal fluid showed WBC's but was negative for bacteria and TB.
3. Staph infection (Subject 302-563-2063) of the clavicle in a 44 year old woman after 21 treatment cycles. It is unlikely that the infection is related to taking tranexamic acid.

b(6)

Other:

1. Pseudotumor cerebri (Subject 302-548-2043) in a 38 year old white woman after five treatment cycles. She was noted to have left eye papilledema on eye exam, moderate in severity, and probably not related to study medication. No further information is available.

Reviewer's comment:

Although it is difficult to ascertain if the above events are related to the use of tranexamic acid, it seems unlikely. It is important to note that the treatment is taken on average only 3-4 days per month, so the subjects are not exposed to tranexamic acid continuously. Moreover, the three cancers and infections do not appear to be anatomically related to each other except for possibly the clavicle and abdominal wall infections.

Allergic Reaction:

1. (Subject 304-724-1009) - is a 45 year old nurse who completed 3 cycles taking 3.9 g/day in Study 301 and then started in Study 304 in September 2007. She

took tranexamic acid at doses varying from 1.3 to 3.9 g/day between September 20-24 with the last recorded dose taken at 7:45 am on the 24th. While at work on _____, she experienced a "full sensation in the throat, intermittent tingling sensations throughout her body, facial flushing, palpitations, and some shortness of breath" and was taken to the Emergency Room (ER) at 2 pm for further evaluation. She denied chest tightness, wheezing, facial or tongue swelling, rash or pruritus, feeling faint. Her BP remained normal or elevated, pulse normal or elevated, and all lab parameters (cardiac, chemistries, CBC, Chest X-ray, and ECG) were normal, except to note the tachycardia. She was treated for an "allergic reaction" with lorazepam 1mg po x1, diphenhydramine 25 mg IV x1 and methylprednisolone 125 mg IV x1, and was observed until ~8 pm / _____, and then discharged to home after approximately 6 hours in the ER. Discharge medications included prednisone 50mg tabs po x 5 days. Also, diphenhydramine and an epinephrine 0.3mg IM pen PRN were dispensed for difficulty breathing (only if such a reaction occurred again). The final impression of the ER physician was an allergic reaction and possible adverse medication reaction.

b(6)

b(6)

Reviewer's comment:

I have reviewed the additional information submitted by the Applicant on 10-30-09, which included the following:

1. Note by the Clinical Research Coordinator of a phone call received from the subject 45 minutes before the ER visit and another note made two days later
2. ER medical records
3. Note by the Independent Medical Monitor, _____, who concluded that this was not an acute allergic reaction to tranexamic acid; he actually recommended a rechallenge test if the subject volunteered to do so
4. Applicant's summary of the subject's medical history, dosing history, ER visit, and additional information

b(4)

The main differential diagnosis in this case is between a panic attack (for which there is a bonafide past history) or an allergic reaction. In any case, I do not believe this was an anaphylactic reaction or a severe (life-threatening) reaction.

On 10-30-09, the Applicant also submitted global postmarketing data regarding reports of severe allergic or anaphylactic reactions to tranexamic acid, whether given orally or intravenously. A recent IMS MIDAS data query suggests that approximately _____ worldwide prescriptions for tranexamic acid are written per year. The World Health Organization safety database from 1969 to August 2009 included 857 unique adverse events for tranexamic acid; of these, 80 are compatible with some form of an allergic reaction with 21 being recorded as either "anaphylactic shock, anaphylactoid reaction, or shock."

b(4)

On 11-02-09, the Applicant submitted a 52-page summary of other subjects in the clinical trials who experienced any level of allergic, hypersensitivity or anaphylactic reactions to Lysteda in the clinical trials, regardless of whether they were considered SAEs. Other than subject 724-1009 above, there were 12 subjects out of 1,205 women who possibly had an allergic reaction to Lysteda while taking the drug. Four subjects withdrew from

the trial because of the “moderate severity” adverse event, while 8 continued in the trial (5 with “mild” and 3 with “moderate” severity reactions). It is difficult to determine if these reactions were truly allergic reaction to tranexamic acid. There were no cases of anaphylaxis as determined by the Applicant. There were also 33 subjects for whom the onset and duration of their adverse events did not coincide with Lysteda dosing, so the Applicant believed these events were not attributable to taking Lysteda. I agree that there were no cases of anaphylaxis and that the 33 cases with possible allergic type reactions should not be attributed to Lysteda.

On 10-29-09 the Division sent to the Applicant some suggested changes to the label concerning the possibility of hypersensitivity to Lysteda. The changes were placed in the following sections of the label: 1) Contraindications, 2) Warnings and Precautions, 3) Adverse Reactions and 4) patient labeling. I agree that there need to be statements in the label about not prescribing Lysteda to women with a known hypersensitivity to tranexamic acid, and information about the possibility of severe allergic reaction to Lysteda. Final wording was agreed to on November 06, 2009.

7.3.5 Submission Specific Primary Safety Concerns

There were three specific areas with potential safety concerns based on pre-clinical and postmarketing data. These topics are covered in this review in the sections noted here: incidence of VTE (7.7 and 8.0), ophthalmologic AEs (7.4.5), and QT changes on ECGs (7.4.4). The final label addresses these issues in the sections titled Contraindications, Warnings and Precautions, Postmarketing Experience, and Clinical Pharmacology.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Selected, first reported, dosing-emergent, and related (possibly, probably, or definitely) AEs in the short-term exposure studies are summarized in Table 35. Headache and nausea were the most frequently reported dosing-emergent AEs related to study drug in all treatment groups. The percentages of subjects reporting these AEs were similar among treatment groups. Abdominal pain, dizziness, and vomiting were reported by small percentages of subjects, such that no patterns within or among treatment groups were detected with those AEs as well.

In the long-term exposure group, by first report of an AE, most GI AEs, assessed to be probably or possibly, or definitely related to study drug, were reported by less than 2% of subjects across cycles 0-27, except for nausea and diarrhea. The percentage of subjects first reporting GI adverse events decreased as cycles progressed (see Table 36).

Table 35: Treatment-Related AEs in Studies 301 and 303

MedDRA Coded (a) Adverse Event	3.9 g/day XP12B-MR N=232 n (%)	1.95 g/day XP12B-MR N=115 n (%)	Placebo N=139 n (%)
Headache	22 (9.48)	12 (10.43)	15 (10.79)
Nausea	12 (5.17)	6 (5.22)	6 (4.32)
Abdominal pain (b)	9 (3.88)	3 (2.61)	4 (2.88)
Dizziness	2 (0.86)	3 (2.61)	3 (2.16)
Vomiting	3 (1.29)	0	1 (0.72)

Source: Section 5.3.3.3 in Applicant's ISS, Appendix 2.2, Table 54.

(a) MedDRA Coding Version 7.1; (b) Combines preferred terms abdominal pain, abdominal pain upper, and abdominal pain lower.

Reviewer's comment:

As can be seen in the table here, the most common adverse events that were believed to be at least possibly related to treatment show no major difference between the 3.9 g/day dose and placebo. What is difficult to explain are the women taking the lower tranexamic acid dose, yet experiencing a slightly higher percentage of headache, nausea, and dizziness, although the difference is not statistically significant and probably not clinically significant.

Common AEs occurring at any time in $\geq 5\%$ of subjects taking Lysteda in the two long-term studies are listed in Table 36.

Table 36: AEs in ≥ 5% of Subjects Taking Lysteda – Studies 302 and 304

Preferred Term	N	%
Study 302 (27 months, Safety Population N=723)		
Headache + tension headache	448	62.0
Menstrual discomfort + dysmenorrhea	438	60.6
Back pain	227	31.4
URI + viral URI	205	28.4
Abdominal discomfort + pain + pain lower + pain upper + tenderness	199	27.5
Sinusitis + acute sinusitis + sinus headache	165	22.8
Musculoskeletal pain + discomfort + myalgia	158	21.9
Nasal congestion + nasal discomfort + respiratory tract congestion + sinus congestion	157	21.7
Arthralgia + joint stiffness + joint swelling	115	15.9
Multiple allergies + seasonal allergies	105	14.5
Nausea	104	14.4
Throat irritation	100	13.8
Diarrhea	88	12.2
Cough + productive cough	81	11.2
Migraine	78	10.8
Insomnia	74	10.2
Neck pain	61	8.4
Dyspepsia	60	8.3
Fatigue	57	7.9
Cystitis + UTI	56	7.7
Vaginal candidiasis + vaginal infection + genital infection fungal + vaginitis + vaginitis bacterial	54	7.5
Muscle cramp + muscle spasms	52	7.2
Dizziness + dizziness postural	52	7.2
Post-procedural pain	51	7.1
Vomiting	43	5.9
Toothache	42	5.8
Menorrhagia	40	5.5
Study 304 (9 months, Safety Population N= 260)		
Menstrual discomfort + dysmenorrhea	125	48.1
Headache + tension headache	116	44.6
Back pain	60	23.1
Sinusitis + acute sinusitis + sinus headache + allergic sinusitis + sinus pain	44	16.9
Abdominal discomfort + pain + pain lower + pain upper	43	16.5
URI + viral URI	40	15.4
Nasal congestion + respiratory tract congestion + sinus congestion	27	10.4
Musculoskeletal pain + discomfort + myalgia	24	9.2
Multiple allergies + seasonal allergies	22	8.5
Migraine	20	7.7
Nausea	17	6.5
Arthralgia + joint stiffness	16	6.2
Flu-like illness	15	5.8

Source: From the CDTL review- Table 17, pp 23 - 50, and Table 2, pp 117-128, Applicant's Submission of September 30, 2009.

Reviewer's comment:

Here again it is hard to interpret the findings. The listed AEs occurred at any time during the extended trials and are not considered to be necessarily due to tranexamic acid. Furthermore, the women in the trials took tranexamic acid on average for < 4 days per menstrual cycle and not continuously throughout the cycle. The pattern and relative frequency of AEs are similar in the two extended uncontrolled safety studies, although, as would be expected, the overall numbers are higher in the longer study, Study 302. The ten most frequent AEs are virtually identical in both groups and represent conditions likely to be commonly experienced in the general population.

Looking at the AE profiles over all four studies, it appears that the most common AEs likely to be related to Lysteda exposure are:

- headache/tension headache (40-59% of Lysteda subjects)
- back pain (17-29% of Lysteda subjects)
- musculoskeletal pain/discomfort/myalgia (8-20% of Lysteda subjects)
- muscle cramps/spasm (5-8% of Lysteda subjects)
- arthralgia/joint stiffness/joint swelling (4-15% of Lysteda subjects)
- fatigue (4-7% of Lysteda subjects)

For labeling, AEs that were reported by at least 5% of Lysteda subjects and more frequently than in placebo-treated subjects are presented in tabular form (with slightly different formatting) using the pooled data from the two short-term placebo-controlled studies for the 3.9 g/day Lysteda vs. placebo arms, as shown in Table 37 below.

Table 37: AEs Reported by ≥ 5% of Lysteda Subjects and More Often than in Placebo

Preferred Term	Lysteda 3.9 g/day N=232		Placebo N=139	
	N	%	N	%
Headache + tension headache	117	50.4	65	46.8
Sinus/nasal/allergy	59	25.4	24	17.3
Back pain	48	20.7	21	15.1
Abdominal discomfort/pain/ pain lower/pain upper/ tenderness	46	19.8	25	18.0
Musculoskeletal pain/ discomfort/myalgia	26	11.2	4	2.9
Arthralgia/joint stiffness/joint swelling	16	6.9	7	5.0
Muscle cramps/spasm	15	6.5	8	5.8
Migraine	14	6.0	8	5.8
Anemia	13	5.6	5	3.6
Fatigue	12	5.2	6	4.3

Source: From the CDTL review, section 8.2, Common Adverse Events

Reviewer's comment:

Table 2 in the final label for Lysteda Table 2 contains the above table information, but in a slightly different format

7.4.2 Laboratory Findings

Hemoglobin values:

In the short-term exposure group, greater percentages of subjects with hemoglobin values below the normal range at baseline shifted to normal at Visit 5 (MR-301) or Visit 8 (MR-303) in the 3.9 g/day active treatment group compared with the placebo group. In the long-term exposure group, of hematology values below normal range, low hemoglobin was most commonly seen over the cycles analyzed (0, 6, 9, 15, and 27). The percentage of subjects with hemoglobin values below the normal range decreased over time, from 30.5% of subjects (329 of 1080) at cycle 0 to 21.4% of subjects (15 of 70) at cycle 27. While the numbers of subjects with improvements in hemoglobin were greater in the long-term exposure group compared with the short-term exposure group, regardless of iron supplementation or multivitamin use; overall, the numbers were too small to determine if tranexamic acid had an indirect effect on improvements in hemoglobin levels. Although findings were mixed across the Phase 3 program regarding improvements in iron deficiency anemia, this is not entirely unexpected due to the design of the Phase 3 studies: Iron supplementation could have been initiated at **the Investigators' discretion if the subjects' hemoglobin was <12 g/dL at enrollment or if subjects' hemoglobin declined to <11 g/dL while on study.** Diet was not controlled in the Phase 3 program and few women were anemic at study entry in the Phase 3 clinical trials.

Reviewer's comment:

Based on the Applicant's summary of hemoglobin data stated above, it is certain that no labeling claims can be made concerning the amelioration of anemia with the treatment by tranexamic acid. Similar trends were seen with ferritin values which were likewise followed in the studies.

7.4.3 Vital Signs

No clinically meaningful changes in vital signs were noted among the treatment groups in the short term and long term studies.

Reviewer's comment:

After reviewing the data for vital signs, this reviewer agrees with the Applicant's conclusion.

7.4.4 Electrocardiograms (ECGs)

There were no clinically meaningful ECG abnormalities noted in the two clinical trials. In addition, the thorough QT prolongation study showed no effect on both therapeutic and supra-therapeutic doses of tranexamic acid on the QT interval.

Reviewer's comment:

The designated QT Interdisciplinary Review Team within the Agency's Division of Cardiovascular and Renal Products evaluated the TQT single-center, randomized, blinded, placebo- and active-controlled crossover study in 48 subjects. The dose selection was considered reasonable. Their conclusion agrees with the Applicant's that no significant ECG abnormalities or prolongation effects were associated with the use of tranexamic acid (1300 mg and 3900 mg). The following text is the QT Interdisciplinary Team's recommendation for the proposed label:

"In a randomized, placebo- and active-controlled crossover study, 48 healthy female subjects were administered a single oral dose of LYSTEDA 1300 mg, LYSTEDA 3900 mg (3 times the recommended dose), placebo, and moxifloxacin 400 mg. At both LYSTEDA doses, there was no significant effect on the QTc interval. At the 3900 mg dose, peak tranexamic acid concentrations were approximately 2-fold higher than peak concentrations following a 1300 mg dose."

7.4.5 Special Safety Studies/Clinical Trials

Ocular Adverse Events:

The Applicant believes that no patterns or differences between treatment groups were detected in the two randomized studies, because the numbers of subjects reporting ocular AEs (eye disorders SOC) that were at least possibly related to treatment were small, with 2 subjects (0.9%) reporting AEs in the 3.9 g/day active treatment group, 0 subjects reporting in the 1.95 g/day active treatment group, and 4 subjects (2.9%) reporting in the placebo group. However, since many more ocular adverse events were reported overall, and retinal changes were seen in long-term toxicity studies in dogs and cats, and impaired color vision and other visual disturbances have been reported with the use of tranexamic acid, the Division requested three separate consults from the following Agency sources:

1. Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance II (DPV II)
2. Safety Statistical team in the Division of Biometrics VII
3. Division of Anti- Infective and Ophthalmology Products (DAIOP)

DPV II consult:

DPV II found that the FDA AERS database contains 7 cases of possible ophthalmological adverse events associated with tranexamic acid (Cyklokapron®). Serious ophthalmological events possibly associated with oral tranexamic acid use requiring interventions and leading to disabilities have been reported but are poorly characterized and lack formal ophthalmological testing. However, the previous FDA labeling for oral tranexamic acid and the current labeling for intravenous tranexamic acid (Cyklokapron®) includes a Warning for ophthalmological adverse events. DPV II believes warnings of ophthalmological events **should also be added to the Lysteda™** label. DPV II initially recommended that the Applicant include visual abnormalities and an ophthalmological examination advisory in the Warnings and Precautions section of **the proposed label for Lysteda™**. However, following further review of information provided by the Applicant (discussed further below), DPV II agreed with DRUP and Dr. Chambers that visual examinations in the absence of symptoms did not need to be recommended in labeling.

Reviewer's comment:

DPV II reviewed only the postmarketing reports in the AERS database. Because tranexamic acid has had very limited use in the US and for a totally different patient population and indication, the above findings and recommendations are of limited value. Of greater relevance are the recommendations of the Ophthalmology consult discussed below.

Safety Statistical Team:

The primary reviewer Olivia Lau, PhD, reported the following ophthalmic events:

1. Visual acuity was the most common event in the two 3-6 month randomized studies: 9.7% of tranexamic acid subjects and 8% of placebo subjects experienced a decrease in visual acuity in one eye. In the 9-27 month open-label studies, 17% of 50 subjects experienced decreased visual acuity at one or more times.
2. Abnormal color vision was experienced by 2 (0.8%) of tranexamic acid subjects and 1 (1.3%) placebo subject in the two randomized trials. In the open-label trials, 6 (2.1%) of subjects experienced a change to abnormal color vision.
3. Retinal changes were seen in 1 (0.4%) tranexamic acid subject and in no placebo subjects in the two randomized trials. In the open-label studies, 9 (3.2%) subjects were observed to have a change from normal to abnormal retinal status.
4. Other eye-related adverse events were reported in the randomized and open-label trials. Specifically, in the 9-27 month open-label trials, 180 instances of eye adverse events (66 different preferred terms) were reported in 33 patients.

Reviewer's comment:

It is important to remember that the mean and median age of the women in the two placebo-controlled trials was between 39-40 years. In this population one would expect to see eye-related adverse events, especially changes in visual acuity. Although many ophthalmic adverse events were reported, it is my impression that compared to the placebo subjects, they are not clinically significant because there is no significant difference in the percentage of ophthalmic adverse events between the tranexamic acid subjects and the placebo subjects. In the longer 9-27 month open-label trials, one would expect a larger number of adverse events in all categories, so this data is much more difficult to interpret. **Dr. Lau's Table 10 (p 18 of her review) 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).** I concur with this finding, as visual AEs generally occurred with greater frequency in the 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 much shorter duration.

For labeling and safety purposes, I believe the ophthalmology consult is the most meaningful and should be given the most weight.

Ophthalmology Consult:

In his review dated June 30, 2009, Dr. Wiley Chambers, Director of the Division of Anti-infective and Ophthalmologic Products, concluded that the clinical testing was appropriate for the potential signals noted in non-clinical studies and based on the past historical use of tranexamic acid. The most serious ocular events following the use of tranexamic acid are expected to include ligneous conjunctivitis, venous stasis retinopathy and thromboembolic events of the eye. The expected frequency of these adverse events is very low and the clinical data submitted in the NDA is not expected to adequately characterize the exact frequency of these uncommon events. He concluded that some of the retinal findings were consistent with either venous stasis retinopathy or small vessel thromboembolic events and that the cases of conjunctivitis could not be differentiated from ligneous conjunctivitis. With the exception of the three most serious events, he concluded that no significant ophthalmology findings were clearly identified in the clinical trials. Most of the eye findings are considered incidental ones typically found in the population studied.

Beyond the potential concern for ligneous conjunctivitis, venous stasis retinopathy and thromboembolic events of the eye, there were no other signals of concern that he believed should be labeled. Dr Chambers specifically stated there is no scientific basis for the recommendation to routinely follow tranexamic acid consumers with color vision tests, or to contraindicate the product for women with acquired color vision defects.

Concerning visual and ocular effects, the Applicant submitted proposed revisions to the **Division's recommended labeling and provided a review** of relevant literature and two expert opinions on September 11, 2009. The Applicant proposed adding a Contraindication of Lysteda use in patients with a history of retinal vein or artery occlusion, and revising the Warning and patient labeling sections regarding visual

effects. Dr. Chambers agreed with the Applicant's proposed revisions in the Contraindication and Warning and Precaution sections of the label. Women with a history of retinal vein or artery occlusion should not take tranexamic acid. Tranexamic acid should be discontinued if visual symptoms occur and the patient referred to an ophthalmologist for a complete ophthalmic evaluation.

Reviewer's comment:

For a more extensive discussion of the ophthalmology assessments done in the four Phase 3 trials, see the CDTL review. After evaluating all the data from the clinical trials and other postmarketing sources, the group consensus for the final label is the following:

4 Contraindications subsection 4.1 Thromboembolic Risk states:

"Do not prescribe Lysteda to women who are known to have the following conditions: A history of thrombosis or thromboembolism, including retinal vein or artery occlusion."

5.2 Ocular Effects

Retinal venous and arterial occlusion has been reported in patients using tranexamic acid. Patients should be instructed to report visual and ocular symptoms promptly. In the event of such symptoms, patients should be instructed to discontinue LYSTEDA immediately and should be referred to an ophthalmologist for a complete ophthalmic evaluation, including dilated retinal examination, to exclude the possibility of retinal venous or arterial occlusion. Ligneous conjunctivitis also has been reported in patients taking tranexamic acid. The conjunctivitis resolved following cessation of the drug.

7.4.6 Immunogenicity

There is no indication that immunogenicity is a potential issue with the use of tranexamic acid.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

According to the Applicant, in the comparative MR-301 study no increase in frequency of subjects experiencing AEs, SAEs, treatment-related TEAEs, or moderate or severe TEAEs was seen in the 3.9 g/day active treatment group compared with the 1.95 g/day active treatment group. No important differences were seen between the active treatment groups in the percentages of subjects with reports of selected dosing-emergent, treatment-related AEs headache, nausea, abdominal pain, dizziness, and vomiting.

Reviewer's comment:

It is of note that the UK label for tranexamic acid tablets states (Section 4.8 Undesirable effects), "Gastrointestinal disorders (nausea, vomiting, diarrhoea) may occur but disappear when the dosage is reduced." Likewise, the Canadian label states under Adverse Reactions, "Gastrointestinal symptoms (nausea, vomiting, diarrhea) occur but

disappear when the dose is reduced.” According to the investigators’ evaluations in the MR-301 study, the women (N= 117) taking the lower tranexamic acid dose experienced a slightly higher percentage of treatment related headache, nausea, and dizziness than women (N= 118) taking the higher daily dose. Although the difference is not statistically significant, this finding does not agree entirely with the statement in the UK and Canadian labels.

7.5.2 Time Dependency for Adverse Events

For all AEs, there was an overall trend for the first report to occur during the first interval (cycles 0-6), with a smaller proportion of subjects experiencing the first report of an AE during the later intervals (cycles 7-12, 13-18, and 19-27). The majority of the first reports of AEs in the long-term exposure population were considered by the Investigator to be unrelated (probably not or definitely not) to treatment. For the most common AEs there was no trend that showed an increase incidence with time. For example, during the two short-term trials nausea, diarrhea, and abdominal discomfort were the most frequently reported treatment emergent GI adverse events by $\geq 3\%$ of subjects. In the long-term trials, treatment emergent GI adverse events were reported by less than 2% of subjects.

7.5.3 Drug-Demographic Interactions

Subgroup evaluation of AE data for various parameters (age and race) were conducted by the Applicant and no clinically meaningful differences were noted for the short-term for the long-term exposure groups.

7.5.4 Drug-Disease Interactions

There were none studied. The label does have a section on drug dosage decreases based on renal function as tranexamic acid is excreted primarily in urine by the kidney.

7.5.5 Drug-Drug Interactions

No formal studies have been conducted to identify specific drugs that might potentially interact with tranexamic acid because of its limited metabolism and excretion primarily by the kidneys. In women taking combination hormonal contraceptives, no controlled studies have been performed to evaluate the safety of tranexamic acid taken concomitantly. Because combination hormonal contraceptives increase the risk of blood clots, stroke, or myocardial infarction, caution should be exercised when prescribing tranexamic acid to patients taking combination hormonal contraceptives.

Although no clinical studies were performed to examine the effects of alcohol on the pharmacokinetics of tranexamic acid tablets, the impact of different ratios of alcohol in the dissolution media on the release profile was explored. Results from this study concluded that tranexamic acid tablets are not expected to show dose dumping in the presence of alcohol.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

From the Canadian label (September 2003):

In one of the carcinogenicity studies in which rats were given tranexamic acid in high doses, biliary hyperplasia, cholangioma and adenocarcinoma of the liver were found. These findings have not been reproduced in a number of subsequent carcinogenicity studies. An increased incidence of leukemia (although not statistically significant) occurred in one study in mice given 4.8 percent Tranexamic acid for 20 months. In other studies, the frequency and histologic appearance of the observed tumors were similar in the test groups and in the untreated animals.

From the DRUP Pharmacology/Toxicology review:

Kim Hatfield, PhD, recommended that no additional non-clinical carcinogenicity studies are required. She recommended no changes in the carcinogenicity section of the **Applicant's proposed label**.

7.6.2 Human Reproduction and Pregnancy Data

In Study 301, one subject on Lysteda 1.95 g/day became pregnant on-study, after two cycles on medication. She delivered a healthy, full-term girl.

In Study 303, two subjects, both on Lysteda 3.9 g/day, became pregnant on-study. One conceived after two cycles on treatment, and delivered healthy, full-term twin boys. The second became pregnant after five cycles of treatment and delivered a healthy male.

In Study 302, there were 13 pregnancies reported; of these, one was ectopic, two were spontaneous abortions, two were missed abortions, two were elective abortions, two resulted in healthy full-term births, and one resulted in a 32 week delivery of healthy twins. Three subjects were lost to follow-up, two with no outcome information available, and one who reported loss of the pregnancy about six weeks after a positive pregnancy test, but provided no medical records.

There were no pregnancies in Study 304.

Reviewer's comment:

It is difficult to interpret these results. No congenital anomalies were identified. Two sets of twins is more than might be expected and the four spontaneous and missed abortions is more than would be expected.

From the Australian label for tranexamic acid (amended March 11, 2008):

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Reproduction studies performed in mice, rats and rabbits have not

revealed any evidence of impaired fertility or adverse effects on the fetus due to tranexamic acid.

The long-term clinical experience is limited to 21 pregnant women, treated for one to 18 weeks, in most cases to prevent further hemorrhage in connection with ablatio placenta [placental abruption]. All women delivered alive and normal children except for prematurity. The short-term experience comprises 67 women with abruptio placenta treated with a single dose just before delivery by cesarean section. All deliveries went well and were not further complicated by hemorrhage.

There are no adequate and well-controlled studies in pregnant women. However, tranexamic acid is known to cross the placenta and appears in cord blood at concentrations approximately equal to maternal concentration. Because animal reproduction studies are not always predictive of human response, tranexamic acid should be used during pregnancy only if clearly needed.

7.6.3 Pediatrics and Assessment of Effects on Growth

Tranexamic acid was not studied in subjects less than 18 years old. However, per FDA agreements at both the end-of-Phase 2 and pre-NDA meetings, Xanodyne has proposed to conduct a pediatric PK study in children aged 12 to 17 years as a Phase 4 commitment. A synopsis of this proposed study is provided with the NDA and was discussed with the PeRC (Pediatric Review Committee) on May 27, 2009. The committee expressed some concern for the following issues:

1. Safety of the participants
2. Need to study the very young adolescents (ages 12-14)
3. Inclusion and exclusion criteria

The reference drug product, Cyklokapron, is currently indicated for intravenous use in the pediatric population for tooth extraction without dose adjustment. Even if tranexamic acid (Lysteda) is administered to pediatric patients off-label, no additional safety risk is anticipated.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No reports have been made to indicate abuse potential or a rebound or re-exposure effect after drug withdrawal. Overdose data are limited. The March 2008 Australian label states, "There is one report of overdosage in which a 17 year old ingested 37 g of tranexamic acid and after receiving treatment with gastric lavage, mild intoxication was reported."

7.7 Additional Submissions / Safety Issues

Safety Updates:

At the time of the initial NDA submission on 1-30-09, the open label safety studies MR-302 and 304 were ongoing and were still ongoing at the time of the required Safety Update submitted on April 30, 2009. The update includes data from all subject visits that occurred through 28 February 2009 for both studies. This cut-off date meets the **Division's 31 October 2008 Pre-NDA Meeting** request regarding the timing of the safety cut-off for the Safety Update. At the late February cutoff date, 749 of the 784 subjects (96%) in study MR-302 had completed the study (including 534 early withdrawals) and 275 of the 292 subjects (94%) in study MR-304 had completed (including 89 early withdrawals). A second safety update was submitted on 9-28-09 at the request of the Division. The second update included the following:

- new (not previously reported) deaths, SAEs, premature terminations for all causes and for specific AEs
- new summary of exposure to tranexamic acid over time (3-month intervals) for studies 302 and 304
- composite summary of combined exposure to tranexamic acid across the four Phase 3 studies over time (3-month intervals)
- overall dosing summary for studies 302 and 304
- revised summary tables for subject completion/disposition for studies 302 and 304
- revised summary tables for treatment emergent SAEs for studies 302 and 304
- tables showing disposition of subjects in studies 303 and 304 for each 3-month treatment interval

Deaths: No deaths have occurred since the 2-28-09 data cutoff for the first safety update.

SAEs: No additional SAEs have been reported in either safety update since the initial NDA submission. In the first update, there were 7 additional SAEs reported in 5 subjects that in fact were described in the initial NDA submission, were considered not treatment related, but were not included in the original study databases; the data for the 7 SAEs are now reflected in the updated study databases.

Discontinuations: Three new discontinuations due to an adverse event are included in the first update and 11 in the second update (8 in Study 302 and 3 in 304).

Reviewer's comment:

The two Safety Updates were reviewed and no additional safety issues were raised. The brief narrative summaries for additional subjects who stopped the trial because of adverse events are included as well as new (summary or follow-up notes) information for subjects with previously reported SAEs. The first safety update (4-30-09) included the line listings of adverse events, summary table of deaths, discontinuations due to adverse

events and SAEs, and supportive datasets in SAS transport format. The Applicant's analysis is that the revised tables and listings show the rate of adverse events per treatment cycle remained stable in both extended studies. No clinically meaningful changes are seen that would impact the safety profile of tranexamic acid. I concur with the Applicant's analysis.

The second update includes the bulleted items listed above. Adequate exposure to tranexamic acid over time is clearly demonstrated and no new safety signals are seen in the updates.

Literature Search:

The Applicant's clinical literature search found 88 new publications with no new data to have a potential to change the proposed label for tranexamic acid. There was one new publication by Sundström (2009), based on data from the UK General Practice Research Database from 1992-1998, that suggests the use of mefenamic acid (OR_{adj} 5.54 [95% CI 2.13–14.40]) or norethisterone (OR_{adj} 2.41 [95% CI 1.00–5.78]) among women with a diagnosis of menorrhagia was associated with a statistically significant increased risk of venous thromboembolism (VTE). An increased risk of VTE with tranexamic acid (OR_{adj} 3.20 [95% CI 0.65– 15.78]) was also observed, but it did not reach statistical significance. The author also hypothesizes that patients with low hemoglobin levels, which is a proxy for more severe menorrhagia, are associated with an increased risk of VTE.

In the April 2008 *Drug Safety* article titled Benefit-Risk Review of Systemic Haemostatic Agents (for HMB) by Ian Fraser, et al, the following safety conclusion is made:

The incidence of VTE during the first 19 years (equating to 238,000 patient years) in which tranexamic acid was prescribed in Sweden for the treatment of excessive or heavy menstrual bleeding did not differ from that in women in the general population (0.0046% vs 0.0043-0.005%). A review of the Swedish national registry of VTE events did not show an increased rate after tranexamic acid became available OTC for the management of heavy menstrual bleeding. On the basis of the 10 years' experience in Sweden, oral tranexamic acid is currently under consideration for reclassification from prescription-only to pharmacy availability in the UK for this indication.

Reviewer's comment:

The 2009 epidemiology article by Sundström et al found a total of 134 cases of VTE associated with the treatment of menorrhagia (using three different medications) and 552 matched controls; the biggest weakness of the study is the fact that "recent use of tranexamic acid was scarce." Nonetheless, it is reassuring that this study did not find a statistically significant increase in the VTE risk. The recent review article by Fraser et al is comprehensive with 70 references and compares five different categories of oral agents (tranexamic acid, NSAIDs, COCs, cyclical progestogens, and desmopressin) for the treatment of HMB. The safety and efficacy profile for tranexamic acid as reviewed by Fraser is adequate and acceptable.

Potential Safety Issue:

The one theoretical safety concern that was not addressed in the clinical trial is the association between concomitant use of tranexamic acid and hormonal contraception and the risk of VTEs. From the medical literature, there are no clinical or epidemiology studies or reviews that looks primarily at this risk. Given that both products are indicated for women of reproductive age, and that hormonal contraceptives are often used off-label to manage heavy menstrual bleeding, it is unknown to what extent the two products will be used concomitantly. Because women using hormonal contraceptives were excluded from the clinical trials supporting the approval of Lysteda, it is not known whether the population of women using both products concomitantly is large enough to study, should further study be warranted. Therefore, a postmarketing commitment (PMC) was requested by the Division to conduct a pharmacoepidemiologic study based on drug use information to assess the patterns of concomitant use of Lysteda and hormonal contraception, including assessment of the ages of women using both products as compared to women using Lysteda alone. The Applicant agreed to the PMC on 10-21-09.

8 Postmarket Experience

There has been extensive postmarketing experience with tranexamic acid in Canada, Europe, Australia, and Asia. A review of reports submitted to the FDA AERS database over the past 16 years listing tranexamic acid and possible VTE events was performed by the Division of Pharmacovigilance II (DVP II) in the Office of Surveillance and Epidemiology (OSE). There were 40 reports (37 foreign, 3 unknown country) of possible VTE events associated with tranexamic acid, 34 in females (average age 49 years), and 12 associated with treating menorrhagia. No new signals of concern were identified other than the ones already known from postmarketing surveillance. The reports included serious thromboembolic adverse events (pulmonary embolism, DVT, cerebral thrombosis, retinal vein and artery thrombosis).

EMA (European Medical Evaluation Agency) Experience:

In July 2000, the EMA's Committee for Proprietary Medicinal Products (CPMP) issued an official opinion concerning the dosage and safety of Cyklo-f (tranexamic acid). This was in response to a potential public health risk raised by Germany related to the scientific basis of the dose recommendation, specifically the lack of clinical trials performed according to current standards confirming the recommended dose schedule. The overall summary of the EMA evaluation regarding the dose justification for tranexamic acid for treating menorrhagia noted that it:

... would be considered insufficient for a new medicinal product, because the available studies are not in accordance with the current requirements. However, the totality of the data accumulated over a period of more than three decades is comprehensive and provides adequate evidence for the efficacy and safety of tranexamic acid in the treatment of menorrhagia. Regarding... the scientific justification of the recommended

dose, it was concluded that the available studies suggest that the recommended dose of 2 [500 mg] tablets 3 times daily for 3 to 4 days (and a maximum daily dose of 4 grams) induces a clinically relevant reduction in menstrual blood by approximately 40% without inducing significant adverse effects.

... the overall benefit-risk of Cyklo-f in the treatment of menorrhagia can be considered positive.

Reviewer's comment:

This EMEA 2000 summary statement, based on over 30 years of use, is very reassuring and supports the daily dose of 4 grams tranexamic acid for 4 days for the treatment of menorrhagia. Data from six clinical trials and postmarketing experience was evaluated. The data indicated that 3 grams tranexamic acid per day is the lowest clinically significant effective dose and that higher doses reduce the menstrual blood loss to a greater degree. The risk for experiencing GI adverse events, although mild in nature, is increased at six grams per day.

9 Appendices

9.1 Literature Review/References

The safety and efficacy of tranexamic acid in the treatment of HMB has been widely reported in the published literature over the past 30 years. The most recent article concerning VTE risk is by Sundstrom et al (BJOG November 2008) using the General Practice Research Database for 1992-98. Although “the recent use of tranexamic acid was scarce and the risk estimate did not reach statistical significance”, the adjusted odds ratio for VTE was 3.20 (95% CI 0.65-15.78). Their finding that anemia or a low hemoglobin (a proxy for more severe menorrhagia) was associated with an increased risk of VTE suggested that menorrhagia could be a prothrombotic condition in itself. This confounding factor makes interpretation of the findings more difficult.

The published literature on the safety and efficacy of tranexamic acid is discussed in detail in two review articles (Lethaby, 2002; Wellington, 2003). A third review (Dunn, 1999) summarized the published literature on the use of tranexamic acid in a range of therapeutic uses, including treatment of menorrhagia. All three reviews concluded that oral tranexamic acid at a dose of 4 g per day, for up to 5 days, was effective in reducing MBL in women with menorrhagia, and a greater reduction in objective measures of HMB was shown when compared to placebo or other medical therapies (e.g., NSAIDS, oral luteal phase progestogen, and ethamsylate). **The reviews suggest that “tranexamic acid may be considered a first-line treatment for the initial management of HMB associated with idiopathic menorrhagia, especially for women in whom hormonal treatment is either not recommended or not wanted.”**

A list of 13 references is included in the Applicant's 23-page summary of clinical safety and 47 references are included in the Integrated Summary of Efficacy.

Clinical Review
Daniel Davis, MD
NDA 22-430
Lysteda- tranexamic acid

Reviewer's comment:

In section 7.7, see subsection Literature Search for additional comments.

9.2 Labeling Recommendations

The Applicant proposed the trade name Lysteda. The Division of Medication Error Prevention and Analysis (DMEPA) found this trade name acceptable in its review dated September 22, 2009, and the Division concurred with this decision.

Carton and container labeling was reviewed and was revised by the Applicant in accordance with recommendations made by DMEPA and by the CMC reviewer. The final carton and container labeling submitted by the Applicant on September 15, 2009 was acceptable to the DMEPA and CMC reviewers.

The Lysteda label was submitted in the format prescribed by the Physician Labeling Rule (PLR). Consults on the proposed label were obtained from the Division of Risk Management and the Division of Drug Marketing, Advertising and Communication (DDMAC). Their comments were incorporated into the label as appropriate.

Tentative agreement was reached on 10-27-09 for the final indication, contraindications, warnings and precautions, and clinical sections of the label. The final indication is: **"LYSTEDA (tranexamic acid) tablets is indicated for the treatment of cyclic heavy menstrual bleeding."** After several discussions with the Applicant, two key warning statements in the label were agreed to:

- **"Women using hormonal contraception should use Lysteda only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event."**
- **"Patients should be instructed to report visual and ocular symptoms promptly. In the event of such symptoms, patients should be instructed to discontinue LYSTEDA immediately and should be referred to an ophthalmologist for a complete ophthalmic evaluation, including dilated retinal examination, to exclude the possibility of retinal venous or arterial occlusion."**

On November 06, 2009, further agreement was reached concerning the labeling for the rare occurrence of hypersensitivity to tranexamic acid. Appropriate changes were made in the Contraindications, Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections of the final label.

Reviewer's comment:

There are no further changes that I would recommend for the label. It is complete and provides satisfactory clinical trial and safety information for the prescriber and the consumer.

9.3 Advisory Committee Meeting

The Division concluded that there was no need to have an Advisory Committee meeting for this product. It has been approved in the US since 1986 for limited indications, and

in other countries for many years for the treatment of menorrhagia. The product has not been taken off the market in any country for safety reasons; furthermore, treatment with oral tranexamic acid up to six grams per day for 6-12 days is approved in other countries for indications such as epistaxis, post-conization of the cervix, post-prostatectomy, and dental operations.

9.4 Extra Materials

Menstrual Impact Questionnaire (MIQ)-

The 3-page MIQ included six items that were designed to capture data on variations in the following six areas:

- 1) **patients' perception of amount of blood loss,**
- 2) the extent to which bleeding limited work outside or inside the home,
- 3) the extent to which bleeding limited physical activities,
- 4) the extent to which bleeding limited social or leisure activities,
- 5) listing of activities which patients felt were limited, and
- 6a-c) the amount and meaningfulness of change from the previous menstrual period.

The MIQ items were analyzed separately as each item was designed to measure a different concept as noted in the review. The questionnaire is found on the next three pages.

Menorrhagia PRO Item Questionnaire

These questions are about your most recent menstrual period.

Please refer to the entire period from the time you began your period to the point where it was completely finished.

1. During your most recent menstrual period, your blood loss was:

(Please circle the number of your answer)

1. LIGHT
2. MODERATE
3. HEAVY
4. VERY HEAVY

2. During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home? *(Please circle the number of your answer)*

1. NOT AT ALL
2. SLIGHTLY
3. MODERATELY
4. QUITE A BIT
5. EXTREMELY

3. During your most recent menstrual period, how much did your bleeding limit you in your physical activities? *(Please circle the number of your answer)*

1. NOT AT ALL
2. SLIGHTLY
3. MODERATELY
4. QUITE A BIT
5. EXTREMELY

4. During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities? *(Please circle the number of your answer)*

1. NOT AT ALL
2. SLIGHTLY
3. MODERATELY
4. QUITE A BIT
5. EXTREMELY

5. Please mark all activities that were limited by bleeding during your most recent menstrual period.

Mark all that apply

- Walking
- Standing
- Climbing stairs
- Squatting or bending down
- Childcare (playing with children, attending school functions)
- Shopping (mall, grocery)
- Home Management (cooking, cleaning, yard work, laundry)
- Leisure (dancing, dinner, movies)
- Exercise (running, biking, swimming, gym, aerobics, yoga)
- Sports (tennis, golf)
- Gardening
- Traveling/Vacation
- Other? _____
- Other? _____

6. Compared to your previous menstrual period, would you say your blood loss during this period was:

(Please circle one response, and then follow the arrows for your next step)

0 ABOUT THE SAME

1 BETTER *(go to 6a)*

2 WORSE *(go to 6b)*

(If you answered "about the same", please stop here, your survey is completed)

6a. If your menstrual bleeding 'improved' since your last period, please indicate how much.
(Please circle the number of your answer)

- 7 A VERY GREAT DEAL BETTER
- 6 A GREAT DEAL BETTER
- 5 A GOOD DEAL BETTER
- 4 AN AVERAGE AMOUNT BETTER
- 3 SOMEWHAT BETTER
- 2 A LITTLE BETTER
- 1 ALMOST THE SAME, HARDLY BETTER AT ALL

6b. If your menstrual bleeding 'worsened' since your last period, please indicate how much.
(Please circle the number of your answer)

- 7 A VERY GREAT DEAL WORSE
- 6 A GREAT DEAL WORSE
- 5 A GOOD DEAL WORSE
- 4 AN AVERAGE AMOUNT WORSE
- 3 SOMEWHAT WORSE
- 2 A LITTLE WORSE
- 1 ALMOST THE SAME, HARDLY WORSE AT ALL

6c. Was this a meaningful or important change for you:

(Circle the number next to your answer)

- 0 NO
- 1 YES

Daily Diary-

The Menstrual Cycle Bleeding Diary Card was designed to collect the total number of small blood clots, large blood clots, small stains, large stains, times of spotting, times of bleeding, and times sleep was interrupted during the menstrual period. It was the primary instrument for determining the prespecified key secondary endpoint of a **significant reduction in large stains** ["Number of times you stained your outer clothes, furniture or bedding."]. Subjects were instructed to record the actual number of times each day (from 0 to the actual number) throughout the entire menstrual cycle.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22430	ORIG-1	XANODYNE PHARMACEUTICS INC	Lysteda

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

/s/

DANIEL DAVIS
11/06/2009

LISA M SOULE
11/06/2009

I concur with Dr. Davis' conclusions and recommendation to approve NDA 22-430 for the treatment of cyclic heavy menstrual bleeding.

Medical Officer's Consult Review of NDA 22-430
Ophthalmology Consult

NDA 22-430
Ophthalmology Consult

Submission date: 1/30/09
Review date: 6/30/09

Sponsor: Xanodyne Pharmaceuticals, Inc.

Drug: Tranexamic Acid

Proposed Indications: Reduction in heavy menstrual bleeding (menorrhagia)

Submitted: NDA including clinical studies 301, 302, 303, and 304

Questions by Division of Reproductive and Urologic Drug Products:

We are requesting your consultative review of the pending electronic NDA with regards to the ophthalmology testing done.

Please answer the following questions:

1. Was the testing appropriate and comprehensive enough to evaluate the potential signals noted in animals?

Review Comment: *The clinical testing was appropriate for the potential signals noted in non-clinical studies and based on the past historical use of tranexamic acid. The most serious ocular events following the use of this product are expected to include ligneous conjunctivitis, venous stasis retinopathy and thromboembolic events of the eye. The expected frequency of these events is low and the clinical trials are not of sufficient size (and were not expected to be) to adequately characterize the exact frequency of these events. These events are also known to occur in human and non-human animals with plasminogen deficiencies. Some of the retinal findings in the clinical studies are consistent with either venous stasis retinopathy or small vessel thromboembolic events. The reported cases of conjunctivitis are not described in sufficient detail to differentiate from ligneous conjunctivitis. These cases of conjunctivitis would be expected to resolve following discontinuation of the drug product.*

2. Do you agree with the Sponsor's interpretation of the ophthalmology testing results?

Review Comment: *I do not completely agree with the sponsor's interpretation of the ophthalmology testing results, however, 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.*

3. Do you have any concerns whether any adverse events reports suggest a signal other than/beyond that identified in the ophthalmology evaluations?

Review Comment: *None, beyond the potential for ligneous conjunctivitis, venous stasis retinopathy and for thromboembolic events.*

4. Do you see signals of concern that should be labeled?

Review Comment: *Potential for ligneous conjunctivitis, venous stasis retinopathy and thromboembolic events including those in the eye. As noted in my consult from 2004, the administrative files for NDA 19-280 and NDA 19-281 were reviewed with respect to the ocular findings submitted in the NDA and the basis for including the ocular Warnings, Contraindications and Adverse Reactions. The administrative files indicate a misunderstanding of the use of color vision tests. There is no scientific basis for the recommendation to follow patients with color vision tests, nor with the contraindication for patients with acquired color vision defects.*

5. Would you recommend any postmarketing evaluation of ophthalmologic signals or adverse events?

Review Comment: *None at this time.*

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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

/s/

Wiley Chambers
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MEDICAL OFFICER

Wiley Chambers
6/30/2009 05:33:47 PM
MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA & IND	NDA 22-430 & IND 68-096
Brand Name	LYSTEDA™
Generic Name	Tranexamic acid modified-release (XP12B-MR)
Sponsor	Xanodyne Pharmaceuticals, Inc.
Indication	Menorrhagia
Dosage Form	650 mg modified release tablets
Drug Class	Anti-fibrinolytic
Therapeutic Dosing Regimen	1.3 g po tid for up to 5 days
Duration of Therapeutic Use	Up to 5 days for each menstrual period for a maximum of 24 months
Maximum Tolerated Dose	Not determined in human
Submission Number and Date	N 000 & SDN 121 January 30 th , 2009
Review Division	DRUP / HFD 580

1 SUMMARY

No significant QT prolongation effect of tranexamic acid (1300 mg and 3900 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between tranexamic acid (1300 mg and 3900 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guideline. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTcF$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that the assay sensitivity of the study was established.

The sponsor's dose selection is reasonable. The suprathapeutic dose (3900 mg) is 3 times the therapeutic dose (1.3 g) but produces mean C_{max} approximately 2-fold higher. Tranexamic acid is primarily excreted via the kidneys by glomerular filtration. Therefore the worst case scenario is when tranexamic acid is administered to patients with the renal impairment. The sponsor has proposed dose adjustments in these patients. There are no other intrinsic or extrinsic factors known that can increase exposure to tranexamic acid.

In this single-center, randomized, blinded, placebo- and active-controlled crossover study, 48 healthy subjects were randomized to receive tranexamic acid 1300 mg, tranexamic acid 3900 mg, placebo, and 400 mg moxifloxacin. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs corresponding to the Largest Upper Bounds for Tranexamic acid (1300 mg and 3900 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Tranexamic acid 1300 mg	10 hour	3.8	(0.1, 7.4)
Tranexamic acid 3900 mg	10 hour	3.2	(-0.4, 6.9)
Moxifloxacin 400 mg*	3 hour	14.2	(10.5, 17.8)

*Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 5 timepoints is 8.9 ms.

2 PROPOSED LABEL

The sponsor has not included any information regarding QT effects in the proposed label. The following text is our suggestions for labeling. We defer all labeling decisions to the review division.

In a randomized, placebo- and active-controlled crossover study, 48 healthy female subjects were administered a single oral dose of LYSTEDA 1300 mg, LYSTEDA 3900 mg (3 times the recommended dose), placebo, and moxifloxacin 400 mg. At both LYSTEDA doses, there was no significant effect on the QTc interval. At the 3900 mg dose, peak tranexamic acid concentrations were approximately 2-fold higher than peak concentrations following a 1300 mg dose.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Xanodyne Pharmaceuticals, Inc. has developed tranexamic acid (LYSTEDATM with a modified-release oral dose formulation (also known as XPB12-MR), a new tablet strength (650 mg), and a new dosage regimen (two 650-mg tablets administered 3 times daily) for treatment of menorrhagia.

The Sponsor has submitted the NDA as a 505(b)(2) application.

3.2 MARKET APPROVAL STATUS

In the United States, oral and IV tranexamic acid (Cyclokapron®) was approved in 1986 to treat patients with hemophilia for short term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. Tranexamic acid is used extensively in Europe, Canada, Australia, and New Zealand to treat menorrhagia, but is not approved for this indication in the United States.

3.3 PRECLINICAL INFORMATION

Reviewer's Comment: Non-Clinical studies per the ICH S7B guidelines were not carried out. The Sponsor is relying on the FDA's finding of safety for Cyklokapron as reflected in the approved Cyklokapron labeling.

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety eCTD Module 2.7.4

“The safety and efficacy of tranexamic acid in the treatment of HMB has been widely reported in the published literature over the last 30 years (Dunn, 1999; Lethaby, 2002; Wellington, 2003). These reviews conclude that oral tranexamic acid at a dose of 4 g per day, for up to 5 days, is effective in reducing menstrual blood loss in women with menorrhagia and a greater reduction in objective measures of heavy menstrual bleeding is shown when compared to placebo or other medical therapies (i.e., NSAIDS, oral luteal phase progestogen, and ethansylate) (Rybo, 1991). According to a published review article (Wellington, 2003), oral tranexamic acid is well tolerated by most patients with menorrhagia. No consistent serious adverse events have emerged with the tranexamic acid immediate-release, 500-mg oral tablet formulation (FDA, 2000). However, gastrointestinal (GI) side effects (e.g., nausea, dyspepsia, vomiting, and diarrhea) are frequently (approximately 15%) reported (e.g., Gleeson, 1994; Preston, 1995).

“The safety of tranexamic acid modified-release tablets was assessed in a total of 8 human clinical studies (4 in healthy volunteers and 4 in patients). The safety of LYSTEDATM in the treatment of heavy menstrual bleeding (HMB) was demonstrated in 2 randomized double-blind placebo-controlled studies and 2 open label studies. The ITT population included all randomized subjects who ingested ≥ 1 dose of study medication. Of these 1,205 ITT subjects, 486 were included in the short-term exposure group. Of the 1,205 ITT subjects, 1101 were included in the long-term exposure group.

“Three deaths occurred, 1 each during the screening period in Study XP12B-MR-301 (Subject 732-1001) and Study XP12B-MR-302 (Subject 561-2024), and 1 during Study XP12B-MR-302 (Subject 525-2005-cardiac arrest, pneumonia and sepsis).

Reviewer’s Comments: There are no reports of sudden cardiac death seizures or significant ventricular arrhythmias associated with QT prolongation. The sponsor reports that there were no clinically meaningful ECG abnormalities noted in their clinical program.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of tranexamic acid’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study in September 2007.

The sponsor submitted the thorough QT study report XP12B-104 for tranexamic acid (XP12B-MR), including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Single-Dose, Double-blind, Placebo- and Positive-controlled, 4-way Crossover Study of the Electrocardiographic (ECG) QT Interval Prolongation Effect of (XP12B-MR) Tranexamic Acid in Healthy Fasting Adult Female Subjects

4.2.2 Protocol Number

XP12B-104

4.2.3 Study Dates

2 February 2008 — 1 March 2008

4.2.4 Objectives

Primary

- To evaluate the effect of tranexamic acid on ventricular repolarization in healthy female subjects. In particular, to assess the effects of two dose levels of tranexamic acid, the approximate therapeutic dose (1300 mg), and a suprathreshold dose (3900 mg) administered as single doses.

Secondary

- To evaluate the safety and tolerability of tranexamic acid at the anticipated therapeutic level and at a suprathreshold level.
- To evaluate the pharmacokinetics of tranexamic acid (at two dose levels).
- To determine the relationship between C_{max} and change in QT_c from baseline.
- To perform exploratory analysis on the linearity of tranexamic acid pharmacokinetics based on these two dose levels.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, single-dose, double-blind, 4-way crossover study with a placebo, an active control (400 mg moxifloxacin), 1300 mg and 3900 mg tranexamic acid single doses. Doses were separated by a washout period of 8 days.

4.2.5.2 Controls

The sponsor used both placebo and positive (400 mg moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were blinded including moxifloxacin. The randomization scheme was blinded to the subjects, doses, investigator, laboratory analysts and personnel who monitored adverse reactions in the clinic. Pharmacy personnel were un-blinded, as they are independent from the study team. Study drug preparation and dosing were performed in separate rooms.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Each subject who completed the study screening assessments and met all the eligibility criteria was assigned a unique identification number. 48 subjects were enrolled in 2 enrollment groups of 24 subjects each. Within each enrollment group, 6 subjects were assigned to each of the 4 randomization sequences presented below:

Table 2: Four Randomization Treatment Sequence

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
2	B	D	A	C
3	C	A	D	B
4	D	C	B	A

A = therapeutic dose (1300 mg tranexamic acid)

B = suprathreshold dose (3900 mg tranexamic acid)

C = placebo

D = positive control (400 mg moxifloxacin)

4.2.6.2 Sponsor's Justification for Doses

Sponsor state in their study report XP12B-104:

“The proposed suprathreshold dose for the conduct of this TQT trial was a single oral 3900 mg dose of tranexamic acid. This dose was expected to produce a maximum C_{max} of approximately 65 mcg/mL (mean 40 mcg/mL) and a maximum AUC of approximately 332 mcg·h/mL (mean 219 mcg·h/mL) of tranexamic acid. This tranexamic acid exposure is three fold greater than the expected therapeutic dose, and covers the highest exposure expected after administration of the therapeutic dose, including scenarios of dosing in subjects with renal impairment. This study design should be adequate to characterize the potential cardiac effect”. (Source: XP12B-104 Study Report, Section 9.2, Pg 27)

Reviewer's Comments: Sponsor's choice of 3.9 g as the suprathreshold dose is reasonable. The suprathreshold dose (3.9 g) is 3-fold the therapeutic dose (1.3 g) but produces C_{max} approximately 2-fold higher.

Tranexamic acid is primarily excreted via the kidneys by glomerular filtration with more than 95% excreted unchanged drug in urine. Therefore, the high exposure scenario is when multiple doses of tranexamic acid are administered to patients with the renal impairment. The $T_{1/2}$ of tranexamic acid is expected to increase with decreasing renal function. The sponsor has not conducted such a renal impairment study with oral tranexamic acid; therefore it is not clear the extent of accumulation with multiple doses. The sponsor has proposed dose adjustment for patients with renal impairment based on IV data. There are no other intrinsic or extrinsic factors known that can increase exposure to tranexamic acid greater than what was observed following the suprathreshold dose (Clinical Pharmacology Table, section 6.1).

The sponsor mentions that expected mean C_{max} in subjects with renal impairment having 1.3 g tid oral dose is 31-36 mcg/ml which is approximately a three-fold increase in exposure compared to subjects with normal renal function. The renal impairment study

was performed after 10 mg/kg i.v. administration (equivalent to 20 mg/kg (1.3g) oral in a 65 kg individual). A concentration of 31-36 mcg/ml is the C_{max} after i.v. bolus dose that the sponsor compares with the C_{max} achieved after p.o administration and therefore is an invalid comparison.

4.2.6.3 Instructions with Regard to Meals

“Subjects were required to fast for at least 8 hours before dosing and for at least 5 hours post-dose. Water was not allowed from 1 hour before until 1 hour after dosing, but was allowed at all other times”. (Source: XP12B-104 Study Report, Section 9.1, Pg 26)

Reviewer’s Comment: Acceptable.

4.2.6.4 (ClinPharm) ECG and PK Assessments

Study Day	-1	1
Intervention	No treatment (Baseline)	1.3 or 3.9 g single oral dose
12-Lead ECGs	None collected	Pre-dose (60, 40 and 20 min) and 0.5, 1, 2, 3, 4, 5, 6.5, 10, 14 and 24 hours after dosing
PK Samples for drug	None collected	Pre-dose and 0.5, 1, 2, 3, 4, 5, 6.5, 10, 14 and 24 hours after dosing

Reviewer’s Comment: Acceptable

4.2.6.5 Baseline

Baseline value is defined as the ECG measurements before dose on the same day.

4.2.7 ECG Collection

Cardiodynamic sampling was performed using continuous cardiac monitoring via a 12 lead digital holter from 1 hour before dosing until 24 hours post-dose. Following 10 minutes of quiet, but awake rest in the supine position, triplicate ECGs were extracted at the time points specified above.

The ambulatory 12-lead data acquired with the holter device from 1 hour pre-dose until 24 hours post-dose was transferred to the central ECG laboratory for the cardiodynamic analyses. Three 10-second ECGs were extracted at the pre-specified time points, approximately 2 minutes apart. The interval data used for the analyses were taken from three consecutive raw beats from each ECG. On each extracted ECG, heart rate, PR-interval, QRS duration and QT-interval were measured in the Computer Assisted Measurement of Intervals (CAMI) system. At each time point, the value of the interval was considered as the average of the three ECGs.

b(4)

b(4)

Extracted ECGs were blinded to subject ID, date, time, sequence and treatment code, and were read by a Cardiologist. A clinical interpretation was also given for each ECG.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 48 female subjects (18-49 yrs of age) with a normal baseline ECG and BMI between 18-28 kg/m² were enrolled in the study and 46 subjects completed the clinical phase of the study. The following subjects did not complete the study:

- Subject No. 13 withdrew from the study on Day -1 of Period 3, due to family emergency. The subject had received a dose of 1300 mg of tranexamic acid in Period 1 and 3900 mg of tranexamic acid in Period 2.
- Subject No. 37 was dropped by the Principal Investigator on Day -1 of Period 4 due to an ovarian cyst. The subject had received 1300 mg of tranexamic acid in Period 1, 3900 mg of tranexamic acid in Period 2 and all placebos in Period 3.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Change of QTcF from baseline and placebo is considered as the primary endpoint for the interpretation. The difference between each active treatment group and placebo group and its 95% CI in least squares means from the ANOVA model are presented in the following table for QTcF. Both of the 1300-mg and 3900-mg tranexamic acid (XP12B-MR) treatment groups had the largest upper bounds to be less than 10 ms, while the moxifloxacin group had largest lower bound to be 10.2 ms, indicating a negative QT prolongation effect for both doses of the test drug tranexamic acid and a positive effect of the active control for moxifloxacin.

Table 3: QTcF Comparison Between All Treatment Cohorts

Time Pts	1.3g XP12B – PLC A-C			3.9g XP12B – PLC B-C			400mg Moxi – PLC D-C		
	Lower 95% CI	Msec Mean Diff	Upper 95% CI	Lower 95% CI	Msec Mean Diff	Upper 95% CI	Lower 95% CI	Msec Mean Diff	Upper 95% CI
0.5	-4.22	-0.93	2.35	-2.29	0.65	3.59	-4.55	3.45	11.44
1	-4.6	-0.27	4.06	-4.19	-0.25	3.68	-0.82	5.2	11.21
2	-4.53	-0.28	3.96	-4.58	-1.29	2.01	5.86	*10.42	14.99
3	-1.82	2.34	6.51	-0.94	2.72	6.39	9.72	*14.11	18.49
4	-4.66	-0.15	4.37	-3.42	0.36	4.14	6.29	*10.9	15.5
5	-5.7	-1.72	2.25	-1.03	2.78	6.59	7.91	*12.28	16.64
6.5	-4	0.29	4.57	-4.37	1.45	7.27	-2.3	4.72	11.75
10	-0.26	3.57	7.4	-1.26	3.1	7.45	3.18	*7.42	11.66
14	-4.79	-0.5	3.78	-3.91	0.83	5.56	-0.32	*4.78	9.88
24	-1.77	1.54	4.84	-4.2	-0.11	3.97	2.58	*5.7	8.83

Treatment: A = 2 x 650 mg TA (XP12B-MR), B = 6 x 650 mg TA (XP12B-MR), C = Placebo, D = 1 x 400 mg Moxifloxacin (Active “positive” control).

The difference (Active – Placebo) in least squares (LS) means and its 95% CI were calculated from an ANOVA model with fixed effects for sequence, treatment, period, and random effect for subject nested within sequence.

* = Statistically significant (p<0.05).

Source: sponsor’s table 11.2.1

4.2.8.2.2 Additional Analysis

The impact of treatment drug on heart rate was analyzed. No significant heart rate effect was seen in response to tranexamic acid. A modest increase in heart rate was seen at the 1 and 3 hour time points (< 5 bpm) with moxifloxacin treatment. The sponsor also provided QTcB results which were similar to those of QTcF.

4.2.8.2.3 Categorical Analysis

No QTcF value was greater than 480 ms. Percentages of QTcF values between 450 and 480 ms are 0%, 0.19%, 0% and 2.77% for treatment A, B, C and D as specified under Table 3, respectively. More QTcF prolongation was observed for moxifloxacin compared with other treatment groups. No other significant difference between treatments was observed.

4.2.8.3 Safety Analysis

No deaths were reported in this study. One subject (Subject No. 37) was discontinued from the study by the Investigator due to the serious AE of moderate endometriosis (verbatim term: right ovarian endometrioma). No other SAEs or significant AEs were reported.

No clinically significant ECG abnormalities were reported.

4.2.8.4 Clinical Pharmacology

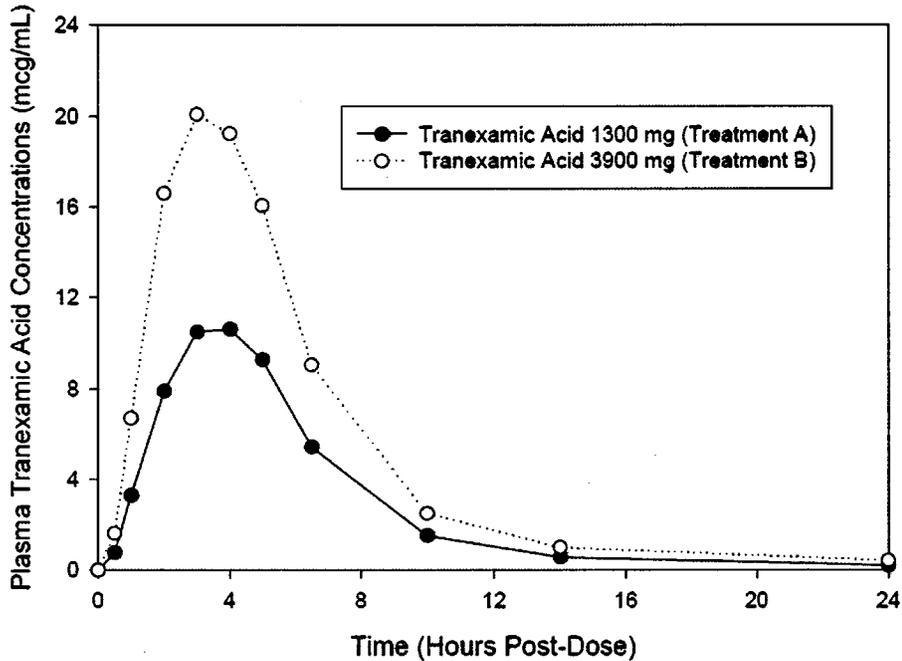
4.2.8.4.1 Pharmacokinetic Analysis

Mean plasma concentration time profile for tranexamic acid is shown in Figure 1.

Summary statistics of the pharmacokinetics of tranexamic acid is provided in

Table 4

Figure 1: Mean Plasma tranexamic acid concentration time profile following 1.3 and 3.9 g single dose of tranexamic acid.



(Source: XP12B-104 Study Report, Figure 11.5.5:1, Pg 45)

Table 4: Pharmacokinetic parameters (Arithmetic mean \pm SD) following 1.3 and 3.9g of Tranexamic acid

PK parameters	Treatment A (1300 mg)	Treatment B (3900 mg)
AUC 0-t (mcg·h/mL)	67.7 \pm 19.5	123 \pm 37.0
AUC _{inf} (mcg·h/mL)	69.4 \pm 19.6	127 \pm 37.2
AUC 0-t/AUC _{inf} (%)	97.3 \pm 1.20	96.8 \pm 1.15
C _{max} (mcg/mL)	11.6 \pm 3.50	21.5 \pm 5.63
t _{max} (h)	3.60 \pm 0.835	3.20 \pm 0.788
Half-life (h)	5.52 \pm 1.21	6.21 \pm 1.12
k _{el} (1/h)	0.135 \pm 0.0545	0.115 \pm 0.0206

(Source: XP12B-104 Study Report, Table 11.5.5:1, Pg 45)

The C_{max} and AUC_{inf} following supratherapeutic dose (3.9 g) in the thorough QT study were 1.8 and 1.9 fold, respectively when compared to the therapeutic dose (1.3 g). The increase in 3-fold dose produced approximately 2-fold increase in exposures indicating less than dose proportional PK of tranexamic acid at the studied doses.

4.2.8.4.2 Exposure-Response Analysis

Sponsor performed linear mixed effect modeling to account for relationship between plasma concentration of tranexamic acid and $\Delta\Delta QTcF$ and $\Delta\Delta QTcB$. The linear relationship with tranexamic acid concentration was not statistically significant for $\Delta\Delta QTcF$ and $\Delta\Delta QTcB$. The linear relationship with moxifloxacin concentration was statistically significant for both $\Delta\Delta QTcF$ and $\Delta\Delta QTcB$.

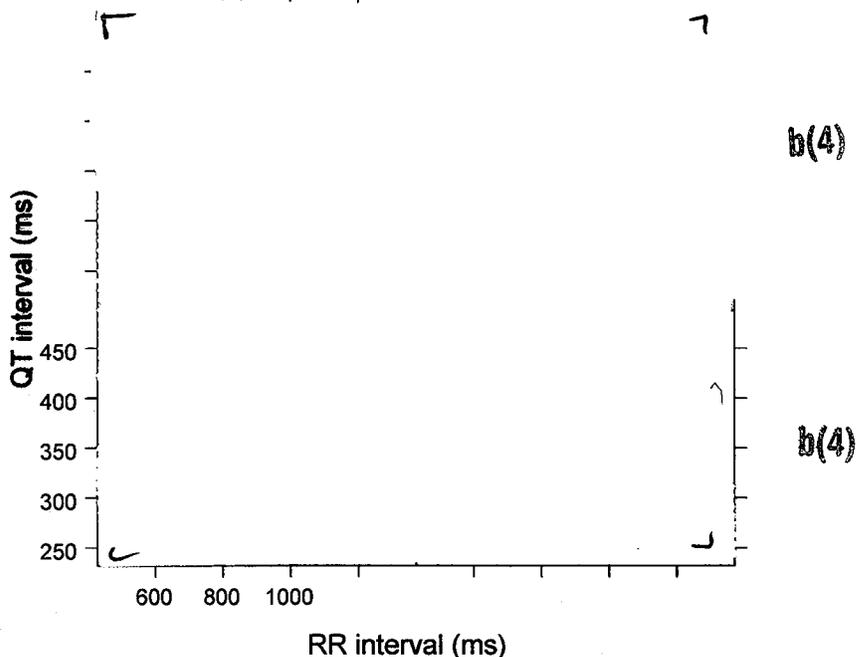
For details please see study report XP-12B-104, Section 11.4.4, Page 44.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

It appears that QTcF corrects heart rate reasonably well (Figure 2). Therefore, QTcF has been used for the primary endpoint for the statistical analysis.

**Figure 2: QT, QTcB, QTcF vs. RR
(Each Subject's Data Points are Connected with a Line)**



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Tranexamic Acid

The statistical reviewer used mixed model to analyze the $\Delta\Delta QTcF$ effect. The model includes treatment, time points and period as fixed effects and subject as a random effect. Interactions between treatment and time points were used to construct the LS means.

Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group of 1300 mg Tranexamic Acid

Time/(hr)	1300 mg Tranexamic Acid	Placebo	$\Delta\Delta$ QTcF	
	Mean	Mean	Mean	90% CI
0.5	-4.9	-4.2	-0.7	(-4.4, 2.9)
1	-1.7	-1.7	-0.1	(-3.7, 3.6)
2	-1.0	-0.9	-0.1	(-3.7, 3.6)
3	-1.5	-4.0	2.6	(-1.1, 6.2)
4	-0.6	-0.6	0.1	(-3.6, 3.7)
5	-2.7	-1.2	-1.5	(-5.2, 2.1)
6.5	-10.7	-11.2	0.5	(-3.2, 4.2)
10	-10.2	-14.0	3.8	(0.1, 7.4)
14	-11.5	-11.2	-0.3	(-3.9, 3.4)
24	-9.2	-11.0	1.8	(-1.9, 5.4)

Table 6: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group of 3900 mg Tranexamic Acid

Time/(hr)	3900 mg Tranexamic Acid	Placebo	$\Delta\Delta$ QTcF	
	Mean	Mean	Mean	90% CI
0.5	-3.5	-4.2	0.8	(-2.9, 4.4)
1	-1.8	-1.7	-0.1	(-3.8, 3.5)
2	-2.1	-0.9	-1.2	(-4.8, 2.5)
3	-1.2	-4.0	2.8	(-0.8, 6.5)
4	-0.1	-0.6	0.5	(-3.2, 4.1)
5	1.7	-1.2	2.9	(-0.8, 6.6)
6.5	-9.6	-11.2	1.6	(-2.1, 5.2)
10	-10.8	-14.0	3.2	(-0.4, 6.9)
14	-10.3	-11.2	0.9	(-2.7, 4.6)
24	-11.3	-11.0	-0.3	(-4.0, 3.4)

The largest upper bounds of the 2-sided 90% CI for the mean difference between 1300 mg tranexamic acid and placebo, and between 3900 mg tranexamic acid and placebo were 7.4 ms and 6.9 ms at 10 hours after dose, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same model to analyze moxifloxacin and placebo data from half hour to 4 hours after dose. The whole time course post-dose for $\Delta\Delta\text{QTcF}$ is displayed in Figure 3. The largest unadjusted 90% lower confidence interval is 10.5 ms at 3 hours after dose. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 8.9 ms at 3 hours after dose, which indicates that an at least 5 ms $\Delta\Delta\text{QTcF}$ effect due to moxifloxacin can be detected from the study.

Table 7: Analysis Results of ΔQTcF and $\Delta\Delta\text{QTcF}$ for Treatment Group of 400mg Moxifloxacin at Time Point 0.5 hour – 4 hours

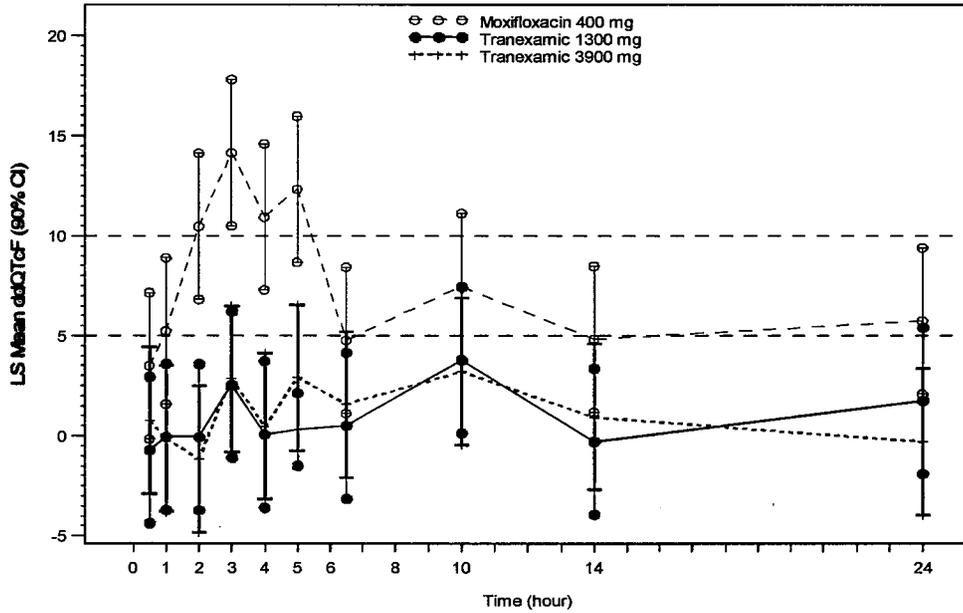
	400 mg Moxifloxacin	Placebo	$\Delta\Delta\text{QTcF}$	
Time/(hr)	Mean	Mean	Mean	90% CI
0.5	-0.8	-4.1	3.3	(-1.8, 8.5)
1	3.5	-1.6	5.1	(-0.0, 10.2)
2	9.5	-0.8	10.3	(5.2, 15.4)
3	10.1	-3.9	14.0	(8.9, 19.1)
4	10.2	-0.5	10.8	(5.7, 15.9)

* Bonferroni method was applied for multiple endpoint adjustment for 5 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcF over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose absolute QTcF values are ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 8: Categorical Analysis of QTcF

Treatment Group	Total N		Value ≤ 450 ms		450 ms < Value ≤ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	41	164	40 (97.6%)	163 (99.4%)	1 (2.4%)	1 (0.6%)
Moxifloxacin 400 mg	41	410	35 (85.4%)	398 (97.1%)	6 (14.6%)	12 (2.9%)
Placebo	41	410	41 (100%)	410 (100%)	0 (0.0%)	0 (0.0%)
Tranexamic 1300 mg	41	410	41 (100%)	410 (100%)	0 (0.0%)	0 (0.0%)
Tranexamic 3900 mg	41	409	40 (97.6%)	408 (99.8%)	1 (2.4%)	1 (0.2%)

Table 9 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 9: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin 400 mg	41	410	33 (80.5%)	400 (97.6%)	8 (19.5%)	10 (2.4%)
Placebo	41	410	41 (100%)	410 (100%)	0 (0.0%)	0 (0.0%)
Tranexamic 1300 mg	41	410	41 (100%)	410 (100%)	0 (0.0%)	0 (0.0%)
Tranexamic 3900 mg	41	409	40 (97.6%)	408 (99.8%)	1 (2.4%)	1 (0.2%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limits of 90% CI for the PR mean differences between 1300 mg tranexamic acid and placebo, and between 3900 mg tranexamic acid and placebo are 4.8 ms and 3.0 ms, respectively.

Table 10: Analysis Results of Δ APR by Treatment Group

Time/(hr)	1300 mg Tranexamic Acid		3900 mg Tranexamic Acid	
	LS Mean	90% CI	LS Mean	90% CI
0.5	-0.4	(-3.7, 2.9)	-0.4	(-3.7, 3.0)
1	-0.1	(-4.2, 2.5)	-1.9	(-6.0, 0.7)
2	1.0	(-1.9, 4.8)	-2.9	(-5.8, 0.9)
3	-1.3	(-4.3, 2.3)	-2.6	(-5.6, 1.0)
4	-2.8	(-4.4, 2.3)	-2.7	(-4.3, 2.3)
5	-3.8	(-5.2, 1.5)	-2.9	(-4.3, 2.3)
6.5	-4.5	(-4.5, 2.1)	-5.9	(-6.0, 0.7)
10	-8.4	(-11.6, -5.0)	-10.0	(-13.2, -6.6)
14	-3.7	(-4.1, 2.6)	-4.8	(-5.1, 1.5)
24	-1.8	(-3.5, 3.2)	-4.2	(-5.9, 0.8)

The outlier analysis results for PR are presented in Table 11. Only one subject experience PR > 200 ms for the study drug.

Table 11: Categorical Analysis for Observations PR >200 ms under Treatment

Treatment Group	ID	Time 0.5	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6.5	Time 14	Time 24	Baseline
Tranexamic 3900 mg	001-0005	223	208	206	207	206	208	218	203	221	223

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the QRS mean differences between 1300 mg tranexamic acid and placebo, and between 3900 mg tranexamic acid and placebo are 2.1 ms and 3.4 ms, respectively. There is no subject who experienced absolute QRS interval greater than 120 ms in any treatment group.

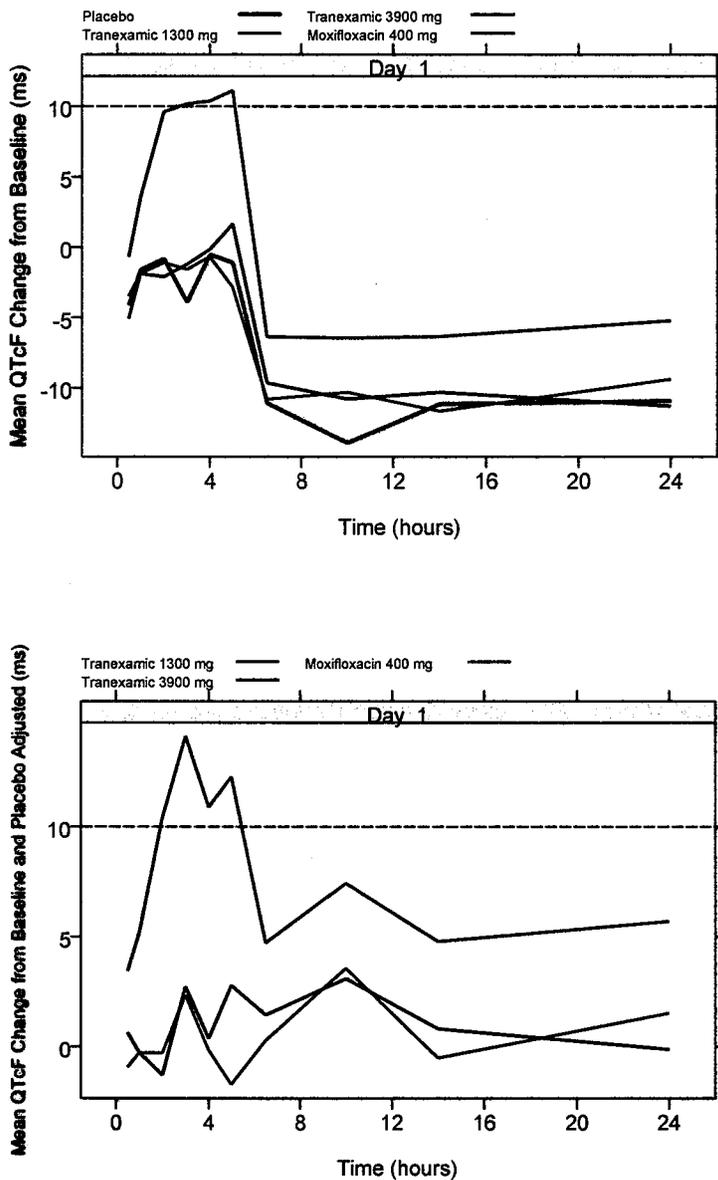
Table 12: Analysis Results of $\Delta\Delta$ QRS by Treatment Group

Time/(hr)	1300 mg Tranexamic Acid		3900 mg Tranexamic Acid	
	LS Mean	90% CI	LS Mean	90% CI
0.5	-1.9	(-2.6, 0.8)	-0.7	(-1.4, 1.9)
1	-2.8	(-2.8, 0.6)	-0.3	(-0.2, 3.1)
2	-2.5	(-2.5, 0.9)	-0.4	(-0.4, 3.0)
3	-2.4	(-1.2, 2.1)	-1.1	(0.0, 3.4)
4	-2.9	(-2.5, 0.8)	-1.2	(-0.8, 2.5)
5	-3.0	(-2.2, 1.1)	-1.1	(-0.3, 3.0)
6.5	-1.9	(-2.2, 1.2)	0.2	(-0.1, 3.3)
10	-3.3	(-1.8, 1.5)	-1.7	(-0.2, 3.1)
14	-2.2	(-2.1, 1.3)	-0.3	(-0.2, 3.1)
24	-4.0	(-4.3, -0.9)	-1.5	(-1.9, 1.5)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 Δ QTcF and $\Delta\Delta$ QTcF Time Profiles

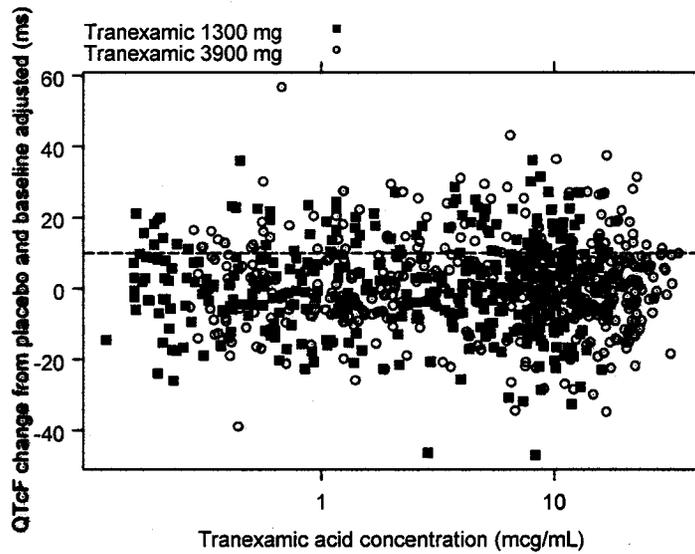
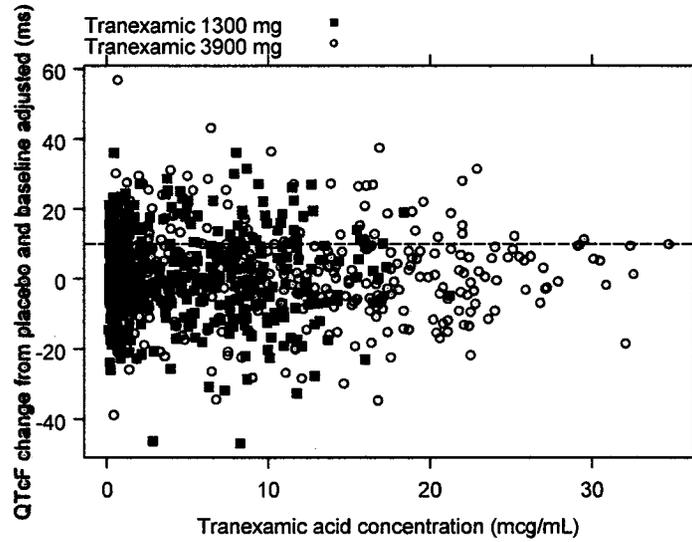
Figure 4. Mean Δ QTcF (change from baseline) (top), $\Delta\Delta$ QTcF (placebo-adjusted change from baseline) (bottom), for Tranexamic acid 1.3 g (blue line), Tranexamic acid 3.9 g (red line), moxifloxacin (green line), and placebo (black line).



5.3.2 Tranexamic Acid Concentration-QTcF Analysis

The relationship between $\Delta\Delta\text{QTcF}$ and tranexamic acid concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5. $\Delta\Delta\text{QTcF}$ vs. Tranexamic acid concentration.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG Assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 84% of the ECGs were annotated in the primary lead (II) with V2 and V5 being the most frequent backup leads. A large number of ECGs (33%) had T-offset high frequency noise with a QT bias of 1.49% in this study with female subjects, according to the ECG warehouse automated algorithm. Although a large number of ECGs had T-offset high frequency noise, ECG interpretation and annotation placement appeared satisfactory on review of a subset. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Intervals

There were no clinically relevant effects on the PR or QRS intervals due to tranexamic acid. Only one subject had a PR of over 200 ms post-dose with tranexamic acid 3900 mg. This subject also had a baseline PR of over 200 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose	Maximum Proposed Clinical Regimen	1.3g modified-release (MR) tranexamic acid (XP12B-MR) po TID (3.9 g/day) administered for up to 5 days for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure and physical activities		
Maximum Tolerated Dose	NOAEL'	Repeat-Dose Toxicity (dog): 600 mg/kg/day		
		Reproductive Toxicity (rat): 1500 mg/kg/day		
		Reproductive & Development Toxicity (rat): 1500 mg/kg/day		
Principal Adverse Events	ADRs During Dosing in ≥3% of Subjects	Nausea (5.2%), Diarrhea (3.0%), Headache (9.5%), Menstrual Discomfort (3.9%; e.g. cramping and menstrual pain) occurred in 2 pivotal efficacy & safety Phase 3 trials in subjects receiving 1.3 g MR po TID for up to 5 days		
Maximum Dose Tested	Single Dose	3.9g MR'' po (fasting)		
		1g IV'''		
	Multiple Dose	1.3g MR po q 8h (3.9g/day for 5 days)		
Exposures Achieved at Maximum Tested Dose [Mean (%CV)]	Single Dose		C _{max} ^a	AUC ₍₀₋₂₄₎ ^a
			mcg/mL	mcg ^a h/mL
		Study XP12B-101		
		1g IV ^b	95.24 (22.8)	122.96 (11.7)
		1.3g MR po (fasting)	11.25 (29.1)	69.64 (27.2)
		1.3g IR'''' po (fasting)	12.26 (23.0)	72.66 (16.4)
		Study XP12B-102		
		1.3g MR po (fasting)	12.28 (31.3)	73.03 (25.0)
		1.3g IR po (non-fasting)	12.95 (25.4)	83.23 (22.5)
		Study XP12B-104		
	1.3g MR po (fasting)	11.60 (30.2)	69.39 (28.3)	
	3.9g MR po (fasting)	21.50 (26.2)	126.55 (29.4)	
	Maximum C _{max} Observed	34.80		
	Multiple Dose		C _{max} ss	AUC _{0-24,ss}}
			mcg/mL	mcg ^a h/mL
		Study XP12B-103		
		1.3g MR po q 8h (5days)	15.80 (30.1)	74.79 (29.0)
			C _{max}	AUC _{0-24}}
		Study XP12B-103	mcg/mL	mcg ^a h/mL
1.3g MR po x 1 (single dose)		13.18 (33.1)	76.86 (30.4)	
Range of linear PK	Linear PK expected for doses of 1.95 – 5.85 g/day, administered in divided, TID doses Dosing regimen: 1.3g MR po TID (3.9 g/day) administered during heavy menstrual bleeding for up to 5 days for the management of menorrhagia			
Accumulation at steady state [Mean (%CV)]	No significant accumulation demonstrated (see Multiple Dose information above from Xanodyne protocol XP12B-103);			
	Study XP12B-103	C _{max} ss	C _{min} ss	AUC _{0-24,ss}}
	1.3g po q8h (5days)	15.80 (30.1)	5.16 (31.2)	74.79 (29.0)

Metabolites	>95% of the dose is excreted in the urine as unchanged drug: Metabolites: 1% deaminated dicarboxylic acid (inactive) and 0.5% acetylated tranexamic acid (inactive) compounds excreted after oral administration		
Absorption	Absolute/Relative Bioavailability		Mean (%CV)
		Females – Study XP12B-101	44.9% (25.3)
	Tmax	Study XP12B-101	Median (range)
		2.94h (2h – 4h)	
Distribution	Vd/F or Vd	Study XP12B-103 Vdss/F (Compartmental Analysis)	Mean (%CV) 70.4 L (32.9)
		% Bound	Protein Bound/Bound+Unbound <3%
	Elimination	Route	Primary route
Percent dose eliminated			>95% of the dose is excreted in the urine as unchanged drug
Other routes			N/A
Terminal t½			Mean (SD)
		Post-distributional	2.06h ± 0.21h
		Study XP12B-101 Terminal t½	Mean (%CV) 11.37h (17.6)
CL/F or CL		Study XP12B-103 CL/F	Mean (%CV) 17.7 L/h (27.9)
Intrinsic Factors	Age	Not indicated in the elderly, therapy only indicated in women of childbearing age. AUC _{0-24h} and C _{max} in the targeted population of menstruating reproductive women, approximate: 75 ± 10 mcg ² h/mL and 15 ± 3.5 mcg/mL, respectively	
	Sex	Not indicated in males, female administration only (see above)	
	Race	AUC & C _{max} not specifically studied	
	Renal Impairment	In patients with various degrees of renal impairment administered 10mg/kg IV of tranexamic acid, comparable to 20mg/kg of oral XP12B-MR (i.e.1.3g for a 65 kg subject), achieved post-distribution mean C _{max} values of 31.3-36.4 mcg/mL Percent renal excretion of tranexamic acid correlates to GFR	

		Renal Function Impairment	% Excreted over 24h
		Normal (<1.36 mg/dL)	95%
		Moderate (1.36-2.83 mg/dL)	38%
		Severe (2.84 -5.66mg/dL)	20%
		The dosage regimen adjustments in the current US package insert for tranexamic acid (Pharmacia and Upjohn's Cyklokapron® Package Insert) will be adopted for XP12B-MR	
	Hepatic Impairment	N/A – not significantly metabolized (<5%); and produced metabolites are inactive	
Extrinsic Factors	Drug interactions	Tranexamic acid is not metabolized and/or influenced by CYP450 isoenzymes. No formal drug-drug interaction studies conducted in the XP12B-MR development program (agreement per the End of Phase 2 meeting, September 20, 2004)	
	Food effects	Study XP12B-102	Ratio of LSM (90% confidence interval)
		C _{max} (mcg/mL)	106.8% (97.2-117.3%)
		AUC _(0-∞) (mcg ² h/mL)	115.4% (106.5-124.9%)
Expected High Clinical Exposure Scenarios	<p>Dosage Regimen (targeted for indication): 1.3g MR Tranexamic Acid po TID (3.9 g/day) administered during heavy menstrual bleeding for up to 5 days for the management of menorrhagia. Patients participating in 2 randomized control trials (RCT) with menorrhagia averaged 3.5 days of XP12B-MR therapy per menstrual cycle</p> <p>High clinical exposure scenarios;</p> <p>a. <u>Previously unknown renal impairment:</u> A patient who is started on tranexamic acid (1.3 g MR po TID), unadjusted dose for renal impairment is expected to achieve a mean C_{max} of ~31-36 mcg/mL, which is approximately a three fold increase compared to subjects with normal renal function. A supra-therapeutic single-dose of 3.9g, which is 3X the recommended therapeutic single-dose, produced a maximum C_{max} of approximately 35 mcg/mL with a mean of 21.5 mcg/mL.</p> <p>b. <u>Renal impairment occurs while on therapy:</u> If a patient's renal function deteriorates while on therapy, the expected maximum mean C_{max} of ~31-36 mcg/mL would be approximately a three fold increase compared to subjects with normal renal function. A supra-therapeutic single-dose of 3.9g, which is 3X the recommended therapeutic single-dose, produced a maximum C_{max} of approximately 35 mcg/mL and a mean of 21.5 mcg/mL.</p> <p>c. <u>Patient takes an entire daily dose as a single dose</u> (i.e. 3.9g as 6 x 650mg tablets). This scenario is unlikely given the pill burden. A supra-therapeutic single-dose of 3.9g will cover the expected increased exposure in this patient (as studied in the TQT study)</p>		

* NOAEL = no observed adverse effect level; ** MR = modified-release formulation; *** IV = intravenous formulation; **** IR = immediate-release formulation;

- Unless otherwise specified, values reflect ln-transformed parameters and the antilog of the means (i.e. geometric means) is reported.
- Arithmetic mean

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