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APPLICATION NUMBER:

22-430

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 6, 2009
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-430
Applicant	Xanodyne Pharmaceuticals, Inc.
Date of Submission	January 30, 2009
PDUFA Goal Date	July 30, 2009 (Priority), extended to October 30, 2009
Proprietary Name / Established (USAN) names	Lysteda™ Tranexamic acid tablets
Dosage forms / Strength	Tablet; 650 mg
Proposed Indication(s)	Treatment of cyclic heavy menstrual bleeding
Recommended:	Approval

1. Introduction

This NDA seeks marketing approval for tranexamic acid, or Lysteda™ (hereinafter referred to as Lysteda), for the indication of treatment of cyclic heavy menstrual bleeding.

Currently approved treatments for heavy menstrual bleeding (HMB) include both interventional and medical options. Relatively definitive treatments include hysterectomy and endometrial ablation or resection. Uterine artery embolization and myomectomy may be used to treat fibroid-related HMB. Four oral progestins have received US approval for similar indications; the only two remaining on the market are Aygestin® (NDA 18-405), which is norethindrone acetate, 2.5-10 mg for 5-10 days and Provera® (NDA 11-839) or medroxyprogesterone acetate, 5-10 mg for 5-10 days. The indications for both products read “to treat...abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.” On October, 1, 2009, the levonorgestrel-releasing intrauterine device Mirena® (NDA 21-225) was approved for a secondary indication to treat HMB in women who choose to use intrauterine contraception. Oral contraceptives have also been used off-label in extended/continuous regimens to control HMB.

The Applicant has submitted a 505(b)(2) application, which relies in part on the Agency’s findings of safety for tranexamic acid with respect to nonclinical data, which was based on review of data contained in NDAs 19-280 and 19-281 for Cyklokapron (tranexamic acid).

The Applicant requested and was granted priority status for the submission, on the basis of having received Fast Track designation earlier in the development process. Fast Track status was granted based on the potential to fill an unmet need (i.e., a nonhormonal treatment for HMB).

The Applicant conducted four phase 3 studies in support of this marketing application, two were pivotal three- to six-month randomized, placebo-controlled, double-blind safety and

efficacy trials, while two were open label studies that provided longer-term safety data and some confirmatory efficacy data.

The major issues addressed in this review involve the development and use of a novel patient-reported outcome instrument to support key secondary endpoints; safety issues, particularly with respect to thrombogenic and ophthalmologic risk and risk of severe allergic reactions; and labeling. In addition, areas in which there were variant opinions by members of the review team are discussed.

2. Background

2.1 DESCRIPTION OF PRODUCT

Lysteda is a synthetic lysine derivative and an antifibrinolytic agent that acts by forming a reversible complex with plasminogen. This results in formation of a plasmin/tranexamic acid complex that prevents the binding of plasmin to the surface of fibrin and thereby inhibits fibrinolysis.

Tranexamic acid was first approved in the U.S. (as an orphan drug) in 1986, in both tablet and injectable formulations as Cyklokapron (NDA 19-280 for 500 mg tablet; NDA 19-281 for 100 mg/ml injectable). The approved indication was for treatment of patients with hemophilia for short term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. The oral formulation was discontinued and the NDA withdrawn in 2002 for reasons unrelated to safety; the injectable formulation continues to be marketed.

Tranexamic acid has also been approved for marketing for the currently requested indication in a number of European countries including the United Kingdom, as well as in Canada, Japan, New Zealand and Australia. It has been available over-the-counter in Sweden for about ten years.

2.2 Regulatory History

A preIND meeting was held with Xanodyne on November 3, 2003. The Applicant had previously met with the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) in March 2003, prior to the transfer of the indication of heavy menstrual bleeding to the Division of Reproductive and Urologic Products (DRUP). DGCDP had concurred that a 505(b)(2) application, referencing NDAs 19-280 and 19-281 would be appropriate; DRUP confirmed this. At the preIND meeting, DRUP noted that the toxicology studies supporting the previous NDAs were inadequate by current standards, and requested that the Applicant conduct a chronic repeat-dose toxicity study in the most sensitive species, and a combined embryo-fetal development/pre- and postnatal development study. These protocols were subsequently reviewed in 2004, and found acceptable.

At the preIND meeting, the Applicant was also advised to address food effect, potential effect on QT prolongation, and justification of renal dose adjustment. Regarding clinical development, the Division recommended two adequate and well-controlled trials, although a single multicenter trial with very strong efficacy results could suffice. The efficacy data should cover six months to demonstrate a durable effect. The appropriate study population was agreed to be women with at least 80 ml menstrual blood loss (MBL) per cycle.

The IND (68,096) was opened in December 2003 and a guidance meeting was held on August 25, 2004 to discuss dose-ranging. The Applicant presented literature to support a dose of 3.9 g/day as the optimal dose. DRUP did not agree, and, citing concern about potential venous thromboembolic events (VTEs) with a drug in this class, recommended that the Applicant determine the LED in a randomized, controlled, and blinded study. This ideally would be done by evaluating more than one dose, and showing that one dose then failed to meet the prespecified efficacy endpoints. Historically, the EMEA had issued a Committee Opinion in 2000 regarding the dose justification for tranexamic acid for menorrhagia and 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 tablets 3 times daily for 3 to 4 days (and a maximum daily dose of 4 g) induces a clinically relevant reduction in menstrual blood by approximately 40% without inducing significant adverse effects.

DRUP also provided guidance about the size of the safety database, requesting data on 200 women completing one year of treatment and 10,000 cycles of use. Health-related quality of life instruments proposed for use would need to be validated and included in the statistical analysis plan if they were intended to support labeling claims.

DRUP and the Applicant met again for an End-of-Phase 2 meeting on September 20, 2004. Reviewing a protocol for the initial phase 3 trial, the Division recommended conduct of a second safety and efficacy study, but noted that it could be shorter than the six-month study proposed. The following recommendations were discussed regarding entry criteria:

- Do not exclude women based on the size of fibroids, as women with fibroids of any size will likely be in the target population once the product is marketed
- Remove weight restrictions
- DRUP agreed with the exclusion of women using oral contraceptives (OCs), and would likely include OC use as a contraindication in labeling
- Include IUD users

Based on information submitted in the meeting package, DRUP agreed that no drug-drug interaction studies were needed between tranexamic acid and other drugs that are primarily renally excreted.

The Division noted that the causes of heavy menstrual bleeding may differ in the adolescent population as compared to adults; therefore, a clinical trial in adolescents would be requested. This could be done as a phase 4 commitment.

The product was granted Fast Track designation in October 2004.

Comments regarding ophthalmologic assessments to be conducted in the phase 3 trials (recommended on the basis of toxicology findings) were provided by an FDA ophthalmologist and conveyed to the Applicant in December 2004.

The protocol for a one-year safety study (Study 302) was reviewed in February 2005; this study would enroll *de novo* (rather than extending women studied in one of the two efficacy and safety studies) and inclusion criteria would be based on medical judgment about the diagnosis of HMB, rather than on documented MBL (as done in the primary efficacy and safety studies). The Applicant was informed that the efficacy analyses in this study would be considered exploratory.

The primary efficacy and safety study protocols were submitted under Special Protocol Assessment (SPA) requests and comments were conveyed in June 2005. Study 301 was proposed as a three-month trial comparing two doses of tranexamic acid and placebo, with the goal of 160 evaluable subjects in each treatment arm and 80 in the placebo arm. Study 303 was proposed as a six-month trial comparing the 3.9 g/day dose of tranexamic acid with placebo, with the goal of 140 evaluable subjects in the treatment arm and 70 in the placebo arm. For both studies, the two primary endpoints were proposed to be 1) reduction in MBL (measured by alkaline hematin methodology) during five consecutive days of the period, assessed from baseline to the final cycle on treatment, with clinical significance defined as at least a 50 ml reduction in MBL; and 2) improvement in quality of life as measured by the Vitality domain of the SF-36, version 2. The Applicant proposed that a statistically significant outcome on either endpoint would constitute success; the Division required that reduction in MBL of at least 50 ml from baseline be demonstrated for a successful outcome.

Statistical reviews of the primary efficacy and safety studies (Studies 301 and 303) were completed in June 2005 and comments were conveyed to the Applicant.

Study Endpoints and Label Development (SEALD) team comments on the SF-36 Vitality Scale were conveyed on August 2005, and indicated that the scale was not acceptable to support a labeling claim. Literature submitted by the Applicant regarding areas of importance to women with menorrhagia did not define the concept(s) that are measured by the SF-36. Concerns identified by patients in the Applicant's **focus groups (lack of control/spontaneity, impaired work performance, reduced work/school attendance, inability to enjoy physical activity/exercise, exhaustion and sleep loss, reduced interpersonal/sexual relationships, feeling unhygienic, irritability/depression, embarrassment due to leakage/soiling of clothing)** were not adequately measured by the SF-36.

A Type A meeting to discuss the SPA comments was held on October 14, 2005. Concerning **the determination of a "clinically meaningful" reduction in MBL, the Applicant proposed an anchoring technique based on a global satisfaction question.** This was acceptable to DRUP and SEALD. The Applicant was encouraged to find additional study endpoints, in lieu of the SF-36 Vitality Scale, that are closely linked to MBL and of universal concern to women with menorrhagia. Three criteria for study success were agreed upon for the MBL endpoint:

- Statistically significant difference between active and placebo groups in the change from baseline in MBL
- The point estimate of the reduction from baseline in MBL is ≥ 50 ml greater in the active group than the placebo group
- The point estimate of the reduction from baseline for MBL is at least as great as the decrease found to be clinically meaningful to women with menorrhagia

The Applicant also proposed a secondary responder analysis, with a response defined as achieving the greater of a 50 ml decrease or the decrease determined to be clinically meaningful; DRUP noted that failure to show statistically significant difference between groups on this analysis would be a review issue. **In addition, the Applicant's proposal to impute missing data using data from other subjects was not acceptable.**

Following this meeting, 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 in those instruments 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.

The revised protocols for Studies 301 and 303 were again submitted for SPA, and comments were provided in September 2006. The following key secondary endpoints, accounted for in the statistical analysis plan, were acceptable to the Division:

- Limitation of physical activity (MIQ Question 3)
- Limitation of social and leisure activities (MIQ Question 4)
- Reduction in large stains (daily diary)

The Division advised that if these endpoints were intended to support labeling claims, they would need to be evaluated individually in each study, not as pooled data. Statistical comments were provided regarding step-down hypothesis testing (the primary endpoint of MBL reduction should be evaluated at the higher dose first, followed by the primary endpoint at the lower dose, with the secondary endpoints then evaluated for each dose level if the corresponding primary endpoint was statistically significant). Comments also addressed the **Applicant's plan to conduct interim analyses of each study to adjust the sample size based upon conditional power for the key secondary endpoints.**

SEALD reviewed the plan to identify a clinically meaningful reduction in MBL using Question 6 from the MIQ, and was generally supportive, with caveats that the change in MBL should be assessed at the end of the first on-treatment period as compared to last pretreatment period, and that the change in bleeding rated **at least "much better" (i.e., the top two response options based on a hypothetical 7-point scale ranging from "very much worse" to "very much better") should provide the anchor.**

A teleconference was held on February 21, 2007 to discuss the statistical analysis plan and imputation of missing data. The Applicant agreed to analyze the three key secondary endpoints separately for each study. DRUP accepted the primary efficacy population as all randomized subjects who have at least one efficacy data point (MBL from one menstrual period).

A preNDA meeting was held on October 31, 2008. No unresolved issues remained.

2.3 Primary Clinical Reviewer's Recommendation

The primary medical reviewer, Dr. Daniel Davis, made the following recommendation in his review dated November 6, 2009:

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.

2.4 Issues Raised in Other Reviews

A number of consultative reviews were requested for this NDA, and, in some cases, the conclusions and recommendations of the reviewers were not initially consistent with those reached by the clinical reviewers.

Regarding efficacy, the statistical reviewer, Dr. Xin Fang, concluded that the validity and reliability of the MIQ supporting the key secondary endpoints had not been demonstrated, and recommended inclusion of these endpoints in labeling “**should be exercised with caution.**” I discuss the Applicant’s program to develop and validate the MIQ in Section 7.4.2, and the label mentions these endpoints only in the Clinical Studies section, which Dr. Fang has reviewed.

In early communications associated with his consultative review of the ophthalmology data, Dr. Chambers of the Division of Anti-infective and Ophthalmologic Products recommended that women using Lysteda undergo pretreatment and interval ophthalmologic examinations. Following review of additional information submitted by the Applicant, Dr. Chambers agreed that such monitoring was not needed, and labeling regarding ocular safety was revised in accordance with his recommendations. This is further discussed in Section 8.2.1.1.

The Division of Pharmacovigilance II (DPV II) reviewed the AERS database for ophthalmologic and VTE events associated with tranexamic acid. The labeling regarding VTEs is consistent with their recommendations. Like Dr. Chambers, DPV II initially recommended pretreatment visual examinations, but concurred with the currently proposed labeling as revised following review of the Applicant’s **additional submission, as indicated in the memorandum by Melissa Truffa dated October 28, 2009.**

A statistical review of safety data was conducted by the Division of Biometrics VII, focusing particularly on ophthalmologic, renal and VTE safety issues, along with other AEs. This review raised concern about the overall sufficiency of the data to permit adequate assessment of the long-term safety of Lysteda, and expressed concern about the adequacy of the ophthalmologic evaluations. My assessments of a number of the issues evaluated in this review are divergent, and are further discussed in Sections 8.2.1.1, 8.2.1.2 and 8.2.2. A secondary review by Dr. Paul Schuette, dated October 27, 2009, addresses many of the areas of disagreement, and concluded:

We cannot comment on whether the totality of the other existing data together with the submitted clinical trials data is adequate to establish the long term safety and risk/benefit profile for Lysteda, but will defer to the judgment of the review division in this matter.

3. CMC/Device

The primary Chemistry Reviewer, Gene Holbert, Ph.D., made the following recommendations in his review dated September 24, 2009:

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."

No postmarketing commitments or risk management steps were recommended.

3.1 General product quality considerations

Regarding drug substance, the specifications are based on those of the European and Japanese Pharmacopeia; there is no USP monograph for tranexamic acid. Specifications for the drug substance are acceptable.

The Applicant initially provided multiple time points for dissolution acceptance criteria, but revised this (in a major amendment submission that resulted in a three-month clock extension) to a single time point criterion of no less than $\frac{1}{2}$ (Q) at 90 minutes. The revised specification was acceptable. Tablets are not expected to show dose dumping in the presence of alcohol. The product was originally posited by the Applicant to be a "modified release" formulation, however, review of the plasma concentration profile led to the determination that the product is virtually identical to immediate release formulations. Thus, the "modified release" description was denied.

b(4)

The Applicant proposed only a single test for identity; this was initially considered a deficiency. However, the active pharmaceutical ingredient (API) specification includes two tests for identity – HPLC and IR. This was determined to be sufficient, so that a second identity test for the drug product was not required. The drug product specification was acceptable.

Four excipients require microbial testing, but such testing is not performed on the final product because the starting materials undergo microbial controls.

Stability testing demonstrated that the tablets are stable through the proposed shelf life. The post-approval stability protocol was adequate. Packaging DMFs were reviewed and found to be adequate. The following expiry was granted when stored at room temperature:

- 36 months for 100 count bottles
- 3 months for bulk tablets
- 24 months for all other packaging configurations

3.2 Facilities review/inspection

The $\frac{1}{2}$ 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)

3.3 Other notable issues (resolved or outstanding)

The Applicant described the product as a "modified release tablet." A consult was requested from the biopharmaceutics reviewer in the Office of New Drug Quality Assessment (ONDQA)

as to whether the product was properly described as “**modified release.**” The reviewer, Patrick Marroum, Ph.D., concluded in his review dated May 14, 2009 that

In the opinion of the [ONDQA], Lysteda is not a modified release formulation because it has a pharmacokinetic plasma concentration profile that is very similar to the already approved Cyklokapron IR formulation. The results of the study conducted by the sponsor show that Lysteda and Cyklokapron are bioequivalent to each other. In summary, Lysteda does not exhibit release characteristics that are typical of a modified release formulation.

This determination was conveyed to the Applicant, and the description in labeling was appropriately revised.

4. Nonclinical 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

The primary Toxicology Reviewer, Kim Hatfield, Ph.D., made the following recommendations in her review dated June 22, 2009:

Recommendations on approvability: Nonclinical data support approval of tranexamic acid (Lysteda), 1.3 g (2 x 650 mg tablets) three times daily, for treatment of heavy menstrual bleeding.

Recommendations for nonclinical studies: No additional nonclinical studies are required.

Recommendations on labeling: The Sponsor’s submitted labeling for Sections 8.1, 8.3, 13.1 and 13.2 are acceptable with minor changes.

In a memorandum dated October 27, 2009, Dr. Hatfield noted that:

Nonclinical recommendations for labeling were made for NDA 22-430 in my review submitted to the NDA and signed on 6-22-09. Subsequent changes that were made during label negotiation to Sections 8.1, 8.2, 8.3, 13.1 and 13.2 are all appropriate, and I concur with the final label submitted to the Sponsor on 10-26-2009.

Dr. Hatfield notes that tranexamic acid was found in fetal plasma at each dose used in the reproductive toxicity study, indicating *in utero* exposure during maternal dosing. Tranexamic acid is also detected in breast milk at a level 1% of that of the peak serum concentration.

The Applicant conducted a 39 week chronic toxicity study in male and female dogs, which demonstrated transient treatment-related ocular toxicity mainly at doses six times the recommended human dose of 3.9 g/day. Effects include reddening and discharge in the eyes, changes in the nictating membrane/conjunctiva, altered reflectivity in the fundus of the eye, conjunctival inflammation and inflammatory exudate in the eye. In prior studies, dose- and time-related ophthalmologic effects were observed in rats, cats and dogs at doses six to 40 times the human dose, at durations of six days to one year. Incidence of these effects ranged from 25-100% of animals. The NOAEL determined in the chronic toxicity study in the dog was primarily based on ocular toxicity, and was five times the recommended human exposure,

based on AUC. The ocular toxicities of exudate and conjunctivitis are believed to be an effect of exaggerated pharmacology of tranexamic acid, related to its antifibrinolytic mechanism of action.

Genotoxicity was addressed with a literature study that concluded that tranexamic acid is negative for genotoxicity based on the rec-assay on *Bacillus subtilis*, the Ames test, *in vitro* and *in vivo* chromosomal aberration assays and the dominant lethal test. Carcinogenicity is discussed in the current Cyklokapron label, which indicates an increased incidence of leukemia in male mice that is likely drug-related, along with hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system in rats at doses exceeding the maximum tolerated dose. Hyperplasia, but not neoplasia, was observed at lower doses, and similar changes were not observed when a different strain of rat was used. Carcinogenicity may be strain-specific in the rat, and limited to exceedingly high doses.

Team Leader Comment

Further discussion with Dr. Lynnda Reid, the Pharmacology/Toxicology Team Leader, revealed that in the published carcinogenicity studies cited in the label, the increased rate of leukemia did not meet criteria for statistical significance. Biliary hyperplasia and adenocarcinomas were seen only in a strain of rats no longer commonly used in carcinogenicity testing; when retested in a strain commonly used, there were no findings of biliary hyperplasia. In addition, there were no findings of adverse effects on hematology parameters or hyperplastic lesions in the chronic six-month rat study or the 12-month dog study.

No dose-related toxicity relating to maternal or fetal health was demonstrated in the embryofetal and pre/postnatal development studies.

Dr. Hatfield identified the following nonclinical safety concerns and issues and discussed their relevance to human use:

- **Ocular toxicity – a relevant clinical concern, as a reversible case of conjunctivitis in a human patient has been reported in the literature. Visual abnormalities were the most commonly reported postmarketing adverse event (AE) in Swedish patients.**
- **Placental transfer – of low concern, as reprotoxicity studies have not shown any adverse effects of treatment with tranexamic acid during pregnancy**
- **Central nervous system effects – of low concern, as clinical studies have only demonstrated headache, dizziness and migraine at clinical doses, and have not noted hyperexcitability and convulsions, as seen in rats.**
- **Cardiovascular events – there are no known nonclinical data to support the labeled contraindication in patients with active thromboembolic disease.**

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology Reviewer, Hyunjin Kim, Ph.D., stated the following in his review dated October 16, 2009:

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.

Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 22-430 acceptable from a Clinical Pharmacology perspective.

No phase 4 commitments were requested, although Dr. Kim noted that a pediatric study is required under PREA (see Section 10).

Pharmacokinetic (PK) evaluation of Lysteda demonstrated a t_{max} of 3 hours, with a $t_{1/2}$ of 11 hours. Elimination is predominantly urinary excretion through glomerular filtration. Steady state was reached in 32 hours after first dose. Absolute bioavailability was 44%; there is very limited protein binding, mostly to plasminogen. PK was linear, independent of time following repeated administration.

No PK study was conducted in renally impaired subjects, but renal dose adjustment was accepted, based upon the adjustment available in the Cyklokapron label. No dose adjustment is needed for hepatic impairment, as very little metabolism of tranexamic acid occurs.

Food effect was found to be negligible, with about a 7% increase seen in AUC and C_{max} when administered with food vs. fasting. Subjects in phase 3 trials were advised to dose without regard to meals.

Results of the thorough QT study are discussed in Section 8.2.1.3.

6. Clinical Microbiology

As the product is an oral tablet, no clinical microbiology review was warranted.

7. Clinical/Statistical- Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The pivotal efficacy trials were Studies 301 and 303, with Study 302 intended to provide supportive efficacy data on health-related quality of life and long-term safety information. Study 304 was conducted only as a safety study, and did not provide any efficacy data. Study 301 was a three-month trial evaluating a 1.95 g/day dose of Lysteda, a 3.9 g/day dose of Lysteda and placebo, in a randomized, double-blind, multicenter design. One objective of this study was to establish the lowest effective dose of Lysteda. Study 303 was a six-month randomized, double-blind, multicenter trial that compared only the 3.9 g/day dose of Lysteda to placebo. Study 303 also evaluated the durability of the treatment effect. Study 302 enrolled 781 subjects, 239 (30.6%) of whom completed the 27 months of treatment.

The studies were conducted entirely in the US; Study 301 at 63 sites, and Study 303 at 40 sites. The entry criteria were the same for Studies 301 and 303, and are discussed in Dr. Davis' review. Briefly, entry criteria required an average MBL of 80 ml or greater over two pretreatment menstrual periods as assessed by alkaline hematin, and regular menstrual cycles. Fibroids were not exclusionary unless the investigator determined they were of sufficient size

and number to warrant surgical management. Use of a copper IUD was also acceptable. Active or history of arterial or venous thromboembolic disease was exclusionary, as was known thrombophilia. In addition, use of hormonal contraception was also excluded. For Study 302, women were not screened for eligibility based on alkaline hematin-determined MBL, but were considered eligible based upon the investigator's diagnosis of cyclic HMB based on review of history, physical examination and laboratory findings, and menstrual period evaluation during screening.

Team Leader Comment

The Applicant's clinical development program was consistent with the recommendations made by DRUP during preNDA interactions.

7.2 Demographics

The demographics and baseline characteristics of the subjects in Studies 301, 303 and 302 are displayed in Table 1 through Table 3. Subjects ranged in age from 18 to 50 years, with the average between 39-41 years. Duration of HMB ranged as great as 30+ years, with the average around 10 years. Between 36-44% of subjects in the two pivotal trials had fibroids visualized on ultrasound examination. Two-thirds or more of subjects over all three trials were Caucasian, with about 20-33% African American and small numbers of Asian, Native American, Pacific Islander and "other" subjects. Overall, the demographics of the subjects were similar across study arms and over trials. Demographic information for Study 304 is not shown, as the subjects were all rolled over from Study 301 or 303.

Table 1 Demographics and Baseline Characteristics – Study 301

Demographic Variable	XP12B-MR 3.9 g/day N = 115	XP12B-MR 1.95 g/day N = 115	Placebo N = 67
Age – years (a)			
n	115	115	67
Mean (SD)	39.19 (6.248)	40.18 (6.296)	38.93 (6.056)
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)
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)			
Present	51 (44.35)	44 (38.26)	24 (35.82)
Absent	64 (55.65)	71 (61.74)	43 (64.18)
Race, n (%)			
White	77 (66.96)	76 (66.09)	43 (64.18)
Black	34 (29.57)	31 (26.96)	22 (32.84)
Asian	0	3 (2.61)	0
Native American	1 (0.87)	0	0
Pacific Islander	0	1 (0.87)	0
Other	3 (2.61)	4 (3.48)	2 (2.99)

Source: Table 1.3.1-1, p 15, Applicant's Summary of Clinical Efficacy

Table 2 Demographics and Baseline Characteristics – Study 303

Demographic Variable	XP12B-MR 3.9 g/day N = 117	Placebo N = 72
Age – years (a)		
n	117	72
Mean (SD)	38.74 (6.324)	38.85 (6.837)
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)
Median	7.00	7.08
Range (min – max)	0.58 – 35.00	0.42 – 36.00
Presence of Fibroids (b)		
Present	44 (37.61)	27 (36.49)
Absent	73 (62.39)	43 (64.18)
Race, n (%)		
White	86 (73.50)	51 (70.83)
Black	23 (19.66)	18 (25.00)
Asian	1 (0.85)	1 (1.39)
Native American	0	0
Pacific Islander	0	0
Other	7 (5.98)	2 (2.78)

Source: Table 1.3.1-2, p 16, Applicant's Summary of Clinical Efficacy

Table 3 Demographics and Baseline Characteristics – Study 302

Demographic Variable	XP12B-MR 3.9 g/day N = 719
Age - years (a)	
n	719
Mean (SD)	38.32 (6.572)
Median	39.00
Range (min – max)	18.00 – 50.00
Heavy menstrual bleeding duration (years)	
n	718
Mean (SD)	9.85 (8.545)
Median	6.25
Range (min – max)	0.00 (b) – 38.00
Race, n (%)	
White	544 (75.66)
Black	147 (20.45)
Asian	10 (1.39)
Native American	1 (0.14)
Other	17 (2.36)

Source: Table 1.3.2-1, p 19, Applicant's Summary of Clinical Efficacy

7.3 Disposition of Subjects

Subject disposition for the two short-term trials is shown in Table 4 and Table 5.

Table 4 Subject Disposition – Study 301

	Lysteda 3.9 g/day N (%)	Lysteda 1.95 g/day N (%)	Placebo N (%)	Overall N (%)
Screening				
Failure				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				
Failed to return	6 (5.1)	5 (4.3)	1 (1.4)	12 (3.9)
Other	3 (2.5)	2 (1.7)	2 (2.9)	7 (2.3)
Protocol violation	3 (2.5)	1 (0.9)	1 (1.4)	5 (1.6)
Subject request	2 (1.7)	0	1 (1.4)	3 (1.0)
Adverse Event	1 (0.9)	3 (2.6)	1 (1.4)	6 (2.0)

Source: Based on Table 10.1-1, p 40 of 504, Study Report for Study 301

Table 5 Subject Disposition – Study 303

	3.9 g/day n (%)	Placebo n (%)	Overall n (%)
Screening			
Failure			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			
Failed to return	10 (8.1)	6 (8.2)	16 (8.2)
Other	8 (6.5)	1 (1.4)	9 (4.6)
Subject request	6 (4.9)	2 (2.7)	8 (4.1)
Protocol violation	2 (1.6)	5 (6.8)	7 (3.6)
Adverse Event	3 (2.4)	3 (4.1)	6 (3.1)

Source: Based on Table 10.1-1, p 39 of 489, Study Report for Study 303

Team Leader Comment

In Study 301, the withdrawal rate for the lower dose (1.95 g/day) was similar to that for placebo, while it was higher in the 3.9 g/day arm. Comparing only the high dose and placebo, placebo subjects more commonly withdrew for adverse events or “other,” while 3.9 g/day Lysteda subjects more often withdrew for “failed to return.” In Study 303, which included only the 3.9 g/day dose and lasted six cycles, the withdrawal rate was similar for study drug and placebo and was actually numerically higher in the placebo group. A greater proportion of placebo subjects terminated for protocol violations, unsatisfactory efficacy and adverse events, while more Lysteda subjects withdrew due to “other,” and “subject request.”

Subject disposition for Study 302 is shown in Table 6 and for Study 304 in Table 7.

Table 6 Subject Disposition – Study 302

Outcome	N	%
Enrolled	781	100
Completed	239	30.6
Withdrawn	542	69.4
Failed to Return	156	20.0
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 7 Subject Disposition – Study 304

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

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

Team Leader 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 both 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.

Further breakdown of premature terminations by three-month intervals in the long-term safety studies is provided in Table 8 and Table 9.

Table 8 Premature Discontinuations 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		Months 25-27	
	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	33.0
# 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	7.4
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	2.3
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	1.2
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	1.9
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	1.2
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	0.4
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	0.4
Death	0		1	0.2	0		0		00		0		0		0		0	

*% is based on N at start of interval

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

Table 9 Premature Discontinuations 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: Based on Tables 1.1 – 1.3, pp 14 -16 of 16, Applicant's Submission of September 30, 2009

Team Leader Comments

- **Withdrawal patterns for the first nine months of treatment were similar across the two long-term studies, with about 30% withdrawing in that period.**
- **In both studies, the proportion withdrawing decreased with time. Relatively few discontinuations were attributed to AEs, particularly in Study 304, in which subjects had previously been enrolled in either Study 301 or Study 303; however, given the vague descriptions of the predominant reasons for withdrawal (failed to return, subject request, other), it is possible that additional withdrawals were associated with AEs, although not primarily attributed to AEs. Withdrawal due to unsatisfactory efficacy did not increase with time; this provides indirect evidence of the durability of treatment benefit.**

7.4 Efficacy Findings

7.4.1 Assessment of Efficacy

The Applicant agreed on the following criteria for an efficacy claim:

- The comparison between change from baseline in MBL between tranexamic acid and placebo would be statistically significant
- The point estimate for the reduction from baseline in MBL in the tranexamic acid group would be at least 50 ml
- The point estimate for the reduction from baseline in MBL in the tranexamic acid group would be greater than or equal to a clinically meaningful reduction, as determined by a Receiver Operator Characteristic (ROC) analysis in Study 301

Team Leader Comment

There appears to be a discrepancy over the definition of one of the success criteria in early discussions with the Applicant, in that some communications between the Division and the Applicant state that the point estimate for the reduction from baseline in MBL in the tranexamic acid group would be at least 50 ml, while others state that the difference between treatment arms in reduction from baseline MBL should be at least 50 ml. However, the Applicant used the former definition in the Statistical Analysis Plan for Studies 301 and 303. In addition, a recent approval of the IUD Mirena for a similar indication used a 50 ml reduction from baseline MBL as one criterion for success.

The primary efficacy endpoint was the reduction from baseline in MBL during the entire menstrual period, as assessed by the alkaline hematin method. For Study 301, MBL was averaged over all three treatment periods. In Study 303, MBL was averaged over Treatment Cycles 1, 2, 3 and 6.

Team Leader Comment

Alkaline hematin evaluation of MBL is considered the “gold standard.”

The Division and the Applicant agreed upon three prespecified key secondary endpoints that were accounted for in the statistical plan and were intended to support labeling claims; these were:

- Limitations in physical activities (LPA, based on Question 3 from the MIQ)
- Limitations in social and leisure activities (LSLA, based on Question 4 from the MIQ)
- Large stains (based on responses in the daily subject diary)

The primary efficacy population was the modified Intent to Treat (mITT), which comprised all randomized subjects who took at least one dose of study medication, had a baseline primary efficacy evaluation and had enough primary efficacy data to construct one period of data after the first dose.

If MBL data were missing (e.g., if sanitary products were not collected for a day), the subject's bleeding diary was examined for the missing day; if it indicated either spotting or no bleeding occurring, a 0 was imputed for MBL. If the diary indicated that it was a bleeding day, the alkaline hematin values were imputed from adjacent non-missing values. If MBL for an entire menstrual period was missing, no data were imputed.

Analysis used an ANCOVA model with fixed effects of treatment and baseline as covariates. Receiver operator characteristic (ROC) analysis was used to determine a level of MBL reduction that was clinically meaningful to subjects. This is further discussed in Section 7.4.1.2. To control for multiple comparisons, hierarchical hypothesis testing was utilized: first the primary endpoint for the comparison of the 3.9 g/day Lysteda vs. placebo arms was evaluated; if this was statistically significant, then the key secondary endpoints were sequentially evaluated for the same dose in the hierarchy of LSLA, LPA and large stains. If the null hypothesis was accepted at any point in the hierarchy, further hypothesis testing was not done. If all four endpoints for the 3.9 g/day dose of Lysteda were significant, then the same pathway was followed for the 1.95 g/day dose of Lysteda (in Study 301 only).

Both studies underwent an interim analysis after MBL data were available on 50% of the subjects, in order to re-estimate sample size for the LSLA and LPA endpoints. Based on the interim analysis, the sample size for Study 303 was increased. Interim analyses were performed by the Data Monitoring Committee using the conditional power method; no statistical penalty was taken.

Team Leader Comments:

- **The sequential analysis plan was changed from the original DRUP recommendations; the original plan would not have allowed the Applicant to evaluate the key secondary endpoints for the 3.9 g/day Lysteda dose if the 1.95 g/day dose failed on the primary endpoint. Because one of the objectives of Study 301 was to demonstrate the lowest effective dose, the Applicant did not expect the**

1.95 g/day dose to succeed, and it did not make sense to tie the evaluation of key secondary endpoints on the higher dose to success for the lower dose.

- **In other respects, the Applicant's statistical analysis was consistent with the recommendations made by DRUP during preNDA interactions.**

7.4.1.1 Primary Efficacy Results

The reduction in MBL in Study 301 was 65 ml in the 3.9 g/day Lysteda arm, 44 ml in the 1.95 g/day Lysteda arm and 7 ml in the placebo arm. Both Lysteda doses were statistically significantly better than placebo in MBL reduction from baseline; however, only the 3.9 g/day dose met the criterion of a change of at least 50 ml from baseline. Therefore, the 3.9 g/day dose of Lysteda was considered the lowest effective dose, was the dose carried into Studies 302-304, and is the only dose for which the Applicant seeks marketing approval.

In Study 303, the reduction from baseline in MBL was 66 ml in the 3.9 g/day Lysteda arm and 18 ml in the placebo arm. The difference was statistically significant. Again, the Lysteda dose met the 50 ml change from baseline criterion.

Tabular displays of the data for each study, as confirmed by the FDA statistician, are shown in Table 13 and Table 14.

To determine the clinically meaningful reduction in MBL, the Applicant developed a global rating of change question with a seven-point response option (this is Question 6 in the MIQ):

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

Source: Final Study Report, MIQ Validation in Women with Heavy Menstrual Blood Loss, p 28

Based on subjects' response to this question, asked at the end of the first on-treatment cycle in Study 301, a receiver operator characteristic (ROC) curve analysis was performed to identify the reduction in MBL that was clinically meaningful to subjects. The analysis was blinded to treatment assignment.

Team Leader Comment

The description of how the clinically meaningful value of MBL reduction was determined is **confusing**. The Applicant states "A blinded analysis of the amount of change in MBL from the pretreatment menstrual periods to the end of the first on-study bleeding period (associated with a change in menstrual bleeding that a subject had considered at least 'much better') provided the data for the analysis." The rating "much better" is not a response option for Question 6b on the MIQ, so it is unclear where this evaluation is coming from. This description was apparently based on the advice provided by SEALD in

presubmission communications, but it is questionable whether this “much better” categorization was actually used, as it is not described in the protocol (amendment 3). It appears that subjects had to answer “better” to Question 6 and then “yes” to Question 6c in order to be used in the ROC analysis. In this case, even subjects rating themselves as “almost the same, hardly better at all” would be included, which would likely decrease the value of the clinically meaningful MBL reduction.

Based on the mITT population, it was found that a 36 ml reduction in MBL optimized the sensitivity and specificity of the cutpoint on the ROC curve. At this value, the sensitivity is 65% and the specificity is 66%. The actual distribution of subjects dichotomized at this level is shown in Table 10.

Table 10 Subject Distribution by 36 ml MBL Reduction Cutpoint and Meaningfulness of Change

	Change > 36 ml	Change ≤ 36 ml	Total
Change was Meaningful	109 True positives	58 False negatives	167
Change was Not Meaningful	36 False positives	69 True negatives	105
Total	145	127	272

Team Leader Comment

The fairly poor sensitivity and specificity may be attributable to the inclusion of women who had minimal positive change in MBL in the calculations. Given the population assessed, the ROC did identify the optimal cutpoint, but a more sensitive and specific cutpoint would likely have been identified if the analysis population had been selected as requested by SEALD, to include only women who described their improvement perhaps at levels 5-7 on Question 6a. However, since both studies also met the higher bar of demonstrating an improvement of at least 50 ml in MBL, this criterion for success becomes less important.

7.4.1.2 Key Secondary Efficacy Results

Development and Validation of the Menorrhagia Impact Questionnaire

As discussed with the Division during various meetings over the clinical development program, the Applicant sought to evaluate several key secondary endpoints based upon a Patient-Reported Outcome (PRO) instrument, and also proposed to use the same instrument to help determine the magnitude of a reduction in MBL that was clinically meaningful to women with HMB, through an anchoring technique.

One of the objectives of Study 302 was to validate the Menorrhagia Impact Questionnaire (MIQ) to be used in Studies 301 and 303 to evaluate the key secondary endpoints LSLA and LPA and to determine the level of MBL reduction that is meaningful to women. The Applicant began by identifying concepts and domains that would form the conceptual framework for the generation of items to be included in the PRO. This started by open-ended qualitative interviews with 26 women enrolled in Study 302 at five different US sites to determine what they perceived as the impact of HMB and what they desired from medical therapy. These subjects identified a number of areas in which HMB had a significant impact; among these, need for frequent changes of sanitary products, limitations on activity or daily function and frequency of soiling were highest ranked. From these findings, a preliminary PRO measure and a preliminary monthly diary were developed and tested on a second subgroup of subjects (N=20) from Study 302, then refined using information from cognitive debriefing interviews. The initial PRO contained six items, covering qualitative description of

blood loss, limitations in work activity, physical activity, social or leisure activity, a checkbox of activities in which the subject participated during menses, and a global assessment question of change in blood loss since the previous period.

The major change instituted following this debriefing was to clarify that the MIQ should be answered based on the woman's experience over her entire period. For the diary, it was clarified that data should be entered daily from the day of a clinic visit until the next clinic visit. The specific items were unchanged.

Team Leader Comments:

- **The interviews that generated the initial items for the MIQ appear to have been appropriately open-ended and non-directive.**
- **The demographics of the subjects who participated in the interviews and the cognitive debriefing were generally similar to the demographics of subjects in Studies 301 and 303.**
- **The Study 302 subjects were qualified for study entry on the basis of physician determination that they had HMB, whereas the subjects in Studies 301 and 303 had to meet alkaline hematin MBL criteria for eligibility. It is unclear whether this would be likely to impact the generation and confirmation of items for inclusion in the MIQ. However, the target population of users once Lysteda is marketed will not undergo strict quantification of their MBL before receiving a prescription, so it is likely that the Study 302 subjects are representative of the target population.**
- **The Applicant does not discuss why the construct concerning limitations in work activities was not included in the MIQ, as this was ranked as the activity most limited during menses by about 50% of subjects. It was also ranked as one of the most important concepts.**
- **It is not clear that saturation of item development was reached.**
- **The cognitive debriefing group indicated that clarity and ease of use of the MIQ and the daily diary were good.**

The MIQ was then validated in a subgroup of 131 subjects in Study 302 diagnosed with menorrhagia, and an age-matched control group of 131 women with normal menstrual periods by self-report. The validation study also evaluated the bleeding diary.

Data from the 262 subjects in the validation cohort provided data at baseline and following the first treatment (or non-treatment for normal controls) period, which was used to evaluate variability, the conceptual framework, construct-related validity, ability to detect change and respondent burden. Data from the 80 menorrhagia subjects who volunteered for test-retest was used to assess test-retest reliability. The first four questions on the MIQ were evaluated separately for validation; the last two (Questions 5 and 6) were considered descriptive variables and were not formally validated. [Question 1 concerns self-perceived blood loss, Question 2 limitations in work activities, Question 3 limitations in physical activities and Question 4 limitations in social and leisure activities.]

Variability measures the extent to which the full range of responses is used. At baseline, the combined study group utilized the entire range of response options for MIQ Questions 1-4, indicating adequate variability.

For test-retest reliability, a score above 0.7 indicates stability of responses over time. The intraclass coefficient score for the treatment group ranged from 0.72 to 0.77, indicating good reliability over repeated administrations in the menorrhagia population.

Construct-related validity evaluates whether relationships among items, domains and concepts conform to what is predicted by the conceptual framework, including convergent and discriminant validity, as measured by correlation coefficients between each MIQ item and items and scales from other PRO instruments believed to be relevant to menorrhagia (i.e., the Short Form 36 [SF-36] and Ruta Menorrhagia Questionnaire). The MIQ items showed strong correlation with the menorrhagia-specific instrument, the Ruta, while the correlation was weaker with the SF-36, which is a generic health status instrument.

Known-groups validity determines the ability of the instrument to distinguish between groups known to be distinct (i.e., menorrhagic and normal subjects). For each MIQ item at baseline, there was a statistically significant difference between mean scores for the HMB vs. normal cohorts, with the menorrhagic subjects reporting scores about one point higher on the four-point item (Question 1) and 1.7 points higher on the five-point items (Questions 2-4).

Ability to detect change evaluates the extent to which scores change when the concept measured changes. This was assessed on the change from baseline to Month 1 scores. For each of the first four MIQ questions, normal subjects reported almost identical mean scores at baseline and Month 1, while subjects with HMB tended to decrease by about one point on a four or five-point scale from baseline to Month 1. The calculated effect sizes for the four items in the HMB group ranged from -0.9 to -1.2 (negative indicates improvement), while for the normal group, the effect sizes ranged from 0.05 to -0.2.

For the bleeding diary, the decline from baseline to Month 1 was statistically significantly greater for the HMB group than for the normal group on number of bleeding days, number of large clots, and number of large stains.

Team Leader Comments:

- **The demographics of the menorrhagic subjects were similar to those in the phase 3 studies generally in terms of age and duration of HMB.**
- **The PROs used to evaluate construct-related validity have not themselves been accepted by SEALD as valid instruments to assess menorrhagia impact. For this reason, I place little weight on this assessment. However, I believe that the development of the MIQ based on patient input starting with the initial focus groups provides reasonable assurance that it is assessing appropriate domains that concern women with heavy menstrual bleeding.**
- **I concur that the validation study demonstrated acceptable psychometric properties for the MIQ, and that it is an acceptable instrument for use in measuring the key secondary endpoints of limitation in physical activity (LPA, MIQ Question 3), limitation in social and leisure activity (LSLA, MIQ Question 4). The bleeding diary appears appropriate for assessment of large stains.**

Secondary Efficacy Analysis Results

The prespecified secondary endpoints of LSLA, LPA and large stains were analyzed in both studies for the 3.9 g/day Lysteda arm compared to placebo. Response options for LSLA (MIQ Question 4: During your most recent menstrual period, how much did your bleeding limit

your social and leisure activities?) and LPA (MIQ Question 3: During your most recent menstrual period, how much did your bleeding limit your physical activities?) were:

- 1: Not at all
- 2: Slightly
- 3: Moderately
- 4: Quite a bit
- 5: Extremely

For large stains, a responder analysis was performed, with a responder defined as a subject with a decrease in the number of large stains reported in the diary.

Results are presented in Table 11 and Table 12. The endpoints of LSLA and LPA were statistically significantly improved for the 3.9 g/day Lysteda arm as compared to the placebo arm. The difference between treatment groups on large stains was not statistically significant.

Table 11 Study 301: Key Secondary Endpoints in the mITT Population

Treatment Arm	N	Baseline Mean (SD)	Least Squares Mean Change	p-value
LSLA (MIQ Question 4)				
3.9 g/day Lysteda	112	3.0 (1.08)	0.98	< 0.0001
Placebo	66	2.9 (0.97)	0.39	
LPA (MIQ Question 3)				
3.9 g/day Lysteda	112	3.1 (1.04)	0.94	< 0.0001
Placebo	66	3.0 (0.87)	0.34	
Large Stains				
% Responders				
3.9 g/day Lysteda	111	64		0.16
Placebo	67	52		

Source: Based on Tables 11.4.2, and 11.4.3, page 48, Final Study Report of Study 301 and Tables 3.2.4.1 – 3.2.4.3, Statistical review of Dr. Fang, dated June 15, 2009

Table 12 Study 303: Key Secondary Endpoints in the mITT Population

Treatment Arm	N	Baseline Mean (SD)	Least Squares Mean Change	p-value
LSLA (MIQ Question 4)				
3.9 g/day Lysteda	115	2.9 (1.02)	0.85	< 0.0001
Placebo	72	2.7 (0.98)	0.44	
LPA (MIQ Question 3)				
3.9 g/day Lysteda	115	3.1 (0.95)	0.87	< 0.0001
Placebo	72	2.9 (0.95)	0.40	
Large Stains				
% Responders				
3.9 g/day Lysteda	115	57		0.45
Placebo	72	51		

Source: Based on Tables 11.4.2 and 11.4.3, page 47, Final Study Report of Study 303 and Tables 3.3.4.1 – 3.3.4.3, Statistical review of Dr. Fang, dated June 15, 2009

7.4.2 Statistician's Review and Conclusion

The statistical reviewer, Xin Fang, Ph.D., analyzed the data from the two phase 3 safety and efficacy studies (Studies 301 and 303). There were no major statistical issues regarding the analysis of the primary or three key secondary endpoints. Dr. Fang noted that the three pre-specified secondary endpoints were based on a patient-reported outcome instrument, the MIQ, for which he did not believe validity and reliability had been documented.

Team Leader Comment

I disagree with Dr. Fang's evaluation of the MIQ as an instrument without documented validity and reliability. As discussed in Section 7.4.1.2, I concur that the Applicant conducted an appropriate development and validation of the instrument, and that it, along with the bleeding diary, are acceptable for use in assessing the key secondary endpoints. However, Dr. Fang was not asked to review the validation substudy in Study 302, so he was probably not familiar with the methodology employed by the Applicant to develop and validate the instrument. His recommendation was that "inclusion of such secondary endpoints in the label should be exercised with caution." The Applicant's proposed endpoints as been denied, and the endpoints are discussed only in the Clinical Trials section of the label. b(4)

The sample size was calculated to provide 90% power to detect a 50 ml difference in the mean change from baseline in MBL between the active treatment and placebo arms. Assuming a 65 ml reduction in the tranexamic acid arm, and a 15 ml reduction in the placebo arm, with a common standard deviation of 85 ml and an allocation ratio of 2:1, the plan was to randomize 92 subjects to tranexamic acid and 46 to placebo.

Dr. Fang reported results on change in MBL in the mITT population in terms of the least square mean (based on the ANCOVA model), rather than the Applicant's reported sample mean.

The efficacy results as calculated by Dr. Fang for Studies 301 and 303 are shown in Table 13 and Table 14, respectively.

Table 13 Study 301: Mean Reduction from Baseline in MBL (ml) in the mITT Population

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

Source: Table 11.4-1 and reviewer's analysis

Source: Table 3.2.3, Statistical review of Dr. Fang, dated June 15, 2009

Table 14 Study 303: Mean Reduction from Baseline in MBL (ml) in the mITT Population

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

Source: Table 11.4-1

Source: Table 3.3.3, Statistical review of Dr. Fang, dated June 15, 2009

He made the following recommendation in his review dated June 15, 2009:

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

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

Team Leader Comment

Dr. Fang noted that he reported results as Least Squares mean change, rather than the sample means used by the Applicant, because the Least Squares means were adjusted for differences in baseline MBL, and also formed the basis of the statistical testing that generated the p value. I concur that Least Squares means should be reported in labeling.

Dr. Fang also confirmed the Applicant's secondary analyses of the LSLA, LPA and large stains endpoints.

7.4.3 Supportive Efficacy Analysis

The Applicant included supportive efficacy as an objective of long-term safety study 302; however, the instruments used were PRO instruments (the Ruta Menorrhagia Questionnaire and the SF-36) that were not accepted by the Division as validated for evaluation of HMB endpoints. Therefore, no further consideration is given in this review to the supportive efficacy analysis.

7.5 Overall Assessment of Efficacy

The goals of the two safety and efficacy studies were to establish the lowest effective dose by demonstrating an ineffective dose, and then to demonstrate efficacy in the remaining dose. The Applicant succeeded in doing so. Study 301 demonstrated that the lower dose of 1.95 g/day failed to reduce MBL by at least 50 ml from baseline, one of the criteria for success. The higher dose of 3.9 g/day was successful in both studies, meeting all three criteria established by the Division, of showing a statistically significantly greater reduction from baseline MBL, and a reduction that was at least 50 ml and at least the amount determined to be clinically meaningful to women. The clinically meaningful value was determined to be 36 ml in a ROC analysis conducted in Study 301. I would argue that the Applicant should have used a population that experienced a greater level of benefit from treatment to conduct the ROC analysis, which would likely have generated a higher value for "clinically meaningful" MBL reduction. However, I find the consistent reduction of MBL by over 65 ml in the 3.9 g/day

Lysteda arms in both studies, and the fact that this reduction exceeded that seen in placebo subjects by 48 – 58 ml, to be a persuasive demonstration of efficacy.

The Applicant further demonstrated efficacy on two of its three pre-specified secondary endpoints, limitations in social and leisure activities and in physical activity. Lysteda subjects **generally reduced their LSLA and LPA scores from an average of “moderately limited” to an average of “slightly limited.”** Thus, it appears that the reduction in MBL experienced by Lysteda users also addresses some of the impact of HMB that is bothersome to women with this condition. The responder analysis of change in large stains was not statistically significantly different between Lysteda and placebo arms.

8. Safety

The safety population evaluated was the ITT population (all randomized subjects who ingested at least one dose of study medication). In Study 301, the safety population comprised 297 of the 304 randomized subjects (115 in each of the 1.95 g/day and 3.9 g/day Lysteda dose arms, and 67 placebo subjects). In Study 303, the safety population comprised 189 of the 196 randomized subjects (117 in the 3.9 g/day Lysteda dose arm and 72 placebo subjects). Over both placebo-controlled studies, a total of 231 subjects were exposed to the 3.9 g/day dose, and used Lysteda for an average of 3.4 days per menstrual cycle.

Although the two long-term safety studies (Studies 302 and 304) were ongoing at the time of the NDA submission, the Applicant provided two safety updates, in April and September 2009, which provided data through the completion of the studies. The database for Study 304 was under final lock at the time of the last safety update; the database for Study 302 was still being cleaned, but was placed under interim lock. Data regarding exposure, deaths, serious adverse events (SAEs), and discontinuations due to adverse events are discussed in this section of the review based upon all data submitted, not just that in the initial submission. For this reason, numbers of events may vary from those reported in the primary medical review.

For Study 302, of 781 subjects who were randomized, 723 took at least one dose of study drug and therefore comprised the ITT population. Women in Study 302 dosed for an average of 2.9 days per menstrual cycle.

For Study 304, a total of 288 subjects enrolled, with 260 who took at least one dose and comprised the ITT population. Seventy-three of these had already been exposed to the 3.9 g/day dose of Lysteda in Study 301, 67 had received the 3.9 g/day dose of Lysteda in Study 303, and the remainder had rolled over from the 1.9 g/day dose or from placebo in one of the placebo-controlled trials. Women in Study 304 dosed for an average of 3.5 days per menstrual cycle.

In the long-term safety studies, the Applicant provided data from 12,169 cycles (10,213 in Study 302 and 1,956 in Study 304) of exposure to the 3.9 g/day dose. This is equivalent to 936 women-years of exposure. Over all four studies, which included over 1,200¹ women

¹ Only approximate numbers of subjects are provided for exposures ≤ 6 cycles; this is because Study 304 comprised subjects who rolled over from any of the dose arms of Studies 301 and 303. From the tables provided by the Applicant, it is not possible to tell if some of the 3.9 g/day subjects are counted in both the original and the extension study cycles. However, both Studies 301 and 303 were small compared to the long-term studies, so the impact on overall exposure is minimal.

exposed to the 3.9 g/day dose, over 1,000 had at least three cycles of exposure, over 800 had at least six cycles, 387 had at least 12 cycles of exposure, and 227 had at least 24 cycles of exposure.

Team Leader Comment

The exposure evaluated by the Applicant exceeded what was requested by the Division (10,000 cycles and at least 200 women completing one year of treatment). Including the four phase 1 studies that enrolled a total of 144 subjects, the exposure approximated ICH guidelines for drugs to be used on a chronic basis (1,500 subjects total, 300-600 for six months and 100 for 12 months).

8.1 Deaths and Serious Adverse Events

Deaths

One subject died during screening for Study 301, and one during screening for Study 302, both prior to randomization. There was a single on-treatment death in the clinical development program, that of Subject 525-2005 in Study 302. This was a 34 year old woman who took three cycles of treatment with 3.9 g/d of tranexamic acid, and approximately six weeks following her last dose was admitted in respiratory distress and diagnosed with bilateral pneumonia (community acquired) and sepsis. She was intubated and admitted to the ICU, where she was resuscitated following cardiorespiratory arrest. Her condition remained poor. On hospital day 35, a Doppler ultrasound of the lower extremities showed no evidence of DVT. An IVC filter was placed the next day for DVT/PE prophylaxis due to prolonged immobilization. She remained unresponsive to treatment, was placed on DNR status on hospital day 41, and she expired that day. The discharge summary listed pneumococcal sepsis as the primary diagnosis, with secondary diagnoses of pneumonia with respiratory failure and pneumothorax with interstitial emphysema. The death certificate listed primary cause of death as asystole, with additional causes being multiorgan failure, sepsis and pneumococcal bacteremia. An autopsy was not obtained.

Team Leader Comment

The patient had blood and sputum cultures indicating pneumococcus, and no evidence of a thromboembolic event. The IVC filter was placed prophylactically, following a negative Doppler ultrasound study. I do not believe this death was thromboembolic, or drug-related.

Serious Adverse Events

Subjects experiencing one or more SAEs are listed in Table 15. In Study 301, one subject (0.9%) on 3.9 g/day Lysteda experienced three SAEs, and one subject (0.9%) on 1.95 g/day Lysteda experienced a single SAE. No placebo subjects experienced an SAE. In Study 303, two subjects (1.7%) on 3.9 g/day Lysteda experienced an SAE, and three placebo subjects (4.2%) experienced four SAEs. There were 46 SAEs in 32 subjects (4.4%) in Study 302, and seven SAEs in five subjects (1.9%) in Study 304.

Table 15 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
303 616-3009	Acute bronchitis	Placebo	Hospitalization	Unlikely
	Post Traumatic Stress Disorder	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
302 505-2001	Menorrhagia	3.9 g/day	Severe	Possible – lack of efficacy (after 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
	Ventral hernia	3.9 g/day	Hospitalization	Unlikely
	Abdominal wall	3.9 g/day	Hospitalization	Unlikely

Study #, Subject #	SAE (Bold = led to study discontinuation)	Study Drug	Severity	Reviewer Assessment of Association
302 536-2051	abscess			
	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	Unlikely
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 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 treatment cycle; attributed to endometrial polyps; underwent hysteroscopic polypectomy followed by

Study #, Subject #	SAE (Bold = led to study discontinuation)	Study Drug	Severity	Reviewer Assessment of Association
				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: 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

Team Leader Comments:

- **Of the subjects with SAEs that may be related to study medication, Subject 303 653-3010 underwent an elective hysterectomy for heavy menses, which occurred every 14 days, lasting 7-10 days. She had taken one cycle of treatment prior to surgery. Pathology revealed multiple uterine fibroids, the largest 3 cm. This SAE may reflect lack of efficacy of treatment. 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 301 752-1002 went to the ER for complaints of chest pain that occurred three weeks after completing her second cycle of dosing. Despite negative cardiac enzymes, EKG, stress thallium treadmill test and stress myocardial myoview study, she was admitted due to risk factors and the fact that her pain resolved with nitroglycerin. Further work-up the next day by endoscopy demonstrated distal esophagitis and gastritis with superficial gastric ulcerations, and she was diagnosed with chest pain secondary to gastritis, superficial gastric ulcerations, hypertension and anxiety.**
- **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.**
- **Subject 302 547-2016 experienced a syncopal episode three days after completing dosing for her second cycle of treatment. Associated symptoms included diarrhea and chest pain. She was admitted for 23 hour observation, with all testing results normal, and was diagnosed with a GI virus.**
- **Subject 304 774-1004 is discussed in Section 8.2.1.2.**
- **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 8.2).

Withdrawals due to Adverse Events

The number of subjects who withdrew due to an adverse event is shown in Table 4 through Table 7. Specific AEs that led to withdrawal are shown below in Table 16 through Table 19. One specific AE leading to withdrawal is a possible case of severe allergic reaction occurring in a subject (724-1009) from Study 301 who rolled over into Study 304. She experienced throat tightening, shortness of breath and facial flushing after her 10th dose in the first cycle in Study 304; she had previously completed three cycles on 3.9 g/day Lysteda in Study 301. This case is further discussed in Section 8.2.

Table 16 Adverse Events Leading to Withdrawal – Study 301

Preferred Term [Bold = SAE (#)]	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		
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 17 Adverse Events Leading to Withdrawal – Study 303

Preferred Term [Bold = SAE (#)]	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

Table 18 Adverse Events Leading to Withdrawal – Study 302 (3.9 g/day)

Preferred Term [Bold = SAE (#)]	# 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
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
Partial seizures	1
Pelvic pain	1
Peripheral edema	1

Preferred Term [Bold = SAE (#)]	# Subjects withdrawing (Total 97 of 781 or 12.4%)
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: Data listing 4.1, pp 53 to 62, Applicant's Submission of September 30, 2009

Table 19 Adverse Events Leading to Withdrawal – Study 304

Preferred Term [Bold = 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: Data listing 2.1, p 130, Applicant's Submission of September 30, 2009

Team Leader Comments

- The case of dyspnea/throat tightness occurred in a subject during her fourth cycle of exposure to tranexamic acid and could represent a severe allergic reaction (see Section 8.2 for further discussion).
- There otherwise does not appear to be a particular pattern of concern in the AEs leading to withdrawal in either the placebo-controlled or the open label studies.

8.2 Other Adverse Events

Common Adverse Events

Common AEs for each study are listed in Table 20 for the short-term placebo-controlled efficacy trials and in Table 21 in the long-term uncontrolled safety trials.

Table 20 Adverse Events Occurring in ≥ 5% of Subjects Taking Lysteda and More Frequently than in Placebo – Studies 301 and 303

Preferred Term	Lysteda 1.95 g/day		Lysteda 3.9 g/day		Placebo	
	N (total N = 115)	%	N (total N = 115)	%	N (total N = 67)	%
Study 301 (3 months)						
Headache + tension headache	54	47.0	48	41.7	26	38.8
Back pain	20	17.4	20	17.4	7	10.5
URI + viral URI	16	13.9	8	7.0	7	10.4
Musculoskeletal pain + discomfort + myalgia	15	13.0	13	11.3	2	3.0
Nasal congestion + respiratory tract congestion + sinus congestion	13	11.3	5	4.4	2	3.0
Fatigue	13	11.3	4	3.5	3	4.5
Diarrhea	12	10.4	10	8.7	4	6.0
Sinusitis + sinus headache + sinus pain	11	9.6	5	4.4	3	4.5
Multiple allergies + seasonal allergies	10	8.7	6	5.2	2	3.0
Nausea	9	7.8	5	4.4	4	6.0
Arthralgia	7	6.1	5	4.4	1	1.5
Throat irritation	7	6.1	0		2	3.0
Migraine	7	6.1	7	6.1	4	6.0
Muscle cramp	3	2.6	6	5.2	3	4.5
Pain in extremity	6	5.2	3	2.6	3	4.5
Anemia	6	5.2	1	0.9	1	1.5
Study 303 (6 months)						
			N (total N = 117)	%	N (total N = 72)	%
Menstrual discomfort + dysmenorrhea			77	65.8	40	55.6
Headache + tension headache			69	59.0	39	54.2
Back pain			28	23.9	14	19.4
Abdominal discomfort + pain + pain lower + pain upper			23	19.7	10	13.9
Sinusitis + sinus headache + allergic sinusitis + sinus pain			17	14.5	6	8.3
Multiple allergies + seasonal allergies			14	12.0	7	9.7
URI + viral URI			14	12.0	7	9.7
Musculoskeletal pain + myalgia			13	11.1	2	2.8
Anemia			12	10.3	4	5.6
Nasal congestion + respiratory tract congestion + sinus congestion			12	10.3	4	5.6
Arthralgia + joint stiffness			11	9.4	6	8.3
Muscle cramp(s) + muscle spasms			9	7.7	5	6.9
Pain in extremity			8	6.8	2	2.8
Fatigue			8	6.8	3	4.2
Migraine			7	6.0	4	5.6

Bolded cells for Study 301 indicate treatment arm with higher rate of AEs

Source: Table 61, pp 202-211, Final Study Report of Study 301 and Table 49, pp 140-150, Final Study Report of Study 303

Team Leader Comments

- In Study 301, almost all AEs that were higher in Lysteda than placebo arms occurred most frequently in the 1.95 g/day group. The single exception was muscle cramps, which was only slightly more common in the 3.9 g/day arm than the placebo group, which was in turn, higher than the 1.95 g/day arm. Back pain and migraine occurred with equal frequency in both Lysteda arms, and more commonly than in the placebo arm.
- Events in the following System Organ Classes (SOCs) occurred more commonly in placebo than Lysteda subjects in Study 301:
 - Cardiac Disorders (3% in placebo vs. 0% in 3.9 g/day Lysteda; specifically, the Preferred Term (PT) palpitations)
 - Ear and Labyrinth Disorders (3% in placebo vs. 2.6% in 3.9 g/day Lysteda; specifically, the PTs ear pain and tinnitus)
 - Renal and Urinary Disorders (1.5% in placebo vs. 0.9% in 3.9 g/day Lysteda; specifically, the PT polyuria)
 - Reproductive System and Breast Disorders (55.2% in placebo vs. 43.5.0% in 3.9 g/day Lysteda; specifically, the PTs menorrhagia, menstrual discomfort, pelvic pain, PMS and vulvovaginal disorder)
 - Skin and Subcutaneous Tissue Disorders (6.0% in placebo vs. 5.2% in 3.9 g/day Lysteda; specifically, the PTs acne and dandruff)
- Events in the following SOCs occurred more commonly in placebo than Lysteda subjects in Study 303:
 - Eye Disorders (12.5% in placebo vs. 6.0% in Lysteda; specifically, the PTs nuclear cataract, color vision abnormal blue-yellow, conjunctivitis, dry eye, hyalosis asteroid, lens disorder, and vision blurred)
 - GI Disorders (37.5% in placebo vs. 31.6% in Lysteda; specifically, the PTs abdominal discomfort, anal polyp, diarrhea, dyspepsia, epigastric discomfort, food poisoning, gastritis, GERD, mouth ulceration, nausea, oral pruritis, pancreatitis, and vomiting)
 - Hepatobiliary Disorders (2.8% in placebo vs. 0% in Lysteda; specifically, the PTs cholecystitis and cholelithiasis)
 - Injury, Poisoning and Procedural Complications (4.2% in placebo vs. 2.6% in Lysteda; specifically, the PTs joint dislocation, muscle strain and post-procedural pain)
 - Investigations (19.4% in placebo vs. 17.1% in Lysteda; specifically, the PTs blood bicarbonate decreased, blood triglycerides increased, blood urine, color vision test abnormal, hematocrit decreased, hemoglobin decreased, mean cell volume decreased, monocyte count decreased, RBC count decreased, and serum ferritin decreased)
 - Musculoskeletal and Connective Tissue Disorders (38.9% in placebo vs. 34.2% in Lysteda; specifically, the PTs arthritis and flank pain)
 - Skin and Subcutaneous Tissue Disorders (8.3% in placebo vs. 6.0% in Lysteda; specifically, the PTs acne, pruritis, psoriasis and urticaria)
 - Vascular Disorders (5.6% in placebo vs. 4.3% in Lysteda; specifically, the PTs deep vein thrombosis and hypertension)

Table 21 Adverse Events Occurring in \geq 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: Table 17, pp 23 - 50, and Table 2, pp 117-128, Applicant's Submission of September 30, 2009

Team Leader Comments

- The pattern and relative frequency of AEs are similar in the two 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 studies and represent conditions likely to be commonly experienced in the general population.
- Two AEs (Menstrual discomfort + dysmenorrhea and Abdominal discomfort + pain + pain lower + pain upper + tenderness) were actually more common in the placebo arms of the Study 301. In Study 303, Abdominal discomfort + pain + pain lower + pain upper + tenderness was more common in the Lysteda arm.
- In Study 303, diarrhea, nausea and dyspepsia were more common in the placebo arm. Therefore, I believe it is unlikely that these events are drug-related, even though they occur with relative frequency in the open label studies.
- Looking at the AE profiles over all four studies, it appears to me 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, these AEs should be presented in tabular format, and I believe the most useful display is a comparison of rates (as shown below), using the pooled data from the two placebo-controlled studies for the 3.9 g/day Lysteda vs. placebo arms.

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

Serious Allergic Reactions

Subject 304 724-1009 in Study 304 (who had rolled over following three cycles on 3.9 g/day Lysteda in Study 301) experienced what initially appeared to be a severe allergic reaction, or even anaphylaxis, during her 4th cycle of treatment (following dose 10 in her first cycle in Study 304). Approximately six hours after dosing, while at her job in a transplant unit, she complained of a “rush” sensation and a taste of “blood” in her throat. She was mildly

hypertensive and tachycardic, and her colleagues took her down to the ER. Prior to treatment by ER staff, her colleagues started an IV and administered IV diphenhydramine. The subject at this time was reporting a “full sensation in her throat, experiencing intermittent tingling sensations throughout her body, palpitations and some SOB [shortness of breath].” Her chief complaint was noted to be “dyspnea, swelling” and she denied chest tightness, diarrhea, facial swelling, nausea, rash, stridor, tongue swelling, vomiting or wheezing. She was treated with lorazepam, and IV methylprednisone and observed for about 5 hours, then discharged home. Later discussions with the subject revealed that she had previously had an “anxiety attack” with similar symptoms that was treated with Zolof, and that she had had some stressful encounters and little food intake shortly before the current episode.

Further review of records indicated that she had reported an episode of “throat tightening” with her first dose of the third cycle in Study 301, but had continued to dose throughout that cycle without further AE reports. She had also previously reported “jaw clicking” and “ear popping” with earlier doses and noted that these symptoms were “similar to her reaction in the past when taking ASA [aspirin],” to which she reported an allergy.

Team Leader Comments:

- **The time course and the subject’s normal blood pressure, along with lack of respiratory symptoms, argue against this representing an anaphylactic reaction, which is typically characterized by rapid onset following exposure to a potential allergen of skin/mucosal symptoms with either respiratory compromise or hypotension². However, the subject’s prior history of “throat tightening” during her third cycle of use is intriguing, and suggests that there may be an allergic component to her reaction.**
- **One other case report of anaphylaxis associated with bolus intravenous administration of tranexamic acid was found on a literature search, in a 72 year old man undergoing cardiac surgery³.**
- **I believe that these cases warrant discussion in labeling.**

Following review of this case, the Applicant was asked to search the trial databases for any other possible cases of anaphylaxis or severe allergic reactions, and also to provide any information available regarding the extent of global postmarketing reports of such reactions. The Applicant submitted responses on October 30 and November 2, 2009.

The review of the databases was based on a search of 14 relevant CRF Verbatim Terms and MedDRA preferred terms related to possible allergic reactions. This revealed 12 reports that were temporally associated with dosing, and an additional 33 reports that included one or more terms but were not temporally associated with dosing. These latter cases were excluded from further consideration. In addition, there were three reports involving placebo subjects. No reports of anaphylaxis were identified.

Of the 12 reports associated with dosing, the Applicant identified three of them as potential cases:

² Sampson HA et al. Second symposium on the definition and management of anaphylaxis: summary report – second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006, 47: 373-80

³ Lucas-Polomeni MM et al. A case of anaphylactic shock with tranexamic acid (Exacyl). *Ann Fr Anesth Reanim.* 23: 607-09, 2004

- **Subject 302 512-2035** – experienced allergic rash, urticaria and “hives over entire body” 8 and 22 days after dosing in Cycle 5, then experienced itchy rash and/or urticaria and hives during Cycles 7, 8 and 9. She ultimately withdrew due to these AEs.
- **Subject 302 563-2011** – experienced dyspnea and SOB on two sequential cycles and ultimately withdrew due to these AEs.
- **Subject 302 563-2014** – experienced rash on her extremities on the fourth day of dosing in her first cycle; she did not take further doses and withdrew due to this AE.

Team Leader Comments:

- **I reviewed all 12 cases and agree with the Applicant’s conclusion that Subjects 302 512-2035 and 302 563-2011 are likely cases of allergic reaction to tranexamic acid.**
- **I consider that Subject 302 563-2014 is a possible case, but a single reaction is not conclusive evidence to me. In addition to this subject, I consider that Subject 302 560-2015 (one of the 12 cases, but not considered by the Applicant to be a potential case) is a possible case. She experienced moderate SOB with dosing on the 2nd day of the first dosing cycle. She also experienced moderate diarrhea the following day and withdrew from the study for this AE.**
- **Overall, I consider that the database includes three likely cases of allergic reactions (Subjects 304 724-1009, 302 512-2035 and 302 563-2011) and two possible cases (Subjects 302 563-2014 and 302 560-2015). I concur with the Applicant that there were no cases of anaphylaxis.**
- **I also concur with the Applicant that the 33 reports of index symptoms that were not associated with dosing are unlikely to represent drug-related allergic reactions.**

The Applicant also provided data from the WHO safety database, searched from 1969 to August 3, 2009. There were 857 unique events reported in association with tranexamic acid (the estimated exposure was approximately _____ prescriptions per year worldwide). Of these, 80 reports were of potential allergic, hypersensitivity or anaphylactic reactions. Seventeen of these reports were specifically of anaphylactic shock or anaphylactoid reaction.

b(4)

Team Leader Comment

Although the number of events in the WHO database is extremely small, it is notable that almost 10% relate to allergic reactions. Based on this, and the signal in the clinical trials, I believe that discussion of allergy and hypersensitivity should be included in labeling, including Contraindications, Warnings, Adverse Reactions (Clinical Trials and Postmarketing subsections) and patient labeling. The Applicant has agreed to proposed language.

The Applicant also performed a search of the worldwide literature and identified the same case noted above. One other case was found, in which tranexamic acid was one of several suspect medications.

Pregnancies

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.

There were 13 pregnancies reported in Study 302; 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 positive pregnancy test, but provided no medical records.

There were no pregnancies in Study 304.

Laboratory Data and Vital Signs

Laboratory and vital signs data are discussed in Dr. Davis' review, and did not provide any signal of concern.

8.2.1 Special Safety Studies

8.2.1.1 Ophthalmology Assessment

For Studies 301 and 303, the Applicant evaluated the distribution of adverse events over treatment arms by Chi Square test. No significant difference was noted for the Eye Disorder System Organ Class (SOC) overall for either study, or for individual Eye Disorder SOC Preferred Terms (PT) in Study 301. In Study 303, the PT Vision Blurred was statistically significantly increased ($p=0.03$) in the placebo arm (3 subjects [4.2%] vs. none in the 3.9 g/day Lysteda arm). Other visual PTs reported by $\geq 1\%$ of subjects in either arm include:

- **Vision Blurred – 1.5% in placebo arm of Study 301 (none in Lysteda arms)**
- **Cataract Nuclear – 1.4% in placebo arm of Study 303 (none in Lysteda arm)**
- **Color Vision Test Abnormal (Blue-Yellow) – 2.8% in placebo arm of Study 303 (0.9% in Lysteda arm)**
- **Retinal Deterioration – 1.7% in Lysteda arm of Study 303 (none in placebo arm)**

In Study 302, the following PTs in the Eye Disorders SOC were reported by $\geq 1\%$ of subjects:

- **Conjunctivitis – 1.7%**
- **Eye pruritis – 1.2%**
- **Vision Blurred + Visual Acuity Reduced – 1.0%**

In Study 304, the only AE in the Eye Disorder SOC that occurred in more than a single subject was Vision Blurred, experienced by two subjects (0.8%).

Team Leader Comments

- **The pattern of eye-related AEs in the two placebo-controlled studies does not indicate a higher risk of visual AEs in the Lysteda-exposed subjects.**
- **The rate of Vision Blurred in the open-label studies appears consistent with and even lower than that seen among placebo subjects in the placebo-controlled studies, even though the duration of the latter studies was shorter.**
- **The PTs Vision Blurred and Visual Acuity Reduced were bundled in reporting results from Study 302 because these may represent similar symptoms. In the remaining three studies, there were no reports of Visual Acuity Reduced**

The Applicant conducted ophthalmologic examinations as recommended by DRUP's ophthalmology consultant, Dr. Wiley Chambers. These included ocular examinations at

baseline and Week 12 (or early termination) in Study 301; baseline and Week 24 (or early termination) in Study 303; baseline and Weeks 12, 24, 60 and 108 (or early termination) in Study 302; and at Week 36 (or early termination) in Study 304. These exams included visual acuity for each eye measured separately, the HRR test for color blindness, measurement of intraocular pressure and dilated retinal examination.

Team Leader Comments:

- **The ophthalmologic exams provided were consistent with the advice provided by Dr. Chambers, although he did not request color vision testing.**
- **The data provided in the Study Report for Study 304 is uninterpretable, as there is no baseline, and no link is provided to ~~the subject's original baseline~~ back in Study 301 or 303. A total of 86 subjects (33%) had ophthalmologic test results reported. It cannot be determined whether intraocular pressure or visual acuity results were changed from baseline or from a later exam in the previous study. Two retinal fundoscopic exams were categorized as "abnormal;" and had the notations "as before" and "previously noted." A single color vision test was noted as abnormal, but was noted not to be of clinical significance.**

Results of the ophthalmologic exams are shown in Table 22.

Table 22 Results of Ophthalmologic Exams in all 4 Studies

Study 301						
Parameter	N evaluated		Lysteda 3.9 g/day		Placebo	
	Lysteda	Placebo	R eye	L eye	R eye	L eye
IOP	105	64	0.1	-0.1	-0.4	-0.3
Visual acuity decreased	105	64	6.7%	10.5%	6.3%	10.9%
Visual acuity increased	105	64	4.8%	6.7%	4.7%	3.2%
Color vision nl → abnl	104	64	1.0%		0	
Color vision abnl → nl	104	64	1.9%		1.6%	
Retinal exam nl → abnl	104	64	1.0%		0	
Retinal exam abnl → nl	104	64	4.8%		1.6%	
Study 303						
Parameter	N evaluated		Lysteda 3.9 g/day		Placebo	
	Lysteda	Placebo	R eye	L eye	R eye	L eye
IOP	100	60	-0.4	-0.5	0.0	0.1
Visual acuity decreased	100	60	6.0%	6.0%	6.7%	5.0%
Visual acuity increased	100	60	9.0%	7.0%	13.3%	8.3%
Color vision nl → abnl	100	59	1.0%		6.8%	
Color vision abnl → nl	100	59	2.0%		3.4%	
Retinal exam nl → abnl	100	60	0		0	
Retinal exam abnl → nl	100	60	6.0%		3.3%	
Open-Label Safety Study 302						
Parameter	Lysteda N evaluated at Study Termination		R eye		L eye	
IOP	153		0.0		0.3	
Visual acuity decreased	152 (151 L eye)		9.9%		9.9%	
Visual acuity increased	152		9.2%		8.6%	
Color vision nl → abnl	153				1.3%	
Color vision abnl → nl	153				2.0%	
Retinal exam nl → abnl	151				2.7%	
Retinal exam abnl → nl	151				5.3%	

IOP = intraocular pressure (change from baseline to final visit)

Source: Tables 90 – 95, pp 275-280, Final Study Report of Study 301; Tables 77– 82, pp 212-217, Final Study Report of Study 303; Tables 30 – 41, pp 219-230, Final Study Report of Study 302; and Appendix 16.2.9, Data Listing 11, pp 253-267, Final Study Report of Study 304

Team Leader Comments:

- For visual acuity, in the placebo-controlled studies, the proportion with adverse changes in the Lysteda arms was similar to those in the placebo arms.
- For color vision and retinal exams, the Lysteda subjects experienced equivalent changes in both directions (normal to abnormal and abnormal to normal). This suggests there is no overall adverse impact of Lysteda on color vision or retinal findings. This is further confirmed by the findings of increased reports of abnormal color vision in placebo subjects in Study 303.
- Results from the open label Study 302 are somewhat limited by the fact that there was a marked decrease in the number of subjects who underwent ophthalmologic exams over time (from 715 at baseline in Study 302 to 153 at study termination). If subjects withdrew due to ocular adverse events, these results could be seriously biased. However, a total of eight subjects (1.1%)

withdrew for reasons related to visual/ocular AEs, so this does not appear to account for a large amount of the subject attrition.

- **Table 22 displays results in the open-label Study 302 at the study termination visit; however, the pattern of changes noted at earlier evaluations tended to be similar to those reported for the last visit. For visual acuity, at all evaluations, the number of subjects who had improved acuity was about equal to the number whose acuity decreased. For color vision and retinal examination, the percent that changed from abnormal to normal exceeded those who changed from normal to abnormal at all assessment periods.**
- **Overall, I do not find a signal for adverse impact of Lysteda on vision or ocular safety based on the results of the ophthalmologic testing. While the number of subjects tested at the end of each study was significantly less than the number initially enrolled, there is no indication that subjects were discontinuing on the basis of ophthalmologic AEs, which would introduce a serious bias.**

Ophthalmology Consult

The Division requested consultation from Dr. Wiley Chambers, Director of the Division of Anti-infective and Ophthalmologic Products, to assist in interpreting the results of the examinations. In his review dated June 30, 2009, he provided the following responses (in italics) to the Division's consult questions:

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

The clinical testing was appropriate for the potential signals noted in nonclinical 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?

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?

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?

Potential for ligneous conjunctivitis, venous stasis retinopathy and thromboembolic events including those in the eye. As noted in my consult from 2004, the administrative file for NDA 19-280 and 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?

None at this time.

In further discussions following receipt of this consult, Dr. Chambers recommended that labeling recommend visual examination prior to starting Lysteda, with repeat exams at regular intervals for women who use the product regularly. 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. Chamber's assessment of Applicant's proposal is discussed in the Team Leader comment below.

Division of Pharmacovigilance II (DPV II) Consult

DPV II was asked to review the AERS database with respect to VTEs and ophthalmologic AEs reported in association with tranexamic acid (e.g., Cyklokapron). AERS contained seven cases of possible ophthalmologic AEs associated with tranexamic acid. In his review dated May 18, 2009, Mark Miller of DPV II noted that these cases are poorly characterized and lack formal ophthalmologic testing, and **therefore "lacks information to fully evaluate an association."** However, following review of current Cyklokapron labeling, he recommended that visual abnormalities be noted in Warnings and Precautions, and that a recommendation should be made for a baseline eye examination.

Team Leader Comment

The clinical reviewers from DRUP, Dr. Chambers, and DPV II staff met to discuss the Applicant's submission of September 11, 2009. Following review, Dr. Chambers agreed with the Applicant that the ocular AEs of greatest concern would not be detected with baseline and interval visual examinations, and therefore no longer recommended baseline or routine on-treatment examinations. He also concurred with the modification of the Contraindication Section, and with the Applicant's proposed Warnings and Precautions language with slight modifications. This warning now reads:

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.

DRUP and DPV II concurred with Dr. Chambers' recommendations.

8.2.1.2 Assessment of Risk of Venous Thromboembolism (VTE)

There were no pulmonary emboli or deep vein thromboses (DVTs) in Studies 301, 302 or 304. One placebo subject in Study 303 experienced a DVT. In Study 304, Subject 774-1004 was evaluated for a possible cerebrovascular accident following completion of Study 301 and then at least six cycles of 3.9 g/day Lysteda in Study 304. She presented six days after her last dose of Lysteda with left-sided weakness, numbness and tingling, and was found on a cerebral angiogram to have a fusiform basilar artery aneurysm with three daughter aneurysms. She was determined to have a right pontine infarct secondary to the fusiform aneurysm. A transcranial Doppler study showed no emboli in the right posterior circulation. The upper basilar trunk was tortuous and showed underlying atherosclerotic disease, and a perforating artery in the vicinity of this diseased segment was noted to have spontaneously thrombosed. The subject ultimately underwent stent placement followed by successful stent-assisted coiling of the aneurysm.

Team Leader Comments:

- **Regarding Subject 774-1004, a review of Pubmed suggests that hemodynamic factors related to luminal geometry, as well as factors related to hypercoagulability, may affect the risk of spontaneous thrombosis in a fusiform basilar aneurysm, in particular, where the hemodynamics and geometry of the aneurysm result in relatively stagnant flow and/or low shear in one or more areas of the aneurysm⁴. Therefore, I believe that there are features of this case that make it questionable whether treatment with Lysteda had any relationship to the event. Given the relatively short half-life of tranexamic acid (11 hours) and the time course between last dosing and presentation of symptoms, a causal relationship is unlikely in my opinion.**
- **The statistical safety review by Olivia Lau, Ph.D. described six VTE AEs, ascertained on the basis of MedDRA terms, two of which occurred during screening. Of the remaining four AEs, Dr. Lau noted the DVT in the placebo subject, and the brainstem infarction in Study 304, Subject 774-1004, both mentioned above. The other two potential cases both involved subjects on 3.9 g/day of Lysteda, and included a case of abnormal Doppler ultrasound (Subject 622-3009 in Study 303) and a case of transient blindness (Subject 511-2023 in Study 302).**
- **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 May 30, 2007, the date of 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.**

⁴ Rayz VL et al. Numerical Modeling of the Flow in Intracranial Aneurysms: Prediction of Regions Prone to Thrombus Formation. Ann Biomed Eng 36: 1793-1804, 2008

- **In Study 302, Subject 511-2023 had an AE described as “one second loss of vision” on Day 46 of the study, which was also noted to be resolved. It is unlikely that this represents a thrombotic or embolic event.**
- **In summary, I agree with Dr. Davis’ assessment that the only VTE in the phase 3 trials was a single DVT occurring in a placebo subject.**

As noted above, DPV II was asked to review the AERS database with respect to VTEs reported in association with tranexamic acid (e.g., Cyklokapron). Following a search through April 2009, AERS was found to contain 40 cases of possible VTEs associated with tranexamic acid reported over the interval from 1993 to 1998. Of these, 60% were associated with the oral formulation, and none was a US report. One case involved a fatal pulmonary embolism associated with use of oral tranexamic acid for menorrhagia, and 18 cases involved hospitalizations. Three cases of retinal venous or arterial thrombosis were reported. Cases occurred in users with and without prior history of thromboembolic disease. In his review dated May 18, 2009, Mark Miller of DPV II **recommended strengthening the Applicant’s proposed Contraindications section of labeling to address women with active thromboembolic disease, and adding a Warnings and Precautions section regarding possible increased risk of VTE in women with a past history of thromboembolic disease.**

Team Leader Comment

In the agreed-upon labeling, Lysteda is contraindicated in women with active thromboembolic disease, a history of thrombosis or thromboembolism, or an intrinsic risk of thrombosis or thromboembolism. The Warnings and Precautions section discusses potential increased risk of VTEs if Lysteda is used concomitantly with combined hormonal contraceptives, which have a known association with VTE. Retinal vascular thrombosis is also addressed in a Warning.

8.2.1.3 Through QT Study

The Applicant conducted a thorough QT (TQT) study that evaluated the effect on prolongation of the QT interval in a single dose cross-over design. The study evaluated the proposed therapeutic dose of Lysteda (1.3 gm), a suprathreshold dose of Lysteda (3.9 gm), placebo, and a comparator known to have a significant effect on QT prolongation (moxifloxacin 400 mg). The study was reviewed by the Interdisciplinary Review Team (IRT) for QT Studies. The conclusion of the consultative review, dated May 18, 2009, was

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 the ICH E14 guideline. The largest lower bound of the 2-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 IRT made recommendations for labeling regarding the QT effects; slight modifications made by the Applicant were acceptable to the IRT reviewer.

8.2.2 Safety Biometrics Review

As a result of the NDA submission containing datasets in the Clinical Data Interchange Standards Consortium (CDISC) format, the safety data were reviewed by the Division of Biometrics VII. The reviewer, Olivia Lau, Ph.D., focused particularly on ophthalmologic, renal and VTE safety issues, along with other AEs. Although the studies were not powered to test safety-related hypotheses, the presentation of the data in CDISC format allowed for exploratory statistical analysis. Dr. Lau raised concern in her review about the overall sufficiency of the data to permit adequate assessment of the long-term safety of Lysteda. She also expressed concern that the ophthalmologic evaluations constituted a convenience sample, and noted apparent imbalances in adverse findings on the ophthalmologic exams, as well as in the reports of ophthalmologic AEs and VTEs for subjects treated with Lysteda as compared to placebo subjects. Dr. Lau further calculated relative risks for the occurrence of AEs listed by SOC and PT, and identified seven PTs that she determined were statistically significantly elevated in Lysteda subjects. These were: musculoskeletal pain, nasal congestion, anemia, arthralgia, fatigue, back pain, and headache.

Team Leader Comments:

- **I do not agree with Dr. Lau's determination of the VTE cases, as discussed in Section 8.2.1.2. Her assessment of a greater number of cases among Lysteda subjects was based only on a review of MedDRA terms, while Dr. Davis and I were able to review the narratives and verbatim reports, which allowed us to make clinical judgments about the likelihood that the MedDRA term represented a true VTE.**
- **My assessment of the ophthalmologic examination data and AE reports is discussed in Section 8.2.1.1. I find her discussion one-sided, and a review of the reports and shift tables for both Lysteda and placebo groups indicates that there is no signal of concern regarding an adverse impact of Lysteda on ophthalmologic parameters. This conclusion is further supported by Dr. Chambers' evaluation of the ophthalmologic findings.**
- **While I do not agree that statistical significance testing is warranted for these safety data, my independent review of the frequency of AE reports identified all of the AE terms Dr. Lau specified as occurring more frequently among Lysteda subjects than placebo subjects. These will be noted in labeling.**
- **Finally, I disagree with her assessment that the data are insufficient to permit adequate assessment of the long-term safety of Lysteda use. The Division had extensive input into the design of the clinical development program, and the Applicant complied with all DRUP requests with regard to the size of the safety database. The magnitude of exposure was consistent with or in excess of what the ICH guidelines recommend. While recognizing that safety evaluation in clinical trials is seldom intended to characterize the occurrence of rare adverse events, I am also reassured by the long and widespread use of tranexamic acid for this indication, which has not revealed additional safety signals.**

A secondary review by Dr. Paul Schuette, dated October 27, 2009, addressed many of the areas of disagreement, and noted that the trials had been powered for efficacy, not for safety endpoints. Safety analyses should be regarded as exploratory given that safety endpoints were not prespecified. Interpretation of data is compromised by missing data and use of uncontrolled, open label studies for evaluation of longer-term safety. He concluded:

Since all conclusions in the primary review are exploratory in nature, we defer to the review division for the clinical relevance and significance of any observed outcomes or imbalances.

We cannot comment on whether the totality of the other existing data together with the submitted clinical trials data is adequate to establish the long term safety and risk/benefit profile for Lysteda, but will defer to the judgment of the review division in this matter.

8.3 Safety Update

A 90-day safety update was submitted by the Applicant on April 30, 2009. As agreed at the pre-NDA meeting, the ongoing open label safety studies (Studies 302 and 304) were updated with data from all subject visits occurring through February 28, 2009. Following the clock extension, the Applicant was requested to submit a further safety update, given the expected completion of the ongoing studies. Additional updates were submitted on September 28 and September 30, 2009. By this point, both Study 302 and 304 had been completed and the database for Study 304 had been locked. An interim lock had been placed on the Study 302 database, as there remained a few open queries. None of the queries impact the data reported in the safety update, according to the Applicant. As described in earlier sections of this review, the updated safety information has been integrated and presented within each relevant safety section.

8.4 Postmarketing Safety Findings

The Applicant's proposed oral formulation of tranexamic acid is not currently marketed anywhere in the world. However, another oral formulation of tranexamic acid has been marketed for over 40 years for treatment of menorrhagia in Scandinavia, and oral tranexamic acid tablets are widely used in Europe, Japan and Canada. Tranexamic acid tablets has been available over-the-counter in Sweden for over ten years. Labels for tranexamic acid for the treatment of menorrhagia from Australia, Canada, Sweden and the U.K. were reviewed for reports of adverse reactions; these labels are consistent with the labeling proposed for Lysteda.

8.5 Literature Review

Based on a review of the literature and publications submitted by the Applicant, several studies were identified that pertain to the potential for thromboembolic risk associated with use of tranexamic acid. Berntorp et al⁵ conducted a case-control study to evaluate the association of recent use of tranexamic use with a thromboembolic event. Reproductive-aged female cases (N=662) of VTE, verified by radiologic evaluation, were identified from a tertiary care registry for a six-year period and matched by gender, age and geographic location to multiple controls (N=1,506). Cases and controls were interviewed about their use of tranexamic acid and other medications, including hormonal contraceptives, in the month preceding the event (cases) or the month preceding the interview (controls). Based on estimates of drug use in Sweden, the authors estimate that the study was powered to be able to detect a two to threefold higher use of tranexamic acid among cases. The frequency of VTE was higher among control women, resulting in an odds ratio of 0.55 (0.31-0.97) for the association of tranexamic acid with VTEs. In contrast, the odds ratio for oral contraceptives, known to be associated with VTE risk, was

⁵ Berntorp E, Follrud C, Lethagen S. No increased risk of venous thrombosis in women taking tranexamic acid. *Thromb Haemost* 2001; 86: 714-5

2.41 (1.98 – 2.92). Recall bias could have occurred in either direction in this study; typically, cases are more likely to recall past exposures than are controls, but in this case, the medication usage was likely ascertained over a more recent period for controls as compared to cases. Nonetheless, this study gives no indication of an association between of tranexamic acid and VTE.

A single new literature citation was identified in the Safety Update; this was a case-control study by Sundstrom et al⁶ conducted over a seven-year period using the UK's General Practice Research Database, which covers 4% of the UK population. Reproductive-aged women with a diagnosis of menorrhagia formed the study population. Cases were identified from this population by diagnosis of DVT or pulmonary embolus, confirmed by use of anticoagulant therapy or death from a cause consistent with VTE. Cases with known risk factors for VTE, pregnancy within six weeks of the event, or use of combined oral contraceptives were excluded. An average of four controls per case were matched by practice and year of birth, and used the same exclusion criteria. Exposures of interest were medications used to treat menorrhagia, specifically, tranexamic acid, mefenamic acid (an NSAID), or norethisterone, used within 90 days of the index event. A total of 134 cases and 552 matched controls were identified. The point estimate of the risk of VTE associated with each drug was elevated, but the confidence interval around the odds ratio (OR) for tranexamic acid was not statistically significant (adjusted OR 3.20, 95% CI 0.65 – 15.78). Statistically significant associations were observed for mefenamic acid (OR 5.54), and norethisterone (OR 2.41). This may be related to the relatively less frequent use of tranexamic acid: only three of 23 exposed cases used tranexamic acid and only four of 33 exposed controls. The authors also report an association of VTE with anemia or low hemoglobin, considered a proxy for more severe menorrhagia, and suggest that menorrhagia may be a prothrombotic condition, leading to confounding by indication.

Team Leader Comment

There is no clear indication in the literature of an association between use of tranexamic acid and VTE. Only two case-control studies directly evaluate the association, and neither demonstrated a statistically significant increase in risk of VTE, although the studies trended in opposite directions.

8.6 Overall Assessment of Safety

The extent of exposure evaluated in the phase 4 studies exceeded that requested by the Division in preNDA interactions with the Applicant. With safety data from over 12,000 cycles of treatment, and on over 200 women who used the drug for at least two years, I believe the safety database is adequate to support approval of Lysteda and development of appropriate labeling.

The single on-treatment death in the clinical development program occurred in a subject who received the 3.9 g/day Lysteda dose in the open label Study 302. Review of the information provided about her hospital course and diagnostic work-up reassures me that this was not a treatment-related death.

⁶ Sundstrom A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: a case-control study using the General Practice Research Database. BJOG 2009; 116: 91-7.

There was no concerning pattern of SAEs in the four studies; the most commonly reported SAEs included menorrhagia (7), migraine (4) and enlarging fibroids (3). Menorrhagia and fibroids would be expected in a population with HMB, particularly where fibroids did not constitute an exclusion criterion. Migraine is relatively common in the population of reproductive-aged women, and is described in labeling, as it was also a common AE noted more often in Lysteda-treated women than placebo subjects.

Although none were reported by the Applicant as an SAE, a thorough search of the trial databases revealed three likely cases of significant allergic reactions, with another two possible cases. This signal is supported by postmarketing data from the WHO safety database, which also includes a number of likely cases. This class of AE is discussed in labeling.

The pattern of AEs that led to early study withdrawal mirrors that of SAEs in the open label studies, with headache, menstrual complaints and fibroids among the most frequent occurrences. In the placebo-controlled studies, no AE leading to early discontinuation occurred in more than a single Lysteda subject.

Common AEs were reviewed based on both the placebo-controlled and open label studies; the placebo-controlled data help with implications about drug-relatedness, while the open label studies provide information on extended exposure to Lysteda. The pattern and frequency of common AEs are similar across both data sets, and are described in labeling. Those occurring in over 5% of Lysteda subjects and more frequently than in placebo subjects involved headaches, including migraines; sinus/nasal/allergic conditions; abdominal pain; muscle and joint complaints; anemia and fatigue.

The single event (DVT) in the clinical trials that I believe constituted a VTE occurred in a placebo subject. Following review of MedDRA terms potentially indicative of a VTE, I conclude that the three potential cases in Lysteda-exposed subjects were not VTEs. In addition, the limited literature on tranexamic acid and VTE risk does not support an increased risk, although one study reported a nonsignificant OR of 3.2. Given the long and widespread use of tranexamic acid for menorrhagia globally, it is unlikely that there is a significant signal of increased risk that has remained undetected. Recommendations made by DPV II following review of AERS reports of VTE cases associated with tranexamic acid use abroad, including one fatal pulmonary embolism, have been addressed in labeling.

As requested by DRUP, the Applicant provided a comprehensive ophthalmologic examination at various timepoints in the studies. These data are somewhat limited by the attrition of subjects over time, so that far less than 100% of enrolled subjects ultimately underwent the final study examination. In addition, the presentation of data on subjects in 304 is not useful. Overall, I do not find a signal for adverse impact of Lysteda on vision or ocular safety based on the results of the ophthalmologic testing. While the number of subjects tested at the end of each study was significantly less than the number initially enrolled, there is no indication that subjects were discontinuing on the basis of ophthalmologic AEs, which would introduce a serious bias. Review of the Eye Disorder SOC AE reports also provides reassurance, as the frequency of these AE reports did not differ between treatment arms in Study 301, and were actually more common among placebo subjects in Study 303. **Dr. Chambers' consultative review of the ophthalmologic findings and examination results concluded that the major safety concerns pertain to ligneous conjunctivitis, venous stasis retinopathy and thromboembolic events of the eye. These safety issues are described in a labeled Warning.**

An appropriately conducted thorough QT study was submitted and reviewed by the QT IRT, and no signal of QT prolongation was demonstrated by Lysteda at therapeutic and supratherapeutic doses.

The primary reviewer concluded that the safety profile of Lysteda was acceptable, with similar rates of SAEs, gastrointestinal and ophthalmologic AEs in both Lysteda and placebo subjects in the controlled trials. I concur that the safety profile supports approval of Lysteda for treatment of HMB.

9. Advisory Committee Meeting

The Division determined that an Advisory Committee was not needed to review this application, as it was not a new molecular entity and raised no new safety concerns.

10. Pediatrics

The Applicant requested a partial waiver (for premenarcheal girls) and a deferral (for postmenarcheal girls) of pediatric studies. The Division recommended a partial waiver from age 0-12 years on the grounds that necessary studies would be impossible or highly impracticable because (1) the condition does not exist in premenarcheal girls and (2) too few postmenarcheal girls under the age of 12 with HMB exist to allow for a study in this subpopulation. DRUP also recommended that the pediatric studies be conducted postapproval, once this product had been determined to be safe and effective for women 18 years and older for the proposed indication.

The Applicant provided a synopsis of a proposed pediatric PK study, to be conducted as a phase 4 commitment. The study, to enroll 18 adolescent females aged 12 to 17, would evaluate the single dose PK of Lysteda following administration of two 650 mg tablets. **Eligibility requirements would include “evidence of heavy menstrual bleeding,” absence of bleeding or coagulation disorders or other significant chronic illness, and no current use of an IUD or use within three months of other hormonal treatment.** PK sampling would be conducted on an inpatient basis, at baseline, hourly for the first six hours after dosing, and then at 10, 14, 24, 28, 32 and 36 hours post-dose.

The Pediatric Review Committee (PeRC) PREA Subcommittee reviewed the request and the synopsis of the proposed pediatric protocol on May 27, 2009. The Subcommittee agreed with the Division and granted a partial waiver and deferral for this product.

The PeRC Subcommittee did raise a question about the occurrence of HMB in adolescents, and particularly as to whether the enrollment of younger adolescents would be sufficient to reflect their representation in the potential target population. The Division sent an information request to the Applicant requesting data on the prevalence of HMB in adolescents. The Applicant submitted results from a search of the literature, estimating that the prevalence of HMB in adolescents is about 4% of girls aged 13 to 17. Data on 12 year old girls are not available in the literature. This estimate is based upon a Swedish population-based study from **the 1960's that used alkaline** hematin methodology to evaluate menstrual blood loss in women in various age strata. The prevalence of HMB (MBL > 80 ml) was 4.2% among 95 adolescents in the 15 year old stratum. Additional data reviewed was proportion of physician visits for excessive menstruation, obtained from the US Physicians Drug and Diagnosis Audit

(PDDA) from _____ This showed that _____ of visits for women under age 20 were for excessive menstruation. Of the 4.8% of visits for this complaint, the age breakdown was:

b(4)

- Age 13 - _____
- Age 14 - _____ b(4)
- Age 15 - _____
- Age 16 - _____
- Age 17 - _____ b(4)
- Age 18 - _____
- Age 19 - _____

Team Leader Comment

While data are sparse regarding the prevalence of HMB in adolescents, the data from divergent sources are surprisingly consistent. Based on PDDA physician visit data, it appears that healthcare is sought by adolescents for HMB in about equal proportions by 13-15 year olds, 16 year olds and 17-19 year olds. Thus, I believe the Applicant's proposal to enroll 18 subjects in a single dose PK study appears feasible. The Division will review the full protocol for the study when it is submitted, and will likely recommend that the Applicant stratify enrollment to ensure that there is adequate representation of adolescents 16 and under.

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

11. Other Relevant Regulatory Issues

11.1 Potential Financial Conflicts

The Applicant certified that it did not use any investigators debarred under Section 306 of the Federal Food, Drug and Cosmetic Act.

The Applicant submitted financial disclosure information for all investigators; only one, _____, had disclosable information (\$75,000 payment from the Applicant for consulting services on the overall development program. _____ enrolled _____ subjects in Study _____ of whom continued in Study _____. A site inspection by the Division of Scientific Investigation (DSI) was requested on the basis of this financial interest.

b(6)

b(6)

11.2 DSI Inspections

Site inspections by DSI were requested for two additional sites; they were selected on the basis of having enrolled relatively large numbers of subjects. Dr. Baker enrolled 18 subjects in Study 303, 15 of whom continued in Study 304. Dr. Mabey enrolled 44 subjects in Study 302.

Dr. Lukes' inspection revealed no deviations from regulations and received a final classification of no action indicated (NAI). Dr. Baker's inspection revealed deviations regarding Pap smears, and he received a voluntary action indicated (VAI) classification. However, the DSI summary dated September 3, 2009 stated "the deviations noted...would not

appear to have a significant impact on data integrity and the data appear acceptable in support of the respective application.” Dr. Mabey’s inspection revealed that three subjects (Study 302) each took four doses per day on various occasions, a violation of the protocol-specified maximum of three doses per day. He received a VAI classification, and DSI noted “the review division may wish to consider excluding data from Subjects [524] 2014, 2016 and 2022, for the reason noted...above; otherwise, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective application.”

Team Leader Comment

Data from Study 302 were not used in the pivotal assessment of efficacy; therefore, the additional doses taken by three subjects did not have an impact on the Division’s evaluation of the efficacy of Lysteda. Safety data from subjects who take extra doses are useful, as this may occur in actual use as well.

12. Labeling

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 DRUP 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. Their comments were incorporated into the label as appropriate.

Major areas of labeling negotiations included:

- the specifics of the indication statement
- discussion of the risk of serious allergic reactions
- discussion of the potential for exacerbation of the increased risk of VTEs associated with use of combined hormonal if these products were used concomitantly with Lysteda
- warning regarding the risk of visual and ocular adverse events, particularly vascular occlusion in the retina and ligneous conjunctivitis

In addition, foreign labels for tranexamic acid as well as the current Cyklokapron label were reviewed and the current label was revised as needed for consistency with these labels.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that Lysteda be approved for the indication “treatment of cyclic heavy menstrual bleeding.”

13.2 Risk Benefit Assessment

The Applicant has demonstrated efficacy for the 3.9 g/day dose of Lysteda, according to the criteria agreed-upon with the Division, in both of the phase 3 safety and efficacy studies. The average reduction in MBL was about 65 ml in the Lysteda arms, and this exceeded the reduction achieved in placebo subjects by about 50 ml. The Applicant further demonstrated efficacy on two of its three pre-specified secondary endpoints, limitations in social and leisure activities and in physical activity. Lysteda subjects generally reduced their LSLA and LPA scores from an average of “moderately limited” to an average of “slightly limited.” The responder analysis of change in large stains was not statistically significantly different between Lysteda and placebo arms.

The change in MBL with Lysteda is not as dramatic as that seen for the Mirena IUD, which was recently approved for a secondary indication of treatment of HMB in women who desire intrauterine contraception. However, Lysteda will be a useful treatment option for women who wish to avoid hormonal treatment, and/or do not need contraception.

The safety profile of Lysteda is generally reassuring, and risks that have been identified (in part, through the extensive postmarketing experience with tranexamic acid), such as VTEs, ophthalmologic adverse events and serious allergic reactions, can be adequately addressed in labeling.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

The Applicant proposes a risk management plan with the following goals:

- Identify changes in the AE profile as more patients are exposed to Lysteda
- Identify potential safety issues promptly to provide appropriate information to prescribers
- Monitor safety issues and implement appropriate risk mitigation strategies as needed

The Applicant proposes to conduct routine pharmacovigilance activities that include expeditious collection and evaluation of suspected AEs, expedited (15 day) reporting of serious unexpected AEs, and submission of spontaneous AE reports and worldwide literature review to FDA in accord with Agency regulations and guidances, including quarterly reporting for the first three years after approval and annually thereafter.

In view of the lack of studies in adolescents under age 18, the Applicant proposes that it will not detail to pediatricians. However, as Cyklokapron is indicated for use in the pediatric population without dose adjustment, the Applicant believes that off-label use by pediatric patients will not pose any risk. A pediatric PK study is proposed as a phase 4 commitment (see Section 10 and next bulleted section).

Team Leader Comments

- **The Applicant proposes nothing more than routine pharmacovigilance activities, and I believe this is sufficient based upon the safety profile demonstrated for Lysteda in the clinical trials and for tranexamic acid generally in the literature and postmarketing reports as described in foreign labeling.**
- **While I do not believe there is a safety signal associated with Lysteda that warrants development of a REMS, I do believe there is a need for a postmarketing commitment, as detailed in the next bulleted section, to determine the extent to which Lysteda is used**

concomitantly with hormonal contraceptives. Women using hormonal contraceptives, which are associated with an increased risk of VTE, were excluded from the clinical trials, so there are no data on whether concomitant use with Lysteda might result in a further elevation of VTE risk. Postapproval, the AERS database will be monitored, and if there were reports of VTEs in concomitant users, it would be important to know the extent of such concomitant use in the population.

- **I concur that there is not likely to be an increased risk to postmenarcheal adolescents who might use Lysteda, as compared to the adult women studied in the trials.**

13.4 Recommendation for other Postmarketing Requirements and Commitments

The Applicant proposed in the NDA submission a postmarketing commitment to conduct a pediatric PK study. The Division initially requested such a postmarketing study to explore the possibility that the effect of Lysteda might vary in the adolescent population, who may have slightly different underlying etiologies for their HMB, as compared to adult women. The proposed study, to enroll 18 adolescent females aged 12 to 17, would evaluate the single dose PK of Lysteda following administration of two 650 mg tablets. Eligibility requirements would include **“evidence of heavy menstrual bleeding,” absence of bleeding or coagulation disorders** or other significant chronic illness, and no current use of an IUD or use within three months of other hormonal treatment. PK sampling would be conducted on an inpatient basis, at baseline, hourly for the first six hours after dosing, and then at 10, 14, 24, 28, 32 and 36 hours post-dose. The Applicant agreed to conduct this as a postmarketing requirement and this will be documented in the action letter.

In addition, the current studies excluded women using hormonal contraception, so there is no information on concomitant use of Lysteda and hormonal contraceptives. While combined oral contraceptives in particular tend to decrease HMB, there well may be a subset of women who use hormonal contraception but still have bleeding that is bothersome enough that they desire an additional treatment modality, such as Lysteda. In the absence of data on such concomitant use, I cannot assess whether there might be a potential that use of tranexamic acid concomitantly with hormonal contraceptives might elevate the already increased risk of VTE described in hormonal contraceptive users. While I do not believe there is a safety signal associated with Lysteda that warrants development of a REMS, I do believe there would be value in a postmarketing commitment to evaluate the extent of concomitant use of Lysteda and hormonal contraceptives. This could be done in a claims database, which would allow evaluation of the patterns of concomitant use, including issues such as whether there is an age differential between women who use both products as compared to women who use only Lysteda. Postapproval, the AERS database will be monitored, and if there were reports of VTEs in concomitant users, it would be important to know the extent of such concomitant use in the population.

On October 21, 2009, the Applicant agreed to the postmarketing commitment as described above, and agreed to the following milestones:

Protocol Submission Date:	January 2010
Study Completion Date:	July 2012
Final Report Submission Date:	January 2013

Cross Discipline Team Leader Review
Final 11/6/09
22-430 Lysteda

Given that the Applicant has agreed to such a commitment, I am willing to address concomitant use with hormonal contraceptives with a strong Warning rather than

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13.5 Recommended Comments to Applicant

None

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/

LISA M SOULE
11/06/2009

SCOTT E MONROE
11/06/2009

I concur with Dr. Soule's overall assessment and her recommendation that Lysteda be approved for the indication of treatment of cyclic heavy menstrual bleeding.