OBSTETRICS

Tafoxiparin, a novel drug candidate for cervical ripening and labor augmentation: results from 2 randomized, placebo-controlled studies

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BACKGROUND: Slow progression of labor is a common obstetrical problem with multiple associated complications. Tafoxiparin is a depolymerized form of heparin with a molecular structure that eliminates the anticoagulant effects of heparin. We report on 2 phase II clinical studies of tafoxiparin in primiparas. Study 1 was an exploratory, first-in-pregnant-women study and study 2 was a dose-finding study.

OBJECTIVE: Study 1 was performed to explore the effects on labor time of subcutaneous administration of tafoxiparin before onset of labor. Study 2 was performed to test the hypothesis that intravenous treatment with tafoxiparin reduces the risk for prolonged labor after spontaneous labor onset in situations requiring oxytocin stimulation because of dystocia.

STUDY DESIGN: Both studies were randomized, double-blind, and placebo-controlled. Participants were healthy, nulliparous females aged 18 to 45 years with a normal singleton pregnancy and gestational age confirmed by ultrasound. The primary endpoints were time from onset of established labor (cervical dilation of 4 cm) until delivery (study 1) and time from start of study treatment infusion until delivery (study 2). In study 1, patients at 38 to 40 weeks of gestation received 60 mg tafoxiparin or placebo daily as 0.4 mL subcutaneous injections until labor onset (maximum 28 days). In study 2, patients experiencing slow progression of labor, a prolonged latent phase, or labor arrest received a placebo or 1 of 3 short-term tafoxiparin regimens (initial bolus 7, 21, or 35 mg followed by continuous infusion at 5, 15, or 25 mg/hour until delivery; maximum duration, 36 hours) in conjunction with oxytocin.

RESULTS: The number of participants randomized in study 1 was 263, and 361 were randomized in study 2. There were no statistically significant differences in the primary endpoints between those receiving tafoxiparin and those receiving the placebo in both studies. However, in study 1, the risk for having a labor time exceeding 12 hours was significantly reduced by tafoxiparin (tafoxiparin 6/114 [5%] vs placebo 18/101 [18%]; P=.0045). Post hoc analyses showed that women who underwent labor induction had a median (range) labor time of 4.44 (1.2−8.5) hours with tafoxiparin and 7.03 (1.5−14.3) hours with the placebo (P=.0041) and that co-administration of tafoxiparin potentiates the effect of oxytocin and facilitates a shorter labor time among women with a labor time exceeding 6 to 8 hours (P=.016). Among women induced into labor, tafoxiparin had a positive effect on cervical ripening in 11 of 13 cases (85%) compared with 3 of 13 participants (23%) who received the placebo (P=.004). For women requiring oxytocin because of slow progression of labor, the corresponding results were 34 of 51 participants (66%) vs 16 of 40 participants (40%) (P=.004). In study 2, tafoxiparin had no positive effects on the secondary endpoints when compared with the placebo.

Except for injection-site reactions in study 1, adverse events were no more common for tafoxiparin than for the placebo among either mothers or infants. There were few serious or treatment-related adverse events.

CONCLUSION: Subcutaneous treatment with tafoxiparin before labor onset (study 1) may be effective in reducing the labor time among women undergoing labor induction and among those requiring oxytocin for slow progression of labor. Moreover, tafoxiparin may have a positive effect on cervical ripening. Short-term, intravenous treatment with tafoxiparin as an adjunct to oxytocin in patients with labor arrest (study 2) did not affect labor time or other endpoints. Both studies suggest that tafoxiparin has a favorable safety profile in mothers and their infants.

Key words: dystocia, infants, labor induction, labor time, neonates, oxytocin, slow progress of labor

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Introduction

Prolonged labor (dystocia) and labor arrest are common, with >30% of first-time deliveries being affected.[1−6] These problems are associated with maternal and fetal complications, including fetal asphyxia, infection, instrumental delivery, postpartum hemorrhage, vaginal tears, anal sphincter injuries, and uterine ruptures.[7−9] Moreover, prolonged labor is the leading cause of emergency cesarean deliveries, which put the mother and baby at risk for additional complications.[10−12]

During late-stage pregnancy, the uterine extracellular matrix (ECM) is remodeled to facilitate contractions. Cervical ripening, an inflammatory reaction associated with remodeling of the ECM, ensures adequate softness and distensibility for parturition.[13−18] Insufficiencies in either of these processes can cause prolonged or delayed labor. Standard treatments, such as oxytocin

AJOG at a Glance

Why was this study conducted?

This study aimed to explore the effects of tafoxiparin, a depolymerized form of heparin without anticoagulant effects, administered before labor or as an adjunct to oxytocin in women with dystocia.

Key findings

Tafoxiparin may reduce the risk for highly extended labor times (>12 hours) and may be effective in promoting cervical ripening. Thus, it has potential to reduce labor duration in the context of labor induction or when given as an adjunct to oxytocin in patients with dystocia. Tafoxiparin has a favorable safety profile in mothers and infants.

What does this add to what is known?

In harnessing the potential benefits of low molecular weight heparin without its anticoagulant effects, tafoxiparin seems to be a promising treatment option for cervical ripening and augmentation of labor.

and prostaglandins, are not always effective, and these may cause adverse events (AEs) such as hyperstimulation or maternal fever.[19−22] Consequently, alternative therapeutic options are needed.

Low molecular weight heparin (LMWH), structurally similar to heparan sulfate, may reduce labor time by increasing myometrial activity in the uterus and by increasing secretion of the cytokine interleukin-8 in the cervix.[23−25] However, routine application of LMWH is precluded because of the antithrombin (AT)-mediated anticoagulant effects that increase the risk for hemorrhage.[26,27]

Tafoxiparin is a depolymerized form of heparin with a molecular weight of 5 to 7 kDa. Oxidation of the glucuronic acid moiety in the pentasaccharide sequence that binds AT means that tafoxiparin (unlike LMWH) does not activate AT and therefore has no anticoagulant effects.[25,28] Preclinical studies have shown that tafoxiparin stimulates cytokine release from cervical fibroblasts in a similar manner to LMWH.[25,28] In addition, similarly to LMWH, tafoxiparin may act in conjunction with oxytocin to increase the contractile activity of myometrial smooth muscle, addressing any reduction in heparan sulfate levels.[19,25,28] Thus, tafoxiparin may support parturition by facilitating cervical ripening and increasing the strength of uterine contractions. Importantly, tafoxiparin, like LMWH, does not cross the placental barrier and therefore does not affect the unborn fetus.[29,30]

Dilafor AB sponsored 2 randomized, double-blind, placebo-controlled phase II clinical studies of tafoxiparin in primiparas. Study 1 was an exploratory, first-in-pregnant-women study assessing subcutaneous (SC) tafoxiparin treatment for ≤28 days in primipara women planning vaginal delivery. The following 2 hypotheses emerged from this study: "tafoxiparin reduces the risk of prolonged labor after spontaneous onset in situations where oxytocin stimulation is needed due to dystocia" and "tafoxiparin reduces labor time when labor induction is performed with prostaglandin to induce cervical ripening and/or with amniotomy/oxytocin to stimulate uterine contractions." Study 2 was performed in women requiring treatment for slow progression of labor, a prolonged latent phase, or labor arrest to test the hypothesis that "tafoxiparin reduces the risk of prolonged labor after spontaneous onset in situations where oxytocin stimulation is needed due to dystocia." Tafoxiparin was administered as an adjunct to oxytocin, and to ensure sufficiently rapid onset of action, both drugs were administered intravenously (IV).

Materials and Methods

Study design

Both phase II studies were prospective, multicenter, randomized, double-blind, and placebo-controlled. Study 1 (PPL02; ClinicalTrials.gov identifier, NCT00710242; EudraCT identifier, 2006-005839-20) assessed multiple SC doses of tafoxiparin, whereas study 2 (PPL07; ClinicalTrials.gov identifier, NCT03001193; EudraCT identifier, 2016-002118-40) was an IV dose-finding study. The studies were performed in accordance with the Good Clinical Practice and the Declaration of Helsinki. The protocols were approved by the relevant authorities and regional ethics boards. All participants provided signed informed consent. Study 1 was conducted between April 4, 2007 and May 15, 2009, and study 2 was conducted between December 27, 2016 and March 5, 2019. Both studies were closed for enrolment on reaching the intended sample size.

Participants of both studies were healthy, nulliparous females aged 18 to 45 years with a normal singleton pregnancy and gestational age confirmed by second trimester ultrasound. Exclusion criteria were similar in the 2 studies, and all were applied from the outset, including breach or abnormal presentation, serious infectious disease (eg, HIV, hepatitis), previous vaginal bleeding, moderate to severe hypertension, eclampsia, coagulation disorders, heparin-induced thrombocytopenia, heparin allergy, alcohol or drug abuse, and large or small for gestational age fetus. Furthermore, women with a body mass index (BMI) >30 kg/m^2 (study 1) or ≥35 kg/m^2 (study 2) were excluded. Patients with infections (eg, HIV, hepatitis, sexually transmitted diseases) during the last 10 weeks of pregnancy were also excluded from study 1, whereas those with uterine scars or induction of labor were excluded from study 2.

In study 1, patients who experienced a normal pregnancy and were at 38 to 40 weeks of gestation were recruited at maternal healthcare units (ie, when they were outpatients). A 60 mg dose of tafoxiparin or a placebo was administered

TABLE 1
Demographic and baseline characteristics (safety populations in studies 1 and 2)

Study 1	Placebo (n=125)	Tafoxiparin (n=138)
Age (y)	29.1±4.2	28.8±4.2
Body mass index prepregnancy (kg/m^2)	23.4±2.9	23.5±2.7
Gestational age at screening (wk)	38.9±0.7	38.9±0.7
Gestational age at start of treatment with study medication (wk)	39.4±0.6	39.4±0.6
Gestational age at delivery	40.8±0.8	40.8±0.8

Study 2	Placebo (n=91)	Tafoxiparin 5 mg/h (n=88)	Tafoxiparin 15 mg/h (n=87)	Tafoxiparin 25 mg/h (n=90)
Age (y)	29.3±4.7	29.8±5.0	29.1±5.0	30.2±4.6
Body mass index at screening (kg/m^2)	24.2±3.7	24.5±3.9	24.4±3.9	24.7±4.3
Gestational age (wk)	40.3±1.0	40.1±1.2	40.3±1.0	40.2±1.1
Main indication				
- Primary slow progression of labor[a]	41 (45)	40 (46)	44 (51)	43 (48)
- Prolonged latent phase[b]	31 (34)	28 (32)	27 (31)	29 (32)
- Primary labor arrest[c]	19 (21)	20 (23)	16 (18)	18 (20)

Data are shown as the mean ± standard deviation or number (percentage).

[a] Slow progress of labor was defined as <1 cm/hour increase in cervical dilatation for a period of 3 hours. A cervical dilation of 3–6 cm was required at the time of inclusion; [b] Prolonged latent phase defined as painful contractions during at least 18 hours without progress into established labor. To be included in the study, a cervical dilatation of 2–3 cm and amniotomy or spontaneous rupture of membranes were required. If still no progress 1 hour after amniotomy, the subject could be enrolled; [c] Primary labor arrest was defined as no increase in cervical dilatation during 3 hours. A cervical dilatation of 3–6 cm was required.

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daily as 0.4 mL SC injections until labor (maximum treatment duration, 28 days). Labor was induced in cases with preeclampsia, hepatosis, or postterm pregnancy at 42 weeks of gestation. At labor onset, study treatment was discontinued and the women were treated according to standard clinical practice.

Study 2 patients experiencing slow progression of labor, a prolonged latent phase, or labor arrest (see definitions under Table 1) were recruited while at the delivery ward. There were 4 study arms, namely 1 placebo and 3 tafoxiparin arms (initial IV bolus [7, 21, or 35 mg] followed by continuous infusion [5, 15, or 25 mg/hour until delivery; maximum duration 36 hours]). This was administered in addition to IV oxytocin according to standard clinical practice.

In both studies, a follow-up visit was scheduled 8 to 16 weeks postpartum. In study 2, participants were contacted telephonically 6 months after study inclusion for questionnaire-based documentation of the infant's development.

Assessments

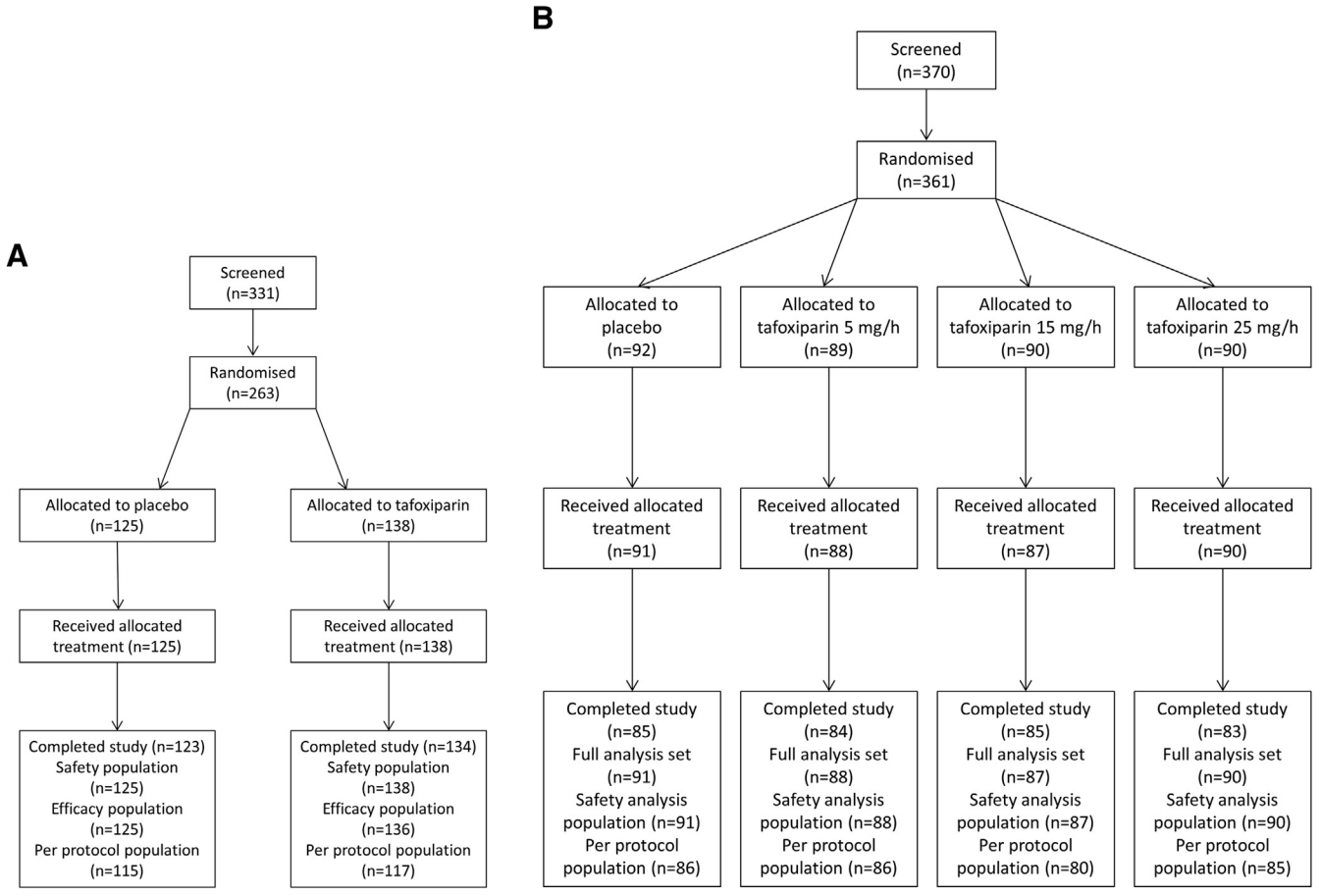
The primary endpoint in study 1 was labor delivery time, defined as the time from onset of established labor (cervical dilation of 4 cm)[6] to delivery. Secondary efficacy assessments included proportion of women with labor time >12 hours, use of epidural anesthesia (EDA), labor augmentation, labor induction, and Westin score[31] (scale 0–10; 0–5, unripe cervix; 6–10, ripe cervix) on days 0, 7, 14, 21, and 28. The primary endpoint in study 2 was time from start of infusion of study treatment until delivery. Secondary efficacy assessments were proportion of women with prolonged labor, time from cervical dilation of 4 cm until delivery, proportion of women receiving EDA, and delivery by cesarean delivery.

In both studies, blinded evaluation of partograms was performed by an independent obstetrician. Safety assessments included AEs, physical examinations, vital signs, hematology and clinical chemistry results, rate of withdrawal, and neonatal outcomes.

Statistics

The null hypothesis in study 1 was that there is no difference in labor delivery time between the treatment groups. For the primary analysis, the labor delivery time was transformed by square root and analyzed using analysis of covariance with adjustment for center and use of EDA. Based on unpublished observational data, a delivery time of 8 hours was assumed, and a reduction of 1.8 hours was considered clinically meaningful. We calculated that 170 eligible patients would be required to reach 90% power to detect a difference. Assuming a dropout rate of 35%, we aimed to randomize 260 patients. The primary analysis was done on the safety population (all randomized participants who received ≥1 dose of study treatment). We anticipated no missing data for the primary endpoint. Post hoc analyses were performed in subgroups of study participants (women who underwent induction of labor and women who received and who did not receive

FIGURE 1
Patient disposition



A, Study 1. **B**, Study 2. Six patients who underwent randomization withdrew before completing study 1 (reasons: loss to follow-up, protocol deviation), and 24 patients withdrew early from study 2 (consent withdrawal, discretion of the principal investigator). In study 1, two patients who received tafoxiparin were excluded from the efficacy population (reasons: protocol deviation, inability to participate in the study).

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oxytocin) using time-to-event methodology (proportional hazard Cox regression and nonparametric log-rank test; no adjustments for covariates). The Westin score was assessed using chi-square tests. All statistical tests for differences between study arms were 2-sided and performed at the 5% significance level.

For study 2, the null hypothesis was that the time from first infusion to delivery is equal for all treatment groups. The sample size required to achieve 90% power to detect a 20% reduction in this endpoint was 90 participants per dose group (360 participants in total). Results were analyzed using the full analysis set (FAS) (all eligible and randomized participants who received ≥1 dose of study treatment), the per-protocol population, and the safety population (all participants who received ≥1 dose of study treatment). No interim analyses were planned or undertaken. In accordance with the European Medicines Agency guidance, the primary endpoint was analyzed using Multiple Comparison Procedure—Modelling. The model included treatment dose and was adjusted for other covariates.

Results

Participants

The number of women randomized in studies 1 and 2 were 263 and 361, respectively. The safety population in study 1 included all 263 participants of whom 138 received tafoxiparin (Figure 1). Two tafoxiparin recipients were excluded from the efficacy population. In study 2, the FAS and safety populations were identical (n=356), and 265 women received tafoxiparin (5, 15, or 25 mg/h). In both studies, baseline characteristics were similar in the tafoxiparin and placebo groups (Table 1). All women participating in both studies were White. In study 1, the mean number of injections (standard deviation [SD]) of the study treatment was 10.2 (6.0) in the placebo arm and 10.1 (6.2) in the tafoxiparin arm.

TABLE 2
Efficacy results of study 1

Labor outcome	Placebo	Tafoxiparin
Labor induction	n=16	n=14
Labor time in women undergoing labor induction[a] (h), median (range)	7.03 (1.5–14.3)	4.44 (1.2–8.5)[b]
Vaginal delivery	n=101	n=114
Time from cervical dilatation of 4 cm until vaginal delivery (h), mean ± standard deviation	7.52±3.97	6.84±3.15
Number (%) of women with prolonged labor (>12 hours)	18 (18)	6 (5)[c]
Total efficacy population	n=125	n=136
Number (%) of cesarean deliveries	23 (18)	22 (16)
Number (%) of vacuum-assisted deliveries	24 (19)	22 (16)

[a] Women with nonspontaneous start of labor; [b] Indicates a *P* value of.0041 when compared with the placebo; [c] Indicates a *P* values of.0045 when compared with the placebo.

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Efficacy: study 1

There was no statistically significant difference in the outcomes between the tafoxiparin and placebo treatment groups in the primary analysis. Mean (±SD) vaginal delivery times were 6.84±3.15 hours for tafoxiparin and 7.52±3.97 hours for the placebo (*P*=.48) (Table 2). Notably, 32% of the study participants had normal labor progression and therefore did not receive oxytocin. The proportion of women with a labor time exceeding 12 hours was smaller in the tafoxiparin group than in the placebo group (5% vs 18%; *P*=.0045). Furthermore, in the subgroup of women who underwent labor induction (ie, those with nonspontaneous onset of labor), the median labor time with tafoxiparin treatment was 4.44 hours (range, 1.2–8.5 hours) and 7.03 hours (range, 1.5–14.3) with placebo treatment. Time-to-event analysis showed a statistically significant difference between these 2 groups (log-rank test, *P*=.0041) (Table 2 and Figure 2, A). Furthermore, co-administration of tafoxiparin seemed to potentiate the effect of oxytocin and to facilitate a shorter labor time among women with a labor time exceeding 6 to 8 hours (log-rank test, *P*=.016) (Figure 2, B).

At the beginning of treatment, the mean Westin score (SD) was similar in the 2 study groups (tafoxiparin, 2.4 [1.8] vs placebo, 2.5 [2.0]). A positive change of ≥1 point in the Westin score after 7 days of treatment was significantly more likely with tafoxiparin treatment than with the placebo: this was observed in 11 of 13 (85%) subjects induced into labor who received tafoxiparin compared with 3 of 13 (23%) subjects who received the placebo (*P*=.004) (Figure 3, C). The corresponding percentages were 66% and 40% (*P*=.004), respectively, among women who needed oxytocin for slow progression of labor, and 84% and 57% (*P*=.07), respectively, among subjects who did not require oxytocin. On days 14, 21, and 28, the number of women who remained undelivered was too small to provide meaningful Westin score data.

Among subjects with a vaginal delivery and spontaneous onset of labor, 94% and 98% received N_2O and 56% and 53% received EDA in the placebo and tafoxiparin groups, respectively. The percentage of women who delivererd by cesarean delivery and vacuum extraction were similar in the 2 study groups (Table 2).

Efficacy: study 2

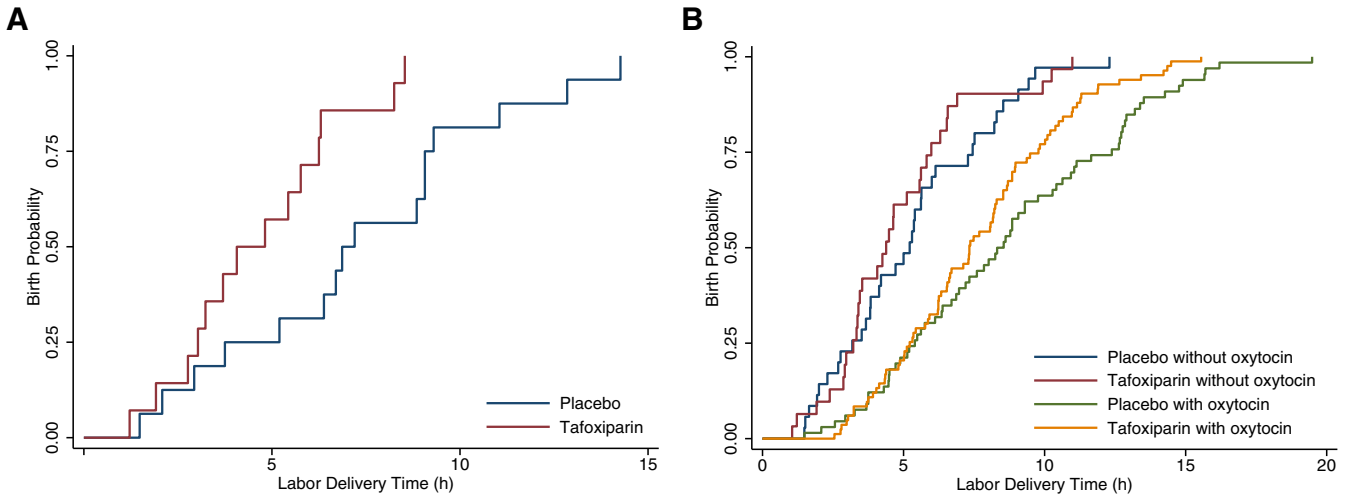
In the primary analysis (time from the start of infusion of study treatment until delivery), no statistically significant between-group differences and no dose-response signal were detected. In addition, there were no differences between the treatment groups in the secondary endpoints (Table 3). The percentage of women who delivered by cesarean delivery and vacuum extraction were similar in all study groups (Table 3). Between 91% and 94% of subjects in the 4 treatment groups received EDA.

Safety: studies 1 and 2

Across the 2 studies (6 study arms), AEs were reported by 68% to 86% of mothers (Table 4, Supplemental Tables 1 and 5). Most AEs were mild to moderate and unrelated to the study treatment. In study 1, the incidence of injection-site reactions (mainly bruising) was higher in the tafoxiparin group than in the placebo group (19% vs 6%). This led to a difference between tafoxiparin and placebo treatment at the system organ class level (general disorders and administrative site conditions: 28% vs 14%). All other AE rates at both the preferred term and system organ class levels and across both studies were similar for tafoxiparin and placebo treatment (Supplemental Tables 1 and 2). Importantly, there was no evidence that tafoxiparin increased the risk for clinically significant postpartum hemorrhage and there were no epidural or spinal hematomas in either of the studies. In study 1, the percentage of women with bleeding >1000 mL in the tafoxiparin group was 9% (12/138) compared with 12% (15/125) in the placebo group. The corresponding percentages in study 2 were 15%, 10%, and 8% (tafoxiparin 5, 15, and 25 mg/h) vs 8% (placebo).

Serious AEs (SAEs) were reported in a minority of women (Table 4, Supplemental Tables 2 and 6). In study 1, uterine hemorrhage was the most common SAE (occurring in 2 tafoxiparin-treated women and 2 placebo-treated subjects). A total of 7 SAEs were possibly related to the study treatment. These occurred in 2 women who received the placebo (1 had anemia and uterine hemorrhage, and the other had uterine hemorrhage and retained placenta or membranes) and in 2 who received tafoxiparin. The related SAE in

FIGURE 2
Subgroup analyses of labor delivery time in study 1



A, Women with induction of labor (placebo n=16; tafoxiparin n=14). **B,** Women who received and did not receive oxytocin (placebo without oxytocin n=35; tafoxiparin without oxytocin n=31; placebo with oxytocin n=66; tafoxiparin with oxytocin n=84).

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the first tafoxiparin-treated woman was hemorrhage associated with a cesarean delivery. The second tafoxiparin-treated woman had a normal delivery but subsequently presented with a vaginal hematoma. The vaginal hematoma and an occurrence of uterine hemorrhage were reported as SAEs, which were both deemed possibly related to the tafoxiparin treatment by the investigator. The patient was later diagnosed with Von Willebrand's disease and should not have been included in the study. The most common SAEs in study 2 were postpartum hemorrhage (reported in 5 study participants: 2 in each of the 5 mg/h and 15 mg/h tafoxiparin groups and 1 in the 25 mg/h tafoxiparin group). All these SAEs were assessed to be unrelated to the study treatment. In study 2, 1 SAE was deemed to be related to the tafoxiparin treatment. This was cervical laceration; the outcome was deemed to be resolved and recovered. In study 2, the incidence of uterine hyperstimulation with fetal heart rate changes requiring tocolytic treatment was slightly higher with the placebo treatment (9%) than with the tafoxiparin treatment (1% to 7%). No uterine hyperstimulation requiring treatment with tocolytics was reported in study 1.

In both studies, the incidence and severity of AEs in infants were similar between the tafoxiparin and placebo treatment groups (Table 4, Supplemental Tables 3 and 7). Most AEs in infants were mild or moderate, and none was related to the study treatment. The most common AEs among infants in both studies were neonatal infections and gastrointestinal disorders. SAEs were uncommon among the infants (Table 4, Supplemental Tables 4 and 8). No infant-related safety concerns were reported at 8 to 16 weeks or at the 6-month teleconference.

Most laboratory evaluations showed no clinically significant deviation from the normal range. Fetal acidosis (base excess <-12 mmol/L) was reported in 10% of infants in the placebo group of study 1 and in 5% of infants in the tafoxiparin group. The corresponding percentages in study 2 were 0% (placebo) and 1%, 3%, and 0% in the respective tafoxiparin groups (5, 15, and 25 mg/h). In both studies, Apgar scores were similar in infants born to women treated with either the placebo or tafoxiparin.

Discussion

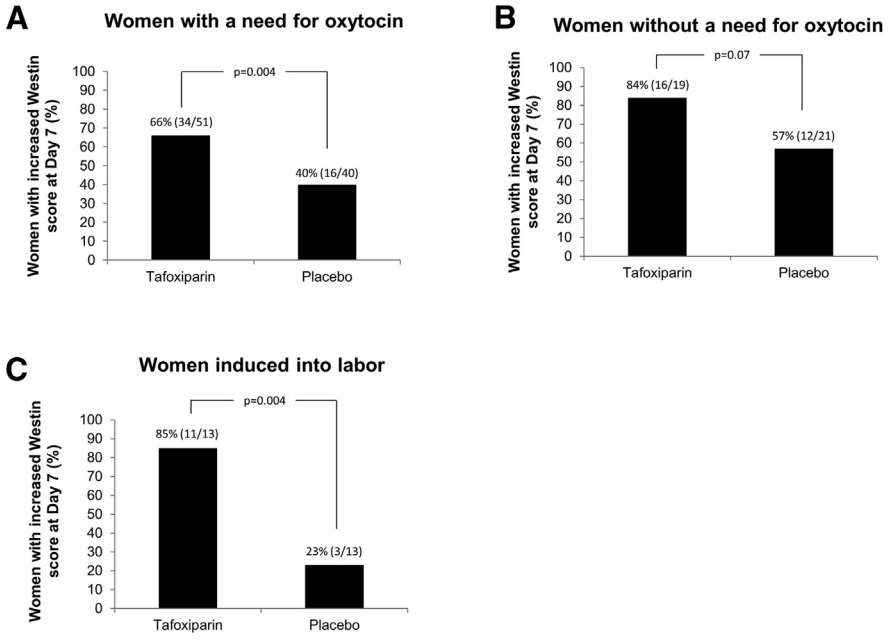
Principal findings

In study 1, the risk for having a labor time exceeding 12 hours was significantly reduced by tafoxiparin, and reduced labor time was evident in women whose labor time exceeded 6 to 8 hours and who received oxytocin treatment. The reduction in labor time was most pronounced among women who underwent labor induction. Cervical ripening, measured by improvement in the Westin score, was more likely to progress in women who received tafoxiparin. In study 2, no statistically significant benefits were observed among those who received tafoxiparin when compared with those who received the placebo.

Results in the context of what is known

The findings reported here are in line with previous in vitro data suggesting that tafoxiparin increases myometrial contractility and cervical ripening.[25] Three previous phase I studies of tafoxiparin were conducted in healthy, nonpregnant volunteers.[28] IV or SC doses of 2 to 4 times the intended clinical

FIGURE 3
Subgroup analyses of cervical ripening in study 1



A, Women who received oxytocin. **B,** Women who did not receive oxytocin to stimulate uterine contractions. **C,** Women for whom labor was induced by cervical ripening and/or by amniotomy and oxytocin treatment. Women who delivered before day 7 had no Westin score reported at day 7 and were therefore not included in these analyses. The Westin score was defined according to a 10-point scale according to which 0 to 5 represents an unripe cervix and 6 to 10 represents a ripe cervix.

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dose were administered. Tafoxiparin did not influence the coagulation system and demonstrated a good overall safety profile.

Research and clinical implications

Study 1 was the first-in-pregnant-women investigation of tafoxiparin, conducted to investigate administration of the drug before labor, across a range of different conditions. Therefore, the inclusion criteria were broad, and a number of post hoc analyses were performed to extract all relevant information and to create new hypotheses. More than 30% of participants had normal labor progression without a need for labor augmentation by oxytocin and additional tafoxiparin, which limited the scope for demonstrating the effectiveness of tafoxiparin in the primary endpoint.

As stated earlier, the results of study 1 led to the formulation of 2 new hypotheses. The hypothesis that tafoxiparin reduces the risk for prolonged labor after spontaneous onset in situations requiring oxytocin stimulation owing to dystocia was tested in study 2. Nulliparous women requiring labor augmentation received IV tafoxiparin or placebo as an adjunct to oxytocin. Study 2 failed to show that tafoxiparin was effective; this may have been because the treatment time was too short for tafoxiparin to influence remodeling of the ECM. However, a longer treatment period would be difficult to implement during ongoing labor. Future studies probably need to focus on treatment as performed in study 1 and on treatment in specific, high-risk groups. The second hypothesis stemming from study 1, that tafoxiparin reduces labor time when labor induction is performed with prostaglandin to induce cervical ripening and/or with amniotomy or oxytocin to stimulate uterine contractions, is being tested in a placebo-controlled study (PPL17) in which tafoxiparin is being administered SC for up to 7 days in term pregnant women scheduled for labor induction.[32]

From a clinical perspective, the primary endpoints of the studies presented here did not show statistically significant benefits with tafoxiparin treatment when compared with the placebo, but it remains possible that tafoxiparin may be

TABLE 3
Efficacy results of study 2

Labor outcome	Placebo (n=91)	Tafoxiparin 5 mg/h (n=88)	Tafoxiparin 15 mg/h (n=87)	Tafoxiparin 25 mg/h (n=90)
Time from start of infusion of study treatment until delivery (h), median (interquartile range)	6.07 (4.60–10.38)	7.00 (4.67–10.40)	7.48 (4.98–10.65)	7.32 (4.95–11.48)
Number (%) of women with prolonged labor (≥14 hours) with odds ratios (95% confidence interval) when compared with placebo	11 (12)	9 (10) 0.804 (0.304–2.129)	7 (8) 0.843 (0.307–2.317)	6 (7) 0.457 (0.155–1.345)
Number (%) of cesarean deliveries	13 (14)	13 (15)	13 (15)	14 (16)
Number (%) of vacuum extractions	16 (18)	24 (27)	19 (22)	16 (18)

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TABLE 4
Summary of adverse events occurring in studies 1 and 2

Adverse events	Study 1		Study 2			
	Placebo (n=125)	Tafoxiparin (n=138)	Placebo (n=91)	Tafoxiparin 5 mg/h (n=88)	Tafoxiparin 15 mg/h (n=87)	Tafoxiparin 25 mg/h (n=90)
Maternal						
Any adverse event	85 (68)	108 (78)	69 (76)	76 (86)	72 (83)	72 (80)
Adverse event possibly or probably related to study treatment	15 (12)	25 (18)	3 (3)	19 (22)	2 (2)	7 (8)
Injection-site reaction[a]	8 (6)	26 (19)	N/A	N/A	N/A	N/A
Severe adverse event	3 (2)	10 (7)	5 (6)	1 (1)	3 (3)	4 (4)
Serious adverse event	4 (3)	10 (7)	4 (4)	6 (7)	7 (8)	11 (12)
Infant						
Any adverse event	44 (35)	46 (33)	69 (76)	62 (70)	63 (72)	64 (71)
Severe adverse event	3 (2)	3 (2)	4 (4)	1 (1)	1 (1)	3 (3)
Serious adverse event	16 (13)	14 (10)	10 (11)	18 (20)	11 (13)	20 (22)

[a] This adverse event has been included in the table because in study 1, it had the highest incidence rate and it helps to characterize the difference between the treatment groups in the overall adverse event rate.

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effective in reducing labor time in specific groups (eg, women undergoing labor induction). Both studies showed that tafoxiparin was well tolerated by women and their infants. Most AEs were no more common with tafoxiparin treatment than with the placebo, and there were few severe, serious, or treatment-related AEs. Small differences were observed in the AE profiles between the 2 studies, and these could be related to differences in the dosing regimens (eg, timing and route of administration). No increased risk for bleeding or hyperstimulation was documented in either study and no safety concerns were apparent even when high doses of tafoxiparin were administered during labor. Therefore, no contraindications related to anesthetic procedures or cesarean delivery are anticipated.

Strengths and limitations

A major strength of the data reported here is their robustness: both studies were randomized and relatively large (263 women were included in study 1 and 361 in study 2). A substantial dose expansion was explored in study 2. Other strengths were the multicenter designs, making the results generalizable, and the comprehensive statistical models underlying the sample size estimations. The most apparent weakness of study 1 was that >30% of the subjects had a normal labor and no need for augmentation with oxytocin and therefore there was no need for tafoxiparin treatment; this limited the scope for tafoxiparin to exhibit an effect. Lack of treatment effect in study 2 may be related to the treatment duration being too short.

Conclusion

The results of the first study presented here (study 1) suggested that tafoxiparin treatment may be effective in reducing the labor time in specific groups, particularly among women undergoing labor induction, possibly by promoting cervical ripening, and among those requiring oxytocin for slow progression of labor. Both studies confirmed that tafoxiparin has a favorable safety profile in both mothers and their infants. Further studies are planned to determine the optimum strategy for utilizing tafoxiparin in clinical practice to reduce morbidity among mothers and children. ■

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