Advisory Committee for Reproductive Health Drugs

NDA 22-139

for

Progesterone Gel 8%

15 Dec 2011 – Briefing Materials

Columbia Laboratories, Inc.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Table of Contents

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Table of Tables

Table of Figures

Table of Appendices

LIST OF ABBREVIATIONS

ASD	atrial septal defect
BMI	body mass index
BPD	bronchopulmonary dysplasia
CDC	Centers for Disease Control
CI	confidence interval
FDA	Food and Drug Administration
IND	Investigational New Drug Application
ISE	Integrated Summary of Efficacy
ITT	Intent-To-Treat
IUFD	intrauterine fetal death
IVH	intraventricular hemorrhage
MITT	Modified Intent-To-Treat
NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
NIH	National Institute of Health
NDA	New Drug Application
PTB	preterm birth
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome
RR	relative risk
SD	standard deviation
TEAE	treatment emergent adverse event
TVU	transvaginal ultrasound
VSD	ventricular septal defect

1   EXECUTIVE SUMMARY

This briefing package has been prepared in support of the January 20, 2012 meeting of the Reproductive Health Drugs Advisory Committee Meeting. The meeting will review New Drug Application (NDA) 22-139 submitted by Columbia Laboratories Inc. (hereafter, "Columbia") to the Food and Drug Administration (FDA) requesting approval of progesterone gel 8% for the following indication: *the reduction of risk of preterm birth in women with a singleton gestation and a short uterine cervical length in the mid-trimester of pregnancy. The key clinical study enrolled women with a uterine cervical length of 1 to 2 cm.* The application is based on an adequate and well-controlled randomized clinical study (COL-1620-302, hereafter, "Study 302"), supportive information from Study COL-1620-300 (hereafter, "Study 300"), and independent substantiation of the approach to reducing the risk of preterm birth in women with short cervix through the use of vaginal progesterone from Fonseca, et al, 2007.[1] A pharmacokinetic study was also performed (COL-1620-301, hereafter, "Study 301"). Results from Study 300 were published by O'Brien, et al[2] and DeFranco, et al,[3] while Study 302 results were published by Hassan, et al.[4] All three of these studies are described and discussed in further detail within this briefing package, while Section 6 of this briefing package contains abstracts of other published vaginal progesterone trials in short cervix subjects. A schematic of Columbia's clinical development program is shown in Figure 1.1.

---

[1] **Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007 Aug 2;357(5):462-9.**

[2] O'Brien JM, Adair CD, Lewis DF, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial, Ultrasound Obstet Gynecol 2007;30:687-96.

[3] DeFranco, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007;30:697-705.

[4] Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial, Ultrasound Obstet Gynecol 2011;38:18-31.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Figure 1-1   Columbia's Clinical Development Program
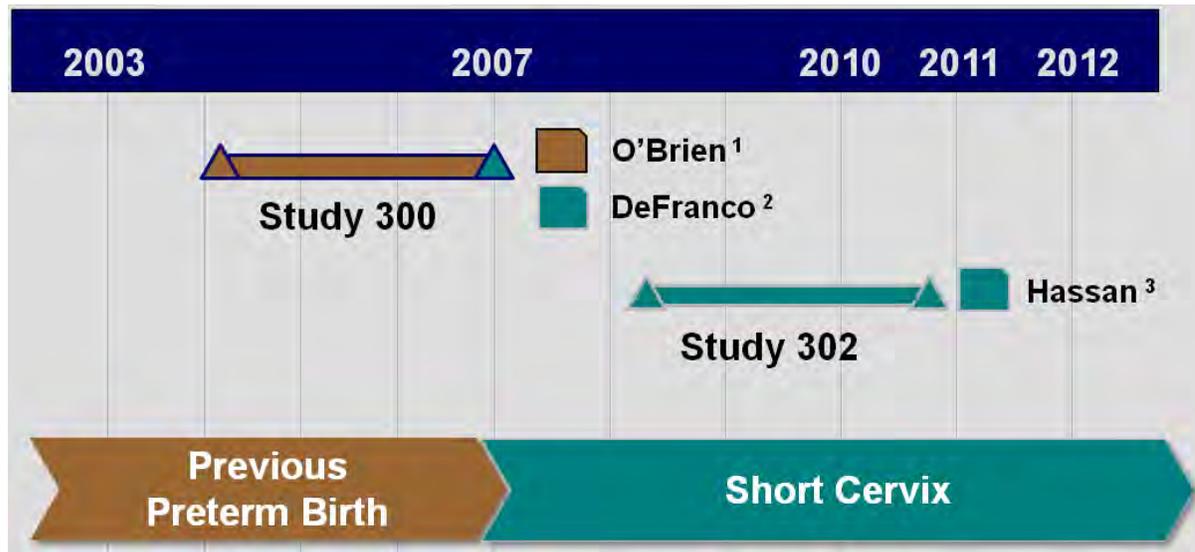
Progesterone gel 8%, containing natural progesterone, is currently an approved drug in the United States (US), having been approved for vaginal use in 1997 by the FDA for progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency. In this indication, progesterone gel 8% has been approved for use up to the 12th week of pregnancy and has been marketed under the names Crinone® and Prochieve®. The mechanism of benefit in this indication results from augmentation of low levels of endogenous progesterone, or complete replacement, in order to maintain pregnancy during the first trimester. The current submission for reduction of risk of preterm birth pertains to the product and formulation that are identical to the previously approved product and formulation.

Preterm birth, or delivery less than 37 weeks gestation, has continued to increase in the US over the last 20 years, and represents approximately 12% of all births according to the Centers of Disease Control (CDC).[5] Preterm birth accounts for 34% of infant mortality, and 95% of this mortality occurs in births <32 weeks gestation.[6] Short-term consequences of preterm birth include severe detrimental medical conditions such as respiratory distress syndrome (RDS), sepsis, intraventricular hemorrhage, and necrotizing enterocolitis. As early as the 1960s obstetricians attempted to reduce preterm contractions as the main therapeutic

---

[5] www.cdc.gov/.
[6] Callaghan WM, et al. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics. 2006 Oct;118(4):1566-73.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

approach to reduce preterm birth.[7] Tocolytics such as ethanol, terbutaline, nonsteroidal anti-inflammatory drugs and calcium channel blockers have been evaluated; however, these approaches have not been successful in reducing preterm birth rates.

More recently, risk factors for preterm birth have emerged that may in fact identify the potential disease processes at an earlier stage to enable interventions to effectively extend gestational age. A landmark study by Iams in 1996 clearly defined that cervical length in the second trimester is an important predictor of preterm birth.[8] Iams described the distribution of cervical lengths and calculated the risk of a preterm birth by comparing the preterm births for cervical lengths below the 75th percentile to those cervical lengths above this point. In this study, the 75th percentile was 4.0 cm. The relative risk of a preterm birth was double for cervical lengths shorter than 4.0 cm compared with cervical lengths longer than 4.0 cm. When the cervix measured <3.0 cm the relative risk for preterm birth was nearly four. Moreover, there was a 6-fold increase risk at 2.6 cm, a 9-fold increase risk at 2.2 cm, and a 14-fold increase at <1.3 cm. Figure 1-2 presents Iams data in graphical form.

Figure 1-2   Risk of Premature Delivery by Cervical Length
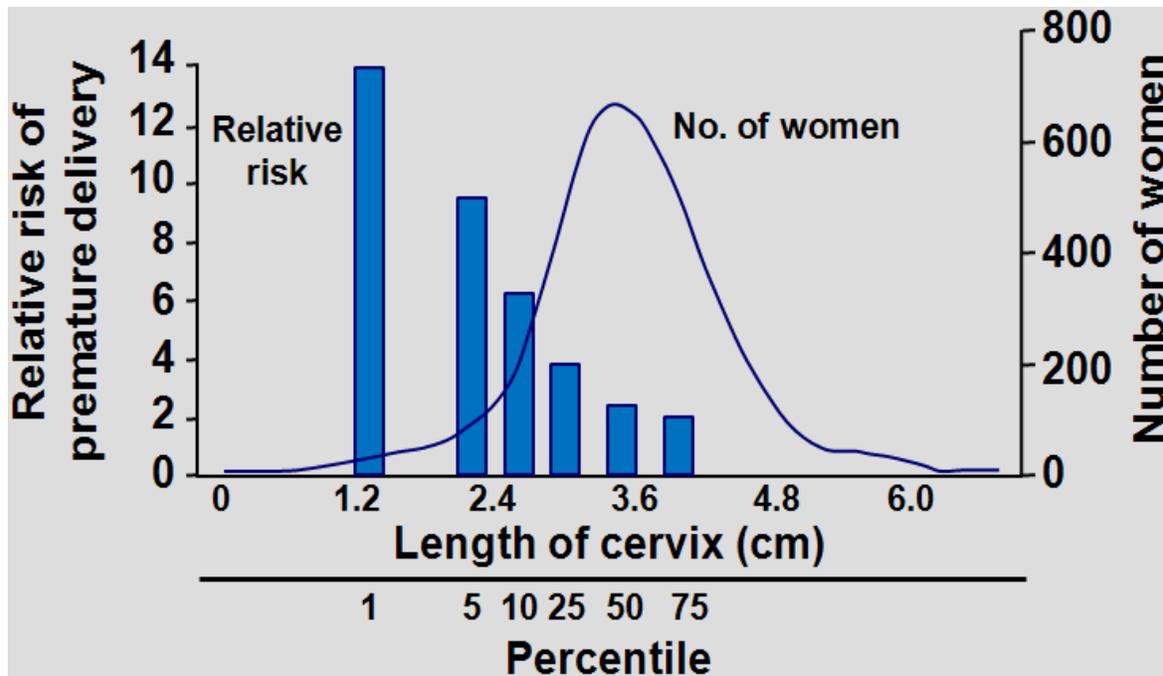
From Iams JD, et al, Figure 4.

---

[7] Fuchs F, Stakemann G. Treatment of threatened premature labor with large doses of progesterone. Am J Obstet Gynecol. 1960 Jan;79:172-6.
[8] Iams JD, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996;334(9):567-72.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

As a result of this research by Iams and similar data from other investigations,[9] cervical length is now considered to be the most important predictor of preterm birth. Nevertheless, because of the absence of an appropriate therapeutic intervention to address this risk factor, measurement of cervical length has had limited clinical utility to date.

Because of its known role in the maintenance of pregnancy, progesterone has long been of interest to clinicians as a therapeutic intervention for preterm birth. Premature cervical shortening in the mid-trimester is a clinical observation of a pathophysiologic process that causes changes that would normally occur over several months to occur over weeks. Findings that have been associated with cervical changes in pregnancy include an increase in inflammatory cells into the cervical stroma with resultant production of cytokines, and an increased activity of prostaglandins and matrix metalloproteinases that disrupt extracellular matrix.[10] Whether these observations are the cause or effect of cervical shortening are unclear; however, progesterone has been shown to abrogate these effects.[11]

In the late 1990s, the strategy to reduce preterm birth began shifting from intervention to repress premature uterine contractions to prophylaxis at an earlier stage in pregnant women with a known risk factor for preterm birth. In 2003, the results from two trials were published that continued to shift the treatment strategies from tocolytics to prevention. These two studies were randomized controlled trials of a progestin versus placebo in women with a history of preterm birth. One trial evaluated a weekly injectable formulation of a synthetic progestin[12] and the other investigation by Fonseca evaluated daily vaginal administration of natural progesterone in a compounded suppository formulation.[13] Both of the trials published in 2003 demonstrated a reduction in preterm birth with active treatment. These results led to the initiation of Columbia's Study 300 in 2004 with its proprietary vaginal progesterone gel 8% formulation.

---

[9] To MS, et al. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. Ultrasound Obstet Gynecol 2006;27:362-7.

[10] Sato T, et al. Hormonal regulation of collagenolysis in uterine cervical fibroblasts. Modulation of synthesis of procollagenase, prostromelysin and tissue inhibitor of metalloproteinases (TIMP) by progesterone and oestradiol-17 beta. Biochem J. 1991 May 1;275 (Pt 3):645-50.
  Imada K, et al. Hormonal regulation of matrix metalloproteinase 9/gelatinase B gene expression in rabbit uterine cervical fibroblasts. Biol Reprod. 1997 Mar;56(3):575-80.
  Imada K, et al. An antiprogesterone, onapristone, enhances the gene expression of promatrix metalloproteinase 3/prostromelysin-1 in the uterine cervix of pregnant rabbit. Biol Pharm Bull 2002;25:1223-7.

[11] Xu H, et al. Preventing cervical ripening: the primary mechanism by which progestational agents prevent preterm birth? Am J Obstet Gynecol. 2008 Mar;198(3):314.e1-8.
  Hassan SS, et al. The molecular basis for sonographic cervical shortening at term: identification of differentially expressed genes and the epithelial-mesenchymal transition as a function of cervical length. Am J Obstet Gynecol. 2010 Nov;203(5):472.e1-472.e14.

[12] Meis PJ, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Jun 12;348(24):2379-85.

[13] Fonseca EB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Study 300 was a randomized controlled trial conducted in pregnant women with a singleton gestation and a history of a previous preterm birth. Subjects were randomized to either placebo or progesterone gel 8% treatment. Although Study 300 did not achieve the primary goal of reducing preterm birth in the enrolled population of women with a history of preterm birth, a subgroup analysis from that study identified a subgroup of responders to natural progesterone administered vaginally: women with a sonographic short uterine cervix. After understanding the responsiveness of this subgroup, it was suggested in the 2007 publication by O'Brien, et al, that the baseline measurement of cervical length and resultant exclusion of patients with cerclage dramatically reduced the number of potentially treatment-responsive short cervix patients in the study, with a negative impact on the overall trial result. Interestingly, a second independent trial conducted by Fonseca using vaginally administered progesterone in oil capsules that was also published in 2007 provided additional substantiation of the effect of intravaginal progesterone in preventing preterm birth in women with a short cervix.

All of this information led Columbia to initiate Study 302 to test the hypothesis of whether treatment with progesterone gel 8% could reduce the incidence of preterm birth in women with a short cervix. This adequate and well-controlled study was conducted in collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) through a Clinical Trials Agreement (National Institute of Health [NIH] Study 09-CH-N014) since a trial evaluating the efficacy of vaginal progesterone in women with a short cervix was also being planned by that group at the same time. The progesterone gel 8% formulation produced by Columbia offered advantages over the progesterone in oil capsules tested by Fonseca; the Columbia formulation is specifically designed for vaginal administration and utilizes a novel bioadhesive technology that may provide prolonged local progesterone administration, resulting in elevated progesterone tissue concentrations at the target organ while minimizing systemic exposure.[14] Overall summaries of Study 300, Study 302, and Fonseca, et al, 2007, now follow in this Executive Summary section, with more details being provided in subsequent sections of this briefing package.

Study 300 primarily enrolled women with previous preterm birth, while Study 302 enrolled pregnant women with a short cervical length of 1 to 2 cm. Both were randomized, multicenter, double-blind, placebo-controlled studies; other design features, such as study visits, study drug administration, follow-up visit schedule, as well as baseline and follow-up assessments, were virtually identical, although Study 300 also included a 2-year infant follow-up period that was not included in Study 302.

---

[14] Cicinelli E, et al. Direct transport of progesterone from vagina to uterus.

The percentage of subjects with gestational age at delivery ≤32 weeks, the primary efficacy endpoint in Study 300, although numerically lower, was not statistically significantly different between the progesterone gel 8% and placebo groups in the total population (10.0% versus 11.3%, respectively, p = 0.694). However, a planned secondary analysis showed a decrease in the rate of cervical shortening between baseline and 28 weeks. Subsequently, a post-hoc analysis was performed on the subset of women (n=58 progesterone gel 8%, 58 placebo) with short cervixes (defined as ≤3.0 cm) using gestational age at delivery. In this analysis, the log-rank test for a difference between the Kaplan-Meier time-to-event curves censored at 37 weeks was nominally significant (p=0.043). Moreover, in this short cervix subset of women, there were also important differences with respect to the proportion of neonates admitted to the neonatal intensive care unit (NICU, 14% in the progesterone group vs. 26% in the placebo group, p=0.299), total number of neonatal hospital days per admission (7 versus 14 days, p=0.095), and occurrence of neonatal RDS (7% versus 19%, p=0.092).

In Study 302, a total of 465 pregnant women with a cervical length of 1.0 to 2.0 cm were randomized from ten countries (23 US sites, 21 non-US sites). The primary efficacy variable was the frequency of preterm birth at <33 weeks gestation in the intent-to-treat (ITT) analysis set. Secondary efficacy variables included frequency of preterm birth at <28 weeks, <35 weeks, <37 weeks, and term delivery (≥37 weeks). Once randomized, the subjects began daily administrations no earlier than 20 0/7 weeks of gestational age and continued treatment until 36 6/7 weeks, development of preterm rupture of membranes, or delivery. Progesterone gel 8% was associated with a statistically significant reduction in preterm birth for the primary variable when compared with placebo (8.9% versus 15.2%, p=0.022). Several additional sensitivity analyses supported the finding of the primary endpoint including adjustments for alternative pooling of study sites and US and non-US regional effects in two analyses, and adjustment for seven covariates in an additional analysis. Moreover, a preplanned test for interaction between primary pooled study sites and treatment was not significant (p=0.185). The incidence of preterm births at other gestational age endpoints as presented in Table 1-1 further attested to the robustness of the finding.

Table 1-1   Study 302 Incidence of Preterm Birth (ITT Analysis Set)

	Placebo n=224 PTB (%)	Prog gel 8% n=235 PTB (%)	Risk Difference (95% CI)	p Value*
Primary endpoint <33 weeks	**34 (15.2%)**	**21 (8.9%)**	**-6.2 (-12.2, -0.3)**	**p=0.022**
Secondary endpoint <28 weeks	21 (9.4%)	12 (5.1%)	-4.3 (-9.0, 0.5)	p=0.075
Secondary endpoint <35 weeks	50 (22.3%)	34 (14.5%)	-7.9 (-14.9, -0.8)	p=0.012
Secondary endpoint <37 weeks	74 (33.0%)	71 (30.2%)	-2.8 (-11.3, 5.7)	p=0.377

*based on Cochran-Mantel-Haenszel adjusted for primary pooled study sites and risk strata.
PTB=preterm birth
Source: Study 302 clinical study report, Table 14.2.1.1.

The gestational age at delivery results are displayed as a Kaplan-Meier curve in Figure 1-3.

Figure 1-3   Study 302 Kaplan-Meier Curve for Gestational Age at Delivery (ITT Analysis Set)

Source: Study 302 clinical study report, Figure 14.2.1.3.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE
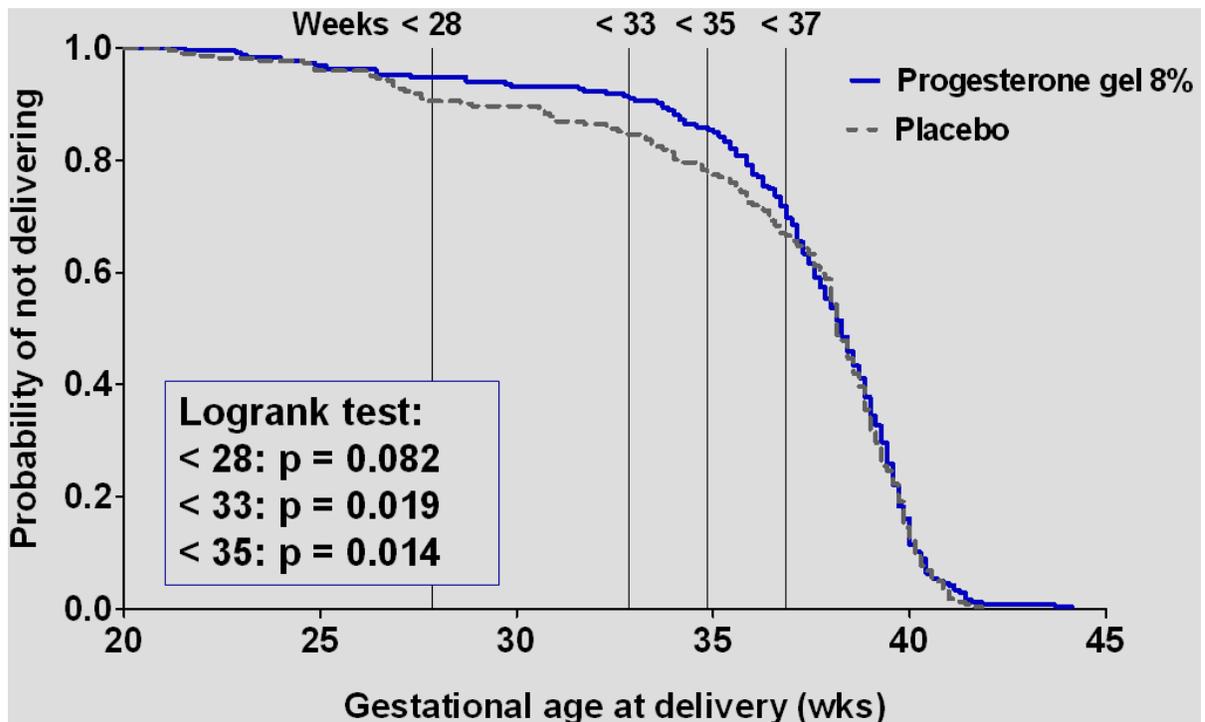
As a further assessment of the robustness of the finding for the primary endpoint, several planned secondary analyses of infant outcomes were performed. Composite scores were defined *a priori* that were composed of mortality and selected morbidity events. A key composite endpoint for perinatal mortality and neonatal morbidity was a 0-4 point score based on the ITT analysis set. Although the study was not powered for statistical comparisons on secondary endpoints, clinically meaningful reductions were nevertheless observed. For example, the results of the 0-4 point composite endpoint favored the progesterone gel 8% group in the reduction of perinatal mortality/neonatal morbidity with a statistical trend (p=0.113); in addition, the non-weighted composite score of "any morbidity & mortality" also favored the progesterone gel in support of the primary endpoint (p=0.088). In the ITT analysis set for the progesterone gel 8% group, there was a nominally significant reduction in RDS, the most common complication of prematurity and the leading cause of death of prematurity, when compared with the placebo group (nominal p=0.036). Other planned secondary endpoints of infant well-being also supported the finding of improvement in infant outcome such as increased length, weight, and head circumference. Overall the infant outcomes were consistent with the finding of the primary endpoint, and a comparison of the results from Studies 300 and 302 demonstrated a similar effect of progesterone gel 8% in the population of women with a short cervical length.

In addition to the multiple sensitivity analyses done on the primary endpoint, the analyses of multiple gestational cut points, and the infant outcome analyses, a number of prespecified and post-hoc subgroup analyses were also performed for the primary endpoint. In the review of these subgroup analyses it should be noted that this trial was not powered to show significance in any subgroup. Moreover, subgroup analyses are expected to display some variability around the overall result and may even show an opposite result by chance. It is known that as the number of individual tests increases the probability of falsely rejecting the null hypothesis increases when not adjusted for multiplicity. For example, if ten tests are performed, the chance of showing a significant result is 0.4 or approximately 1 in 2.5. In addition, when the sample size is halved for a subgroup (such as by the median) an original planned power of 80% is reduced to 50%.[15] Nevertheless, with all such caveats in mind, these subgroup analyses are presented and discussed in this briefing package. Subgroups explored in these investigations were as follows:

Pre-specified

- US region versus non-US region

---

[15] Rosner B. In *Fundamentals of Biostatistics*, 2nd Edition (1986). Chapter 7: Hypothesis Testing. Duxbury Press, Boston, Massachusetts.

- History of preterm birth versus no history of preterm birth

- Baseline cervical length ≤1.7 cm (median) versus baseline cervical length >1.7 cm

- History of cervical surgery

Post-hoc

- Gestational age at first dose ≤21 5/7 weeks (median) versus gestational age at first dose >21 5/7 weeks

- Maternal age ≤25.4 years (median) versus maternal age > 25.4 years

- Asian Race, Black Race, White Race

- Body mass index (BMI) ≤23.9 kg/m^2 (median) versus BMI >23.0 kg/m^2.

The results of these analyses all favored progesterone, with one exception (maternal age), and this pattern for subgroups therefore supported the positive finding on the primary endpoint.

Finally, another post-hoc analysis was performed combining short cervix (≤3.0 cm) subjects from Study 300 with all Study 302 subjects to explore efficacy in the largest group of short cervix women possible from the submission database. A reduction in the incidence of preterm birth (<33 weeks) was observed in the progesterone gel 8% treatment group compared with the placebo group (9.9% versus 16.7%, p=0.012). Risk reductions were also observed for the secondary efficacy variables of birth at <28 weeks (4.8% versus 8.7%, p=0.053), <35 weeks (16.3% versus 24.4%, p=0.007), and <37 weeks (33.0% versus 37.6%, p=0.181). Nominal statistical differences (p≤0.05, unadjusted for multiple comparisons) were noted for outcomes of RDS (3.7% versus 9.4%, p=0.011) and Any Mortality/ Morbidity Event (8.2% versus 14.3%, p=0.032). A nominally significantly higher birth weight was also noted in the progesterone infants (2,732.8 g versus 2,572.2 g for placebo, p=0.014), and a trend was observed for fewer NICU admissions (p=0.082).

Independent substantiation of the efficacy of vaginal progesterone in reducing the risk of preterm birth in women with short cervix was provided in research sponsored by the Fetal Medicine Foundation conducted from September 2003 through May 2006 in maternity hospitals in the United Kingdom, Chile, Brazil, and Greece, as published by Fonseca, et al in 2007. In this randomized, double-blind, placebo-controlled trial, 250 women with a cervical length of ≤1.5 cm received vaginally administered 200 mg capsules of micronized progesterone in peanut oil or identical appearing capsules of placebo containing safflower

oil, every night from 24 to 33 6/7 weeks of gestation. Follow-up visits for ultrasound assessment of fetal growth and cervical length were carried out every 2 weeks until 34 weeks of gestation. The primary outcome measure was spontaneous delivery before 34 weeks. The secondary outcome measures were birth weight, fetal or neonatal death, major adverse outcomes before discharge from the hospital, and need for neonatal special care. A strong treatment effect was noted for the use of vaginal progesterone in this study, with the percentage of preterm birth being 19.2% in the progesterone group versus 34.4% in the placebo group (p=0.007). The authors concluded that the results of this randomized trial demonstrated that in women with a short cervix, the daily vaginal administration of 200 mg of progesterone significantly reduced the rate of spontaneous preterm delivery.

The safety of progesterone gel 8% was demonstrated in 1,119 pregnant women who were considered at risk for preterm birth in the two Columbia safety and efficacy clinical studies, and in the additional pharmacokinetic study. In these three clinical studies, 579 subjects were exposed to progesterone gel 8% and 540 subjects received placebo. The occurrence of treatment-related adverse events was low and comparable between progesterone gel 8% and placebo, the most common adverse events being preterm labor-related complications of pregnancy. The most common adverse events that led to discontinuation of study drug were premature baby, premature labor and preterm rupture of membranes. There were no maternal deaths in any of the studies. Analysis of infant outcomes showed that there was no evidence of a fetal or infant mortality safety signal associated with progesterone gel 8% treatment. Additionally, in the two-year infant follow-up from Study 300, there was no evidence of infant harm when examining growth and development parameters. Finally, a review of 14 years of post-marketing safety data from the use of the approved progesterone gel 8% during the first trimester in support of ART has not uncovered any safety signals.

In summary, the data from this program using progesterone gel 8% in women with a short cervix to reduce the risk of preterm birth demonstrated a statistically significant and clinically meaningful reduction in preterm birth in women at high risk with an associated improvement in infant outcome. This benefit was accompanied by no meaningful risk to the mother or the fetus or infant. If broadly applied, use of this therapy could eliminate thousands of preterm births annually in the US with no meaningful risk. From a public health standpoint, the daily administration of Columbia's bioadhesive formulation of progesterone gel 8% in women with a short cervix would provide a valuable new treatment option in the armamentarium of treating preterm birth.

2   BACKGROUND

2.1   Introduction

Progesterone gel 8% is a well-known product that was first approved for vaginal use in 1997 by the US FDA for progesterone supplementation or replacement as part of an ART treatment for infertile women with progesterone deficiency. In this indication, progesterone gel 8% has been approved for use from two weeks prior to implantation up to the 12th week of pregnancy. The mechanism of benefit in this indication results from augmentation of low levels of endogenous progesterone, or complete replacement, in order to achieve and maintain the pregnancy during this first trimester. Progesterone gel 8% has been marketed in the United States and over 60 countries under the trade names Crinone and Prochieve. Over 50 million doses have been prescribed worldwide for use in pregnancy up to the 12th week, and excellent safety in early pregnancy has been demonstrated during this highly sensitive period of fetal development. Columbia submitted and received approval for this formulation under NDAs #20-701 and #20-756, for infertility and secondary amenorrhea respectively. These NDA's are currently held by Watson Laboratories, Inc.

NDA 22-139 was submitted by Columbia to the FDA on April 26, 2011 requesting approval of progesterone 8% vaginal gel to be administered once daily for *the reduction of risk of preterm birth in women with a singleton gestation and a short uterine cervical length in the mid-trimester of pregnancy. The key clinical study enrolled women with a uterine cervical length of 1 to 2 cm.* Progesterone gel 8% has not previously received approval in any country for the indication requested in this application and no marketing application for this indication has been submitted outside of the United States as of this date.

The active ingredient of progesterone gel 8%, progesterone, is the same molecule as the naturally occurring hormone in women. The product is a sustained-release formulation containing 90 mg progesterone per dose in a polycarbophil-based gel contained in a pre-filled single-use vaginal applicator; the applicator allows for easy vaginal dosing. The investigational product and applicator for this new indication are identical to the previously approved products Crinone and Prochieve. In the currently approved use in infertility, one pre-filled vaginal applicator is used either once daily for progesterone supplementation, or twice daily for progesterone replacement, to achieve and support a pregnancy as part of an ART treatment regimen. In the new use in preterm birth, the dose is proposed to be once daily. The progesterone gel 8% formulation produced by Columbia offers advantages over the progesterone in oil capsules tested by Fonseca, et al, 2007 in that the Columbia formulation was specifically designed for vaginal administration and utilizes a novel bioadhesive technology that may provide prolonged local progesterone administration,

resulting in elevated progesterone tissue concentrations at the target organ while minimizing systemic exposure.[16] As such, it allows for effective progesterone supplementation with just 90 mg of progesterone administered once daily whereas with other studied vaginal formulations, 300 to 600 mg daily doses of progesterone have been required for comparable efficacy.[17]

2.2   Information on Preterm Birth

Preterm birth, or delivery less than 37 weeks gestation, has shown a general trend for increase in the US over the last 20 years. Importantly, the rates of preterm birth prior to 34 weeks gestation have remained stable despite efforts specifically directed at reducing those rates. It is this earlier birth group that has the highest rate of major morbidity and mortality in newborns. Despite the objectives of Healthy People 2010, the US continues to have one of the highest infant mortality rates, ranking 48th in world ranking.[18] Importantly, preterm birth accounts for 34% of infant mortality and 95% of those who die are born <32 weeks gestation. Short-term consequences of preterm birth include death, RDS, sepsis, intraventricular hemorrhage, and necrotizing enterocolitis. The highest incidence of these complications occur in infants born to women who delivered prior to 32 weeks. Although the majority of these complications come from infants born between 34 and 37 weeks (70%) where the frequency of preterm birth is much higher, the incidence of complications is lower and less severe.[19]

Preterm birth is costly in many ways both for the individual and for society. Infants who are born preterm are more likely to have chronic lung disease, visual or hearing impairments, cerebral palsy, and developmental delay. Importantly, there are other more subtle but substantial long term consequences of prematurity. For example, in the Norwegian national registry, even infants born preterm without the obvious physical disabilities mentioned above still had lower education level attained, life income, and establishment rates of a family.[20]

Understanding the etiology of preterm birth is complicated by its multifactorial nature. About 70% of all preterm births are categorized as spontaneous preterm birth and are the result of infection and inflammation, spontaneous rupture of membranes, preterm contractions, and idiopathic cervical shortening. The remaining 30% of preterm births are

---

[16] Cicinelli E, et al. Direct transport of progesterone from vagina to uterus.
[17] Doody KJ, et al. Endometrin for luteal phase support in a randomized, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation. Fertil Steril. 2009 Apr;91(4):1012-7. Epub 2008 Apr 18.
  Geber S, et al. Comparison between two forms of vaginally administered progesterone for luteal phase support in assisted reproduction cycles. Reprod Biomed Online. 2007 Feb;14(2):155-8.
[18] https://www.cia.gov/library/publications/the-world-factbook/rankorder/2091rank.html.
[19] Callaghan WM, et al. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics. 2006 Oct;118(4):1566-73.
[20] Moster D. Long-term medical and social consequences of preterm birth. N Engl J Med. 2008 Jul 17;359(3):262-73.

the result of elective inductions due to either maternal or fetal complications including preeclampsia and fetal growth restriction.

The historical approach to reducing preterm birth has focused on the reduction of preterm contractions with the evaluation of tocolytics such as ethanol, terbutaline, nonsteroidal anti-inflammatory drugs and calcium channel blockers, none of which have been approved for this use by the FDA. This approach has not been successful and likely reflects, at least in part, the fact that the process resulting in preterm contractions is the end stage of the preterm birth process. More recently, attempts have been made to identify individuals at greatest risk for preterm delivery and then employ interventions directed to reduce their specific risks. The recent focus on what was felt to be an important risk factor, history of preterm birth, has met with some success as evidenced by the recent approval of a 17- hydroxyprogesterone caproate injection indicated to reduce the risk of preterm birth in women with a singleton pregnancy with a history of a singleton spontaneous preterm birth. However, this risk factor does not address individuals having their first pregnancy or those with a prior term delivery where, in fact, most preterm births originate.

More recently, cervical length has become recognized as an important risk factor that may identify the disease process in an early enough stage that allows interventions to be effective. A landmark study by Iams in 1996 clearly defined cervical length in the second trimester as an important predictor of preterm birth.[21] In the Iams data, the risk of preterm birth with cervical length shorter than the 75th percentile (4.0 cm) was twice the risk of preterm birth compared to those with a longer cervical length above the 75th percentile, and as the cervical length decreased, the risk of preterm birth dramatically increased. When the cervix measured <3 cm the relative risk for preterm birth was nearly four. Moreover, there was a 6-fold increased risk at 2.6 cm, a 9-fold increased risk at 2.2 cm, and a 14-fold increased risk at <1.3 cm. Figure 1.1 presents Iams data in graphical form.

---

[21] Iams JD, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996;334(9):567-72.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Figure 2.2-1 Risk of Premature Delivery by Cervical Length
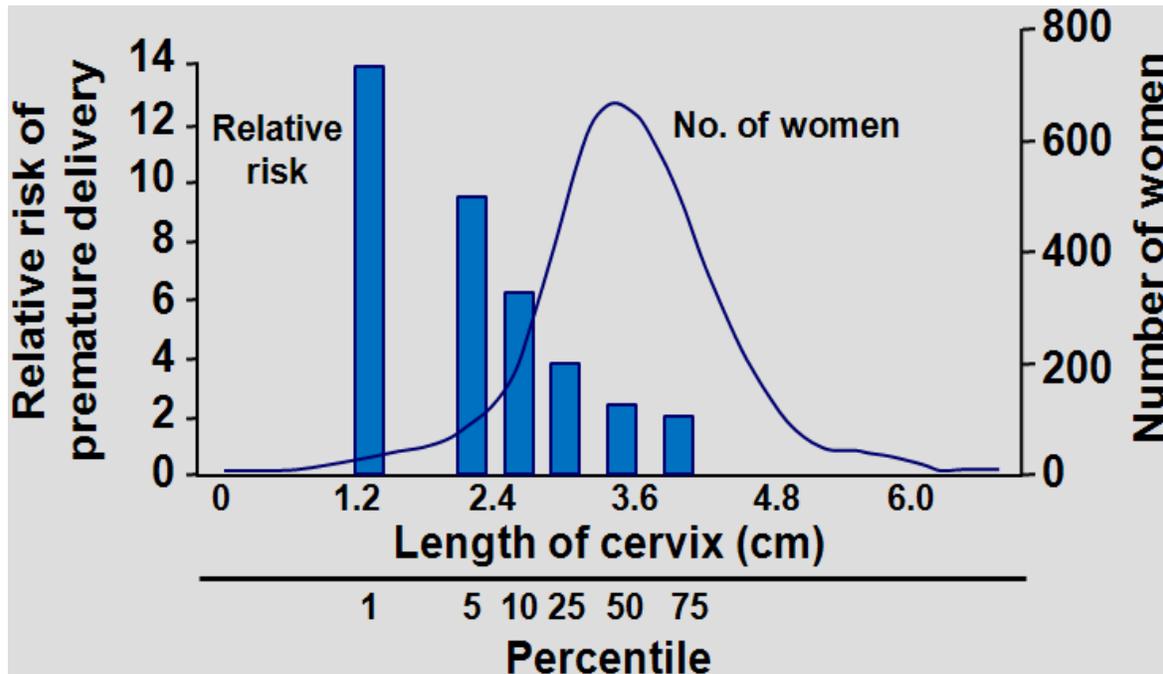
From Iams JD, et al, Figure 4.

As a result of research such as this performed by Iams and others,[22] cervical length is now considered the most important predictor of preterm birth, and short cervix as a risk factor represents a large unmet medical need for women. A therapy offering the degree of risk reduction demonstrated by Columbia's vaginal progesterone gel 8% in this development program could prevent approximately 20,000-30,000 preterm births annually, as shown in Table 2.2-1.

---

[22] Berghella, et al. Gestational age at cervical length measurement and incidence of preterm birth. Obstet Gynecol. 2007 Aug;110(2 Pt 1):311-7.

Table 2.2-1 Potential Preterm Births Avoided Through the Use of Progesterone Gel 8%

Cervical Length	Approximant Total Singleton Annual US Births (a)	Incidence of Cervical Length (b)	Preterm Birth Rate at this Cervical Length (c)	Reduction with Treatment (d)	Reduction in Preterm Births <35 Weeks
<2 cm	4,000,000	0.05	0.30	0.35	21,000
<2.5 cm	4,000,000	0.10	0.23	0.33	30,360

(a) CDC website.
(b) Iams, et al, 1996.
(c) Berghella, et al, 2007.
(d) Hassan, et al, 2011; Romero, et al, 2011, http://www.ajog.org/article/S0002-9378(11)02358-1/abstract.

2.3   The Role of Progesterone in Pregnancy

Progesterone's role in the establishment and maintenance of pregnancy is well understood. Progesterone is first produced by the corpus luteum of the ovary. Prior to implantation of the fertilized ovum, progesterone from the corpus luteum prepares the lining of the uterus for implantation of the fertilized egg. After implantation, progesterone from the corpus luteum is necessary for the maintenance of the first 8 weeks of pregnancy. From implantation of the embryo onwards for the rest of pregnancy, the placenta produces increasing amounts of progesterone and serum levels of progesterone increase dramatically into the third trimester of pregnancy. The administration of an anti-progestin in late pregnancy will accelerate cervical softening and shortening in the absence of uterine contractions and this observation suggests that these high levels of progesterone may have an effect on maintaining cervical integrity.[23] Because of this postulated role in the maintenance of pregnancy, progesterone has long been of interest to clinicians as a therapeutic intervention for preterm birth. It should be noted here that natural progesterone is virtually free of any teratogenic, metabolic, or hemodynamic effects, although this is not true for certain artificial progestagens and β-mimetics.[24]

---

[23] Word RA, et al, Dynamics of cervical remodeling during pregnancy and parturition: mechanisms and current concepts. Semin Reprod Med. 2007 Jan;25(1):69-79.

Chwalisz K, et al. The effect of antigestagen ZK 98,199 on the uterine cervix. Acta Endocrinol 1987;283:113.

Norman J, et al. Antiprogesterones. Br J Hosp Med. 1991 Jun;45(6):372-5. Review.

Elliott CL, et al. The effects of mifepristone on cervical ripening and labor induction in primigravidae. Obstet Gynecol. 1998 Nov;92(5):804-9.

Stenlund PM, et al. Induction of labor with mifepristone--a randomized, double-blind study versus placebo. Acta Obstet Gynecol Scand. 1999 Oct;78(9):793-8.

Giacalone PL, et al. The effects of mifepristone on uterine sensitivity to oxytocin and on fetal heart rate patterns. Eur J Obstet Gynecol Reprod Biol. 2001 Jul;97(1):30-4.

[24] Fonseca EB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24.

2.4   Proposed Mechanism of Action

Overly rapid cervical shortening is a clinical observation of a pathophysiologic process that reduces the time of cervical shortening from months to weeks. Understanding the mechanisms that may result in a short cervix provides an opportunity for a therapeutic intervention. The cervix has abundant extracellular matrix including collagen and elastin. In term pregnancies, cervical ripening, or shortening occurs as a result of decreased collagen content, increased collagen solubility and increased collagenolytic activity. In women at risk for preterm birth these same cervical changes occur at an earlier gestational age. There is often an increase in inflammatory cells into the cervical stroma with resultant production of cytokines, prostaglandins and matrix metalloproteinases that disrupt the extracellular matrix.[25] Importantly, steroid hormones, including progesterone, can abrogate these effects.[26] Although the specific biologic and/or cellular mechanisms of action in the prolongation of pregnancy from natural progesterone administered vaginally to women with a short cervical length are only currently being elucidated, a recent report suggests that an intracellular mechanism related to changes in specific gene expressions may be partly responsible for these beneficial actions.[27] A diagram summarizing the potentially beneficial effects of progesterone is presented in Figure 2.2-2.

---

[25] Sato T, et al. Hormonal regulation of collagenolysis in uterine cervical fibroblasts. Modulation of synthesis of procollagenase, prostromelysin and tissue inhibitor of metalloproteinases (TIMP) by progesterone and oestradiol-17 beta. Biochem J. 1991 May 1;275 (Pt 3):645-50; Imada K. Hormonal regulation of matrix metalloproteinase 9/gelatinase B gene expression in rabbit uterine cervical fibroblasts. Biol Reprod. 1997 Mar;56(3):575-80.
  Imada K, et al. An antiprogestereon, onapristone, enhances the gene expression of promatrix metalloproteinase 3/prostromelysin-1 in the uterine cervix of pregnant rabbit. Biol Pharm Bull 2002;25:1223-7.
[26] Xu H, et al. Preventing cervical ripening: the primary mechanism by which progestational agents prevent preterm birth? Am J Obstet Gynecol. 2008 Mar;198(3):314.e1-8.
  Hassan SS, et al. The molecular basis for sonographic cervical shortening at term: identification of differentially expressed genes and the epithelial-mesenchymal transition as a function of cervical length. Am J Obstet Gynecol. 2010 Nov;203(5):472.e1-472.e14.
[27] Zakar T, Mesiano S. How does progesterone relax the uterus in pregnancy? N Engl J Med. 2011 Mar 10;364(10):972-3.

Figure 2.2-2 Proposed Mechanisms of Action of Progesterone
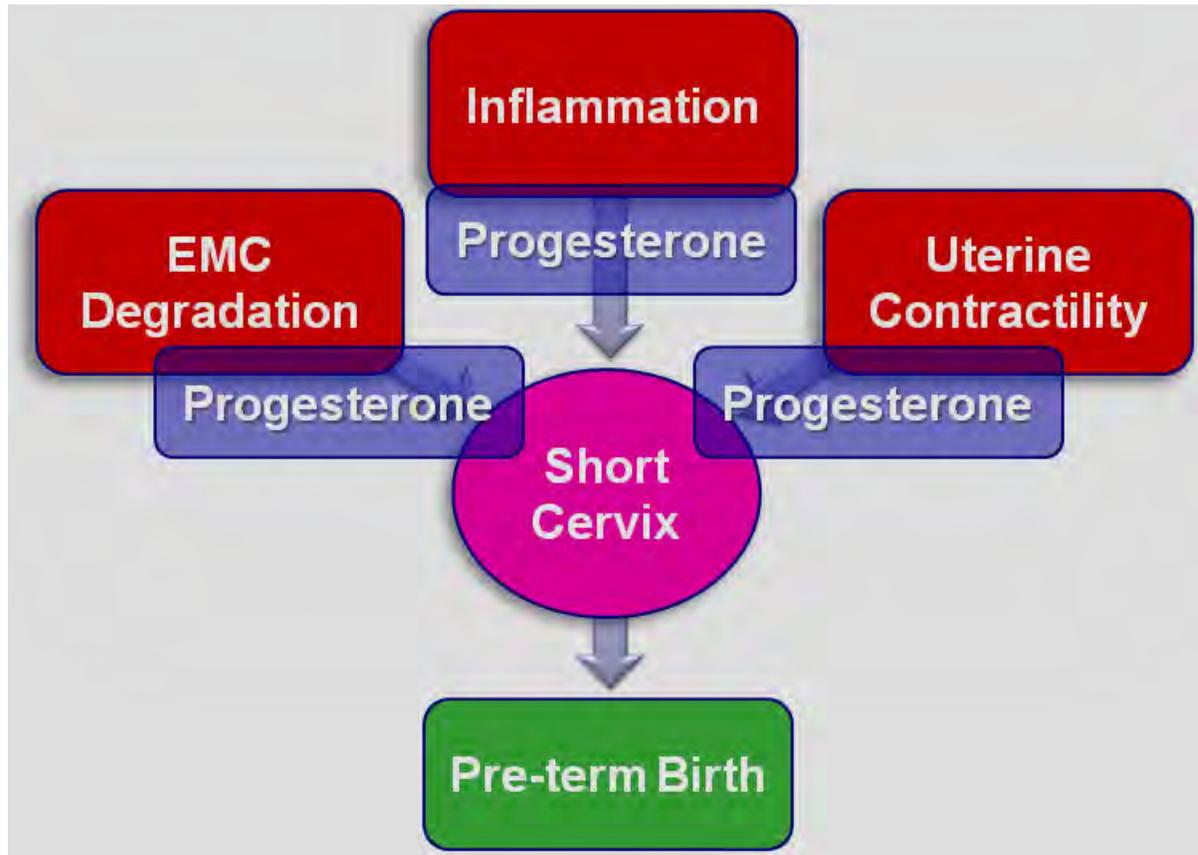
ECM=extracellular

2.5 Non-Clinical Information

No new nonclinical studies were performed for NDA 22-139, the NDA currently under consideration, since progesterone is a naturally occurring major steroid secreted by women during pregnancy. An agreement was made with the FDA during previous development programs for the approved indications to limit the nonclinical studies to single-dose toxicity and local tolerance studies. The nonclinical studies that were performed in support of the approved NDA 20-701 included acute toxicity studies, local tolerance toxicity studies, and an antigenicity study. The acute oral toxicity studies were performed in mice and rats and demonstrated a median lethal dose (sexes combined) to be greater than 5000 mg/kg of body weight. An eye irritation study in rabbits indicated that the compound had minimal irritative effects, which cleared in less than 24 hours. A primary dermal irritation study, also in rabbits, showed no formulation-related effects. Three vaginal irritation studies, all performed in rabbits, showed the formulation to be acceptable overall under the conditions of the test. A sensitization maximization test in guinea pigs showed no dermal sensitization.

2.6   Key Clinical Development Program Decisions

A schematic of Columbia's overall clinical development program is represented in Figure 2.6-1.

Figure 2.6-1 Columbia Clinical Development Program
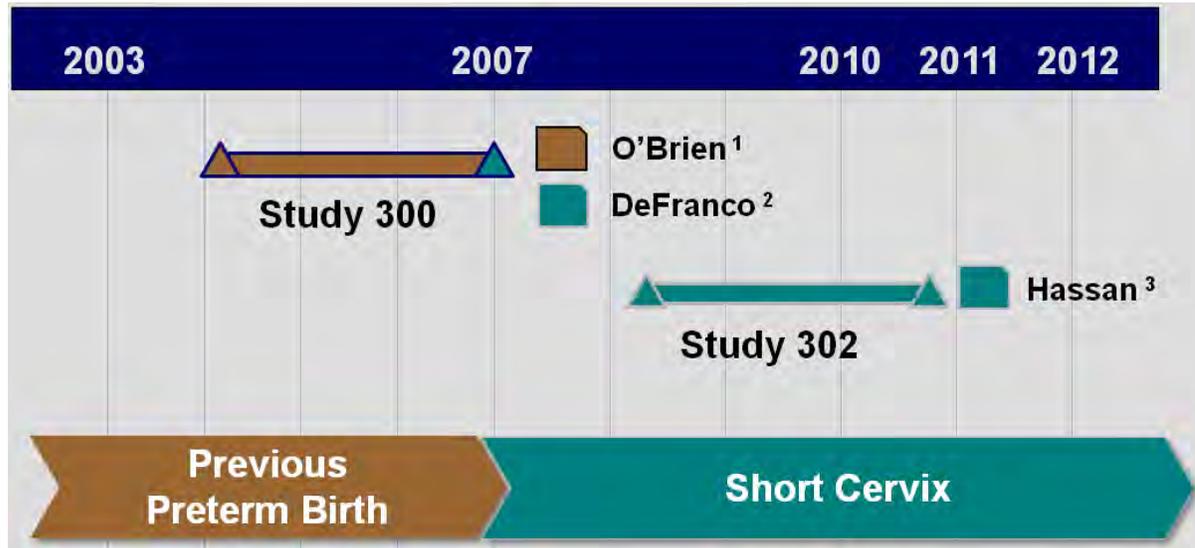
The clinical studies that Columbia conducted to develop progesterone gel 8% for the proposed indication are described in detail in Section 3.1 and 3.2. These studies consist of Study 302 as the adequate and well-controlled Phase 3 study for the proposed indication, and Study 300, the precursor to Study 302, which investigated the effects of progesterone gel 8% in women with a history of preterm birth. As mentioned in the Executive Summary, although Study 300 did not achieve the primary goal of reducing preterm birth in women with a history of preterm birth, a planned secondary analysis showed a decrease in the rate of cervical shortening between baseline and 28 weeks, and a further subgroup analysis identified women with short uterine cervix as responders to natural progesterone administered vaginally. The second trial conducted by Fonseca[28] using vaginally administered progesterone in oil capsules that was published in 2007 also provided independent substantiation of the effect of intravaginal progesterone in preventing preterm birth in women with short cervix. All of these results led Columbia to initiate Study 302 to test the hypothesis of whether treatment with progesterone gel 8% could reduce the incidence of preterm birth in women with a short cervix.

---

[28] **Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007 Aug 2;357(5):462-9.**

Study 302 was conducted under collaboration with the NICHD through a Clinical Trials Agreement (NIH Study 09-CH-N014) since a similar vaginal progesterone trial was also being planned by that group at the same time. During collaboration with the NIH and FDA, two major decisions were part of the creation of this investigative protocol: the determination of cervical length to be studied and the gestational age cut-off used for the primary analysis. After a review of all data available, it was determined to include women with a cervical length of 1.0 – 2.0 cm at 19 to 23 6/7 weeks of gestation. Although data strongly suggested that women with longer cervical lengths would benefit from vaginal progesterone therapy, the upper limit of cervical length in this trial was limited to what was considered the most sensitive subject population. Such an approach is consistent with design considerations usually undertaken during clinical trials since placebo rates in subjects who are less sensitive to intervention create impractical sample sizes. The lower limit of cervical length was chosen since women with cervixes <1 cm are likely to have already entered the terminal phase of labor, may require cerclage, and have a higher risk of infection and inflammation,[29] and all such conditions would have confounded the evaluation of treatment effect in this trial.

Regarding selection of the primary endpoint, there has been little historical agreement among researchers regarding the most clinically-relevant gestational age. However, it is well established that the burden of morbidity and mortality increases dramatically with each one week interval from the 28 to 37 week gestational age window, and in fact, the highest frequency of preterm birth complications occur in babies delivered before 33 weeks.[30] Therefore, <33 weeks was selected in order to create a conservative gestational age which would be considered by the vast majority of the medical community as being unequivocally clinically meaningful. This choice of <33 weeks is also consistent with guidance provided by the Reproductive Health Drugs Advisory Committee in 2006 where a primary endpoint of <35 weeks or lower was recommended.[31]

Transvaginal ultrasound (TVU) has played an integral role in this clinical development program and its use is important for appropriate patient selection in the proposed indication. TVU has been described several times in the literature and by now is a well-known technique that is widely available and part of obstetrical training and routine clinical practice.[32] In 2009, Mella[33] published an article concluding that cervical length measurement by TVU is one of the most effective screening methods for the prediction of preterm birth, and in that

---

[29] Vaisbuch E, et al. Patients with an asymptomatic short cervix (<or=15 mm) have a high rate of subclinical intraamniotic inflammation: implications for patient counseling. Am J Obstet Gynecol. 2010 May;202(5):433.e1-8.

[30] Callaghan WM, et al. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics. 2006 Oct;118(4):1566-73.

[31] http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4227M1.pdf.

[32] Educational Objectives: A Core Curriculum in Obstetrics and Gynecology, 9th Edition. 2009, published byProfesional Publishing Group, Ltd.

[33] Mella MT, Berghella V. Prediction of preterm birth: cervical sonography. Semin Perinatol. 2009 Oct;33(5):317-24.

publication he described the simple, accurate, and proper technique to measure cervical length. This same technique had been described earlier in 1996 by Iams[34] and in 2003 by Owen.[35] Currently, the 2007 ACOG Guidelines for Perinatal Care require obstetricians to provide ultrasound procedures and allow for the use of TVU in first-trimester imaging and in the measurement of cervical length when needed.[36] It is worth noting that the Society for Maternal Fetal Medicine is also finalizing guidelines for making cervical length screening and treatment with vaginal progesterone a standard part of obstetric care.[37]

2.7   Pharmacokinetics/Pharmacodynamics

Clinical pharmacology information in pregnant women was provided from one pharmacokinetic study, Study 301, while pharmacodynamic information was provided from a planned analysis from Study 300.

2.7.1   Study 301 - Pharmacokinetics

Study 301 was an open-label, multicenter bioavailability trial in pregnant women at high risk of spontaneous preterm delivery. Twenty-three pregnant women between 18 and 45 years of age, and between 16 0/7 and 22 6/7 weeks gestation, received daily progesterone gel 8% treatment for 14 to 22 weeks, until 37 weeks of gestation. Two subjects withdrew from the study prior to week 28; one was lost to follow-up and one withdrew voluntarily. All 23 subjects were included in the tabulation of the demographic and safety data. The mean age was 29 years and 61% of subjects were Caucasian, 26% were African American, 9% were Hispanic and 4% were Asian/Pacific Islander. Results are shown in Table 2.7-1.

---

[34] Iams JD, et al. The length of the cervix and the risk of spontaneous premature delivery. N Engl J Med 1996;334(9):567-72.

[35] Owen J. Evaluation of the cervix by ultrasound for the prediction of preterm birth. Clin Perinatol. 2003 Dec;30(4):735-55.

[36] Guidelines for Perinatal Care, 6th Edition. 2007, published byAmerican Academy of Pediatrics and American College of Obstetricians and Gynecologists.

[37] Fareeduddin R, Han C. Clinical update: vaginal progesterone to prevent preterm birth. Special Delivery (newsletter of the Society for Maternal-Fetal Medicine), Volume 3, Issue 4, Fall 2011.

Table 2.7-1   Study 301 Progesterone Plasma Level Results

	Progesterone Conc. Week 28 pre-dose (ng/mL)	Progesterone Conc. Week 28 post-dose (ng/mL)	Change from pre-dose (ng/mL)
Average	111.60	127.45	15.9
Maximum	175.40	210.90	57.5
Minimum	57.30	79.60	-13.7
Median	104.70	121.50	16.8
Standard Deviation	33.72	37.91	n/a
n	19	21	19

n/a=not available
Source: Study 301 clinical study report, Table 11.2.

The levels of progesterone varied considerably among subjects, however, all progesterone concentrations measured during the study were within the lab's normal reference range for the third trimester (48.40 – 422.50 ng/mL). Serum progesterone concentrations at Week 28 of pregnancy increased slightly following dosing with progesterone gel 8% in 17 of the 19 women for whom data were available. It was concluded that the changes seen in this study resulted in part from dosing with the vaginal gel product, as well as the normal intra-subject daily fluctuations from placental production. For reference, concentrations from other progesterone products and administration routes can be higher. For instance, package labeling for Prometrium® (progesterone 200 mg capsule) states that the maximum mean systemic concentration after five daily oral doses is more than twice this amount (i.e., 38.1 ± 37.8 ng/mL), but there is no published pharmacokinetic data on vaginal dosing during pregnancy with Prometrium. Finally, it is important to note that intramuscular administration of hydroxyprogesterone caproate does not result in significant systemic concentrations of natural progesterone since *in vitro* data indicate that the caproate group is retained during metabolism of the molecule.

2.7.2   Study 300 - Pharmacodynamics

A pharmacodynamic effect from the intravaginal administration of progesterone gel 8% was demonstrated in Study 300. Measurement of the change in cervical length from screening to Week 28 by TVU demonstrated that the progesterone gel 8% group had a nominally significant (p=0.038) decrease in cervical shortening compared with the placebo group: least squares means: -0.61 and -0.44 for placebo and progesterone gel 8%, respectively, as shown in Table 2.7-2.

Table 2.7-2   Study 300 Change in Cervical Length from Screening to Week 28 (cm) (Intent-to-Treat Analysis Set)

Statistic	Placebo (N=302)	Progesterone gel 8% (N=309)
N	274	273
Mean (SD)	-0.6 (0.90)	-0.46 (0.87)
Median	-0.5	-0.3
Minimum, Maximum	-3.6, 1.9	-3.9, 1.7
Dif. in least squared means	-0.16	
95% CI	-0.31, -0.01	
p-value*	0.038	

*p-value based on ANCOVA with terms for baseline and treatment.
Source: Study 300 clinical study report, Table 14.2.6.1.

Although the existence and degree of this pharmacodynamic effect may not be important for women with normal cervixes, this slowing of cervical length shortening is considered beneficial for women who already have short cervixes and who are at risk for delivering early because of this risk. Importantly, the degree of this effect was more marked in women with the shortest cervixes: in the women with cervixes ≤3.0 cm there was a mean difference of -0.34 cm between treatment groups (95% CI -0.61, -0.06).

2.8   Brief Regulatory History and Agreements

During the development of progesterone gel 8% for reduction of risk of preterm birth, Columbia met with the FDA multiple times to discuss the requirements for approval as well as Phase 3 protocol designs. Meetings to discuss development program points and the Study 300 design occurred in February and April 2004, while meetings to discuss Study 301 occurred in June and September 2006. Agreements on Study 302 were reached in meetings held with the FDA in July 2007 and April 2010. In addition, a pre-NDA meeting was held in February 2011 to come to agreement on the contents of the application. The most important specific and key agreements for the development program, particularly Study 302, are detailed below.

1. Vaginal ultrasound would be a valid and reliable measurement for assessing cervical length when performed with appropriate quality control procedures. The timeframe of 18 to 22 weeks gestation would be an acceptable timeframe for the measurement of baseline cervical length.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

2. A statistically robust finding of a treatment effect on preterm birth at <33 weeks
    gestation in a high risk population defined at any pre-specified shortened cervical
    length would be a clinically important result. (As previously mentioned, in the
    August 2006 Advisory Committee Meeting for another preterm birth prevention
    project, 17-hydroxyprogesterone caproate, the committee recommended that
    gestational age cutpoints <35 weeks would be appropriate.)

3. In addition to the reduction in the rate of preterm delivery, an improvement in a
    composite clinical endpoint measuring neonatal/infant morbidity/mortality would be
    important. It was agreed that an acceptable composite measure would count any
    infant who experienced death, RDS, bronchopulmonary dysplasia, periventricular
    leukomalacia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing
    enterocolitis. This neonatal morbidity/mortality composite score, as a single pre-
    specified analysis with a trend indicating treatment benefit, would be supportive.

4. The safety data collected for Study 300, which included infant follow-up to two years
    of age, together with the safety data from Study 302, would be adequate to support
    submission of an NDA.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

3   CLINICAL EFFICACY

Evidence of efficacy for progesterone gel 8% in women with short cervix is provided from an adequate and well-controlled clinical study, Study 302, with supportive information from Study 300, and independent substantiation of the approach to reducing the risk of preterm birth in women with short cervix through the use of vaginal progesterone from Fonseca, et al, 2007.[38] The first clinical investigation, Study 300, was a randomized, double-blind, multicenter, placebo-controlled study that primarily included women with previous preterm birth (with both short cervix and normal cervix). Study 302 was also a randomized, multicenter, double-blind, placebo-controlled study that included only pregnant women with a short cervix, defined as 1-2 cm (with or without a previous preterm birth). Both studies utilized academic and non-academic centers worldwide. Fonseca 2007 was also a randomized, double-blind, placebo-controlled, clinical study conducted by an independent sponsor, the Fetal Medicine Foundation, and tested 200 mg micronized progesterone capsules.

The designs of Columbia's two studies were nearly identical in terms of study visits, study drug administration, follow-up visit schedule, as well as baseline and follow-up assessments. There were minor differences between the studies regarding the screening and dosing periods; however, these differences are not considered meaningful. A comparison of study designs is presented in Table 3.1-1.

---

[38] **Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007 Aug 2;357(5):462-9.**

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Table 3.1-1 Comparison of Study Designs

Parameter	Study 300	Study 302
Population	Women with a singleton pregnancy and history of documented preterm delivery (at 20 to 35 weeks gestation) in the immediate preceding pregnancy regardless of baseline cervical length; women with a cervical length of ≤2.5 cm without a history of preterm birth were enrolled under a separate randomization (N=9)	Women with a singleton pregnancy and a cervical length between 1 - 2 cm, regardless of obstetrical history
Screening period	16 to 22 6/7 weeks gestational age	19 to 23 6/7 weeks gestational age
Dosing period	18 to 22 6/7 weeks until 37 0/7 weeks, preterm rupture of membranes, or delivery; (short cervix only subjects were dosed from 20 to 22 6/7 weeks)	20 to 23 6/7 weeks until 36 6/7 weeks, premature rupture of membranes, or delivery.
Preterm birth endpoints	Primary: ≤32 weeks Secondary: ≤28, ≤35, and <37 weeks	Primary: <33 weeks Secondary: <28, <35, and <37 weeks

Source: Final clinical study protocols.

3.1   Study 300

3.1.1   Methodology

3.1.1.1 Design

Study 300 was a prospective, randomized, double-blind, parallel group, placebo-controlled multi-center study. Subjects were randomized in a 1:1 ratio. Once randomized, the subjects were to begin treatment no earlier than 18 0/7 (for women with a history of preterm birth) or 20 0/7 (for women with a short cervix only; no history of preterm birth) weeks of gestational age. The study participants were followed at 2-week intervals after randomization. Study drug was administered daily until 37 0/7 weeks, development of preterm rupture of membranes, or delivery.

3.1.1.2 Population

This study recruited a population of women between 18 and 45 years of age with an estimated gestational age between 16 0/7 weeks and 22 6/7 weeks and a history of preterm birth in the previous pregnancy, defined as ≤35 0/7 weeks gestation. However, a small second population of women with cervical lengths ≤2.5 cm with a separate randomization was also conducted as a pilot study within this investigation. Cervical length was measured at baseline in all women who were recruited. Subjects were excluded if they had a multifetal gestation, cervical cerclage or pessary, acute cervical insufficiency with bulging membranes passing the external os, uterine anatomic malformation (bicornuate uterus, septate uterus),

preterm rupture of membranes, vaginal bleeding, known or suspected amnionitis, signs or symptoms of preterm labor at the time of enrollment, complete placenta previa, or the pregnancy was complicated by a major fetal anomaly or known chromosomal abnormality.

3.1.1.3 Treatment Administered

Subjects received 90 mg of progesterone gel 8% (1.125 g of the gel product) or placebo gel once daily in the morning. This dose was selected since it had previously been demonstrated to be safe and effective in maintaining pregnancy during the first trimester, and because a previous randomized clinical trial showed efficacy with a 100 mg non-bioadhesive vaginal formulation.[39]

3.1.1.4 Endpoints

The primary efficacy endpoint was the frequency of preterm birth at ≤32 weeks gestation in the ITT analysis set.

Secondary efficacy endpoints included frequency of preterm birth at ≤28 weeks, ≤35 weeks, <37 weeks, and term delivery (≥37 weeks), changes in cervical length at week 28, incidence of hospital admission for preterm birth, and the number of infant hospital days (NICU, intermediate care, and regular newborn nursery).

3.1.1.5 Sample Size

A sample size of at least 630 was estimated to provide a power of 88% using a 2-sided significance level of 5% for the primary efficacy variable based on an overall placebo rate of 20% and a 50% reduction with progesterone gel 8%.

3.1.2   Results

Fifty-three investigative sites (14 non-US, 39 US) worldwide participated. In the safety analysis set, 224 subjects were from non-US region and 413 were from the US. Of these, 302 subjects in the placebo treatment group and 309 subjects in the progesterone gel 8% treatment group were included in the ITT analysis set; these subjects were able to provide a delivery date (for this study there was no *a priori* imputation scheme as was later developed for Study 302). The percentage of subjects with gestational age at delivery ≤32 weeks, the primary efficacy endpoint in Study 300, although numerically lower, was not statistically significantly different between the progesterone gel 8% and placebo groups in the ITT analysis set (10.0% versus 11.3%, respectively, p=0.694). However, a planned secondary analysis showed a decrease in the rate of cervical shortening between baseline and 28 weeks

---

[39] Fonseca EB, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24.

(as previously described in Section 2.7.2). Subsequently, a post-hoc analysis was performed on the subset of 116 women (58 progesterone, 58 placebo) with baseline cervical lengths of ≤3.0 cm using gestational age at delivery. In this analysis, the log-rank test for a difference between the Kaplan-Meier time-to-event curve censored at 37 weeks was nominally significant (p=0.043) as shown in Figure 3.1-1. Moreover, in this subset, there were also important differences with respect to the proportion of neonates admitted to the NICU (14% versus 26%, p=0.299), total number of neonatal hospital days (7 versus 14 days, p=0.095), and occurrence of neonatal RDS (7% versus 19%, p=0.092).

Figure 3.1-1 Study 300 Gestational Age at Delivery for Subjects with Cervixes ≤3.0cm.
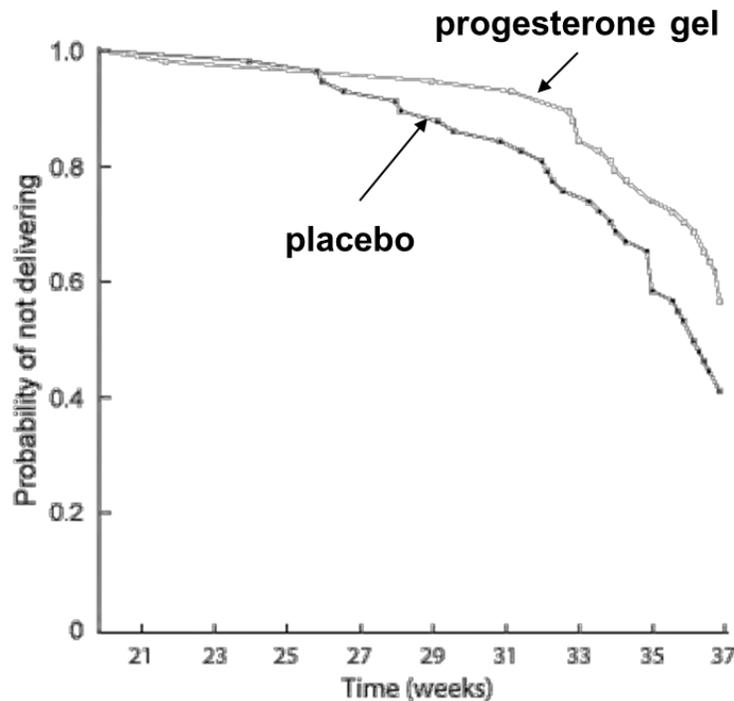
Source: Figure 3 of DeFranco, et al. 2007.

3.1.3   Conclusions

In Study 300, women with a history of a previous preterm birth did not have a reduction in the risk of recurrent preterm birth with progesterone treatment beginning as early as 18 weeks gestation. However, progesterone gel 8% treatment was associated with a nominally significant reduction in cervical shortening. More importantly in women with cervixes ≤3.0 cm, a time-to-event analysis demonstrated that progesterone gel 8% also had a nominally significant delay in delivery through 37 weeks with accompanying improvements in infant outcomes.

3.2   Study 302

3.2.1   Methodology

3.2.1.1 Design

Study 302 was a prospective, randomized, double-blind, parallel group, placebo-controlled multi-center study. Subjects were randomized in a 1:1 ratio stratified by risk group (previous preterm birth versus no previous preterm birth) to begin treatment no earlier than 20 0/7 weeks of gestational age. After randomization, the study participants were followed at two-week intervals and study drug was administered daily until 36 6/7 weeks, development of preterm rupture of membranes, or delivery.

3.2.1.2 Population

Singleton gestation subjects with an estimated gestational age between 19 0/7 weeks and 23 6/7 weeks, and a maternal age between 15 (or local age of majority/emancipation) and 45 years of age were recruited from a population of women with cervical length between 1.0 and 2.0 cm as determined by TVU at mid-trimester. Subjects with or without a previous preterm birth were offered the opportunity to participate. Subjects were excluded if they had a multifetal gestation, cervical cerclage or pessary, acute cervical insufficiency with bulging membranes passing the external os, uterine anatomic malformation (bicornuate uterus, septate uterus), preterm rupture of membranes, vaginal bleeding, known or suspected amnionitis, signs or symptoms of preterm labor at the time of enrollment, complete placenta previa, or the pregnancy was complicated by a major fetal anomaly or known chromosomal abnormality.

3.2.1.3 Treatment Administered

Subjects received 90 mg of progesterone gel 8% (1.125 g of the gel product) or placebo gel once daily in the morning to match the dose used in Study 300.

3.2.1.4   Endpoints

The primary efficacy endpoint was the frequency of preterm birth at <33 weeks gestation in the ITT analysis set. The primary analysis of this variable was performed using a Cochran-Mantel-Haenszel (CMH) test stratified by primary pooled study sites and preterm birth history risk strata. Planned sensitivity analyses for the primary endpoint included analysis of the primary endpoint adjusting for: secondary pooled study site and preterm birth history risk strata; US vs non-US study sites and preterm birth history risk strata; and logistic regression including adjustment for 7 covariates (primary pooled study site, risk strata, gestational age at first dose, maternal age, baseline cervical length, BMI, race). A test for interaction between primary pooled study site and treatment was also planned. The ITT population was

defined as all randomized subjects that received at least one dose of study drug. The following imputation scheme was used for the gestational age categories:

- All placebo subjects with no documented delivery date were counted as term deliveries (37 weeks gestational age at delivery).

- For progesterone gel 8% subjects with no documented delivery date, the date of last contact was used as the delivery date.

This strategy provided a 'worst case' analysis with respect to eliminating any perceived advantage for progesterone gel for subjects without a delivery date.

Secondary efficacy endpoints were selected for demonstration of the robustness of the primary endpoint and included: the frequency of preterm birth at <28 weeks, <35 weeks, <37 weeks, and term delivery (≥37 weeks); infant outcomes both individually and as composite scores; and other parameters of infant well-being such as length, weight, and head circumference. In order to increase diagnosis reliability during the development program, standard definitions were used for selected infant outcomes and are provided in Appendix 1. The infant outcomes were as follows:

- Respiratory Distress Syndrome (RDS)
- Bronchopulmonary Dysplasia (BPD)
- Intraventricular Hemorrhage (IVH)
- Proven Sepsis
- Necrotizing Enterocolitis (NEC)
- Periventricular Leukomalacia (PVL)
- Perinatal mortality

A 0-4 point score for perinatal mortality/neonatal morbidity score was considered a key secondary efficacy variable. This composite score was calculated as follows, counting events as RDS, BPD, grade III or IV IVH, proven sepsis, NEC, or PVL:

    0 = no events
    1 = one event and no perinatal mortality
    2 = two events and no perinatal mortality
    3 = three or more events and no perinatal mortality
    4 = perinatal mortality

In addition, three other alternative composite scoring algorithms were also pre-defined (Table 3.2-4). Finally, APGAR scores, congenital abnormalities, NICU admission, infant hospital days, and number of days in the NICU were also evaluated.

3.2.1.5 Sample Size

A sample size of at least 450 was estimated to provide a power of 93% using a 2-sided significance level of 5% for the primary efficacy variable based on an overall placebo rate of 22% and a 55% reduction with progesterone gel 8% based on Fisher's exact test.

3.2.2   Results

3.2.2.1 Disposition

A total of 465 pregnant women were randomized in Study 302 from 10 countries with the majority (96%) completing the study. Six subjects never received study drug (5 on placebo, 1 on progesterone gel 8%) and were not included in the ITT analysis set. Forty-five percent of the study enrollment was from the US. Forty-four centers worldwide enrolled subjects with 206 US subjects from 23 US sites, and 253 non-US subjects from 21 non-US sites in the ITT/Safety population. As mentioned, the study was stratified for the presence or absence of a previous preterm birth in the last pregnancy, and this stratification resulted in a balanced proportion of subjects with a history of a previous preterm birth between treatment groups. A total of 15.5% of the subjects had a previous preterm birth. The majority of subjects (94% of the placebo-treated subjects and 97% of the progesterone gel 8%-treated subjects) completed the study. Table 3.2-1 summarizes subject disposition from this study.

Table 3.2-1 Study 302 Summary of Subject Disposition

Number of Subjects	Descriptive Statistic	Placebo			Prochieve			Overall Total
		Preterm	No Preterm	Total	Preterm	No Preterm	Total	
Randomized [1] [2]	n (%)	34 (7%)	195 (42%)	229 (49%)	38 (8%)	198 (43%)	236 (51%)	465 (100%)
Completed Study [3]	n (%)	30 (88%)	185 (95%)	215 (94%)	36 (95%)	194 (98%)	230 (97%)	445 (96%)
Discontinued Study Drug [3]	n (%)	4 (12%)	10 (5%)	14 (6%)	2 (5%)	4 (2%)	6 (3%)	20 (4%)
Reason for Discontinuation of Study Drug [3]								
Adverse Event: Stillbirth	n (%)	2 (6%)	2 (1%)	4 (2%)	2 (5%)	1 (<1%)	3 (1%)	7 (2%)
Adverse Event: IUFD	n (%)	1 (3%)	1 (<1%)	2 (<1%)	0	2 (1%)	2 (<1%)	4 (<1%)
Lost to Follow-up	n (%)	0	4 (2%)	4 (2%)	0	0	0	4 (<1%)
Subject Voluntarily Withdrew	n (%)	0	2 (1%)	2 (<1%)	0	1 (<1%)	1 (<1%)	3 (<1%)
Other Reason	n (%)	1 (3%)	1 (<1%)	2 (<1%)	0	0	0	2 (<1%)

[1] Three screen failures entered in the database are not included in the analysis. These subjects' data are included in the data listings.
[2] Percentage based on the total number of subjects randomized.
[3] Percentage based on the number of subjects randomized within each corresponding treatment group, strata, or total.
Source: Study 302 clinical study report, Table 14.1.1.1.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

3.2.2.2 Demographics

Demographics were balanced between treatment groups as shown in Table 3.2-2.

Table 3.2-2   Study 302 Summary of Subject Demographics

		Placebo			Progesterone Gel 8%			Overall
	Descriptive Statistic	**Preterm History N=33**	**No Preterm History N=191**	**Total N=224**	**Preterm N=38**	**No-Preterm N=197**	**Total N=235**	**N=459**
Age (years)	Mean (SD)	28.0 (5.98)	25.8 (4.87)	26.1 (5.10)	28.0 (6.60)	26.2 (5.65)	26.5 (5.83)	26.3 (5.48)
Race Asian (a) Black White Other	n (%)	15 (45%) 9 (27%) 7 (21%) 2 (6%)	62 (32%) 58 (30%) 62 (32%) 9 (5%)	77 (34%) 67 (30%) 69 (31%) 11 (5%)	15 (39%) 11 (29%) 9 (24%) 3 (8%)	61 (31%) 65 (33%) 64 (32%) 7 (4%)	76 (32%) 76 (32%) 73 (31%) 10 (4%)	153 (33%) 143 (31%) 142 (31%) 21 (5%)
Body Mass Index (kg/m^2)	Mean (SD)	24.9 (6.66)	25.2 (6.73)	25.2 (6.70)	26.1 (7.18)	25.5 (6.15)	25.6 (6.31)	25.2 (6.50)
Cervical Length (cm)	Mean (SD)	1.75 (0.281)	1.69 (0.287)	1.70 (0.286)	1.74 (0.225)	1.72 (0.260)	1.72 (0.254)	1.71 (0.270)
Gestational Age at First Dose (Weeks)	Mean (SD)	22.2 (1.38)	21.7 (1.40)	21.8 (1.40)	21.7 (1.24)	21.9 (1.39)	21.9 (1.37)	21.8 (1.39)
Fetal Anatomy Normal	N (%)	32 (97%)	190 (>99%)	222 (>99%)	38 (100%)	197 (100%)	235 (100%)	457 (>99%)

(a) Primarily subjects from India.
Source: Clinical study report Table 14.1.2.1; Listings 16.2.4.1 and 16.2.4.6.

3.2.2.3 Primary Efficacy Results

Progesterone gel 8% was associated with a statistically significant and clinically meaningful reduction in preterm birth for the primary variable when compared with placebo. The incidence of preterm birth at various gestational ages are presented in Table 3.2-3, while Figures 3.2-1 and -2 present a graphical representation of these data and a Kaplan-Meier curve for gestational age at delivery, respectively.

Table 3.2-3 Study 302 Incidence of Preterm Birth (ITT Analysis Set)

	Placebo n=224 PTB (%)	Prog gel 8% n=235 PTB (%)	Risk Difference (95% CI)	P Value*
Primary endpoint **<33 weeks**	**34 (15.2%)**	**21 (8.9%)**	**-6.2** **(-12.2, -0.3)**	**p=0.022**
Secondary endpoint <28 weeks	21 (9.4%)	12 (5.1%)	-4.3 (-9.0, 0.5)	p=0.075
Secondary endpoint <35 weeks	50 (22.3%)	34 (14.5%)	-7.9 (-14.9, -0.8)	p=0.012
Secondary endpoint <37 weeks	74 (33.0%)	71 (30.2%)	-2.8 (-11.3, 5.7)	p=0.377

*based on Cochran-Mantel-Haenszel adjusted for primary pooled study sites and risk strata.
PTB=preterm birth
Source: Study 302 clinical study report, Table 14.2.1.1.

Figure 3.2-1 Study 302 Incidence of Preterm Birth (ITT Analysis Set)
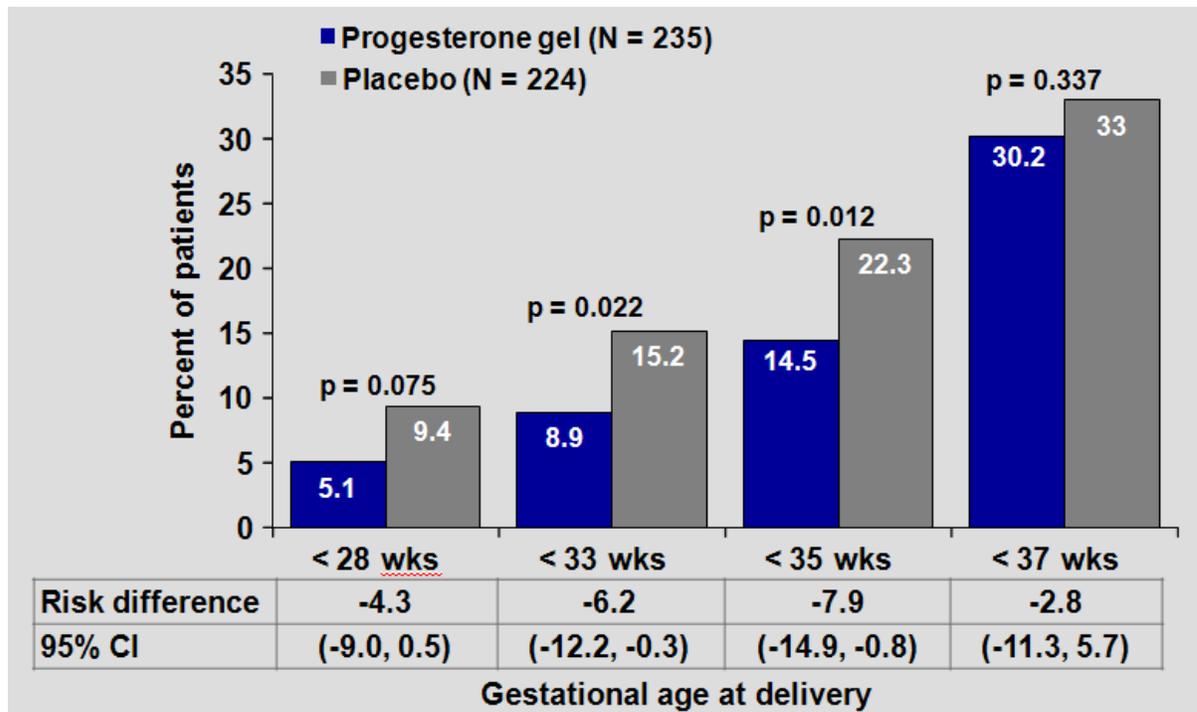
Source: Study 302 clinical study report, Table 14.2.1.1

Figure 3.2-2 Study 302 Kaplan-Meier Curve for Gestational Age at Delivery (ITT Analysis Set)
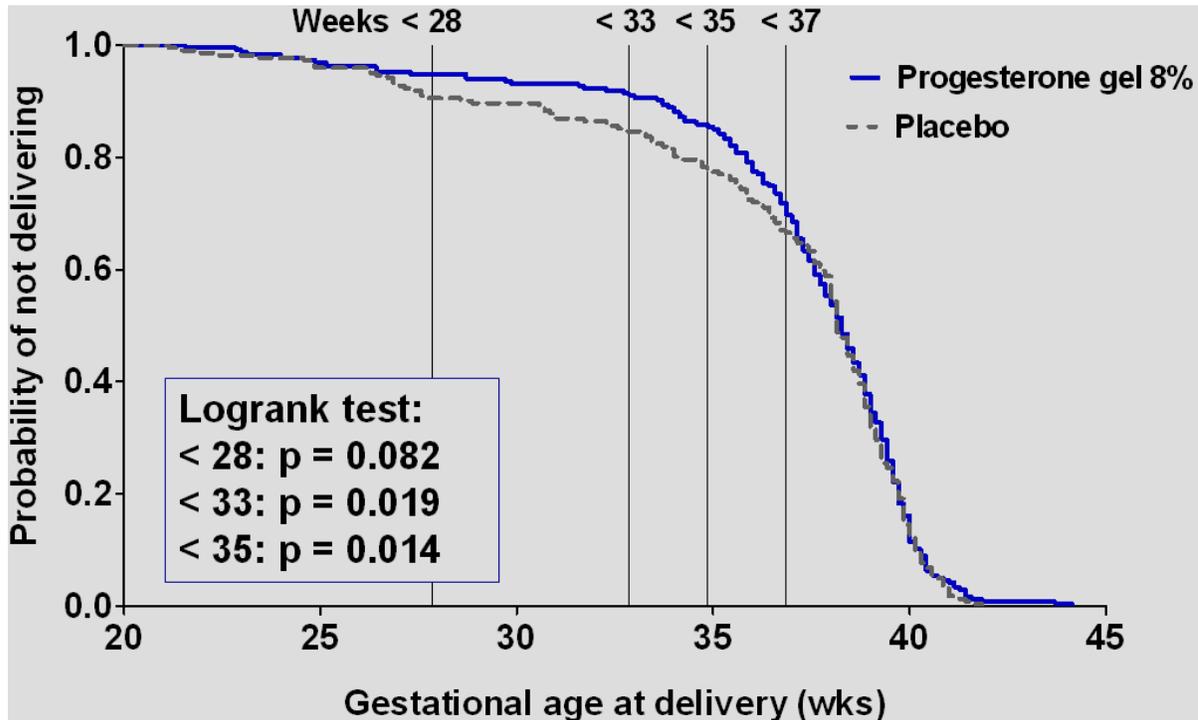
Source: Study 302 clinical study report, Figure 14.2.1.3.

Several sensitivity analyses were also performed on the primary endpoint and the result of each is shown below:

- p = 0.017: Treatment comparison for CMH adjusted for secondary pooled study sites and risk strata. Secondary pooled study sites were developed *a priori* as a sensitivity assessment for the primary pooled study sites (also *a priori* defined). Whereas the nine primary pooled study sites contained between 45-56 subjects, the 16 secondary pooled study sites contained approximately half these sample sizes.

- p = 0.031: Treatment comparison for CMH adjusted for US and non-US sites and risk strata. All 206 US subjects and 253 non-US subjects were pooled into two groups for this analysis.

- p = 0.044: Treatment comparison for logistic regression including 7 co-variates. This pre-specified logistic regression model contained terms for primary pooled study sites, risk strata, gestational age at first dose, maternal age, cervical length, BMI, race, and treatment group.

- p = 0.185: Interaction between primary pooled study sites and treatment. The interaction analysis was obtained from a logistic regression model with terms for

primary pooled study sites, risk strata, treatment group, and primary pooled study sites by treatment interaction.

3.2.2.4 Secondary Efficacy Results

An additional evaluation of the robustness of the finding of the primary endpoint was the reduction in the frequency of preterm birth at adjacent gestational age cut points, as shown previously in Table 3.2-3. Further assessment of the robustness of the primary endpoint was conducted through analysis of the planned secondary endpoints of infant outcomes. As previously defined, the key composite score for perinatal mortality and neonatal morbidity was the 0-4 point composite score based on the ITT analysis set. The 0-4 composite score, as well as the three alternative pre-defined composite scores in the ITT analysis set, all favored the progesterone gel 8% group in the reduction of perinatal mortality/neonatal morbidity, as shown in Table 3.2-4. In the assessment of "Any Mortality/Morbidity Event", the risk of any mortality/morbidity event favored the progesterone gel 8% group (p = 0.088).

Table 3.2-4 Study 302 Perinatal Mortality and Neonatal Morbidity and Composite Sources (ITT Analysis Set)

Analysis	Value	Placebo n (%)	Prog gel 8% n (%)	p-value
Any Morbidity or Mortality Event	Yes	28 (12.5%)	18 (7.7%)	0.088 (a)
0-4 Point Scale Composite Score (b)	0	192 (86%)	217 (92%)	0.113 (a)
	1	11 (5%)	5 (2%)	
	2	7 (3%)	2 (<1%)	
	3	0 (0%)	3 (1%)	
	4	10 (4%)	8 (3%)	
0-4 Point Scale with NICU Days Composite Score (c)	0	168 (75%)	194 (83%)	0.103 (a)
	1	11 (5%)	6 (3%)	
	2	17 (8%)	19 (8%)	
	3	14 (6%)	8 (3%)	
	4	10 (4%)	8 (3%)	
0-6 Point Scale Composite Score (d)	0	192 (86%)	217 (92%)	0.113 (a)
	1	11 (5%)	2 (2%)	
	2	7 (3%)	2 (<1%)	
	3	0 (0%)	0 (0%)	
	4	0 (0%)	3 (1%)	
	5	0 (0%)	0 (0%)	
	6	10 (4%)	8 (3%)	

(a) Based on Cochran-Mantel-Haenszel test adjusted for primary pooled study site and risk strata. Composite scores used modified ridits.
(b) 0 = no events; 1= one event for (RDS, grade III or IV IVH, proven sepsis, PVL, NEC, BPD) and no perinatal mortality; 2 = two events and no perinatal mortality; 3 – three or more events and no perinatal mortality; 4 = perinatal mortality.
(c) 0 = no events; 1 = one event for (RDS, grade III or IV IVH, proven sepsis, PVL, NEC, BPD) or <5 days in the NICUE and no perinatal mortality; 2 = two events or between 5 and 20 days in the NICU and no perinatal mortality; 3 = three or more events or >20 days in the NICU and no perinatal mortality; 4 = perinatal mortality.
(d) 0 = no events; 1 = one event for (RDS, grade III or IV IVH, proven sepsis, PVL, NEC, BPD) and no perinatal mortality; 2 = two events and no perinatal mortality; 3 = three events and no perinatal mortality; 4 = four events and no perinatal mortality; 5 = five events and no perinatal mortality; 6 = perinatal mortality.
 Source: Study 302 clinical study report, Table 14.2.3.1.

Moreover, there were favorable infant outcomes with the use of progesterone gel 8% versus placebo, including, most importantly, a reduction in RDS, the most common complication of prematurity and the leading cause of death of prematurity. These outcomes are shown in Table 3.2-5. It is worth noting that this treatment effect for RDS infants is the first such benefit demonstrated in a clinical trial since the introduction of surfactant, demonstrating that the benefit of progesterone gel 8% is additive to the substantial treatment effect of surfactant therapy in this condition.

Table 3.2-5 Study 302 Perinatal Mortality and Neonatal Morbidity (ITT Analysis Set)

Morbidity and Mortality	Descriptive Statistic	Placebo N = 224	Prog gel 8% N = 235	Nominal p Value*
RDS	n (%)	16 (7.1)	7 (3.0)	0.036
BPD	n (%)	5 (2.2)	4 (1.7)	0.701
IVH	n (%)	5 (2.2)	4 (1.7)	0.676
Proven Sepsis	n (%)	5 (2.2)	7 (3.0)	0.577
NEC	n (%)	4 (1.8)	5 (2.1)	0.769
PVL	n (%)	0 (0)	0 (0)	---
Hydrocephaly	n (%)	0 (0)	0 (0)	---
Congenital Abnormalities	n (%)	3 (1.3)	1 (0.4)	0.288
Perinatal Death	n (%)	10 (4.5)	8 (3.4)	0.596
Fetal Death		5 (2.2)	5 (2.1)	
Neonatal Death		5 (2.2)	3 (1.3)	
NICU Admission	n (%)	43 (19.2)	35 (14.9)	0.152
Hospital Admission for Preterm Labor	n (%)	55 (24.6)	52 (22.1)	0.490

*Based on CMH test adjusted for primary pooled study site and risk strata.
Source: Study 302, clinical study report, Table 14.2.3.1.

Finally, evidence for improvement in infant outcome was also supported by an increase in the size of the infants at birth, and a reduction in infants with birth weight <1500 grams (6.4% versus 13.3%, p=0.014). For the <2500 grams category, there was a numerical difference between progesterone and placebo (25.6% versus 30.7%, p=0.229). Neonatal information is shown in Table 3.2-6.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Table 3.2-6   Study 302 Neonatal Characteristics

	Placebo N = 224	Prog gel 8% N = 235	Nominal p-value
Birth weight (g)	2634.6	2770.7	0.059
Birth weight <1500 g, n (%)	13.3	6.4	0.014
Length (cm)	46.3	47.6	0.013
Head circumference (cm)	31.9	32.7	0.021
APGAR 1 min	7.4	7.7	0.067
APGAR 5 min	8.7	8.7	0.476
Neonatal intensive care admission, n (%)	43 (19.2)	35 (14.9)	0.152
Total NICU days (median)	15 (*n=43*)	9 (*n=35*)	0.827

Source: Study 302 clinical study report, Table 14.2.3.1, Table 14.2.5.1, Appendix 16.1.9.

3.2.3   Additional Analyses

In addition to the multiple sensitivity analyses done on the primary endpoint, the analyses of multiple gestational cut points, and the infant outcome analyses, a number of prespecified and post-hoc subgroup analyses were also performed for the primary endpoint. In the review of these subgroup analyses it should be noted that this trial was not powered to show significance in any subgroup. Moreover, subgroup analyses are expected to display some variability around the overall result and may even show an opposite result by chance. It is known that as the number of individual tests increases the probability of falsely rejecting the null hypothesis increases when not adjusted for multiplicity. For example, if ten tests are performed, the chance of showing a significant result is 0.4 or approximately 1 in 2.5. In addition, when the sample size is halved for a subgroup (such as by the median) an original planned power of 80% is reduced to 50%.[40] Nevertheless, with all such caveats in mind, these subgroup analyses are presented and discussed in this briefing package. Subgroups explored in these investigations were as follows:

Pre-specified

- US region versus non-US region

- History of preterm birth versus no history of preterm birth

- Baseline cervical length ≤1.7 cm (median) versus baseline cervical length >1.7 cm

- History of cervical surgery

[40] Rosner B. In *Fundamentals of Biostatistics*, 2nd Edition (1986). Chapter 7: Hypothesis Testing. Duxbury Press, Boston, Massachusetts.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Post-hoc

- Gestational age at first dose ≤21 5/7 weeks (median) versus gestational age at first dose >21 5/7 weeks

- Maternal age ≤25.4 years (median) versus maternal age > 25.4 years

- Asian Race, Black Race, White Race

- Body mass index (BMI) ≤23.9 kg/m^2 (median) versus BMI >23.0 kg/m^2

The subgroup estimates all favored progesterone, with one exception (maternal age), and this pattern of results for subgroups therefore strongly supported the positive finding on the primary endpoint. All race subgroups favored progesterone treatment, with Blacks demonstrating a risk reduction very close to the overall treatment effect (-6.6 for Blacks versus -6.2 for Overall), Caucasians demonstrating a stronger risk reduction of -9.0, and Asians demonstrating a smaller risk reduction of -3.8. Figure 3.2-3 summarizes the results of all subgroup analyses, and discussions of the four subgroups that showed the smallest treatment effects will be presented in the sections that follow.

Figure 3.2-3 Study 302 Forest Plot of Preterm Birth <33 Weeks Risk Differences, Overall and by Subgroups

	Estimate	(95% CI)		Placebo N	% Preterm Birth	Treated N	% Preterm Birth
Sites: All	-6.2	(-12.2,-0.3)		224	15.2	235	8.9
Sites: US Only	-2.4	(-12.9,8.1)		99	19.2	107	16.8
Sites: Non US Only	-9.7	(-15.9,-3.4)		125	12	128	2.3
Previous Preterm Birth: Yes	-2.4	(-19.9,15.1)		33	18.2	38	15.8
Previous Preterm Birth: No	-7	(-13.3,-0.8)		191	14.7	197	7.6
Cervical Length: <=1.7 cm	-9.3	(-20.5,1.9)		94	24.5	99	15.2
Cervical Length: >1.7 cm	-4	(-9.9,1.8)		130	8.5	136	4.4
History of Cervical Surgery: Yes	-10.8	(-27.2,5.5)		26	15.4	22	4.5
History of Cervical Surgery: No	-5.8	(-12.1,0.6)		198	15.2	213	9.4
Gest. Age at 1st Dose: <=21 5/7 weeks	-0.8	(-9.5,7.9)		112	13.4	119	12.6
Gest. Age at 1st Dose: >21 5/7 weeks	-11.8	(-19.8,-3.8)		112	17	116	5.2
Maternal Age: <=25.4 years	0.6	(-7.3,8.6)		108	10.2	120	10.8
Maternal Age: >25.4 years	-12.9	(-21.5,-4.3)		116	19.8	115	7
Race: Asian	-3.8	(-11.3,3.6)		77	7.8	76	3.9
Race: Black	-6.6	(-19.5,6.3)		67	22.4	76	15.8
Race: Caucasian	-9	(-18.8,0.8)		69	14.5	73	5.5
BMI: <=23.9 kg/m^2	-6.5	(-13.5,0.5)		116	11.2	107	4.7
BMI: >23.9 kg/m^2	-7	(-16.7,2.6)		103	19.4	121	12.4

-25   -20   -15   -10   -5   0   5   10   15

Favors Progesterone   Risk Difference   Favors Placebo

Source: Efficacy Analysis of US and Non-US Sites, Progesterone Gel 8% Appendix 1 Section 2 Table 2.2-2.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

3.2.3.1 Region Subgroups

In the subgroup analyses for Study 302, the results for the U.S. (risk reduction -2.4) and non-U.S. (risk reduction -9.7) regions both favored progesterone, although the size of the treatment effect was greater in the non-US regions. However, Study 300 provided another opportunity to evaluate the regional effects of vaginal progesterone gel 8% in the U.S. and non-U.S. subgroups, particularly since many of the same sites participated in both studies. Figure 3.2-4 demonstrates that for Study 300, an opposite regional effect was observed, supporting the conclusion that the Study 302 regional effect can be attributed to normal variability among subgroups when considering an endpoint of low incidence.

Figure 3.2-4 Study 300 Delivery <33 Weeks (All Subjects)
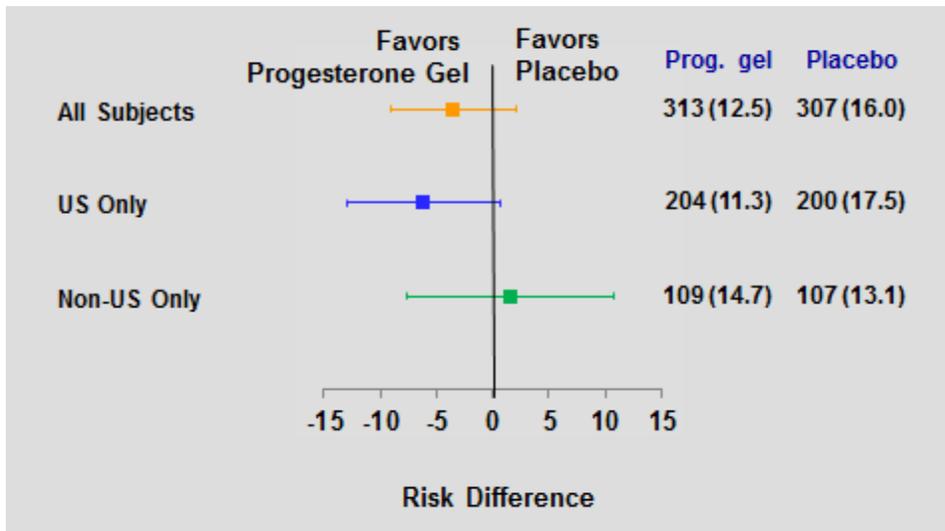
Source: White paper to FDA entitled "Efficacy Analysis of US and Non-US Sites", Appendix Table 1.1-1.
Note: Study 302 imputation scheme was applied to the Study 300 data.

It should be noted that when Study 300 data are limited to the more relevant category of women with short cervix, the US and non-US results become even more favorable for progesterone, including positive effects in the adjacent gestational age cut points. Figure 3.2-5 displays all of these positive progesterone treatment effects in the US across all gestational age cut points from both studies.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

**Figure 3.2-5 Studies 302 and 300 (≤3.0 cm) Summary of Regional Effects at
Various Weeks**
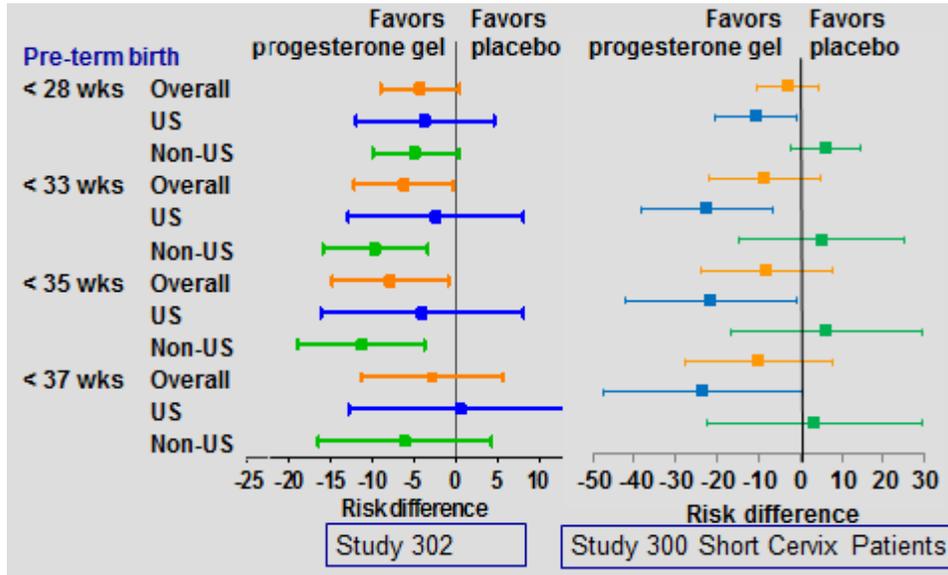
Source: Study 302 clinical study report, Tables 14.2.1.1, Table 14.2.1.4; White paper to FDA entitled "Efficacy Analysis of US and Non-US Sites", Appendix Table 1.2-1, Table 1.2-2, Table 1.2-3.
Note: Study 302 imputation scheme was applied to the Study 300 data.

In summary, regional subgroup analyses from Studies 300 and 302 support the benefit of this therapy for subjects in the US region.

3.2.3.2   Previous Preterm Birth Subgroups

In the subgroup analyses for Study 302, the results for "previous preterm birth- yes" and "previous preterm birth -no" both favored progesterone, although the size of the treatment effect was greater for those without a previous preterm birth (-7.0 risk reduction versus -2.4 for those with such history). Again, Study 300 provided another opportunity to evaluate the effects of vaginal progesterone gel 8% in women with a history of preterm birth since nearly all women in Study 300 had such a history. In Figure 3.2-6, the results for Study 300 short cervix subjects (≤3.0) are shown in a Kaplan-Meyer plot. Note that the curves separate and that the log-rank test of p=0.043 provides evidence that the separation is meaningful. These results suggest that progesterone gel 8% offers benefit to women with short cervixes, regardless of their history of preterm birth.

Figure 3.2-6 Study 300 Probability of Remaining Undelivered (Subjects ≤3.0 cm)
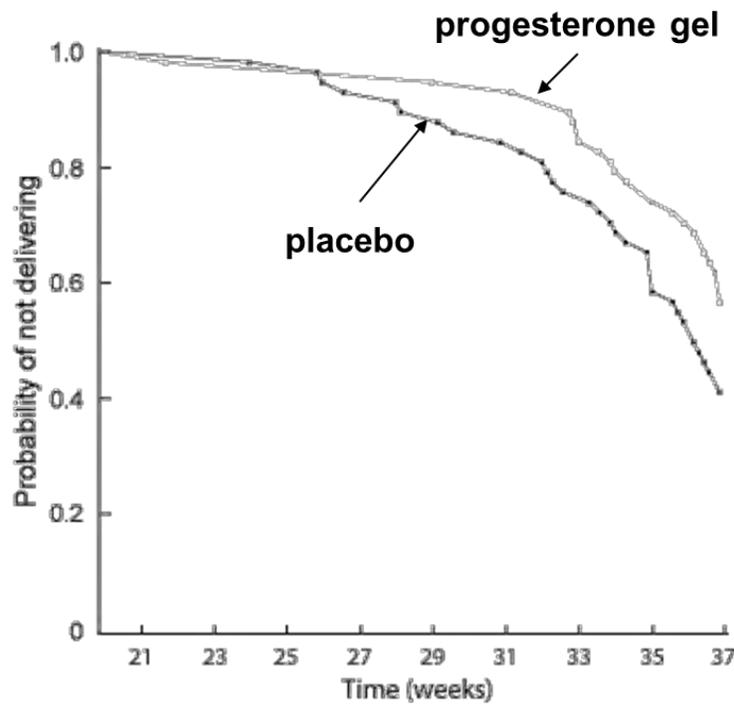
Source: Figure 3 of DeFranco, et al. 2007.

In summary, information from Study 300 suggests that the Study 302 history of preterm birth regional results could be attributed to normal variability among subgroups when considering an endpoint of low incidence.

3.2.3.3 Gestational Age at First Dose Subgroups

In the subgroup analyses for Study 302, the results for gestational age at first dose were assessed for subgroups above and below the median. Both favored progesterone; although, the subgroup starting at a relatively later gestational age had an estimated effect that was greater than the overall trial result (-11.8 risk reduction versus -6.2 for overall) and the subgroup starting at a relatively earlier gestational age had an estimated effect that was less than the overall trial result (-0.8 versus -6.2 for overall). As known statistical principles caution that subgroup results in a randomized clinical trial can be misleading, one test of the relevance of such results is the test of plausibility.

It has been previously presented that vaginal progesterone delayed cervical shortening from baseline to 28 weeks in Study 300, and that this pharmacodynamic effect was the basis for

the delay in delivery in women with short cervixes. It is intuitive that the earlier treatment begins, the more likely this pharmacodynamic effect would be observed, particularly in women with a short cervix (see Section 2.7.2), and it is counter-intuitive to have results that suggest that less treatment would be more effective. Subgroup analysis results such as this are precisely why appropriate caution is necessary when considering such subgroup outcomes. Beyond this test of plausibility, it also remains a possibility that the Study 302 early gestational age at first dose effect could be attributed to normal variability among subgroups when considering an endpoint of low incidence.

3.2.3.4   Maternal Age Subgroups

In the subgroup analyses for Study 302, the results for maternal age were assessed for subgroups above and below the median. While women in the higher age subgroup had the highest estimate of favorable progesterone effect of any subgroup in the trial (-12.9 risk reduction), women in the lower age subgroup had a lower estimate of effect and were, in fact, the one subgroup that favored placebo (0.6 risk reduction). As a consequence of the many subgroup analyses conducted (seventeen total), this result may merely be one in which a false negative has been observed, even if progesterone gel 8% had positive treatment effects.

Nevertheless, when the subgroup analysis of age for the short cervix patients in Study 300 is reviewed, subgroups above and below the median (25.3 years, very similar to the median 25.4 years in Study 302) have estimates that favor progesterone. The older subgroup had a progesterone response of -10.8 and the younger subgroup had a response of -6.4. Therefore, the efficacy estimates for the younger subgroup in Study 300 do not support the possibility from Study 302 that younger subgroups favor placebo. These Study 302 maternal age subgroup results may again represent normal variability among subgroups when considering an endpoint of low incidence.

3.2.3.5   Combined Study 300 and Study 302 Data

Because the designs of Study 300 and 302 were nearly identical, efficacy data from the short cervix subjects in both Phase 3 studies (Study 300 ≤3.0 cm subset with Study 302 1.0-2.0 cm ITT analysis set) were integrated into common datasets for a combined summary and analysis. A cervical length of ≤3.0 cm was chosen for this analysis in order to include women from the Colombia investigations that were at or below the 25th percentile of cervical length according to the previously mentioned research from the NICHD Maternal Fetal Medicine Unit Network, published by Iams, et al. This definition is also consistent with that

used by the NICHD Maternal Fetal Medicine Unit Network for the SCAN trial.[41] A brief summary of this analysis is presented in the following paragraphs.

The combined analysis set consisted of 581 subjects (287 placebo, 294 progesterone), 122 of whom were from Study 300 and 459 from Study 302. Whereas the previous analyses of subjects from Study 300 with cervical length ≤3.0 cm included only a total of 116 subjects, this analysis included the additional 6 subjects from 300 in this cervical length subgroup who had a missing delivery date. These missing delivery dates were imputed using the same algorithm used for Study 302. The mean age was 26.3 years, with 32% Asian, 30% Black, 29% White, and 9% Other. The mean BMI was 25.4 mg/kg^2 and the mean cervical length was 1.92 cm. For the primary efficacy variable in the combined analysis set, a statistically significant reduction in the incidence of preterm birth (<33 weeks) was observed in the progesterone gel 8% treatment group compared with the placebo group (9.9% versus 16.7%, p=0.012). Risk reductions were also observed for the secondary efficacy variables of birth at <28 weeks (4.8% versus 8.7%, p=0.053), <35 weeks (16.3% versus 24.4%, p=0.007), and <37 weeks (33.0% versus 37.6%, p=0.181).

Meaningful risk differences were also noted for infant outcomes of RDS and Any Mortality/Morbidity Event. Additionally, lower percentages of infants born to women treated with progesterone gel 8% were observed for the below 2500 and 1500 grams categories, respectively. Infant outcome data is presented in Table 3.2-7.

Table 3.2-7   Study 300 (≤3.0 cm) and Study 302 Data Neonatal/Infant Outcomes

Neonatal Outcomes	Placebo (N=287) %	Prog gel 8% (N=294) %	Risk Difference (95% CI)
RDS	27 (9.4)	11 (3.7)	-5.7 (-9.7, -1.7)
BPD	8 (2.8)	4 (1.4)	-1.4 (-3.7, 0.9)
Proven Sepsis	4 (3.1)	9 (3.1)	-0.1 (-2.9, 2.7)
NEC	5 (1.7)	5 (1.7)	0.0 (-2.2, 2.1)
IVH	7 (2.4)	5 (1.7)	-0.7 (-3.1, 1.6)
PVL	0 (0)	0 (0)	Non estimable
Perinatal Death	12 (4.2)	9 (3.1)	-1.1 (-4.2, 1.9)
Neonatal Death	6 (2.1)	3 (1.0)	-1.1 (-3.1, 0.9)
Any Mortality/Morbidity Event	41 (14.3)	24 (8.2)	-6.1 (-11.2, -1.0)
Birthweight < 2500g	98 (35.5)	82 (28.1)	-7.4 (-15.1, 0.2)
< 1500g	37 (13.4)	19 (6.5)	-6.9 (-11.8, -2.0)

Perinatal Death = infant death, intrauterine fetal death, and stillbirth, Neonatal Death = infant death.
Source: Integrated Summary of Efficacy Table 2.3.1, Statistical Document Output/Supplemental Analysis

[41] http://clinicaltrials.gov/ct2/show/NCT00439374?term=short+cervix+trial&rank=2.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

In conclusion, this combined analysis provided evidence that pregnant women with mid-trimester cervical lengths above 2 cm benefited from treatment with progesterone gel 8% through both a reduction in the risk of preterm birth and an improvement in infant outcomes. The totality of data from this combined analysis demonstrated meaningful improvements for these high risk women and their offspring.

3.3   Fonseca, et al, 2007

Independent substantiation of the approach to reducing the risk of preterm birth in women with short cervix through the use of vaginal progesterone was provided in research sponsored by the Fetal Medicine Foundation conducted from September 2003 through May 2006 in maternity hospitals in the United Kingdom, Chile, Brazil, and Greece (clinicaltrials.gov #NCT00422526). All women with singleton or twin pregnancies who were undergoing routine ultrasonography at 20 to 25 weeks of gestation for examination of fetal anatomy and growth were given the option of TVU measurement of cervical length as a predictor of spontaneous early preterm delivery. Gestational age was determined from the menstrual history and confirmed from the measurement of fetal crown-rump length at a first trimester scan, which was carried out routinely in the participating hospitals. The subset of women with a cervical length of 1.5 cm or less were invited to take part in the randomized, double-blind, placebo-controlled trial. The exclusion criteria were major fetal abnormalities, painful regular uterine contractions, a history of ruptured membranes, or a cervical cerclage. Women were randomized through central randomization to achieve 125 women in each treatment group. The test product used was either 200 mg capsules of micronized progesterone in peanut oil (Utrogestan, Besins International Belgium) or identical appearing capsules of placebo containing safflower oil (Medicaps®). Subjects were instructed to insert one capsule into the vagina every night before going to sleep from 24 to 33 weeks 6 days of gestation. Follow-up visits for ultrasound assessment of fetal growth and cervical length were carried out every 2 weeks until 34 weeks of gestation. The primary outcome measure was spontaneous delivery before 34 weeks. The secondary outcome measures were birth weight, fetal or neonatal death, major adverse outcomes before discharge from the hospital, and need for neonatal special care. The analysis was performed according to the intention-to-treat principle. Comparisons between groups were performed with the use of the Mann-Whitney U test. Univariate comparisons of dichotomous data were performed with the use of Fisher's exact test. The risk of spontaneous preterm birth before 34 weeks was quantified by the relative risk and 95% confidence interval. Effect modification was assessed with the use of the Mantel-Haenszel test for homogeneity. Multivariable analysis was performed by logistic

regression. The risk of spontaneous preterm birth from randomization until 34 weeks was assessed using Kaplan-Meier analysis.

Of the 250 women who were randomized, 226 were singleton and 24 were twin pregnancies. The median age of the randomized population was 29 years, with balance between groups for races (overall approximately 38% White, 55% Black, 7% Other). The overall median BMI was approximately 24 kg/m^2, the overall median gestational age at randomization was approximately 23 4/7 weeks, and the overall median cervical length of the randomized groups was approximately 1.2 cm. A strong treatment effect was noted for the use of vaginal progesterone. Summary results from this published investigation are presented in Figure 3.3-1 and Table 3.3-1.

Figure 3.3-1 Fonseca, et al, 2007 Kaplan-Meier Presentation of Cumulative Percentage of Continued Pregnancies
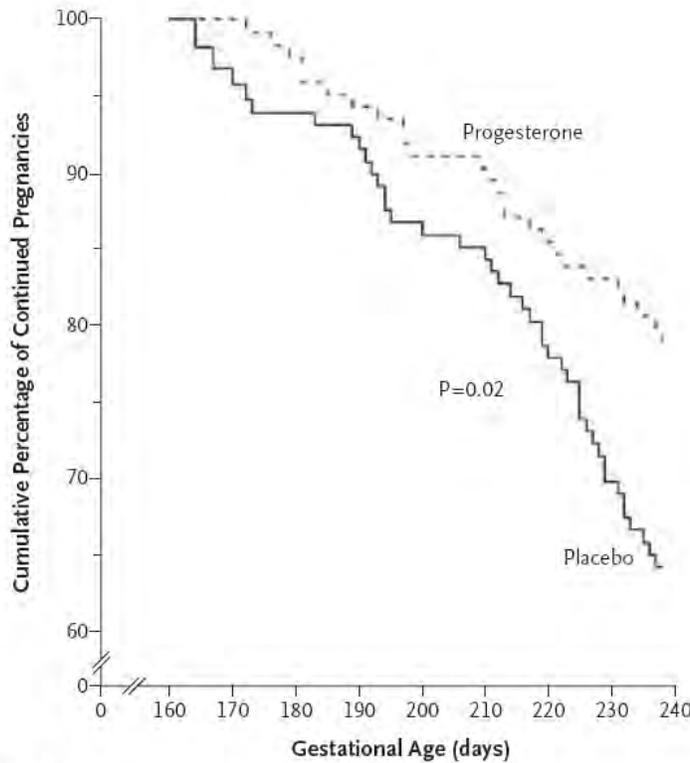
Source: Figure 2 from Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007 Aug 2;357(5):462-9.

Table 3.3-1   Fonseca, et al, 2007 Other Study Outcomes

Outcome	Progesterone Group†	Placebo Group‡	Relative Risk (95% CI)	P Value	Adjusted Relative Risk (95% CI)	P Value
	no. (%)					
Maternal						
Spontaneous delivery at <34 wk	24 (19.2)	43 (34.4)	0.56 (0.36–0.86)	0.007	0.56 (0.32–0.91)	0.02
Any delivery at <34 wk	26 (20.8)	45 (36.0)	0.58 (0.38–0.87)	0.008	0.60 (0.35–0.94)	0.02
Perinatal						
Fetal death	1 (0.7)	1 (0.7)		0.98		
Neonatal death	2 (1.5)	7 (5.1)	0.29 (0.06–1.42)	0.13	0.34 (0.06–1.81)	0.22
Birth weight <2500 g	56 (41.2)	59 (42.8)	0.96 (0.69–1.26)	0.81	0.97 (0.68–1.29)	0.85
Birth weight <1500 g	18 (13.2)	27 (19.6)	0.68 (0.36–1.21)	0.20	0.74 (0.36–1.37)	0.35
Composite adverse outcomes	11 (8.1)	19 (13.8)	0.59 (0.26–1.25)	0.17	0.57 (0.23–1.31)	0.19
Intraventricular hemorrhage§	1 (0.7)	2 (1.4)	0.51 (0.05–5.30)	0.58	0.33 (0.01–8.84)	0.52
Respiratory distress syndrome	11 (8.1)	19 (13.8)	0.59 (0.26–1.25)	0.17	0.57 (0.23–1.31)	0.19
Retinopathy of prematurity	2 (1.5)	0				
Necrotizing entercolitis	0	1 (0.7)				
Composite therapy	34 (25.0)	45 (32.6)	0.77 (0.48–1.15)	0.21	0.75 (0.44–1.16)	0.20
Neonatal intensive care	33 (24.3)	42 (30.4)	0.80 (0.49–1.21)	0.30	0.80 (0.47–1.24)	0.34
Ventilation	16 (11.8)	25 (18.1)	0.65 (0.33–1.21)	0.18	0.64 (0.30–1.25)	0.20
Phototherapy	16 (11.8)	14 (10.1)	1.16 (0.56–2.25)	0.68	1.09 (0.50–2.19)	0.82
Treatment for sepsis	3 (2.2)	11 (8.0)	0.28 (0.07–1.01)	0.05	0.29 (0.07–1.10)	0.07
Blood transfusion	4 (2.9)	5 (3.6)	0.81 (0.22–2.86)	0.75	0.79 (0.19–3.10)	0.74

 * For perinatal outcomes, the relative risks, 95% confidence intervals, and P values were estimated by logistic regression clustered on maternal identifiers to account for nonindependence between twin pairs. Relative risks were adjusted for maternal age, body-mass index, smoking status, race, history of preterm birth, and cervical length at the time of randomization.
 † There were 125 pregnancies and 136 infants in the progesterone group.
 ‡ There were 125 pregnancies and 138 infants in the placebo group.
 § Intraventricular hemorrhage was grade 2 in all infants.

Source: Table 2 from Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007 Aug 2;357(5):462-9.

The authors noted that the cumulative percentage of patients who did not give birth spontaneously before 34 weeks was significantly higher in the progesterone group than in the placebo group, and multivariable analysis demonstrated that adjustment for maternal characteristics at the time of randomization did not attenuate the protective effect of progesterone. The relative risk of preterm birth did not vary significantly according to maternal age, BMI, race, obstetrical history, or whether the pregnancy was singleton or twin. The authors concluded that the results of this randomized trial demonstrated that, in women with a short cervix, the daily vaginal administration of 200 mg of progesterone from 24 to 34

weeks of gestation significantly reduced the rate of spontaneous preterm delivery, and that there was no increased risk of mortality or neonatal morbidity.

3.4   Efficacy Discussion and Conclusions

Evidence for the efficacy of Columbia's progesterone gel 8% is provided in the adequate and well-controlled Study 302, with supportive evidence from Study 300. Independent substantiation of the approach to reducing the risk of preterm birth in women with short cervix through the use of vaginal progesterone is also provided by Fonseca, et al, 2007.

In Study 300, progesterone gel 8% was shown to decrease the rate of cervical shortening from baseline to 28 weeks gestation. This effect on cervical shortening led to the observation that the subset of subjects with baseline cervical length ≤ 3.0 cm experienced a benefit from progesterone gel 8% treatment with a nominally significant difference between the Kaplan-Meier time-to-event curves when censored at 37 weeks. In addition, numerical improvements in infant outcomes were observed. The adequate and well-controlled Study 302 demonstrated that progesterone gel 8% was associated with a statistically significant and clinically meaningful reduction in preterm birth for the primary variable <33 weeks ($p=0.022$) when compared with placebo. The result of the primary endpoint was supported by multiple sensitivity analyses and secondary endpoints that included progesterone effects at adjacent gestational age cut points and associated improvement in infant outcomes. The results of various subgroup analyses also supported the finding of the primary result of this randomized clinical trial. Finally, the results of both of these studies were substantiated by a key investigation of vaginal progesterone in women with short cervixes published in 2007 by Fonseca, et al, in which the authors noted that the cumulative percentage of patients who did not give birth spontaneously before 34 weeks was significantly higher in a vaginal progesterone treatment group than in a placebo group.

In conclusion, a review of the results from Columbia's vaginal gel studies demonstrates that pregnant women with mid-trimester short cervical lengths benefit from daily treatment with a bioadhesive formulation of progesterone gel 8% with a delay in delivery, and that this delay is associated with improved infant outcomes.

4   CLINICAL SAFETY

4.1   Collection and Analysis of Safety Data

During the clinical development program of Columbia's progesterone gel 8% for this new indication, safety was evaluated by maternal adverse event reporting, brief physical/obstetrical examinations conducted during the progress of the study, and infant follow-up at delivery. Adverse events and physical/obstetrical examinations data were collected during the maternal study visits and during post infant delivery hospitalization. Other assessments included physical examination at baseline, fundal height measurement, fetal heart rate, and concomitant medication usage. It should be noted that clinical laboratory values were not assessed in this clinical development program since these had been previously evaluated thoroughly for previous indications and were seen to be unaffected by intravaginally delivered progesterone gel 8%. Additionally, the same infant outcomes that were previously described in the efficacy section were evaluated as safety variables, and in Study 300, infant follow-up of development and morbidity assessments were collected at 6-, 12-, and 24 months after birth.

4.2   Exposure to Progesterone Gel 8%

In the three clinical studies (Studies 3001, 301, 302), 579 subjects were exposed to progesterone gel 8% and 540 subjects received placebo. For the Integrated Summary of Safety (ISS) safety analysis set (Studies 300 [n=637] and 302 [n=459]), exposure in the progesterone gel 8% group ranged from 0 to 22 weeks; exposure in the placebo group was not materially different, ranging from 0 (less than 4 days) to 22 weeks. Average exposure for progesterone gel 8% was 85.3 mg per day and the exposure was similar for the placebo group. The average progesterone gel 8% exposure per day in milligrams did not differ materially between the US sites and non-US sites. The exposure in the bioavailability study (Study 301) ranged from 14 to 19 weeks; however, safety data from this study were not integrated into the ISS safety analysis set.

Table 4.2-1   Studies 300 and 302 Extent of Exposure (Combined Safety Analysis Set)

Parameter	Descriptive Statistic	Placebo US	Placebo Non-US	Placebo Overall	Prog gel 8% US	Prog gel 8% Non-US	Prog gel 8% Overall
Duration of Treatment (weeks)	N	306	234	540	313	242	555
	Mean	13.2	14.8	13.9	13.3	15.1	14.1
	SD	4.68	3.87	4.42	4.68	3.33	4.25
	Minimum	0	1	0	0	1	0
	Median	14.4	15.7	14.9	14.7	15.7	15.0
	Maximum	20	22	22	20	22	22
Average Exposure per Day (mg)	N	302	231	533	306	242	548
	Mean	82.9	89.1	85.6	82.4	89.0	85.3
	SD	11.55	2.82	9.40	12.32	5.21	10.35
	Minimum	26	70	26	5	23	5
	Median	87.2	90.0	90.0	86.8	90.0	90.0
	Maximum	96	95	96	105	100	105

Source: Integrated Summary of Safety, Table 2.1.1, Table 2.1.4.

4.3   Maternal Safety - Study 301

In this bioavailability study, twenty subjects experienced 115 adverse events, including four subjects who experienced 15 serious adverse events. None of these serious adverse events were considered related to study drug. No subjects died during the study and no subjects discontinued due to an adverse event.

The most frequently reported adverse events were uterine contraction abnormality (60.9%), fetal disorder (21.7%), abdominal pain (21.7%), premature labor (17.4%), urinary tract infection (17.4%), back pain (17.4%), and vaginal hemorrhage (17.4%). Of the 115 adverse events, two subjects reported three adverse events that were possibly or probably related to study treatment: vaginal burning, vaginal dryness, and hair loss. The subjects recovered from these adverse events without further treatment.

4.4   Maternal Safety - Adverse Events (Studies 300 and 302)

In the combined data set of the two randomized clinical studies, the incidence and profile of adverse events were similar between progesterone gel 8% and placebo. Seventy-six percent of subjects in the progesterone gel 8% group and 77% in the placebo group experienced at least one Treatment Emergent Adverse Event (TEAE, Table 4.4-1). The percentage of subjects experiencing any serious TEAEs was also similar between treatment groups (42% progesterone gel 8% and 44% placebo). The percentage of subjects who discontinued study drug due to a TEAE was the same for both groups (18% progesterone gel 8% and 18% placebo), and there were no maternal deaths reported in these studies. The percentage of subjects with related TEAEs was also comparable between the two groups (16%

progesterone gel 8% and 15% placebo). Subjects reporting severe TEAEs in the
progesterone gel 8% and placebo groups represented 16% and 18%, respectively.

Table 4.4-1   Studies 300 and 302 Summary of Maternal TEAEs (Combined Safety Analysis Set)

Parameter	Placebo n (%)	Prog gel 8% n (%)
Any TEAE	418 (77%)	420 (76%)
Any Serious TEAE	237 (44%)	234 (42%)
Any TEAE leading to discontinuation	99 (18%)	102 (18%)
Any related TEAE	83 (15%)	88 (16%)
Any severe TEAE	98 (18%)	90 (16%)

Source: Integrated Summary of Safety, Table 2.2.1.1.

The most common TEAEs reported were related to pregnancy, puerperium, and perinatal
conditions (52% progesterone gel 8% and 54% placebo). Other commonly reported TEAEs
were infections, gastrointestinal disorders and reproductive system and breast disorders
(Table 4.4-2).

Table 4.4-2   Studies 300 and 302 Summary of Maternal TEAEs by System Organ Class in Descending Order (Combined Safety Analysis Set)

System Organ Class	Placebo (N=540) n (%)	Prog gel 8% (N=556) n (%)
Any TEAE	418 (77%)	420 (76%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	289 (54%)	288 (52%)
INFECTIONS AND INFESTATIONS	170 (31%)	192 (35%)
GASTROINTESTINAL DISORDERS	146 (27%)	161 (29%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	124 (23%)	124 (22%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	66 (12%)	68 (12%)
NERVOUS SYSTEM DISORDERS	64 (12%)	67 (12%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	44 (8%)	53 (10%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	62 (11%)	45 (8%)
METABOLISM AND NUTRITION DISORDERS	29 (5%)	41 (7%)
INVESTIGATIONS	10 (2%)	26 (5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	27 (5%)	24 (4%)
PSYCHIATRIC DISORDERS	21 (4%)	19 (3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	28 (5%)	15 (3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	13 (2%)	13 (2%)
SURGICAL AND MEDICAL PROCEDURES	11 (2%)	13 (2%)
RENAL AND URINARY DISORDERS	12 (2%)	12 (2%)
CARDIAC DISORDERS	7 (1%)	7 (1%)
VASCULAR DISORDERS	9 (2%)	6 (1%)
EYE DISORDERS	10 (2%)	5 (<1%)
IMMUNE SYSTEM DISORDERS	7 (1%)	3 (<1%)
EAR AND LABYRINTH DISORDERS	4 (<1%)	2 (<1%)
HEPATOBILIARY DISORDERS	2 (<1%)	2 (<1%)
ENDOCRINE DISORDERS	1 (<1%)	1 (<1%)
NEOPLASMS BENIGN MALIGNANT AND UNSPECIFIED	0	2 (<1%)
SOCIAL CIRCUMSTANCES	1 (<1%)	1 (<1%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (<1%)	0

Source: Integrated Summary of Safety, Table 2.2.1.1, Table 2.2.1.2.

For inter-study comparison purposes, Table 4.4-3 shows the incidence of TEAEs in ≥5% of subjects in either progesterone gel 8% or placebo groups by study. Some expected variability exists between studies, however, in both studies the most frequent events were

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

complications of high-risk pregnancy and included "premature baby" "uterine contractions abnormal" and "premature labor".

Table 4.4-3   Studies 300 and 302 Summary of Maternal Treatment-Emergent Adverse Events (≥5% in either treatment group) by Preferred Term by Study

Preferred Term	COL-1620-300		COL-1620-302	
	Placebo N=316	Prog gel 8% (N=321)	Placebo N=224	Prog gel 8% N=235
Premature labor	66 (20.9%)	63 (19.6%)	33 (15%)	17 (17%)
Uterine contractions abnormal	34 (10.8%)	46 (14.3%)	40 (18%)	34 (14%)
Uterine contractions during pregnancy	37 (11.7%)	40 (12.5%)	--	--
Premature baby	38 (12.0%)	33 (10.3%)	47 (21%)	44 (19%)
Bleeding peripartum	22 (7.0%)	23 (7.2%)	14 (6%)	9 (4%)
Premature rupture of membranes	19 (6.0%)	22 (6.9%)	10 (4%)	13 (6%)
Vomiting in pregnancy	15 (4.7%)	17 (5.3%)	12 (5%)	10 (4%)
Vulvovaginal Mycotic Infection	32 (10.1%)	25 (7.8%)	11 (5%)	17 (7%)
Urinary tract infection	18 (5.7%)	36 (11.2%)	9 (4%)	11 (5%)
Nasopharyngitis	18 (5.7%)	16 (5.0%)	--	--
Upper respiratory tract infection	16 (5.1%)	13 (4.0%)	--	--
Abdominal pain	29 (9.2%)	25 (7.8%)	11 (5%)	13 (6%)
Nausea	27 (8.5%)	30 (9.3%)	23 (10%)	23 (10%)
Dyspepsia	26 (8.2%)	24 (7.5%)	12 (5%)	15 (6%)
Abdominal pain lower	8 (2.5%)	22 (6.9%)	--	--
Vaginal discharge	29 (9.2%)	27 (8.4%)	--	--
Cervix disorder	35 (11.1%)	20 (6.2%)	17 (8%)	23 (10%)
Pelvic pain	16 (5.1%)	15 (4.7%)	--	--
Back pain	27 (8.5%)	35 (10.9%)	11 (5%)	12 (5%)
Cough	15 (4.7%)	17 (5.3%)	--	--
Headache	29 (9.2%)	31 (9.7%)	18 (8%)	16 (7%)
Oedema peripheral	15 (4.7%)	22 (6.9%)	--	--
Anemia	--	--	14 (6%)	15 (6%)
Vaginal infection	--	--	11 (5%)	15 (6%)
Chorioamnionitis	--	--	12 (5%)	12 (5%)
Gestational diabetes	--	--	9 (4%)	14 (6%)
Vaginitis bacterial	--	--	6 (3%)	12 (5%)
Fetal growth retardation			11 (5%)	5 (2%)

Source: Study 300 clinical study report, Table 14.3.1.3; Study 302 clinical study report, Table 14.3.1.4.

For further assistance in reviewing the TEAEs, the adverse events that were reported in ≥5% of subjects treated with progesterone gel 8% and that were at a higher rate than placebo are listed in Table 4.4-4. Note that the term "urinary tract infection" does not include the adverse

event of "pyelonephritis"; there were four cases of pyelonephritis in this program (<1%), with two cases on placebo and two cases on progesterone gel 8%.

Table 4.4-4   Studies 300 and 302 Summary of Treatment Emergent Adverse Events Reported in ≥5% of Progesterone Gel 8% Subjects and at a Higher Rate than Reported in Placebo Subjects (Combined Safety Analysis Set)

Adverse Events by Preferred Term	Placebo N = 540 n (%)	Prog gel 8% N = 556 n (%)
Nausea	50 (9.3)	53 (9.5)
Urinary tract infection	27 (5.0)	48 (8.6)
Back pain	39 (7.2)	47 (8.5)
Premature rupture of membranes	29 (5.4)	35 (6.3)
Abdominal pain lower	17 (3.1)	30 (5.4)
Vaginal infection	23 (4.3)	29 (5.2)
Oedema peripheral	18 (3.3)	29 (5.2)

Source: Integrated Summary of Safety, Table 2.2.1.4.

4.5   Maternal Safety - Serious Adverse Events (Studies 300 and 302)

In the ISS safety analysis set, rates for serious adverse events were similar for the progesterone gel 8% (42%) and placebo groups (44%). Most common serious adverse events were related to pregnancy, puerperium, and perinatal conditions and were reported in 37% of subjects in the progesterone gel 8% group and 38% of subjects in the placebo group. Only twelve of these serious adverse events were considered related to study drug by the investigator. A full listing of all serious adverse events is included in Appendix 2, as well as the listing of those considered related by the investigator.

4.6   Infant Safety - Safety Outcomes

Infant outcomes were evaluated by the incidence of perinatal mortality and neonatal morbidities including RDS, BPD, grade III or IV IVH, PVL, proven sepsis, NEC and NICU days. Table 4.6-1 summarizes the infant outcome data for the combined 300 and 302 safety analysis set.

Table 4.6-1   Studies 300 and 302 Summary of Infant Safety Data (Combined Safety Analysis Set)

Outcomes	Placebo (N=540) N (%)	Prog gel 8% (N=556) N (%)
RDS	54 (10.0)	41 (7.4)
BPD	8 (1.5)	5 (0.9)
Proven Sepsis	12 (2.2)	12 (2.2)
NEC	9 (1.7)	7 (1.3)
IVH	10 (1.9)	10 (1.8)
PVL	0 (0)	0 (0)
Perinatal Death	19 (3.5)	18 (3.2)
Neonatal Death	11 (2.0)	8 (1.4)
Any mortality/morbidity event	74 (13.7)	62 (11.2)
Birthweight <2500g	175 (33.6)	154 (28.2)
<1500g	51 (9.8)	39 (7.1)

Perinatal Death = infant death, intrauterine fetal death, and stillbirth, Neonatal Death = infant death.
Source: Integrated Summary of Safety, Table 2.3.1, Output 1 – Supplemental Analysis.

These results demonstrated no evidence of fetal/neonatal harm with the progesterone gel 8% treatment compared with placebo. Table 4.6-2 compares the infant outcome data from the 300 and 302 studies. The infant data from Study 300 is from a subpopulation of subjects, with a baseline cervical length of 3 cm or less. Therefore, the infant data from study 300 included in Table 4.6-2 are a subset of the entire safety analysis set for the study.

Table 4.6-2   Studies 300 and 302 Summary of Infant Safety by Study

Outcomes	Study 300 Cervical Length ≤3 cm %		Study 302 Safety Analysis Set %	
	Placebo N=63	Prog gel 8% N=59	Placebo N=224	Prog gel 8% N=235
RDS	11 (17.5)	4 (6.8)	16 (7.1)	7 (3.0)
BPD	3 (4.8)	0 (0)	5 (2.2)	4 (1.7)
Proven Sepsis	4 (6.4)	2 (3.4)	5 (2.2)	7 (3.0)
NEC	1 (1.6)	0 (0)	4 (1.8)	5 (2.1)
IVH	0 (0)	0 (0)	5 (2.2)	4 (1.7)
PVL	0 (0)	0 (0)	0 (0)	0 (0)
Perinatal Death	2 (3.2)	1 (1.7)	10 (4.5)	8 (3.4)
Congenital Abnormalities	1 (1.6)	2 (3.4)	3 (1.3)	1 (0.4)
NICU Admission	18 (28.6)	9 (15.3)	43 (19.2)	35 (14.9)

Source: Study 302 clinical study report, Table 14.2.3.1; Study 300 clinical study report, Table 11.10, Supplemental Table 300.3, Integrated Summary of Safety listing 3.9.

4.7   Infant Safety - Intrauterine Fetal Deaths, Stillbirths, and Infant Deaths

Table 4.7-1 presents a summary of all fetal/infant death data from the entire clinical development program.

Table 4.7-1   Studies 300 and 302 Summary of Intrauterine Fetal Deaths, Stillbirths, and Infant Deaths

Study	Category	Placebo n/n (%)	Prog gel 8% n/n (%)
300	Intrauterine Fetal Deaths	1 / 316 (0.3)	4 / 321 (1.2)
	Stillbirths	2 / 316 (0.6)	1 / 321 (0.3)
	Infant Death	6 / 316 (1.9)	5 / 321 (1.6)
	Total	*9 / 316 (2.8)*	*10 / 321 (3.1)*
302	Intrauterine Fetal Deaths	2 / 224 (0.9)	2 / 235 (0.9)
	Stillbirths	3 / 224 (1.3)	3 / 235 (1.3)
	Infant Death	5 / 224 (2.2)	3 / 235 (1.3)
	Total	*10 / 224 (4.5)*	*8 / 235 (3.4)*
Combined	Intrauterine Fetal Deaths	3 / 540 (0.6)	6 / 556 (1.1)
	Stillbirths	5 / 540 (0.9)	4 / 556 (0.7)
	Infant Death	11 / 540 (2.0)	8 / 556 (1.4)
	Total	*19 / 540 (3.5)*	*18 / 556 (3.2)*

Source: Study 302 clinical study report, Table 14.2.3.1; Integrated Summary of Safety Table 2.3.1.

In Study 302, there were four intrauterine fetal deaths (IUFD), two in the placebo group and two in the progesterone gel 8% group. In the same study there were also seven stillbirths (three in progesterone gel 8% group and four in placebo group). One of the stillbirths in the placebo group occurred in a subject prior to receiving study drug; this subject has been excluded from the Safety analysis set. There were five IUFDs in Study 300, with four in the progesterone gel 8% group and one in the placebo group. There were four stillbirths in study 300, with three reported in the placebo group and one in the progesterone gel 8% group. One of the stillbirths in the placebo group occurred in a subject prior to receiving study drug; this subject is not in the Safety analysis set.

In Studies 300 and 302, there were eight infant deaths reported in the progesterone gel 8% group and eleven in the placebo group between 1-28 days post delivery. One subject in each of the progesterone gel 8% and placebo groups reported an infant death between 1-28 days prior to receiving study drug; these two subjects are not in the Safety analysis set. Six infant deaths (3 each for progesterone gel 8% and placebo) were reported >28 days post delivery (range 48 days to 11 months). Thus, there were a total of 12 infant deaths reported in the progesterone gel 8% group and 15 infant deaths in the placebo group in studies 300 and 302.

A review of these data suggests that no fetal or infant mortality safety signal was present for progesterone gel 8% in any of the three studies conducted with progesterone gel 8%.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

4.8   Infant Safety - Congenital Anomalies

Tabulations of all congenital anomalies in the clinical development program are presented in Tables 4.8-1 and -2. In Table 4.8-1 represents findings that, based on known embryological development processes, would have been in existence prior to participation in the study.

Table 4.8-1   Studies 300 and 302 Congenital Anomalies Combined Data: Etiology Prior to Dosing

Placebo	Progesterone gel 8%
Talipes, 3 cases	Talipes, 1 case
Extra Digits, 3 cases	Extra Digits, 3 cases
Patent Ductus, 1 case	Micrognathia, 1 case
High Arched Palate, 1 case	Tetralogy of Fallot, 1 case
Thumb Macrodactaly, 1 case	Hypospadius, 2 cases
ASD, 1 case	VSD, 1 case
Craniosynostosis, 1 case	Annular Pancreas, 1 case
	Syndactaly, 1 case
	Ureterocele, 1 case

Source: Studies 302 and 300 multiple listings.

Table 4.8-2 displays anomalies with uncertain embryological etiology and which may have developed during the course of the study. Numerically, there was a higher number of cases in the progesterone gel 8% women; however, no clustering within an organ system, which might suggest a specific teratogenic effect, is apparent.

Table 4.8-2   Studies 300 and 302 Congenital Anomalies Combined Data: Etiology Uncertain

Placebo	Progesterone gel 8%
Pulmonary Stenosis, 1 case	Pulmonary Stenosis, 2 cases
Hip Subluxation, 1 case	Underdeveloped Hips, 2 cases
Strabismus, 2 cases	Amblyopia/Strabismus, 3 cases
Hemiparises, 1 case	Exostoses, 1 case
Hemangioma skin, 2 cases	Heart Murmur, 1 case
Hemangioma liver, 1 case	Ankyloglossi, 1 case
	Vesico-Utero Reflux, 1 case
	Inguinal Hernia, 1 case
	Abdominal Calcifications, 1 case

Source: Studies 302 and 300 multiple listings.

A review of these data does not suggest a pattern of risk associated with the use of progesterone gel 8% during the third trimester of pregnancy.

4.9   Infant Safety - Study 300 Two-Year Infant Follow-Up

Infant safety parameters and developmental milestones for the neonatal population were assessed at 6-, 12-, and 24-month follow-up visits for infants born to subjects in Study 300. Data included head circumference (Figure 4.9-1), weight (Figure 4.9-2), length (Figure 4.9-3), and congenital abnormalities, chronic morbid conditions, and Denver II developmental screening results (Table 4.9-1). Review of these infant outcome parameters over the 2-year follow up period did not demonstrate any association of progesterone gel 8% treatment with detrimental effects.

Figure 4.9-1 Study 300 Mean Head Circumference (cm) 2-Yr Infant Follow-up

	6 months	12 months	24 months
Progesterone gel, n =	212	179	128
Placebo, n =	214	193	136
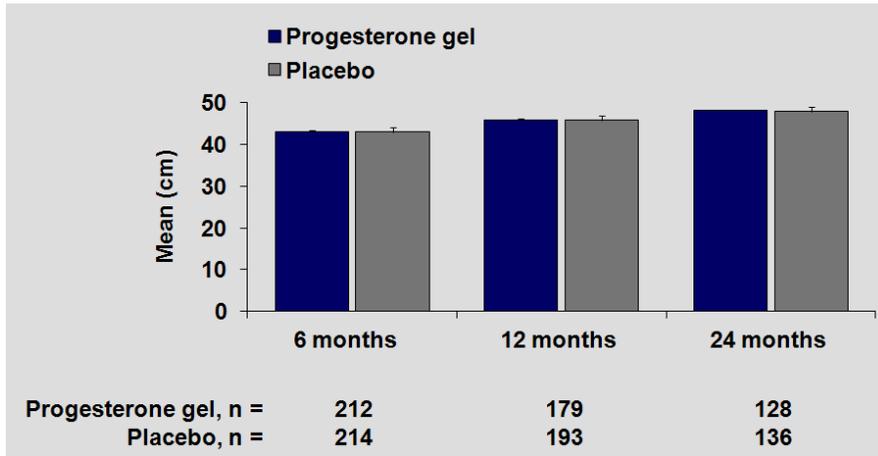
Source: Study 300 clinical study report, Table 14.3.5.1

Figure 4.9-2 Study 300 Mean Weight (gr) 2-Yr Infant Follow-up

	6 months	12 months	24 months
Progesterone gel, n =	218	178	138
Placebo, n =	218	201	149

Source: Study 300 clinical study report, Table 14.3.5.1

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

Figure 4.9-3 Study 300 Mean Length (cm) 2-Yr Infant Follow-up
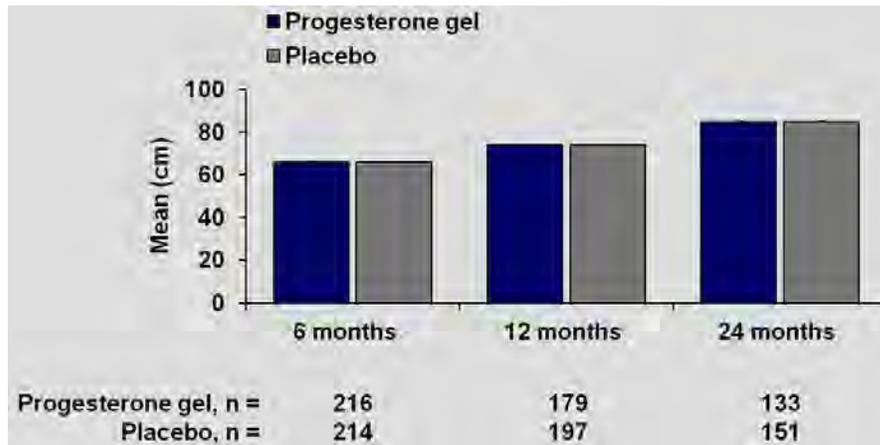
Source: Study 300 clinical study report, Table 14.3.5.1

Table 4.9-1   Study 300 Summary of Other Data 2-Yr Infant Follow-up

	Placebo N = 316	Prog gel 8% N = 321
Congenital anomalies, n (%)	12 (3.8)	11 (3.4)
Chronic morbid conditions, n (%)	17 (5.4)	19 (5.9)
Suspect Denver II, n	23	20

Source: Study 300 clinical study report, Table 12.10 based on expert medical review, Table 14.3.5.1.
Note: Suspect Denver II scores are based on the last available assessment, as presented in Study 300 clinical study report addendum.

4.10 Post Marketing Safety Data for Assisted Reproductive Technology Indication

Postmarking safety information from the use of progesterone gel 8% has been collected since its first approval in 1997. Because the first trimester of pregnancy is considered the most sensitive period for xenobiotic adverse fetal effects, these data from usage in the ART indication would be a stringent evaluation of the use of progesterone gel 8% for the requested use during the third trimester. During the 14 years of in-market experience, 3.66 million doses have been dispensed for the currently approved indications. The total number of spontaneously reported adverse event cases in the Crinone/Prochieve post-marketing safety database maintained by Watson Pharmaceuticals Inc. covering the time period from first approval to 15 October 2011 has been 440, of which 41 were categorized as Serious, and 399

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

as Non-Serious. These cases represent 677 events (75 Serious and 602 Non-Serious). There have been nine spontaneously reported event terms of congenital abnormality representing eight cases, as described below:

> 3 cases – cleft palate
> 1 cases – congenital cardiovascular anomaly
> 1 case – exomphalos
> 1 case – gastrointestinal malformation
> 1 case – hernia congenital
> 1 case – hypospadias
> 1 case – trisomy 21

A review of this safety information from this long period of use does not suggest a safety signal is present with the use of progesterone vaginal gel, even during the more sensitive first trimester.

4.11 Safety Discussion and Conclusions

Every fetus is exposed to progesterone from the time of implantation to the time of delivery, and this exposure to progesterone increases from conception to delivery as maternal progesterone levels rise substantially. Fetal exposure to progesterone is even greater in multiple gestations. Progesterone gel 8% has been previously used in early pregnancy for progesterone supplementation or replacement as part of an ART treatment for infertile women with progesterone deficiency, and after many years of clinical use in the first trimester through this route of administration, no safety signals in the mother or fetus/infant have been detected. Indeed, the USP Drug Information book currently states that "the significant concentration of endogenous natural progesterone produced during pregnancy is devoid of teratogenic effects."[42] In comparison to intramuscular or oral use, systemic levels following vaginal dosing with progesterone gel 8%, approved for ART are low and physiologic. Additionally, vaginal administration would not be expected to result in an altered metabolic profile of the progesterone compared to naturally produced progesterone. Progesterone from the ovaries and from the placenta enters the maternal circulation through the pelvic veins, arteries, and lymphatic system--the same route of entry that occurs with vaginally delivered progesterone. This is dramatically different from the profile of orally or intramuscularly delivered progesterone. For these reasons, the additional small dose and short-term exposure during the third trimester from the vaginal administration of progesterone gel 8% as administered in this clinical development program would not be

---

[42] Drug Information for the Health Care Professional, Thomson Healthcare; 27 edition (January 2007).

expected to increase the risk of adverse events to the mother or fetus. In fact, data from this development program confirms the lack of safety concerns for mother or infant.

In conclusion, all available safety information demonstrates that daily vaginal administration of a bioadhesive formulation of progesterone gel 8% from 18 to 37 weeks gestation is safe and well-tolerated.

5   RISK/BENEFIT ASSESSMENT AND CONCLUSIONS

5.1   Overall

The data from this program showed a statistically significant and clinically meaningful reduction in preterm birth and evidence for improvement in infant outcome, along with no meaningful risk to the mother or the fetus or infant. The benefits of progesterone gel 8% clearly outweigh the minimal risk of its use in women with short cervix, and US marketing authorization of this therapy may safely eliminate 20,000 to 30,000 of preterm births annually in the US.

5.2   Risk Assessment

The safety profile of progesterone gel 8% was demonstrated in three clinical studies conducted by the Sponsor, Study 300 (which included 2 year infant follow-up), Study 301, and Study 302. This program exposed 1,119 pregnant women who were considered at risk for preterm birth. In this database, the occurrence of treatment-related adverse events was low and comparable between progesterone gel 8% and placebo treatment groups. The most common adverse events were preterm labor-related complications of pregnancy, and the most common adverse events that led to discontinuation of study drug were premature baby, premature labor and preterm rupture of membranes. There were no maternal deaths in any of the studies. Analysis of infant outcomes showed that there was no evidence of infant harm associated with the use of progesterone gel 8% treatment, nor any fetal or infant mortality signal. Additionally, in a two-year infant follow-up, there was no evidence of infant harm when examining growth and development parameters. These findings are consistent with post-marketing safety data from the use of progesterone gel 8% during the first trimester which has not uncovered any safety signal during its use in a more vulnerable period of fetal development under the previously approved ART indications.

In conclusion, this bioadhesive formulation of progesterone gel 8% has very low risk when administered intravaginally during the third trimester.

5.3   Benefit Assessment

Evidence of efficacy for progesterone gel 8% in women with short cervix is provided from an adequate and placebo controlled, randomized clinical study, Study 302, with supportive information from Study 300, and independent substantiation of the use of vaginal progesterone in reducing the risk of preterm birth in women with short cervix from Fonseca, et al, 2007.

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

As observed in the adequate and well-controlled clinical trial, Study 302, progesterone gel 8% reduced the incidence of preterm birth in women with short uterine cervical length in the mid-trimester of pregnancy. Compared with placebo, treatment with progesterone gel 8% showed a statistically significantly lower proportion of women who delivered preterm at <33 weeks. This finding was supported by sensitivity analyses and positive effects in other gestational age cut points. Taken together, the incidence of infant outcomes and the composite scores showed evidence of improvement in infant outcomes in the progesterone gel 8% group compared to placebo, reinforcing the clinical relevance of the primary endpoint treatment effects. The 0-4 composite score, as well as three alternative pre-defined composite scores in the ITT analysis set, all favored the progesterone gel 8% group in the reduction of perinatal mortality/neonatal morbidity. In the assessment of "Any Mortality/Morbidity Event", the risk of any mortality/morbidity event also favored the progesterone gel 8% group. Further, there was a reduction in RDS, the most common complication of prematurity and the leading cause of death of prematurity, when compared with the placebo group. Additional evidence for improvement in infant outcome was observed in the increase in size of the infants at birth and the reduction in infants in low birth weight categories. Various similar positive treatment effects were also observed in the results of analyses from Study 300, and in the independent clinical investigation published by Fonseca, et al in 2007.

In the efficacy results from Study 302, the US and non-US regions both favored progesterone, although the size of the treatment effect was greater in the non-US regions. In contrast, in Study 300 the results for the US subgroup favored progesterone, whereas the non-US results favored placebo. This finding supports the conclusion that the Study 302 regional effect can be attributed to normal variability among subgroups when considering an endpoint of low incidence; the totality of data from the program suggests beneficial treatment effects in the US.

In summary, the results from the two Columbia randomized clinical trials of vaginal progesterone gel 8% formulation establish the benefits of this formulation in preventing preterm birth in women with a short cervix. This finding was well supported by results on additional secondary variables. Furthermore, the use of progesterone gel 8% in women with short cervix in the mid-trimester resulted in improvements in infant outcome and standard neonatal assessments of size and development. In conclusion, a bioadhesive formulation of progesterone gel 8% was highly beneficial in preventing preterm birth in women with short cervixes when administered intravaginally during the third trimester.

5.4   Risk/Benefit Conclusions

This NDA requests approval of a bioadhesive vaginal progesterone gel 8% formulation that has been evaluated in two placebo-controlled, randomized clinical trials to reduce the risk of preterm birth. The data from this program showed a reduction in preterm birth and evidence for improvement in infant outcome, along with no meaningful risk to the mother or the fetus or infant. These substantial benefits and minimal risk were observed in both the US and the non-US regions. Moreover, there is published independent substantiation of the approach to reducing the risk of preterm birth in women with short cervix by using intravaginal progesterone. The medical need for such a therapy is particularly acute in the US, where preterm birth is one of the main causes of infant mortality and the preterm birth rate in the US has risen to 12% where it has remained for almost 10 years. The US currently ranks 48th worldwide in the rate of infant mortality and this rank has been worsening steadily since the 1960's. The majority of preterm births occur in women who are pregnant for the first time or have had a prior term pregnancy, and there is currently no approved treatment to reduce the risk of preterm birth in this group. In current clinical practice, identifying the subset of pregnant women who would benefit from progesterone 8% vaginal gel is easily implementable through the use of the widely available and commonly performed TVU procedure. US marketing authorization of this therapy could eliminate 20,000-30,000 preterm births annually in the US, and the benefits of progesterone 8% vaginal gel clearly outweigh the minimal risk of its use in women with short cervix.

6   PUBLISHED VAGINAL PROGESTERONE TRIALS IN SHORT CERVIX SUBJECTS

In addition to the two randomized clinical trials sponsored by Columbia,

> Study 300, published as O'Brien JM, Adair CD, Lewis DF, et al. *Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial,* Ultrasound Obstet Gynecol 2007;30:687-96, and,

> Study 302, published as Hassan SS, Romero R, Vidyadhari D, et al. *Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial,* Ultrasound Obstet Gynecol 2011;38:18-31,

along with the 2007 Fonseca, et al investigation,

> published as *Progesterone and the risk of preterm birth among women with a short cervix,* Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. N Engl J Med. 2007 Aug 2;357(5):462-9,

there are data from two other randomized clinical trials where women were administered vaginal progesterone and where outcomes are known. Abstracts of these two trials are provided in this section. Additionally, the full text of a just-released publication by Romero et al of a meta-analysis discussing the vaginal use of progesterone for the prevention of preterm birth in women with short cervixes is available.

Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial.

Arch Gynecol Obstet. 2011 Mar;283(3):423-9. Epub 2010 Jan 22.

Cetingoz E, Cam C, Sakallı M, Karateke A, Celik C, Sancak A.

Source: Department of Obstetrics and Gynecology, Zeynep Kamil Women and Children Diseases Education and Research Hospital, Uskudar, Istanbul, Turkey.

PURPOSE: The purpose of this study was to evaluate whether the prophylactic administration of vaginal progesterone would reduce the preterm birth rate in high-risk population including singleton and twin pregnancies.

METHODS: This was a randomized, double blind, placebo-controlled study that included 150 high-risk pregnancies. Risk groups included prior spontaneous preterm birth, twin pregnancy, and uterine malformation. Micronized progesterone or placebo (100 mg) was administered daily by vaginal suppository between 24 and 34 weeks of gestation. We compared progesterone and placebo groups for incidence of preterm labor and preterm delivery. Data were compared by χ^2 analysis and Fisher exact test.

RESULTS: There was a statistically significant difference in the rate of preterm labor between placebo and progesterone groups (45.7 vs. 25%, respectively; $p < 0.05$). More women delivered before 37 weeks in placebo group (57.2%) than in progesterone group (40%; $p < 0.05$). Administering progesterone also reduced the preterm birth before 34 weeks of gestation. The difference between placebo and progesterone group was statistically significant (24.3 vs. 8.8%; $p < 0.05$). However, there was no significant difference in neonatal death between placebo and progesterone groups.

CONCLUSION: Prophylactic vaginal progesterone reduced the rate of preterm labor and preterm delivery in high-risk pregnancies.

Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis.

Klein K, Rode L, Nicolaides KH, Krampl-Bettelheim E, Tabor A; PREDICT Group.

Collaborators (18): Vogel I, Larsen H, Holmskov A, Riis Andreasen K, Uldbjerg N, Ramb J, Bødker B, Skibsted L, Sperling L, Hinterberger S, Krebs L, Zingenberg H, Weiss EC, Strobl I, Laursen L, Christensen JT, Mølholm Hansen B, Lando A.

Source: Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria. katharina.klein@meduniwien.ac.at

OBJECTIVES: Progesterone treatment reduces the risk of preterm delivery in high-risk singleton pregnancies. Our aim was to evaluate the preventive effect of vaginal progesterone in high-risk twins.

METHODS: This was a subanalysis of a Danish-Austrian, double-blind, placebo-controlled, randomized trial (PREDICT study), in which women with twin pregnancies were randomized to daily treatment with progesterone or placebo pessaries from 20-24 weeks until 34 weeks' gestation. This subpopulation consisted of high-risk pregnancies, defined by the finding of cervical length ≤ 10th centile at 20-24 weeks' gestation or history of either spontaneous delivery before 34 weeks or miscarriage after 12 weeks. Primary outcome was delivery before 34 weeks. Secondary outcomes were complications for infants including long-term follow-up by Ages and Stages Questionnaire (ASQ) at 6 and 18 months of age.

RESULTS: In 72 (10.6%) of the 677 women participating in the PREDICT study, the pregnancy was considered to be high-risk, including 47 with cervical length ≤ 10th centile, 28 with a history of preterm delivery or late miscarriage and three fulfilling both criteria. Baseline characteristics for progesterone and placebo groups were similar. Mean gestational age at delivery did not differ significantly between the two groups either in subjects with a short cervix (34.3 ± 4.1 vs. 34.5 ± 3.0 weeks, P = 0.87) or in those with a history of preterm delivery or late miscarriage (34.6 ± 4.2 vs. 35.2 ± 2.7 weeks, P = 0.62). Similarly, there were no significant differences between the treatment groups in maternal or neonatal complications and mean ASQ score at 6 and 18 months of age.

CONCLUSION: In high-risk twin pregnancies, progesterone treatment does not significantly improve outcome.

7   APPENDICES

Appendix 1:   Selected Definitions of Infant Outcomes

Respiratory Distress Syndrome
- Clinical - symptoms (one or more of the following):
  - tachypnoea (respiratory rate > 60 breaths per minute)
  - intercostal, subcostal, and sternal recession
  - expiratory grunting
  - cyanosis
  - diminished breath sounds
- plus oxygen therapy (FiO2 ≥ 0.40) until infant death or ≥ 24 hours

Bronchopulmonary Dysplasia
- Treatment with > 21% O2 for at least 28 days, or
- O2 dependence after 36 weeks post-conceptional age

Intraventricular Hemorrhage
Grade I – subependymal hemorrhage
Grade II – intraventricular hemorrhage, uncomplicated
Grade III – intraventricular hemorrhage with ventricular dilatation
Grade IV – intraventricular hemorrhage with ventricular dilatation and parenchymal extension

Proven Sepsis
- Clinically ill infant with suspected infection plus
- Positive blood, CSF, or catheterized/suprapubic urine culture or cardiovascular collapse or unequivocal X-ray finding

Necrotizing Enterocolitis
Surgical – Stage III – Advanced
- perinatal stress (i.e., preterm birth)
- systemic manifestations such as temperature instability, lethargy, apnea, bradycardia, occult or gross GI bleeding, abdominal distension, plus septic shock
- radiographs show: intestinal distension with ileus, small bowel separation, rigid bowel loops, pneumatosis intestinalis, portal vein gas, pneumoteritoneum
- Treatment was surgical

Clinical – Stage II – Definite
- perinatal stress (i.e., preterm birth)
- systemic manifestations such as temperature instability, lethargy, apnea, bradycardia, occult or gross GI bleeding, abdominal distension
- radiographs show: intestinal distension with ileus, small bowel separation, rigid bowel loops, pneumatosis intestinalis, portal vein gas
- Treatment was medical

Other – Stage I – Suspect
- perinatal stress (i.e., preterm birth)
- systemic manifestations such as temperature instability, lethargy, apnea, bradycardia
- radiographs show: intestinal distension with ileus
- Treatment was observation

Appendix 2:   Combined Study 300 and Study 302 Serious Adverse Events

The following serious adverse events (SAEs) from this listing were considered *related* to study drug by the investigator:

Related SAEs in Study 300

141004	Placebo	PREMATURE LABOUR
164002	Placebo	PREMATURE LABOUR
107007	Progesterone Gel	PREMATURE RUPTURE OF MEMBRANES
112006	Progesterone Gel	VOMITING IN PREGNANCY
115020	Progesterone Gel	UTERINE CONTRACTIONS ABNORMAL
133003	Progesterone Gel	CHORIOAMNIONITIS
133003	Progesterone Gel	INTRA-UTERINE DEATH
133003	Progesterone Gel	PREMATURE LABOUR
149001	Progesterone Gel	BLEEDING PERIPARTUM
154003	Progesterone Gel	POSTPARTUM HAEMORRHAGE

Related SAEs in Study 302

29006	Placebo	HYPERSENSITIVITY
29019	Placebo	UTERINE CONTRACTIONS ABNORMAL

ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

**Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302
(Safety Analysis Set)**

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
Any Serious TEAE	n (%)	150 (44%)	87 (44%)	237 (44%)	160 (45%)	74 (37%)	234 (42%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	n (%)	131 (38%)	72 (37%)	203 (38%)	146 (41%)	57 (28%)	203 (37%)
PREMATURE LABOUR	n (%)	64 (19%)	28 (14%)	92 (17%)	65 (18%)	12 (6%)	77 (14%)
PREMATURE BABY	n (%)	41 (12%)	42 (21%)	83 (15%)	46 (13%)	31 (15%)	77 (14%)
PREMATURE RUPTURE OF MEMBRANES	n (%)	22 (6%)	6 (3%)	28 (5%)	23 (6%)	10 (5%)	33 (6%)
UTERINE CONTRACTIONS ABNORMAL	n (%)	12 (3%)	5 (3%)	17 (3%)	19 (5%)	4 (2%)	23 (4%)
CERVICAL INCOMPETENCE	n (%)	7 (2%)	2 (1%)	9 (2%)	9 (3%)	3 (1%)	12 (2%)
PREGNANCY INDUCED HYPERTENSION	n (%)	6 (2%)	1 (<1%)	7 (1%)	6 (2%)	2 (<1%)	8 (1%)
FOETAL DISTRESS SYNDROME	n (%)	0	4 (2%)	4 (<1%)	5 (1%)	4 (2%)	9 (2%)
PRE-ECLAMPSIA	n (%)	6 (2%)	3 (2%)	9 (2%)	2 (<1%)	2 (<1%)	4 (<1%)
OLIGOHYDRAMNIOS	n (%)	6 (2%)	2 (1%)	8 (1%)	3 (<1%)	1 (<1%)	4 (<1%)
PREMATURE SEPARATION OF PLACENTA	n (%)	7 (2%)	3 (2%)	10 (2%)	1 (<1%)	1 (<1%)	2 (<1%)
CHORIOAMNIONITIS	n (%)	1 (<1%)	4 (2%)	5 (<1%)	3 (<1%)	2 (<1%)	5 (<1%)
INTRA-UTERINE DEATH [1]	n (%)	2 (<1%)	1 (<1%)	3 (<1%)	5 (1%)	2 (<1%)	7 (1%)
UTERINE CONTRACTIONS DURING PREGNANCY	n (%)	6 (2%)	0	6 (1%)	4 (1%)	0	4 (<1%)
FOETAL GROWTH RETARDATION	n (%)	0	4 (2%)	4 (<1%)	3 (<1%)	1 (<1%)	4 (<1%)

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.

Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302 (Safety Analysis Set) (Continued)

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS (cont'd)							
BLEEDING PERIPARTUM	n (%)	3 (<1%)	0	3 (<1%)	3 (<1%)	0	3 (<1%)
STILLBIRTH [1]	n (%)	2 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)
VOMITING IN PREGNANCY	n (%)	1 (<1%)	1 (<1%)	2 (<1%)	3 (<1%)	0	3 (<1%)
FOETAL HEART RATE DECELERATION	n (%)	1 (<1%)	1 (<1%)	2 (<1%)	0	2 (<1%)	2 (<1%)
FOETAL MOVEMENTS DECREASED	n (%)	3 (<1%)	1 (<1%)	4 (<1%)	0	0	0
ECLAMPSIA	n (%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)
FUNISITIS	n (%)	0	2 (1%)	2 (<1%)	0	1 (<1%)	1 (<1%)
POSTPARTUM HAEMORRHAGE	n (%)	0	2 (1%)	2 (<1%)	1 (<1%)	0	1 (<1%)
THREATENED LABOUR	n (%)	2 (<1%)	0	2 (<1%)	1 (<1%)	0	1 (<1%)
BREECH PRESENTATION	n (%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
DELIVERY	n (%)	0	0	0	2 (<1%)	0	2 (<1%)
HELLP SYNDROME	n (%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
UMBILICAL CORD PROLAPSE	n (%)	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0
BRADYCARDIA FOETAL	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
CHOLESTASIS OF PREGNANCY	n (%)	0	0	0	0	1 (<1%)	1 (<1%)
FACE PRESENTATION	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
FALSE LABOUR	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
OBSTRUCTED LABOUR	n (%)	0	0	0	0	1 (<1%)	1 (<1%)
PLACENTA ACCRETA	n (%)	0	0	0	0	1 (<1%)	1 (<1%)

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.

Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302 (Safety Analysis Set) (Continued)

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS (cont'd)							
PLACENTA PRAEVIA	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
PLACENTAL INSUFFICIENCY	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
PREGNANCY	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
TACHYCARDIA FOETAL	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
UTERINE HYPOTONUS	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
UTERINE RUPTURE	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	n (%)	24 (7%)	14 (7%)	38 (7%)	24 (7%)	13 (6%)	37 (7%)
CERVIX DISORDER	n (%)	21 (6%)	13 (7%)	34 (6%)	19 (5%)	13 (6%)	32 (6%)
VAGINAL DISCHARGE	n (%)	3 (<1%)	0	3 (<1%)	5 (1%)	0	5 (<1%)
OVARIAN CYST	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
UTERINE PAIN	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
VAGINAL LACERATION	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
GASTROINTESTINAL DISORDERS	n (%)	9 (3%)	4 (2%)	13 (2%)	11 (3%)	5 (2%)	16 (3%)
ABDOMINAL PAIN	n (%)	5 (1%)	1 (<1%)	6 (1%)	3 (<1%)	1 (<1%)	4 (<1%)
ABDOMINAL PAIN LOWER	n (%)	0	2 (1%)	2 (<1%)	5 (1%)	2 (<1%)	7 (1%)
NAUSEA	n (%)	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)
DIARRHOEA	n (%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
GASTRITIS	n (%)	0	0	0	1 (<1%)	1 (<1%)	2 (<1%)
VOMITING	n (%)	0	0	0	1 (<1%)	1 (<1%)	2 (<1%)
ABDOMINAL DISCOMFORT	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
CONSTIPATION	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
PAROTID GLAND ENLARGEMENT	n (%)	1 (<1%)	0	1 (<1%)	0	0	0

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.

Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302 (Safety Analysis Set) (Continued)

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
INFECTIONS AND INFESTATIONS	n (%)	6 (2%)	5 (3%)	11 (2%)	8 (2%)	4 (2%)	12 (2%)
URINARY TRACT INFECTION	n (%)	3 (<1%)	2 (1%)	5 (<1%)	1 (<1%)	0	1 (<1%)
UPPER RESPIRATORY TRACT INFECTION	n (%)	0	2 (1%)	2 (<1%)	0	2 (<1%)	2 (<1%)
GASTROENTERITIS	n (%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0	2 (<1%)
PYELONEPHRITIS	n (%)	2 (<1%)	0	2 (<1%)	1 (<1%)	0	1 (<1%)
VAGINAL INFECTION	n (%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0	2 (<1%)
CELLULITIS	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
CYTOMEGALOVIRUS INFECTION	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
PNEUMONIA	n (%)	0	0	0	0	1 (<1%)	1 (<1%)
PNEUMONIA PRIMARY ATYPICAL	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
UREAPLASMA INFECTION	n (%)	0	0	0	0	1 (<1%)	1 (<1%)
VAGINAL CANDIDIASIS	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
SURGICAL AND MEDICAL PROCEDURES	n (%)	3 (<1%)	5 (3%)	8 (1%)	3 (<1%)	7 (3%)	10 (2%)
CERVIX CERCLAGE PROCEDURE	n (%)	2 (<1%)	4 (2%)	6 (1%)	2 (<1%)	7 (3%)	9 (2%)
MATERNAL THERAPY TO ENHANCE FOETAL LUNG MATURITY	n (%)	0	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)
CAESAREAN SECTION	n (%)	1 (<1%)	0	1 (<1%)	0	0	0

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.

Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302 (Safety Analysis Set) (Continued)

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	n (%)	2 (<1%)	2 (1%)	4 (<1%)	5 (1%)	0	5 (<1%)
PYREXIA	n (%)	2 (<1%)	2 (1%)	4 (<1%)	3 (<1%)	0	3 (<1%)
CHEST PAIN	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
OEDEMA PERIPHERAL	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
METABOLISM AND NUTRITION DISORDERS	n (%)	3 (<1%)	1 (<1%)	4 (<1%)	3 (<1%)	0	3 (<1%)
GESTATIONAL DIABETES	n (%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)
DEHYDRATION	n (%)	2 (<1%)	0	2 (<1%)	0	0	0
DIABETES MELLITUS	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
DIABETES MELLITUS INADEQUATE CONTROL	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	n (%)	0	1 (<1%)	1 (<1%)	1 (<1%)	3 (1%)	4 (<1%)
FALL	n (%)	0	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)
ABDOMINAL INJURY	n (%)	0	0	0	1 (<1%)	1 (<1%)	2 (<1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	n (%)	2 (<1%)	0	2 (<1%)	3 (<1%)	0	3 (<1%)
BACK PAIN	n (%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0	2 (<1%)
ARTHRALGIA	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
MYALGIA	n (%)	1 (<1%)	0	1 (<1%)	0	0	0

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.

Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302 (Safety Analysis Set) (Continued)

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
CARDIAC DISORDERS	n (%)	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	0	1 (<1%)
AORTIC VALVE INCOMPETENCE	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
ATRIAL FIBRILLATION	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
FOETAL HEART RATE DECELERATION	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
MITRAL VALVE INCOMPETENCE	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
TACHYCARDIA FOETAL	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	n (%)	2 (<1%)	0	2 (<1%)	2 (<1%)	0	2 (<1%)
ASTHMA	n (%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)
DYSPNOEA	n (%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)
COUGH	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	n (%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)
ANAEMIA	n (%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)
INVESTIGATIONS	n (%)	0	0	0	2 (<1%)	1 (<1%)	3 (<1%)
FOETAL HEART RATE ABNORMAL	n (%)	0	0	0	2 (<1%)	0	2 (<1%)
FOETAL MONITORING	n (%)	0	0	0	0	1 (<1%)	1 (<1%)

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.

Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302 (Safety Analysis Set) (Continued)

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
NERVOUS SYSTEM DISORDERS	n (%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0	2 (<1%)
HEADACHE	n (%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0	2 (<1%)
HEPATOBILIARY DISORDERS	n (%)	0	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
CHOLECYSTITIS ACUTE	n (%)	0	0	0	0	1 (<1%)	1 (<1%)
GALLBLADDER DISORDER	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
IMMUNE SYSTEM DISORDERS	n (%)	2 (<1%)	0	2 (<1%)	0	0	0
HYPERSENSITIVITY	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
RHESUS INCOMPATIBILITY	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
SOCIAL CIRCUMSTANCES	n (%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
PHYSICAL ASSAULT	n (%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)	1 (<1%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
ERYTHROBLASTOSIS FOETALIS	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
EYE DISORDERS	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
VISION BLURRED	n (%)	1 (<1%)	0	1 (<1%)	0	0	0

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.

**Summary of Serious Maternal Treatment-Emergent Adverse Events for Studies COL-1620-300 and COL-1620-302
(Safety Analysis Set) (Continued)**

System Organ Class/ Preferred Term	Descriptive Statistic	Placebo			Progesterone Gel 8%		
		Preterm (N=344)	No Preterm (N=196)	Total (N=540)	Preterm (N=355)	No Preterm (N=201)	Total (N=556)
PSYCHIATRIC DISORDERS	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
ANXIETY	n (%)	1 (<1%)	0	1 (<1%)	0	0	0
RENAL AND URINARY DISORDERS	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
HYDRONEPHROSIS	n (%)	0	1 (<1%)	1 (<1%)	0	0	0
VASCULAR DISORDERS	n (%)	0	0	0	1 (<1%)	0	1 (<1%)
LYMPHOEDEMA	n (%)	0	0	0	1 (<1%)	0	1 (<1%)

Note: Preterm=PTB (<=35 0/7 weeks) risk group; No Preterm=short cervix only (<=2.5 cm) risk group.