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# 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial

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## Abstract

**Background** Women with a history of spontaneous preterm birth (SPTB) are at a significantly increased risk for recurrent preterm birth (PTB). To date, only one large U.S. clinical trial comparing 17-OHPC (17-α-hydroxyprogesterone caproate or "17P") to placebo has been published, and this trial was stopped early due to a large treatment benefit.

**Objective** This study aimed to assess whether 17-OHPC decreases recurrent PTB and neonatal morbidity in women with a prior SPTB in a singleton gestation.

**Study Design** This was a double-blind, placebo-controlled international trial involving women with a previous singleton SPTB (*clinicaltrials.gov*: NCT 01004029). Women were enrolled at 93 clinical centers (41 in the United States and 52 outside the United States) between $16^{0/7}$ to $20^{6/7}$ weeks in a 2:1 ratio, to receive either weekly intramuscular (IM) injections of 250 mg of 17-OHPC or an inert oil placebo; treatment was continued until delivery or 36 weeks. Co-primary outcomes were PTB < 35 weeks and a neonatal morbidity composite index. The composite included any of the following: neonatal

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death, grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, or proven sepsis. A planned sample size of 1,707 patients was estimated to provide 98% power to detect a 30% reduction in PTB < 35 weeks (30% to 21%) and 90% power to detect a 35% reduction in neonatal composite index (17%–11%) using a two-sided type-I error of 5%. Finally, this sample size would also provide 82.8% power to rule out a doubling in the risk of fetal/early infant death assuming a 4% fetal/early infant death rate. Analysis was performed according to the intention-to-treat principle.

**Results** Baseline characteristics between the 1,130 women who received 17-OHPC and 578 women who received placebo were similar. Overall, 87% of enrolled women were Caucasian, 12% had >1 prior SPTB, 7% smoked cigarettes, and 89% were married/lived with partner. Prior to receiving study drug, 73% women had a transvaginal cervical length measurement performed and <2% had cervical shortening <25 mm. There were no significant differences in the frequency of PTB < 35 weeks (17-OHPC 11.0% vs. placebo 11.5%; relative risk = 0.95 [95% confidence interval (CI): 0.71–1.26]) or neonatal morbidity index (17-OHPC 5.6% vs. placebo 5.0%; relative risk = 1.12 [95% CI: 0.68–1.61]). There were also no differences in frequency of fetal/early infant death (17-OHPC 1.7% vs. placebo 1.9%; relative risk = 0.87 [95% CI: 0.4–1.81]. Maternal outcomes were also similar. In the subgroup of women enrolled in the United States ($n = 391$; 23% of all patients), although the rate of PTB < 35 weeks was higher than the overall study population, there were no statistically significant differences between groups (15.6% vs. 17.6%; relative risk = 0.88 [95% CI: 0.55, 1.40].

**Conclusion** In this study population, 17-OHPC did not decrease recurrent PTB and was not associated with increased fetal/early infant death.

In 2003, Meis and colleagues, on behalf of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD), Maternal-Fetal Medicine Units (MFMU) Network, published the results of a randomized controlled trial (RCT) which demonstrated that 250 mg weekly intramuscular (IM) injection of 17-α-hydroxyprogesterone caproate (17-OHPC) could reduce the risk of recurrent preterm birth (PTB) in women with a prior spontaneous PTB (SPTB) by approximately 34% compared with placebo (relative risk [RR] = 0.66 [95% confidence interval (CI): 0.54–0.81]).[1] This trial was conducted across 19 sites which were university-based academic medical centers. Originally planned with a sample size of 500 women, it was stopped early by the Data Safety Monitoring Committee (DSMC) based on prespecified rules, when it was considered unethical to continue recruitment given the robust evidence of efficacy with PTB < 37 weeks. Although underpowered to assess neonatal morbidities, the RR point estimates for neonatal death, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing dysplasia were all <1.0 and ranged from 0.25 to 0.63.

Also published in 2003, Fonesca and colleagues[2] reported the results of their RCT of vaginal progesterone to prevent PTB. This trial, conducted in Brazil and involving 142 women at high-risk for PTB, reported that vaginal progesterone decreased PTB < 37 and < 34 weeks. The positive treatment benefits from these two RCT's prompted the American College of Obstetricians and Gynecologists (ACOG) to state "recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women (i.e., those with a prior spontaneous birth at <37 weeks of gestation)."[3] In 2008, ACOG and the Society for Maternal Fetal Medicine (SMFM) coauthored a document that stated, "progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and prior SPTB."[4]

In 2011, the U.S. Food and Drug Administration (FDA) granted conditional approval of 17-OHPC for commercial use in the United States under the Subpart-H accelerated approval pathway.[5] Accelerated approval under the Subpart-H regulatory pathway is allowed for new drugs that are intended to treat serious or life-threatening conditions and provide meaningful benefit to patients over existing treatments.[6] In addition to accelerated approval, 17-OHPC was granted Orphan Drug Designation, as its indicated population affects less than 200,000 patients in the United States annually. In an analysis of the potential impact of 17-OHPC on PTB rates in the United States, based on 2002 natality data Petrini et al estimated there were approximately 132,000 women per year who would be eligible for 17-OHPC therapy.[7] In general, the FDA requires a new drug to have data from two adequate and well-controlled clinical trials as substantial evidence of effectiveness. Although not planned or conducted as a drug approval trial, the NICHD study was a key aspect to provide evidence of 17-OHPC effectiveness; a

condition of FDA approval was that the sponsor had to complete a confirmatory trial.

This confirmatory trial was designed with the input of the FDA to assess the efficacy of 17-OHPC based on both PTB and neonatal morbidity and to assess the safety based on fetal/early infant death. The FDA also required a long-term infant follow-up study. As it was recognized that 17-OHPC had largely become an acceptable standard of care in the United States for this indication, FDA required that at least 10% of study participants be enrolled from North American sites. This study report describes the confirmatory trial, called the PROLONG study (Progestin's Role in Optimizing Neonatal Gestation)[8]; the efficacy objective was to assess whether 17-OHPC decreases recurrent PTB and neonatal morbidity in women with a prior SPTB in a singleton gestation and a safety objective was to rule out an increase in the risk of fetal and/or early infant death.

## Materials and Methods

### Trial Oversight

The PROLONG study was a multicenter, randomized, controlled, parallel group, double-blind trial at 93 total centers across nine countries (see Supplementary Material [available in the online version] for all participating clinical sites). Clinical sites were required to be associated with a hospital which had access to level-3 or greater neonatal intensive care unit (NICU). This trial was conducted in accordance with Good Clinical Practices guidelines and the provisions of the Declaration of Helsinki. Qualified representatives of the Sponsor monitored the study according to a predetermined monitoring plan to verify protocol adherence and accuracy and completeness of data. The protocol was approved by the institutional review board at each hospital before participants' enrollment. The protocol was developed in consultation with the FDA and mirrored the study protocol from the NICHD MFMU trial. The trial was registered at *clinicaltrials.gov* (NCT01004029)[9] along with an infant follow-up study which is still ongoing (NCT01146990).[10] The protocol and other study materials are available in Supplementary Material (available in the online version). Written informed consent was obtained from all participants before randomization. As part of the consent process, participants were informed in their native language of the results of the NICHD MFMU study and after 2011 that 17-OHPC had been approved for use by the FDA.

### Screening and Recruitment

Women $\geq$18 years old, with a singleton pregnancy who had a documented previous pregnancy complicated by a singleton SPTB and who were $16^{0/7}$ to $20^{6/7}$ weeks in the current pregnancy were eligible for the trial. SPTB was defined as delivery from $20^{0/7}$ to $36^{6/7}$ weeks following spontaneous preterm labor or preterm rupture of membranes (PROM). Women were excluded for the following reasons: multifetal gestation, known major fetal anomaly, heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, a seizure disorder, or use of progesterone treatment in any form (i.e., vaginal, oral, and IM) during current pregnancy. In 2013, the study protocol was modified to allow for enrollment of women if they received micronized progesterone (orally or vaginally) provided it was stopped at least 4 weeks prior to the first dose of study medication. An obstetric ultrasonographic examination was required at $14^{0/7}$ to $20^{3/7}$ weeks for gestational dating and evaluation for fetal anatomic abnormalities.

### Randomization and Treatment

After informed consent, women were administered a trial injection of placebo and asked to return in 1 week at which time eligibility was reassessed to determine if they could be randomized. Women were randomly allocated 2:1 to receive 17-OHPC or placebo once per week from randomization through $36^{6/7}$ weeks or delivery, whichever occurred first. Randomization was performed via an interactive voice response system using a computer-generated schedule with a block sequence of random blocks of size 3 and 6, stratified by study site and gestational age at randomization ($16^{0/7}$–$17^{6/7}$ weeks and $18^{0/7}$–$20^{6/7}$ weeks).

The 17-OHPC was supplied as a sterile solution containing the active ingredient (hydroxyprogesterone caproate, 250 mg/mL), benzyl benzoate, castor oil, and benzyl alcohol. Placebo was identical, minus the active ingredient, and was matched in color and appearance compared with 17-OHPC. Both the 17-OHPC and placebo were identical to the formulations used in the MFMU network trial. The study drug was given by the study site personnel as a 1 mL intramuscular injection in the upper outer quadrant of the gluteus maximus. The women, their caregivers, and research personnel were not informed of the study-group assignment. Other than administration of the study drug, the research protocol did not dictate any specific treatment regimen and pregnancy management was at the discretion of the treating clinician. Transvaginal ultrasound cervical length measurement was performed following local clinical care guidelines and was not prescribed by the study protocol. Management of shortened cervix was at the discretion of the patient's attending physician.

### Trial Outcomes

PROLONG had co-primary efficacy outcomes; PTB $<$ 35 weeks (all deliveries occurring from randomization until $35^{0/7}$ weeks of gestation, including miscarriages or abortions occurring from $16^{0/7}$ through $19^{6/7}$ weeks) and a composite neonatal morbidity and mortality index. The composite index included any of the following: neonatal death, grade-3 or-4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, or proven sepsis. Secondary outcomes were neonatal death, PTB $<$ $32^{0/7}$ weeks and PTB $<$ $37^{0/7}$ weeks, as well as spontaneous and medically indicated PTB $<$ $32^{0/7}$, $<$$35^{0/7}$, and $<$$37^{0/7}$ weeks.

The primary safety outcome was fetal/early infant death defined as any of the following: spontaneous abortion/miscarriage (delivery from $16^{0/7}$–$19^{6/7}$ weeks of gestation), stillbirth delivering after $20^{0/7}$ weeks through term, or early infant death. Early infant death was defined as death after

birth until 28 days of life occurring in live-born neonates delivered $<24^{0/7}$ weeks of gestation. The secondary safety outcomes analyzed were the individual components of the primary safety outcome as well injection reactions, maternal complications, and other adverse events. Standardized definitions for neonatal and safety outcomes can be found in the PROLONG protocol (see ►**Supplementary Material**, available in the online version). Neonates were followed through 28 days of life or discharged from the NICU, whichever was later. All cases of miscarriage, stillbirth, and neonatal death were reviewed blinded to study drug in a standardized process and categorized by both local investigator and by an MFM expert for causality related to study medication (definite, probable, possible, unlikely/remote, and definitely not).

### Statistical Analysis

The study was designed to have adequate power for the coprimary efficacy analyses and the primary safety analyses. Baseline outcome rates (PTB, neonatal outcomes, and safety measures) and treatment effects (17-OHPC vs. placebo) utilized for sample size estimates were extrapolated from the NICHD MFMU network trial. A total of 1,665 live-born infants were required to detect a reduction of 35% in the rate of the composite index (17%–11%) with a power of 90% and a two-sided type-I error of 5%. Assuming 2.5% of pregnancies would result in miscarriage or stillbirth, an additional 42 patients were planned to be enrolled for a total of 1,707 (1,138 active and 569 placebos). A total sample size of 1,707 patients provided 98% power to detect a reduction of approximately 30% in the rate of PTB $<35^{0/7}$ weeks (from 30% to 21%) using a two-sided type-I error of 5%. This sample size assumed there would be adequate power (>92%) to detect clinically significant reductions in the secondary outcomes of PTB $<32^{0/7}$ and $<37^{0/7}$ weeks. Finally for the primary safety outcome, assuming a 4% fetal/early infant death rate in both treatment groups with a two-sided type-I error of 5%, a sample size of 1,707 patients would provide 82.8% power to rule-out a doubling in the risk of fetal/early infant death (i.e., the upper bound of the confidence interval [CI] for the RR of 17P compared with placebo will be $\leq$2.0).

Evaluation for statistical differences between the 17-OHPC and placebo groups in the percentage of patients who delivered $<35^{0/7}$ weeks gestation and the percentage of neonates with the neonatal composite index were determined using Cochran–Mantel–Haenszel (CMH) tests stratified by gestational age at randomization. Analyses were performed according to the intention to treat principle. Patients with missing delivery or neonatal composite index data had the endpoint imputed, using a multiple imputation analysis, assuming a monotone missing data pattern. A logistic regression with treatment, gestational age at randomization, the interaction of treatment and gestational age at randomization, and the number of previous preterm deliveries including miscarriages and abortions were used for imputation. The combined CMH statistic from the imputed datasets was determined using the Wilson–Hilferty transformation. Since PTB $<35^{0/7}$ weeks and the neonatal composite index were coprimary outcomes, no adjustment for multiplicity were planned.

For the primary safety outcome of fetal/early infant death an adjusted RR (for gestational age at randomization) and a 95% CI for the RR was calculated using the CMH procedure. If the upper bound of the CI was $<2.0$, it would be interpreted that 17P-OHPC did not increase the risk of fetal/early infant death.

Descriptive statistics were provided by treatment group for baseline variables, primary, secondary, and additional efficacy and safety outcomes. Adjusted (for gestational age at randomization) RRs and 95% CIs for the RRs were calculated based on the observed data (i.e., not using an imputation procedure) using the CMH procedure. Prespecified subgroup analyses for the primary outcome and exploratory sub analyses for selected secondary outcomes included evaluating treatment effects by maternal race, location of recruitment (the United States vs. the non–United States), and gestational age of qualifying prior preterm birth. The statistical analysis plan is provided (see ►**Supplementary Material**, available in the online version).

An independent DSMC monitored the trial for safety and met annually and reviewed safety and side-effect data. Given the necessity to complete this study as part of FDA approval, no interim analyses were performed for efficacy and there were no futility parameters.

### Role of the Funding Source

This study was designed and conducted by the Sponsor, originally Hologic and KV Pharmaceutical, then Lumara Health and subsequently AMAG Pharmaceuticals. During the 9-year period that the trial was conducted, there were two contract research organizations overseeing the study, PRA International and ResearchPoint Global. Analyses were performed by biostatistician (AFD) in conjunction with the authors. Study authors had access to all study data and independence regarding data analyses, interpretation of findings, and manuscript preparations.

## Results

### Characteristics of the Participants

The first patient was randomized on November 12, 2009 and the last study visit was October 8, 2018. After prescreening, based on medical record and chart review, 1,877 women were assessed more thoroughly for eligibility. Due to the nature of chart screening and eligibility assessment, the specific number of women who were evaluated for potential eligibility and/or declined participation was not tracked. A total of 1,740 women were eligible, consented, and agreed to the test injection (►**Fig. 1**). Of these, 1,708 remained eligible for the study and returned for the randomization visit; 1,130 women were allocated to 17-OHPC and 578 were allocated to placebo (►**Fig. 1**). There were 391 women randomized in the United States and 1,317 women randomized non-United States (see ►**Supplementary Material** [available in the online version] for recruitment by site).

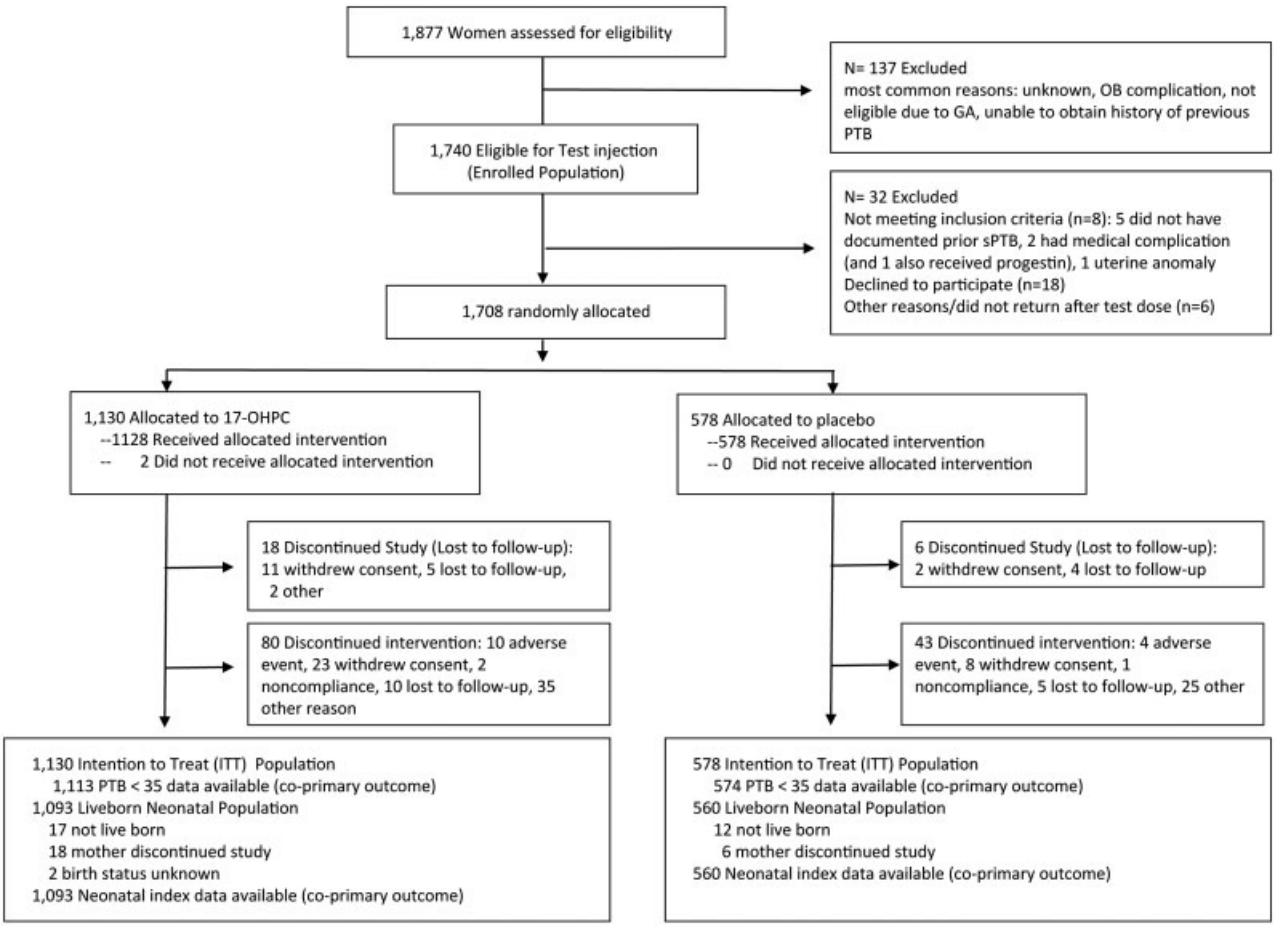


**Fig. 1** Patient eligibility, randomization, and assessment. HPC, hydroxyprogesterone caproate; PROLONG, Progestin's Role in Optimizing Neonatal Gestation; PTB, preterm birth, sPTB, spontaneous PTB.

There were no differences in demographic or clinical characteristics between study groups (►**Table 1**). Most of the participants were white (87%), few had >1 prior SPTB (13%), 89% were married, and 8% smoked. There were no differences in number of study medication injections between those receiving 17-OHPC (median = 18, range: 1–22) or placebo (median, 18, range: 1–22) or the rate of full compliance (91.4 vs. 92.4%).

## Primary Outcomes and Other Perinatal Outcomes

No difference between treatment groups was found for either coprimary efficacy outcome; PTB $< 35^{0/7}$ weeks (17-OHPC 11.0% vs. placebo 11.5%; RR = 0.95 [95% CI: 0.71–1.26]; $p = 0.72$) and neonatal composite index (17-OHPC 5.6% vs. placebo 5.0%; RR = 1.12 [95% CI: 0.70–1.66]; $p = 0.73$). A review of the individual components of the neonatal composite index indicates no differences between the treatment groups for any of the components assessed. The frequency of respiratory distress syndrome drove the composite outcomes for both groups.

Similarly, the rate of PTB < 37 and < 32 weeks were not different (►**Table 2**). Maternal outcomes including need for cerclage placement, tocolysis, antenatal corticosteroid therapy, gestational diabetes, preeclampsia, chorioamnionitis, and abruption were also not different (►**Table 3**). In the PROLONG, the rates of PTB were higher in the United States patients compared to the non-U.S. patients (data presented in ►**Supplementary Material**, available in the online version). Outside the United States, the rates of PTB in the regions with the highest enrollments (i.e., Russia and Ukraine that accounted for 60% of all patients enrolled) were among the lowest observed.

The fetal/early infant death rates were lower than expected and not different between treatment groups (17-OHPC 1.7 vs. placebo 1.9%; RR = 0.87 [95% CI: 0.4–1.81]). Patients receiving 17-OHPC had a lower risk of miscarriage (17 OHPC 0.5% vs. 1.6%; RR = 0.28 [95% CI: 0.08–0.94]) and there was no statistically significant difference in the frequency of stillbirth (17-OHPC 1.1% vs placebo 0.5%; RR 2.07 [95% CI 0.59–7.29]) (►**Table 4**). Assessment of causality of the relationship of study drug in the cases of miscarriage, stillbirth, and neonatal outcomes is described in ►**Supplementary Material** (available in the online version).

A total of 1,253 women had transvaginal ultrasound cervical length performed prior to receiving study medication and 18 (1.4%) had measurement <25 mm. Of them, 22.2% (4/18) in the 17-OHPC group and 44.4% (4/9) in the placebo group had PTB < 35 weeks. Of women with cervical length >25 mm, 9.6% (78/810) in the 17-OHPC group and 9.5% (39/410) in the placebo group had PTB <35 weeks.

**Table 1** Demographic and clinical characteristics

| | 17-OHPC $n = 1,130$ | Placebo $n = 578$ |
|---|---|---|
| Maternal age (y) | 30.0 ± 5.2 | 29.9 ± 5.2 |
| Race | | |
| Black | 73 (6.5) | 41 (7.1) |
| Caucasian | 1,004 (88.8) | 504 (87.2) |
| Asian | 23 (2.0) | 22 (3.8) |
| Other | 30 (2.7) | 11 (1.9) |
| Hispanic or Latino ethnicity | 101 (8.9) | 54 (9.3) |
| No. of prior spontaneous PTB > 1 | 148 (13.1) | 70 (12.1) |
| Prior elective abortion | 281 (24.9) | 142 (24.6) |
| Prior indicated PTB | 19 (1.7) | 13 (2.3) |
| Gestational age at qualifying prior SPTB (wk) | 32 (28–35) | 33 (29–35) |
| Prepregnancy BMI (kg/m$^2$) | 23 (21–27) | 23 (21–27) |
| Marital status | | |
| Married/living with a partner | 1,013 (89.6) | 522 (90.3) |
| Never married | 86 (7.6) | 40 (6.9) |
| Divorced/widowed/separated | 31 (2.7) | 16 (2.8) |
| Years of education | 13 (11–15) | 13 (11–15) |
| Smoked during current pregnancy | 92 (8.1) | 41 (7.1) |
| Drank alcohol during current pregnancy | 24 (2.1) | 18 (3.1) |
| Used any "street drugs" during current pregnancy | 16 (1.4) | 8 (1.4) |
| Transvaginal cervical length <25 mm, *n*/N1[a] (%) | 10/833 (1.2) | 8/420 (1.9) |
| Prior vaginal progesterone therapy in pregnancy | 16 (1.4) | 10 (1.7) |

Abbreviations: BMI, body mass index; OHPC, α-hydroxyprogesterone caproate; PTB, preterm birth; SPTB, spontaneous preterm birth.
Note: *n* is number of patients in the Intent to Treat population. Data expressed as *n* (%), median (inter-quartile range), or mean (± standard of deviation).
[a]N1 = number of patients with cervical length measurement performed prior to first dose of study drug; measured prior to the first dose of study drug.

## Discussion

The PROLONG trial was conducted in consultation with the FDA (as part of FDA approval for the use of 17-OHPC) for the purpose of serving as a confirmatory study following the MFMU trial. However, unlike the robust positive findings of the NICHD MFMU trial, the PROLONG study had a much lower event rate of PTB (almost 50% lower) and did not confirm treatment efficacy. Given the much lower than expected event rates, PROLONG, despite its large sample size, was underpowered to assess treatment efficacy related to PTB endpoints and neonatal outcomes. Event rates for pregnancy loss (fetal/early infant death) were lower than expected and not different between groups. Although not statistically significant, there was an increase in the frequency of stillbirth in the 17-OHPC group. A detailed clinical review of these cases noted factors unassociated with 17-OHPC as the suspected cause in the majority of cases. There were also no differences in the rates of gestational diabetes.

Despite having the same eligibility criteria and study protocol, the MFMU trial and PROLONG ended up having very dissimilar patient populations which may explain the marked difference in PTB event rates. In the MFMU trial, women were recruited from United States academic medical centers and had a high-baseline risk for PTB.[1] In the NICHD trial, the women receiving placebo had PTB < 37, PTB < 35, and PTB < 32 weeks of 54.9%, 30.7%, and 19.6%, respectively, while in PROLONG, the rates were 21.9%, 11.5%, and 5.2%, respectively. In PROLONG, most women were recruited from outside the United States (75%). In Russia and Ukraine, where >60% patients were enrolled, PTB < 37 weeks occurred in 17.2% and 21.1%, respectfully. Differences in race and socioeconomic status between women in the NICHD trial and PROLONG non-United States are clear, but there may also be another explanation for the lower PTB event rates seen in PROLONG. When PROLONG started recruitment in 2009, many physicians in the United States were already prescribing 17-OHPC (or vaginal progesterone) as routine care. Their interest and ability to participate in a placebo-controlled trial was therefore limited. Few, if any, United States major medical centers participated in PROLONG because they had access to 17-OHPC or a comparable treatment. Most sites who chose to participate in PROLONG did not have access to 17-OHPC for their patients, and therefore a two-thirds chance of receiving 17-OHPC was better than no chance. Over time, and especially with the FDA approval of 17-OHPC in 2011, it is possible than women with a higher risk

**Table 2** Obstetrical outcomes

| | 17-OHPC $n = 1{,}130$ | Placebo $n = 578$ | RR (95% CI) |
|---|---|---|---|
| Number assessed for outcome, N1 | 1,113 | 574 | 0.95 (0.71–1.26) |
| PTB $< 35^{0/7}$ wk[a] | 122 (11.0) | 66 (11.5) | |
| Spontaneous | 93 (8.4) | 51 (8.9) | 0.93 (0.67–1.30) |
| Indicated | 28 (2.5) | 14 (2.4) | 1.03 (0.55–1.93) |
| Number assessed for outcome, N1 | 1,112 | 572 | |
| PTB $< 37^{0/7}$ wk | 257 (23.1) | 125 (21.9) | 1.06 (0.88–1.28) |
| Spontaneous | 209 (18.8) | 98 (17.1) | 1.10 (0.88–1.36) |
| Indicated | 46 (4.1) | 26 (4.5) | 0.91 (0.57–1.46) |
| Number assessed for outcome, N1 | 1,116 | 574 | 0.92 (0.60–1.42) |
| PTB $< 32^{0/7}$ wk | 54 (4.8) | 30 (5.2) | |
| Spontaneous | 38 (3.4) | 22 (3.8) | 0.88 (0.52–1.48) |
| Indicated | 15 (1.3) | 7 (1.2) | 1.11 (0.46–2.63) |
| Cerclage | 6 (0.5) | 7 (1.2) | 0.44 (0.15–1.32) |
| Preterm labor[b] | 187(16.5) | 84 (14.5) | 1.14 (0.90–1.44) |
| Tocolysis | 134 (11.9) | 63 (10.9) | 1.09 (0.82–1.44) |
| Antenatal corticosteroid therapy | 105 (9.3) | 61(10.6) | 0.88 (0.65–1.20) |
| Maternal GDM | 35 (3.1) | 21 (3.6) | 0.91 (0.54–1.54) |
| Preeclampsia | 47 (4.2) | 30 (5.2) | 0.86 (0.51–1.46) |
| Chorioamnionitis | 9 (0.8) | 2 (0.3) | 2.24 (0.48–10.41) |
| Abruption | 16 (1.4) | 4 (0.7) | 2.04 (0.69–6.06) |
| Cesarean delivery | 292 (25.8) | 140 (24.2) | 1.07 (0.90–1.27) |

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; OHPC, α-hydroxyprogesterone caproate; PTB, preterm birth; RR, relative risk.

Note: $n$ = number of subjects in the intent to Treat population. N1 = number of subjects with non-missing delivery data or with missing delivery data who were known to be pregnant at the specified gestational age. Relative risk (RR) and confidence interval (CI) adjusted for gestational age at randomization stratum and based on observed data (no imputation for missing data). Data expressed as $n$ (%).Type of delivery (spontaneous and indicated) is not available for women with missing delivery data.

[a]$p$-Value = 0.72 and is from the Cochran–Mantel–Haenszel test based on the sample sizes within each gestational age at randomization stratum. Missing outcome data were imputed using a multiple imputation analysis.

[b]Not including episode of delivery event.

for recurrent PTB did not get enrolled in PROLONG but were rather steered to open label therapy, to avoid the chance of receiving a placebo. With these combinations of events, PROLONG enrolled a lower risk profile of women, both in the United States and outside the United States. The lower rate of prior SPTB > 1 and the very low rate of shortened cervix (<2%) are indicators that women with more severe obstetrical histories or conditions may have been (consciously or unconsciously) steered away from participation. Since PTB is not a singular disease, but a syndrome with multiple pathways and etiologies,[11,12] it is not unexpected that the disease severity, as measured by the rate of recurrent PTB, has a wide range. As an example, in the PROLONG United States study population ($n = 391$), PTB < 37 weeks occurred in 28.8% of those who received placebo. This is substantially greater than those outside the United States, but still much lower than the NICHD trial. Another factor is that not all women may be "responders" to 17-OHPC as there may be pharmacogenomic variations (e.g., in the NICHD trial 36.3% of women treated with 17-OHPC had PTB < 37 weeks)[13,14]

## Limitations and Strengths

One of the limitations of PROLONG is that the majority of women were enrolled outside the United States and their characteristics were quite different, which leads to uncertainty on the applicability to a higher risk United States population. The second major limitation is the fact that the study was underpowered given the much lower than expected event rates. The sample size estimates were based on the NICHD trial which had very high event rates for both PTB and neonatal morbidity. Assuming the same estimates for sample size calculation, given the observed event rates, PROLONG would have required 3,600 women to have 90% power for PTB < 35 weeks and 6,000 women for the neonatal composite outcome. Another limitation is the paucity of women in PROLONG who had a short cervix. In the trial, there were only 2% who had a short cervix, which is lower than expected in a population of women with a prior SPTB.[15–17] The number of women in this subgroup does not provide an adequate sample to assess treatment effect.

**Table 3** Neonatal outcomes—live-born neonatal population

| | 17-OHPC $n = 1{,}093$ | Placebo $n = 559$ | RR (95% CI) |
|---|---|---|---|
| Composite neonatal morbidity and mortality index[a] | 61 (5.6) | 28 (5.0) | 1.12 (0.72–1.72) |
| Neonatal death | 6 (0.5) | 3 (0.5) | 0.98 (0.24–3.91) |
| Bronchopulmonary dysplasia | 6 (0.5) | 1 (0.2) | 3.02 (0.38–24.1) |
| Respiratory distress syndrome | 54 (4.9) | 26 (4.7) | 1.06 (0.67–1.68) |
| Necrotizing enterocolitis | 2 (0.2) | 2 (0.4) | 0.5 (0.07–3.40) |
| IVH, grade 3 or 4 | 2 (0.2) | 1 (0.2) | 0.99 (0.09–10.52) |
| Proven sepsis | 5 (0.5) | 3 (0.5) | 0.84 (0.20–3.56) |
| NICU admission | 137 (12.5) | 58 (10.4) | 1.21 (0.90–1.62) |
| Birth weight (g) | $3{,}076.6 \pm 630.0$ | $3{,}080.1 \pm 609.2$ | NA |
| TTN | 37 (3.4) | 11 (2.0) | 1.72 (0.89–3.33) |
| Number of neonates on ventilator support/receiving supplemental oxygen | 130 (11.9) | 54 (9.7) | 1.23 (0.91–1.67) |
| PDA | 4 (0.4) | 4 (0.7) | 0.53 (0.14–2.06) |
| ROP | 5 (0.5) | 7 (1.3) | 0.37 (0.12–1.16) |
| Neonatal LOS (for those admitted to the NICU) (d) | $18.6 \pm 20.4$ | $23.3 \pm 24.5$ | NA |

Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; LOS, length of stay; NA, not applicable; NICU, neonatal intensive care unit; OHPC, α-hydroxyprogesterone caproate; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk; TTN, transient tachypnea of the newborn.

Note: Data expressed as *n* (%), median (interquartile range), or mean ($\pm$ standard of deviation). *n* = number of neonates in the live-born neonatal population. RR and CI are adjusted for gestational age at randomization stratum.

[a]*p*-Value = 0.62 and is from the Cochran–Mantel–Haenszel test based on the sample sizes within each gestational age at randomization stratum.

**Table 4** Pregnancy loss, stillbirth, and neonatal death outcomes

| | 17-OHPC n/N1 (%) | Placebo n/N1 (%) | RR (95% CI)[a] |
|---|---|---|---|
| Fetal/early infant death[b] | 19/1128 (1.7) | 11/578 (1.9) | 0.87 (0.4–1.81) |
| Miscarriage[c] | 4/866 (0.5) | 7/448 (1.3) | 0.28 (0.08–0.94) |
| Stillbirth[d] | 12/1124 (1.1) | 3/571 (0.5) | 2.07 (0.59–7.29) |
| Early infant death[e] | 3/1112 (0.3) | 1/568 (0.2) | 1.48 (0.14–15.24) |

Abbreviations: CI, confidence interval; OHPC, α-hydroxyprogesterone caproate; RR, relative risk.

[a]Relative risk is from the CMH test adjusted for gestational age at randomization stratum.

[b]Denominator is number of patients who received study drug. Fetal/early infant death is defined as a miscarriage, stillbirth, or neonatal death through 28 days of life occurring in a live-born neonate at $< 24$ weeks of gestation.

[c]Denominator is number of patients who received study drug and were randomized $20^{0/7}$ weeks of GA. Miscarriage is defined as spontaneous delivery from $16^{0/7}$ to $19^{6/7}$ weeks of gestation.

[d]Denominator is number of patients who received study drug and were pregnant beyond $\geq 20^{0/7}$ weeks of GA. Stillbirth is defined as antepartum or intrapartum death from $20^{0/7}$ weeks of gestation through term.

[e]Denominator is number of patients who received study drug and did not have a miscarriage or stillbirth. Patients with missing data are assumed not to have the specified outcome.

Strengths of the PROLONG trial include its placebo-controlled design, large sample size, low lost to follow-up rate and planned infant follow-up study (on-going). Another strength is that the study protocol mirrored the MFMU trial which has allowed for direct comparisons with that trial. There was a planned prespecified subgroup analysis to assess treatment effects for the U.S. versus non-U.S. subgroups. In the U.S.-only subgroup ($n = 391$) which had a higher baseline PTB rate compared with the non-U.S. (i.e., PTB < 37 weeks in U.S.-only placebo group 28.2 vs. 20% in non-U.S. placebo group), there were nonsignificant trends for treatment efficacy with PTB < 32 weeks (point estimate RR = 0.58) and < 35 weeks (RR = 0.88) but not <37 weeks (RR = 1.16). There was also a nonsignificant trend for the neonatal composite (RR = 0.81). These analyses should be considered exploratory and hypothesis generating only. Finally, PROLONG included an on-going follow-up study to determine whether there is a difference in development status between children, aged 23 to 25 months corrected gestational age, whose mothers received 17-OHPC or placebo (*clinicaltrial.gov*: NCT01146990).

## Conclusion

In conclusion, current clinical guidelines in the United States recommend the use of 17-OHPC in women with prior SPTB.[18] How best to adjudicate the findings of the PROLONG trial, given it was underpowered and inconclusive regarding assessment of treatment efficacy, will be challenging for clinicians, patients, and policy makers. Combining data in systematic reviews and/or meta-analyses[19,20] to attempt to differentiate a population with the most optimal benefit/risk ratio will be important. The absence of other evidence-based interventions to offer this orphan population (women with prior SPTB) combined with the reality that 17-OHPC has been widely used for over 15 years adds to the complexity. Finally, the feasibility of conducting another placebo controlled RCT seems improbable, especially in the United States.

### Condensation

In women with a prior spontaneous preterm birth, weekly 17-OHPC compared with placebo did not reduce recurrent preterm birth or decrease neonatal morbidity.

### Clinical Trial Registration

Date of registration: October 27, 2009.
Date of initial participant enrollment: November 12, 2009.
Clinical trials ID: NCT01004029.
URL: https://clinicaltrials.gov/ct2/show/NCT01004029?term=17P+AMAG&rank=2.

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### Conflict of Interest

P.N., J.B., O.M.Y., G.I.R., N.Y.R., O.P., N.T. are PROLONG clinical site investigators.
C.G.-B. and J.R.B. have received grant funding for other project(s) from the sponsor (AMAG Pharmaceuticals, Inc.).
G.R.S. and H.S.M. have received consulting fees from AMAG Pharmaceuticals, Inc.
A.F.D. has received consulting/personal fees related to her work on the project from the sponsor (AMAG Pharmaceuticals, Inc.).
J.G., R.B., M.J.J., M.D., L.W., J.K. are current or former employees of AMAG Pharmaceuticals, Inc.

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