

# Re-examining the Meis Trial for Evidence of False-Positive Results

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U.S. Food and Drug Administration (FDA)-approved 17 $\alpha$ -hydroxyprogesterone caproate therapy is currently available to reduce recurrent preterm birth in the United States. This commentary reviews the original landmark Meis trial (“Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate”), which led to conditional approval of 17 $\alpha$ -hydroxyprogesterone caproate by the FDA in 2011. The recent PROLONG (Progesterin’s Role in Optimizing Neonatal Gestation) trial failed to confirm the original findings. The Meis trial was rigorously designed and conducted, with highly statistically significant results that should not be undermined by the negative results of PROLONG. Given that the United States has among the highest preterm birth rates in the world and that the predominant enrollment in PROLONG was outside the United States, the results of the “old” Meis trial should not be summarily dismissed. It would be detrimental to high-risk pregnant patients to

inappropriately prioritize results of PROLONG over the Maternal-Fetal Medicine Units Network’s Meis trial (funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development). We assert PROLONG was underpowered, based on substantially lower observed preterm birth rates than anticipated, and therefore was a false-negative study, rather than the Meis trial being a false-positive study. Careful assessment of these two trials is critical as removal of 17 $\alpha$ -hydroxyprogesterone caproate from the U.S. marketplace may have substantial effects on public health.

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In 2003, Meis and colleagues from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network published their landmark trial in the *New England Journal of Medicine*.<sup>1</sup> This was the first rigorous, placebo-controlled trial to demonstrate an intervention reduced preterm birth in women with a history of spontaneous preterm birth. This finding expanded on the results of a meta-analysis of five randomized trials that demonstrated a 42% reduction in the rate of recurrent preterm birth with 17 $\alpha$ -hydroxyprogesterone caproate.<sup>2</sup>

The Meis trial was heralded as a major advance in the field of obstetrics and led to U.S. Food and Drug Administration (FDA) approval of Makena in 2011. A requirement by the FDA was the initiation of a second confirmatory trial, known as PROLONG (Progesterin’s Role in Optimizing Neonatal Gestation), which began in 2009. PROLONG, conducted largely outside the United States, failed to confirm the benefit of 17 $\alpha$ -hydroxyprogesterone caproate in women with the same eligibility criteria as the Meis trial.<sup>3</sup> In October 2019, an FDA Advisory Committee voted 9–7 to recommend the FDA pursue withdrawal of 17 $\alpha$ -hydroxyprogesterone caproate. Notably, this action would apply to the original Makena intramuscular formulation, any FDA-approved generic equivalents,

as well as the Makena Auto-Injector for subcutaneous use.

During the recent Advisory Committee meeting and elsewhere,<sup>4</sup> concerns were raised regarding the Meis trial. As one of the investigators and co-authors of the Meis trial (B.S.), the biostatistician for the Meis trial (A.F.D.), and an independent maternal-fetal medicine specialist currently involved in the Maternal-Fetal Medicine Units Network (G.R.S.), we feel compelled to address these criticisms. For transparency, we acknowledge that the three of us have affiliations with AMAG, the manufacturer of Makena. We also address the PROLONG trial data for context of the current dilemma.

### **EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT MATERNAL-FETAL MEDICINE UNITS NETWORK MEIS TRIAL**

Women at 19 academic centers were randomized 2:1 to receive 17 $\alpha$ -hydroxyprogesterone caproate or placebo. A sample size of 500 women was needed to detect a 33% reduction (from 37% to 25%) in the rate of preterm birth at less than 37 weeks of gestation with 80% power. A prespecified stopping criterion for efficacy based on the Lan-DeMets procedure using an O'Brien-Fleming spending function was included in the study design.

At the second interim analysis reviewed by an independent data and safety monitoring board, the prespecified criterion threshold of  $\alpha = 0.015$  was met based on 370 randomized patients. Women who were randomized up to that point remained in the trial until delivery, resulting in a data set of 463 women (92.6% of the planned sample size). The relative risk (RR) was 0.66 (95% CI 0.54–0.81) for preterm birth at less than 37 weeks of gestation in favor of 17 $\alpha$ -hydroxyprogesterone caproate ( $P < .001$ ). Secondary outcomes of preterm births at less than 35 and less than 32 weeks of gestation also showed benefit with 17 $\alpha$ -hydroxyprogesterone caproate with RRs of 0.67 (95% CI 0.48–0.93) and 0.58 (95% CI 0.37–0.91), respectively. Although the trial was not powered to detect direct neonatal benefits, results were encouraging, with trends across the spectrum of reducing composite neonatal morbidity, and reduction in rates of necrotizing enterocolitis and intraventricular hemorrhage.

Despite these compelling results, the findings were criticized because of the preterm birth rate in the placebo group, an imbalance in number of prior preterm births between 17 $\alpha$ -hydroxyprogesterone caproate and placebo, the use of castor oil as a diluent, the large number of patients enrolled from one site,

and the use of 37 weeks of gestation as the primary endpoint.

Critics of the Meis trial have cited concerns that the 54.9% rate of preterm birth at less than 37 weeks of gestation in the placebo group was higher than projected. A previous Maternal-Fetal Medicine Units Network study, HUAM (the Home Uterine Activity Monitoring study), was used to estimate the placebo preterm birth rate for the sample size calculation.<sup>5</sup> However, the higher than anticipated preterm birth rate in the Meis trial can be explained by fundamental differences between the HUAM and the Meis studies. In HUAM, women simply consented to external monitoring of their uterine activity. In contrast, in the Meis trial, women consented to weekly intramuscular injections of an experimental treatment. Thus, the patient burden was higher in the Meis trial and likely skewed enrollment toward patients who were more motivated to participate owing to a negative obstetric outcome in their prior pregnancy (eg, only 22% in HUAM had more than one prior preterm birth, vs 32% in the Meis trial).

In a 2010 editorial,<sup>6</sup> Dr. Iams notes three historical factors associated with recurrent preterm birth: maternal race (black vs nonblack); gestational age of the index preterm birth, and the number of previous preterm births. Each risk factor confers a 1.5- to 2-fold increase in the risk of recurrent preterm birth beyond the 1.5- to 2-fold risk associated with a prior preterm birth. In retrospect, the preterm birth rate in the placebo arm of the Meis trial was not unexpected given the high participation by black patients, the early gestational age of the prior preterm birth, and the proportion of women with more than one prior preterm birth.

A higher than expected outcome rate in the placebo group is not a flaw and does not invalidate the trial, but it does raise the question of generalizability. To address this issue, subgroup analyses were conducted including by number of prior preterm birth, race, marital status, and smoking or substance use (Table 1). In these subgroups, 17 $\alpha$ -hydroxyprogesterone caproate reduced the risk of preterm birth at less than 37 weeks of gestation with RRs ranging from 0.52 to 0.72, indicating that the results were generalizable to a wide range of women with previous spontaneous preterm birth. In addition, treatment-subgroup interactions were assessed by logistic regression, and none of the interaction terms were significant. Thus, there was consistent benefit of 17 $\alpha$ -hydroxyprogesterone caproate across subgroups, which is further evidence of the robust findings.

**Table 1. Preterm Birth at Less Than 37 Weeks of Gestation by Subgroup (Meis Trial)\***

Preterm Birth at Less Than 37 wk	17P	Placebo	RR (95% CI)
Overall	111/306 (36.3)	84/153 (54.9)	0.66 (0.54–0.81) <sup>†</sup> 0.70 (0.57–0.85) <sup>**</sup>
More than 1 prior preterm birth	41/86 (47.7)	44/63 (69.8)	0.68 (0.52–0.90)
Only 1 prior preterm birth	70/220 (31.8)	40/90 (44.4)	0.72 (0.53–0.97)
Black	64/181 (35.4)	47/90 (52.2)	0.68 (0.51–0.90)
Nonblack	47/125 (37.6)	37/63 (58.7)	0.64 (0.47–0.87)
Unmarried	50/150 (33.3)	43/82 (52.4)	0.64 (0.47–0.86)
Married	61/156 (39.1)	41/71 (57.7)	0.68 (0.51–0.90)
Smoke or substance use	28/85 (32.9)	23/36 (63.9)	0.52 (0.35–0.76)
No smoke or substance use	83/221 (37.6)	61/117 (52.1)	0.72 (0.57–0.92)
Southeast site	23/86 (26.7)	18/40 (45.0)	0.59 (0.36–0.97)
Other sites	92/224 (41.1)	66/113 (58.4)	0.70 (0.56–0.88)

17P, 17 $\alpha$ -hydroxyprogesterone caproate; RR, relative risk.

Data are n/N (%), where n=number of patients in the specified category and N=number of patients in the treatment group (overall or in the specified subgroup) with nonmissing delivery data.

\* Table created from the Meis data set (includes previously unpublished data).<sup>1</sup>

<sup>†</sup> The CI is a 96.5% CI to adjust for the interim analysis.

<sup>\*\*</sup> Adjusted for more than one prior preterm birth using the Cochran-Mantel-Haenszel procedure.

Although the overall demographics and clinical characteristics in the Meis trial were balanced between the groups, the placebo group had more prior preterm births compared with the 17 $\alpha$ -hydroxyprogesterone caproate group (mean, 1.6 vs 1.4, respectively;  $P=.007$ ). An analysis which adjusted for this variable confirmed the significant reduction in preterm birth at less than 37 weeks of gestation in the 17 $\alpha$ -hydroxyprogesterone caproate group (RR 0.70; 95% CI 0.57–0.85,  $P<.001$ ) (Table 1). In addition, 17 $\alpha$ -hydroxyprogesterone caproate reduced preterm birth in the subgroups of those who with more than one prior preterm birth (RR 0.68; 95% CI 0.52–0.92) and those with only one prior preterm birth (RR 0.72; 95% CI 0.53–0.97).

Some questioned the use of castor oil as the diluent because oral castor oil can stimulate labor through a mechanism where intestinal lipases release ricinoleic acid, a hydroxylated fatty acid.<sup>7</sup> However, there is no evidence that castor oil stimulates labor when administered parenterally.

Preterm birth rates have long been higher in the Southeast compared with other U.S. regions.<sup>8</sup> Thus, it is not unexpected that one site in that region had the highest enrollment rate (27% of the women) (Table 1). Nevertheless, this institution did not bias the results of the Meis trial: 17 $\alpha$ -hydroxyprogesterone caproate demonstrated a significant reduction in preterm birth at other sites with a RR of 0.70 (95% CI 0.56–0.88). Therefore, the trial results remained significant, even when all the women from the Southeast site were excluded from the analysis. Further, the  $P$  value (0.82) from an interaction term in a logistic regression

analysis indicates that the Southeast site results were not significantly different from the other sites.

The primary efficacy outcome of the Meis trial was preterm birth at less than 37 weeks of gestation, with preterm birth at less than 35 weeks and preterm birth at less than 32 weeks as secondary outcomes. The trial was not powered for neonatal morbidity and mortality or for a composite neonatal endpoint. At the initial 2006 FDA Advisory Committee meeting, the majority of committee members voted that preterm birth at less than 37 weeks of gestation was not an adequate surrogate for reduction in fetal or neonatal morbidity or mortality, and that preterm birth at less than 35 weeks of gestation was an adequate surrogate.<sup>9</sup> Since then, multiple studies have found that neonates born between 34 and 37 weeks of gestation (ie, “late” preterm birth) were physiologically and metabolically less mature than term neonates, resulting in a higher risk of morbidity and mortality.<sup>10–13</sup> Thus, FDA determined that preterm birth at less than 37 weeks of gestation was an acceptable surrogate endpoint, reasonably likely to predict clinical benefit.<sup>9</sup>

The Meis trial demonstrated consistent reductions in preterm birth regardless of gestational age endpoint (Table 2), with RRs of 0.66 for preterm birth at less than 37 weeks of gestation, 0.67 for preterm birth at less than 35 weeks, and 0.58 for preterm birth at less than 32 weeks. Composite neonatal morbidity and mortality was also lower in the 17 $\alpha$ -hydroxyprogesterone caproate group (11.9%) compared with the placebo group (17.2%).<sup>14</sup> Although not statistically significant, the RR of 0.69 for a neonatal outcome that included death and serious complications often

**Table 2. Efficacy Outcomes for the Meis\* and PROLONG<sup>†</sup> Trials**

Endpoint	Meis* <sup>†</sup>		PROLONG <sup>‡</sup>		U.S. PROLONG* <sup>§</sup>	
	17P	Placebo	17P	Placebo	17P	Placebo
PTB at less than 37 wk RR (95% CI) <sup>  </sup>	36.3 (111/306) 0.66 (0.54–0.81)	54.9 (84/153) 0.81 (0.68–0.94)	23.1 (257/1,112) 1.06 (0.88–1.28) <sup>¶</sup>	21.9 (125/572) 0.95 (0.71–1.26)	33.2 (85/256) 1.16 (0.84–1.61)	28.2 (37/131) 0.88 (0.55–1.40)
PTB at less than 35 wk RR (95% CI)	20.6 (63/306) 0.67 (0.48–0.93)	30.7 (47/153) 0.67 (0.48–0.93)	11 (122/1,113) 0.95 (0.71–1.26)	11.5 (66/574) 0.92 (0.60–1.42)	15.6 (40/256) 0.58 (0.27–1.21)	17.6 (12/131) 0.84 (0.41–1.72)
PTB at less than 32 wk RR (95% CI)	11.4 (34/306) 0.58 (0.37–0.91)	19.6 (30/153) 0.58 (0.37–0.91)	4.8 (54/1,116) 1.12 (0.68–1.61)	5.2 (30/574) 0.84 (0.41–1.72)	5.5 (14/256) 0.84 (0.41–1.72)	9.2 (12/131) 0.84 (0.41–1.72)
NCI <sup>‡</sup> RR (95% CI)	11.9 (35/295) 0.69 (0.43–1.10)	17.2 (26/151) 0.69 (0.43–1.10)	5.6 (61/1,093) 1.12 (0.68–1.61)	5.0 (28/559) 1.12 (0.68–1.61)	7.1 (18/252) 0.84 (0.41–1.72)	8.8 (11/125) 0.84 (0.41–1.72)

17P, 17 $\alpha$ -hydroxyprogesterone caproate; PTB, preterm birth; RR, relative risk; NCI, neonatal composite index. Data are % (n/N) unless otherwise specified. N=number of patients in the specified category; N for PTB=number of patients in the treatment group with nonmissing delivery data (Meis and PROLONG) or with missing delivery data who were known to be pregnant at the specified gestational age (PROLONG); for NCI=number of liveborn neonates of patients in the treatment group.

\* See Table 2 in reference 1, Meis et al, for Meis preterm birth data.

<sup>†</sup> AMAG Pharmaceuticals, Inc. Makena, prescribing information. 2018 (for Meis NCI data).

<sup>‡</sup> See Table 2 in reference 3, Blackwell et al, for PROLONG PTB data, Figure S2 for U.S. PROLONG PTB data, and Table 3 for PROLONG NCI data.

<sup>§</sup> AMAG Pharmaceuticals, Inc. Advisory Committee Meeting, October 29, 2019. Slide #CO60 (for U.S. PROLONG NCI data).

<sup>||</sup> RR and CI for the Meis study are adjusted for the number of prior PTBs. RR and CI for the PROLONG study are adjusted for gestational age at randomization stratum.

<sup>¶</sup> The CI is a 96.5% CI to adjust for the interim analysis.

<sup>#</sup> NCI includes death, respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, necrotizing enterocolitis, and proven sepsis.

associated with long-term health consequences was reassuring.

## PROLONG TRIAL

PROLONG was an international, double-blind, randomized, placebo-controlled trial in women with a history of spontaneous preterm birth and was conducted from 2009 through 2018.<sup>3</sup> The study was designed in conjunction with the FDA to serve as a confirmatory trial, with preterm birth at less than 35 weeks of gestation and a neonatal composite index as co-primary endpoints. The study enrolled approximately 1,700 women, more than 75% in countries outside the United States (eg, Bulgaria, the Czech Republic, Hungary, Italy, Russia, Ukraine, and Spain). Notably, no site that participated in the Meis study participated in PROLONG, presumably because of ethical concerns of a placebo-controlled trial when a standard of care existed.

PROLONG did not demonstrate a statistically significant difference between the arms for the co-primary endpoints; the incidence of preterm birth at less than 35 weeks of gestation (17 $\alpha$ -hydroxyprogesterone caproate-treated group 11.0% vs placebo 11.5%,  $P=.72$ ) and the percentage of neonates with the morbidity and mortality composite index (5.6% vs 5.0%,  $P=.73$ ). There were also no differences between treatments in preterm birth rates at less than 37 and less than 32 weeks of gestation.

Despite the same eligibility criteria, the Meis and PROLONG trials enrolled vastly different patient populations.<sup>1,3</sup> When comparing demographics and baseline characteristics, the differences among socioeconomic status surrogates linked to higher rates of preterm birth (eg, substance use, education level, race) stand out, with most differences driven by patients enrolled in PROLONG outside the United States. Given the health disparities that exist in obstetric care and preterm birth rates in the United States, these differences are noteworthy.

The PROLONG trial results appear to have been significantly influenced by the patient enrollment outside the United States, with a lower background preterm birth rate and different access to prenatal care than in the United States. Furthermore, both study groups had a lower than expected preterm birth rate and neonatal composite index. The sample size estimates were based on the Meis trial, which had higher event rates for both preterm birth and neonatal morbidity. Given the observed event rates, PROLONG would have required 3,600 women and 6,000 women, respectively, to achieve 90% power for preterm birth at less than 35 weeks of gestation and the neonatal composite outcome.<sup>3</sup>

Although there are inherent issues with subgroup analyses (eg, PROLONG was not powered for subgroup analysis), it is worthwhile to consider the U.S. subgroup. In the U.S. PROLONG population,

preterm birth rates were higher than those outside the United States. Importantly, the direction and magnitude of the RR for preterm birth at less than 32 weeks of gestation and the neonatal composite index were similar to the Meis study, although these results were not statistically significant.

The key safety outcome of PROLONG was to rule out a doubling of risk of fetal or early infant death in the 17 $\alpha$ -hydroxyprogesterone caproate group.<sup>15</sup> This endpoint specifically addressed the FDA's concern of a potential safety signal relative to the numerically higher rate of both miscarriage and stillbirth from the Meis study. In both treatment arms, the rate of fetal or early infant death was low, 1.7% and 1.9% in the 17 $\alpha$ -hydroxyprogesterone caproate and placebo groups, respectively. Importantly, because some published data suggest that 17 $\alpha$ -hydroxyprogesterone caproate increases rates of gestational diabetes,<sup>16</sup> the rates observed in the PROLONG study were similar (3.1% in 17 $\alpha$ -hydroxyprogesterone caproate and 3.6% in the placebo group).<sup>3</sup> Additional adverse events were low and comparable between treatment groups.

After the publication of PROLONG, both the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine issued updated interim guidance. The American College of Obstetricians and Gynecologists stated that it is not changing clinical recommendations at this time and continues to recommend 17 $\alpha$ -hydroxyprogesterone caproate.<sup>17</sup> The Society for Maternal-Fetal Medicine noted that it is reasonable for health care professionals to use 17 $\alpha$ -hydroxyprogesterone caproate in women with a risk profile more similar to those in the Meis trial.<sup>18</sup>

## CONCLUSIONS

Although the results of PROLONG failed to confirm the findings of the Meis trial, it is of paramount importance to dispel misconceptions, and for the medical community to understand the original trial. The Meis trial was rigorously designed and conducted, with highly statistically significant results that should not be undermined by PROLONG. If both Meis and PROLONG are valid trials, the more important question to address is which of the studies is more generalizable to the U.S. patient population. The predominant enrollment outside the United States in PROLONG (necessary because 17 $\alpha$ -hydroxyprogesterone caproate had been incorporated into routine U.S. clinical care), and the marked differences in the PROLONG trial population compared with Meis, undoubtedly factor into the discordant results.

It would be detrimental to high-risk pregnant patients to inappropriately prioritize the results of

PROLONG over that of a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network trial. The lower-risk population in PROLONG leads us to believe that it is more likely that PROLONG was underpowered based on the observed outcome rates, and therefore a false-negative study, rather than the Meis trial being a false-positive study.

A few nonrandomized U.S. studies of 17 $\alpha$ -hydroxyprogesterone caproate in women with prior spontaneous preterm birth have been published since the Meis trial, with conflicting results.<sup>19,20</sup> The observational nature of these studies may have introduced bias making their interpretation difficult. We believe it is critical for the Makena sponsor to identify feasible, timely and appropriate ways to generate additional U.S.-based effectiveness data to better elucidate the particular risk factors—beyond simply a history of spontaneous preterm birth—that predict who will benefit most from 17 $\alpha$ -hydroxyprogesterone caproate in the United States. Until then, the best approach is to use 17 $\alpha$ -hydroxyprogesterone caproate in women who are similar to those who participated in the Meis trial, which was definitively positive in this population.

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