17 α-Hydroxyprogesterone Caproate (Makena®) for Women with Singleton Pregnancy and Prior Spontaneous Preterm Birth

FDA Advisory Committee Meeting

Division of Bone, Reproductive and Urologic Products

AMAG Pharmaceuticals, Inc.

October 29, 2019

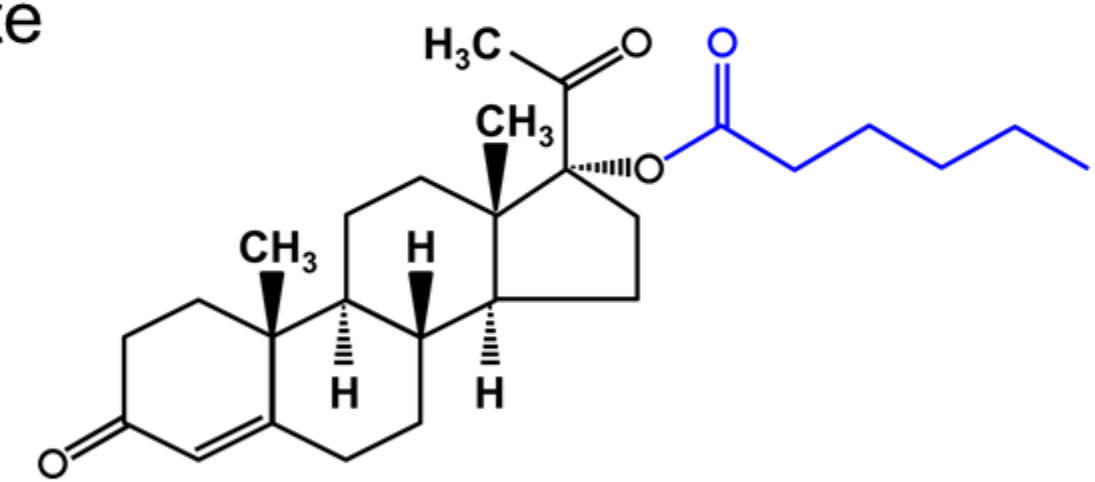
Introduction

Julie Krop, MD
Chief Medical Officer
EVP Clinical Development and Regulatory Affairs
AMAG Pharmaceuticals, Inc.

Makena and Generic 17P Formulations: Only FDA-Approved Therapy to Reduce Recurrent Preterm Birth

- Synthetic progestin
- Active pharmaceutical ingredient: 17 α-hydroxyprogesterone caproate
  - Not same as progesterone
- Proposed MOA
  - Decreases inflammation
  - Inhibits uterine activity
- Not metabolized into androgens, estrogen, or corticosteroids

17P



17P is an Orphan Drug

- Indicated for women with singleton pregnancy and prior spontaneous preterm birth
- Subset of all preterm birth
  - Affects ~ 3% (130,000) of all pregnancies
- Orphan Drug designation received

17P's Prolonged Half-Life Allows Once-Weekly Administration

- 17P treatment
  - Begins between 16^0 and 20^6 weeks pregnancy
  - Continued until 37 weeks or delivery
- Previously only available through pharmacy compounding

17P Approved Under Subpart H Accelerated Approval Pathway in 2011

- Subpart H applies to therapies that
  - Treat serious or life-threatening conditions with unmet need
  - Demonstrate efficacy on surrogate endpoint reasonably likely to predict clinical benefit
- Preterm birth (PTB) < 37 weeks accepted surrogate endpoint
  - Multiple studies established preterm infants at high risk of morbidity and mortality
- Required confirmatory trial of clinically relevant endpoints

FDA 21CFR314

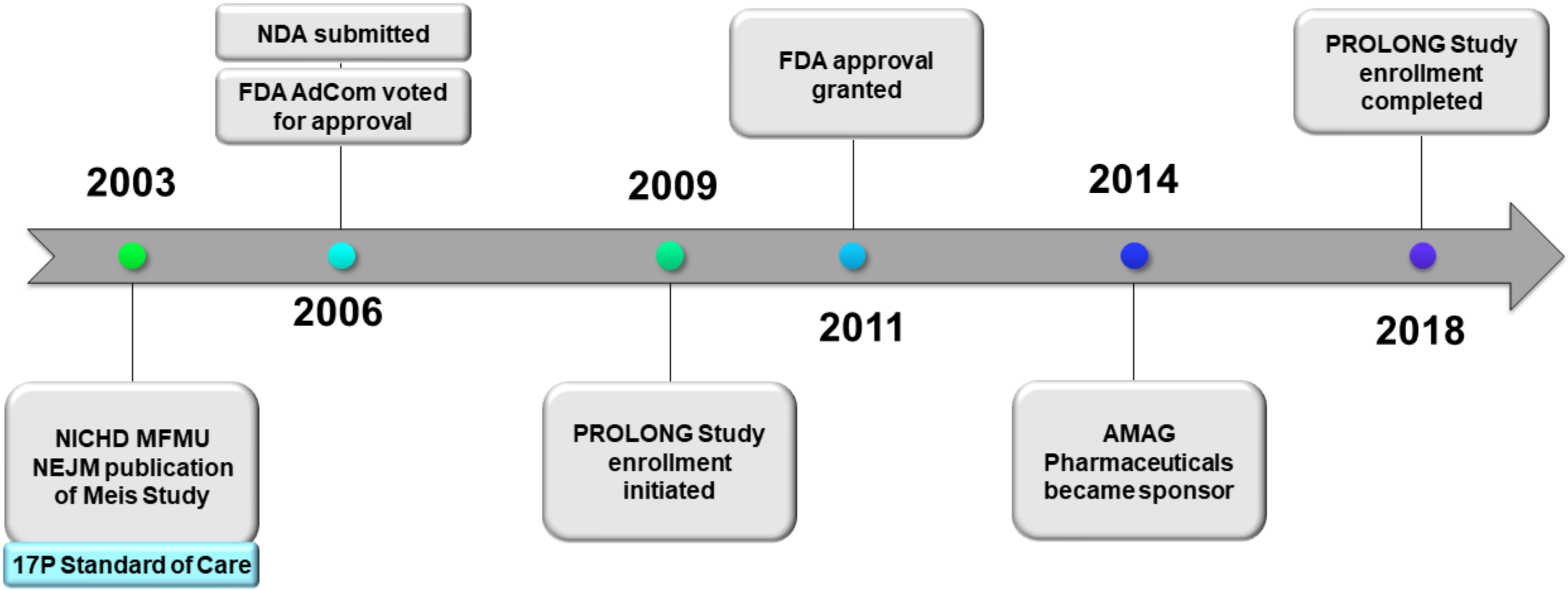
17P Approved Based on Compelling Results of Study 002 (Meis)

- Meis study conducted through NICHD MFMU
  - All US population
- Established substantial evidence of 17P efficacy
  - Highly statistically significant reduction in PTB rate vs. placebo < 37 weeks (p=0.0003)
  - Also reduced PTB < 35 weeks and < 32 weeks
    - Associated with highest incidence of neonatal complications

Meis, NEJM, 2003

NICHD = National Institute of Child Health and Human Development Health; MFMU = Maternal Fetal Medicine Units

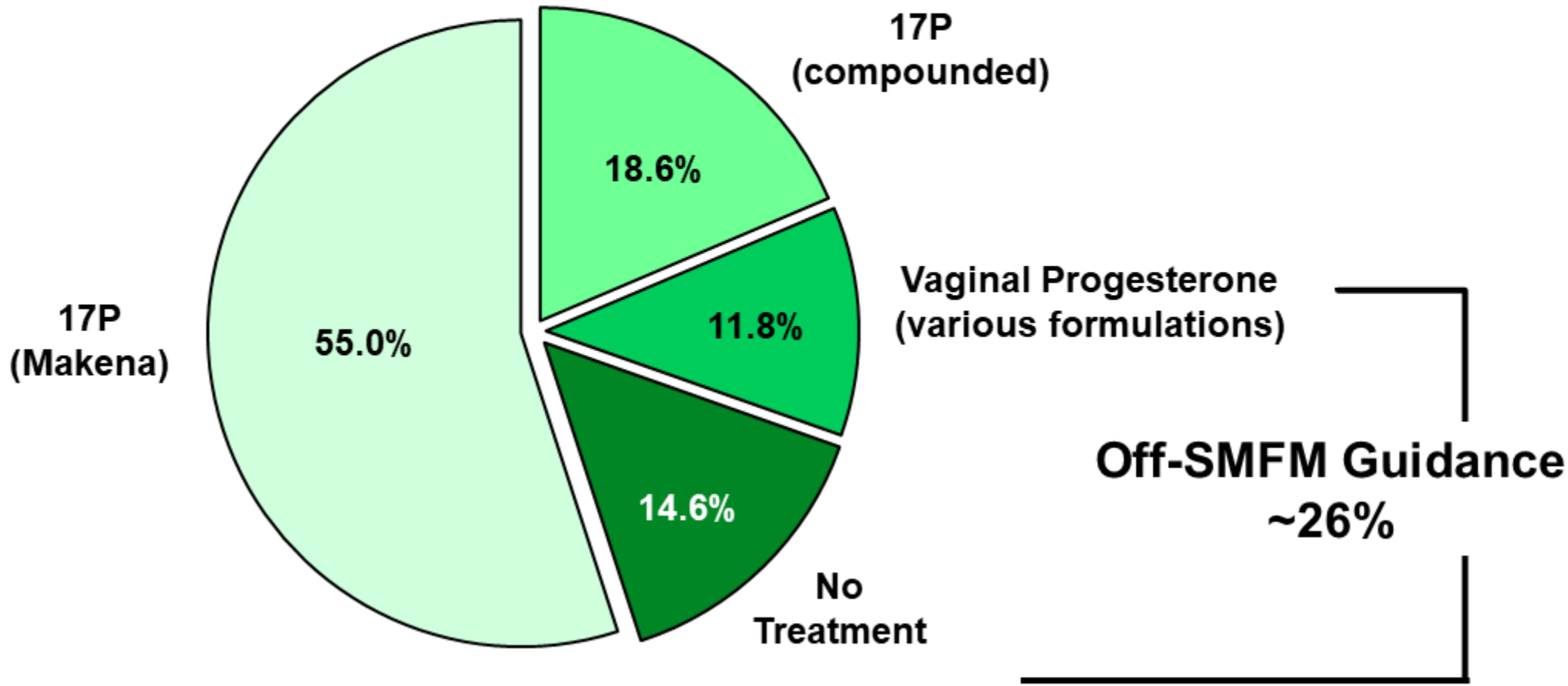
Key Events in 17P Approval Pathway



Preterm Birth is Major US Public Health Concern

- Leading cause of infant morbidity and mortality
- Can lead to serious long-term health complications
- Recurrent PTB represents only a small proportion of all PTBs

~75% of Indicated Patients Treated with 17P in 2017



Gallagher AJP Reports, 2018

Generalizability of PROLONG Efficacy Data to US is Challenging

- Key differences in study populations and background rates
- Meis trial enrolled in US inner city academic medical centers
  - ~30% background rate of PTB < 35 weeks
- PROLONG enrolled population with low PTB rate
  - ~11% background rate of PTB < 35 weeks
- Strong efficacy from Meis and other clinical trials along with favorable safety profile

Agenda

Clinical Background / Unmet Need	**Michelle Y. Owens, MD** Professor and Medical Director School of Medicine Department of Obstetrics and Gynecology The University of Mississippi Medical Center
Meis Study Design and Results	**Baha M. Sibai, MD** Professor Department of Obstetrics, Gynecology and Reproductive Sciences McGovern Medical School-UTHealth Principal Investigator, MFMU
PROLONG Efficacy and Safety	**Laura A. Williams, MD, MPH** Sr Vice President, Clinical Development AMAG
Clinical Perspective / Benefit / Risk	**Sean C. Blackwell, MD** Professor and Chair Department of Obstetrics, Gynecology, and Reproductive Sciences McGovern Medical School-UTHealth Principal Investigator, MFMU
AMAG Actions Following PROLONG	**Julie Krop, MD** CMO, EVP Clinical Development and Regulatory Affairs, AMAG

Additional Expert Consultants

Hugh Miller, MD	Principal Investigator, PROLONG Founder, Watching Over Mothers & Babies (WOMB)
Anita Das, PhD	Statistician AD Stat Consulting
Eugene Poggio, PhD	Statistician Biostatistical Consulting

Clinical Background and Need

Michelle Y. Owens, MD
Professor and Medical Director
School of Medicine Department of Obstetrics and Gynecology
The University of Mississippi Medical Center

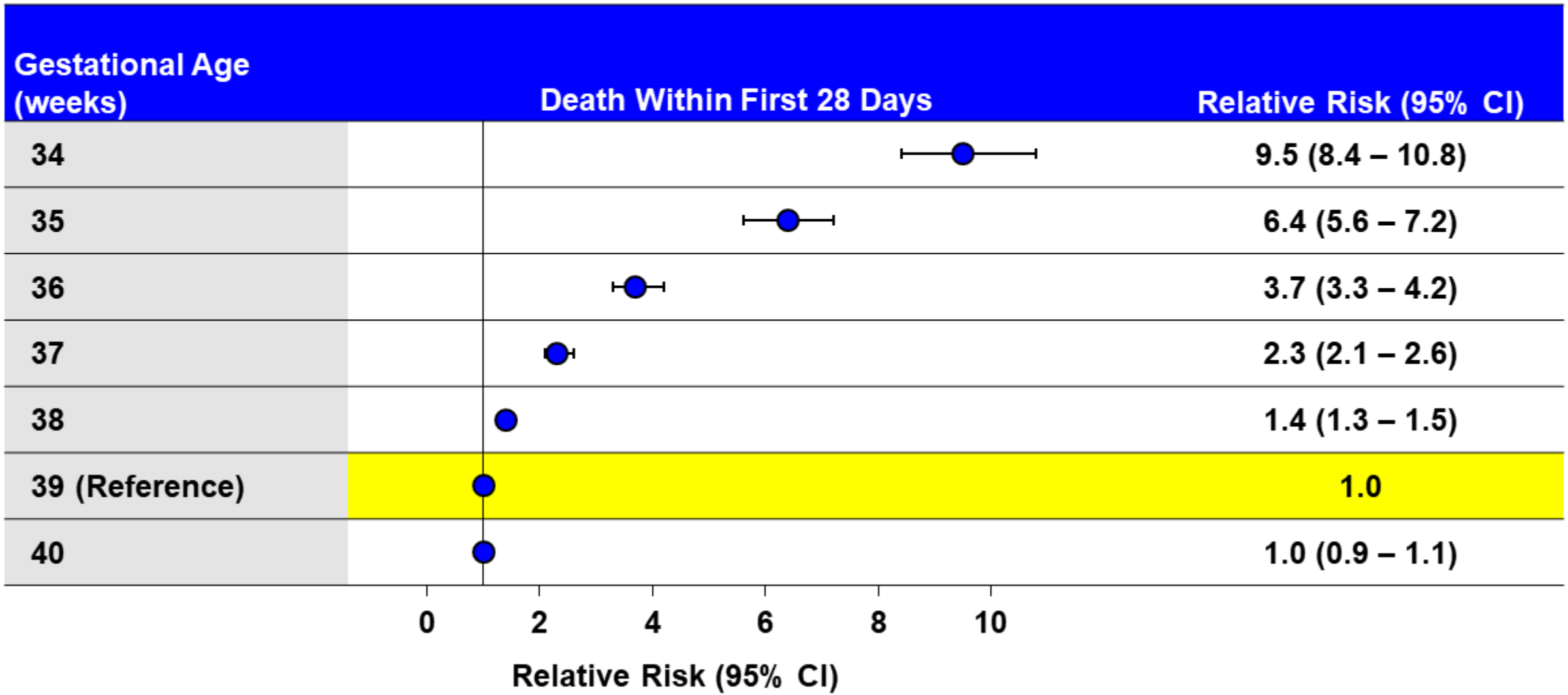
Preterm Birth: Significant Problem in US

- 1 in 10 babies born prematurely in US
- Disadvantaged women – socioeconomically, educationally, limited healthcare access
- PTB puts infant at substantial risk
- Critical to have access to FDA-approved 17P for subset of women with prior PTB

What is at Stake: The Health of Infants

Photo: https://nyuwinthrop.org/newsroom/cornerstone/winter-spring-2018/nyu-winthrop-neonatal-breakthroughs/

Neonatal and Infant Mortality Significantly Higher for Babies Born at 34 – 36 Weeks Gestation



Reddy, et al., Pediatrics 2009

Preterm Birth and Complications #1 Cause of Death of Babies in US

Short-Term Complications

- Respiratory distress syndrome (RDS)
- Bronchopulmonary dysplasia (BPD)
- Intraventricular hemorrhage (IVH)
- Periventricular leukomalacia (PVL)
- Necrotizing enterocolitis (NEC)
- Apnea
- Jaundice
- Anemia
- Infections

Long-Term Consequences

- Chronic respiratory problems
- Rehospitalization
- Metabolic disorders
- Neurodevelopmental problems
  - Cerebral palsy
  - Cognitive deficits
  - Hearing and vision impairment
  - Learning disorders

Spong CY. Obstet Gynecol 2003, Stoll, et al, Pediatrics, 2010, Gyamfi-Bannerman, NEJM, 2016

Babies Born at Lower Gestational Ages Have Higher Rates of Neonatal Morbidity and Mortality

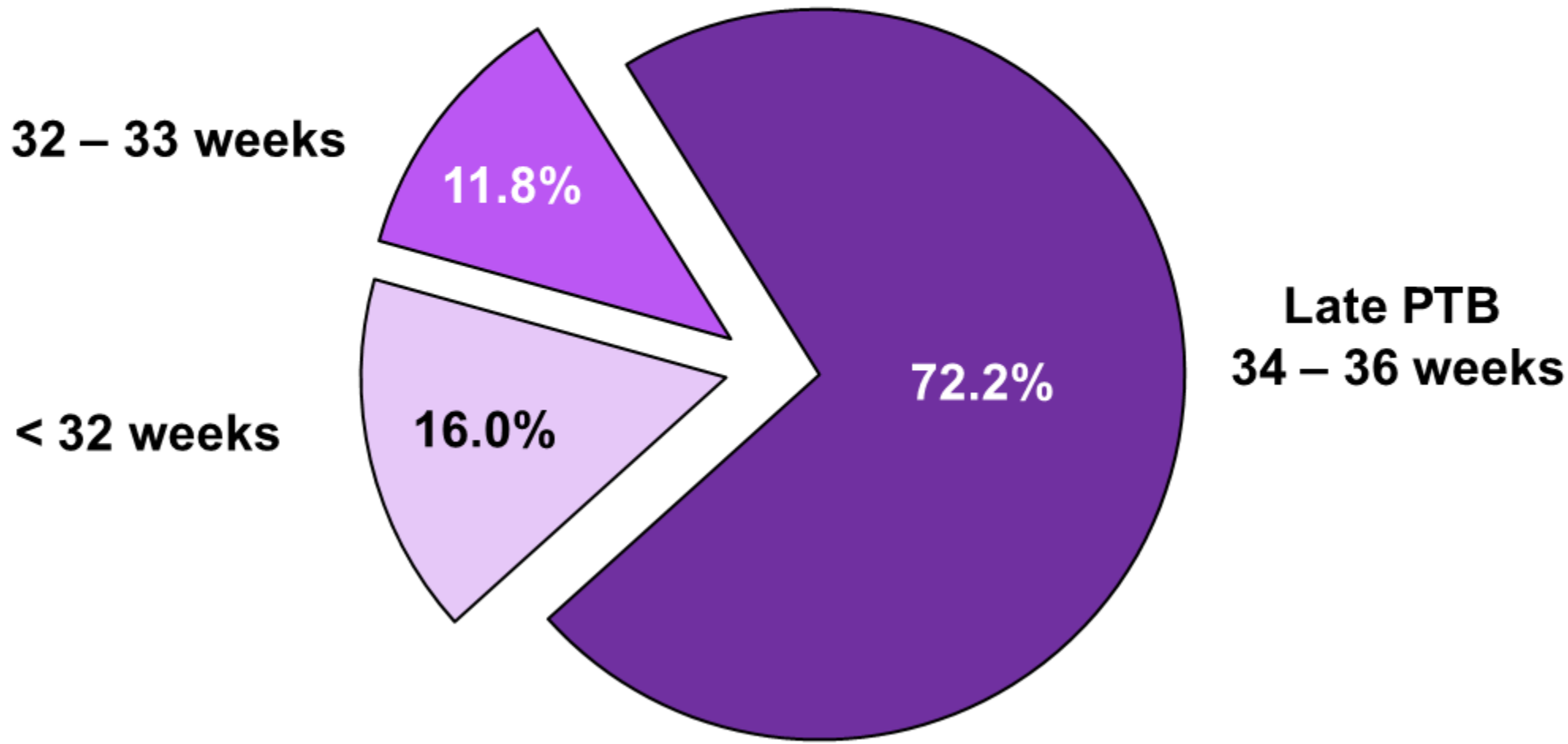
Delivery Gestational Age (Weeks)	Death n (%)	Major Morbidity n (%)	Death or Major Morbidity n (%)
< 32	117 (3)	448 (11)	565 (14)
< 35	119 (2)	560 (9)	679 (11)
36	0 (0)	55 (2)	55 (2)

Major morbidities

- Persistent pulmonary hypertension
- IVH grade 3 / 4
- Seizures
- Hypoxic-ischemic encephalopathy
- NEC stage II / III
- Bronchopulmonary dysplasia

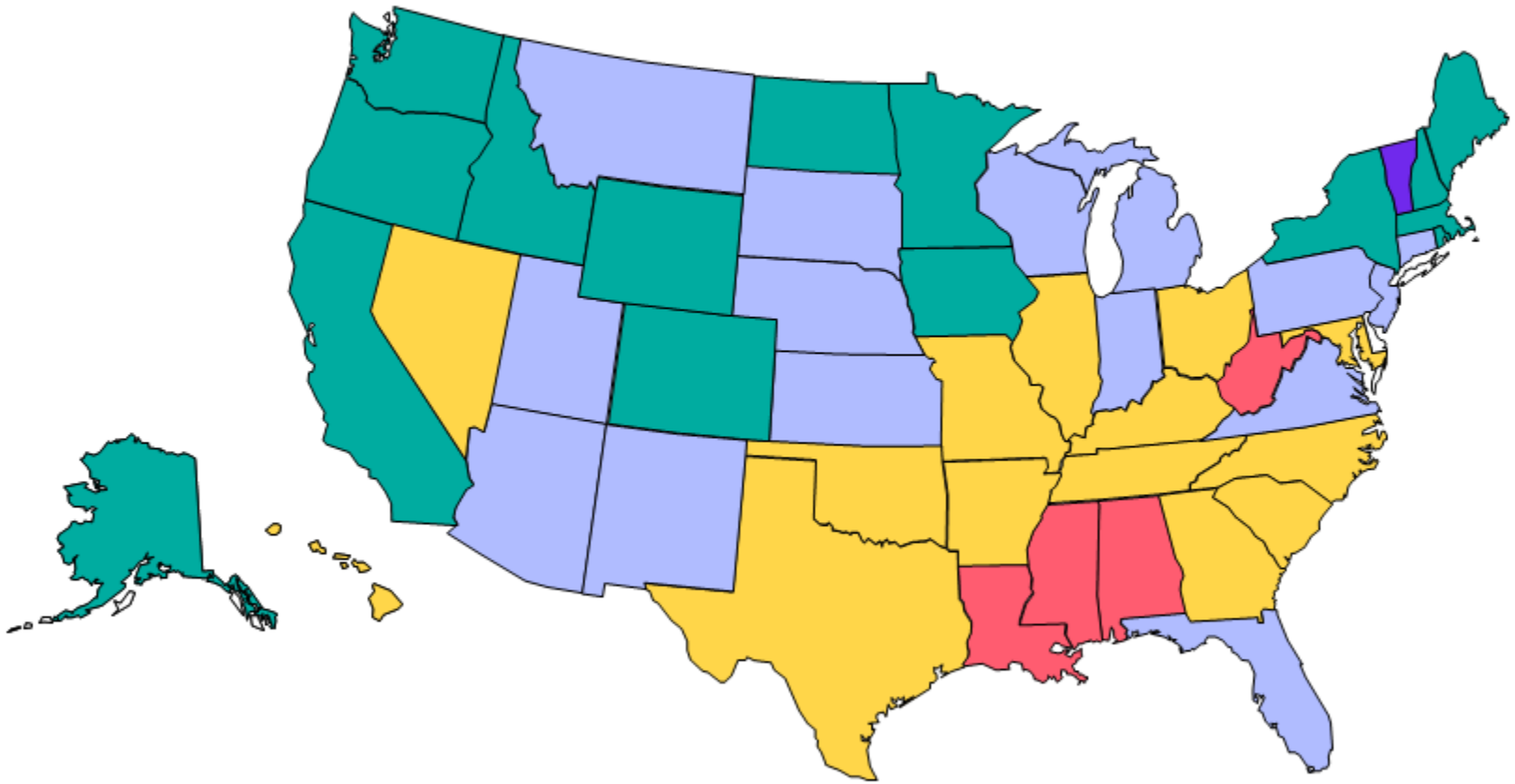
Manuck, AJOG 2016

Preterm Birth by Gestational Age



National Vital Statistics Reports “Births: Final Data for 2017”

US Ranks 131st of 184 Countries for Preterm Birth



Preterm Birth Rate

- Grade A: ≤ 8.1%
- Grade B: 8.2 – 9.2%
- Grade C: 9.3 – 10.3%
- Grade D: 10.4 – 11.4%
- Grade F: ≥ 11.5%

March of Dimes, 2018 Premature Birth Report Card
National Vital Statistics Reports "Births: Preliminary Data for 2015"

Risk Factors for Singleton Preterm Birth

Maternal Characteristics

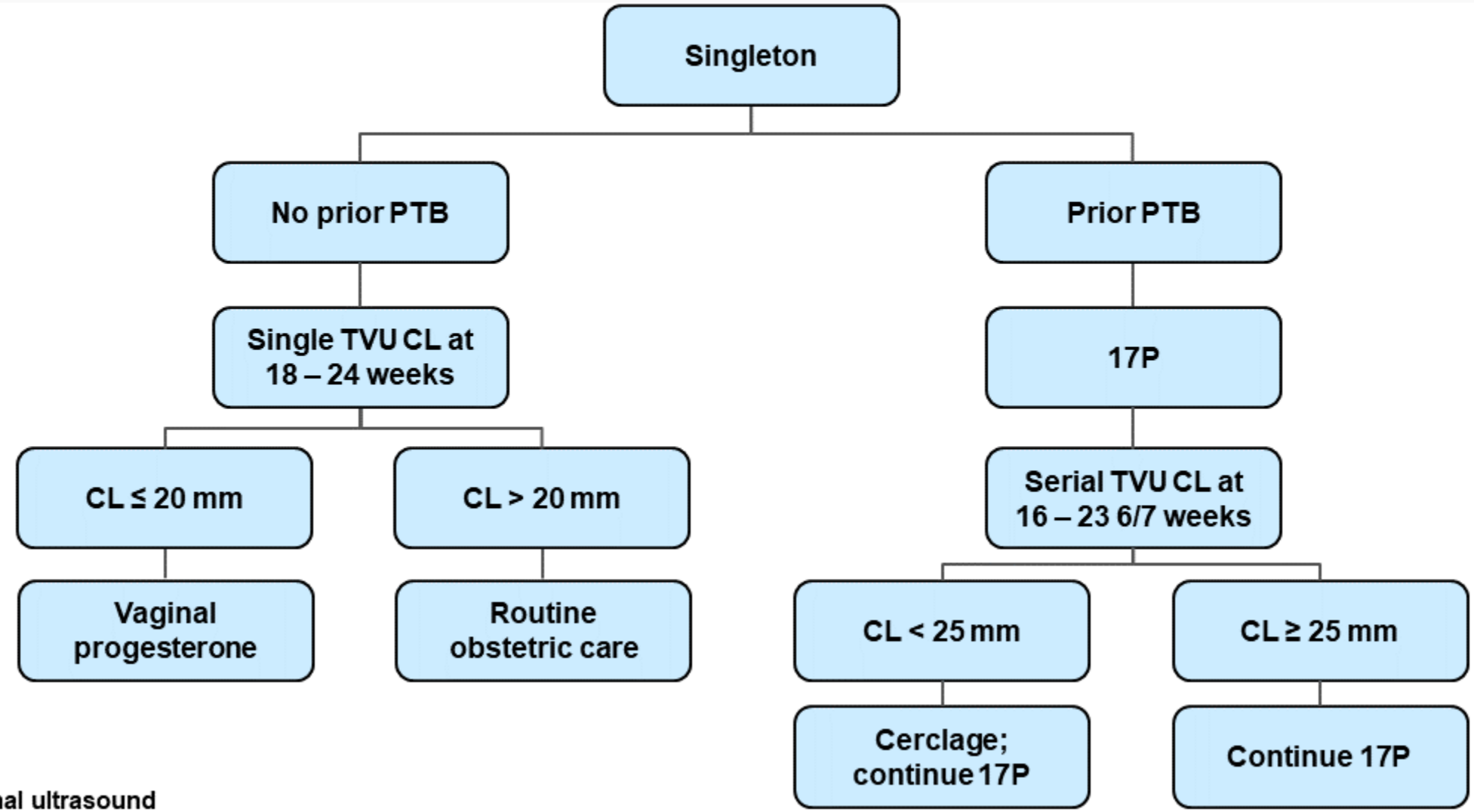
- **History of SPTB < 37 weeks**
- Short cervix
- African American
- Genitourinary infections
- Short intervals between pregnancies
- Advanced maternal age
- Low pre-pregnancy BMI

Social Determinants of Health

- Low socioeconomic status (i.e., education, income, marital status, nutrition)
- Stress (e.g., domestic violence, housing instability)
- Nicotine, alcohol, or drug use

Goldenberg Lancet 2008
ACOG Committee Opinion #729 2018

SMFM 2012 Clinical Guidelines



TVU = transvaginal ultrasound

SMFM Publications Committee, with assistance of Vincenzo Berghella AJOG 2012

Preterm Birth is Major US Public Health Concern, Disproportionately Affecting Lower SES Groups

- Infants spend weeks or months in NICU
- Must reduce preterm birth rate and prevent complications
- Physicians and patients need continued access to 17P

Meis Study Design and Results

Baha Sibai, MD

Professor, Department of Obstetrics, Gynecology and Reproductive Sciences

McGovern Medical School-UTHealth

Investigator, MFMU Network

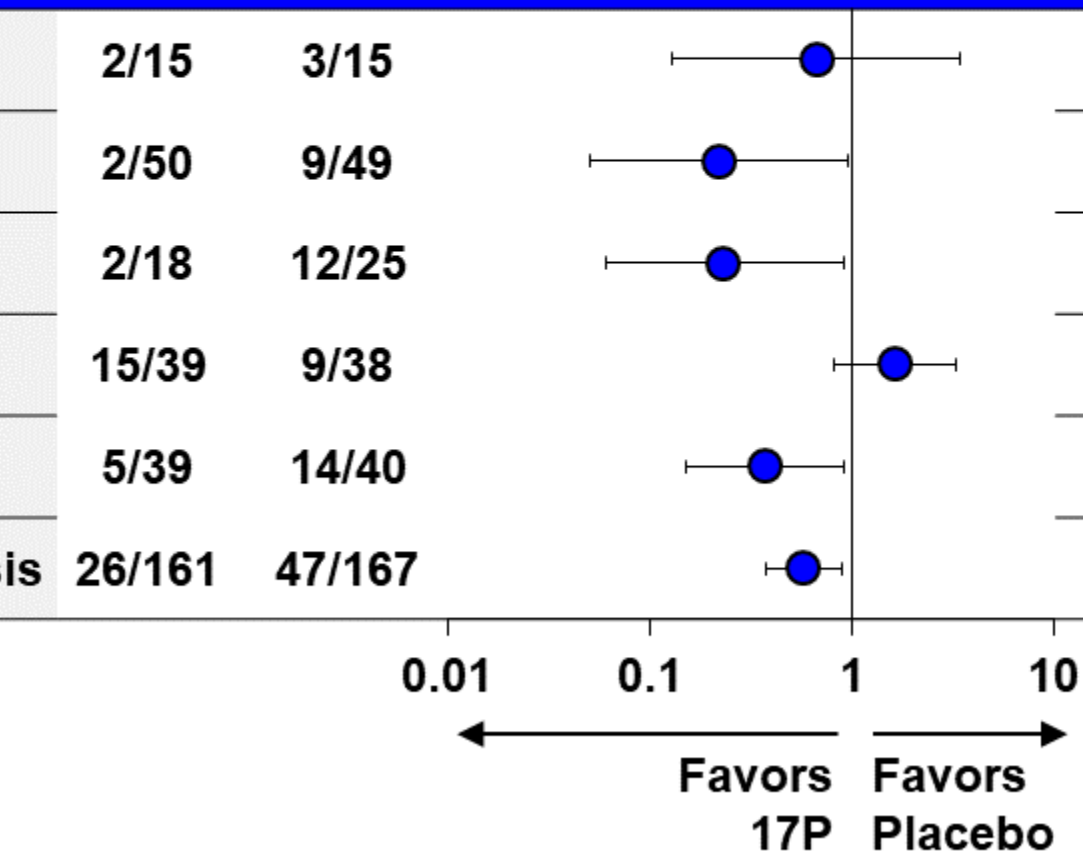
MFMU Network Established to Promote Rigorous Clinical Trials in Pregnancy

- Primary aim to reduce rate of preterm birth
- Rigorous process to select centers and studies
  - Network centers with ≥ 40% high-risk obstetric population
  - Diverse patient populations

MFMU established in 1986 by NICHD

Meta-Analysis of 17P Demonstrated 42% Reduction in Recurrent PTB

Study	17P n/N	Placebo n/N	17P vs. Placebo Relative Risk (95% CI)
LeVine (1964)	2/15	3/15	0.67 (0.13 – 3.44)
Papiernick-Berkhauer (1970)	2/50	9/49	0.22 (0.05 – 0.96)
Johnson (1975)	2/18	12/25	0.23 (0.06 – 0.91)
Hartikainen-Sorri (1980)	15/39	9/38	1.62 (0.81 – 3.25)
Yemini (1985)	5/39	14/40	0.37 (0.15 – 0.92)
Meta-Analysis	26/161	47/167	0.58 (0.38 – 0.90)



Adapted from Keirse, BJOG 1990

Meis Study Designed to Evaluate 17P in Women with History of SPTB

- Women ≥ 18 years
- Singleton pregnancy
- Hx of previous singleton SPTB
- Enrolled 16^0 - 20^6 week of pregnancy

Randomization 2:1

17P
250 mg IM q7 days

Weekly injections of study drug until 36^6 week of pregnancy OR delivery

Placebo (vehicle)
IM q7 days

Meis, et al. NEJM. 2003

Meis Study High-Risk Population for Preterm Birth

Demographics and baseline characteristics	17P (N=310)	Vehicle (N=153)
Age (years), mean ± SD	26.0 ± 5.6	26.5 ± 5.4
> 1 Previous PTB	27.7%	41.2%
Black or African American	59.0%	58.8%
White	25.5%	22.2%
Non-Hispanic or Latino	86.1%	83.0%
Married or living with partner	51.3%	46.4%
BMI before pregnancy (kg/m^2), mean ± SD	26.9 ± 7.9	26.0 ± 7.0
Educational level (years), mean ± SD	11.7 ± 2.3	11.9 ± 2.3
Gestational age of qualifying delivery (weeks), mean ± SD	30.6 ± 4.6	31.3 ± 4.2
Any substance use* during pregnancy	27.4%	23.5%

2 – 4% of patients were Asian, 2 – 3% were Other (Native Hawaiian/Pacific Islander, American Indian or Alaska native, mixed race and other)
*Smoking, alcohol or illicit drugs

Meis et al. NEJM 2003

Meis Study Primary Outcome: Preterm Delivery < 37 Weeks

- < 37 weeks gestation current definition of prematurity
- Sample size N = 500 women
  - Based on expected recurrent PTB rate of 37% in placebo group
  - Expected 1/3 reduction of recurrence with 17P

Meis, et al. NEJM 2003

Meis Study: High Rate of Completion and Compliance

	17P (N=310)	Vehicle (N=153)
Completed study, %	98.7%	100%
Number of injections (mean)	14.1	13.7
Full compliance (< 10 days between doses)	91.5%	91.5%

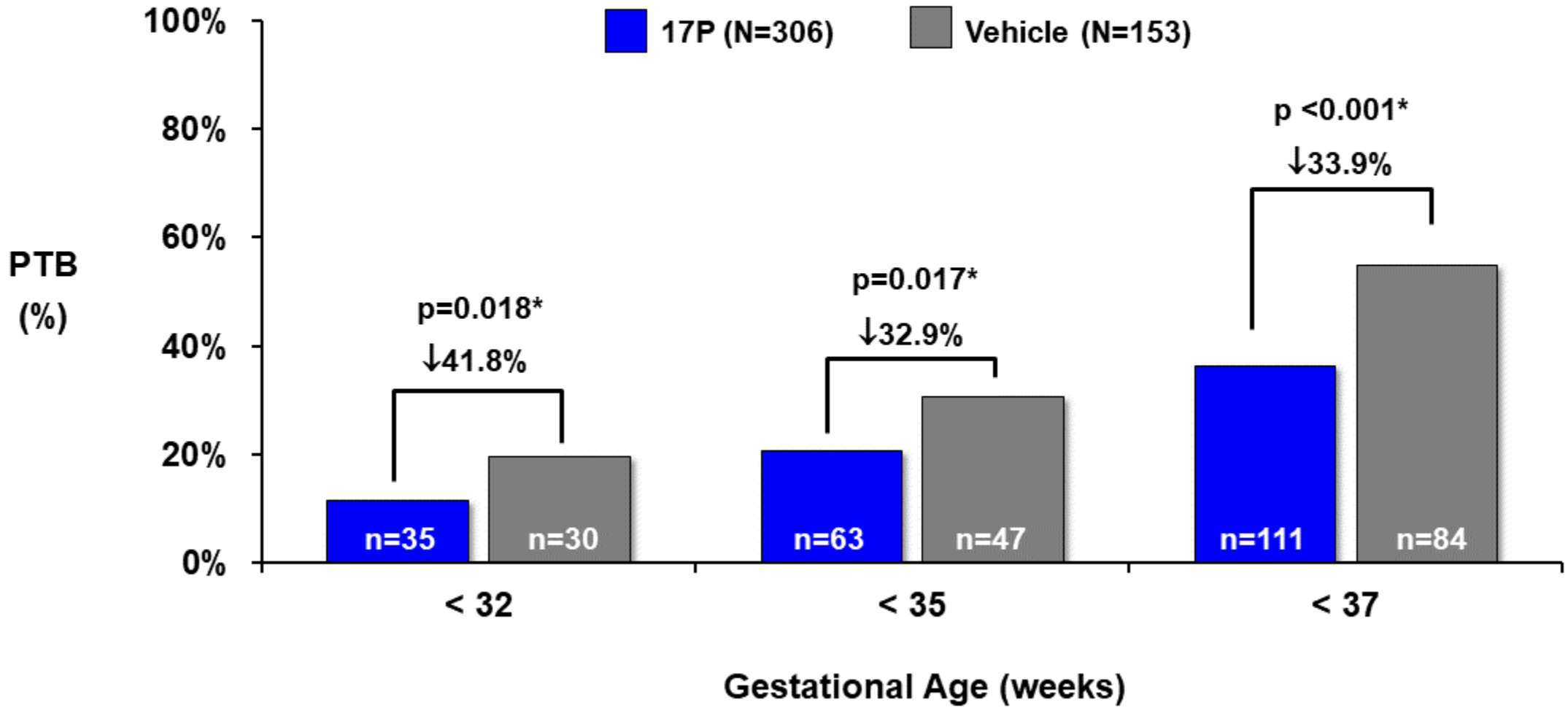
Meis, et al. NEJM 2003

Meis Study Stopped Early Due to Clear Evidence of 17P Benefit

- Study conducted from 1999 – 2002
- Planned interim analysis with pre-specified stopping criterion for efficacy (p=0.015)
  - Study halted at second interim analysis
  - Data available for 93% of planned sample (463/500)

Meis, et al. NEJM 2003

Meis Study Demonstrated Significant Reduction of PTB with 17P Compared to Vehicle

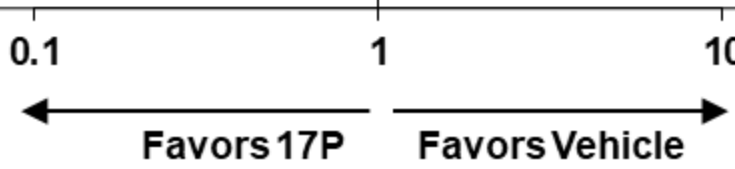


*p-values unadjusted for imbalance in prior PTBs

Meis, et al. NEJM 2003

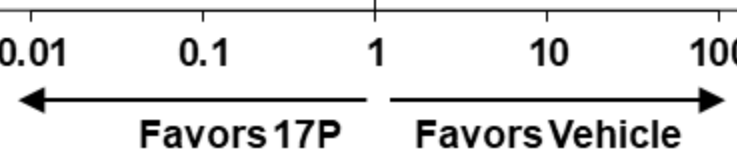
Meis Study: Consistent Reduction in PTB < 37 Weeks with 17P Across Subgroups

Subgroup	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
All patients	111/310	84/153	0.66 (0.54, 0.81)
> 1 Prior PTB	41/86	44/63	0.68 (0.52, 0.90)
Only 1 prior PTB	70/220	40/90	0.72 (0.53, 0.97)
Black	64/181	47/90	0.68 (0.51, 0.90)
Non-Black	47/125	37/63	0.64 (0.47, 0.87)
Unmarried	50/150	43/82	0.64 (0.47, 0.86)
Married	61/156	41/71	0.68 (0.51, 0.90)
Smoke or substance use	28/85	23/36	0.52 (0.35, 0.76)
No smoke or substance use	83/221	61/117	0.72 (0.57, 0.92)
Education ≤ 12 years	80/223	55/103	0.67 (0.52, 0.86)
Education > 12 years	31/83	29/50	0.64 (0.45, 0.93)



17P Reduced Neonatal Complications vs. Placebo

Subgroup	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
Necrotizing enterocolitis	0/305	4/152	0 (p<0.05)
IVH Any Grade	4/305	8/153	0.25 (0.08, 0.82)
Retinopathy	5/305	5/152	0.50 (0.15, 1.70)
Bronchopulmonary dysplasia	4/305	5/152	0.40 (0.11, 1.46)
Ventilatory support	26/303	22/151	0.59 (0.35, 1.00)
Respiratory distress syndrome	29/305	23/152	0.63 (0.38, 1.05)
Transient tachypnea	11/305	11/152	0.50 (0.22, 1.12)
Supplemental oxygen	45/303	36/151	0.62 (0.42, 0.92)
Proven sepsis	9/305	4/152	1.12 (0.35, 3.58)
Patent ductus arteriosus	7/305	8/151	0.43 (0.16, 1.17)



Meis, et al., NEJM 2003

Reduced Neonatal Intensive Care Unit (NICU) Admissions and Days With 17P Compared to Vehicle

	17P	Vehicle	17P vs Vehicle
Admitted to NICU, n/N (%)	82/295 (27.8%)	55/151 (36.4%)	Relative Risk = 0.76 95% CI (0.58, 1.01)
Number of NICU days, mean ± SD	23.9 ± 32.4	29.2 ± 37.6	Δ = -5.3 95% CI (-17.5, 6.9)

Perinatal Death in Meis Study

Complication	17P (N=306)[1] n (%)	Vehicle (N=153) n (%)
Total deaths	19 (6.2)	11 (7.2)
Neonatal deaths	8 (2.6)	9 (5.9)
Miscarriages < 20 weeks gestation [2]	5 (2.4)	0
Stillbirth	6 (2.0)	2 (1.3)

1. 4 patients in the 17P group were lost to follow-up and perinatal death status could not be determined
2. Percentage adjusted for the number at risk (17P n=209, Vehicle n=107) enrolled at <20 weeks gestation.

Follow-Up Observational Study of Meis Trial Babies Confirmed Long-Term Safety of 17P

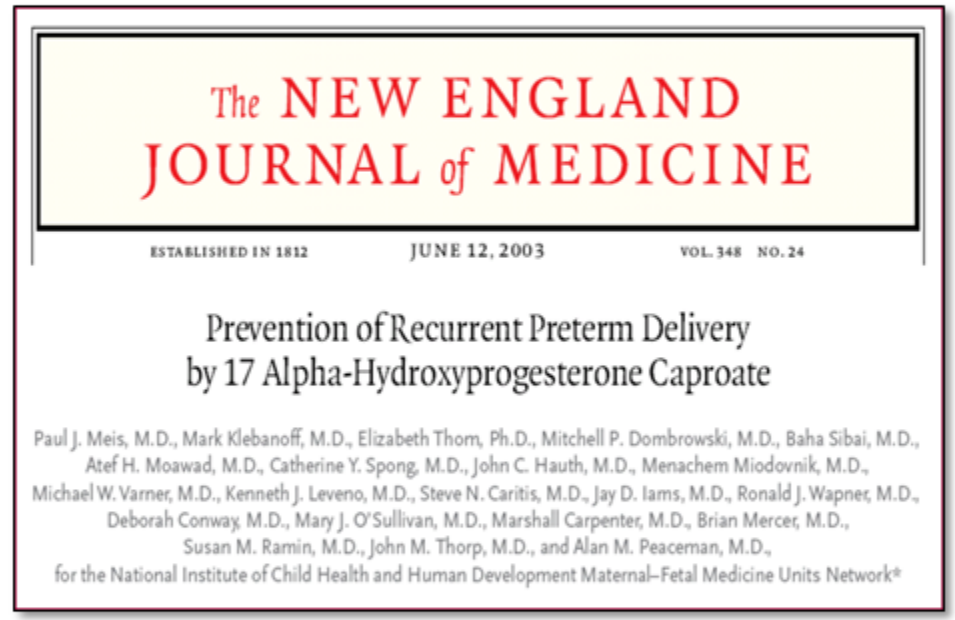
Ages and Stages Questionnaire (ASQ) Scored below cutoff on	17P (N=193)	Vehicle (N=82)	p-value
At least one area	27%	28%	0.9
Communication	11%	11%	0.9
Gross motor	3%	4%	0.7
Fine motor	21%	18%	0.6
Problem solving	10%	11%	0.9
Personal-social	4%	1%	0.4
Preschool Activities Inventory (PAI)			
Mean score for boys	67	67	0.3
Mean score for girls	33	32	0.5

Northen et al., Am J Obstet Gynecol, 2007

Median age (48 months, 41.8 to 55.0, 25th to 75th percentile)

Meis Results Considered Significant Advance in Obstetrics

- Relative risk
  - 0.66 (95% CI, 0.54 to 0.81)
- Absolute difference in preterm
  - 18.6%
- Number Need to Treat
  - 5.4 women to prevent 1 PTB



Meis, NEJM 2003

Meis Study Established Substantial Evidence of 17P Efficacy and Formed Foundation of PTB Prevention

- Clinicians have relied on 17P since 2003
- Only FDA-approved treatment to reduce risk of recurrent PTB since 2011
- Patients and clinicians need 17P as available option to prevent recurrent PTB

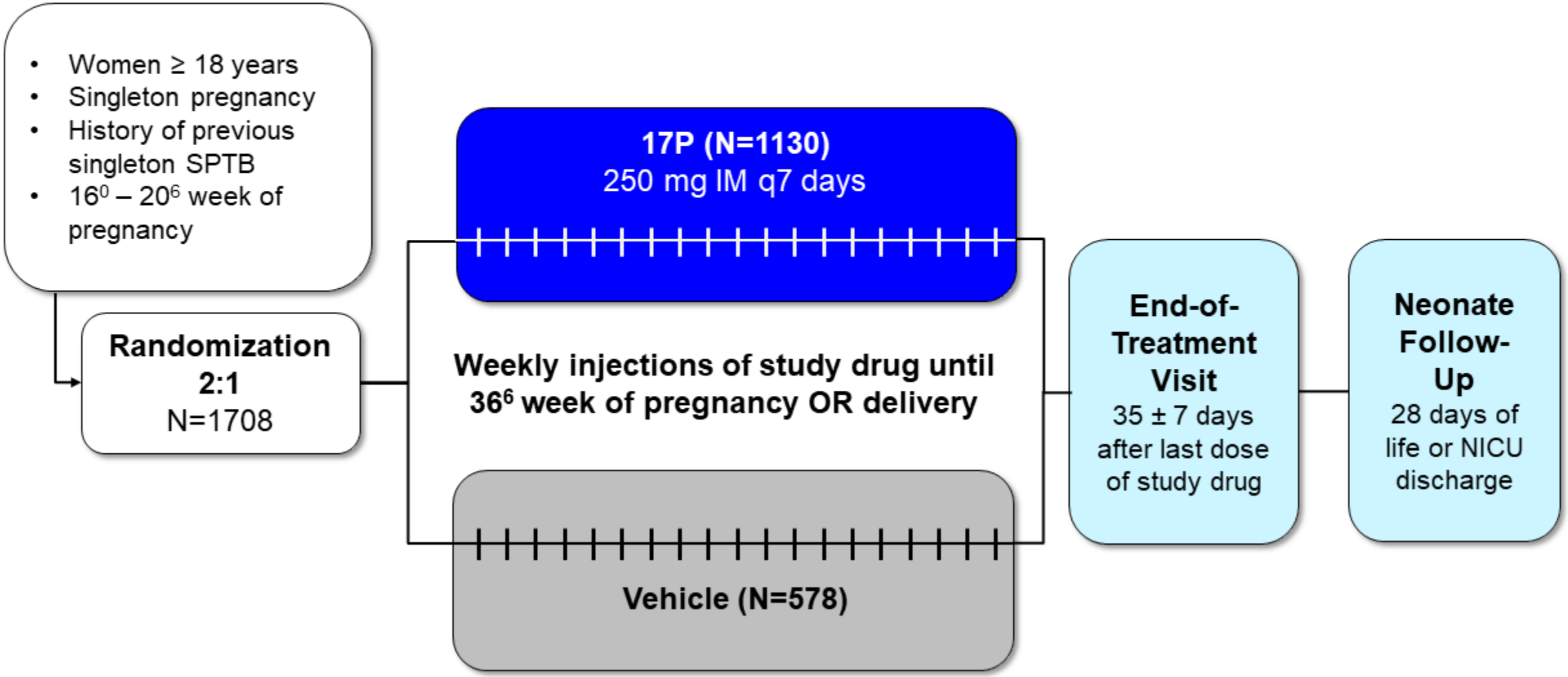
PROLONG: Efficacy and Safety

Laura A. Williams, MD, MPH
Senior Vice President, Clinical Development & Biostatistics
AMAG Pharmaceuticals, Inc.

PROLONG Designed to Mirror Meis Trial

- PROLONG did not meet its co-primary outcomes
  - Lower background PTB rates in PROLONG compared to Meis

PROLONG: Double-Blind, Vehicle-Controlled, Multi-Center, Randomized Study



PROLONG: Co-Primary Outcomes

- Reduction of PTB < 35 weeks gestation
- Reduction in composite neonatal morbidity and mortality index
  - Respiratory distress syndrome
  - Bronchopulmonary dysplasia
  - Grade 3 or 4 intraventricular hemorrhage
  - Necrotizing enterocolitis
  - Proven sepsis
  - Neonatal death

PROLONG: Key Secondary Efficacy and Primary Safety Outcomes

Secondary Outcomes

- Reduction of PTB by gestational age at delivery

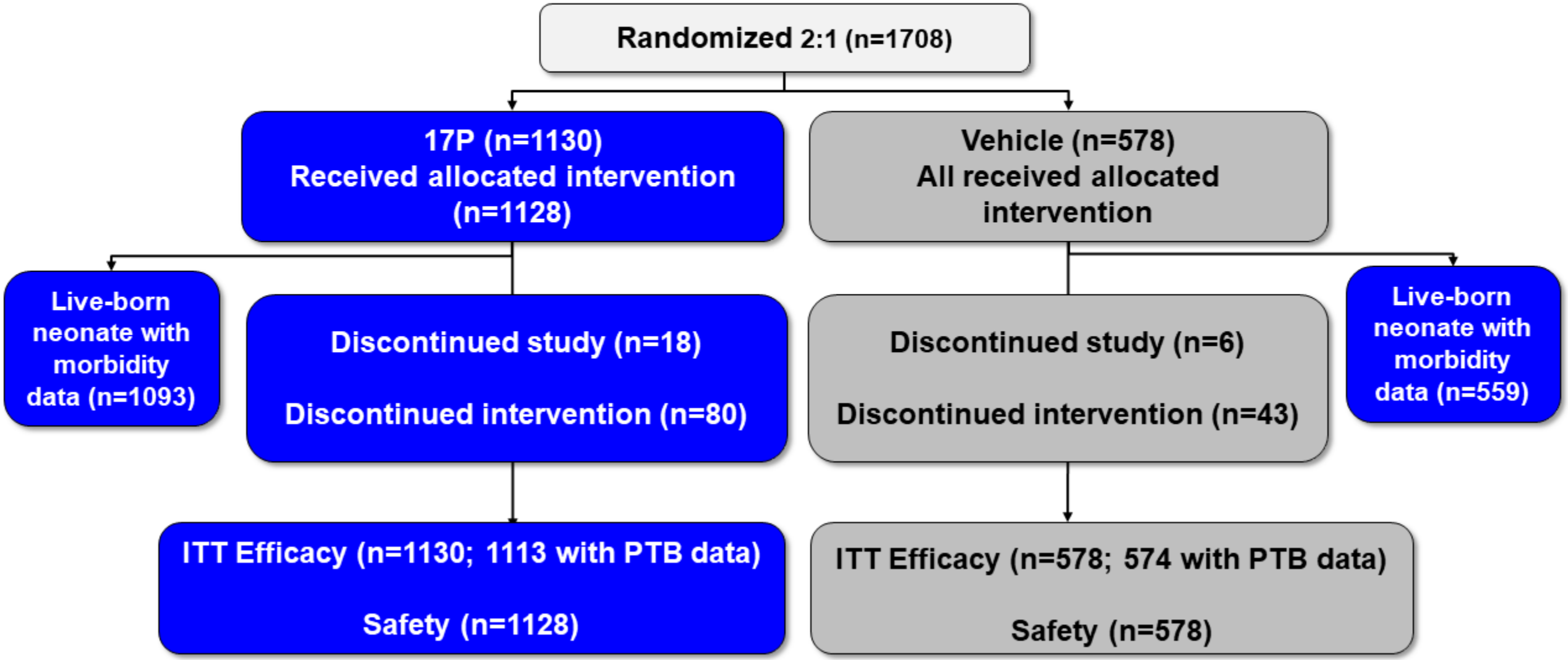
Primary Safety Outcome

- Exclude doubling in risk of fetal or early infant death

PROLONG: Sample Size and Powering Based on Conservative Estimates of Meis Results

- Sample size of 1707 provide
  - 98% power to detect 30% reduction in PTB < 35 weeks
  - 90% power to detect 35% reduction in neonatal composite index
  - 83% power to rule out doubling in risk of fetal/early infant death

PROLONG Patient Disposition: ~ 99% of Patients Completed Study



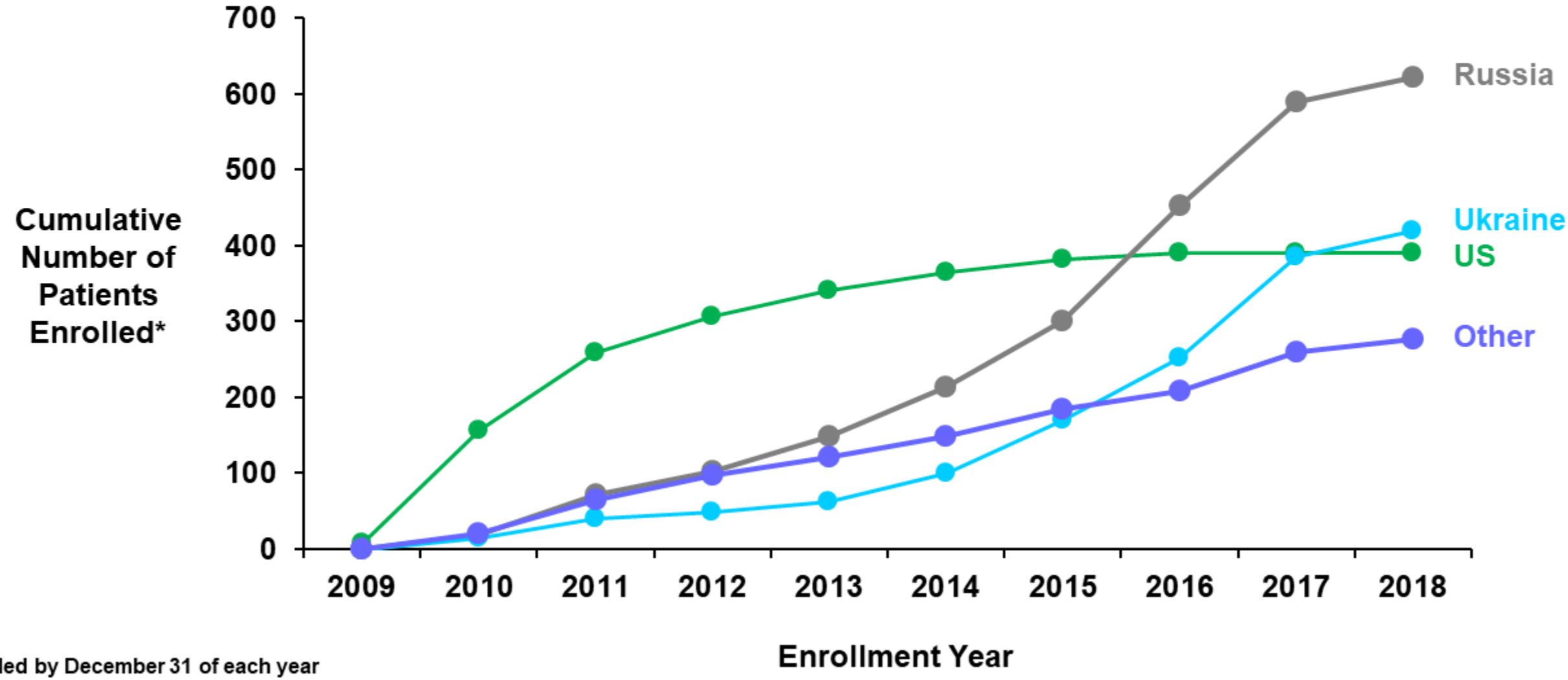
PROLONG: Enrollment by Geographic Region ~ 75% of Patients Enrolled Ex-US

Country	Number of Patients (N=1708) n (%)
United States	391 (22.9)
Ex-US	1,317 (77.1)
Russia	621 (36.4)
Ukraine	420 (24.6)
Hungary	91 (5.3)
Spain	85 (5.0)
Bulgaria	50 (2.9)
Canada	31 (1.8)
Czech Republic	14 (0.8)
Italy	5 (0.3)

61% of patients from Russia/Ukraine

16% (n=276 total) from other Ex-US Countries

PROLONG: Enrollment (Year End)



*Enrolled by December 31 of each year
Other: Bulgaria, Canada, Czech Republic, Hungary, Italy, Spain

PROLONG: Demographics and Baseline Characteristics Similar Across Treatment Groups

Demographics & Baseline Characteristics	17P (N=1130)	Vehicle (N=578)
Age (years), mean ± SD	30.0 ± 5.17	29.9 ± 5.22
Race / ethnicity		
White	88.8%	87.2%
Black, African American / African heritage	6.5%	7.1%
Non-Hispanic or Latino	91.1%	90.7%
Married or living with partner	89.6%	90.3%
BMI before pregnancy (kg/m^2), mean ± SD	24.3 ± 7.1	24.7 ± 8.7
Educational level (years), mean ± SD	13 ± 2.4	13 ± 2.4
Transvaginal cervical length < 25 mm at ≤ 20 weeks	1.2%	1.9%
Any substance use* during pregnancy	9.3%	8.8%

2 – 4% of patients were Asian, 2 – 3% were Other (Native Hawaiian/Pacific Islander, American Indian or Alaska native, mixed race and other) *Smoking, alcohol or illicit drugs

PROLONG: Prior Pregnancy History Similar Across Treatment Groups

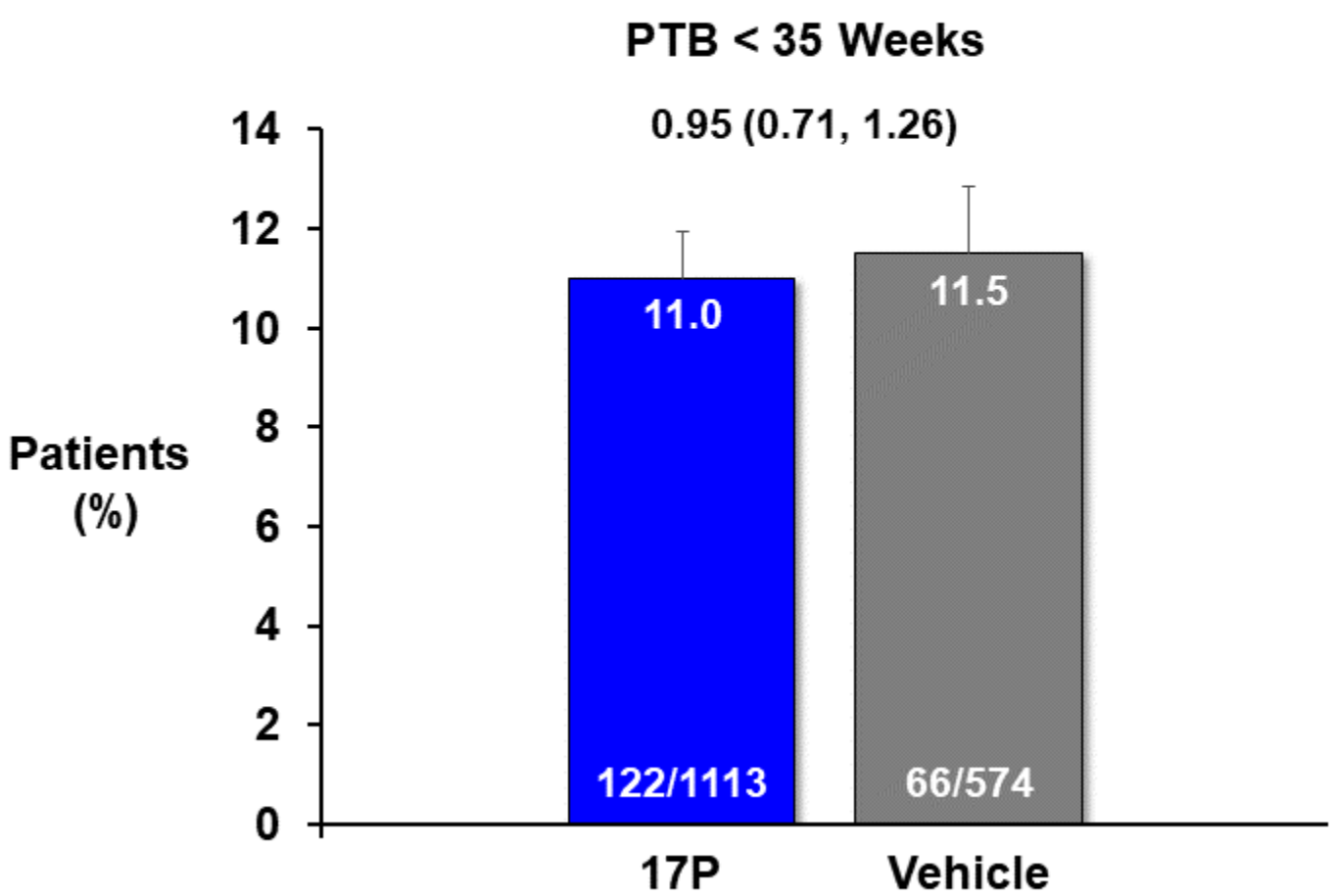
Pregnancy Characteristics	17P (N=1130)	Vehicle (N=578)
Prior SPTB – median (min, max)	1.0 (1, 7)	1.0 (0*, 5)
> 1 previous SPTB n (%)	148 (13.1)	70 (12.1)
Gestational age of prior qualifying delivery (weeks) mean ± SD median (min, max)	 31.3 ± 4.35 32 (20, 36)	 31.6 ± 4.16 33 (20,36)

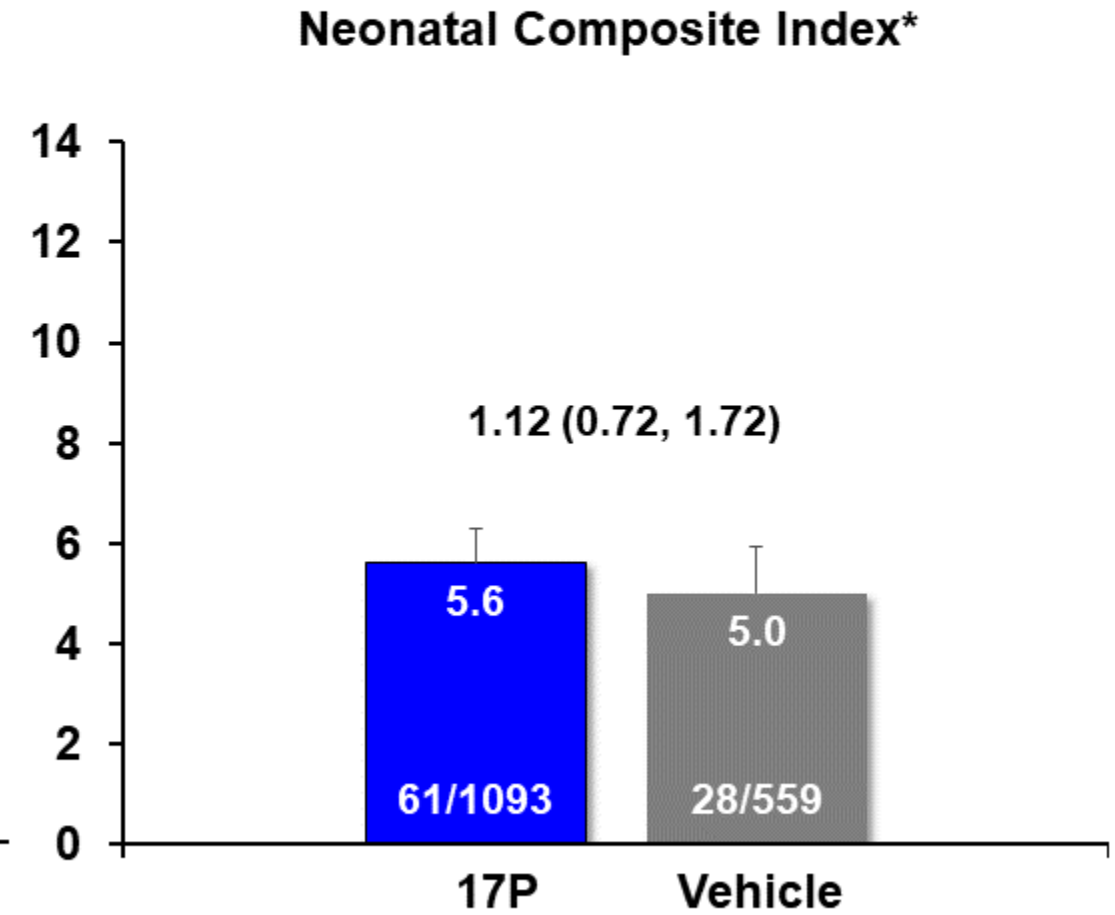
*1 patient in vehicle arm did not have SPTD (protocol deviation)

PROLONG: Comparable Study Drug Compliance Across Treatment Groups

Study Drug Exposure	17P (N=1128)	Vehicle (N=578)
Injections received		
Mean (SD)	17.6 (3.65)	17.5 (3.81)
Median	18	18
Min, Max	(1, 22)	(1, 22)
Patients with full compliance	91.4%	92.4%

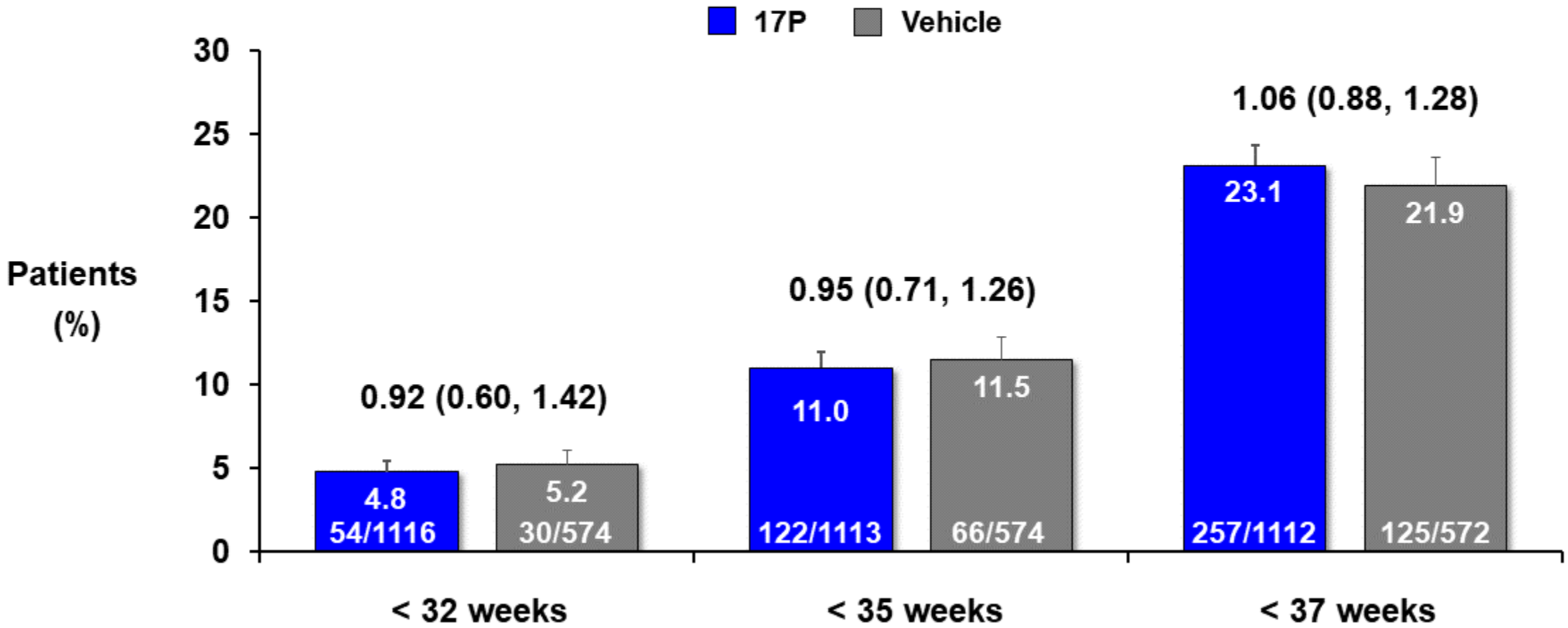
PROLONG: Co-Primary Endpoint Results
PTB < 35 Weeks and Neonatal Composite Index





*Composite included: Death, RDS, BPD, Grade 3 or 4 IVH, NEC and proven sepsis

PROLONG: Key Secondary Endpoint Results (PTB by Gestational Age at Delivery)



PROLONG: Co-Primary Efficacy Outcome Event Rates Higher in US Compared to Ex-US

Preterm Birth < 35 weeks

	17P (N=1130)	Vehicle (N=578)
US, n/N (%)	40/256 (15.6)	23/131 (17.6)
Ex-US, n/N (%)	82/857 (9.6)	43/443 (9.7)

Neonatal Composite Index

	17P (N=1093)	Vehicle (N=559)
US, n/N (%)	18/252 (7.1)	11/125 (8.8)
Ex-US, n/N (%)	43/841 (5.1)	17/434 (3.9)

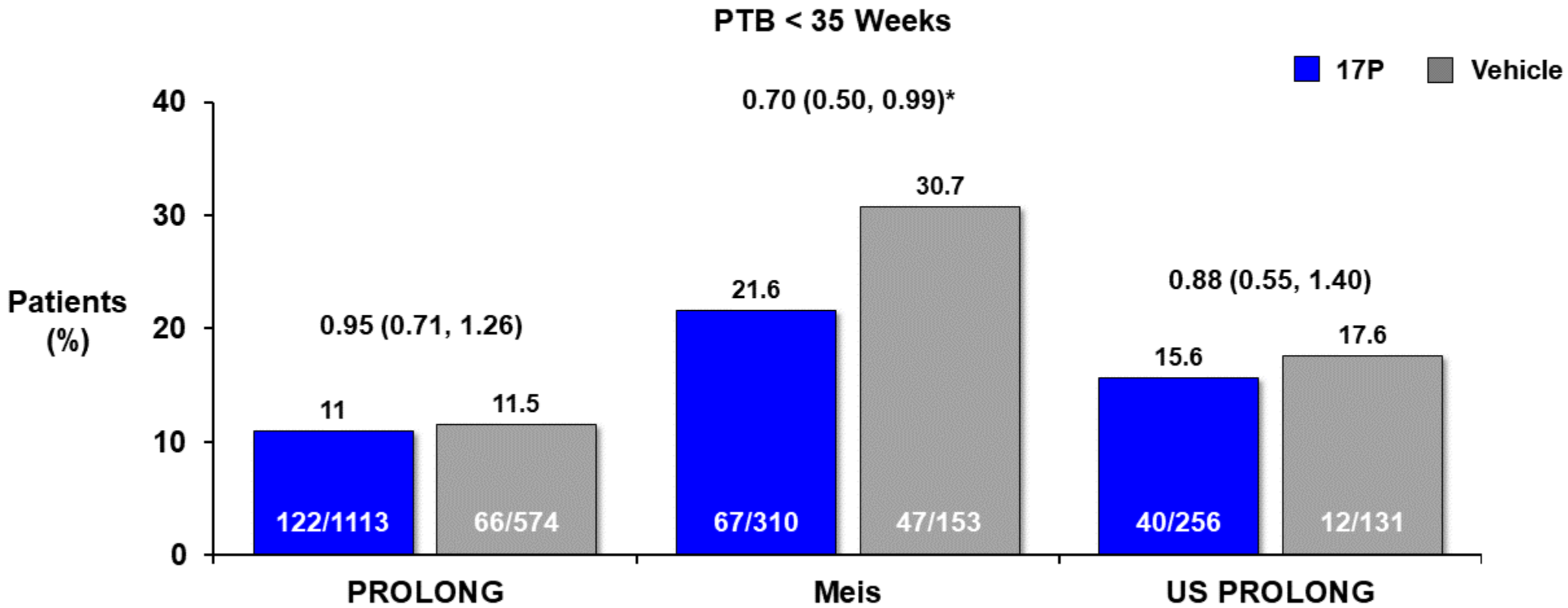
Differences Between PROLONG and Meis Study Populations Less Notable in US PROLONG Subset

Demographics/Baseline Characteristics	PROLONG (N=1708) %	Meis (N=463) %	US PROLONG (N=391) %
Age (years), mean ± SD	30.0 ± 5.2	26.2 ± 5.6	27.6 ± 5.1
> 1 previous SPTB	14.5	28.9	27.4
Black / African American	6.7	59.0	28.9
Hispanic or Latino	9.1	14.9	13.8
Unmarried with no partner	10.1	50.3	30.7
Educational status (≤ 12 years)	43.7	71.3	50.5
Any substance use during pregnancy	9.3	26.1	28.4
Smoking	7.8	21.6	22.8
Alcohol	2.5	8.0	9.2
Illicit drugs	1.4	3.2	5.9

Multifactorial Causes of PTB Make it Challenging to Identify Markers of Response

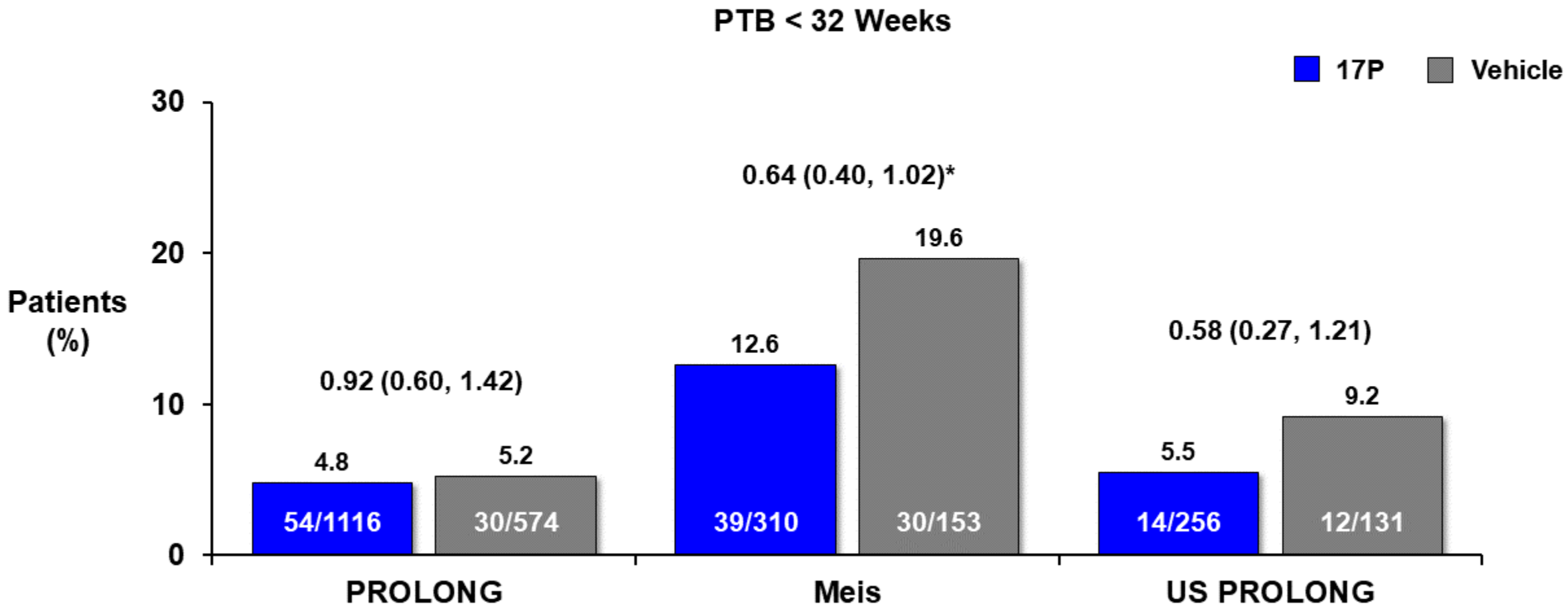
- Additional post hoc analyses conducted
- US PROLONG subset more similar demographics and background characteristics to Meis

Trends for Reductions in PTB Rates at < 35 Weeks in US PROLONG Align (Directionally) with Meis



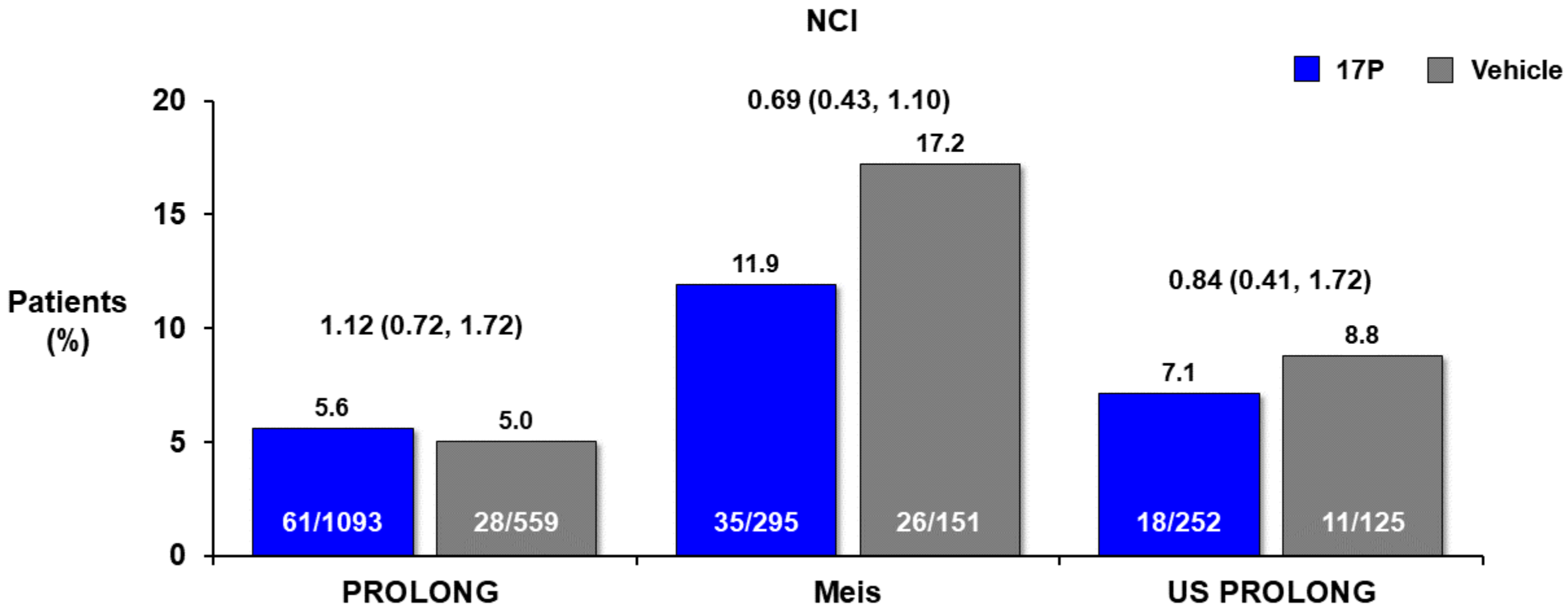
*The CI is a 96.5% CI to adjust for the interim analyses.
Relative risks (RR) and confidence intervals (CI) for the PROLONG study are adjusted for gestational age at randomization stratum.

Trends for Reductions in PTB Rates at < 32 Weeks in US PROLONG Align (Directionally) with Meis



*The CI is a 96.5% CI to adjust for the interim analyses.
Relative risks (RR) and confidence intervals (CI) for the PROLONG study are adjusted for gestational age at randomization stratum.

Trends for Reductions in Neonatal Composite Index* Rates in US PROLONG Align (Directionally) with Meis



*Composite included: Death, RDS, BPD, Grade 3 or 4 IVH, NEC and proven sepsis

PROLONG Efficacy Summary

- Study did not meet co-primary endpoints
  - Findings do not refute robust efficacy seen in Meis
  - Lower background PTB rates in PROLONG compared to Meis
- Trends for benefit favoring 17P seen in smaller subset study population (US PROLONG)

PROLONG Safety

PROLONG: Primary Safety Outcomes

- **Exclude doubling in risk of fetal or early infant death in 17P group vs. vehicle, defined as**
  - Spontaneous abortion/miscarriage (delivery 16^0 – 19^6)
  - Stillbirth at ≥ 20 weeks
  - Early infant death at ≤ 24 weeks (occurring minutes after birth until 28 days of life)

- **Overall perinatal death most relevant outcome**

PROLONG: Overall Rates of Perinatal Death Low and Similar Across Treatment Groups

Fetal or Early Infant Deaths		17P (N=1128)	Vehicle (N=578)	RR (95% CI)[1]
Non-Liveborn	Miscarriages (< 20 weeks)	4/866 (0.5)	7/448 (1.3)	0.28 (0.08, 0.94)
	Stillbirths (≥ 20 weeks)	12/1124 (1.1)	3/571 (0.5)	2.07 (0.59, 7.29)
Liveborn	Early Infant Deaths (≥ 20 to ≤ 24 weeks)	3/1112 (0.3)	1/568 (0.2)	1.48 (0.14, 15.24)
Total Fetal/Early Infant Deaths		19/1128 (1.7)	11/578 (1.9)	0.87 (0.42, 1.81)

1. Relative risk for 17P relative to Vehicle (Placebo) and is from the Cochran-Mantel-Haenszel test adjusted for gestational age at randomization.

PROLONG: Overall Incidence of Treatment Emergent Adverse Events (TEAEs) Comparable Between 17P and Vehicle

Summary of TEAEs	17P (N=1128) n (%)	Vehicle (N=578) n (%)
Any AEs	646 (57.3)	334 (57.8)
Any maternal pregnancy complication (MPC)	115 (10.2)	64 (11.1)
Any AEs leading to study drug withdrawal	11 (1.0)	5 (0.9)
Any SAEs	34 (3.0)	18 (3.1)
Maternal deaths	0	0

PROLONG: No Clinically Meaningful Differences in AEs or Maternal Pregnancy Complications (MPCs)* Between Treatment Groups

AEs and MPCs (≥ 3%) Preferred Term	17P (N=1128) / n (%)	Vehicle (N=578) / n (%)
Patients with ≥1 TEAE or MPC	653 (57.9)	336 (58.1)
Anemia	104 (9.2)	56 (9.7)
Headache	68 (6.0)	28 (4.8)
Nausea	55 (4.9)	26 (4.5)
Back pain	50 (4.4)	20 (3.5)
After birth pain	48 (4.3)	24 (4.2)
Urinary tract infection	44 (3.9)	23 (4.6)
Abdominal pain	40 (3.5)	27 (4.7)
Vomiting	42 (3.7)	19 (3.3)
Injection site pruritis	42 (3.7)	23 (4.0)
Vaginal infection	41 (3.6)	21 (3.6)
Nasopharyngitis	39 (3.5)	27 (4.7)
Constipation	38 (3.4)	17 (2.9)
Dyspepsia	37 (3.3)	25 (4.3)
Insomnia	36 (3.2)	13 (2.2)
Injection site pain	36 (3.2)	24 (4.2)
Vaginitis bacterial	35 (3.1)	21 (3.6)
Gestational diabetes	35 (3.1)	22 (3.8)
Cervical incompetence*	34 (3.0)	16 (2.8)

*MPC = maternal pregnancy complication

PROLONG: TEAEs and MPCs* Leading to Premature Discontinuation of Study Medication

TEAE/MPC Leading to Discontinuation Preferred Term	17P (N=1128)	Vehicle (N=578)
Patients with ≥ 1 TEAE/MPC leading to discontinuation	11 (1.0)	5 (0.9)
Hypothyroidism*	1 (0.1)	0
Nausea/vomiting[1]	1 (0.1)	0
Injection site AEs (erythema, nodule, pruritus, rash, reaction)	4 (0.4)	1 (0.2)
Cholestasis*	0	2 (0.3)
Headache	0	1 (0.2)
Fetal growth restriction*	1 (0.1)	0
Preeclampsia*	0	1 (0.2)
Mood altered[1]	1 (0.1)	0
Shortened cervix*	1 (0.1)	0
Vaginal hemorrhage	1 (0.1)	0
Dermatitis allergic	1 (0.1)	0
Dry skin	1 (0.1)	0

*MPC [1]AE occurred in same patient

PROLONG: Most Commonly Reported Serious Adverse Events (SAEs) and MPCs*

SAEs and MPCs (≥ 2 patients) Preferred Term	17P (N=1128) n (%)	Vehicle (N=578) n (%)
Patients ≥ 1 SAE/MPC	34 (3.0)	18 (3.1)
Cholestasis*	0	3 (0.5)
Endometritis	1 (0.1)	1 (0.2)
Escherichia coli sepsis	2 (0.2)	0
Migraine	1 (0.1)	1 (0.2)
Placental insufficiency*	4 (0.4)	1 (0.2)
Pneumonia	3 (0.3)	0
Premature separation of placenta*	5 (0.4)	2 (0.3)
Pyelonephritis	2 (0.2)	1 (0.2)
Wound infection	2 (0.2)	0

2 patients each had 1 SAE considered possibly related to study drug: 1 in 17P group hospitalized for mild nephrolithiasis; 1 in vehicle group with severe cholestasis

Post-Marketing Surveillance: Safety Consistent with Clinical Trial Data

- Cumulative exposure of 294,781 patients since approval
- Post-marketing data consistent with safety data obtained from Meis and PROLONG
  - No new or unexpected safety findings
- Most frequent AE reports consistent with registration studies
  - Injection site pain and/or other injections site localized reactions (e.g., pruritus, nodule, swelling)

Post-Marketing Surveillance: Makena SAEs Around Perinatal Mortality

SAE: Death		Estimated Post-marketing Reporting Rate*
Non-Liveborn	Abortion spontaneous	0.1%
	Stillbirth	0.1%
Liveborn	Death Neonatal	0.003%
Total Perinatal Deaths		0.2%

*Reporting Rate is computed based on cumulative patient exposure of 294,781 as of Aug 2019

PROLONG Reaffirmed Safety of 17P Demonstrated in Meis Study

- No new or unexpected safety findings
- No clinically meaningful difference in safety profile between treatment arms
- Consistent, favorable maternal and fetal safety comparable to vehicle
- Consistent findings in post-marketing surveillance data

Prevention of Preterm Births: Clinical Perspective

Sean C. Blackwell, MD

Professor and Chair, Department of Obstetrics, Gynecology, and Reproductive Sciences

McGovern Medical School-UTHealth

3 Key Clinical Questions

1. Why did PROLONG efficacy results differ from Meis results?

2. Is it feasible to do another confirmatory trial?

3. What do we do from here?

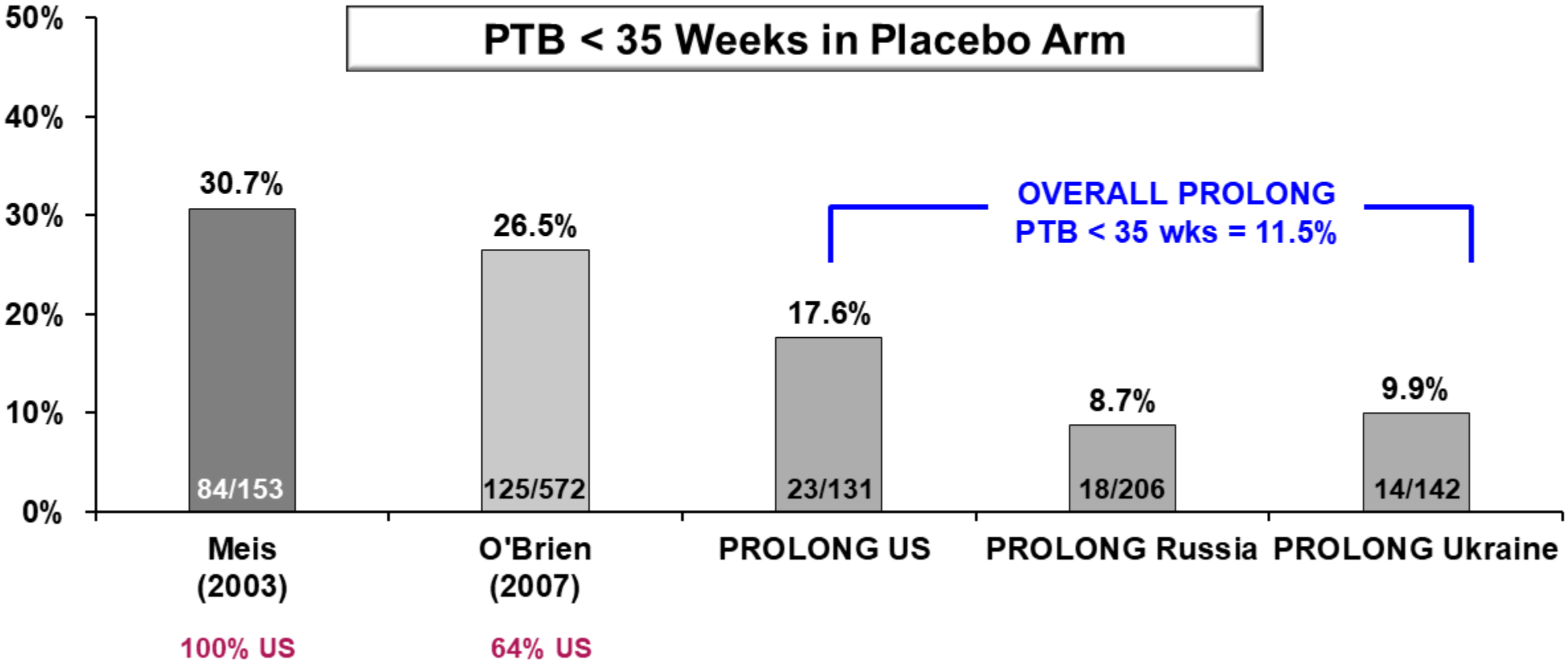
Question #1

Why did PROLONG efficacy results differ from Meis?

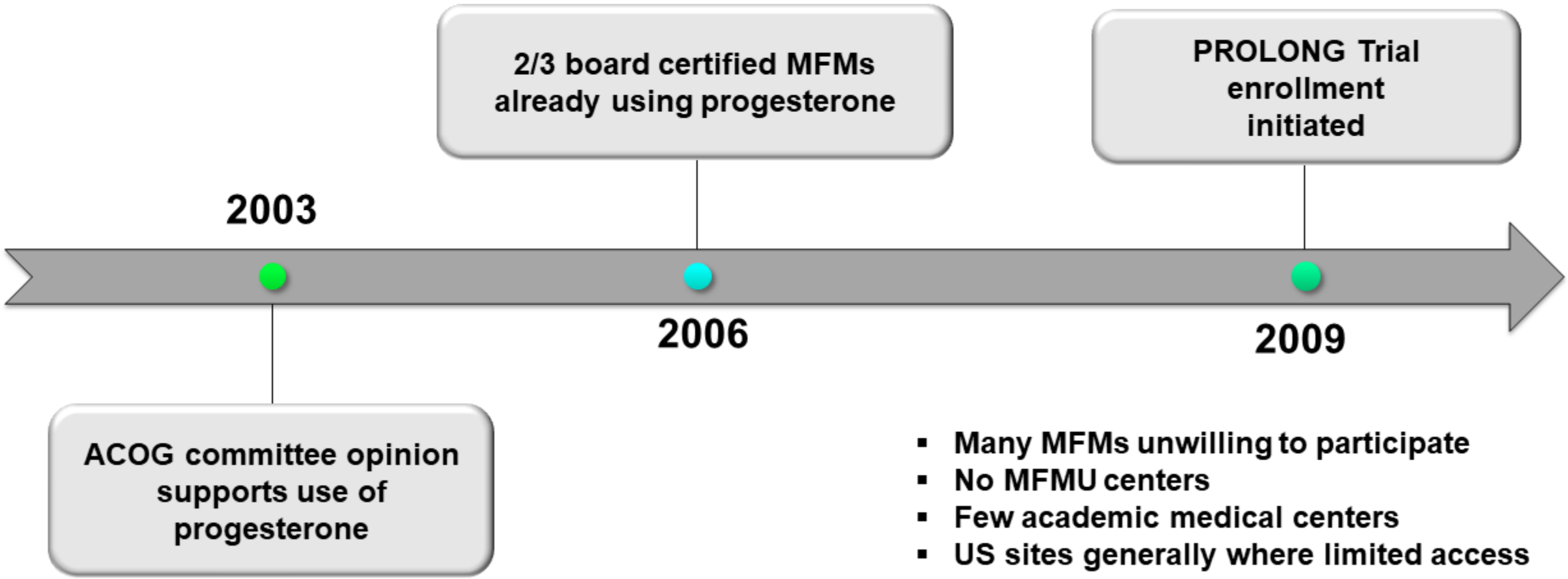
Differences in Clinical Characteristics Between Meis And PROLONG Study Populations

	Meis	PROLONG
Recruitment	100% US Academic Medical Centers	75% ex-US 60% Russia & Ukraine
Race	60% Black	7% Black
Surrogates of SES		
Unmarried with no partner	50%	10%
Smoking	22%	8%
≤ 12 years of education	71%	44%
> 1 prior PTB	27%	14%
PTB in placebo groups		
< 32 wks	19.6%	5.2%
< 35 wks	30.7%	11.5%
< 37 wks	54.9%	21.9%

Placebo Arm PTB Rates Across Different Clinical Trial Populations



PROLONG US: Recruitment Challenges



- Many MFMs unwilling to participate
- No MFMU centers
- Few academic medical centers
- US sites generally where limited access to 17P

Ness, AJOG, 2006

PROLONG US: Enrollment Challenges

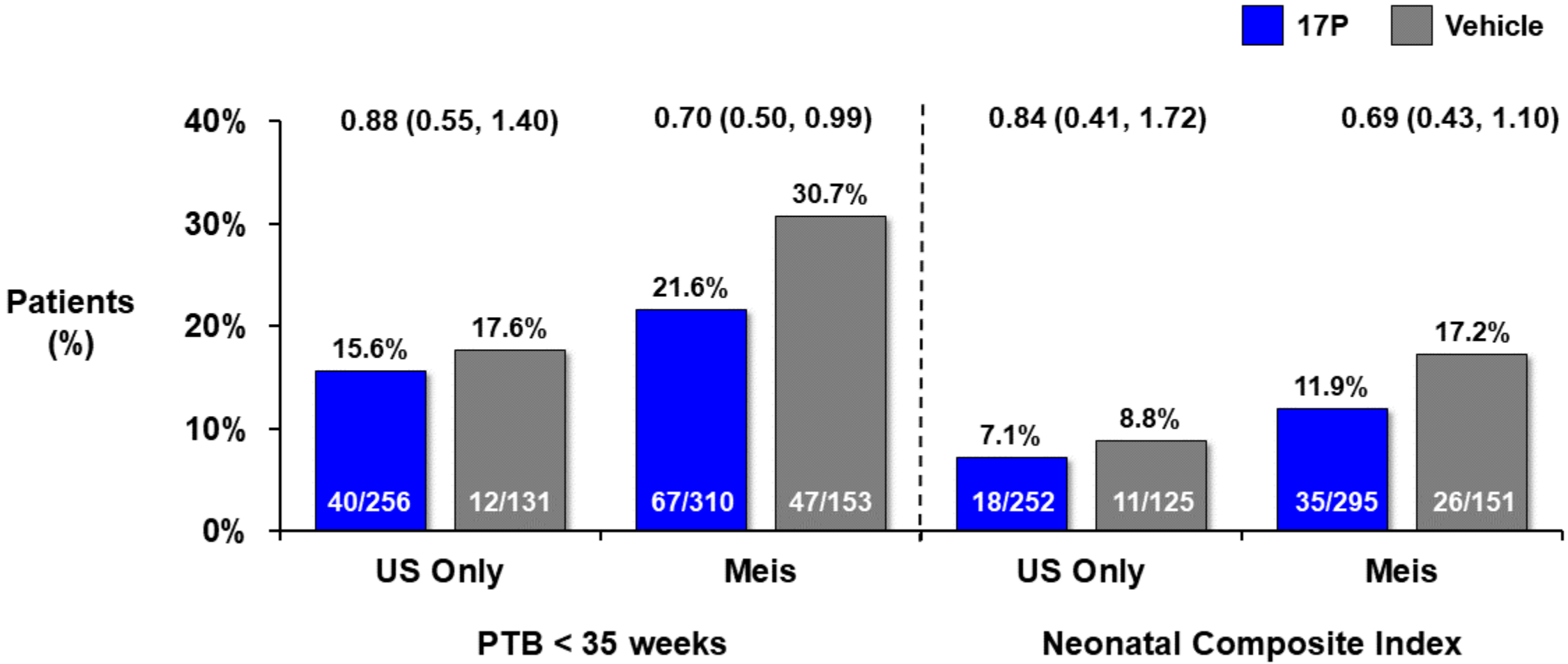
- Patients potentially steered from RCT to get open-label therapy (compounded 17P, vaginal progesterone, other)

- PROLONG
  - Low rate PTB > 1
  - Very low rate short cervix (< 2%)

PROLONG: Low Event Rates

- Sample size and expected event rate based on Meis trial
- 50% lower rates in PROLONG than Meis
- To design a trial today based on these low rates
  - 90% power would require
    - 3,600 women for PTB < 35 weeks
    - 6,000 for neonatal composite morbidity
- Population differences and low event rates make PROLONG results inconclusive

PROLONG: Treatment Effect Trends in US Only



96.5% CI to adjust for the interim analyses and number of prior preterm birth for PTB<35
95%CI adjusted for number of prior preterm birth for NCI

Question #2

Is it feasible to do another confirmatory trial?

Another Confirmatory Trial is Not Feasible

- US physicians won't accept placebo controlled RCT

- Where could we do another placebo controlled RCT?
  - Difficulty finding combination of
    - High-risk women
    - No access to 17P
    - Research infrastructure to conduct major trial

Feasibility of Another Confirmatory Trial: Trial of Two Therapies?

- No evidence-based therapies vs. 17P
- Vaginal progesterone: no benefit in 3 large RCTs
- Cervical cerclage and pessary also no proven benefit

	N	Endpoint	Vaginal progesterone	Placebo	95% CI
O'Brien	659	PTB ≤ 32 weeks	10%	11.3%	OR 0.9 (0.52 to 1.56)
OPPTIMUM*	1,053	PTB < 34 weeks or fetal death	15.9%	18.8%	OR 0.82 (0.58 to 1.16)
PROGRESS*	787	PTB < 37 weeks	36.5%	37.2%	aRR 0.97 (0.81 to 1.17)

*Included 12 women with twin pregnancies

1.O'Brien et al., 2007. 2. Norman et al., The Lancet. 2016. 3. Crowther et al., 2017

Question #3

What should we do from here?

SMFM Statement (October 25, 2019)

"Based on the evidence of effectiveness in the Meis study, which is the trial with the largest number of US patients, and given the lack of demonstrated safety concerns, SMFM believes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very high-risk population reported in the Meis trial."

ACOG Practice Advisory (October 25, 2019)

"ACOG is not changing our clinical recommendations at this time and continues to recommend offering hydroxyprogesterone caproate as outlined in Practice Bulletin # 130, Prediction and Prevention of Preterm Birth."

What Will Happen if FDA-Approved 17P is Not Available?

- Many clinicians will use compounded 17P
  - Lack of GMP
  - Potential variance/sterility issues
  - No labeling
- Most physicians will not tolerate NO TREATMENT
  - Other off-label therapies (non-evidence based)
  - Many will choose cerclage (surgical therapy)

What Will I Do?

- Meis and PROLONG not contradictory
  - Meis showed efficacy in population similar to my patients
  - PROLONG reaffirms safety
  - Overall positive benefit/risk ratio

- Essential to be able to offer FDA-approved 17P

AMAG Actions Following PROLONG

Julie Krop, MD
Chief Medical Officer
EVP Clinical Development and Regulatory Affairs
AMAG Pharmaceuticals, Inc

Totality of Evidence Support Continued 17P Access

- Meis study demonstrated substantial evidence of efficacy
  - Basis of medical societies recommending 17P as standard of care
- PROLONG results inconclusive given differences in patient populations

What Have We Learned from PROLONG?

- Impossible to conduct confirmatory trial once 17P was recommended by medical societies as standard of care
  - Lead to bias towards lower risk population
- PROLONG confirmed favorable safety profile
  - Supported by 8 years of post-marketing surveillance

Does Meis Trial Alone Meet Criteria for Single Trial as Basis for Approval?

- FDA guidance for single trial approval
  - Second trial not feasible or ethical
  - Statistically persuasive findings
  - Clinically relevant endpoint
  - Robust, consistent results across multiple subgroups
- PTB at <37, < 35 and < 32 weeks increases risk to neonate
  - Should no longer require a confirmatory trial
- Orphan disease with NO alternative treatment options

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998

17P is an Important Treatment Option for Pregnant Women With History of Preterm Birth

- Physicians and patients can make informed decisions together
- PROLONG results recently published in American Journal of Perinatology
- Label update with PROLONG safety and efficacy data

Considerations for Another Confirmatory Study

- Randomized placebo-controlled trial
  - Not feasible given current clinical practice guidelines
- Observational study
  - Challenging to control for known and unknown PTB risk factors

Positive Benefit-Risk Profile of 17P Supports Continued Access for Physicians and Patients

- Preterm birth remains major US public health concern
- Critical to keep 17P available to patients who need it most

17 α-Hydroxyprogesterone Caproate (Makena®) for Women with Singleton Pregnancy and Prior Singleton Spontaneous Birth

FDA Advisory Committee Meeting

Division of Bone, Reproductive and Urologic Products

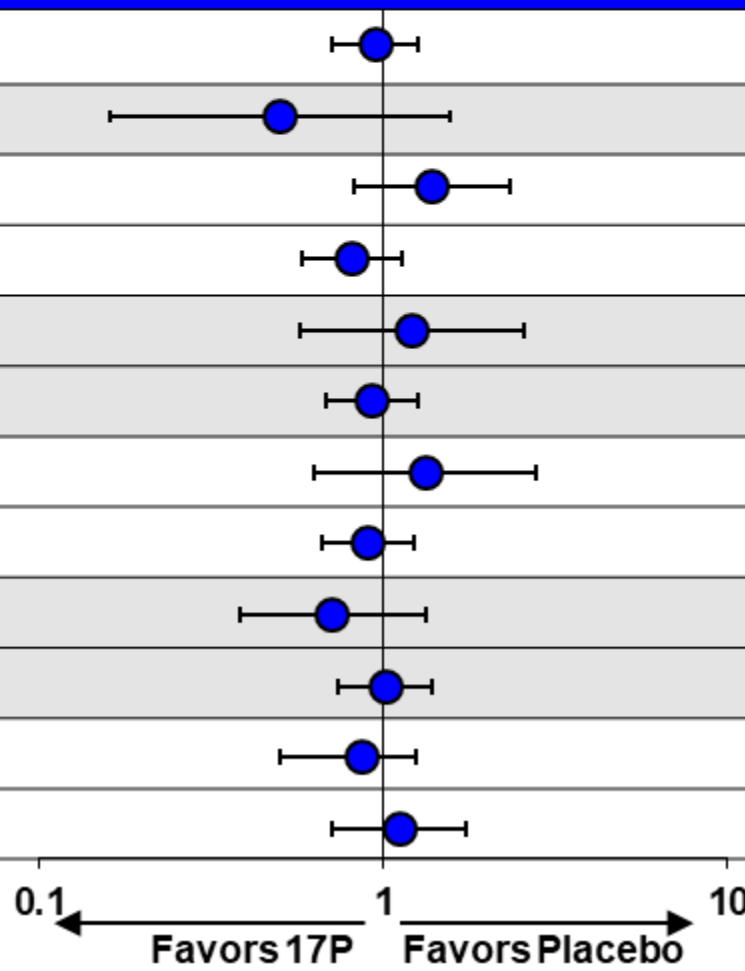
AMAG Pharmaceuticals, Inc.

October 29, 2019

Back-up Slides Shown

PROLONG Study: PTB < 35 Weeks with 17P Across Multiple Subgroups

Subgroup	17P (n/N)	Vehicle (n/N)	Relative Risk (95% CI)
All patients	122/1113	66/574	0.95 (0.71, 1.26)
Cervical Length < 25 mm	4/18	4/9	0.50 (0.16, 1.55)
> 1 Prior SPTB	42/164	15/81	1.38 (0.82, 2.34)
Only 1 Prior SPTB	80/949	51/491	0.81 (0.58, 1.13)
Black	17/72	8/41	1.21 (0.57, 2.56)
Non-Black	105/1041	58/533	0.93 (0.68, 1.26)
Unmarried	22/117	8/56	1.32 (0.63, 2.77)
Married	100/996	58/518	0.90 (0.66, 1.22)
Smoke or substance use	19/105	13/51	0.71 (0.38, 1.32)
No smoke or substance use	103/1008	53/523	1.01 (0.74, 1.38)
Education ≤ 12 years	64/474	40/256	0.86 (0.50, 1.24)
Education > 12 years	58/638	26/318	1.11 (0.71, 1.73)



Stillbirth: PROLONG and Meis MFM Review

Stillbirth affects 1 in 160 pregnancies each year in general population
Several underlying fetal/maternal causes[1]

- **PROLONG**:
  - 17P: 12/1128 (1.1%)
    - 11 underlying factors; 1 unknown
  - Vehicle: 3/578 (0.5%)
    - All had underlying factors
- **Meis**:
  - 17P: 6/306 (2.0%)
    - 5 underlying factors; 1 unknown
  - Vehicle: 2/153 (1.3%)
    - 1 underlying factor; 1 unknown

1. Silver JAMA 2011