U.S. FOOD & DRUG ADMINISTRATION

Presentation by the

Center for Drug Evaluation and Research (CDER)

Agenda

- Opening Remarks – Patrizia Cavazzoni, M.D.
  Director, Center for Drug Evaluation and Research
- Legal Framework – Sara Rothman, J.D., M.P.H.
  Associate Chief Counsel, Office of the Chief Counsel
- Rationale for Withdrawal
  - Part 1 – Christina Chang, M.D., M.P.H.
    Acting Director, Division of Urology, Obstetrics and Gynecology, Office of New Drugs
    Center for Drug Evaluation and Research
  - Part 2 – Laura Lee Johnson, Ph.D.
    Director, Division of Biometrics III, Office of Biostatistics, Office of Translational Sciences
    Center for Drug Evaluation and Research
  - Part 3 – Christine P. Nguyen, M.D.
    Deputy Director, Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
    Office of New Drugs, Center for Drug Evaluation and Research
- Closing Remarks – Peter Stein, M.D.
  Director, Office of New Drugs, Center for Drug Evaluation and Research

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Opening Remarks

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

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- **Retaining Makena's approval likely hinders study of more promising treatments for preterm birth**

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Legal Framework

Sara Rothman, J.D., M.P.H.
Associate Chief Counsel
Office of the Chief Counsel
Food and Drug Administration

Approval Pathways

- **Traditional**
  - Based on (a) measurement of clinical benefit or (b) effect on a surrogate endpoint *known* to predict clinical benefit (i.e., "validated")
  - Authority: Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA); FDA Regulations
- **Accelerated**
  - Based on drug's effect on a surrogate or intermediate clinical endpoint "*reasonably likely* . . . to predict [a drug's] clinical benefit"
  - Sponsor to conduct a confirmatory trial to verify clinical benefit
  - Authority: FDCA sec. 506; FDA Regulations (21 CFR Part 314, Subpart H)
- **Both traditional and accelerated**
  - Must be substantial evidence of effectiveness for proposed conditions of use at the time of approval
  - See FDCA secs. 505(d); 506(e)(2)

Accelerated Approval Can Provide Earlier Access to New Therapies

- Can provide patients with serious and life-threatening diseases **access to new therapies sooner** by expediting drug approval for conditions for which there is unmet need for treatment
- Based on an effect on a surrogate or intermediate clinical endpoint that is *reasonably likely* to predict clinical benefit
- Accepts some uncertainty to provide earlier access
- FDA has required post-approval studies to "**verify and describe [the drug's] clinical benefit**"

Accelerated Approval Eligibility

FDCA 506; 21 CFR 314.500, 314.510

- Under the accelerated approval pathway, FDA considers:
  - "The severity, rarity, or prevalence of the condition," including whether the proposed indication is for a "serious or life-threatening illness," and
  - "The availability or lack of alternative treatments," including any evidence of "meaningful therapeutic benefit to patients over existing treatments . . ."
- Recurrent singleton preterm birth is a serious condition, and there is unmet need for a treatment shown to be effective
- Accelerated approval of Makena:
  - Based on an effect on an intermediate clinical endpoint (gestational age <37 weeks) that was considered "reasonably likely to predict" clinical benefit to neonates
  - Required the sponsor to conduct an adequate and well-controlled trial to verify Makena's predicted clinical benefit to neonates

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Balancing of Public Health Interests in Accelerated Approval Framework

- Give patients with serious or life-threatening diseases access to new therapies sooner by expediting approval, while protecting patients from products:
  - That are not shown to provide clinical benefit
  - With unfavorable benefit/risk profile
- Where the legal standard for withdrawal is met, and CDER determines that approval should be withdrawn, retaining approval would:
  - Unnecessarily expose patients to the risks, with no counterbalancing evidence of benefit, associated with a drug that is not shown to be both safe and effective for its approved indication
  - Upset the delicate balance of earlier patient access to new therapies and protection from drugs that are not shown to be both safe and effective
  - Undermine the integrity of the accelerated approval framework

Withdrawal Standard

FDCA 506(c), 21 CFR 314.530

- The law authorizes FDA to expedite withdrawal of drug approved under the accelerated approval framework
- FDA may withdraw approval, among other reasons, if:
  - "(1) A post-marketing clinical study fails to verify clinical benefit," **OR**
  - "(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use"
- The legal standard for withdrawal is met for **two independent reasons**:
  - (1) The confirmatory trial failed to verify the predicted clinical benefit of reducing neonatal morbidity and mortality from complications of preterm birth
  - (2) Given the available evidence, Makena is no longer shown to be effective at reducing the risk of recurrent singleton preterm birth

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Rationale for Withdrawal

Part 1

Christina Chang, M.D., M.P.H.
Acting Director, Division of Urology, Obstetrics and Gynecology
Office of New Drugs
Center for Drug Evaluation and Research

Question No. 1

Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

Response: No

Trial 003, the required post-marketing confirmatory study, failed to verify Makena's predicted clinical benefit

Preterm Birth Is a Significant Public Health Concern

- Preterm birth (PTB) - delivery prior to 37 weeks of gestation
  ~8% singleton pregnancies
- Most important PTB consequence: mortality, significant morbidity, and long-term physical and developmental impairment
- No approved therapies that demonstrate a direct clinical benefit in neonatal morbidity and mortality

Preterm Birth is Poorly Understood

- Many possible causes – *infection, underlying maternal disease (diabetes, hypertension), uterine overdistension (polyhydramnios, multiple gestation), weak cervix, etc.* – the exact cause is often unknown
- Preterm labor leading to PTB may be triggered by an unrecognized toxic uterine environment
- Allowing spontaneous delivery to occur may result in better neonatal outcome than continuing pregnancy

Improving Neonatal Outcomes is the Relevant Clinical Benefit

- With *spontaneous* PTB, risk of neonatal adverse outcomes generally decreases with increasing gestational age (GA) at delivery

- Unclear whether artificially prolonging pregnancy with *drug treatment* will result in improved neonatal outcomes for the same GA

- Uncertainty whether a GA endpoint can reliably predict neonatal outcome
  - Such uncertainty generally increases with increasing GA

Makena

A progestin (hydroxyprogesterone caproate, HPC)

- Weekly injection starting between 16 to 20 weeks 6 days through 36 weeks 6 days or delivery
- Received Accelerated Approval based on the endpoint reasonably likely to predict clinical benefit (of PTB <37 weeks) to reduce the risk of PTB *in women with a singleton pregnancy with history of singleton spontaneous preterm birth*
- Makena is **not approved to reduce**:
  - neonatal mortality and morbidity from prematurity
  - risk of PTB in women without prior PTB history (e.g., with a short cervix)
  - risk of PTB in multiple gestations

See FDA-approved prescribing information for Makena (INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021945s013lbl.pdf.

Trial 002 (1999 to 2002)

- Randomized (2:1 ratio), double-blind, placebo-controlled trial in U.S.
- Planned sample size of 500 women to detect a 33% reduction in PTB rate (from 37% to 25%) with 80% power
- Outcome data from 463 women (59% Black, 24% White, 15% Hispanic)
  - University of Alabama enrolled 27% of the study population and 43% of Black women

Proportion of Trial 002 Subjects Delivering at <37, <35, and <32 Weeks Gestational Age (ITT Population)

Efficacy Outcome	HPC (Makena) (N = 310[1])	Placebo (N = 153)	Absolute % Treatment Difference (95% CI)[2]	Relative Risk (95% CI)[2]
Birth < 37 weeks	**37%**	**55%**	**-18% (-28, -7)**	0.68 (0.54, 0.84)
Birth < 35 weeks	21%	31%	-9% (-19, -0.4)	0.69 (0.49, 0.98)
Birth < 32 weeks	12%	20%	-8% (-16, -0.3)	0.61 (0.38, 0.98)

Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348(24):2379-85.

[1]Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact.

[2]Adjusted for interim analysis.

In Trial 002, Treatment with Makena Did Not Reduce Fetal/Neonatal Deaths

Outcomes	HPC (Makena) (N = 306)	Placebo (N = 153)	Nominal p-value[1]
Miscarriage < 20 weeks	1.6%	0	0.1746
Stillbirths (antepartum and intrapartum)	2.0%	1.3%	0.7245
Neonatal deaths	2.6%	5.9%	0.1159
Total deaths	6.2%	7.2%	0.6887

Source: Table 8, FDA Background Document for the 2006 Reproductive Health Drugs Advisory Committee Meeting, dated August 2, 2006

[1] No adjustment for multiplicity

In Trial 002, Treatment with Makena Did Not Reduce Neonatal Morbidity

Morbidity Among Live Births	HPC (Makena) (N = 295)	Placebo (N = 151)	Nominal p-value[1]
Composite neonatal morbidity score	11.9%	17.2%	0.1194

- The composite neonatal morbidity measure counted any liveborn who experienced death, respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis.

Source: extracted from Table 10, FDA Background Document for the 2006 Reproductive Health Drugs Advisory Committee

[1] P-values have not been adjusted for multiple comparisons.

Significant Issues Noted During Review

- Issue #1: clinical relevance of delivery at a given GA
- Issue #2: only one adequate and well-controlled clinical trial for demonstration of substantial evidence of effectiveness

Issue #1:
Clinical Relevance of Delivery at a Given GA

- No statistically significant effect of Makena seen on neonatal outcomes
- GA-related endpoint (e.g., delivery at < 37 weeks) not known to predict clinical benefit

Issue #2:
Only One Adequate and Well-Controlled Clinical Trial

- We require substantial evidence of effectiveness showing that the drug is effective for its proposed conditions of use
- Generally, substantial evidence of effectiveness requires data from *two* adequate and well-controlled (AWC) trials
  - But a single AWC trial may be sufficient to provide SEE in some circumstances
- CDER determined that
  - Based on Trial 002, there was substantial evidence of effectiveness that Makena reduced PTB < 37 weeks (an endpoint reasonably likely to predict clinical benefit), supporting accelerated approval

FDA Draft Guidance for Industry "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" (December 2019), available at https://www.fda.gov/media/133660/download.

Trial 003 (PROLONG)

- Randomized, double-blind, placebo-controlled trial
- Essentially the same eligibility criteria as Trial 002
- Accelerated approval was based on a GA endpoint “reasonably likely” to predict clinical benefit, Trial 003 specifically designed to **verify** Makena’s clinical benefit
- Co-primary efficacy endpoints:
  - PTB < 35 weeks GA
  - Neonatal morbidity/mortality composite index
- Initiated in the U.S. and Canada to ensure recruitment of ≥ 10% of 1,700 planned subjects before accelerated approval

Trial 003 (2009 to 2018)

- Included 1,708 women from nine countries (compared to 463 U.S. women in Trial 002): 7% Black and 88% White; 9% Hispanic
- Highest enrolling countries:
  - Russia 621 (36%)
  - Ukraine 420 (25%)
  - U.S. 391 (23%)
    - 391 women
    - 113 Black women (29% of US subgroup) (compared to 273 in Trial 002)

Trial 003 Failed to Demonstrate Makena's Effect on Neonatal Composite Index and PTB < 35 weeks

Trial 003 Efficacy Result

Efficacy outcome	Makena (N=1130)	Placebo (N=578)	Treatment Difference** (95% CI)	Relative Risk (95% CI)	Statistically Significant?
Neonatal Composite Index*	5.4%	5.2%	0.2% (-2.0, 2.5)	1.05 (0.68, 1.61)	**No**
Birth < 35 weeks*	11%	12%	-0.6% (-3.8, 2.6)	0.95 (0.71, 1.26)	**No**
Birth < 32 weeks	5%	5%	-0.4% (-2.8, 1.7)	0.92 (0.60, 1.42)	**No**
Birth < 37 weeks	23%	22%	1.3% (-3.0, 5.4)	1.06 (0.88, 1.28)	**No**

*Co-Primary endpoints: Neonatal composite index and PTB < 35 weeks. Secondary endpoints: PTB < 37 weeks; PTB < 32 weeks
Neonatal Composite Index is the proportion of neonates experiencing at least one event of the composite index (if the liveborn neonate had any of RDS, BPD, Grade 3 or 4 IVH, NEC, proven sepsis, death).
**Cochran-Mantel-Haenszel (CMH) method stratified by gestational age at randomization; For treatment difference: p-value = 0.84 (neonatal composite index), p-value=0.72 (birth < 35 weeks)

BRUDAC: Trial 003 Failed to Show Clinical Benefit

October 2019 Bone, Reproductive and Urologic Drugs AC (BRUDAC) reviewed and discussed results from Trial 002 and Trial 003

- All AC members concluded (voted 16 to 0) that Trial 003 failed to verify the anticipated clinical benefit for Makena

- Most AC members concluded (voted 13 to 3) that, based on the findings from Trial 002 and Trial 003, there is not substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth

Conclusions re: Trial 003

- Trial 003 showed no effect on neonatal outcomes – and therefore **did not verify expected benefit of Makena**

- Makena did not prolong pregnancy – **and failed on GA endpoint(s) that supported accelerated approval in 2011**

Trial 002 Could Not Have Supported Traditional Approval

Trial 002 did not support traditional approval based on gestational age endpoints

- While Trial 002 showed reduction in PTB <32 and <35 weeks
  - These outcomes were not statistically persuasive enough to demonstrate SEE for approval based on a single trial
  - Reduction in PTB <37 weeks was statistically persuasive – served as a "reasonably likely" endpoint to support accelerated approval
- Based on available evidence now, there is no longer substantial evidence of Makena's effectiveness
  - Trial 003 negative on all gestational age endpoints
  - Many other studies fail to show any effect of Makena on gestational age

FDA Draft Guidance for Industry "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" (December 2019), available at https://www.fda.gov/media/133660/download.

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Rationale for Withdrawal

Part 2

Laura Lee Johnson, Ph.D.
Director, Division of Biometrics III, Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research

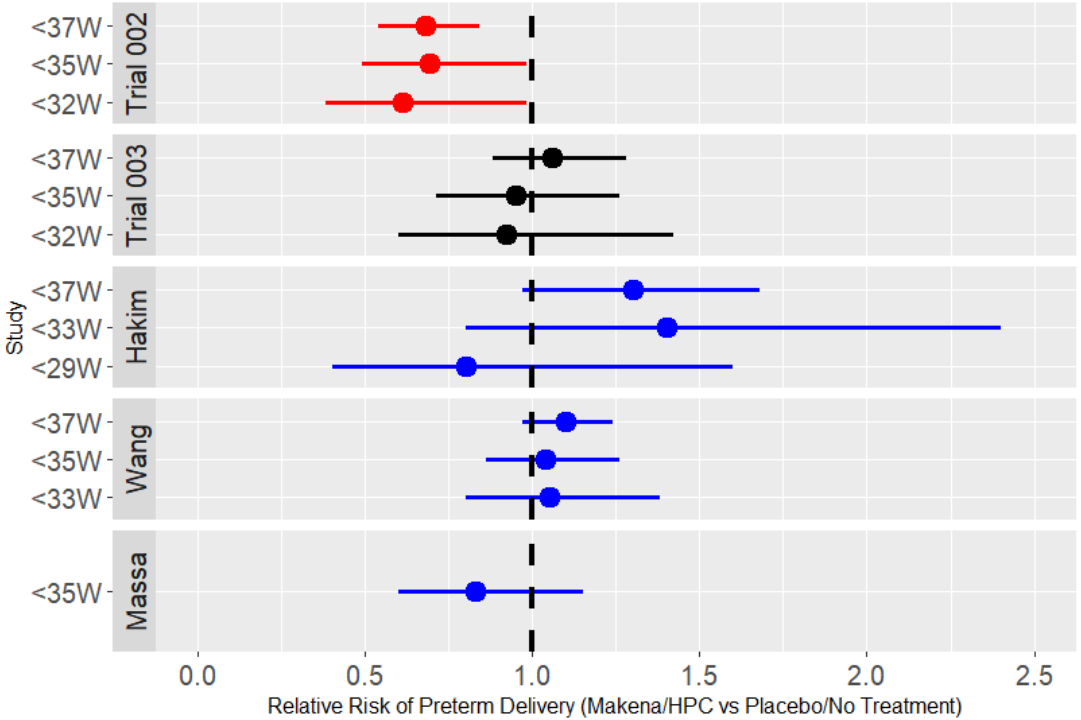
Question No. 2

Does the available evidence demonstrate that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth?

Response: No

Considering the available evidence, Makena is not shown to be effective at reducing the risk of PTB in women with a singleton pregnancy who have a history of singleton sPTB

RCTs and Observational Studies: Indicated Population



- Trial 002 (Meis, N=463) and Trial 003 (PROLONG, N=1,708): Randomized control trials (RCTs) for Makena's intended population
- Hakim (N=4,422), Wang (N=4,781), Massa (N=861): Observational studies with untreated concurrent comparator

Not shown: Bastek and Nelson did not report relative risks; results in both were not statistically significant. PROGFIRST, an RCT, had drug quality issues potentially impacting drug potency and efficacy.

Covis' Assertions Regarding the Different Results of Trials 002 and 003

- Trial 002 shows **higher risk** women had a better response to Makena and Trial 003 failed to sufficiently include this higher risk population
- Trial 003 lacked **power** to detect a difference because conducted in a lower risk population
- **Regional differences** explain failure of 003 – women outside the U.S. were not properly evaluated and were at lower risk of PTB
- Evidence from **other studies** supports response to HPC

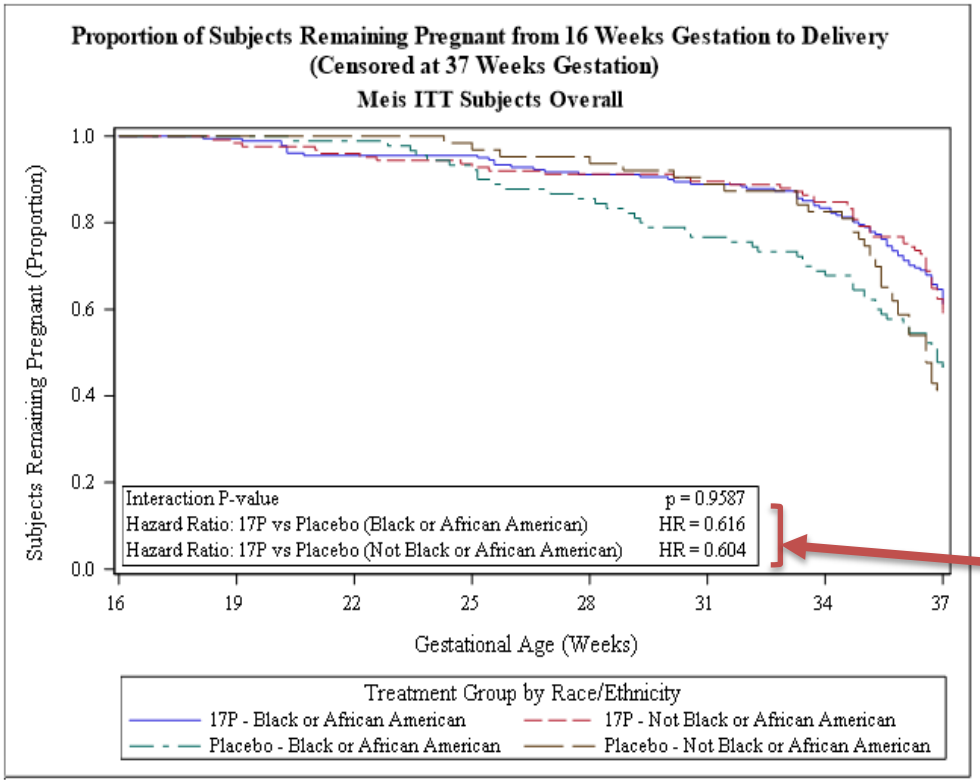
Covis asserts that Trial 002 shows higher risk women have a better response to Makena, and Trial 003 failed to sufficiently include this higher risk population

Black Women and Women with a Prior sPTB < 34 Weeks Do Not Respond Better to Makena in Time-to-Delivery Analyses (Trial 002)

- Time-to-event (delivery) analyses conducted for Trial 002 show that Makena
  - Did not have a better effect in Black women (compared to non-Black women)
  - Did not have a better effect in women who had a prior sPTB <34 weeks (compared to women who did not have a prior sPTB <34 weeks)
- In Trial 002, an effect of Makena is seen in subgroups, but statistically the effect is not better compared to the effect in the complement subgroup

No Differential Treatment Response by Race in Trial 002

Covis (Figure 7) Effect Modifier Analysis of Event Time based on Gestational Age Comparing Black and Non-Black Women by Treatment Arm (Trial 002)



Similar effect of Makena in Black and non-Black women

Source: Covis Briefing Materials @ 53 (Figure 7)

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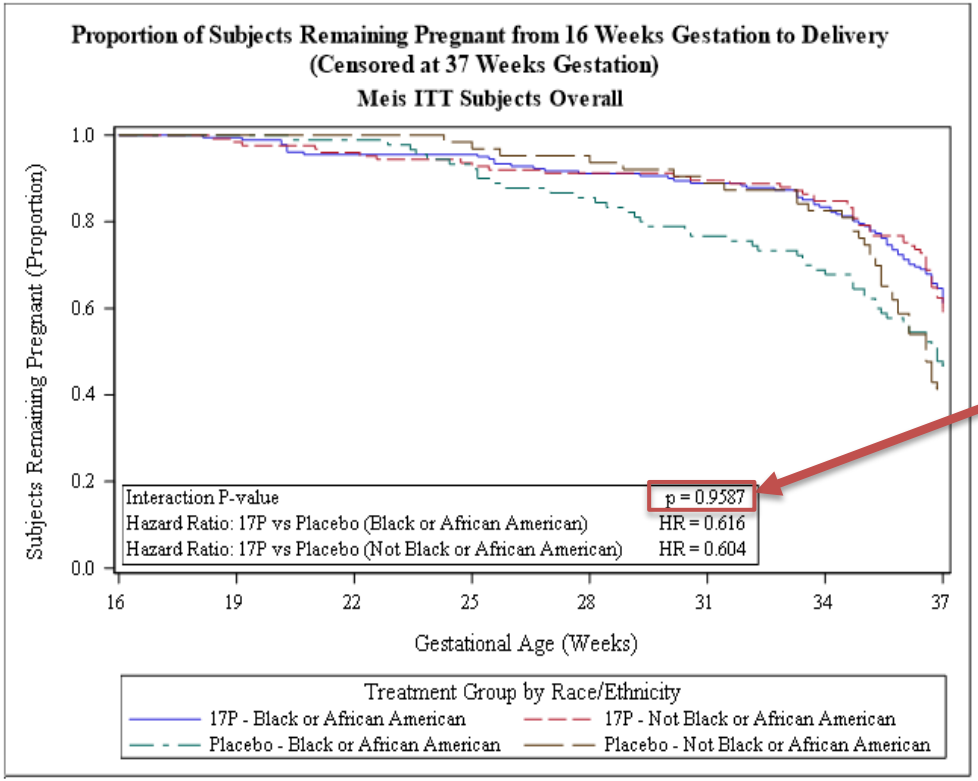


P value for "interaction" not significant

Source: Covis Briefing Materials @ 53 (Figure 7)

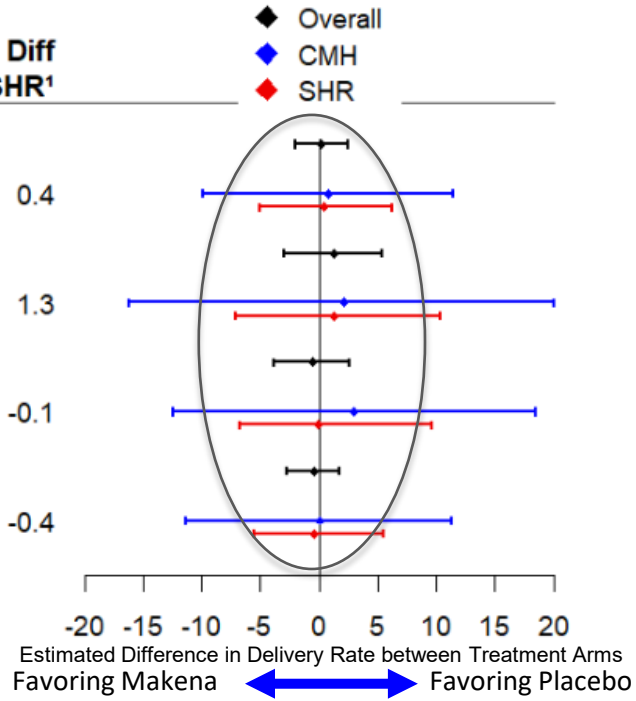
Trial 003 Pre-Specified Subgroups

Subgroup	Categories
Geographic region	U.S., Non-U.S.
Gestational age at randomization	16_0-17_6 weeks, 18_0-20_6 weeks
Gestational age at qualifying delivery*	20_0-<28_0 weeks, 28_0-<32_0 weeks, 32_0-<35_0 weeks, 35_0-<37_0 Weeks
Gestational age at earliest prior PTBs	0-<20_0, 20_0-<28_0, 28_0-<32_0, 32_0-<35_0, 35_0-<37_0
Number of previous PTBs	1, 2, ≥3
Cervical length at randomization	<25 mm ≥25 mm
BMI before pregnancy (kg/m_2)	<18.5, 18.5 - <25, 25-<30, ≥30
Any substance use during pregnancy	Yes, No
Smoking	Yes, No
Alcohol	Yes, No
Illicit drugs	Yes, No
Race	Non-Hispanic Black, non-Hispanic non-Black
Ethnicity	Hispanic, non-Hispanic
Years of education	≤12, >12

* Qualifying delivery is the most recent preterm delivery.

No Evidence of Treatment Effect in Either Black or non-Black Women (Trial 003)

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR[1]
Neonatal Index[2] (%)	5.4	5.2	0.2	
Black (69, 40)	8.7	7.5	0.8	0.4
PTB<37 Weeks (%)	23.1	21.9	1.3	
Black (72, 41)	37.4	34.2	2.1	1.3
PTB<35 Weeks[2] (%)	11.0	11.5	-0.6	
Black (72, 41)	23.6	19.5	3.0	-0.1
PTB<32 Weeks (%)	4.8	5.2	-0.4	
Black (72, 41)	11.1	9.8	0	-0.4

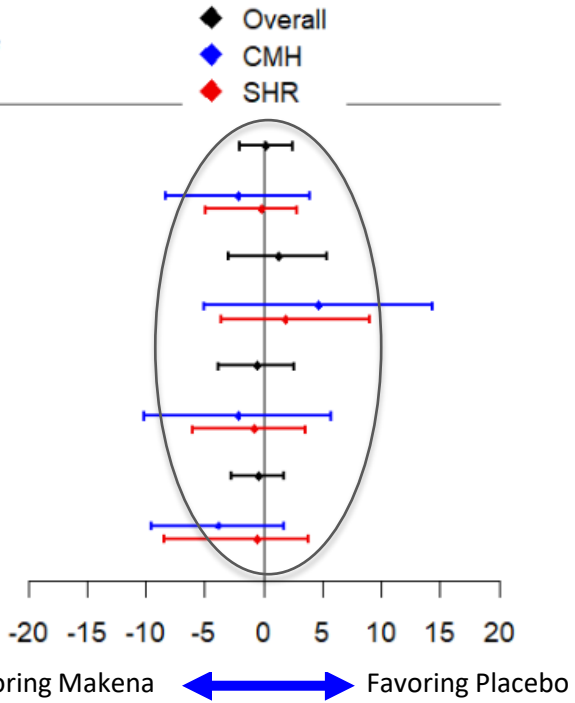


1: Shrinkage using "Non-Black" subgroup
2: Coprimary endpoints

CMH: stratified Cochran-Mantel-Haenszel; SHR: shrinkage estimation; (N Makena, N Placebo)
FDA Slides, 14–20, Figures 1-7, BRUDAC Meeting (Oct. 29, 2019)

No Evidence of Treatment Effect by Region (Trial 003)

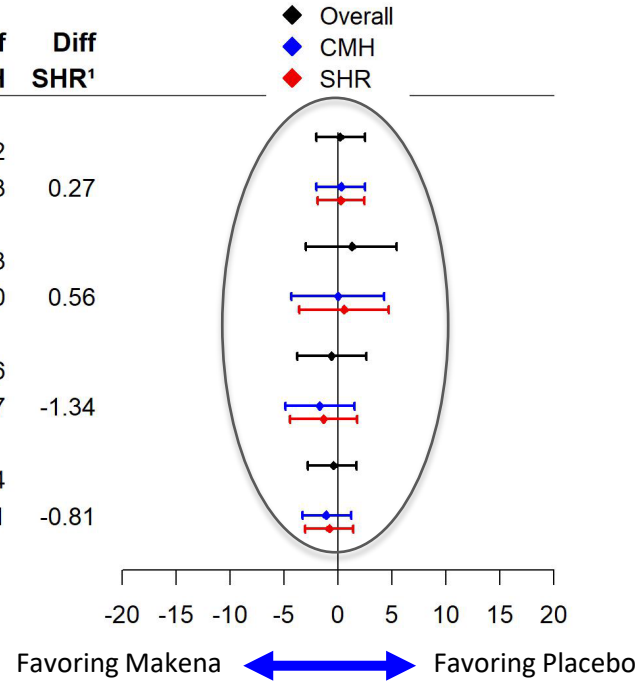
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR[1]
Neonatal Index[2] (%)	5.4	5.2	0.2	
US (252, 126)	7.1	9.5	-2.2	-0.2
PTB<37 Weeks (%)	23.1	21.9	1.3	
US (256, 131)	33.2	28.2	4.7	1.8
PTB<35 Weeks[2] (%)	11.0	11.5	-0.6	
US (256, 131)	15.6	17.6	-2.2	-0.8
PTB<32 Weeks (%)	4.8	5.2	-0.4	
US (256, 131)	5.5	9.2	-3.9	-0.6



1: Shrinkage using "Non-US" subgroup
2: Coprimary endpoints

No Evidence of Treatment Effect by Number of Prior Singleton sPTBs (Trial 003)

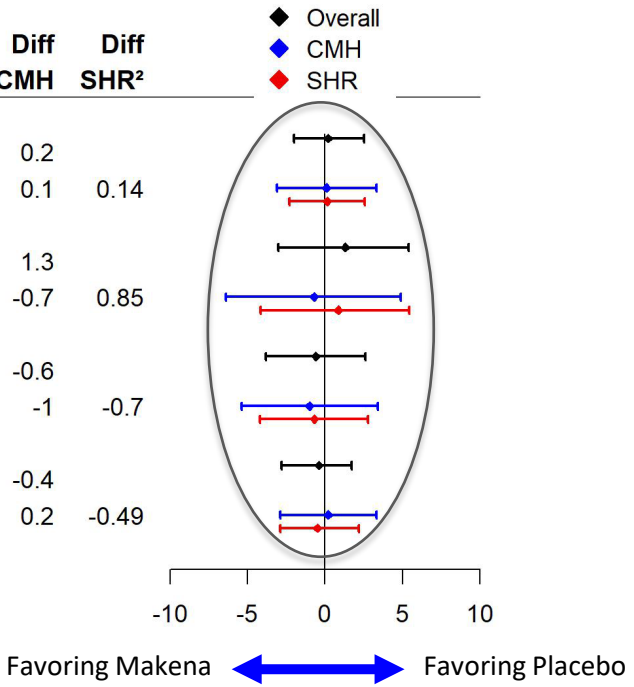
Endpoint Subgroup	Makena (%)	Placebo (%)	Diff CMH	Diff SHR[1]
Neonatal Index[2]	5.4	5.2	0.2	
>1 (145, 70)	4.8	4.5	0.3	0.27
PTB<37 Weeks (%)	23.1	21.9	1.3	
>1 (151, 71)	20	20	0	0.56
PTB<35 Weeks[2] (%)	11	11.5	-0.6	
>1 (151, 71)	8.5	10.1	-1.7	-1.34
PTB<32 Weeks (%)	4.8	5.2	-0.4	
>1 (152, 71)	3.9	5	-1.1	-0.81



1: Shrinkage using "1 prior singleton sPTB" subgroup
2: Coprimary endpoints

No Evidence of Treatment Effect in Those with Prior History of sPTB < 34 weeks (Trial 003)

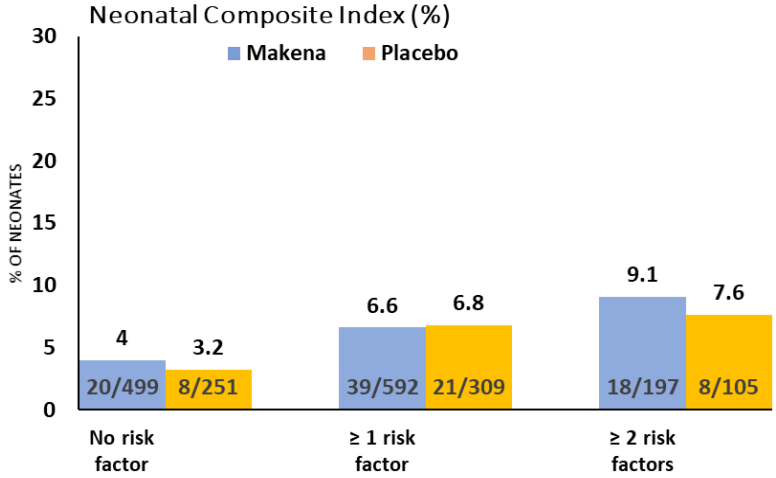
Endpoint Subgroup	Makena (%)	Placebo (%)	Diff CMH	Diff SHR[2]
NCI[1] (interaction p-value : 0.86)	5.4	5.2	0.2	
Any sPTB <34w	6.5	6.4	0.1	0.14
<37w (interaction p-value : 0.30)	23	22	1.3	
Any sPTB <34w	23.9	24.6	-0.7	0.85
<35w (interaction p-value : 0.57)	11	12	-0.6	
Any sPTB <34w	12.1	13.1	-1	-0.7
<32w (interaction p-value : 0.50)	5	5	-0.4	
Any sPTB <34w	6.2	6	0.2	-0.49

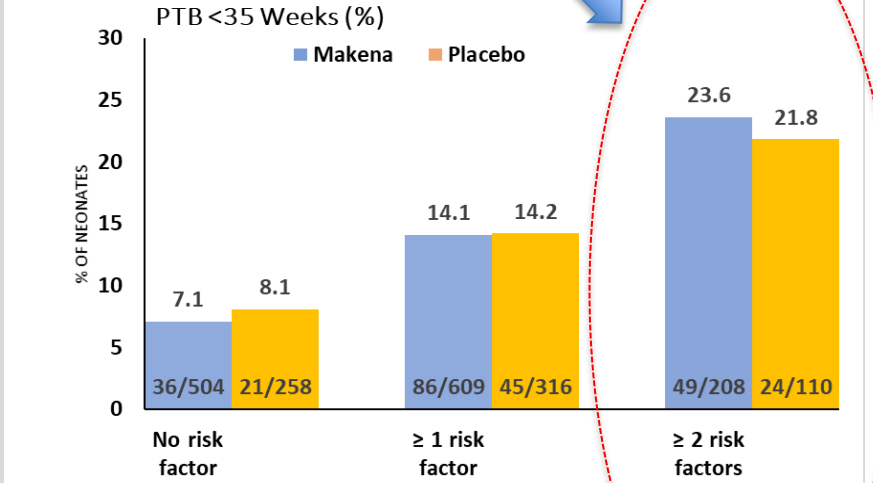


1: NCI: Neonatal Composite Index
2: Shrinkage using "No sPTB <34w" subgroup

No Greater Treatment Response Regardless of Number of Risk Factors in Trial 003

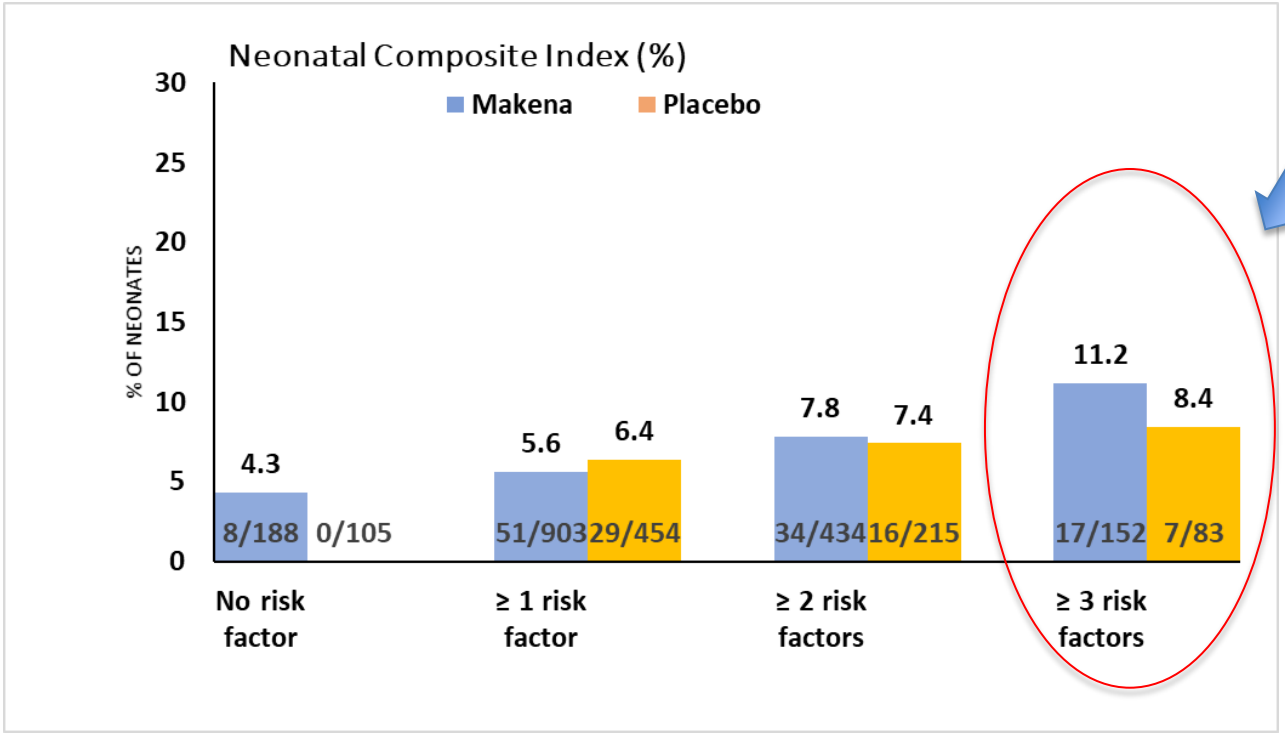
Even with ≥2 RFs, no greater response (also true for 3 or more, etc.)





Risk factors: Black race, history of more than one PTB, single/without partner, substance use in pregnancy, ≤ 12 years education

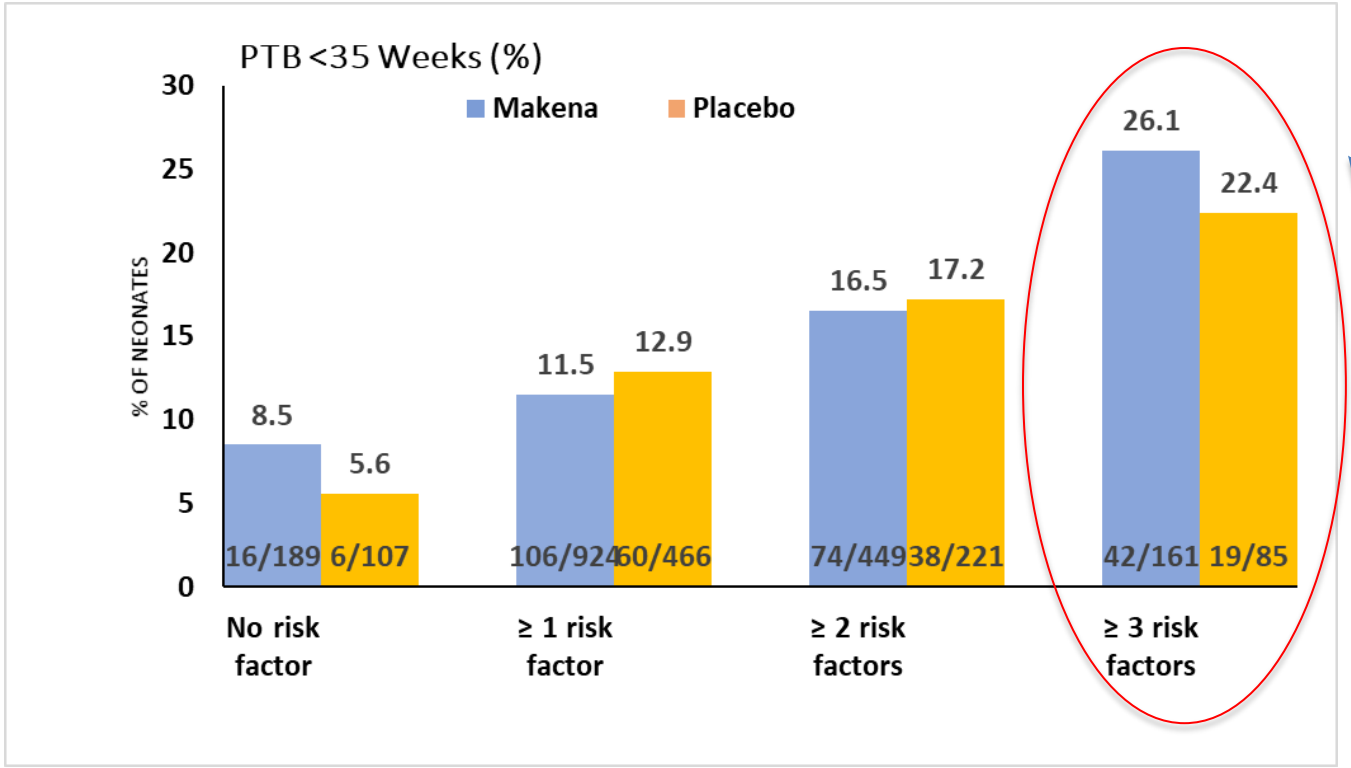
No Improvement for the Neonate in Risk Groups Defined Using 6 Risk Factors (Trial 003)



Even with ≥3 RFs, no improved response

Risk factors: Black race, history of more than one PTB, single/without partner, substance use in pregnancy, ≤ 12 years education, prior sPTB < 34w

No Improvement in PTB Rates in Risk Groups Defined Using 6 Risk Factors (Trial 003)

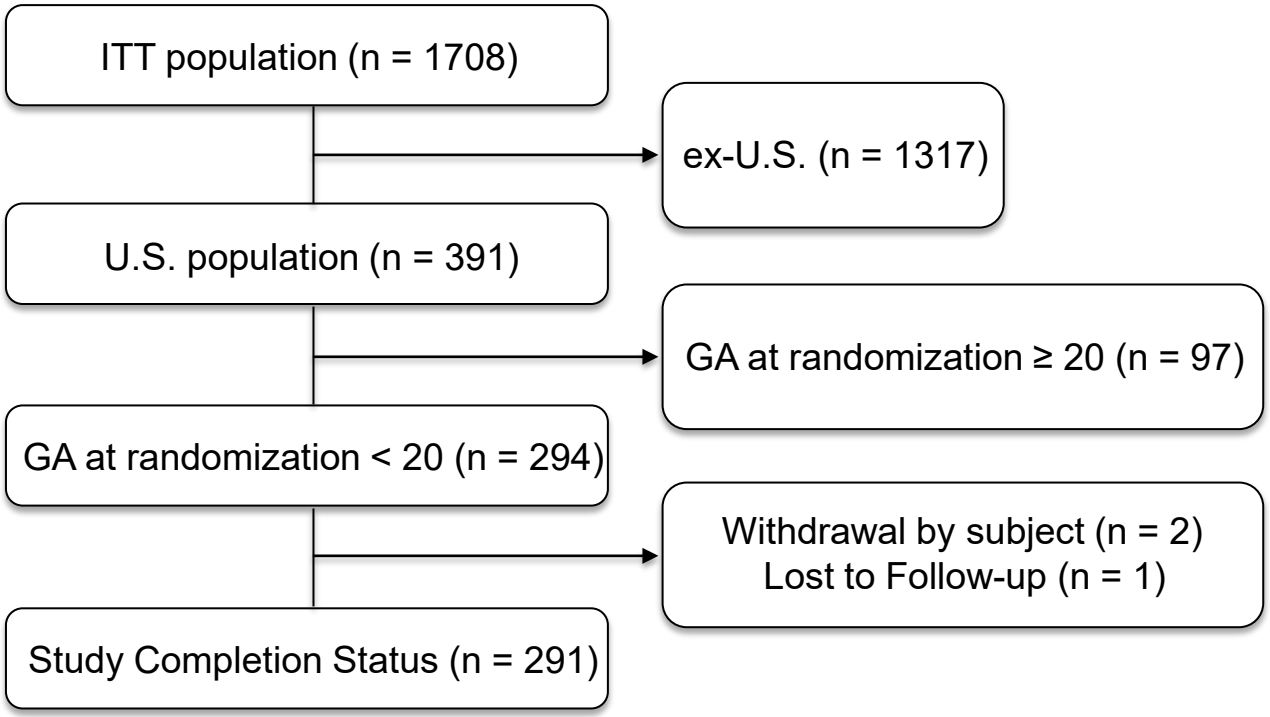


Even with ≥3 RFs, no improved response

Risk factors: Black race, history of more than one PTB, single/without partner, substance use in pregnancy, ≤ 12 years education, prior sPTB < 34w

New Covis Trial 003 subgroup analyses do not demonstrate Makena's efficacy

Covis' New Analyses of Trial 003



Covis' New Analyses of Trial 003

- New continuous endpoint and use of linear regression
- Concerns
  - Not pre-specified (post hoc)
  - Ignores negative outcomes (e.g., stillbirth)
  - Not robust - same analyses of Trial 002 generally do not show the same trends

Covis Table 9 Analyses Re-Run with Trial 002 Data

Estimated Treatment Effect (Weeks Gained) for HPC in Subgroups Defined by Most Recent Prior Gestational Age (mrpGA) of Previous Deliveries Among Subjects Randomized at <20 Weeks GA for Trial 002

m[rp]GA Subgroup	N Total	Estimated treatment effect (weeks gained)	Lower 95% CL	Upper 95% CL	P-value
mrpGA<28	67	**-0.09**	-3.05	2.87	0.9532
mrpGA<29	82	**0.44**	-2.07	2.94	0.7304
mrpGA<30	89	**0.37**	-1.91	2.64	0.7493
mrpGA<31	99	**0.42**	-1.63	2.48	0.6839
mrpGA<32	114	**0.94**	-0.91	2.8	0.3159
mrpGA<33	138	**1.17**	-0.47	2.81	0.1611
mrpGA<34	160	**0.9**	-0.6	2.4	0.2384
mrpGA<35	193	**1**	-0.25	2.26	0.1171
mrpGA<36	226	**0.81**	-0.31	1.93	0.1559
mrpGA<37	249	**0.74**	-0.31	1.79	0.165

Explanations for the Different Results of Trials 002 and 003

Covis Assertions

- Trial 002 shows higher risk women have a better response to Makena and Trial 003 failed to sufficiently include this higher risk population

CDER Assessment

- Little evidence that higher risk women have a higher response to Makena in 002 or 003 including from post-hoc analyses from Covis

Covis asserts that Trial 003 lacked power to detect a difference because it was conducted in a lower risk population

PTB Rates in Women with Prior sPTB: Epidemiological Data and Trial 003 Comparisons

Estimated U.S. recurrent PTB <37 weeks rate (based upon CDC data*)

- 17% = Lower estimate of recurrent PTB in the U.S.
- 20% = PTB < 37w in White women in Georgia (U.S.)
- 21.25% = Upper estimate of recurrent PTB in the U.S.

Range seen in Trial 003

- **22% = PTB < 37w Trial 003 Placebo subjects**
- 22% = sPTB < 37w MFMU Network (1999, U.S.)
- 26% = PTB < 37w in Black women in Georgia (U.S.)
- **28% = PTB < 37w Trial 003 Placebo subjects (U.S.)**
- 28% = PTB < 37w White women in Georgia with prior sPTB < 32w
- **34% = PTB < 37w Black 003 Placebo Subjects (U.S.)**
- 37% = PTB < 37w Black women in Georgia with prior sPTB < 32w

State of Georgia: Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. JAMA. 2000;283(12):1591–1596
MFMU Network: Mercer BM et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am. J. Obstet. Gynecol. 1999;181(5 Pt 1):1216.
Doubling of rate: Hyagriv N. Simhan; Vincenzo Berghella; Jay D. Iams. "Prevention and Management of Preterm Parturition."
Creasy & Resnik's Maternal-Fetal Medicine, Principles and Practice 8th Edition, edited by Robert Resnik; Charles J Lockwood; Thomas R. Moore; Michael F. Greene; Joshua A. Copel; Robert M. Silver, Elsevier, 2018, 679–711.
2.5-fold increase: Mercer BM et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am. J. Obstet. Gynecol. 1999;181(5 Pt 1):1216.
CDC rates: Martin JA, Osterman MJK. Exploring the decline in the singleton preterm birth rate in the United States, 2019–2020. NCHS Data Brief, no 430. Hyattsville, MD: National Center for Health Statistics. 2022, available at https://www.cdc.gov/nchs/data/databriefs/db430.pdf (last visited Sept. 14, 2022).

Women in Trial 002 and Trial 003 Have Similar Distributions of Gestational Age at Prior sPTB Deliveries

Distribution of GA (weeks)	25% Percentile	Mean	Median	75% Percentile
Trial 002 Qualifying sPTB	28	30.8	32	35
Trial 003 Qualifying sPTB	28	31.4	33	35

Trial 002 Has Higher Proportion of Women with Full-term Births between sPTB and Trial Enrollment

	Trial 002		Trial 003	
	n	n/463	n	n/1708
Women with FTBs between qualifying sPTB and trial enrollment	**101**	**22%**	**198**	**12%**

*Qualifying sPTB was determined for the analysis in the following manner: for Trial 002 the latest sPTB was considered the qualifying sPTB (there was no qualifying flag in the dataset); for Trial 003 the qualifying flag in the dataset was used.

Trial 003 Subjects Were Not at "Low Risk" for Recurrent PTB

- Trial 003 rate of PTB *consistent* with rate in U.S. Makena indicated population
- Trial 002 and Trial 003 had *similar* distributions of gestational age for prior sPTB
- Trial 003 participants had a *lower* rate of full-term births between qualifying sPTB and trial
- *No evidence* in subgroup analyses that higher numbers of risk factors lead to a different effect of Makena

90% Power for PTB < 37 weeks Endpoint in Trial 003
Power Table for a Relative Reduction in a Rate (Proportion)

Placebo Rate	5%	10%	20%	25%	30%	35%
21.9%	6.8	18.4	56.0	76.0	**90.1**	97.2

Trial 003 Results
Exclude Clinically Meaningful Effect Differences

Efficacy Outcome	Trial 003 Treatment Difference (95% CI)
Birth < 37 weeks	1.3% (-3.0, 5.4)

Rules out rate reductions greater than 3 percentage points

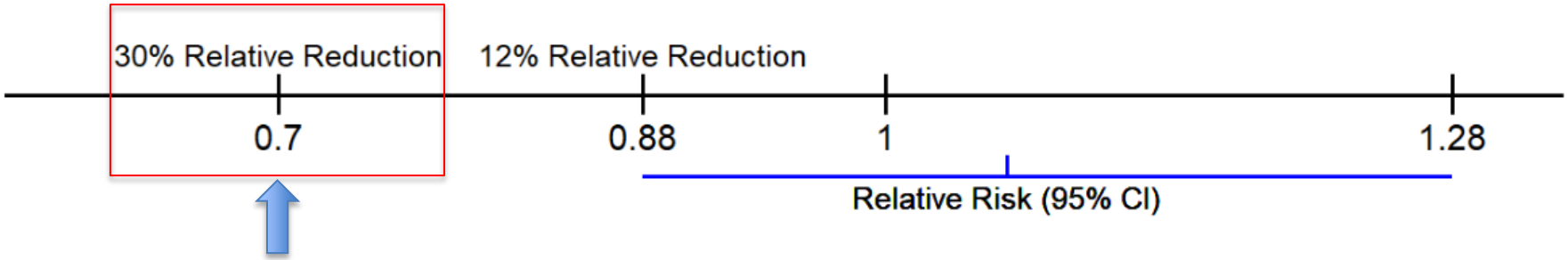
Trial 003 Results
Exclude Clinically Meaningful Relative Differences

Efficacy Outcome	Trial 003 RR (95% CI)
Birth < 37 weeks	1.06 (0.88, 1.28)

Rules out relative rate reductions greater than 12%

Planned Power: PTB: 30% relative reduction → 0.70 RR

Trial 003 Results
Exclude Clinically Meaningful Relative Differences



Explanations for the Different Results of Trials 002 and 003

Covis Assertions

- Trial 002 shows higher risk women have a better response to Makena and Trial 003 failed to sufficiently include this higher risk population

- Trial 003 lacked power to detect a difference because conducted in a lower risk population

CDER Assessment

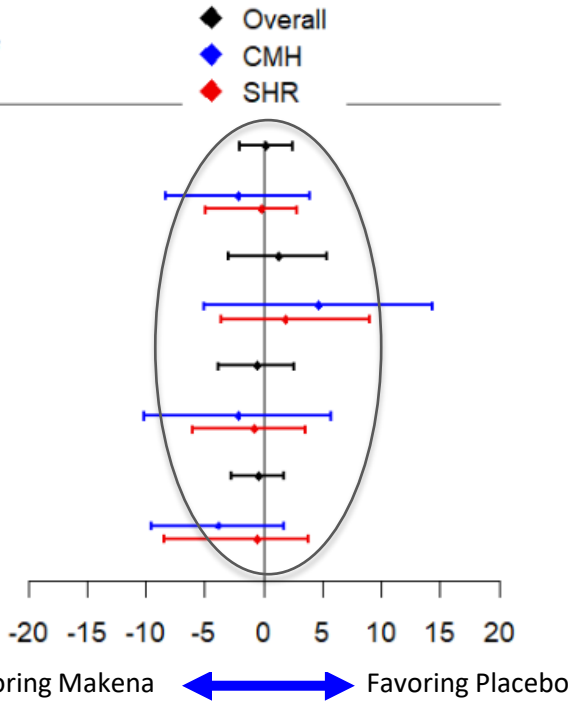
- Little evidence that higher risk women have a higher response to Makena in 002 or 003 including from post-hoc analyses from Covis

- Trial 003 was well powered and excluded a >12% relative reduction in Week 37 PTB rate
- Trial 003 population was not “low risk” – the PTB rate was consistent with the indicated population for Makena

Covis asserts regional differences explain failure of Trial 003 – women outside the U.S. were not properly evaluated and were at lower risk of PTB

No Evidence of Treatment Effect by Region

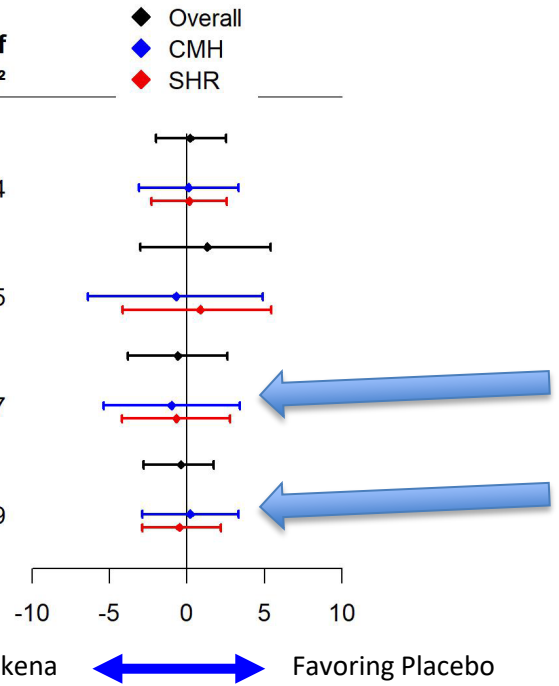
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR[1]
Neonatal Index[2] (%)	5.4	5.2	0.2	
US (252, 126)	7.1	9.5	-2.2	-0.2
PTB<37 Weeks (%)	23.1	21.9	1.3	
US (256, 131)	33.2	28.2	4.7	1.8
PTB<35 Weeks[2] (%)	11.0	11.5	-0.6	
US (256, 131)	15.6	17.6	-2.2	-0.8
PTB<32 Weeks (%)	4.8	5.2	-0.4	
US (256, 131)	5.5	9.2	-3.9	-0.6



1: Shrinkage using "Non-US" subgroup
2: Coprimary endpoints

Any Prior sPTB < 34 Weeks: No Evidence of Treatment Effect

Endpoint Subgroup	Makena (%)	Placebo (%)	Diff CMH	Diff SHR[2]
NCI[1] (interaction p-value : 0.86)	5.4	5.2	0.2	
Any sPTB <34w	6.5	6.4	0.1	0.14
<37w (interaction p-value : 0.30)	23	22	1.3	
Any sPTB <34w	23.9	24.6	-0.7	0.85
<35w (interaction p-value : 0.57)	11	12	-0.6	
Any sPTB <34w	12.1	13.1	-1	-0.7
<32w (interaction p-value : 0.50)	5	5	-0.4	
Any sPTB <34w	6.2	6	0.2	-0.49



1: NCI: Neonatal Composite Index
2: Shrinkage using "No sPTB <34w" subgroup

Explanations for the Different Results of Trials 002 and 003

Covis Assertions	CDER Assessment
• Trial 002 shows higher risk women have a better response to Makena and Trial 003 failed to sufficiently include this higher risk population	• Little evidence that higher risk women have a higher response to Makena in 002 or 003 including from post-hoc analyses from Covis
• Trial 003 lacked power to detect a difference because conducted in a lower risk population	• Trial 003 was well powered and excluded a >12% relative reduction in Week 37 PTB rate • Trial 003 population was not "low risk" – the PTB rate was consistent with the indicated population for Makena
• Regional differences explain failure of 003 – women outside the US were not properly evaluated and were at lower risk of PTB	• No differential effect of drug seen in U.S. or ex-U.S. • No evidence that evaluation of prior PTB was inaccurate (Dr. Nguyen will address) • No evidence that women with an earlier prior PTB (e.g., <34 weeks) had a different response in Trial 003

Covis asserts evidence from other studies supports response to HPC

Makena Real-World, Observational Studies Do Not Show Effectiveness

- Observational analyses – Real World Evidence – can provide supportive evidence for regulatory decision-making
  - Such analyses do not provide the same level of evidence as RCTs
  - Consistency across RWE studies supports stronger conclusions
- For Makena, effectiveness not shown in observational studies with varying study designs, settings, and data sources
- Supports the conclusions from Trial 003 that Makena is not shown to be effective

No Effectiveness Shown in Real-World Studies

- Massa et al. (2020): Academic tertiary care center
  - No association with HPC use and pregnancy prolongation up to 35 weeks
- Wang et al. (2021): Medicaid enrollees in Pennsylvania
  - No benefit in reduction of PTB risk or admission of the neonate into ICU
- Hakim et al. (2021): Commercial insurance claims
  - No benefit for prevention of recurrent PTB

Massa K, Childress K, Vricella LK, et al. Pregnancy duration with use of 17-a-hydroxyprogesterone caproate in a retrospective cohort at high risk of recurrent preterm birth. Am J Obstet Gynecol MFM 2020;2:100219.; Wang X, Garcia S, Kellom K, Boelig R, and Matone M. Eligibility, Utilization, and Effectiveness of 17-Alpha Hydroxyprogesterone Caproate (17OHPC) in a Statewide Population-Based Cohort of Medicaid Enrollees. Am J Perinatol, published online 11-16-2021.; Hakim J, Zhou A, Hernandez-Diaz S, et al. Effectiveness of 17-OHP for Prevention of Recurrent Preterm Birth: A Retrospective Cohort Study. Am J Perinatol, published online: 12-31-2021.

No Effectiveness Shown in Real-World Studies

- Nelson et al. (2017): University teaching hospital in Texas
  - No changes in duration of pregnancy or recurrent PTB ≤35 weeks
- Bastek et al. (2012) – Academic medical center
  - Found no change in institutional PTB rate or gestational delivery age (primary objective)
    - Compared institutional rates before and after implementation of Makena as standard of care
    - In women delivering preterm, a claimed increase in gestational delivery age in Makena period
    - Significant limitations: unknown Makena use, limited confounding control, unclear analysis population and methods
- Neither study shows Makena to be effective

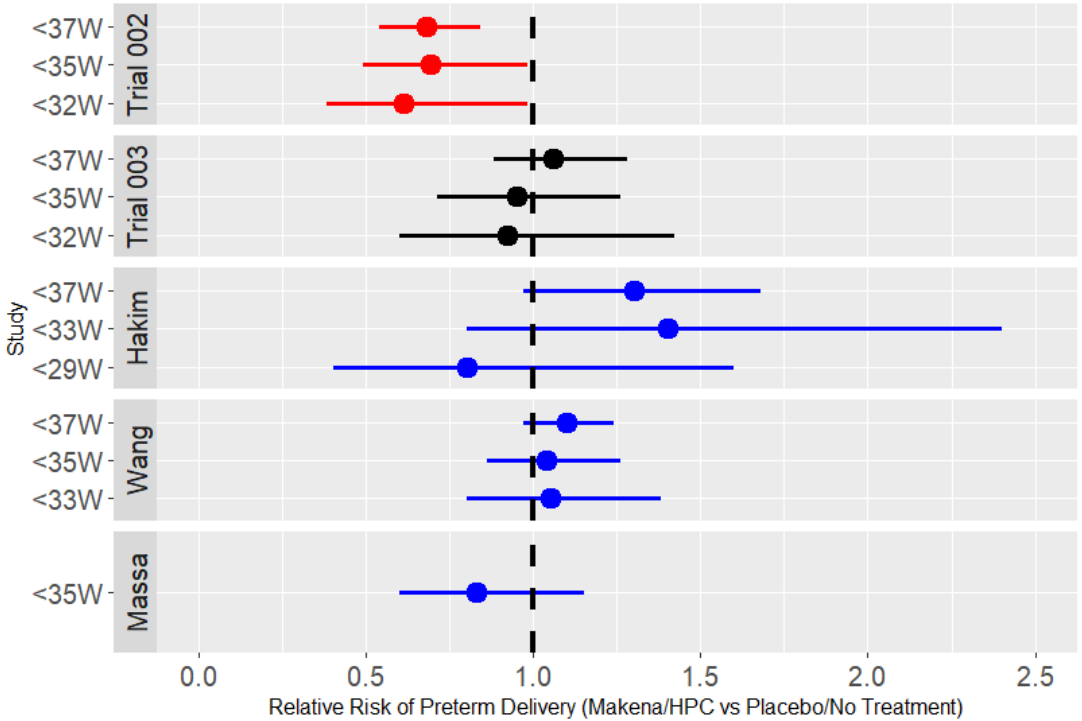
Nelson DB, McIntire DD, McDonald J, Gard J, Turrichi P, Leveno KJ. 17-alpha hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol. 2017;216:600.e1-9.; Bastek JA, Adamczak JE, Hoffman S, Elovitz MA, Srinivas SK. Trends in prematurity: What do changes at an urban institution suggest about the public health impact of 17-alpha hydroxyprogesterone caproate? Matern Child Health J. 2012;16:564-568

Diverse Populations in Real-World Observational Studies

Study (year)	Setting	Maternal age (years)	Predominate race/ethnicity	Region
Hakim (2021)	Commercial claims data	Mean: 33.3	Not provided	US
Wang (2021)	Medicaid claim data	< 20 0.6% 20-34 89.7% ≥ 35 9.7%	White 50% Black 31%	Pennsylvania
Massa (2020)	Academic tertiary care center	Mean: 29.1	Black 66% White 31%	Saint Louis, MO
Nelson (2017)	University teaching hospital	< 20 4% 20-34 77% ≥ 35 19%	Hispanic 80% Black 17%	Dallas, TX
Bastek (2012)	Urban academic medical center	Mean: 27.6	Black 76% White 15%	Pennsylvania

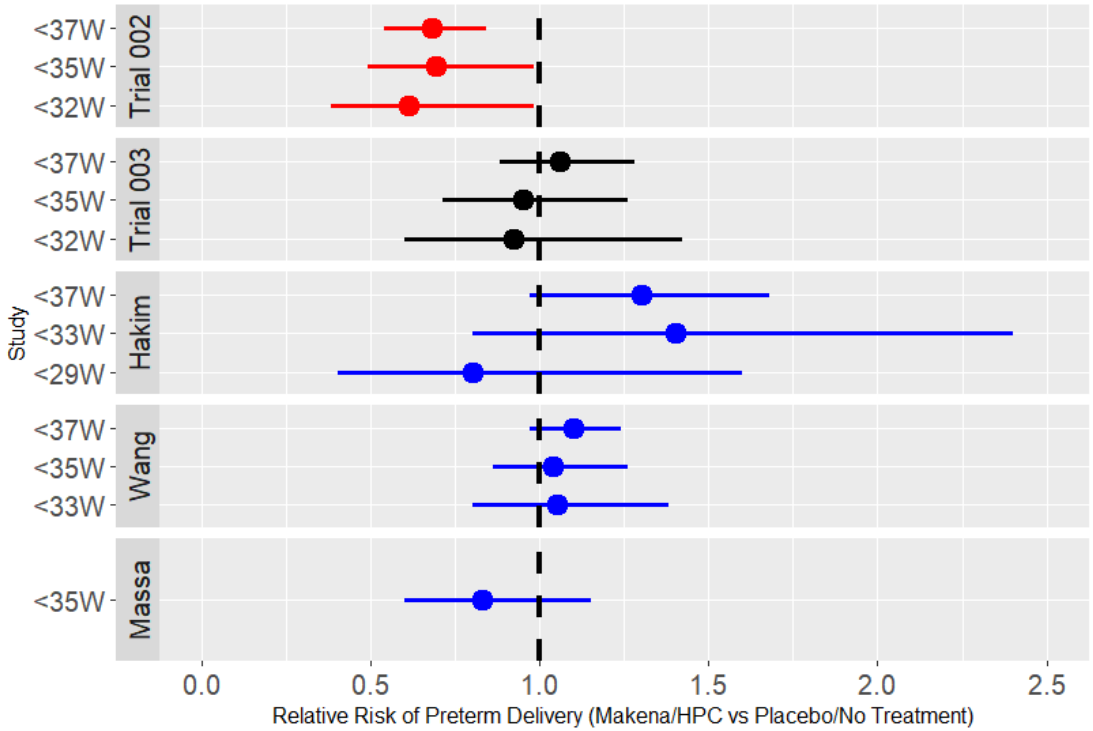
Outlier is Trial 002

RCTs and Observational Studies in Indicated Population



- Trial 002 (Meis, N=463) and Trial 003 (PROLONG, N=1,708): RCTs for Makena's intended population
- Hakim (N=4,422), Wang (N=4,781), Massa (N=861): Observational studies with untreated concurrent comparator

Bastek and Nelson did not report relative risks. Results in both were not statistically significant. PROGFIRST, an RCT, had drug quality issues potentially impacting drug potency and efficacy.



Question No. 2: Does the available evidence demonstrate that Makena is effective for its approved indication…?

No.

RANDOMIZED CONTROLLED TRIALS (RCT) IN OTHER SINGLETON AND MULTI-GESTATION PREGNANCIES DO NOT SHOW A RESPONSE TO MAKENA/HPC

The EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. The Lancet 2021;397 (10280):1183-1194.
Price JT, et al., Weekly 17 alpha-hydroxyprogesterone caproate to prevent preterm birth among women living with HIV: a randomised, double-blind, placebo-controlled trial, The Lancet HIV. 2021; 8(10): e605-e613.

RCTs in Singleton Gestations in Other Populations No Evidence of Effectiveness

- Price et al. (2021): HIV+ women in Zambia (N=800)
  - PTB < 37 weeks or stillbirth: RR (95% CI) = 1.0 (0.6, 1.6)
  - PTB < 37 weeks: RR (95% CI) = 0.9 (0.6, 1.4)
- SCAN: shortened cervix and no prior preterm birth in U.S. (N=657)
  - PTB < 37 weeks: RR (95% CI) = 1.03 (0.79, 1.35)
- PHENIX: shortened cervix plus at least one other risk factor for PTB in France (N=105)
  - Higher dose than Makena (HPC 500 mg not HPC 250 mg); open label
  - PTB < 37 weeks: RR (95% CI) = 1.01 (0.65, 1.57)
  - PTB < 34 weeks: RR (95% CI) = 0.78 (0.40, 1.53)
  - PTB < 32 weeks: RR (95% CI) = 0.64 (0.25, 1.62)

Of the 5 trials in EPPPIC relevant to Makena and singleton pregnancies, two were Trial 002 and Trial 003. A third was PROGFIRST which had known drug quality issues potentially impacting drug potency and efficacy. Price was not in EPPPIC and published after EPPPIC.

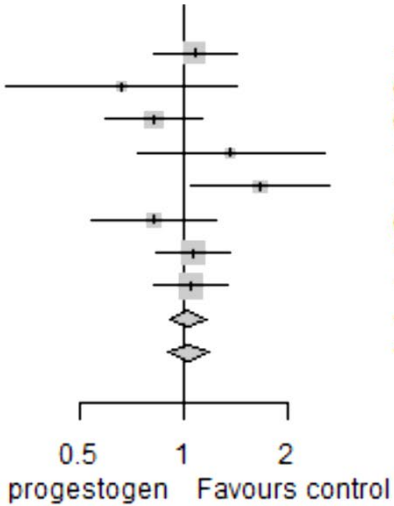
Limitations of EPPPIC Analysis PTB <34 Weeks

- No statistically significant effect in reducing PTB <34 weeks (RR= 0.83, CI= 0.68 - 1.01)
  - Upper bound of the CI notably increased if 002 is removed
- No effect on delivery prior to 37- or 28-weeks gestation, perinatal deaths, or serious neonatal complications
- Results on “high-risk” women based on small and not relevant sample

No Effect: Multiple Gestations (EPPPIC)

Study	Progestogen Events	Progestogen Total	Control Events	Control Total	RR	95%-CI
17-OHPC						
AMPHIA	80	336	73	330	1.08	[0.81; 1.42]
Briery 2009	6	16	8	14	0.66	[0.30; 1.43]
Combs Triplets 2010	33	56	18	25	0.82	[0.59; 1.14]
Combs Twins 2011	31	160	11	78	1.37	[0.73; 2.59]
PHENIX Twins	33	82	19	79	1.67	[1.04; 2.68]
PROGESTWIN	44	194	26	94	0.82	[0.54; 1.24]
SSTARS Triplets	48	71	40	63	1.06	[0.83; 1.36]
SSTARS Twins	93	325	90	330	1.05	[0.82; 1.34]
Fixed effect model		**1240**		**1013**	**1.03**	**[0.92; 1.16]**
Random effects model					**1.03**	**[0.89; 1.19]**

Heterogeneity: I^2 = 25%, τ^2 = 0.0107, p = 0.23



Extracted from Appendix Figure 13: Multifetal pregnancies preterm birth before 34 weeks (two-stage meta-analyses) from Supplement to: The EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet* 2021; 397: 1183–94.

Explanations for the Different Results of Trials 002 and 003

Covis Assertions	CDER Assessment
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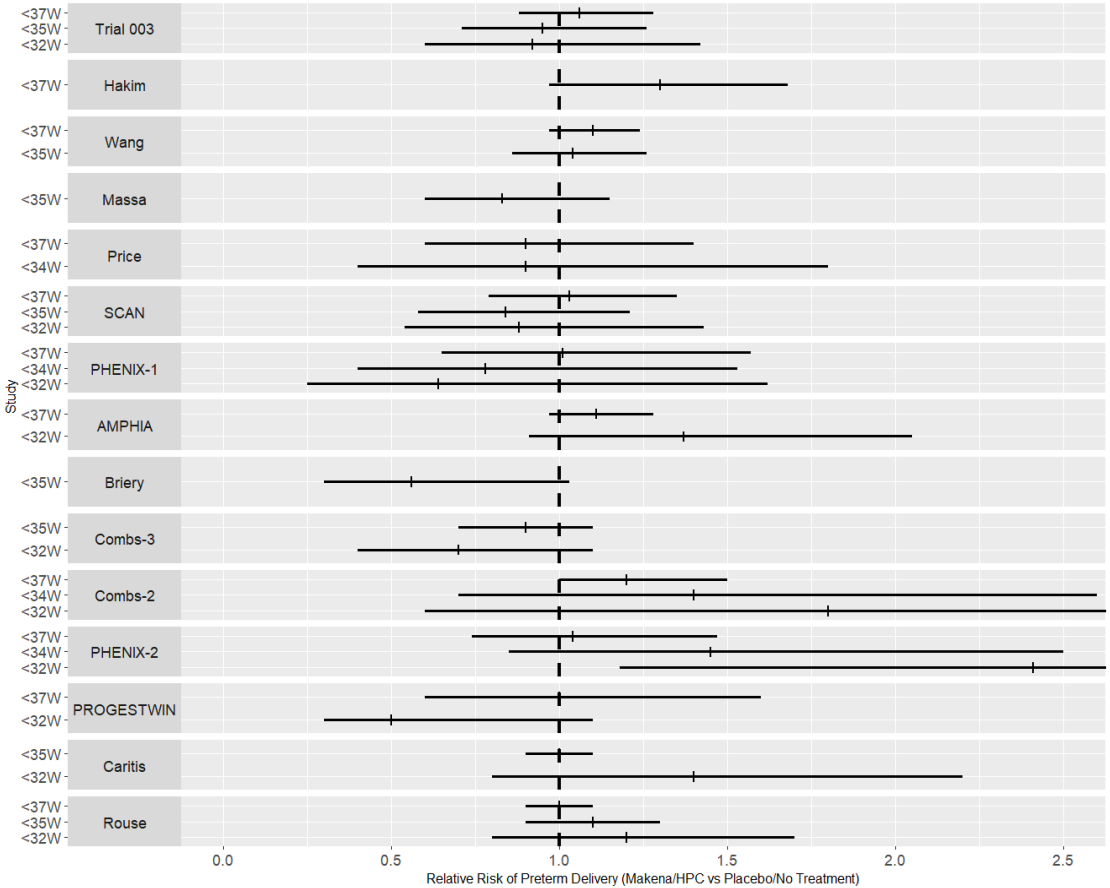
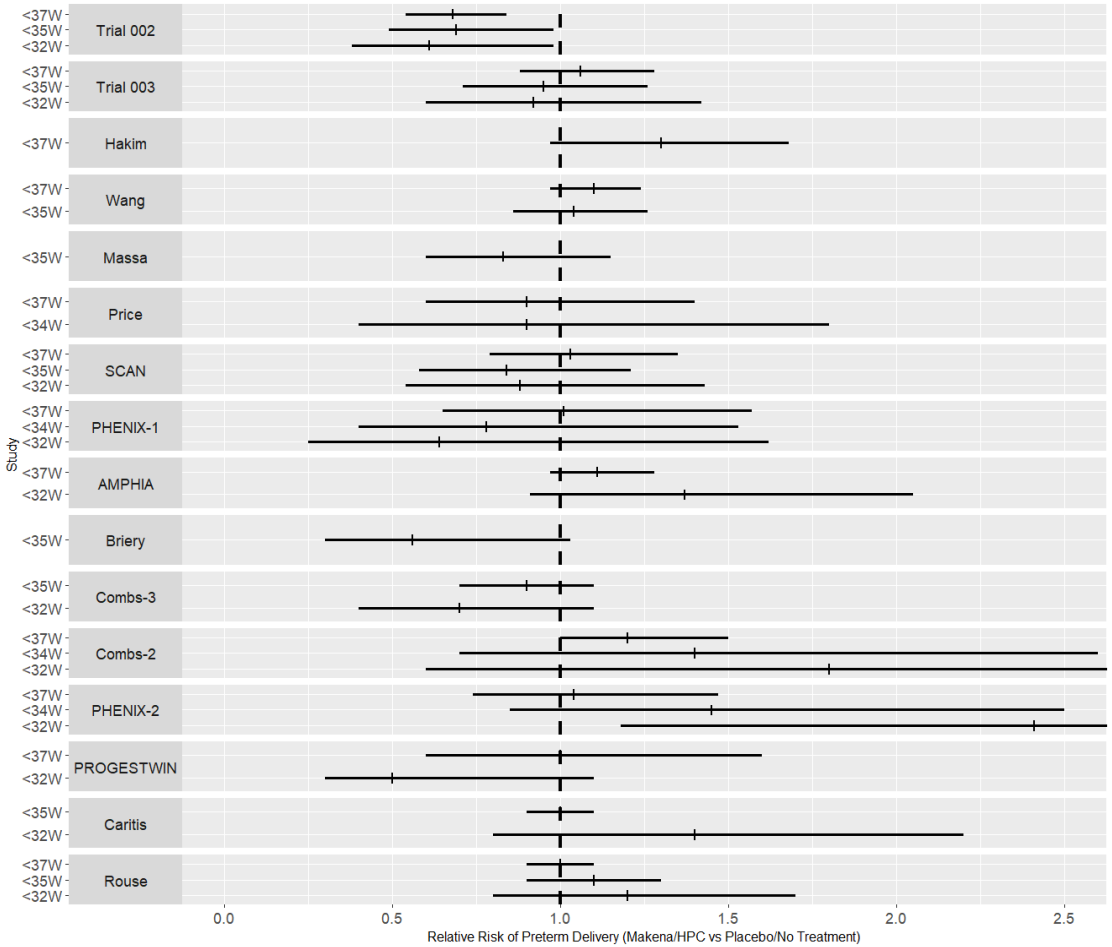
• Evidence from other studies supports response to HPC	• Well conducted observational studies do not show a response to Makena • RCTs in singleton pregnancies – and in multi-gestation pregnancies do not show a response to HPC

Results Across Studies Without Trial 002



Results Across Studies Do Not Support That Makena Is Effective



No evidence of a consistent effect on any gestational age cutpoints

Makena Has Not Been Shown to be Effective

- For indicated population (Question 2), **or**
- For subsets of the indicated population, **or**
- For related non-indicated populations

Rationale for Withdrawal

Part 3

Christine P. Nguyen, M.D.
Deputy Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research

Question No. 3
Should FDA allow Makena to remain on the market?

As part of that discussion, you may discuss:

A. Whether the benefit-risk profile supports retaining the product on the market;

B. What types of studies could provide confirmatory evidence to verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

Question No. 3
Should FDA allow Makena to remain on the market?

As part of that discussion, you may discuss:

A. Whether the benefit-risk profile supports retaining the product on the market;

B. What types of studies could provide confirmatory evidence to verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

Response:

No. Makena's unfavorable benefit-risk profile does not support retaining the product on the market

Makena's Benefit-Risk Profile Is Unfavorable

- Makena has not been shown to be effective
  - No evidence of neonatal benefit
  - No longer shown to be effective for reducing recurrent PTB

- Associated with serious adverse reactions

- Other potential safety issues not yet known, intergenerational safety

Makena's Known Risks Harm Patients

- Reports of thromboembolic events with Makena have been identified
- Allergic reactions can be serious
- Decreased glucose tolerance can exacerbate gestational diabetes, etc.
- Fluid retention may worsen maternal conditions such as pre-eclampsia
- Depression requiring hospitalization has been reported

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- Allergic reactions: Consider discontinuing if allergic reactions occur (5.2)
- Decreased glucose tolerance: Monitor prediabetic and diabetic women receiving Makena (5.3)
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- Depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)

----------ADVERSE REACTIONS----------

- In a study where the Makena instramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥ 2% of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). (6.1)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena auto-injector use (and higher than with Makena intramuscular injection)-was injection site pain (10% in one study and 34% in another). (6.1)

Makena's Known Risks Harm Patients

- Reports of thromboembolic events with Makena have been identified
- Allergic reactions can be serious
- Decreased glucose tolerance can exacerbate gestational diabetes, etc.
- Fluid retention may worsen maternal conditions such as pre-eclampsia
- Depression requiring hospitalization has been reported
- Injection site reactions

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- Allergic reactions: Consider discontinuing if allergic reactions occur (5.2)
- Decreased glucose tolerance: Monitor prediabetic and diabetic women receiving Makena (5.3)
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- Depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)

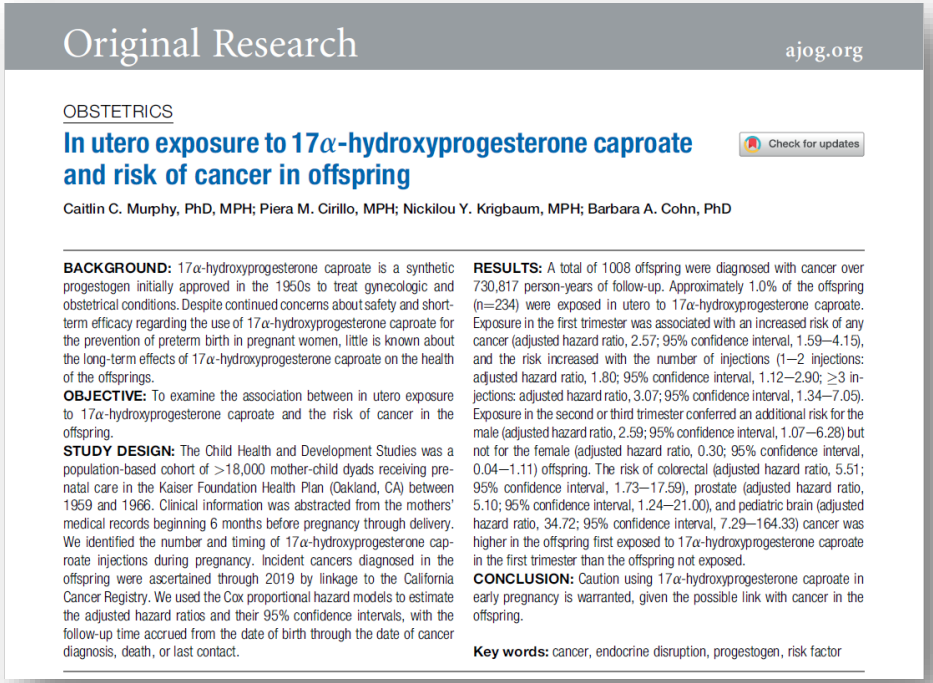
----------ADVERSE REACTIONS----------

- In a study where the Makena instramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥ 2% of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). (6.1)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena auto-injector use (and higher than with Makena intramuscular injection)-was injection site pain (10% in one study and 34% in another). (6.1)

Uncertainty about Intergenerational Safety

- Murphy et al. reported **increased cancer risk in the children** of women treated with HPC, the active ingredient in Makena
  - CDER's evaluation concluded study raised questions of safety meriting further surveillance
  - Highlights uncertainty regarding inter-generational safety for children exposed repeatedly to Makena in utero

Murphy CC, et al. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am. J. Obstet. Gynecol. 2022 Jan;226(1):132.e1–132.e14.



Original Research ajog.org

OBSTETRICS

In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring

Check for updates

Caitlin C. Murphy, PhD, MPH; Piera M. Cirillo, MPH; Nickilou Y. Krigbaum, MPH; Barbara A. Cohn, PhD

BACKGROUND: 17α-hydroxyprogesterone caproate is a synthetic progestogen initially approved in the 1950s to treat gynecologic and obstetrical conditions. Despite continued concerns about safety and short-term efficacy regarding the use of 17α-hydroxyprogesterone caproate for the prevention of preterm birth in pregnant women, little is known about the long-term effects of 17α-hydroxyprogesterone caproate on the health of the offsprings.

OBJECTIVE: To examine the association between in utero exposure to 17α-hydroxyprogesterone caproate and the risk of cancer in the offspring.

STUDY DESIGN: The Child Health and Development Studies was a population-based cohort of >18,000 mother-child dyads receiving prenatal care in the Kaiser Foundation Health Plan (Oakland, CA) between 1959 and 1966. Clinical information was abstracted from the mothers' medical records beginning 6 months before pregnancy through delivery. We identified the number and timing of 17α-hydroxyprogesterone caproate injections during pregnancy. Incident cancers diagnosed in the offspring were ascertained through 2019 by linkage to the California Cancer Registry. We used the Cox proportional hazard models to estimate the adjusted hazard ratios and their 95% confidence intervals, with the follow-up time accrued from the date of birth through the date of cancer diagnosis, death, or last contact.

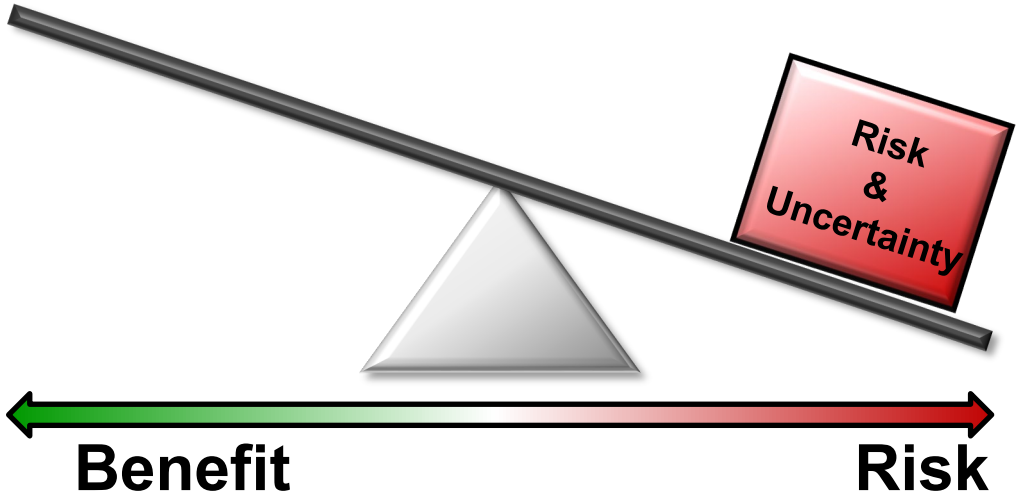
RESULTS: A total of 1008 offspring were diagnosed with cancer over 730,817 person-years of follow-up. Approximately 1.0% of the offspring (n=234) were exposed in utero to 17α-hydroxyprogesterone caproate. Exposure in the first trimester was associated with an increased risk of any cancer (adjusted hazard ratio, 2.57; 95% confidence interval, 1.59–4.15), and the risk increased with the number of injections (1–2 injections: adjusted hazard ratio, 1.80; 95% confidence interval, 1.12–2.90; ≥3 injections: adjusted hazard ratio, 3.07; 95% confidence interval, 1.34–7.05). Exposure in the second or third trimester conferred an additional risk for the male (adjusted hazard ratio, 2.59; 95% confidence interval, 1.07–6.28) but not for the female (adjusted hazard ratio, 0.30; 95% confidence interval, 0.04–1.11) offspring. The risk of colorectal (adjusted hazard ratio, 5.51; 95% confidence interval, 1.73–17.59), prostate (adjusted hazard ratio, 5.10; 95% confidence interval, 1.24–21.00), and pediatric brain (adjusted hazard ratio, 34.72; 95% confidence interval, 7.29–164.33) cancer was higher in the offspring first exposed to 17α-hydroxyprogesterone caproate in the first trimester than the offspring not exposed.

CONCLUSION: Caution using 17α-hydroxyprogesterone caproate in early pregnancy is warranted, given the possible link with cancer in the offspring.

Key words: cancer, endocrine disruption, progestogen, risk factor

Makena's Unfavorable Benefit-Risk Balance Supports Removal from Market

Absent demonstrated effectiveness, using Makena to prevent recurrent PTB in pregnant women exposes them only to risks.



Question No. 3
Should FDA allow Makena to remain on the market?

As part of that discussion, you may discuss:

A. Whether the benefit-risk profile supports retaining the product on the market;

B. What types of studies could provide confirmatory evidence to verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

CDER's Answer:

Only a Randomized, Double-Blind, Placebo-Controlled Trial Could Verify Clinical Benefit

Only a Randomized, Double-Blind, Placebo-Controlled Trial Could Verify Clinical Benefit of Makena

- Not possible to determine Makena's effect without randomization, blinding, placebo control
  - Randomization: balance the known, unknown confounders for PTB
  - Blinding: minimize bias from clinical decisions impacting delivery with knowledge of treatment assignment
  - Placebo control: allows drug attribution as most subjects will have full-term birth without treatment

- No other study design can obtain reliable evidence of Makena's efficacy when:
  - sPTB and recurrent PTB are poorly understood
  - Patients not prescribed Makena differ from those prescribed Makena
  - A 1,708-person RCT has already failed to verify its clinical benefit

Question No. 4 (For Vote)

Considering your responses to the previous questions both in the discussions and votes, should FDA allow Makena to remain on the market while an appropriate confirmatory study is designed and conducted?

Response: No

Conducting Another RCT in U.S. While Makena Remains On The Market Is Infeasible

- An RCT could only be feasible in the U.S. if Makena is first withdrawn

- While Makena stays on market, same or greater recruitment challenges as for Trial 003
  - Trial 003 had significant recruitment difficulties after Makena was approved
  - Providers and patients unlikely to risk patients being randomized into placebo arm when patients can receive Makena by *not* enrolling in a trial

Covis' Surveys Do Not Inform Feasibility of Another RCT in U.S.

- Providers asked, "How likely are you to recommend a pregnant patient enroll in a placebo-controlled study comparing the efficacy of a product vs placebo when the product has been approved by FDA?"
  - Question does not specify the FDA-approved indication (reducing risk of recurrent PTB or another indication?)

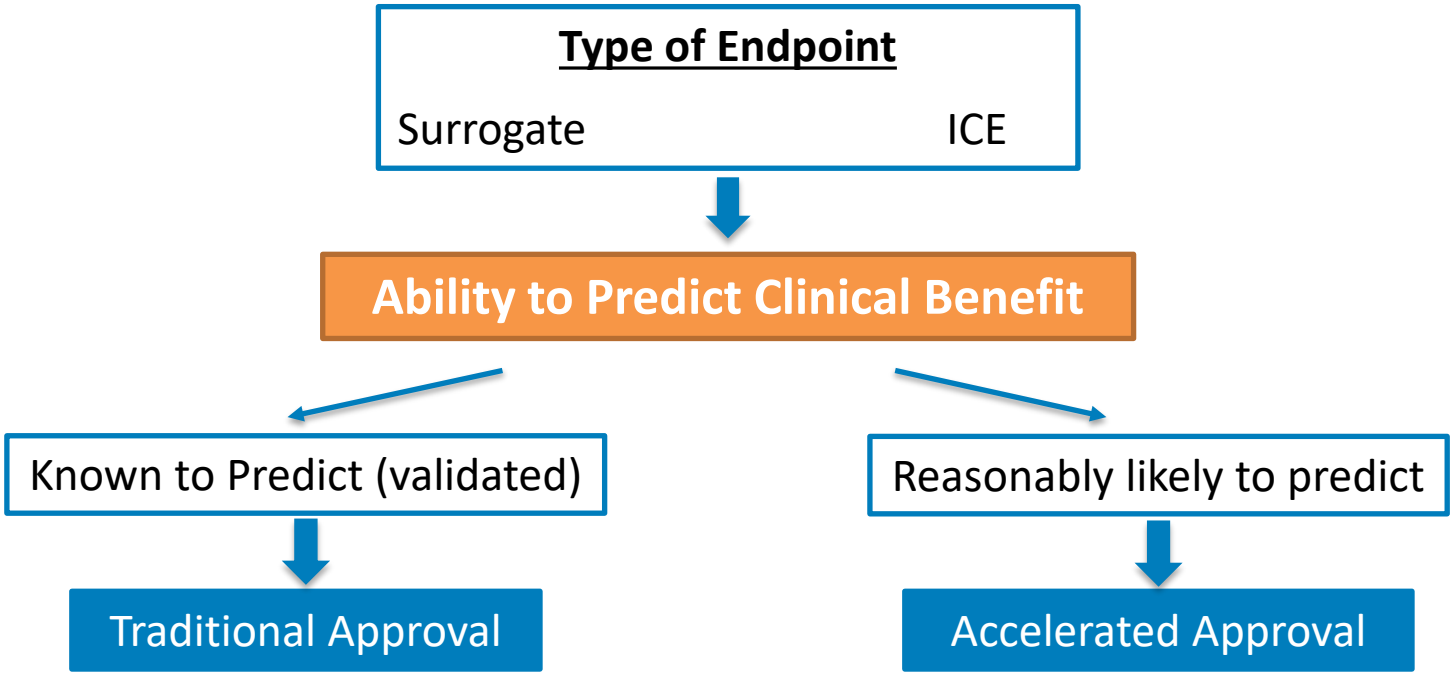
Why would providers recommend, and patients be willing to enroll in RCT that investigates the same use as the indication already approved?

RCT Conducted Outside the U.S. Could Not Be Completed in a Timely Manner

- Even if possible, new trial would likely take at least another decade before results available
- Trial 003 enrolled 1,700 subjects from 93 clinical sites, largely outside the U.S.
  - Almost 10 years to complete
- Sponsor's proposed RCTs estimated sample size from ~1,200 to 3,200 subjects
  - Likely to take *at least* as much time as Trial 003
- Leaving Makena on the market waiting for another RCT would likely mean 20+ years of no verified benefit, known risks

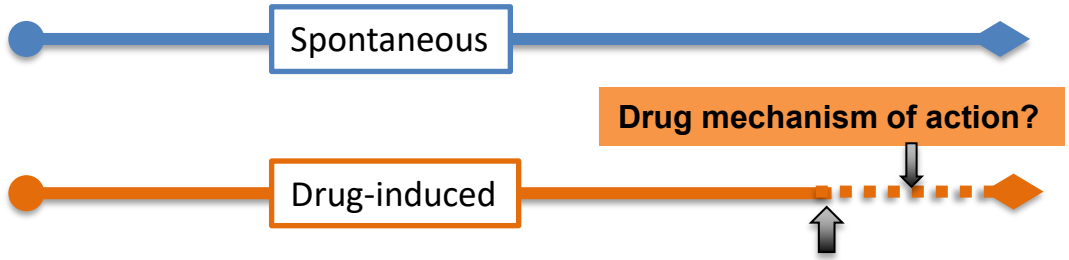
CDER'S RESPONSES TO ADDITIONAL ARGUMENTS BY COVIS

Intermediate Clinical Endpoint (ICE) Does Not Mean Traditional Approval Pathway



Uncertain Whether Drug-Induced Prolongation of Pregnancy Improves Neonatal Outcomes

- Sufficient evidence indicating later age of GA of *spontaneous* delivery correlates with improved neonatal outcomes
- No robust evidence indicating *drug-induced* prolongation of pregnancy correlates with same improved neonatal outcomes at the same GA of spontaneous delivery



Neonatal outcomes 32 weeks delivery

?=?

Neonatal outcomes 32 weeks delivery

- **Subclinical Infection?**
- **Subclinical uteroplacental insufficiency?**
- **Fetal reasons?**
- **Other reasons for which it is better to deliver than remain in utero?**

Qualifying Pregnancy Gestational Age was Reliable in Trial 003

- No evidence indicating qualifying pregnancy gestational age (GA) in Ukraine/Russia was inaccurate
  - GA: documented history of preterm delivery (patient report, medical record, crossed-checked by neonatal birth weight)
  - Neonatal weight validation applied to all countries; treatment groups balanced in neonatal weights of qualifying PTB
  - No reason for information bias

Qualifying Pregnancy Gestational Age Did Not Bias Trial 003

- Qualifying pregnancy gestational age was a **pre-randomization** variable
  - Upon randomization, the proportions of Russian, Ukraine, or U.S. subjects between the Makena and placebo groups balanced
  - Gestational age of qualifying pregnancies comparable between the two treatment groups

Potential for Off-Label Prescribing Does Not Justify Retaining Approval

- Prescribers may use their medical judgment to prescribe approved drugs for unapproved indications

- Potential for off-label prescribing is not a basis to approve or maintain approval of a drug that is no longer shown to be effective
  - CDER's proposal to withdraw is based on Makena's
    - ✓ Failure to demonstrate effectiveness
    - ✓ Unfavorable benefit-risk profile

- Sponsor's assertion about widespread off-label use is speculative

Potential for Compounding Does Not Justify Retaining Approval

- HPC may be eligible for compounding provided certain conditions in the FDCA are met
- Concerns about compounding are not a basis to approve or maintain approval of a drug that is no longer shown to be effective
  - CDER's proposal to withdraw is based on Makena's
    - ✓ Failure to demonstrate effectiveness
    - ✓ Unfavorable benefit-risk profile

Withdrawing Makena is Based on Its Merits

- Withdrawal of accelerated approval is made on each drug's own merits
- Trial 003 did not demonstrate
  1. Clinical benefit
  2. Effect on the endpoint that was the basis of accelerated approval

Makena's failure on both efficacy outcomes is *unique*

Withdrawal Under Accelerated Approval is Not Rare

- Numerous examples of withdrawals after negative confirmatory trials*
  - Iressa (gefitinib)
  - Lartruvo (olaratumab)
  - Ethyol (amifostine)
  - Synercid (quinupristin, dalfopristin)
  - Keytruda (pembrolizumab)
  - Tecentriq (atezolizumab)
  - Opdivo (nivolumab)…

- Makena withdrawal consistent with precedent
  - Avastin's breast cancer indication not voluntarily withdrawn after failed confirmatory trials; no longer shown to be safe or effective
  - CDER proposed withdrawal, hearing held
  - FDA ultimately withdrew indication

*This list also includes approved drugs for which an indication was withdrawn

No Evidence to Narrow Approval to “High-Risk” Women

- No reliable evidence of effectiveness for any identified subgroup, including higher risk of PTB
  - No efficacy consistently seen in any “high-risk” subgroup
  - “High-risk” is ill defined

- For narrowed population, need evidence from RCTs for well-defined population

Leaving Makena on the Market Does Not Address Health Disparities

- No substantial evidence Makena reduces recurrent PTB in Black women or other identified higher risk subgroups
  - Trial 002: effect seen in Black and non-Black women
  - Trial 003: no effect seen in Black and non-Black women
  - Treatment Effect in Trial 002 not corroborated by other evidence since 2011

- No analyzed variable was associated with a consistent treatment effect of Makena across Trial 002 and Trial 003
  - No social determinants of health
  - No factors tied to health disparities

Retaining Makena's Approval Burdens Patients

- Retaining Makena's approval disregards burdens
  - Greatest disservice to patients most at risk for recurrent PTB
  - Drugs without demonstrated benefits amplify those burdens

- In addition to risks, retaining Makena's approval
  - Requires weekly injections
  - Results in utilization of healthcare resources without corresponding benefit

Retaining Makena's Approval Likely Hinders Drug Development

- Likely hinders development of other drugs for Makena's indication
  - Trial enrollment challenges
  - Uncertainties of how to design, conduct, and interpret trials of new products while Makena, not shown to be effective for any group, remains approved
    - May disincentivize development of promising therapies

Patients Need a Drug That Works

- Harmful to retain Makena approval
  - Need for therapy does not mean accepting lack of evidence of efficacy, exposes patients only to risks/burdens
  - Does not address health inequities
  - Contrary to drug approval standard in place to protect, promote public health

- No evidence to support efficacy in Black or other higher risk women

- Leaving Makena on the market would likely impede development of PTB therapeutics
  - Supporting development of safe and effective therapies for PTB is a public health priority

Patients need safe and effective therapy

U.S. FOOD & DRUG ADMINISTRATION

Closing Summary

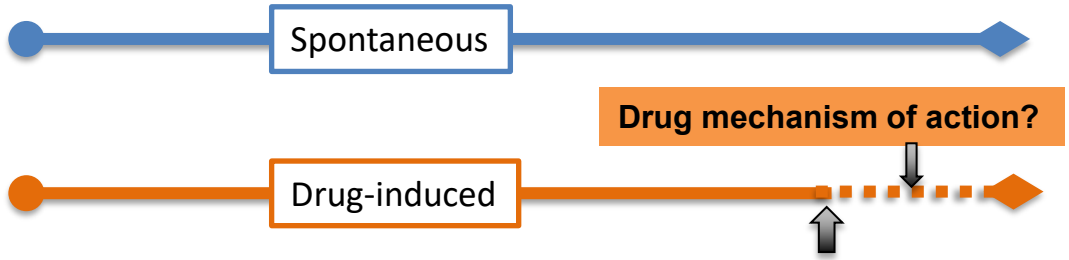
Peter Stein, M.D.
Director, Office of New Drugs
Center for Drug Evaluation and Research

Improving Neonatal Outcomes is the Clinical Benefit to be Assessed

- The causes of PTB are poorly understood - may be triggered by an unrecognized toxic uterine environment
- With spontaneous PTB, risk of neonatal adverse outcomes generally decreases with increasing gestational age (GA) at delivery
- Unclear whether artificially prolonging pregnancy with drug treatment will result in improved neonatal outcomes for the same GA
- Uncertainty whether a GA endpoint can reliably predict neonatal outcome
  - Such uncertainty generally increases with increasing GA

Uncertain Whether Drug-Induced Prolongation of Pregnancy Improves Neonatal Outcomes

- Sufficient evidence indicating later age of GA of *spontaneous* delivery correlates with improved neonatal outcomes
- No robust evidence indicating *drug-induced* prolongation of pregnancy correlates with same improved neonatal outcomes at the same GA of spontaneous delivery



Neonatal outcomes 32 weeks delivery

?=?

Neonatal outcomes 32 weeks delivery

- **Subclinical Infection?**
- **Subclinical uteroplacental insufficiency?**
- **Fetal reasons?**
- **Other reasons for which it is better to deliver than remain in utero?**

Trial 002 Found that Makena Reduced PTB Rates and Supported Accelerated Approval

- A proof-of-concept trial in 463 women who had prior PTB and singleton pregnancy (with one site enrolling 27% of patients)
- Study positive, showed a reduction in PTB (37-, 35-, and 32 weeks) – no statistically significant reduction in neonatal outcome index
- CDER considered the results with the 37-week endpoint sufficiently strong to support approval under **accelerated approval**
  - Response at 37 weeks *reasonably likely* to predict clinical benefit
  - But, a *single* study, based upon an endpoint not validated to support traditional approval
- Subsequent RCT required to **verify** that the drug provides clinical benefit: Trial 003

Trial 003 Failed to Confirm Trial 002

- A multinational Phase 3 trial: included 1,708 women from nine countries (compared to 463 women in Trial 002) – nearly 4-times larger than Trial 002
  - Highest enrolling countries: Russia (621, 36%), Ukraine (420, 25%), and the U.S. (391, 23%) - U.S. subgroup included 113 (29%) Black women
  - No meaningful differences in obstetrical care, **no basis** to expect differential response to treatment across regions
- **Failed to confirm neonatal benefit** and **failed to find effect on PTB rate**
- Results:

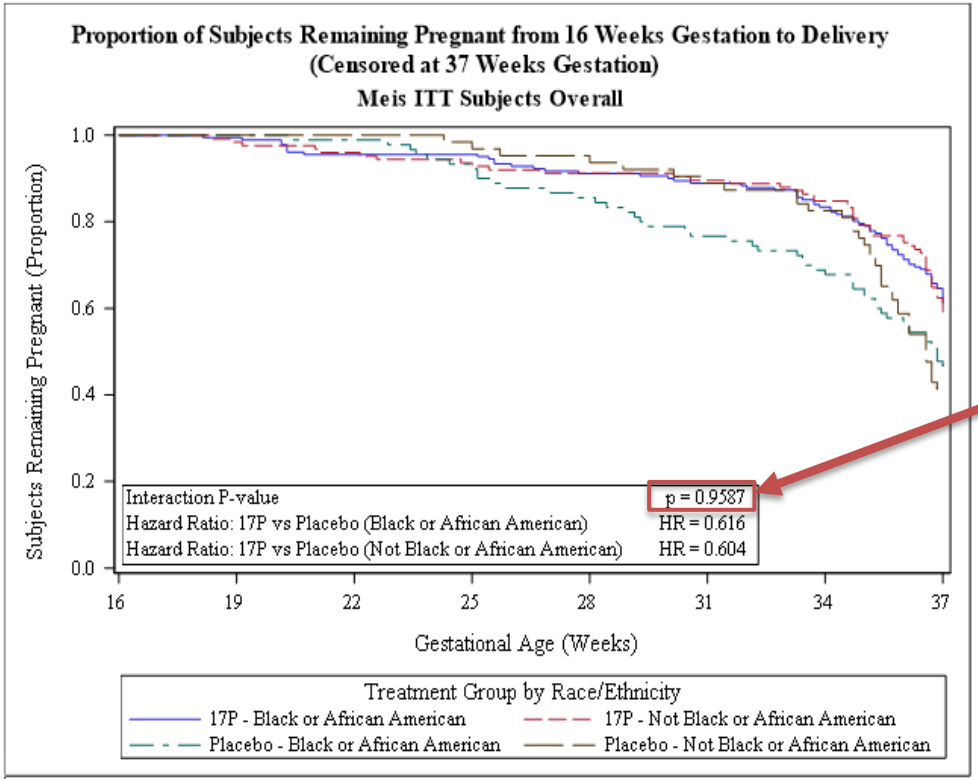
Efficacy outcome	Makena (N=1130)	Placebo (N=578)	Difference (95% CI)	RR (95% CI)	Statistically Significant?
Neonatal Composite Index*	5.4%	5.2%	0.2% (-2.0, 2.5)	1.05 (0.68, 1.61)	**No**
Birth < 35 weeks*	11%	12%	-0.6% (-3.8, 2.6)	0.95 (0.71, 1.26)	**No**
Birth < 32 weeks	5%	5%	-0.4% (-2.8, 1.7)	0.92 (0.60, 1.42)	**No**
Birth < 37 weeks	23%	22%	1.3% (-3.0, 5.4)	1.06 (0.88, 1.28)	**No**

Explanations for the Different Results of Trials 002 and 003

Covis Assertions	CDER Assessment
• Trial 002 shows higher risk women have a better response to Makena and Trial 003 failed to include this higher risk population	• Little evidence that higher-risk women have a higher response to Makena in 002 or 003 <u>including</u> from post-hoc analyses from Covis
• Trial 003 lacked power to detect a difference because conducted in a lower risk population	• Trial 003 was well powered and excluded a >12% relative reduction in Week 37 PTB rate • Trial 003 population was not "low risk" – the PTB rate was consistent with the indicated population for Makena – and had similar risk factors
• Regional differences explain failure of 003 – women outside the U.S. were not properly evaluated and were at lower risk of PTB	• No differential effect of drug seen U.S. vs ex-U.S. • No evidence that evaluation of prior PTB was inaccurate • No evidence that women with an earlier prior PTB (e.g., <34 weeks) had a different response

No Interaction for Treatment Effect by Race in Trial 002

Covis (Figure 7) Effect Modifier Analysis of Event Time based on Gestational Age Comparing Black and Non-Black Subjects by Treatment Arm (Trial 002)

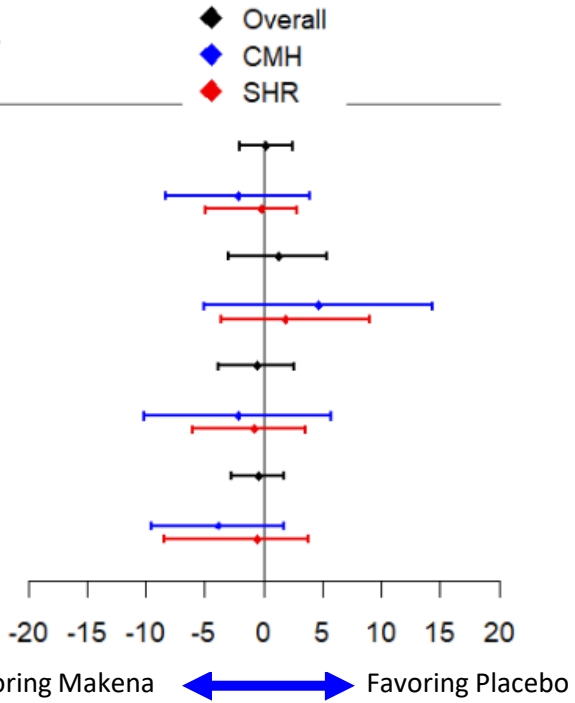


P value for "interaction" not significant

Source: Covis Briefing Materials @ 53 (Figure 7)

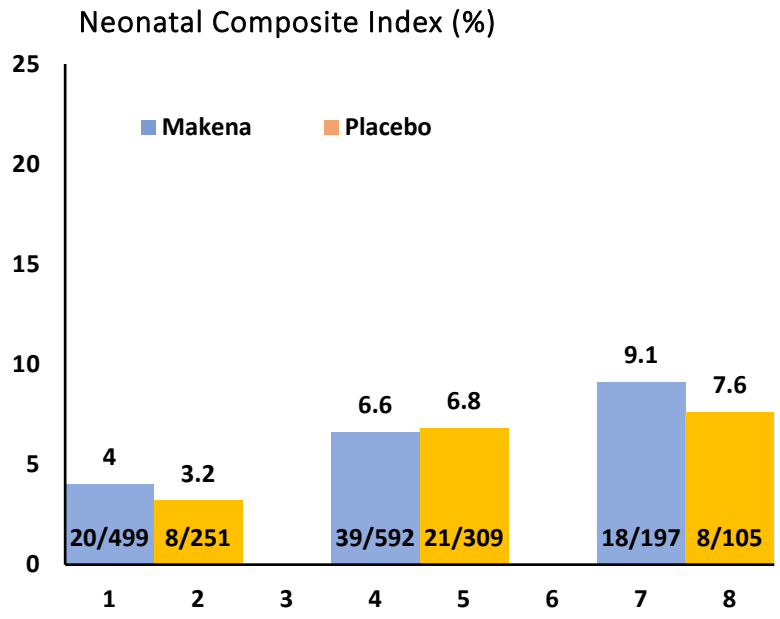
No Evidence of Treatment Effect by Region (Trial 003)

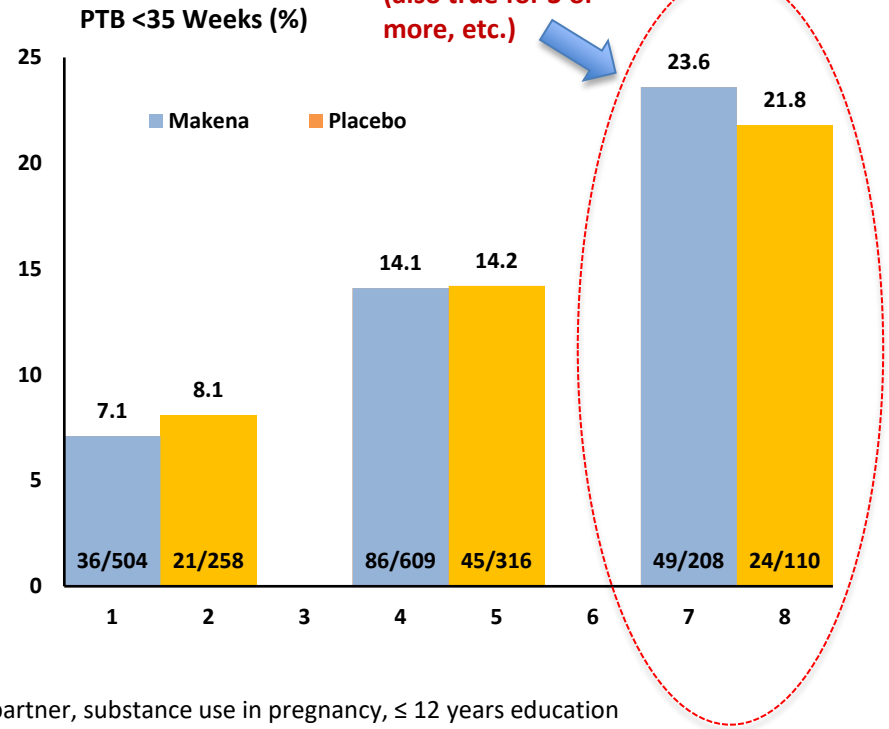
Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR[1]
Neonatal Index[2] (%)	5.4	5.2	0.2	
US (252, 126)	7.1	9.5	-2.2	-0.2
PTB<37 Weeks (%)	23.1	21.9	1.3	
US (256, 131)	33.2	28.2	4.7	1.8
PTB<35 Weeks[2] (%)	11.0	11.5	-0.6	
US (256, 131)	15.6	17.6	-2.2	-0.8
PTB<32 Weeks (%)	4.8	5.2	-0.4	
US (256, 131)	5.5	9.2	-3.9	-0.6



1: Shrinkage using "Non-US" subgroup
2: Coprimary endpoints

No Greater Treatment Response Regardless of Number of Risk Factors in Trial 003





Risk factors: Black race, history of more than one PTB, single/without partner, substance use in pregnancy, ≤ 12 years education

PTB Rates in Women with Prior sPTB: Epidemiological Data and Trial 003 Comparisons

Estimated U.S. recurrent PTB <37 weeks rate (based upon CDC data*)

- 17% = Lower estimate of recurrent PTB in the U.S.
- 20% = PTB < 37w in White women in Georgia (U.S.)
- 21.25% = Upper estimate of recurrent PTB in the U.S.

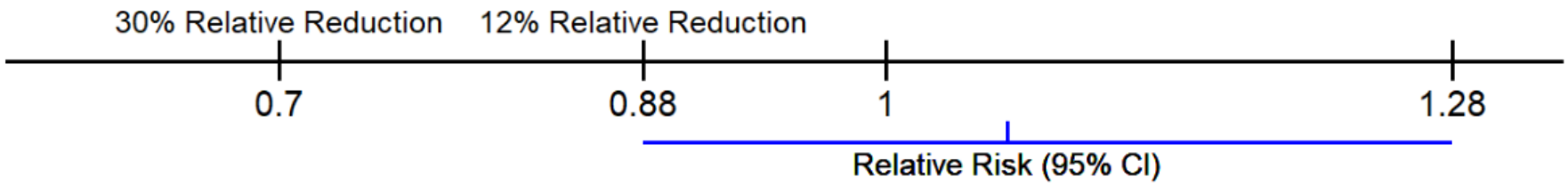
Range seen in Trial 003 U.S. and ex-U.S.

- **22% = PTB < 37w Trial 003 Placebo subjects**
- 22% = sPTB < 37w MFMU Network (1999, U.S.)
- 26% = PTB < 37w in Black women in Georgia (U.S.)
- **28% = PTB < 37w Trial 003 Placebo subjects (U.S.)**
- 28% = PTB < 37w White women in Georgia with prior sPTB < 32w
- **34% = PTB < 37w Black 003 Placebo Subjects (U.S.)**
- 37% = PTB < 37w Black women in Georgia with prior sPTB < 32w

- Based on CDC data (8.5% PTB rate) and the 2- to 2.5-fold increase in risk of a recurrent PTB or sPTB reported in the literature
- For other references, see Slide 59

Trial 003 Results Exclude Clinically Meaningful Effect Sizes

Efficacy Outcome	Trial 003 RR (95% CI)	Trial 003 Treatment Difference (95% CI)
Birth < 37 weeks	1.06 (0.88, 1.28)	1.3% (-3.0, 5.4)



Planned Power: PTB: 30% relative reduction → 0.70 RR

Not Shown to be Effective in Real World Evidence Studies

- Analyses of observational databases (RWE studies) have limitations – but **consistency** across studies supports stronger conclusions
- Here, across 3 different settings, data bases, analytic approaches – **no evidence of Makena effectiveness**

- Wang et al. (2021): Medicaid enrollees in Pennsylvania
  - *No benefit in reduction of PTB risk or admission of the neonate into ICU*
- Hakim et al. (2021): Commercial insurance claims
  - *No benefit for prevention of recurrent PTB*
- Massa et al. (2020): Academic tertiary care center
  - *No association with HPC use and pregnancy prolongation up to 35 weeks*

No Effectiveness Shown in Real-World Studies

- Nelson et al. (2017): University Teaching Hospital in Texas
  - No changes in duration of pregnancy or recurrent PTB ≤35 weeks
- Bastek et al. (2012) – Academic Medical Center
  - Found no change in institutional PTB rate or gestational delivery age (primary objective)
    - Compared institutional rates before and after implementation of Makena as standard of care
    - In women delivering preterm, a claimed increase in gestational delivery age in Makena period
    - Significant limitations: unknown Makena use, limited confounding control, unclear analysis population and methods
- Neither study shows Makena to be effective

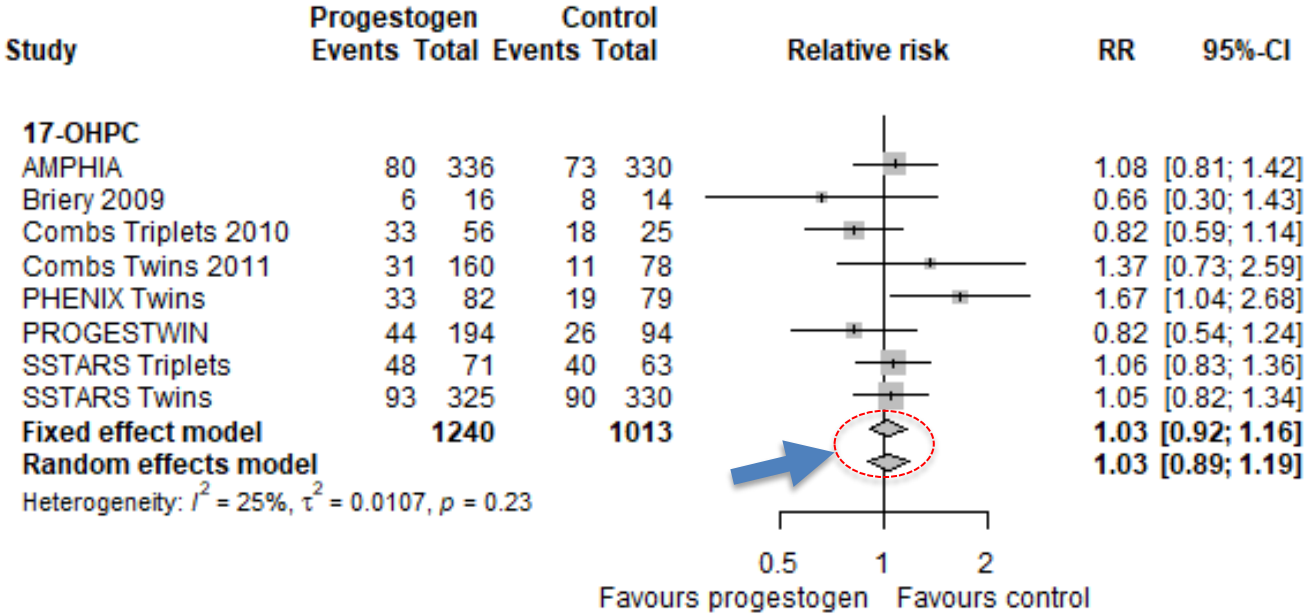
Nelson DB, McIntire DD, McDonald J, Gard J, Turrichi P, Leveno KJ. 17-alpha hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol. 2017;216:600.e1-9.; Bastek JA, Adamczak JE, Hoffman S, Elovitz MA, Srinivas SK. Trends in prematurity: What do changes at an urban institution suggest about the public health impact of 17-alpha hydroxyprogesterone caproate? Matern Child Health J. 2012;16:564-568

No Evidence of Effectiveness of HPC in 3 Other RCTs in Singleton Gestations in Other Populations

- **Price** et al. (2021): studied HIV + women, found no difference in PTB < 37 weeks or stillbirth
  - PTB < 37 weeks or stillbirth: RR (95% CI) = 1.0 (0.6, 1.6); PTB < 37 weeks: RR (95% CI) = 0.9 (0.6, 1.4)
- **SCAN**: shortened cervix and no prior preterm birth
  - PTB < 37 weeks: RR (95% CI) = 1.03 (0.79,1.35)
- **PHENIX**: shortened cervix plus at least one other risk factor for PTB, with higher dose of HPC (500 mg)
  - PTB < 37 weeks: RR (95% CI) = 1.01 (0.65, 1.57)
  - PTB < 34 weeks: RR (95% CI) = 0.78 (0.40, 1.53)
  - PTB < 32 weeks: RR (95% CI) = 0.64 (0.25, 1.62)
- **EPPPIC** meta-analysis: not statistically significant
  - PTB < 34 weeks: RR (95% CI) = 0.83 (0.68, 1.01)
  - Removing Trial 002 notably increases upper bound of CI

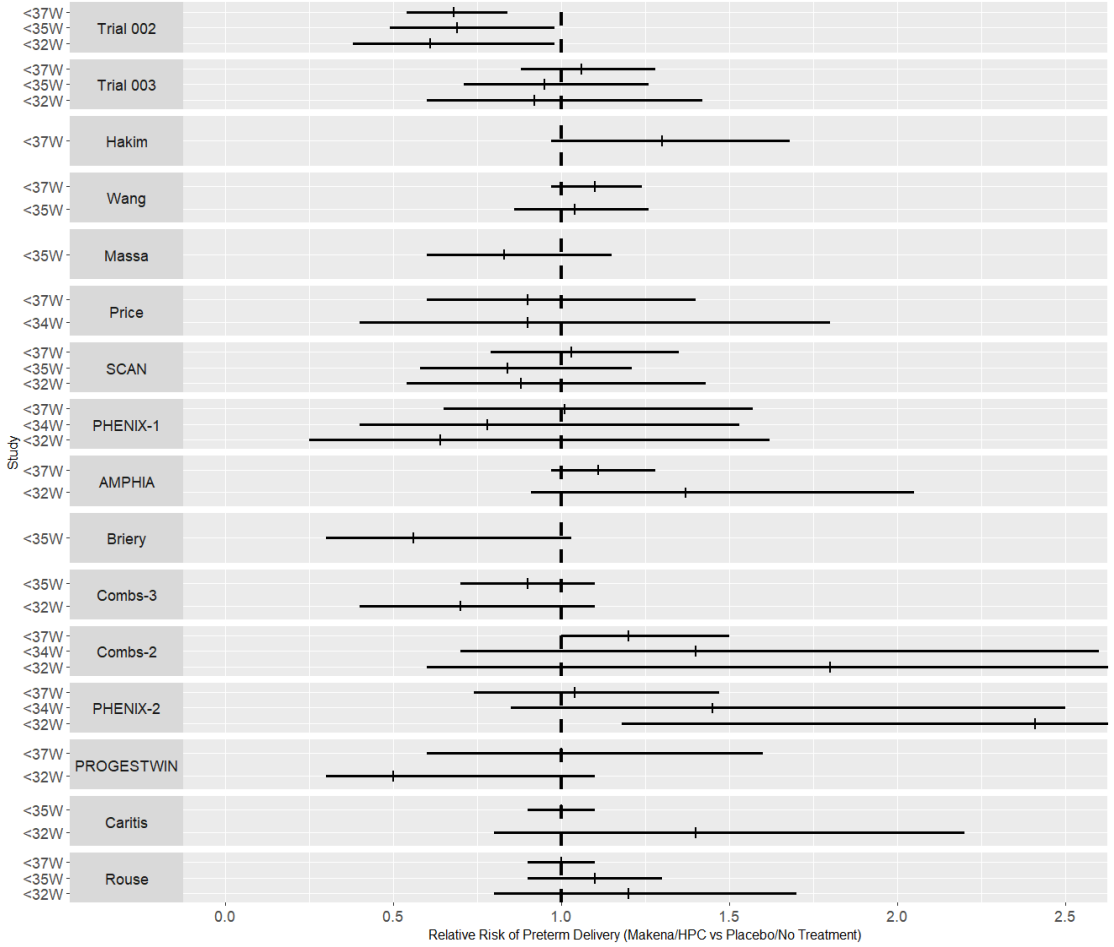
Note: omitting PROGFIRST trial where there were known drug quality issues

No Evidence of Effectiveness of HPC in RCTs in Multiple Gestations in Other Populations (EPPPIC)



Extracted from Appendix Figure 13: Multifetal pregnancies preterm birth before 34 weeks (two-stage meta-analyses) from Supplement to: The EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet* 2021; 397: 1183–94.

Results Across Studies Do Not Support That Makena Is Effective



No evidence of a consistent effect on any gestational age cutpoints

The Available Evidence Does Not Show that Makena Is Effective in Reducing PTB or Improving Neonatal Outcomes

- **Conclusions from the results of Trials 002 and 003**
  - Trial 003 nearly 4x larger than 002, had good precision, and did not find evidence of Makena effectiveness
  - No evident differential treatment effect by subgroup that suggests population differences led to between-trial differences in outcome
  - Placebo PTB rate in Trial 002 above anticipated – risk of a false positive in a smaller, POC trial
- **Other clinical study** results of HPC **do not provide** support for effectiveness
  - No support from observational studies in varying design, setting, and data
  - No support from other RCTs in singleton or multiple gestation pregnancies
- The appropriate **conclusion is that Makena has not been shown to be effective** in reducing PTB or improving neonatal outcomes

Makena Has Risks

- Overall, safety profile in Trials 002 and 003 did not show important imbalances
  - However, clinical trials (unless huge) **do not exclude rare clinically highly impactful events** – such as venous thromboembolism
- Risks of thromboembolic events, allergic reactions, depression in labeling - Warnings and Precautions, injection site reactions – are a concern
- Murphy et al. reported increased cancer risk in the children of women treated with HPC, the active ingredient in Makena
  - CDER's evaluation of study concluded it raised questions of safety meriting further surveillance
  - This points out that long-term risks **not fully understood** – a concern especially when benefit not established

Makena's Benefit-Risk Balance is Unfavorable

- Makena has not been shown to be effective, and has labeled risks and uncertainties with regard to risk
- Absent evidence of clinical benefit, using Makena to prevent recurrent PTB in pregnant women exposes them only to risk, so the risk benefit balance is unfavorable

Conducting Another RCT in U.S. While Makena Remains On The Market Will Require Many Years

- Best evidence of timeline to complete a large RCT, especially one targeting U.S. women, is the **experience from Trial 003**
  - Approximately 10 years to complete - with global recruitment
  - Covis' surveys cannot refute experience of Trial 003 recruitment: a U.S.-based trial is likely to take decade(s) to complete
- If Makena remains on the market, the current lack of evidence of effectiveness could continue for many years/decades
  - Practitioners left exposing their patients to risks and burdens, with no evidence of benefit
  - With Makena off the market, a trial is likely to be able to be rapidly conducted, providing critical information for practitioners and patients

Withdrawal Standard Comes from Statute and Regulations

21 CFR 314.530, FDCA 506(c)

- Accelerated Approval **accepts some uncertainty** – but **requires verification** with post-approval trial – and includes mechanisms to remove drugs when post-approval trial fails to verify benefit
- The law authorizes FDA to expedite withdrawal of drugs approved under the accelerated approval framework
- FDA may withdraw approval, among other reasons, if:
  - "A postmarketing clinical study fails to verify clinical benefit" OR
  - "Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use"

Withdrawal Standard From Statute and Regulations: Two Criteria for Withdrawal of Makena Are Met

- The legal standard for withdrawal is met in two independent ways:

  (1) the confirmatory trial **failed to verify** the predicted clinical benefit of reducing neonatal morbidity and mortality from complications of preterm birth

  (2) other evidence demonstrates Makena **is no longer shown to be effective** at reducing the risk of recurrent singleton preterm birth

Questions and Responses: Question 1

Question 1: Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

- **No, Trial 003 did not verify benefit**

Questions and Responses: Question 2

Question 2: Does the available evidence demonstrate that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth?

- Despite Covis' assertions, no higher responder subgroups demonstrated in either Trials 002 or 003
- Trial 003, nearly 4x the size of Trial 002, was a **well-conducted and fully negative study** - differences in how GA was measured do not explain the differences in trial outcome
- Trial 003 had **good precision** – **excluding a more than a 12% improvement** in PTB < 37 weeks
- **Multiple observational studies** – using different populations and methods – **failed to find an effect of Makena**
- **RCTs in singleton pregnancies** and in **multi-gestation pregnancies failed to find an effect of HPC**

Conclusion: Makena has not been shown to be effective; substantial evidence of effectiveness is lacking

Questions and Responses: Question 3

Question 3: Should FDA allow Makena to remain on the market?

- The statute (FDCA 506(c)) and FDA regulations provide grounds for FDA to withdraw an approved drug from the market
  - **Two legal grounds for withdrawal (either of which can independently support withdrawal) are satisfied here**

Questions and Responses: Question 3

<u>However</u>, since the law says FDA "may"—not must—withdraw a drug when certain criteria are met, why is CDER recommending withdrawal of Makena?

- The **evidence** demonstrates that Makena is **not shown to be effective** for its approved use: the results of the larger trial (Trial 003), multiple observational studies, and RCTs in the indicated and other high-risk populations support this conclusion

- Makena has **risks** (thromboembolic events, hypersensitivity, injection site reactions, etc.) and **uncertainties** (the long-term effects on children of women receiving Makena)

Questions and Responses: Question 3 (cont.)

<u>However</u>, since the law says FDA "may"—not must—withdraw a drug when certain criteria are met, why is CDER recommending withdrawal of Makena?

- With Makena **on the market**, prior recruitment experience (Trial 003) shows that it will take a **decade or more to complete** another trial to provide further information
  - Practitioners will be prescribing a drug **not shown to be effective,** but with attendant **risks** (and uncertainties regarding long-term risk) for a decade more
  - In contrast, with Makena off the market, an answer could be generated more rapidly
- Retaining Makena's approval **likely hinders** study of more promising treatments for preterm birth
- Failure to remove Makena from the market **undermines the accelerated approval pathway**

Questions and Responses: Question 3 (Summary)

<u>However</u>, since the law says FDA "may"—not must—withdraw a drug when certain criteria are met, why is CDER recommending withdrawal of Makena?

- The **evidence** shows that Makena is no longer shown to be effective **– substantial evidence is lacking**
- Makena has known **risks**, and uncertainties regarding risk
- With Makena **on the market**, it will likely take a **decade or more to complete** another trial – but likely can be more rapidly completed with Makena off the market
- Retaining Makena's approval **likely hinders** study of more promising treatments for preterm birth
- Failure to remove Makena **undermines the accelerated approval pathway**
- Retaining approval would be a **disservice to patients** at risk for recurrent PTB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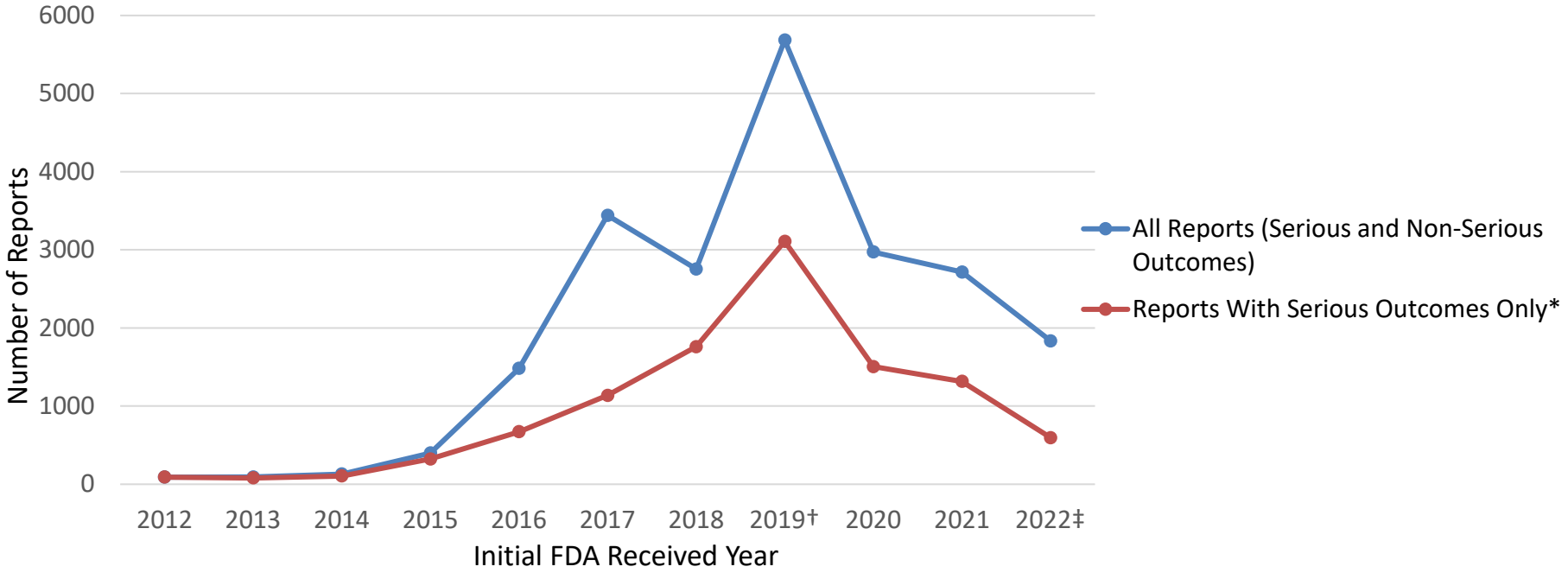
Backup Slides Shown

FAERS Strengths and Limitations

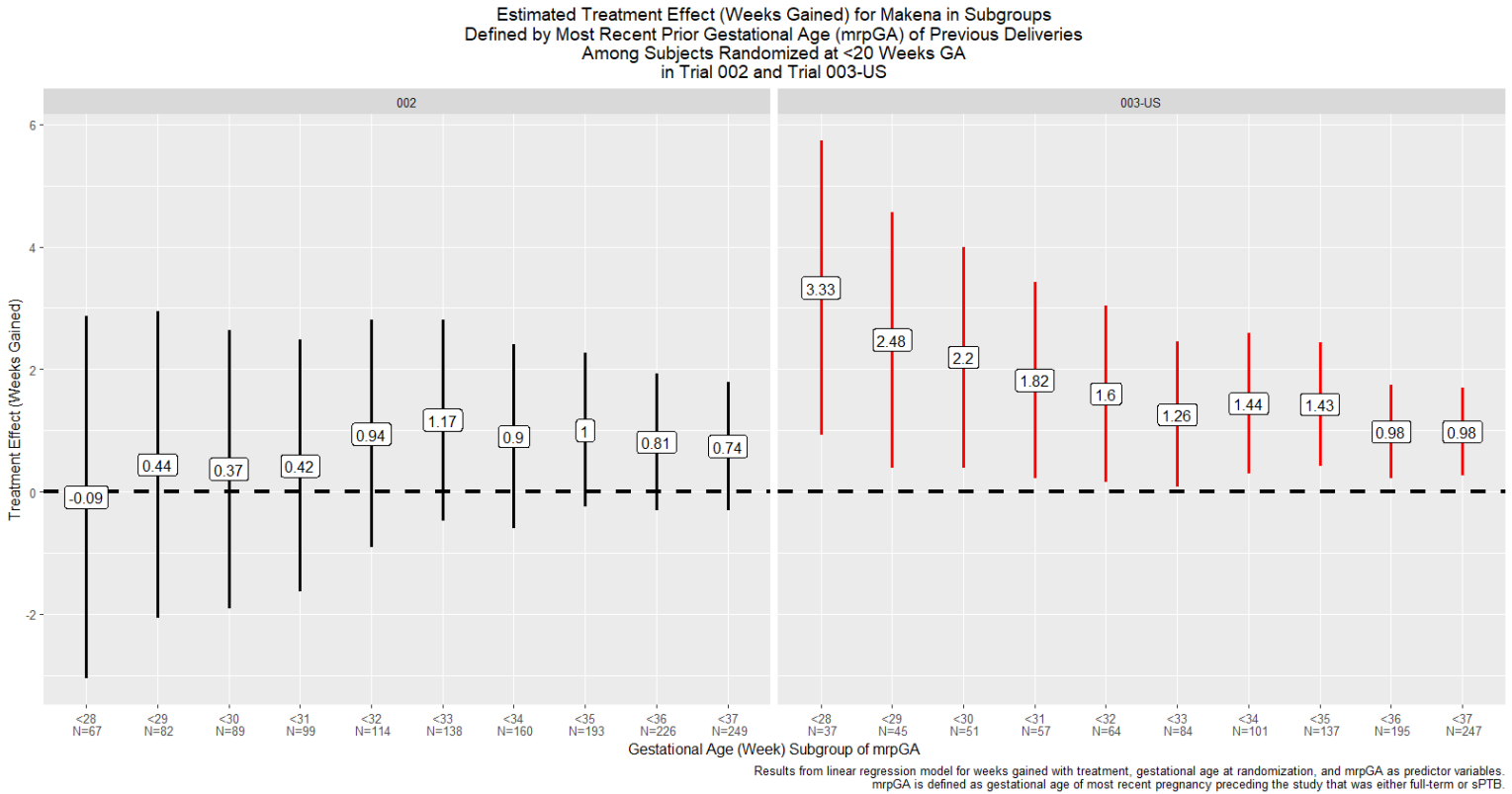
- Strengths include:
  - FAERS data are particularly useful for identifying new (i.e., unexpected or unlabeled), rare, serious adverse events that are temporally associated with a product for which the background rate of events is low.
  - Spontaneous adverse event reports in FAERS can further refine or characterize a known adverse event.
- Limitations include:
  - FAERS data are rarely reliable for analyzing adverse events that have a delayed time to onset or a delayed time to detection (e.g., cancers). This limitation also applies to events that are not unusual in the underlying population (e.g., depression).
  - Known under-reporting - FDA does not receive reports for every adverse event or medication error that occurs with a product because of the voluntary nature of spontaneous reporting.
  - Rates of occurrence cannot be established - Because adverse event reporting is voluntary, information in these reports cannot be used to estimate the incidence (occurrence rates) of the reactions reported or be used to make comparisons between products.

Number of Reports Received per Year, From 2012-2022, in FAERS With Hydroxyprogesterone



* The following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required
intervention, or other serious important medical events. A single report can have one or more outcome.
† Year of the Makena Advisory Committee Meeting
‡ Only reflects data received through July 23, 2022

Defined by mrpGA

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