U.S. FOOD & DRUG ADMINISTRATION

Final Closing Summary

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Closing Summary: A Brief Agenda

- The value of accelerated approval - and the importance of balancing public health interests
- Background on preterm birth, gestational age as an endpoint to predict neonatal outcome
- The results from Trials 002 and 003, and subgroup analyses
- Results from other studies, RWE and RCTs
- Makena: risks and uncertainties
- CDER responses to the Questions

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**"

Balancing of Public Health Interests in Accelerated Approval Framework

- Give patients with serious or life-threatening diseases access to new therapies sooner by expediting the 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- Where the legal standard for withdrawal is met, and CDER determines that approval should be withdrawn, retaining approval would: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

Preterm Birth Is a Significant Public Health Concern

- Preterm birth (PTB) - delivery prior to 37 weeks of gestation
  ~8% singleton pregnancies
- Many possible causes – *infection, underlying maternal disease (diabetes, hypertension), uterine overdistension (polyhydramnios, multiple gestation), weak cervix, etc.* – the exact cause is often unknown
- 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 - Improving Neonatal Outcome is the Relevant Clinical Benefit

- 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
- 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

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.

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

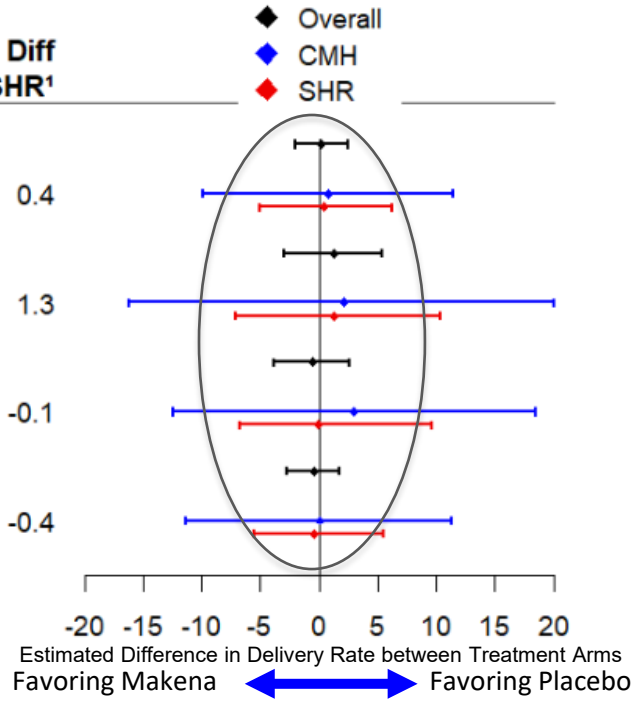
Trial 003 Efficacy Result

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)

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

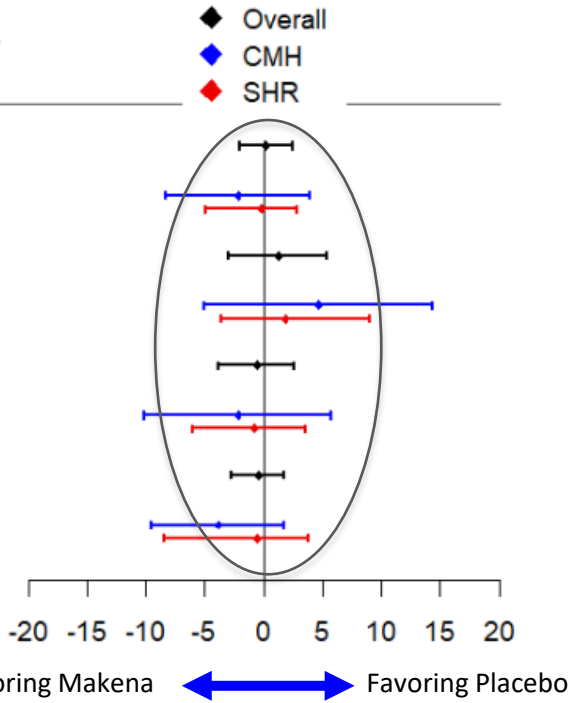


1: Shrinkage using "Non-Black" subgroup
2: Coprimary endpoints

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

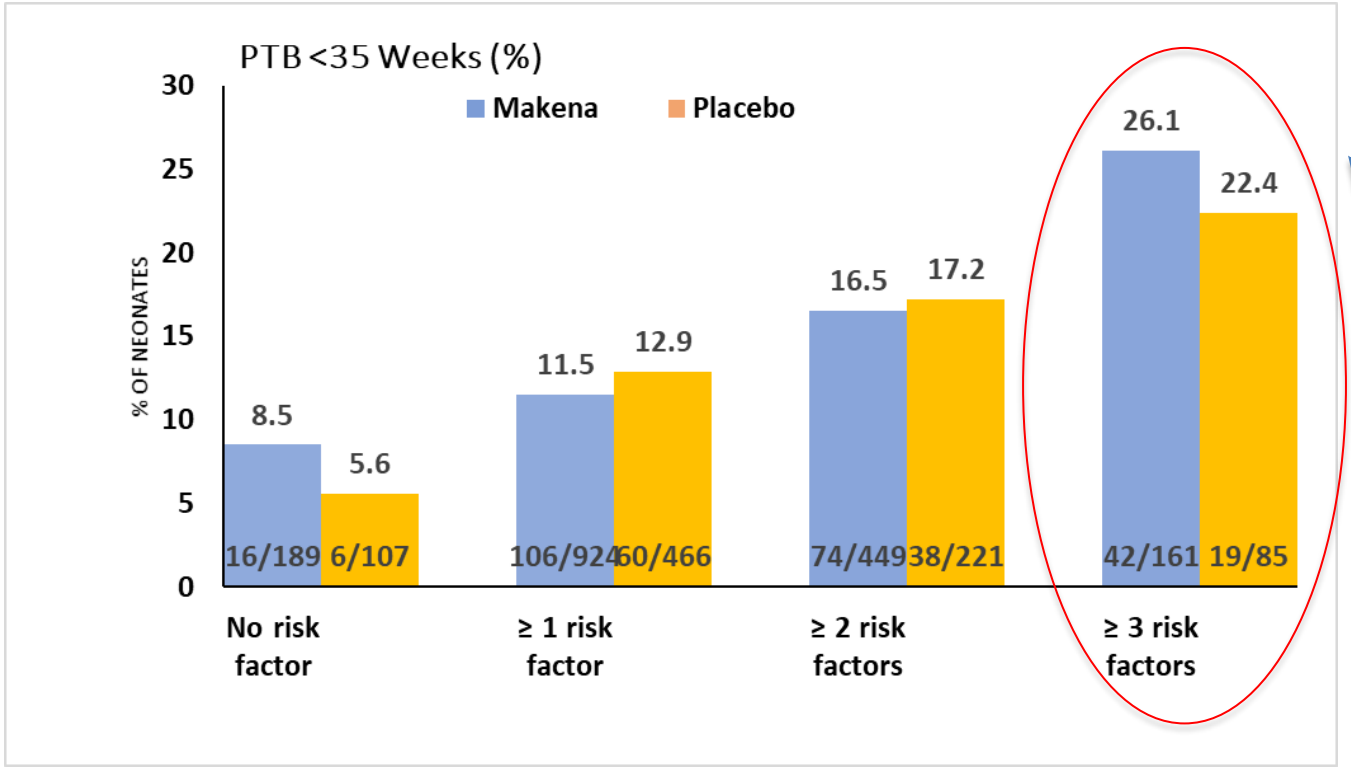
No Evidence of Treatment Effect by Region (Trial 003)

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 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

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).

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

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

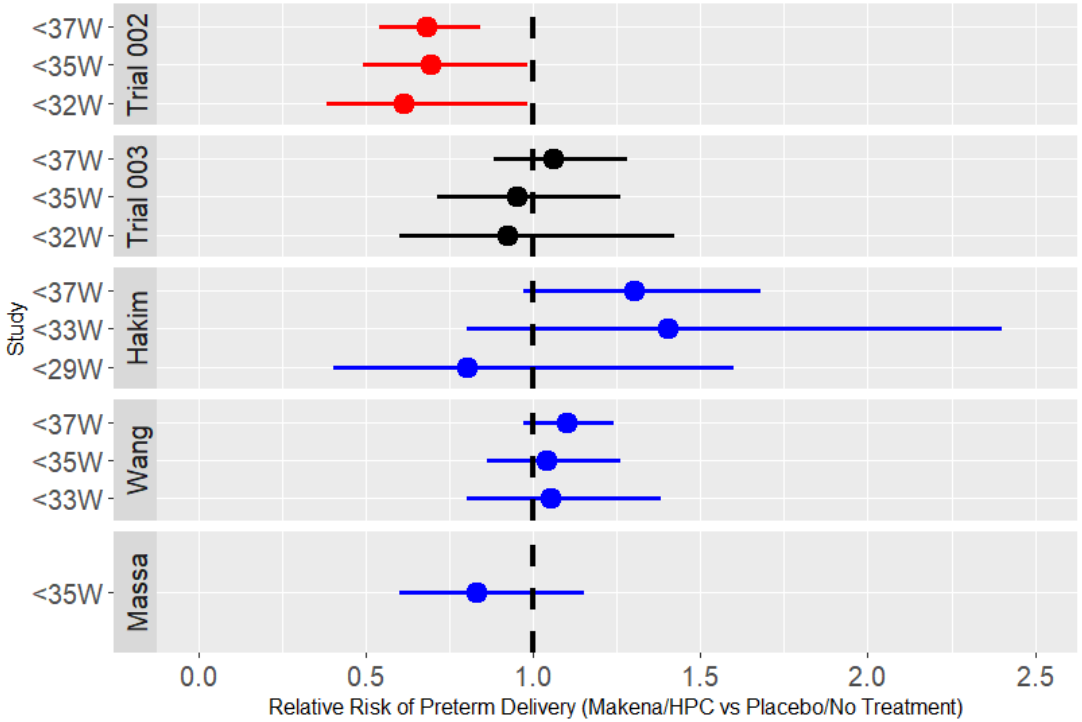
Makena Real-World, Observational Studies Do Not Show Effectiveness

- 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

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

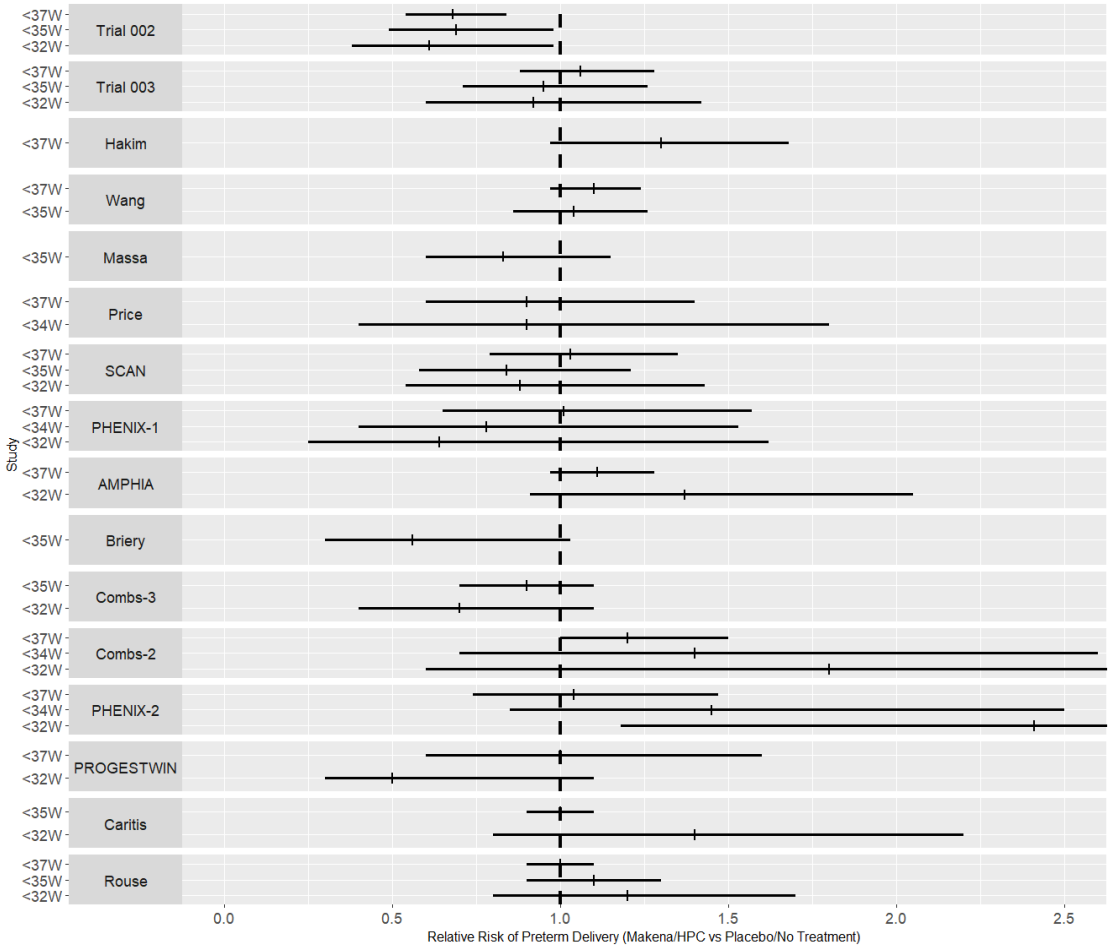
Outlier is Trial 002
RCTs and Observational Studies in Indicated Population



- 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.

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

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

Questions and Responses

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

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** 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
- Failure to remove Makena **undermines the accelerated approval pathway**
- Retaining approval would be a **disservice to patients** at risk for recurrent PTB