COVIS - Questions to CDER

Day 1 – October 17, 2022
CDER Evaluation of the Murphy Article

Division of Epidemiology II – 6/22/22

“Potential for chance findings due to the large number of statistical analyses performed, the small number of exposed cases, lack of an appropriate conceptual framework to justify the proper use of statistical model, and the high likelihood for residual confounding are major study limitations.”

“not of sufficient quality to support regulatory decision-making”

“insufficient evidence to support regulatory action”
**Division of Epidemiology II – 7/15/22**

“DEPI recommends closure of the NISS, classifying the safety signal as indeterminate…”

**Newly Identified Safety Signal (NISS) Closure Memorandum**

Division of Urology, Obstetrics and Gynecology (DUOG) – 7/14/22

“DEPI recommended that this NISS be closed with a finding of an “indeterminate” status. DEPI plans to undertake active surveillance of this issue on an ongoing basis by utilizing PubMed automated search emails. DUOG agrees with this recommendation. The NISS can be closed.”
CDER Evaluation of the Murphy Article


“Indeterminate safety signal (as defined for this MAPP): A safety signal for which current available information is insufficient to support a causal association between a drug and/or an adverse event and does not, based on the current available information, warrant further evaluation.”
“Further Surveillance”

Division of Urology, Obstetrics and Gynecology

“DEPI recommended that this NISS be closed with a finding of an ‘indeterminate status.’ DEPI plans to undertake active surveillance of this issue on an ongoing basis by utilizing PubMed automated search results.”
CDER’s Table 22 from its 2019 Briefing Book: Summary of PTB < 35<sup>0</sup> Weeks by Subgroup

<table>
<thead>
<tr>
<th>Stratification Groups, n/N (%)</th>
<th>Trial 003 Makena (N=1130)</th>
<th>Trial 003 Placebo (N=578)</th>
<th>Trial 003 U.S. Subset Makena (N=258)</th>
<th>Placebo (N=133)</th>
<th>Trial 02 Makena (N=310)</th>
<th>Placebo (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any substance use during pregnancy, N (%)</td>
<td>19/105 (18.1)</td>
<td>13/51 (25.5)</td>
<td>11/69 (15.9)</td>
<td>10/40 (25.0)</td>
<td>16/85 (18.8)</td>
<td>16/36 (44.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>103/1008 (10.2)</td>
<td>53/523 (10.1)</td>
<td>29/187 (15.5)</td>
<td>13/91 (14.3)</td>
<td>47/221 (21.3)</td>
<td>31/117 (26.5)</td>
</tr>
<tr>
<td>No</td>
<td>84/105 (16.8)</td>
<td>38/51 (17.5)</td>
<td>10/69 (14.8)</td>
<td>28/100 (18.4)</td>
<td>13/85 (18.8)</td>
<td>15/38 (39.5)</td>
</tr>
<tr>
<td>Smoking</td>
<td>18/92 (19.6)</td>
<td>11/40 (27.5)</td>
<td>10/58 (17.2)</td>
<td>8/30 (26.7)</td>
<td>13/70 (18.6)</td>
<td>15/30 (50.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>104/1021 (10.2)</td>
<td>55/534 (10.3)</td>
<td>30/198 (15.2)</td>
<td>15/101 (14.9)</td>
<td>50/236 (21.2)</td>
<td>32/123 (26.0)</td>
</tr>
<tr>
<td>No</td>
<td>86/1009 (10.9)</td>
<td>39/503 (16.0)</td>
<td>25/100 (22.0)</td>
<td>28/132 (20.9)</td>
<td>9/104 (9.3)</td>
<td>7/31 (22.6)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1/23 (4.3)</td>
<td>5/18 (27.8)</td>
<td>1/19 (5.3)</td>
<td>4/16 (25.0)</td>
<td>5/27 (18.5)</td>
<td>2/10 (20.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>121/1090 (11.1)</td>
<td>61/556 (11.0)</td>
<td>39/237 (16.5)</td>
<td>19/115 (16.5)</td>
<td>58/279 (20.8)</td>
<td>45/143 (31.5)</td>
</tr>
<tr>
<td>No</td>
<td>116/1069 (10.9)</td>
<td>48/556 (8.6)</td>
<td>20/115 (22.3)</td>
<td>10/100 (10.0)</td>
<td>59/331 (17.6)</td>
<td>20/110 (18.2)</td>
</tr>
<tr>
<td>Illicit drugs</td>
<td>2/15 (13.3)</td>
<td>3/8 (37.5)</td>
<td>2/14 (14.3)</td>
<td>3/8 (37.5)</td>
<td>2/11 (18.2)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>Yes</td>
<td>120/1098 (10.9)</td>
<td>63/556 (11.1)</td>
<td>38/242 (15.7)</td>
<td>20/123 (16.3)</td>
<td>61/295 (20.7)</td>
<td>47/149 (31.5)</td>
</tr>
<tr>
<td>No</td>
<td>118/1069 (10.9)</td>
<td>46/556 (8.1)</td>
<td>22/115 (19.2)</td>
<td>10/100 (10.0)</td>
<td>59/331 (17.6)</td>
<td>20/110 (18.2)</td>
</tr>
<tr>
<td>Race</td>
<td>Non-Hispanic black</td>
<td>17/72 (23.6)</td>
<td>8/40 (20.0)</td>
<td>16/71 (22.5)</td>
<td>8/40 (20.0)</td>
<td>39/183 (21.3)</td>
</tr>
<tr>
<td>Non-Hispanic non-black</td>
<td>92/940 (9.8)</td>
<td>50/480 (10.4)</td>
<td>19/154 (12.3)</td>
<td>10/68 (14.7)</td>
<td>28/127 (22.0)</td>
<td>15/63 (23.8)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic</td>
<td>13/101 (12.9)</td>
<td>8/54 (14.8)</td>
<td>5/31 (16.1)</td>
<td>5/23 (21.7)</td>
<td>10/41 (24.4)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>109/1012 (10.8)</td>
<td>58/520 (11.2)</td>
<td>35/225 (15.6)</td>
<td>18/108 (16.7)</td>
<td>53/265 (20.0)</td>
<td>43/127 (33.9)</td>
</tr>
<tr>
<td>Years of education</td>
<td>≤12</td>
<td>64/474 (13.5)</td>
<td>40/256 (15.6)</td>
<td>24/120 (20.0)</td>
<td>18/74 (24.3)</td>
<td>49/223 (22.0)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>58/639 (9.1)</td>
<td>26/166 (15.6)</td>
<td>16/136 (11.8)</td>
<td>5/57 (8.8)</td>
<td>14/83 (16.9)</td>
<td>15/50 (30.0)</td>
</tr>
</tbody>
</table>

* If more than one prior delivery was <35<sup>0</sup> weeks, qualifying delivery was the most recent.
** The earliest PTB may be indicated or spontaneous.
*** Cervical length measurement was not captured for all subjects in a treatment group.
GA = gestational age
NA = not available
Source: Applicant Analysis. #FDA Analysis.

FDA Briefing Document 2019 ([https://www.fda.gov/media/132003/download](https://www.fda.gov/media/132003/download))
Effectiveness of 17-OHP for Prevention of Recurrent Preterm Birth: A Retrospective Cohort Study

Joe B. Hakim, BSc1, Amy Zhou, MSc2, Sonia Hernandez-Diaz, MD, PhD3, Jessica M. Hart, MD4, Blair J. Wylie, MD, MPH4,# Andrew L. Beam, PhD3,5,#

1Department of Health Sciences and Technology, Harvard-MIT, Cambridge, Massachusetts
2Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts
3Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts
4Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, Massachusetts
5Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts

Am J Perinatol

Address for correspondence Andrew L. Beam, PhD, 820C Kresge Hall 677 Huntington Avenue, Boston, MA 02115 (e-mail: andrew_beam@hms.harvard.edu).

Original Article
Hakim et. al., 2021

**Supplementary Table S2** Summary statistics for the cohort matching inclusion criteria, stratified by treatment assignment

<table>
<thead>
<tr>
<th>Demographic factors, aggregated over zip codes</th>
<th>Treated with 17-OHP</th>
<th>Not treated with 17-OHP</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median income in zip code Mean (SD)</td>
<td>73,486.69 (28,147.72)</td>
<td>72,172.91 (25,763.87)</td>
<td>0.265</td>
</tr>
<tr>
<td>Percentage non-white population in zip code Mean (SD)</td>
<td>0.26 (0.20)</td>
<td>0.28 (0.19)</td>
<td>0.082</td>
</tr>
<tr>
<td>Percentage of population in zip code without high school degree Mean (SD)</td>
<td>0.07 (0.05)</td>
<td>0.07 (0.05)</td>
<td>0.527</td>
</tr>
<tr>
<td>Percentage of population in zip code unemployed Mean (SD)</td>
<td>0.25 (0.05)</td>
<td>0.25 (0.06)</td>
<td>0.399</td>
</tr>
</tbody>
</table>

Abbreviations: 17-OHP, 17α-hydroxyprogesterone caproate; GA, gestational age; ICD, International Classification of Disease; PPROM, preterm premature rupture of membrane; SD, standard deviation.

Note: Categorical variables are reported as n (%). Continuous variables are reported as median (SD). More details including calculation of p-values comparing the treated and untreated groups are described in the “Statistical methods” section, “Quantitative variables” subsection.
Fig. 1 Flow diagram illustrating the number of individuals matching each inclusion criteria. Abbreviations: sPTB, spontaneous preterm birth (including preterm prelabor rupture of membranes).
Eligibility, Utilization, and Effectiveness of 17-Alpha Hydroxyprogesterone Caproate (17OHPC) in a Statewide Population-Based Cohort of Medicaid Enrollees

Xi Wang, PhD¹ Stephanie M. Garcia, MPH¹ Katherine S. Kellom, BS¹ Rupsa C. Boelig, MD²
Meredith Matone, DrPH¹,³

¹PolicyLab, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania
²Department of Obstetrics and Gynecology, Department of Pharmacology and Experimental Therapeutics, Division of Maternal Fetal Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania
³University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Address for correspondence Meredith Matone, DrPH, MHS, University of Pennsylvania Perelman School of Medicine; Scientific Director, PolicyLab, Children’s Hospital of Philadelphia, 2716 South Street, 10-121, Philadelphia, PA 19146 (e-mail: MatoneM@email.chop.edu).

Am J Perinatol
Wang et. al., 2021

Table 3: Use of 17OHP in eligible pregnancies from 2014 to 2016 in Pennsylvania

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among all 17OHP eligible pregnancies</td>
<td>4,781</td>
<td></td>
</tr>
<tr>
<td>Received 17OHP prescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,364</td>
<td>28.5</td>
</tr>
<tr>
<td>No</td>
<td>3,417</td>
<td>71.5</td>
</tr>
<tr>
<td>Among 17OHP recipients</td>
<td>1,364</td>
<td></td>
</tr>
<tr>
<td>Number of 17OHP doses per recipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>199</td>
<td>14.6</td>
</tr>
<tr>
<td>6–10</td>
<td>208</td>
<td>15.2</td>
</tr>
<tr>
<td>11–15</td>
<td>272</td>
<td>19.9</td>
</tr>
<tr>
<td>≥16</td>
<td>685</td>
<td>50.2</td>
</tr>
<tr>
<td>17OHP treatment initiation time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gestational week at the first 17OHP pharmacy claim)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 16 weeks</td>
<td>436</td>
<td>32.0</td>
</tr>
<tr>
<td>16–26 weeks</td>
<td>848</td>
<td>62.2</td>
</tr>
<tr>
<td>≥27 weeks</td>
<td>79</td>
<td>5.8</td>
</tr>
</tbody>
</table>

“Among eligible live births, 28.5% received at least one 17OHP injection. For women with treatment initiation, 15% experienced low adherence of one to five doses, while 50% received more than 16 doses in accordance with clinical guideline recommendations.”
Wang et. al., 2021

**Table 3 Use of 17OHP in eligible pregnancies from 2014 to 2016 in Pennsylvania**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among all 17OHP eligible pregnancies</td>
<td>4,781</td>
<td></td>
</tr>
<tr>
<td>Received 17OHP prescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1,364</td>
<td>28.5</td>
</tr>
<tr>
<td>No</td>
<td>3,417</td>
<td>71.5</td>
</tr>
<tr>
<td>Among 17OHP recipients</td>
<td>1,364</td>
<td></td>
</tr>
<tr>
<td>Number of 17OHP doses per recipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>199</td>
<td>14.6</td>
</tr>
<tr>
<td>6–10</td>
<td>208</td>
<td>15.2</td>
</tr>
<tr>
<td>11–15</td>
<td>272</td>
<td>19.9</td>
</tr>
<tr>
<td>≥16</td>
<td>685</td>
<td>50.2</td>
</tr>
<tr>
<td>17OHP treatment initiation time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gestational week at the first 17OHP pharmacy claim)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 16 weeks</td>
<td>436</td>
<td>32.0</td>
</tr>
<tr>
<td>16–26 weeks</td>
<td>848</td>
<td>62.2</td>
</tr>
<tr>
<td>≥27 weeks</td>
<td>79</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Abbreviation: 17OHP, 17α-hydroxyprogesterone caproate.
### Table 4: Associations of demographic and clinical characteristics with the use of 17OHP among eligible mothers from 2014 to 2016 in Pennsylvania: Adjusted OR and 95% CI from the multivariate logistic regression model

<table>
<thead>
<tr>
<th>Characteristics of previous spontaneous singleton preterm birth</th>
<th>Eligible mothers who received 17OHP (Column %)</th>
<th>Eligible mothers who did not receive 17OHP (Column %)</th>
<th>Adjusted OR for 17OHP use (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age at delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–27 weeks</td>
<td>18.9%</td>
<td>7.4%</td>
<td>2.90 (1.92–4.38)</td>
</tr>
<tr>
<td>28–32 weeks</td>
<td>20.5%</td>
<td>9.3%</td>
<td>3.02 (2.32–3.94)</td>
</tr>
<tr>
<td>33–34 weeks</td>
<td>23.8%</td>
<td>16.1%</td>
<td>2.12 (1.74–2.59)</td>
</tr>
<tr>
<td>35–36 weeks</td>
<td>36.8%</td>
<td>67.3%</td>
<td>Reference</td>
</tr>
<tr>
<td><strong>Child’s birth weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1,500 g</td>
<td>27.3%</td>
<td>11.0%</td>
<td>1.77 (1.21–2.59)</td>
</tr>
<tr>
<td>1,500–2,499 g</td>
<td>46.8%</td>
<td>38.2%</td>
<td>1.60 (1.33–1.92)</td>
</tr>
<tr>
<td>≥2,500 g</td>
<td>25.9%</td>
<td>50.7%</td>
<td>Reference</td>
</tr>
</tbody>
</table>
MAKENA®
(hydroxyprogesterone caproate injection)

October 17-19, 2022
Hearing with Respect to CDER’s Proposal to Withdraw Approval
Introduction

Raghav Chari, PhD
Chief Innovation Officer
COVIS Pharma
Covis Acquired AMAG Pharmaceuticals in Late 2020 and Became Sponsor of Makena in March 2021

- Acquisition occurred after the 2019 BRUDAC meeting and following CDER’s proposal to withdrawal Makena from the market
- Makena is critically important for women at risk of preterm birth

Covis is committed to conducting additional studies and executing a robust plan to address the outstanding questions
Preterm Birth – Points of Agreement

1. Preterm birth is a public health priority
2. Preterm birth impacts a substantial number of women in U.S.
   - Disproportionally impacts women who are Black, other minorities, or socioeconomically disadvantaged
   - 1 in 10 babies are born prematurely in the U.S.
3. Makena and its generics are the only FDA-approved treatment for reducing the risk of preterm birth
4. Gestational age of delivery is an “intermediate clinical endpoint,” which is itself a measurement of a therapeutic effect
   - Strongly correlated with neonatal health
Meis Trial (Trial 002) – Points of Agreement

1. CDER stated Meis was "adequate, well-controlled and very persuasive," and provided "compelling" evidence of clinical benefit\(^1\)
2. Meis trial met its primary endpoint and all pre-specified secondaries for preterm birth
   - Makena significantly reduced preterm births < 37 weeks, < 35 weeks, and < 32 weeks gestation vs. placebo
3. Makena became widely used to reduce the risk of preterm birth in women with a history of spontaneous preterm birth
   - American College of Obstetricians and Gynecologists (ACOG)
   - Society for Maternal-Fetal Medicine (SMFM)

1. CDER 2019 Briefing Document
PROLONG Trial (Trial 003) – Points of Agreement

1. PROLONG did not verify the clinical benefit of Makena on neonatal morbidity and mortality
2. PROLONG did not show an effect on reduction of preterm birth rates
3. PROLONG enrolled different populations in terms of risk factors for preterm birth compared with Meis trial
October 2019, Bone Reproductive and Urologic Drugs Advisory Committee (BRUDAC)

- BRUDAC reached a divided conclusion
- 9 voted for CDER to pursue withdrawal
- 7 voted to leave Makena on the market with the requirement that new confirmatory data be generated
  - Of the 6 OBGYNs, 5 voted to leave Makena on the market
Covis is Committed to Confirming Clinical Benefit of Makena

1. Partial Withdrawal to Higher-Risk Target Population
   - Narrow labeling to use in a higher-risk target population identified through our analysis of Meis and PROLONG
   - No active promotion of Makena

2. Conduct a Randomized Controlled Trial (RCT)
   - Confirm Makena’s effect on intermediate clinical endpoint in the identified higher-risk target patient population – completed within 4- to 6-years

3. Optionally, Also Conduct an Observational Study
   - Further validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment
Available Evidence from Meis and PROLONG Identifies Higher-Risk Target Population of Patients

Partial Withdrawal to Higher-Risk Target Population

- Women with $\geq 1$ recent prior spontaneous preterm birth $< 35$ weeks and
- $\geq 1$ additional risk factor such as
  - Prior spontaneous preterm birth $< 32$ weeks
  - Multiple spontaneous preterm births $< 37$ weeks
  - Last pregnancy within 2 years
  - Other social determinants of preterm birth
Conduct Randomized Controlled Trial

- Extensive multiple stakeholder surveys support feasibility of enrolling
  - Practitioners and patients are willing to participate
- **Proposed population:** Women with $\geq 1$ prior spontaneous preterm birth $< 35$ weeks and $\geq 1$ additional risk factor
- **Trial design:** $\sim 400$ patients randomized 2:1
- **Estimated completion:** 4- to 6-years
Covis Willing to Voluntarily Withdraw Makena Based on Futility and Feasibility Assessments

**Conduct Randomized Controlled Trial**

Pre-specified criteria that would result in voluntary withdrawal:

1. Interim efficacy analysis for futility
2. Assessment of enrollment projections at Month 24 to evaluate feasibility of completing the trial in a 4- to 6-year timeframe
3. Outcome of study is negative
Potential Observational Study to Evaluate Clinical Outcomes

Potential Observational Study

- Establish the relationship between gestational age and neonatal outcomes in treated vs. untreated patients
- Validate benefit of weeks gained on 17P in the RCT
Question at hand, should Makena remain on the market for identified target population of higher-risk patients while additional studies are conducted?
Introduction

Legal and Regulatory Framework

Overview of Preterm Birth

Meis Trial

PROLONG Trial

Totality of Evidence

Identification of a Potential Higher-Risk Patient Population

Additional Publications Supporting Makena’s Efficacy

Safety

Clinical Perspective

Proposed Path Forward While Makena Remains on the Market

Raghav Chari, PhD
Chief Innovation Officer - COVIS Pharma

Rebecca Wood, JD
Partner - Sidley Austin LLP

Yolanda Lawson, MD
Associate Attending Physician – Baylor University Medical Center, Waco, Texas
President Elect – National Medical Association

Baha Sibai, MD
Professor, Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School-UTHealth at Houston

Sean Blackwell, MD
Chair and Professor - Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School-UTHealth at Houston

Michael Greene, MD
Professor - Obstetrics, Gynecology and Reproductive Biology Emeritus
Harvard Medical School, Boston, Massachusetts

Eugene Poggio, PhD
President and Chief Biostatistician
Biostatistical Consulting Inc., Lexington, Massachusetts

Raghav Chari, PhD

Raghav Chari, PhD

Yolanda Lawson, MD

Raghav Chari, PhD

Sean Blackwell, MD
Legal And Regulatory Framework

Rebecca K. Wood
Partner
Sidley Austin LLP
Key Points

1. The accelerated approval standard is flexible
2. Withdrawal of accelerated approval is not mandatory
3. Policy and precedent support keeping Makena on the market while additional study is undertaken
Regulatory Flexibility

- Accelerated approval is “intended to encourage” FDA “to utilize innovative and flexible approaches . . . for patients with serious or life-threatening diseases or conditions and unmet medical needs”

- FDA’s regulations state that standards for drug approval “demand flexibility”

FDCA Section 506(e)(1); 21 CFR 314.105(c)
Permissive Legal Standard for Withdrawal of Approval

- FDA “may withdraw” accelerated approval if
  - a confirmatory trial “fails to verify and describe” the clinical benefit or
  - “other evidence demonstrates that the product is not safe or effective under the conditions of use”
- The statute is permissive, not mandatory
  - CDER acknowledges: “CDER possesses various regulatory options when a confirmatory trial fails to verify clinical benefit”
- FDA has the authority to keep Makena on the market while another trial is conducted

FDCA Section 506(c)(3); CDER Briefing Book page 78
FDA Policy and Precedent Considerations

1. Why did the trial fail?
2. What options are available to patients?
3. Is there a subset of patients for whom the drug may be effective?
FDA – Why did the trial fail?

“There are many reasons that a trial fails and that could be the size of the trial, the endpoint they used, the population that they defined. . . . To remove a drug from the market or even an indication is a big deal and not in the public’s best interest if you can understand why that trial failed. . . . We have to have that flexibility rather than just a draconian approach.”

Dr. Richard Pazdur, Director of FDA’s Oncology Center of Excellence (Dec. 2019)¹

FDA – What Options are Available for Patients?

"FDA must carefully evaluate what other options are available to patients at the time it is considering regulatory action for failure to confirm clinical benefit. In some cases a drug for which clinical benefit has not been confirmed may be the only approved therapeutic option for patients with the disease. Removing the drug from the market and leaving patients with no treatment may be unacceptable."

Dr. Billy Dunn, Director of CDER’s Office of Neuroscience (Sept. 2022)

Opening Statement, Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting (Sept. 7, 2022)
FDA – Is there a Subset of Patients for Whom the Drug is Effective?

“FDA must also consider the possibility that, despite results from confirmatory studies that may appear to indicate that a drug does not provide clinical benefit, there may be a subset of patients for whom the drug may nevertheless be effective.”

FDA Response to Government Accountability Office (September, 2009)
FDA Precedent - Midodrine HCl

1996  Accelerated approval granted
2007  CDER determined that confirmatory studies submitted in 2005 failed to verify clinical benefit
2010  CDER issued NOOH proposing to withdraw midodrine
2012  FDA agreed to hold NOOH in abeyance
2015  Midodrine’s sponsor submitted a supplement with the results of additional studies
   ▪ 19 years after its original approval
   ▪ 10 years after its first “failed” confirmatory studies were submitted to FDA
2022  Midodrine remains on the market

CDER, Midodrine Update (Sept. 2010)
FDA Precedent

“Midodrine is the only drug approved for the treatment of symptomatic orthostatic hypotension (SOH) a rare but serious condition…. If marketing approval for midodrine is withdrawn at this time, patients with SOH will be left with no approved therapeutic options.”¹

“FDA has two goals with respect to midodrine: (1) to obtain high quality data on the effectiveness of the medication and (2) to maintain access for patients to the medication throughout this process.”²

1. Letter from Abigail Brandel, Counsel to CDER and Carla Cartwright, Counsel to CDER to G. Matthew Warren, Senior Regulatory Counsel, Office of the Commissioner of Food and Drugs, Docket No. 2007-N-0475-0036 (Jan. 13, 2012)
2. CDER, Midodrine Update (Sept. 2010)
Compounded 17P

- If FDA withdraws a drug from the market for reasons of safety or efficacy, its active ingredient is added to the list of withdrawn or removed drugs that “may not be compounded”

- In practice, that process is uncertain and may take years
  - Compounding may continue for years following withdrawal

- FDA has stated:
  - “Compounded drugs are not FDA-approved”
  - 503A compounders “are exempt from compliance with cGMPs [current Good Manufacturing Practices] requirements”
  - “Unnecessary use of compounded drug unnecessarily exposes patients to potentially serious health risks”

---

1. 21 U.S.C. § 353a(b)(1)(C); § 353b(a)(4); 21 C.F.R. § 216.24
2. Compounding and the FDA: Questions and Answers (June 29, 2022)
Path Forward

- This is only the second time FDA has held a hearing to address a proposed withdrawal, and the first time a hearing has been held to consider the withdrawal of an entire product
- FDA Chief Scientist granted our request for a hearing

> “Covis has justified a hearing in this matter” given the “genuine and substantial issues of fact appropriate for a hearing.”

- FDA may exercise regulatory flexibility when a confirmatory trial fails in light of the flexible accelerated approval standard, the permissive withdrawal standard, and FDA’s approach to policy and precedent

1. August 18, 2021 FDA Chief Scientist letter to Covis
Preterm Birth

Yolanda Lawson, MD
Associate Attending Physician – Baylor University Medical Center
President Elect – National Medical Association
Preterm Birth is Associated with Significant Neonatal Morbidity and Mortality

- Leading cause of neonatal and infant mortality\(^1\)
- Higher risk of death within first 28 days of life\(^2\)
- Significantly higher risk of short- and long-term complications\(^2\)

**Short-Term Complications**
- Respiratory distress syndrome
- Bronchopulmonary dysplasia
- Intraventricular hemorrhage
- Periventricular leukomalacia

**Long-Term Complications**
- Chronic respiratory problems
- Rehospitalization
- Metabolic disorders
- Neurodevelopment problems

Neonatal Morbidity and Mortality Increase as Gestational Age Decreases

## History of Singleton Preterm Delivery is a Significant Risk Factor for Subsequent Preterm Birth

<table>
<thead>
<tr>
<th>Gestational Age at First Delivery, Weeks</th>
<th>Total n (%)</th>
<th>Preterm in Second Delivery n (%)</th>
<th>Preterm Birth &lt; 37 Weeks in Second Delivery Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 37</td>
<td>46771 (92.4)</td>
<td>2630 (5.7)</td>
<td>Reference</td>
</tr>
<tr>
<td>34 to &lt; 37</td>
<td>2950 (5.8)</td>
<td>838 (28.9)</td>
<td>4.81 (4.48, 5.15)</td>
</tr>
<tr>
<td>28 to &lt; 34</td>
<td>607 (1.2)</td>
<td>226 (37.9)</td>
<td>5.98 (5.37, 6.66)</td>
</tr>
<tr>
<td>24 to &lt; 28</td>
<td>152 (0.3)</td>
<td>61 (40.1)</td>
<td>6.42 (5.33, 7.74)</td>
</tr>
<tr>
<td>20 to &lt; 24</td>
<td>127 (0.3)</td>
<td>35 (27.8)</td>
<td>4.88 (3.66, 6.50)</td>
</tr>
</tbody>
</table>

Laughon et al., 2014  
Trend for gestational age p<0.0001  
RR adjusted for maternal age, race/ethnicity, pre-pregnancy, body mass index, insurance, smoke, alcohol, illicit drug use, chronic medical disease
Preterm Birth Impacts a Substantial Number of Women in the United States

- ~130,000 pregnant women per year in the U.S. have a history of prior singleton spontaneous preterm birth
- Preterm birth disproportionally impacts specific patient populations
  - Women who are Black and other minority groups
  - Other social determinants (i.e., education, income, marital status, nutrition)

Withdrawal of Makena would have greatest impact on at-risk and disadvantaged patient populations
Meis Trial

Baha Sibai, MD
Professor, Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School-UTHHealth at Houston
Houston, Texas
Clinical Experience with Makena and Caring for Higher-Risk Pregnant Women
Meis Trial (Trial 002)
Meis Trial Provides Compelling Evidence of Makena’s Clinical Benefit in Women with History of sPTB

- **Enrollment Criteria**
  - Women ≥ 18 years
  - Singleton pregnancy
  - History of previous singleton sPTB
  - Enrolled 16⁰ – 20⁶ week of pregnancy

- **Makena (17P)**
  - 250 mg IM q7 days
    - *Weekly injections of study drug until 36⁶ week of pregnancy or deliver*

- **Placebo**
  - IM q7 days

- **Second planned interim analysis**: Enrollment stopped early due to significant benefit of Makena compared with placebo
  - Final analyses include 463 women, 92.6% of planned sample size
Makena Met Primary Endpoint Demonstrating Significant Reduction in Preterm Births < 37 Weeks

Patients with Preterm Birth (%)

<table>
<thead>
<tr>
<th>Gestational Age (weeks)</th>
<th>Makena (N = 306)</th>
<th>Placebo (N = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32</td>
<td>N = 35</td>
<td>N = 30</td>
</tr>
<tr>
<td></td>
<td>p = 0.018</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ 41.8%</td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>N = 63</td>
<td>N = 47</td>
</tr>
<tr>
<td></td>
<td>p = 0.017</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ 32.9%</td>
<td></td>
</tr>
<tr>
<td>&lt; 37</td>
<td>N = 111</td>
<td>N = 84</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ 33.9%</td>
<td></td>
</tr>
</tbody>
</table>

Primary Outcome

# Meis Trial Showed Highly Significant Efficacy Across All Major Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Makena (n/N)</th>
<th>Placebo (n/N)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>111/310</td>
<td>84/153</td>
<td>0.66 (0.54, 0.81)</td>
</tr>
<tr>
<td>&gt; 1 Prior PTB</td>
<td>41/86</td>
<td>44/63</td>
<td>0.68 (0.52, 0.90)</td>
</tr>
<tr>
<td>Only 1 prior PTB</td>
<td>70/220</td>
<td>40/90</td>
<td>0.72 (0.53, 0.97)</td>
</tr>
<tr>
<td>Black</td>
<td>64/181</td>
<td>47/90</td>
<td>0.68 (0.51, 0.90)</td>
</tr>
<tr>
<td>Non-Black</td>
<td>47/125</td>
<td>37/63</td>
<td>0.64 (0.47, 0.87)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>50/150</td>
<td>43/82</td>
<td>0.64 (0.47, 0.86)</td>
</tr>
<tr>
<td>Married</td>
<td>61/156</td>
<td>41/71</td>
<td>0.68 (0.51, 0.90)</td>
</tr>
<tr>
<td>Smoking or substance use</td>
<td>28/85</td>
<td>23/36</td>
<td>0.52 (0.35, 0.76)</td>
</tr>
<tr>
<td>No smoking or substance use</td>
<td>83/221</td>
<td>61/117</td>
<td>0.72 (0.57, 0.92)</td>
</tr>
<tr>
<td>Education ≤ 12 years</td>
<td>80/223</td>
<td>55/103</td>
<td>0.67 (0.52, 0.86)</td>
</tr>
<tr>
<td>Education &gt; 12 years</td>
<td>31/83</td>
<td>29/50</td>
<td>0.64 (0.45, 0.93)</td>
</tr>
</tbody>
</table>
Significant Unmet Need and Compelling Evidence of Clinical Benefit Led to Accelerated Approval

- At time of accelerated approval CDER determined Meis was “adequate, well-controlled and very persuasive” and provided “compelling” evidence of clinical benefit
- Meis trial is “sufficiently persuasive to support drug approval based on the findings of a single adequate and well controlled trial”
Meis Trial Results were Considered Significant Advance in the Field of Obstetrics

- Relative Risk (95% CI)
  - 0.66 (0.54, 0.81)
- Absolute difference in preterm birth rate
  - 18.6%
- Number needed to treat
  - 5.4 women to prevent 1 PTB

Meis, NEJM 2003
Meis Trial Results Led to Medical Societies Recommending Progesterone Supplementation for Prevention of Recurrent PTB

“Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes.” ACOG Committee Opinion (2008)

- ACOG concluded results show significant protection for recurrent PTB for all races of women
Meis Trial is Not an Outlier and Not a False Positive

1. Meis results were so compelling that trial stopped early
   - DSMB recommended, given robust efficacy demonstrated with Makena
   - Final data set of 463 women represented 92.6% of the planned sample size

2. Subgroup analyses support that results are generalizable to a wide range of women with previous spontaneous preterm birth
   - Subgroup analyses by number of prior spontaneous preterm births, race, marital status, and smoking or substance use consistently demonstrate the benefits

3. Preterm birth rate in Meis not unexpected
   - High proportion of patients who were Black
   - Early gestational age of prior spontaneous preterm birth
   - High proportion of women with ≥ 1 prior spontaneous preterm birth

Sibai et al, Re-examining the Meis Trial for Evidence of False-Positive Results (2020)
Placebo Arm Preterm Birth Rates Consistent in Meis and O’Brien Trials

PTB < 35 Weeks in Placebo Arm

- Meis (2003): 31% (100% U.S.)
- O’Brien (2007): 27% (64% U.S.)
# Results of Subsequent NICHD Trial Supports Preterm Birth Rate in the Makena Arm of Meis Trial

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Meis Trial</th>
<th>NICHD Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Makena (17P)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 310</td>
</tr>
<tr>
<td>&gt; 1 previous sPTB</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>Black / African American</td>
<td>59%</td>
<td>34%</td>
</tr>
<tr>
<td>Married or living with partner</td>
<td>51%</td>
<td>71%</td>
</tr>
<tr>
<td>Education level, mean (years)</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Gestational age of qualifying sPTB, mean (weeks)</td>
<td>31</td>
<td>32</td>
</tr>
</tbody>
</table>

### Pregnancy Outcome (Preterm Birth)

<table>
<thead>
<tr>
<th></th>
<th>Meis Trial</th>
<th>NICHD Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 37 weeks</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>&lt; 35 weeks</td>
<td>21%</td>
<td>19%</td>
</tr>
<tr>
<td>&lt; 32 weeks</td>
<td>12%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Harper et al., Obstetrics & Gynecology (2010)
NICHD National Institute of Child Health and Human Development
27% Enrollment at One Site in Meis Trial Does Not Undermine the Results

- Preterm birth rates are higher in Southeast vs. other U.S. regions
  - Reasonable to expect one site with high enrollment
- Single Southeast center did not bias the results
  - Significant efficacy of Makena seen at other sites
    Relative Risk (95% CI) = 0.70 (0.56, 0.88)
  - Interaction term in a logistic regression analysis indicates Southeast site results were not significantly different from the other sites (p = 0.82)
PROLONG Trial

Sean Blackwell, MD
Chair and Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School-UTHealth at Houston
Houston, Texas
PROLONG Designed to Mirror Meis

- Identical study protocol
- Expanded recruitment to assess risks of pregnancy loss and neonatal outcomes
- Assumed same treatment effects
  - Effect size = 1/3 reduction
- No interim analyses or assessment of efficacy as trial required to be completed as part of accelerated approval
PROLONG: Baseline Recruitment Challenges

- ACOG/SMFM advocate for progestogen use as best practice
- Meis “convincing” to MFMU and other high-risk academic medical centers
PROLONG: Recruitment Challenges

- Meis published in NEJM
- 2/3 board certified MFM's already using progesterone
- PROLONG Trial enrollment initiated

2003

ACOG committee opinion supports use of progesterone

2006

2009

Ness, AJOG, 2006
PROLONG: Enrollment (Year End)

Cumulative Number of Patients Enrolled*

*Enrolled by December 31 of each year
Other: Bulgaria, Canada, Czech Republic, Hungary, Italy, Spain
PROLONG Primarily Enrolled Patients Outside of the U.S. with 61% Enrolled in Ukraine and Russia

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of Patients (%)</th>
<th>N = 1708</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>391 (22.9)</td>
<td></td>
</tr>
<tr>
<td>Outside the United States</td>
<td>1317 (77.1)</td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>621 (36.4)</td>
<td></td>
</tr>
<tr>
<td>Ukraine</td>
<td>420 (24.6)</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>91 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>85 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td>50 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>31 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td>14 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>5 (0.3)</td>
<td></td>
</tr>
</tbody>
</table>

23% United States
61% Russia / Ukraine
16% Other OUS Countries
### PROLONG Trial PTB Rate < 35 Weeks: Post Hoc Analysis of Top Enrolling U.S. Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Makena</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department of Defense</td>
<td>9.5%</td>
<td>13%</td>
</tr>
<tr>
<td>Madigan Army Medical Center</td>
<td>17%</td>
<td>8.3%</td>
</tr>
<tr>
<td>San Antonio Military Medical Center</td>
<td>0%</td>
<td>29%</td>
</tr>
<tr>
<td>Tripler Army Medical Center</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>Naval Medical Center Portsmouth</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>Top Enrolling U.S. Civilian Sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosemark Women Care Specialist (Idaho Falls, ID)</td>
<td>0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>University of Louisville (KY)</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>Wheaton Franciscan Healthcare (Rancine, WI)</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>University Medical Group (Greenville, SC)</td>
<td>18%</td>
<td>25%</td>
</tr>
<tr>
<td>Watching Over Mothers and Babies Foundation (Tucson, AZ)</td>
<td>20%</td>
<td>43%</td>
</tr>
<tr>
<td>Drug Research and Analysis Corporation (Montgomery, AL)</td>
<td>46%</td>
<td>43%</td>
</tr>
</tbody>
</table>

- Meis Trial PTB rate < 35 weeks placebo arm = 30%
PROLONG Enrolled Lower Risk Population

- Recruitment in U.S.
  - Locations with prior PTB women, but much “lower risk” compared to Meis
- Recruitment outside the U.S.
  - NICU infrastructure & CRO relationships = Russia/Ukraine
  - Lower risk compared to U.S. population and lower than Meis
PROLONG Patients Substantially Different from Patients Enrolled in Meis

What is the Evidence?
PROLONG Did Not Demonstrate Significance on Either of its Prespecified Primary Endpoints

- **PTB < 35 Weeks**
  - Makena: 11.0 (122/1113)
  - Placebo: 11.5 (66/574)
  - Ratio: 0.95 (0.71, 1.26)

- **Neonatal Composite Index¹**
  - Makena: 5.6 (61/1093)
  - Placebo: 5.0 (28/559)
  - Ratio: 1.12 (0.72, 1.72)

---

¹. Composite included: Death, RDS, BPD, Grade 3 or 4 IVH, NEC and proven sepsis
Placebo Arm PTB Rates Across Different Clinical Trial Populations

PTB < 35 Weeks in Placebo Arm

- Meis (2003): 31% (100% U.S.)
- O'Brien (2007): 27% (64% U.S.)
- PROLONG-US: 18%
- PROLONG Russia: 8.7%
- PROLONG Ukraine: 9.9%

Overall PROLONG PTB < 35 wks = 11.5%
Meis Trial Enrolled “Higher-Risk” Patients Prior sPTB < 34 Weeks

- 1 Prior sPTB < 34 wks: Meis 50%, PROLONG-US 40%
- 2 Prior sPTB < 34 wks: Meis 14%, PROLONG-US 6%
# PROLONG Enrolled Vastly Different Population Compared with Meis Trial

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Meis N = 463</th>
<th>PROLONG-OUS N = 1317</th>
<th>PROLONG-US N = 391</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 Previous spontaneous PTB</td>
<td>32% (149)</td>
<td>▶️ 11% (141)</td>
<td>▶️ 27% (107)</td>
</tr>
<tr>
<td>Black / African American</td>
<td>59% (273)</td>
<td>▶️ 0.1% (1)</td>
<td>▶️ 29% (113)</td>
</tr>
<tr>
<td>Unmarried with no partner</td>
<td>50% (233)</td>
<td>▶️ 4% (53)</td>
<td>▶️ 31% (120)</td>
</tr>
<tr>
<td>Educational ≤ 12 years</td>
<td>71% (330)</td>
<td>▶️ 42% (549)</td>
<td>▶️ 50% (197)</td>
</tr>
<tr>
<td>Any substance use during pregnancy</td>
<td>26% (121)</td>
<td>▶️ 4% (47)</td>
<td>△ 28% (111)</td>
</tr>
</tbody>
</table>

- △ Higher risk compared to Meis
- ▶️ Lower risk compared to Meis
Summary: PROLONG Population vs. Meis

- Different clinical characteristics
  - Black race
  - Prior PTB (early PTB and number of prior early PTB)
- Only 2% of women enrolled in PROLONG had short cervix
- Lower rates recurrent PTB in placebo arm
PROLONG was a “Flawed” Trial

Prevention of recurrent PTB in singleton pregnancies

- YES, if trying to study “high-risk” women in U.S.
- THUS, its “negative findings” related to efficacy do not cancel or invalidate the positive findings of Meis
Another Trial is Needed

- Many MFM physicians continue to utilize Makena and believe access to FDA-approved medications is best practice
- SMFM continues to support Makena in the highest-risk population
- Another trial is needed to address efficacy
  - U.S. “higher-risk” population
- Continued access to Makena for clinical care until a trial is completed
Totality of the Evidence

Michael Greene, MD
Professor - Obstetrics, Gynecology and Reproductive Biology Emeritus
Harvard Medical School
Associate Editor of New England Journal of Medicine
Background Principles

1. Makena is indicated only for use with women with a history of a prior spontaneous preterm birth (sPTB)
   - sPTB is significant risk factor for subsequent preterm birth

2. Makena is indicated only for use during singleton pregnancies
   - “Safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.”

3. CDER has asserted that observational studies are not reliable
   - “Inherent limitations to observational studies or externally controlled trials, whether retrospective or prospective… preclude the use of these study designs to obtain reliable evidence of Makena’s efficacy”

1. Laughon et al., 2014
2. Makena Product Labeling
3. CDER Briefing Document 2022
CDER’s Conclusion that the Meis Trial is an Outlier Based on Figure 1 is Inappropriate

Figure adapted from CDER Briefing Document 2022
Observational Studies Have Inherent Limitations

Observational Studies

- RCTs
- Observational

Figure adapted from CDER Briefing Document 2022
Rouse and Caritis Evaluated Efficacy of 17P in Women with Twins and Triplets

**Relative Risk of Preterm Delivery (Makena vs. Placebo/No Treatment)**

- **Twins**
  - RCTs
  - Observational

- **Triplets**
  - RCTs
  - Observational

Figure adapted from CDER Briefing Document 2022
Price Evaluated Women with HIV and Affirmatively Excluded Women with a History of PTB

HIV / No Prior sPTB

Twins

Triplets

Observational Studies

RCTs  Observational

Figure adapted from CDER Briefing Document 2022
Meis (Trial 002) and PROLONG (Trial 003)

Only randomized, controlled trials relevant to Makena’s efficacy

- HIV / No Prior sPTB
- Twins
- Triplets
- Observational Studies

Relative Risk of Preterm Delivery (Makena vs. Placebo/No Treatment)

Figure adapted from CDER Briefing Document 2022
Makena: One Positive RCT, One Failed RCT in a Different Patient Population

- Meis – indisputably robust showing of efficacy
- PROLONG – failed to confirm Meis trial

“There are many reasons that a trial fails and that could be the size of the trial, the endpoint they used, the population that they defined. . . . To remove a drug from the market or even an indication is a big deal and not in the public’s best interest if you can understand why that trial failed. . . . We have to have that flexibility rather than just a draconian approach.”

Dr. Richard Pazdur, Director of FDA’s Oncology Center of Excellence (Dec. 2019)¹

PROLONG Failed to Enroll a Population Capable of Confirming the Results Seen in the Meis Trial

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Meis N = 463</th>
<th>PROLONG-IOUS N = 1317</th>
<th>PROLONG-US N = 391</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 Previous spontaneous PTB</td>
<td>32% (149)</td>
<td>▼ 11% (141)</td>
<td>▼ 27% (107)</td>
</tr>
<tr>
<td>Black / African American</td>
<td>59% (273)</td>
<td>▼ 0.1% (1)</td>
<td>▼ 29% (113)</td>
</tr>
<tr>
<td>Unmarried with no partner</td>
<td>50% (233)</td>
<td>▼ 4% (53)</td>
<td>▼ 31% (120)</td>
</tr>
<tr>
<td>Educational ≤ 12 years</td>
<td>71% (330)</td>
<td>▼ 42% (549)</td>
<td>▼ 50% (197)</td>
</tr>
<tr>
<td>Any substance use during pregnancy</td>
<td>26% (121)</td>
<td>▼ 4% (47)</td>
<td>△ 28% (111)</td>
</tr>
</tbody>
</table>

△ Higher risk compared to Meis ▼ Lower risk compared to Meis
**Preterm Birth Rates in Placebo Groups Were the Most Important Difference Between the Trials**

<table>
<thead>
<tr>
<th>Placebo Groups</th>
<th>Meis N = 153</th>
<th>PROLONG-OUS N = 447</th>
<th>PROLONG-US N = 131</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 37 weeks</td>
<td>55%</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>&lt; 35 weeks</td>
<td>31%</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>&lt; 32 weeks</td>
<td>20%</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Preterm birth rate in placebo group of Meis trial (31%) was used to calculate sample size of PROLONG study.
My Conclusions

- PROLONG failed to confirm Meis, but
  - It is not a definitive negative study
  - It does not rule out efficacy
  - It is not conclusive
- Given the shortcomings of PROLONG
  - It cannot be used to discount Meis as a false positive
  - Meis remains substantial evidence of effectiveness in a higher-risk population
Next Steps

- A further RCT in a higher-risk population is necessary
  - Based on experience in PROLONG, additional enrollment criteria are likely necessary
  - Different endpoints also may be necessary
  - Details should be worked out collaboratively
- Makena should remain on the market while this trial is conducted
- “The widespread use of 17OHP after accelerated approval has not uncovered important safety signals.”¹
- Labeling revisions would be a reasonable accommodation

¹ Greene et al., NEJM 2020
Final Points to Consider

1. Given what we know about risk factors for recurrent preterm birth, were the populations enrolled in Meis and PROLONG sufficiently similar to allow for a meaningful comparison?

2. Are the observed rates of preterm birth in the placebo arms of the two trials sufficiently similar that they can be confidently said to represent two populations at similar risk?
Identification of a Potential Higher-Risk, Target Patient Population

Eugene Poggio, PhD
Founder, President, and Chief Biostatistician
Biostatitical Consulting Inc.
Meis vs. PROLONG

- As discussed, results for Meis and PROLONG studies differed substantially
  - Meis met its primary and secondary endpoints for PTB
  - PROLONG did not meet either of its co-primary endpoints
- As also discussed, Meis and PROLONG enrolled vastly different populations
  - In particular, they differed in risk factors for PTB, Meis patients being at higher risk
- Covis believes difference in results is due to difference in risk
Analyses Investigated Risk Factors of Preterm Birth from Three Data Sources

1. Dorsata medical records database for obstetrics among participating health systems
   - ~1700 pregnancies with confirmed prior preterm birth
   - Only untreated subjects were included (N=1187)
2. Meis trial
   - Placebo patients only (N=153)
3. PROLONG trial
   - Placebo patients only (N=133)
Logistic Regression Models

- **Dependent variable**: Delivery < 34 weeks
- **Factors considered**:
  - Demographic characteristics
  - Medical history (e.g., diabetes, hypertension)
  - Obstetrical history
  - Substance use (smoking, alcohol, drugs)
Identified Risk Factors for Preterm Birth

- Obstetrical history risk factors
  - Mean gestational age of prior spontaneous deliveries (mGA)
  - Gestational age of most recent prior spontaneous delivery (mrpGA)
  - ≥ 1 spontaneous preterm birth < 32 weeks
  - ≥ 2 spontaneous preterm births < 37 weeks

- Other risk factors
  - Race (Black vs. Non-Black)
  - Inter-pregnancy interval (IPINT)
  - Smoking (yes / no)
Endpoints

- Meis and PROLONG had dichotomous primary endpoints
  - Meis: PTB < 37 weeks
  - PROLONG: PTB < 35 weeks (and neonatal composite index)
- In order to increase sensitivity to detecting treatment effects, most of our post hoc analyses used a continuous endpoint
  - Time from randomization to delivery
  - Capped at 35 weeks so that increases would more clearly reflect a clinical benefit
- Analyzed using linear regression model with treatment, GA at randomization, and mrga / mGA as predictor variables
Gestational Age at Randomization

- In its review of the Meis study, FDA noted there was little evidence of any treatment effect in patients randomized at GAs ≥ 20 weeks
  - Covis agrees
- Accordingly, in all the analyses presented below in both Meis and PROLONG, subjects who were randomized at GAs ≥ 20 weeks have been excluded
PROLONG: U.S. vs. Ex-U.S.

- U.S. population more representative of relevant population for FDA decision-making
- Ex-U.S. population is different population with different health care system
- Sample size for U.S. population is sufficient for our purposes
- Ex-U.S. PROLONG represents low-risk population based on risk factors
- Accordingly, all of the analyses presented below for PROLONG are for the U.S. patients only
Important Caveats

- Post hoc analyses
  - Not pre-specified
- Multiple comparison issues
  - Multiple subgroups
  - Multiple endpoints
- Hypothesis generating
PROLONG-US: Treatment Effect Favoring Makena is Higher Among Patients With More Severe Recent Birth History

Weeks Gained for Makena-Treated Patients vs. Placebo*

Gestational Age (Week) of Most Recent Prior Spontaneous Delivery

*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mrgGA as predictor variables.
PROLONG-US: Treatment Effect Also Increases with Risk Based on Mean Gestational Age of Prior Deliveries

**Weeks Gained for Makena-Treated Patients vs. Placebo**

![Graph showing weeks gained for Makena-treated patients vs. placebo](image)

*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mGA as predictor variables.*
Results in PROLONG-US Show Greater Treatment Effect with Greater Risk

- Strong trend in weeks gained from 1 to > 3 as most recent gestational age categories decrease from < 37 to < 28
- Similarly strong trend in weeks gained from 0.5 to > 3 as mean gestational age categories decrease from < 37 to < 28
Selected Potential Higher-Risk Subgroups

- Based on these results and published literature on preterm birth risks, we examined selected higher-risk subgroups
  - Recent spontaneous preterm birth (sPTB) < 32 weeks
  - Recent sPTB < 35 weeks and multiple sPTBs < 37 weeks
  - Recent sPTB < 35 weeks and short interpregnancy interval ($\leq 2$ years)
  - Recent sPTB < 35 weeks and Black race
PROLONG-US Results for Higher-Risk Subgroups

Estimated Weeks Gained (up to 35 Weeks)*

- Overall: N=291, 0.7 weeks
- Recent prior sPTB < 32: N=50, 1.0 weeks
- Recent prior sPTB < 35 + Black: N=31, 0.8 weeks
- Recent prior sPTB < 35 + MTO37: N=15, 1.9 weeks
- Recent prior sPTB < 35 + IPINT ≤ 2 years: N=69, 1.8 weeks

*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mrgGA as predictor variables.
Higher-Risk Target Population Analyzed

- Women with $\geq 1$ recent spontaneous preterm birth $< 35$ weeks and $\geq 1$ additional risk factor
  - Recent prior spontaneous preterm birth $< 32$ weeks
  - Multiple prior spontaneous preterm births $< 37$ weeks
  - Last pregnancy within 2 years
  - Women who are Black
Results in Higher-Risk Target Patient Population for Continuous Endpoint: **Nominally Statistically Significant**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Estimated Difference in Time from Randomization to Delivery (up to 35 weeks)(^1)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROLONG-US</td>
<td>87</td>
<td>1.86</td>
<td>(0.18, 3.54)</td>
</tr>
<tr>
<td>Meis</td>
<td>164</td>
<td>1.33</td>
<td>(0.08, 2.59)</td>
</tr>
</tbody>
</table>

\(^1\) Estimates are from model with time from randomization to delivery (capped at 35 weeks gestation) as outcome variable and treatment, gestational age at randomization, and mrpGA as predictor variables.
## Results in Higher-Risk Target Patient Population for Dichotomous Endpoints: Favorable Point Estimates in PROLONG and Nominally Statistically Significant in Meis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Endpoint</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROLONG-US</td>
<td>87</td>
<td>PTB &lt; 37</td>
<td>0.69</td>
<td>(0.28, 1.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 35</td>
<td>0.55</td>
<td>(0.19, 1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 32</td>
<td>0.36</td>
<td>(0.09, 1.44)</td>
</tr>
<tr>
<td>Meis</td>
<td>164</td>
<td>PTB &lt; 37</td>
<td>0.24</td>
<td>(0.12, 0.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 35</td>
<td>0.35</td>
<td>(0.18, 0.70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 32</td>
<td>0.33</td>
<td>(0.15, 0.70)</td>
</tr>
</tbody>
</table>

Estimates are from logistic regression model with preterm birth (either < 32, < 35, or < 37) as outcome variable and treatment as predictor variable.
Summary

- Have identified a target patient population of higher-risk subjects for which:
  1. New endpoint of weeks from randomization to delivery is nominally statistically significant in both Meis and PROLONG-US
  2. Old primary endpoints of PTB < 35 and PTB < 37 are nominally statistically significant in Meis and have favorable point estimates in PROLONG-US
Additional Publications Supporting Makena’s Efficacy

Raghav Chari, PhD
Chief Innovation Officer
COVIS Pharma
EPPPIC is Largest Existing Individual Patient Data Meta-Analysis of Progestogens Used to Prevent PTB

- Includes participant-level data from 31 trials
  - > 11,000 women
  - > 16,000 offspring
- Includes 5 randomized trials for intramuscular 17P in singleton gestation pregnancies
- First meta-analysis of 17P in singleton gestation pregnancies

The EPPPIC Group, Lancet (2021)
EPPPIC = Evaluating Progestogens for Preventing Preterm Birth International Collaborative
EPPPIC Meta-Analysis Shows Makena Reduces Risk of Early PTB

<table>
<thead>
<tr>
<th>17P</th>
<th>Women (n)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>3053</td>
<td>0.94 (0.78, 1.13)</td>
</tr>
<tr>
<td>Preterm &lt; 34 weeks</td>
<td>3053</td>
<td>0.83 (0.68, 1.01)</td>
</tr>
<tr>
<td>Preterm &lt; 28 weeks</td>
<td>3053</td>
<td>0.73 (0.53, 1.02)</td>
</tr>
<tr>
<td>Maternal complications</td>
<td>2946</td>
<td>1.18 (0.97, 1.43)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>3043</td>
<td>0.88 (0.59, 1.31)</td>
</tr>
<tr>
<td>Serious neonatal complications</td>
<td>3036</td>
<td>0.81 (0.60, 1.09)</td>
</tr>
</tbody>
</table>

The EPPPIC Group, Lancet (2021)
Observational Study by Bastek et al. Further Characterizes Efficacy of 17P

- Comparison of pre-term birth rate and gestational age distribution
  1. Pre-17P (Jan 2004 - Dec 2005)
  2. Post-17P (Jan 2008 - Dec 2009)
    - Policy change in 2006 established 17P as standard of care and it was prescribed to all eligible women

Bastek et al. Shows 17P was Associated with a Meaningful Delay in Preterm Birth

- No difference in proportion of preterm births < 37 weeks
- 17P associated with delay in preterm birth by 10 days
- Authors explained: “evidence that 17-OHPC may have brought us closer towards mitigating the adversity associated with prematurity, which is of great public health significance.”

Bastek et al., Maternal Child Health Journal (2011)
Bastek et al. Shows Women Receiving 17P More Likely to Deliver a Preterm Infant During Late Preterm

<table>
<thead>
<tr>
<th>Gestational Age Range (Weeks)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21^0 – 23^6</td>
<td>0.38 (0.16, 0.90)</td>
<td>0.39 (0.16, 0.93)</td>
</tr>
<tr>
<td>24^0 – 27^6</td>
<td>0.67 (0.31, 1.46)</td>
<td>0.67 (0.31, 1.47)</td>
</tr>
<tr>
<td>28^0 – 32^6</td>
<td>0.56 (0.31, 1.01)</td>
<td>0.53 (0.29, 0.96)</td>
</tr>
<tr>
<td>32^0 – 34^6</td>
<td>0.77 (0.43, 1.39)</td>
<td>0.75 (0.42, 1.36)</td>
</tr>
<tr>
<td>34^0 – 36^6</td>
<td>2.21 (1.45, 3.39)</td>
<td>2.30 (1.49, 3.54)</td>
</tr>
</tbody>
</table>

Bastek et al., Maternal Child Health Journal (2011)
Safety

Raghav Chari, PhD
Chief Innovation Officer
COVIS Pharma
Meis Established Makena’s Favorable Safety Profile

“There were no safety findings in the original NDA submission of April 2006, based on data from Study 002…. Supportive Study 001, Study 17P-FU…. or published medical literature that would have precluded approval of HPC for the proposed indication.”

CDER’s Medical Review of Makena NDA

- Most common AE was injection site reactions
- Non-significant trend toward an increase in 2nd trimester miscarriage rate and stillbirth rate with Makena
- No difference between Makena and placebo arms
  - Incidence of pregnancy complications
  - Overall incidence of combined fetal and neonatal mortality
- Follow-up study showed Makena is safe for fetus when given in 2nd and 3rd trimesters
### PROLONG Reaffirmed Positive Safety Profile of Makena Demonstrated in Meis Trial

<table>
<thead>
<tr>
<th>Summary of TEAE’s</th>
<th>Makena N = 1128</th>
<th>Placebo N = 578</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>57.9%</td>
<td>58.1%</td>
</tr>
<tr>
<td>Any maternal pregnancy complication</td>
<td>10.0%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Any AEs leading to study drug withdrawal</td>
<td>1.0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Any SAEs</td>
<td>3.0%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Maternal deaths</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- No clinically meaningful difference in safety profile between groups
### PROLONG Showed Consistent, Favorable Maternal and Fetal Safety Comparable to Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Makena N = 1130</th>
<th>Placebo N = 578</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal / early infant death</td>
<td>1.7%</td>
<td>1.9%</td>
<td>0.87 (0.42, 1.81)</td>
</tr>
<tr>
<td>Miscarriage (≤ 20 weeks)</td>
<td>0.5%</td>
<td>1.3%</td>
<td>0.32 (0.09, 1.14)</td>
</tr>
<tr>
<td>Stillbirth (≥ 20 weeks)</td>
<td>1.1%</td>
<td>0.5%</td>
<td>2.07 (0.59, 7.29)</td>
</tr>
<tr>
<td>Early infant deaths</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.73 (0.12, 4.48)</td>
</tr>
</tbody>
</table>

**Safety findings:**
- Number of fetal / neonatal deaths were low but were similar between groups
- The study met the prespecified endpoint of excluding a doubling of the risk of fetal / early infant deaths for Makena
## Pooled Safety Data Demonstrate Favorable Safety Profile for Makena Compared to Placebo

<table>
<thead>
<tr>
<th>Condition</th>
<th>Makena (N = 1130)</th>
<th>Placebo (N = 578)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission for preterm labor</td>
<td>16.4%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Preeclampsia or gestational hypertension</td>
<td>5.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>5.1%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>3.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Headache</td>
<td>5.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>4.2%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>4.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.8%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3.0%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Real-World Use for Over A Decade Supports Positive Safety Profile of Makena

- While **more than 350,000 women** have been treated with Makena in the last decade, **no new safety concerns, signals, or risks** have been identified.
- The known potential risks of Makena are already described in its labeling (e.g., thromboembolic events, depression, allergic reactions, decreased glucose retention, fluid retention, injection site reactions).

**Reported AEs in > 350,000 women treated are consistent with Makena’s labeled safety profile**

Covis Data on File (August 31, 2022)
Real-World Use for Over A Decade Supports Positive Safety Profile of Makena

- Estimated Patients Exposed: 356,327
- Injection site reactions: 25,818 (7.25%)
- Allergic reactions: 958 (0.27%)
- Fluid retention with pre-eclampsia: 295 (0.08%)
- Decreased glucose tolerance: 268 (0.08%)
- Depression: 223 (0.06%)
- Thromboembolic events: 36 (0.01%)

Covis Data on File (August 31, 2022)
Murphy Article is Neither Reliable Nor Relevant to Considerations of Safety and Efficacy of Makena

1. Article describes a retrospective analysis of Delalutin, not Makena
   - Both contain 17P but have key differences with respect to indication, timing, and frequency of administration
2. Murphy article has several methodological flaws that undermine the validity of its conclusions
3. Two expert statisticians have submitted declarations pointing to various deficiencies in study design and analysis
4. ACOG announced, "Due to the limitations in the design, the study's findings are not conclusive and should not influence practice"
5. CDER's internal documents also acknowledge the numerous flaws

CDER’s Internal Documents Acknowledge Numerous Flaws In Murphy

“There are significant issues with attempting to apply the results of the Murphy study to the current regulatory and clinical environment”
- CAPT David Money, Director, Division of Epidemiology II (DEPI II), Office of Surveillance and Epidemiology (OSE), CDER

Murphy “provides insufficient evidence to support regulatory action regarding a long-term cancer risk in offspring who were exposed in utero to 17-OHPC”

The study’s limitations “preclude this study from contributing definitively to this drug safety issue”
- Wei Liu, Team Leader, DEPI II, OSE, CDER
Compounded Drugs are Not Subject to Rigorous Safety and Quality Controls

- Compounded drugs do not have FDA-approved labeling
- 503A compounding pharmacies exempt from good manufacturing practices
  - 130 warning letters and more than 100 recalls
- **26 recalls of compounded 17P between 2013-2019**
  - Lack of sterility assurance
  - Product contamination
  - Bacteria and fungi in suspension fluid

Gandell et al., *Current Medical Research and Opinion* (2020)
Clinical Perspective
Medical Community Supports Makena as an Important Treatment Option

Yolanda Lawson, MD
Associate Attending Physician – Baylor University Medical Center
President Elect – National Medical Association
Why Does Makena Matter to Clinicians?

- Preterm birth is a serious medical condition, affecting a significant number of women and their babies
  - Lower gestational age at delivery, greater the risk to the baby
  - 2 weeks of added gestational age before 35 weeks can significantly reduce risks to the baby
- Preterm birth has an enormous impact on the emotional and economic well-being of women and their families
- Greater risk of preterm birth for women who are Black or other minority groups
- It is important for Makena to remain as a treatment option to support clinical decision-making
Compounded 17P is an Imperfect Alternative

- Clinicians are accustomed to compounding when an approved treatment is not available
  - Covis’ recent survey of ~400 obstetricians, gynecologists, and maternal-fetal medicine specialists shows that > 25% would be very likely to recommend compounded medication if there is no approved alternative
- Compounded drugs may have issues with purity, consistency, and quality
- Some communities lack access to compounding pharmacies, creating further equity issues
Safety Profile of Makena as Reported with Real-World Use Consistent with My Clinical Experience

- > 350,000 women have been treated with Makena
- No new safety concerns, signals, or risks have been identified
- Known potential risks of Makena, already described in its labeling
  - Injection site reactions are common with any injected product

Covis Data on File (August 31, 2022)
Medical Community Continues To Support 17P as an Important Treatment Option

Following CDER’s proposal to withdraw Makena (Oct. 5, 2020)

“At this time, ACOG recommendations remain unchanged . . . Current guidelines in the United States recommend the use of progesterone supplementation in women with prior spontaneous preterm birth. Consideration for offering 17-OHPC to women at risk of recurrent preterm birth should continue to take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman and the resources available.”

American College of Obstetricians and Gynecologists (ACOG) Statement on FDA Proposal to Withdraw 17p Hydroxyprogesterone Caproate (Oct. 2020)
Medical Community Continues To Support 17P as Important Treatment Option

Following CDER’s proposal to withdraw Makena (Oct. 5, 2020)

“it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very high-risk population reported in the Meis trial”

Society for Maternal-Fetal Medicine (SMFM) Statement (Oct. 2020)
Many Organizations Agree Makena Should Remain Available as a Treatment Option

- American Association of Birth Centers
- American Society for Reproductive Medicine
- Association of Women’s Health, Obstetric and Neonatal Nurses
- Black Mamas Matter Alliance
- Black Women’s Health Imperative
- Expecting Health
- Healthy Mothers, Healthy Babies
- HealthyWomen
- In Our Own Voice
- Jewish Women International
- Miracle Babies
- Mom Congress
- National Birth Equity Collaborative
- National Black Midwives Alliance
- National Black Nurses Association
- National Coalition for Infant Health
- National Consumers League
- National Medical Association
- National Minority Quality Forum
- National Partnership for Women & Families
- New Voices for Reproductive Justice
- PA Foundation
- Perinatal Health Equity Foundation
- Preterm Birth Prevention Alliance
- Sidelines High-Risk Pregnancy Support
- SisterReach
- SisterSong – The National Women of Color Reproductive Justice Collective
- Southern Birth Justice Network
- SPARK Reproductive Justice Now!
- 1,000 Days
- 2020 Mom

“A decision to withdraw approved 17P products may deepen profound existing maternal and infant health inequities in the U.S. We urge you to not withdraw 17P treatments, so that all pregnant people will continue to be empowered with access to a safe treatment option for preterm birth.”

- Black Women’s Health Imperative
Proposed Path Forward While Makena Remains on the Market

Raghav Chari, PhD
Covis is Committed to Confirming Clinical Benefit of Makena

1. Partial Withdrawal to Higher-Risk Target Population
   - Narrow labeling to use in a higher-risk target population identified through our analysis of Meis and PROLONG
   - No active promotion of Makena

2. Conduct a Randomized Controlled Trial (RCT)
   - Confirm Makena’s effect on intermediate clinical endpoint in the identified higher-risk target patient population – completed within 4- to 6-years

3. Optionally, Also Conduct an Observational Study
   - Further validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment
Proposed Higher-Risk Population

- Women with $\geq 1$ recent prior spontaneous preterm birth $< 35$ weeks \textbf{and}
- $\geq 1$ additional risk factor such as
  - Prior spontaneous preterm birth $< 32$ weeks
  - Multiple spontaneous preterm births $< 37$ weeks
  - Last pregnancy within 2 years
  - Other social determinants of preterm birth
Covis Proposes Conducting an RCT With Time-from-Randomization-to-Birth as the Primary Endpoint

**Proposed Randomized Controlled Trial**

- **Proposed population:** Women with ≥ 1 prior spontaneous preterm birth < 35 weeks and ≥ 1 additional risk factor
- **Trial design:** ~400 patients randomized 2:1
- **Primary endpoint:** Increase in time-from-randomization-to-birth for Makena vs. placebo, capped at 35 weeks gestation
- **Estimated completion:** 4- to 6-years
Clinical Relevance of Efficacy Endpoint of Gestational Age of Prolonging a Pregnancy

Proposed Inclusion Criteria for RCT will Improve Enrollment of Higher-Risk Patients

**Key Inclusion Criteria**

1. Previous singleton qualifying sPTB < 35 weeks occurred within the last 5 years and ≥ 1 additional risk factor
2. Documented medical history of first trimester ultrasound to calculate gestational age of qualifying delivery
### Sample Size Estimates for Endpoint: Time-from-Randomization-to-Delivery (Weeks), Capped at 35 Weeks Gestation

<table>
<thead>
<tr>
<th>Difference in Means</th>
<th>Allocation</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(17P: Placebo)</td>
<td>17P</td>
</tr>
<tr>
<td>1.0</td>
<td>1:1</td>
<td>191</td>
</tr>
<tr>
<td></td>
<td>2:1</td>
<td>286</td>
</tr>
<tr>
<td>2.0</td>
<td>1:1</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>2:1</td>
<td>74</td>
</tr>
</tbody>
</table>

1. Two-sample t-test
2. Two-sided Alpha = 0.05
3. Difference in Means (17P - Placebo): 1.0 or 2.0 weeks
4. Common SD: 3.0
5. Power = 90%
Feasibility Assessments Suggest a Randomized Controlled Trial Can Be Conducted in U.S.
MFMU Network Survey

Sean Blackwell, MD
Chair and Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School-UTHealth at Houston
Houston, Texas
Q1

What is your level of interest in participating in another 17-OHPC Trial? It would be only in the US, placebo-controlled, and involve women with singleton pregnancy and prior sPTB.

Yes, I would consider participating in another RCT with 17-OHPC in order to more clearly establish its role in women with prior sPTB

92% (n=11)

No, I consider PROLONG to have settled the matter of efficacy (in the negative) and I don’t want to participate in another clinical trial

8% (n=1)

No, I consider Meis to have settled the matter of efficacy (in the affirmative) and I don’t want to participate in another clinical trial
If another RCT was conducted in women with a prior sPTB (17-OHPC vs. placebo), in your opinion, how important is the following study design issue? After randomization, a short cervix developed (transvaginal ultrasound ≤ 25 mm) and the protocol allows for (rescue with) cerclage placement.

- Extremely important: 67% (n=8)
- Very important: 17% (n=2)
- Somewhat important: 17% (n=2)
- Not so important: 0%
- Not at all important: 0%
In order to increase the “risk profile” of women eligible for the RCT, having a lower gestational age threshold for a qualifying sPTB has been discussed. This may identify women more likely to respond to 17OHP. In both Meis and PROLONG, women qualified after a prior sPTB < 37 weeks. What is your opinion on the best GA (weeks) entry threshold?

- < 37 Weeks: 33% (n=4)
- < 34 Weeks: 50% (n=6)
- < 32 Weeks: 17% (n=2)
- I don’t know: 0%
Q4 What is your opinion regarding evaluating the primary outcome in a different manner? Would you consider a “delay in delivery” that had clinical meaning (e.g. 7 days difference between placebo vs. 17 OHPC)? This delay in delivery could be a continuous outcome (days) or viewed as a “time to event” metric.

- Yes, I would be open to this approach, assuming there was adequate data to support the measure (50%, n=6)
- No, I would not consider this approach and I believe a GA threshold is required (e.g. < 34 weeks) (33%, n=4)
- No, I would not consider this approach and I believe only an outcome of neonatal morbidity and mortality is required (17%, n=2)
Covis Identified Additional Non-Academic Sites Willing to Participate in an RCT

- Formal RCT feasibility assessment
  - ~100 patients/year available from 19 U.S., 10 OUS sites
    (~66 patients/year if focused on U.S. only)
- Survey conducted within Dorsata practice network
  - ~60-180 patients per year from this network
Covis has Surveyed Providers to Assess Feasibility of Enrolling RCT

- 40% of physicians who use progesterone medication for patients at risk of spontaneous PTB recommend the therapy by injection
- 80% say they are likely to recommend a pregnant patient enroll in a placebo-controlled study when the product is FDA approved
  - 39% if the product has not been approved by the FDA
  - 15% if the product has had its marketing approval withdrawn
Covis Has Surveyed Patients to Assess Feasibility of Enrolling in an RCT

- Survey included 325 patients with a history of spontaneous PTB
- 95% say it is important that treatment options to reduce the risk of another preterm birth be approved by FDA
- 68% would take an approved prescription drug during pregnancy that is intended to prevent recurrent preterm birth and is being studied
  - Only 37% would be willing to take a drug being studied that is not approved
Covis Willing to Voluntarily Withdraw Makena Based on RCT Futility and Feasibility Assessments

Proposed Randomized Controlled Trial

Pre-specified criteria that would result in voluntary withdrawal:

1. Interim efficacy analysis for futility
2. Assessment of enrollment projections at Month 24 to evaluate feasibility of completing the trial in a 4- to 6-year timeframe
3. Outcome of study is negative
Potential Observational Study to Evaluate Clinical Outcomes

Potential Observational Study

- Establish the relationship between gestational age and neonatal outcomes in treated vs. untreated patients
- Validate benefit of weeks-gained on 17P in the RCT
COVIS Position on Questions Presented
Question 1: Do findings from PROLONG verify clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?
Findings from PROLONG Do Not Verify Clinical Benefit of Makena
Question 2: Does available evidence demonstrate that Makena is effective for its approved indication?
Makena Met Primary Endpoint Demonstrating Significant Reduction in Preterm Births < 37 Weeks

Patients with Preterm Birth (%)

- Makena (N = 306)
- Placebo (N = 153)

<table>
<thead>
<tr>
<th>Gestational Age (Weeks)</th>
<th>Patients with Preterm Birth (%)</th>
<th>p-value</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32</td>
<td>N = 35, N = 30</td>
<td>0.018</td>
<td>↓ 41.8%</td>
</tr>
<tr>
<td>&lt; 35</td>
<td>N = 63, N = 47</td>
<td>0.017</td>
<td>↓ 32.9%</td>
</tr>
<tr>
<td>&lt; 37</td>
<td>N = 111, N = 84</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001 ↓ 33.9%

Mels et al., NEJM 2003
PROLONG Failed to Enroll a Population Capable of Confirming the Results Seen in the Meis Trial

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Meis N = 463</th>
<th>PROLONG-OUS N = 1317</th>
<th>PROLONG-US N = 391</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 Previous spontaneous PTB</td>
<td>32% (149)</td>
<td>▶️ 11% (141)</td>
<td>▶️ 27% (107)</td>
</tr>
<tr>
<td>Black / African American</td>
<td>59% (273)</td>
<td>▶️ 0.1% (1)</td>
<td>▶️ 29% (113)</td>
</tr>
<tr>
<td>Unmarried with no partner</td>
<td>50% (233)</td>
<td>▶️ 4% (53)</td>
<td>▶️ 31% (120)</td>
</tr>
<tr>
<td>Educational ≤ 12 years</td>
<td>71% (330)</td>
<td>▶️ 42% (549)</td>
<td>▶️ 50% (197)</td>
</tr>
<tr>
<td>Any substance use during pregnancy</td>
<td>26% (121)</td>
<td>▶️ 4% (47)</td>
<td>▶️ 28% (111)</td>
</tr>
</tbody>
</table>

▶️ Higher risk compared to Meis  ▶️ Lower risk compared to Meis
Analyses Support a Higher-Risk Population

**Proposed Higher-Risk Population**

- Women with $\geq 1$ recent prior spontaneous preterm birth $< 35$ weeks and
- $\geq 1$ additional risk factor such as
  - Prior spontaneous preterm birth $< 32$ weeks
  - Multiple spontaneous preterm births $< 37$ weeks
  - Last pregnancy within 2 years
  - Other social determinants of preterm birth
## Results in Higher-Risk Target Patient Population for Continuous Endpoint: Nominally Statistically Significant

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Estimated Difference in Time from Randomization to Delivery (up to 35 weeks)(^1)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROLONG-US</td>
<td>87</td>
<td>1.86</td>
<td>(0.18, 3.54)</td>
</tr>
<tr>
<td>Meis</td>
<td>164</td>
<td>1.33</td>
<td>(0.08, 2.59)</td>
</tr>
</tbody>
</table>

---

1. Estimates are from model with time from randomization to delivery (capped at 35 weeks gestation) as outcome variable and treatment, gestational age at randomization, and mrgPA as predictor variables.
Results in Higher-Risk Target Patient Population for Dichotomous Endpoints: Favorable Point Estimates in PROLONG and Nominally Statistically Significant in Meis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Endpoint</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROLONG-US</td>
<td>87</td>
<td>PTB &lt; 37</td>
<td>0.69</td>
<td>(0.28, 1.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 35</td>
<td>0.55</td>
<td>(0.19, 1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 32</td>
<td>0.36</td>
<td>(0.09, 1.44)</td>
</tr>
<tr>
<td>Meis</td>
<td>164</td>
<td>PTB &lt; 37</td>
<td>0.24</td>
<td>(0.12, 0.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 35</td>
<td>0.35</td>
<td>(0.18, 0.70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 32</td>
<td>0.33</td>
<td>(0.15, 0.70)</td>
</tr>
</tbody>
</table>

Estimates are from logistic regression model with preterm birth (either < 32, < 35, or < 37) as outcome variable and treatment as predictor variable.
Meis Remains Substantial Evidence of Efficacy

Post Hoc Analyses of PROLONG-US Support Efficacy in a Higher-Risk Patient Population
Question 3A: Should FDA allow Makena to remain on the market?
Question 3B: 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?
Covis is Committed to Confirming Clinical Benefit of Makena

1. Partial Withdrawal to Higher-Risk Target Population
   - Narrow labeling to use in a higher-risk target population identified through our analysis of Meis and PROLONG
   - No active promotion of Makena

2. Conduct a Randomized Controlled Trial (RCT)
   - Confirm Makena’s effect on intermediate clinical endpoint in the identified higher-risk target patient population – completed within 4- to 6-years

3. Optionally, Also Conduct an Observational Study
   - Further validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment
Covis respectfully requests that its proposed path forward receive serious consideration by the Panel and the Agency
MAKENA®
(hydroxyprogesterone caproate injection)

October 17-19, 2022
Hearing with Respect to CDER’s Proposal to Withdraw Approval
COVIS Backup - Slides Shown
Day 2 – October 18, 2022
Meis: Weak Suggestion of Increased Treatment Effect with Increases in Risk Based on Mean Gestational Age of Prior Deliveries

Weeks Gained for Makena-Treated Patients vs. Placebo*

Mean Gestational Age (Week) of Prior Spontaneous Deliveries

*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mGA as predictor variables.
Meis: Large Increase in Treatment Effect Among Blacks (a Risk Factor)

Weeks Gained for Makena-Treated Patients vs. Placebo*

Gestational Age (Week) of Most Recent Prior Spontaneous Delivery

*Results from linear regression model for weeks gained with treatment, gestational age at randomization, and mrpGA as predictor variables.
### Meis (Black): Estimated Treatment Effect (Weeks Gained) for 17P in Subgroups Defined by Mean Gestational Age (mGA) of Prior Deliveries Among Subjects Randomized at <20 Weeks GA

<table>
<thead>
<tr>
<th>mGA Subgroup</th>
<th>Total (N)</th>
<th>Estimated Treatment Effect (weeks gained)</th>
<th>Lower (95% CL)</th>
<th>Upper (95% CL)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mGA&lt; 28</td>
<td>34</td>
<td>2.81</td>
<td>-1.34</td>
<td>6.96</td>
<td>0.1766</td>
</tr>
<tr>
<td>mGA&lt; 29</td>
<td>40</td>
<td>2.83</td>
<td>-1.02</td>
<td>6.68</td>
<td>0.1451</td>
</tr>
<tr>
<td>mGA&lt; 30</td>
<td>48</td>
<td>2.47</td>
<td>-0.78</td>
<td>5.73</td>
<td>0.1328</td>
</tr>
<tr>
<td>mGA&lt; 31</td>
<td>58</td>
<td>2.83</td>
<td>0.07</td>
<td>5.59</td>
<td>0.0448</td>
</tr>
<tr>
<td>mGA&lt; 32</td>
<td>68</td>
<td>2.28</td>
<td>-0.16</td>
<td>4.73</td>
<td>0.0667</td>
</tr>
<tr>
<td>mGA&lt; 33</td>
<td>78</td>
<td>2.06</td>
<td>-0.21</td>
<td>4.33</td>
<td>0.0746</td>
</tr>
<tr>
<td>mGA&lt; 34</td>
<td>100</td>
<td>1.62</td>
<td>-0.28</td>
<td>3.52</td>
<td>0.0939</td>
</tr>
<tr>
<td>mGA&lt; 35</td>
<td>124</td>
<td>1.29</td>
<td>-0.35</td>
<td>2.94</td>
<td>0.1221</td>
</tr>
<tr>
<td>mGA&lt; 36</td>
<td>144</td>
<td>1.66</td>
<td>0.19</td>
<td>3.13</td>
<td>0.0273</td>
</tr>
<tr>
<td>mGA&lt; 37</td>
<td>168</td>
<td>1.41</td>
<td>0.09</td>
<td>2.73</td>
<td>0.0369</td>
</tr>
</tbody>
</table>
Meis (Overall): Visual Inspection of Time-to-Delivery Curves Suggests Differential Treatment Effect by Race

- Black patients: Benefit of 17P apparent early (from ~25 weeks gestation)
- Non-Black patients: Benefit of 17P apparent later (after ~35 weeks gestation)
## Meis: Estimated Weeks Gained (Capped at 37) for High-Risk Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Total (N)</th>
<th>Estimated Treatment Effect (weeks gained)</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>459</td>
<td>0.72</td>
<td>(-0.07, 1.52)</td>
<td>0.0740</td>
</tr>
<tr>
<td>Randomized at GA &lt; 20 - Overall</td>
<td>31</td>
<td>1.26</td>
<td>(0.21, 2.31)</td>
<td>0.0190</td>
</tr>
<tr>
<td>mrpGA &lt; 35</td>
<td>193</td>
<td>1.28</td>
<td>(-0.19, 2.75)</td>
<td>0.0879</td>
</tr>
<tr>
<td>mrpGA &lt; 35 and black</td>
<td>115</td>
<td>1.99</td>
<td>(0.02, 3.96)</td>
<td>0.0478</td>
</tr>
<tr>
<td>mrpGA &lt; 35 and ipint ≤ 5</td>
<td>165</td>
<td>1.87</td>
<td>(0.39, 3.35)</td>
<td>0.0135</td>
</tr>
<tr>
<td>mrpGA &lt; 35 and mto37</td>
<td>62</td>
<td>3.38</td>
<td>(1.03, 5.74)</td>
<td>0.0056</td>
</tr>
<tr>
<td>mrpGA &lt; 35 and ipint ≤ 5 and mto37</td>
<td>56</td>
<td>4.09</td>
<td>(1.80, 6.38)</td>
<td>0.0008</td>
</tr>
<tr>
<td>mrpGA &lt; 35 and ipint ≤ 5 and black</td>
<td>96</td>
<td>2.68</td>
<td>(0.65, 4.72)</td>
<td>0.0104</td>
</tr>
<tr>
<td>mrpGA &lt; 35 and mto37 and black</td>
<td>44</td>
<td>2.36</td>
<td>(-0.57, 5.29)</td>
<td>0.1112</td>
</tr>
</tbody>
</table>
PROLONG – Power Considerations

- Power for PTB < 37 weeks and < 35 weeks in PROLONG by Relative Reduction

<table>
<thead>
<tr>
<th>Placebo Rate</th>
<th>5%</th>
<th>10%</th>
<th>20%</th>
<th>25%</th>
<th>30%</th>
<th>35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.9% (&lt; 37 weeks)</td>
<td>6.8</td>
<td>18.4</td>
<td>56.0</td>
<td>76.0</td>
<td>90.1</td>
<td>97.2</td>
</tr>
<tr>
<td>11.5% (&lt; 35 weeks)</td>
<td>6.4</td>
<td>10.1</td>
<td>29.8</td>
<td>45.0</td>
<td>58.9</td>
<td>74.5</td>
</tr>
</tbody>
</table>
Retrospective Observational Study Comparing Frequencies of Neonatal Morbidity, Death and Length of Stay

- Retrospective individual case review for qualifying subjects

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>17P-Treated Mothers (as indicated per Makena label)</th>
<th>Untreated Mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age Ranges</td>
<td>&lt; 28</td>
<td>28-29</td>
</tr>
</tbody>
</table>

- **Endpoint**: Comparison between event rates (or changes of rates)
  - **Outcomes**: Major morbidity, minor morbidity and death
  - **Timepoints**: All gestational age ranges

*Major and minor morbidities as defined in Manuck (2016) et al.*
IRESSA (gefitinib) Label Change

- Indication was changed to patients “who, in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment.”
- Change in “Indications and Usage” from May 2004 to June 2005:

IRESSA is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from IRESSA.

In light of positive survival data with other agents including another oral EGFR inhibitor, physicians should use other treatment options in advanced non-small cell lung cancer patient populations who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

The effectiveness of IRESSA was initially based on objective response rates (see CLINICAL PHARMACOLOGY-Clinical Studies section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. Subsequent studies intended to demonstrate an increase in survival have been unsuccessful. Specifically, results from a large placebo-controlled randomized trial in patients with advanced NSCLC who progressed while receiving or within 90 days of the last dose of chemotherapy or were intolerant to the most recent prior chemotherapy regimen, did not show an improvement in survival (see CLINICAL PHARMACOLOGY-Clinical Studies section), . . .
# Women with Severe Pre-eclampsia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Expectant Management (N = 49)</th>
<th>Aggressive Management (N = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at delivery (Weeks)</td>
<td>30.8</td>
<td>32.9</td>
</tr>
<tr>
<td><strong>Neonatal outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td>50%</td>
<td>22%</td>
</tr>
<tr>
<td>NEC</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>BPD</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>IVH</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Sibai 1995
## Women with Pre-term rupture of Membranes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antibiotics (N = 300)</th>
<th>Placebo (N = 314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to delivery</td>
<td>6.1</td>
<td>2.9</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>44%</td>
<td>53%</td>
</tr>
<tr>
<td>RDS</td>
<td>41%</td>
<td>49%</td>
</tr>
<tr>
<td>NEC</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>IVH</td>
<td>6%</td>
<td>8%</td>
</tr>
</tbody>
</table>
MAKENA®
(hydroxyprogesterone caproate injection)
October 17-19, 2022
Hearing with Respect to CDER’s Proposal to Withdraw Approval
Proposed Path Forward While Makena Remains on the Market

Raghav Chari, PhD
Chief Innovation Officer
Covis Pharmaceuticals
Covis is Committed to Confirming Clinical Benefit of Makena

1. Partial Withdrawal to Higher-Risk Target Population
   - Narrow labeling to use in a higher-risk target population identified through our analysis of Meis and PROLONG
   - No active promotion of Makena

2. Conduct a Randomized Controlled Trial (RCT)
   - Confirm Makena’s effect on intermediate clinical endpoint in the identified higher-risk target patient population – completed within 4- to 6-years

3. Optionally, Also Conduct an Observational Study
   - Further validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment
Analyses Support a Higher-Risk Population

Proposed Higher-Risk Population

- Women with ≥ 1 recent prior spontaneous preterm birth < 35 weeks and
- ≥ 1 additional risk factor such as
  - Prior spontaneous preterm birth < 32 weeks
  - Multiple spontaneous preterm births < 37 weeks
  - Last pregnancy within 2 years
  - Other social determinants of preterm birth
Covis Proposes Conducting an RCT With Time-from-Randomization-to-Birth as the Primary Endpoint

**Proposed Randomized Controlled Trial**

- **Proposed population:** Women with $\geq 1$ prior spontaneous preterm birth $< 35$ weeks and $\geq 1$ additional risk factor
- **Trial design:** $\sim 400$ patients randomized 2:1
- **Primary endpoint:** Increase in time-from-randomization-to-birth for Makena vs. placebo, capped at 35 weeks gestation
- **Estimated completion:** 4- to 6-years
Covis has Surveyed Providers to Assess Feasibility of Enrolling RCT

- 40% of physicians who use progesterone medication for patients at risk of spontaneous PTB recommend the therapy by injection
- 80% say they are likely to recommend a pregnant patient enroll in a placebo-controlled study when the product is FDA approved
  - 39% if the product has not been approved by the FDA
  - 15% if the product has had its marketing approval withdrawn
Covis Willing to Voluntarily Withdraw Makena Based on RCT Futility and Feasibility Assessments

Proposed Randomized Controlled Trial

Pre-specified criteria that would result in voluntary withdrawal:
1. Interim efficacy analysis for futility
2. Assessment of enrollment projections at Month 24 to evaluate feasibility of completing the trial in a 4- to 6-year timeframe
3. Outcome of study is negative
Potential Observational Study to Evaluate Clinical Outcomes

Potential Observational Study

- Establish the relationship between gestational age and neonatal outcomes in treated vs. untreated patients
- Validate benefit of weeks-gained on 17P in the RCT
COVIS Position on Questions Presented
Question 1: Do findings from PROLONG verify clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?
Findings from PROLONG Do Not Verify Clinical Benefit of Makena
Question 2: Does available evidence demonstrate that Makena is effective for its approved indication?
Makena Met Primary Endpoint Demonstrating Significant Reduction in Preterm Births < 37 Weeks

Makena (N = 306)  Placebo (N = 153)

Primary Outcome

P < 0.001  \(\downarrow 33.9\%

Patients with Preterm Birth (%)

\(p=0.018\)  \(\downarrow 41.8\%

\(p=0.017\)  \(\downarrow 32.9\%

\(N = 35\)  \(N = 30\)  \(N = 63\)  \(N = 47\)  \(N = 111\)  \(N = 84\)

Gestational Age (Weeks)

Mels et al., NEJM 2003
# PROLONG Failed to Enroll a Population Capable of Confirming the Results Seen in the Meis Trial

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Meis N = 463</th>
<th>PROLONG-OUS N = 1317</th>
<th>PROLONG-US N = 391</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 Previous spontaneous PTB</td>
<td>32% (149)</td>
<td>11% (141)</td>
<td>27% (107)</td>
</tr>
<tr>
<td>Black / African American</td>
<td>59% (273)</td>
<td>0.1% (1)</td>
<td>29% (113)</td>
</tr>
<tr>
<td>Unmarried with no partner</td>
<td>50% (233)</td>
<td>4% (53)</td>
<td>31% (120)</td>
</tr>
<tr>
<td>Educational ≤ 12 years</td>
<td>71% (330)</td>
<td>42% (549)</td>
<td>50% (197)</td>
</tr>
<tr>
<td>Any substance use during pregnancy</td>
<td>26% (121)</td>
<td>4% (47)</td>
<td>28% (111)</td>
</tr>
</tbody>
</table>

- **Higher risk compared to Meis**
- **Lower risk compared to Meis**
Analyses Support a Higher-Risk Population

Proposed Higher-Risk Population

- Women with $\geq 1$ recent prior spontaneous preterm birth $< 35$ weeks **and**
- $\geq 1$ additional risk factor such as
  - Prior spontaneous preterm birth $< 32$ weeks
  - Multiple spontaneous preterm births $< 37$ weeks
  - Last pregnancy within 2 years
  - Other social determinants of preterm birth
# Results in Higher-Risk Target Patient Population for Continuous Endpoint: Nominally Statistically Significant

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Estimated Difference in Time from Randomization to Delivery (up to 35 weeks)(^1)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROLONG-US</td>
<td>87</td>
<td>1.86</td>
<td>(0.18, 3.54)</td>
</tr>
<tr>
<td>Meis</td>
<td>164</td>
<td>1.33</td>
<td>(0.08, 2.59)</td>
</tr>
</tbody>
</table>

1. Estimates are from model with time from randomization to delivery (capped at 35 weeks gestation) as outcome variable and treatment, gestational age at randomization, and mrgGA as predictor variables.
Results in Higher-Risk Target Patient Population for Dichotomous Endpoints: Favorable Point Estimates in PROLONG and Nominally Statistically Significant in Meis

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Endpoint</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROLONG-US</td>
<td>87</td>
<td>PTB &lt; 37</td>
<td>0.69</td>
<td>(0.28, 1.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 35</td>
<td>0.55</td>
<td>(0.19, 1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 32</td>
<td>0.36</td>
<td>(0.09, 1.44)</td>
</tr>
<tr>
<td>Meis</td>
<td>164</td>
<td>PTB &lt; 37</td>
<td>0.24</td>
<td>(0.12, 0.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 35</td>
<td>0.35</td>
<td>(0.18, 0.70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTB &lt; 32</td>
<td>0.33</td>
<td>(0.15, 0.70)</td>
</tr>
</tbody>
</table>

Estimates are from logistic regression model with preterm birth (either < 32, < 35, or < 37) as outcome variable and treatment as predictor variable.
Meis Remains Substantial Evidence of Efficacy

Post Hoc Analyses of PROLONG-US Support Efficacy in a Higher-Risk Patient Population
Question 3A: Should FDA allow Makena to remain on the market?
Question 3B: 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?
# Pooled Safety Data Demonstrate Favorable Safety Profile for Makena Compared to Placebo

<table>
<thead>
<tr>
<th></th>
<th>Integrated Safety</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Makena</strong></td>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td><strong>N = 1130</strong></td>
<td><strong>N = 578</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission for preterm labor</td>
<td>16.4%</td>
<td>14.4%</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia or gestational hypertension</td>
<td>5.2%</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5.1%</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>3.6%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>5.0%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>4.2%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>4.0%</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>3.8%</td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.6%</td>
<td>3.3%</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>3.0%</td>
<td>2.3%</td>
<td></td>
</tr>
</tbody>
</table>

Permissive Legal Standard for Withdrawal of Approval

- FDA “may withdraw” accelerated approval if
  - a confirmatory trial “fails to verify and describe” the clinical benefit or
  - “other evidence demonstrates that the product is not safe or effective under the conditions of use”
- The statute is permissive, not mandatory
  - CDER acknowledges: “CDER possesses various regulatory options when a confirmatory trial fails to verify clinical benefit”
- FDA has the authority to keep Makena on the market while another trial is conducted
Covis is Committed to Confirming Clinical Benefit of Makena

1. Partial Withdrawal to Higher-Risk Target Population
   - Narrow labeling to use in a higher-risk target population identified through our analysis of Meis and PROLONG
   - No active promotion of Makena

2. Conduct a Randomized Controlled Trial (RCT)
   - Confirm Makena’s effect on intermediate clinical endpoint in the identified higher-risk target patient population – completed within 4- to 6-years

3. Optionally, Also Conduct an Observational Study
   - Further validate the benefit of prolonging gestational age on neonatal morbidity and mortality with 17P treatment
Covis respectfully requests that its proposed path forward receive serious consideration by the Panel and the Agency.
MAKENA®
(hydroxyprogesterone caproate injection)
October 17-19, 2022
Hearing with Respect to CDER’s Proposal to Withdraw Approval