Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023

Opening Remarks

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

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Clinical Background

• Neonatal mortality and morbidity from preterm birth (PTB) is a significant public health concern

• No therapies approved to reduce the risk of neonatal mortality and morbidity from prematurity

• Progestogens (intravaginal or intramuscular) used to reduce the risk of PTB
  – Only Makena (hydroxyprogesterone caproate injection) approved for reducing the risk of recurrent PTB
• Makena approved in 2011 under accelerated approval to reduce the risk of PTB in women with a singleton pregnancy and a prior spontaneous PTB

• Approval: a single trial conducted 1999-2002 in the U.S., based on surrogate endpoint of gestational age (GA) of delivery <37 weeks

• As required under accelerated approval regulations, the Applicant conducted a postapproval confirmatory trial to verify clinical benefit for the neonate
Confirmatory Trial - 003

• International, randomized, double-blind, placebo-controlled trial in 1708 pregnant women
  – Russia, Ukraine, and U.S. enrolled 36%, 25%, and 23% subjects

• Design, eligibility criteria similar to Trial 002, except for primary endpoints
  – Trial 002: GA at delivery <37 weeks
  – Trial 003: GA at delivery <35 weeks, neonatal morbidity/mortality index

• Conducted 2009-2018
## Trial 003 Results: No Treatment Effect

**Efficacy Endpoints** (% of patients)

<table>
<thead>
<tr>
<th>Efficacy Endpoints*</th>
<th>Makena (N=1130)</th>
<th>Placebo (N=578)</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coprimary: Neonatal composite index (%)</td>
<td>5.4</td>
<td>5.2</td>
<td>0.2 (-2.0, 2.5)</td>
<td>0.84</td>
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<td>Coprimary: PTB &lt;35(^0) weeks (%)</td>
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<td>PTB &lt;32(^0) weeks (%)</td>
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<td>PTB &lt;37(^0) weeks (%)</td>
<td>23.1</td>
<td>21.9</td>
<td>1.3 (-3.0, 5.4)</td>
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*FDA's Analysis
Trial 003 Exploratory Subgroup Analyses

- No statistically significant treatment difference or interaction between treatment effect and these factors:
  - Region (U.S. vs. non-U.S.)
  - Race (Black vs. Non-Black)
  - Elements that may increase PTB risk:
    - 1 vs. >1 prior PTB, substance use in pregnancy, ≤12 years of education, single/no partner
  - These factors may be prognostic, but they do not appear to be effect modifiers

- There was no consistent, convincing evidence of a treatment effect within any particular subpopulation across Trials 002 and 003.
Totality of Evidence: 
Trial 002 and Trial 003

• **Trial 002** - *efficacy on gestational age of delivery (surrogate endpoint)*
  – Conducted 1999-2002 in the U.S.
  – Issues regarding generalizability: ~60% self-identified black, all from academic centers, 27% from a single center, high recurrent preterm birth rate <37 weeks in placebo arm (55%)

• **Trial 003** – *no efficacy on neonatal outcomes (clinical endpoint)* or gestational age at delivery (surrogate endpoint)
  – Conducted 2009-2018, powered to detect treatment effect in Trial 002
  – International (23% from the U.S.), lower risk population, lower recurrent preterm birth rate in placebo arm than in Trial 002
## Totality of Evidence

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Efficacy on Endpoint</th>
<th>Approval Efficacy Requirement Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surrogate endpoint:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA at delivery</td>
<td>Yes (Trial 002)</td>
<td><strong>Issue 1:</strong> Substantial Evidence of Effectiveness</td>
</tr>
<tr>
<td></td>
<td>No (Trial 003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Conflicting efficacy findings</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical endpoint:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal composite index</td>
<td>No (Trial 003)</td>
<td><strong>Issue 2:</strong> Accelerated Approval</td>
</tr>
<tr>
<td></td>
<td>▶ No verification of clinical benefit</td>
<td></td>
</tr>
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</table>
Issue 1: Substantial Evidence of Effectiveness

• Statutory standard of establishing efficacy for FDA drug approval*, including accelerated approval
  – Traditionally, significant findings from $\geq$ 2 adequate and well-controlled trials, each convincing on its own (independent substantiation) on the efficacy endpoint(s), reduces risk false positive from chance or bias

• When appropriate, a single adequate, well-controlled trial with persuasive findings may be accepted as substantial evidence

*Substantial evidence defined in section 505(d) of the Act as “evidence consisting of adequate and well-controlled investigations..”
Issue 1: Substantial Evidence of Effectiveness

- 2011 accelerated approval of Makena based on a single trial
- If there were additional adequate and well-controlled trials in 2011, FDA would have considered those data when deciding about substantial evidence of effectiveness
- Now there are 2 adequate and well-controlled trials (Trials 002 and 003)

**Issue 1:** Trial 003 did not substantiate Makena’s treatment effect on GA of delivery: Is there still substantial evidence of the drug’s effect on reducing the risk of preterm birth?
Issue 1: Substantial Evidence of Effectiveness

Yes

Substantial Evidence of Effectiveness?

Accelerated Approval
(surrogate endpoint)

Traditional Approval
(clinical/validated surrogate endpoint)

No Approval

Issue 1: Conflicting efficacy on surrogate endpoint (GA of delivery)
Issue 2: Accelerated Approval

• Traditional approval: based on *clinical endpoint* (directly measures how patients feel, function, or survive) or *validated surrogate endpoint*

• Accelerated approval: based on a *surrogate endpoint* reasonably likely to predict clinical benefit
  - Expedited drug development pathway
  - Reserved for certain drugs treating serious/life-threatening conditions with unmet medical need
  - Must meet same statutory effectiveness standards as those for traditional approval
Issue 2: Accelerated Approval

• Makena accelerated approval based on treatment effect on **surrogate endpoint (GA of delivery)**
  – GA of delivery is not a direct measure of how neonates feel, function, or survive
  – Spontaneous PTB poorly understood syndrome with potential for multiple pathophysiologic pathways
  – Prolonging GA of delivery may not consistently translate into improved neonatal outcomes
Issue 2: Accelerated Approval

• More uncertainty at the time of approval that the treatment effect on surrogate endpoint (GA at delivery) will translate into clinical benefit (neonatal outcomes)
  – Therefore, must undergo a postapproval confirmatory trial to verify clinical benefit

• FDA can withdraw approval of the drug or indication if the Applicant does not conduct the required trial(s) with due diligence or the trial(s) fail to verify clinical benefit

Issue 2: Trial 003 did not verify Makena’s clinical benefit to the neonate
Issue 2: Accelerated Approval

Substantial Evidence of Effectiveness

Yes

Accelerated Approval (surrogate endpoint)

Clinical Benefit Verified?

Yes

(full) Approval

No

FDA can withdraw approval

Traditional Approval (clinical or validated surrogate endpoint)

Issue 2: Clinical benefit to neonate not verified
Discussion and Voting Questions
Discussion Question 1

• Discuss the effectiveness of Makena on recurrent preterm birth and neonatal morbidity and mortality.
Discussion Question 2

• If a new confirmatory trial were to be conducted, discuss the study design, including control, dose(s) of study medication, efficacy endpoints and the feasibility of completing such a trial.
Discussion Question 3

• Discuss the potential consequences of withdrawing Makena on patients and clinical practice.
Voting Question 4

• Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes?
  – Provide rationale for your vote.
Voting Question 5

• Based on the findings from Trial 002 and Trial 003, is there substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth?
  – Provide rationale for your vote.
FDA approval, including accelerated approval, of a drug requires *substantial evidence of effectiveness (Issue 1).*

For drugs approved under the accelerated approval pathway based on a surrogate endpoint, the Applicant is required to conduct confirmatory trial(s) to *verify clinical benefit (Issue 2).* If the Applicant fails to conduct such a trial(s) or if such trial(s) does not verify clinical benefit, FDA may, following an opportunity for a hearing, withdraw approval.
• Should FDA:

(A) Pursue withdrawal of approval for Makena

(B) Leave Makena on the market under accelerated approval and require a new confirmatory trial

(C) Leave Makena on the market without requiring a new confirmatory trial
Approval: Efficacy Requirement Issues

Substantial Evidence of Effectiveness?

Yes

Accelerated Approval (surrogate endpoint)

Clinical Benefit Verified?

Yes

(full) Approval

No

FDA can withdraw approval

No

Issue 1: Conflicting efficacy on GA of delivery

No Approval

Issue 2: Clinical benefit to neonate not verified

Traditional Approval (clinical/validated surrogate endpoint)
Voting Question 6 Continued

- **Vote A** (withdraw approval) may be appropriate if you believe the totality of evidence does not support Makena’s effectiveness for its intended use.
  - Discuss the consequences of Makena removal
Voting Question 6 Continued

- **Vote B** (require a new confirmatory trial) may be appropriate if you believe the totality of evidence supports Makena’s effectiveness in reducing the risk of recurrent PTB, but that there is no substantial evidence of effectiveness on neonatal outcomes AND you believe that a new confirmatory trial is necessary and feasible.
  
  - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent PTB, based on the surrogate endpoint of gestational age at delivery.
  
  - Also discuss key study elements, including study population, control, dose(s), and efficacy endpoints of the new confirmatory trial (if not previously discussed in Discussion point 2) and approaches to ensure successful completion of such a trial.
Voting Question 6 Continued

- **Vote C** (leave Makena on the market without a new confirmatory trial) may be appropriate if you believe Makena is effective for reducing the risk of recurrent PTB and that it is not necessary to verify Makena’s clinical benefit to neonates.
  - Discuss how the existing data provide substantial evidence of effectiveness of Makena in reducing the risk of recurrent PTB and why it is not necessary to verify Makena’s clinical benefit to neonates.
Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023

Clinical Overview
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

Barbara Wesley, M.D., M.P.H.
Medical Officer
Division of Bone, Reproductive and Urologic Products
Office of New Drugs, Center for Drug Evaluation and Research
Food and Drug Administration
Outline

• Trial 002 and its history (1999-2011)
  – Findings, areas of controversy
• 2006 Advisory Committee
• Accelerated approval postmarketing requirement - Confirmatory Trial 003
Background of Trial 002

• 1999-2002: Funded by National Institute of Child Health and Human Development NICHD; conducted by Maternal-Fetal Medicine Units Network (MFMU).

• 2003: Positive findings of hydroxyprogesterone caproate (HPC) reducing the risk of preterm birth <37 weeks published in the New England Journal of Medicine*

• 2006: Submission of new drug application (NDA) for HPC 250 mg/mL

Makena

Indication
• To reduce the risk of preterm birth in women with a singleton pregnancy and a history of spontaneous preterm birth

Dosage & Administration
• 250 mg once a week beginning between 16⁰ weeks and 20⁶ weeks gestation to week 37 of gestation or birth
Trial 002 Design

Study Medications
• HPC in castor oil
• Placebo

Primary Efficacy Endpoint
• Birth <37\(^0\) weeks

Additional Efficacy Endpoints (post hoc)
• <35\(^0\) weeks and <32\(^0\) weeks
• Composite index of neonatal morbidity
  - Death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), Grade 3 or 4 intraventricular hemorrhage (IVH), proven sepsis, necrotizing enterocolitis (NEC)
Trial 002: Preterm Births <37⁰ Weeks Gestation

**Primary Efficacy Endpoint**  \( P = 0.001 \)

<table>
<thead>
<tr>
<th></th>
<th>HPC</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>310</td>
<td>153</td>
</tr>
<tr>
<td>Number (%) Preterm Births</td>
<td>115 (37%)</td>
<td>84 (55%)</td>
</tr>
</tbody>
</table>

% Difference [Adjusted 95% Confidence Interval] -18% [-28%, -7%]

- PTB rate of **55%** in placebo arm considerably greater than rate in other MFMU Network studies (~36%)
- PTB rate of **37%** in HPC arm similar to PTB rate in placebo arms in other MFMU Network study
## PTB Rate in Placebo Arm by Race in Trial 002

<table>
<thead>
<tr>
<th>Race</th>
<th>Placebo - n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>47/90 (52%)</td>
</tr>
<tr>
<td>Non-black</td>
<td>37/63 (59%)</td>
</tr>
</tbody>
</table>
Percent of Preterm Births at Various Gestational Age Thresholds (Trial 002)

<table>
<thead>
<tr>
<th>Age at Delivery (Weeks)</th>
<th>HPC N=310</th>
<th>Placebo N=153</th>
<th>% Difference [Adjusted 95% Confidence Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;370</td>
<td>37</td>
<td>55</td>
<td>-18.0% [-28%, -7.4%]</td>
</tr>
<tr>
<td>&lt;350</td>
<td>21</td>
<td>31</td>
<td>-9.4% [-19.0%, -0.4%]</td>
</tr>
<tr>
<td>&lt;320</td>
<td>12</td>
<td>20</td>
<td>-7.7% [-16.1%, -0.3%]</td>
</tr>
</tbody>
</table>

Makena prescribing information, Drugs@FDA

Confidence intervals **adjusted for the interim analyses and the final analysis**. To preserve overall Type I error rate of 0.05, p-value boundary of 0.035 used for the adjustment (equivalent to a 96.5% confidence interval).
## Composite Neonatal Morbidity (Trial 002)

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>HPC N=295 n (%)</th>
<th>Placebo N=151 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (live births only)</td>
<td>8 (2.6)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>29 (9.9)</td>
<td>23 (15.3)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>4 (1.4)</td>
<td>5 (3.3)</td>
</tr>
<tr>
<td>Gr. 3/4 intraventricular hemorrhage</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Proven sepsis</td>
<td>9 (3.1)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>0 (0.0)</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td><strong>Composite Index of Morbidity</strong>*</td>
<td><strong>35 (12%)</strong></td>
<td><strong>26 (17%)</strong></td>
</tr>
</tbody>
</table>

* No. subjects with one or more of the listed morbidities
Summary of Effectiveness Issues

• Applicant sought approval for HPC based on
  - Findings from a single clinical trial
  - A surrogate endpoint for infant mortality/morbidity (preterm birth <37 weeks)

• Concern about generalizability to general U.S. population
  - Notably high preterm birth rate in placebo arm (55%)
  - Approximately 60% Black or African American
  - Enrollment from academic centers only; 27% from one academic center
Which gestational age at birth is an adequate surrogate? (21 members voting)

- PTB <37 weeks – yes = 5
- PTB <35 weeks – yes = 13
- PTB <32 weeks – yes = 20
2006 FDA Action: Not Approved

• Major deficiency: New trial to provide substantial evidence of efficacy - direct benefit on neonatal morbidity and mortality or the surrogate PTB <35 and <32 weeks of gestation

• Address the concern regarding early pregnancy loss
Between 2009 and 2011 FDA Actions: Effect of Late-Preterm Birth

- **Late-Preterm Infants** – defined as infants born between 34 0/7 and 36 6/7 weeks of gestation: “are often mistakenly believed to be as physiologically and metabolically as mature as term infants”

- Higher rates of infant mortality and morbidity than term infants.

ACOG Obstetrics Practice Committee Opinion, Number 404, April 2008
2011 FDA Action: Accelerated Approval

• Recent data on effect of FDA to reconsider gestational age at delivery

• FDA concluded that delivering at <37 weeks of gestation was an adequate surrogate endpoint

• Findings of Trial 002 now deemed sufficient to support accelerated approval

• Trial 003 was ongoing and Applicant demonstrated that it could be successfully completed
Applicant’s Obligation

As a condition of accelerated approval, the Applicant was required to complete the confirmatory clinical trial of Makena (Trial 003) to verify the clinical benefit to neonates from the reduction in the risk of PTB.
Makena (hydroxyprogesterone caproate injection)
New Drug Application 021945/Supplement 023

Efficacy in Confirmatory Trial 003

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

October 29, 2019

Jia Guo, Ph.D.
Statistical Reviewer
Division of Biometrics 3
Office of Biostatistics, Center for Drug Evaluation and Research
Food and Drug Administration
Outline

• Overview of Trial 003
  – Trial Design
  – Subject Disposition
  – Demographics and Baseline Characteristics
  – Efficacy Results

• FDA’s Exploratory Analyses

• Concluding Remarks
Trial 003 Study Design

• **Study Design**
  – Multicenter, randomized, double-blind, placebo-controlled
  – Makena or placebo (2:1) stratified by study site and gestational age at randomization (16\(^0\)-17\(^6\) weeks, 18\(^0\)-20\(^6\) weeks)

• **Power**
  – 90% to detect a 35% reduction (from 17% to 11%) in the rate of the neonatal composite index
  – 98% to detect a 30% reduction (from 30% to 21%) in the rate of preterm birth <35\(^0\) weeks of gestation

• **Key Inclusion Criteria**
  – Aged ≥18 years
  – With a previous singleton spontaneous preterm delivery
  – Gestational age between 16\(^0\) to 20\(^6\) weeks

• **Key Exclusion Criteria**
  – Had significant medical disorder
  – Multifetal gestation
  – Known major fetal anomaly or fetal demise
Trial 003 Subject Disposition

- Intent-to-treat (ITT) population: all randomized subjects
- Liveborn neonatal population: all neonates of randomized subjects who were liveborn and had morbidity/mortality data available
Makena and placebo groups were comparable across all demographics and baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Makena (N=1130) n (%)</th>
<th>Placebo (N=578) n (%)</th>
<th>All (N=1708) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1004 (89)</td>
<td>504 (87)</td>
<td>1508 (88)</td>
</tr>
<tr>
<td>Black</td>
<td>73 (6)</td>
<td>41 (7)</td>
<td>124 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>53 (5)</td>
<td>33 (6)</td>
<td>86 (5)</td>
</tr>
<tr>
<td>Single or without a partner</td>
<td>117 (10)</td>
<td>56 (10)</td>
<td>173 (10)</td>
</tr>
<tr>
<td>≤12 years</td>
<td>488 (43)</td>
<td>259 (45)</td>
<td>747 (44)</td>
</tr>
<tr>
<td>Any substance use during pregnancy</td>
<td>106 (9)</td>
<td>52 (9)</td>
<td>158 (9)</td>
</tr>
<tr>
<td>&gt;1 previous SPTB</td>
<td>166 (15)</td>
<td>82 (14)</td>
<td>248 (15)</td>
</tr>
<tr>
<td>Region, United States</td>
<td>258 (23)</td>
<td>133 (23)</td>
<td>391 (23)</td>
</tr>
</tbody>
</table>

SPTB = spontaneous preterm birth
Trial 003 Efficacy Endpoints

• **Coprimary Endpoints**
  – Preterm birth (PTB) prior to 35\(^0\) weeks of gestation (Yes/No)
  – Neonatal composite morbidity and mortality index: Yes, if the liveborn neonate had any of
    - RDS
    - BPD
    - Grade 3 or 4 IVH
    - NEC
    - Proven Sepsis
    - Death

• **Secondary Endpoints**
  – PTB prior to 32\(^0\) Weeks
  – PTB prior to 37\(^0\) Weeks
No statistically significant benefit of Makena (vs. placebo) was demonstrated in either coprimary and secondary efficacy endpoints.

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<td>PTB &lt;37⁰ weeks (%)</td>
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<td>1.3 (-3.0, 5.4)</td>
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</tr>
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N: number of randomized subjects
* CMH method stratified by gestational age at randomization
FDA analysis
FDA’s Position

• Generally FDA does not support subgroup analyses for inference of efficacy when the primary analysis result does not demonstrate efficacy (FDA 1998, FDA 2017b)
  – Inflation of type I error
  – FDA considers such analyses for hypothesis-generating


Draft Guidance for Industry *Multiple Endpoints in Clinical Trials* (January 2017) [https://www.fda.gov/media/102657/download](https://www.fda.gov/media/102657/download)
FDA Exploratory Analyses

• FDA reviewed the Applicant’s post hoc subgroup analyses results to explore if differences in key aspects of Trials 003 and 002 might clarify the divergent results
  – Comparison between Trial 002 and Trial 003
  – Subgroup analyses
Comparison Between Trials 003 and 002 – Study Population

- **Black/African American**: Trial 002: 7%, Trial 003 US subset: 29%, Trial 003: 59%
- **History of >1 SPTB**: Trial 002: 15%, Trial 003 US subset: 27%, Trial 003: 32%
- **Single or without a partner**: Trial 002: 10%, Trial 003 US subset: 31%, Trial 003: 50%
- **Substance use during pregnancy**: Trial 002: 10%, Trial 003 US subset: 28%, Trial 003: 26%
- **≤12 Years education**: Trial 002: 43%, Trial 003 US subset: 50%, Trial 003: 70%
Comparison Between Trials 003 and 002 – Placebo Group

Neonatal Composite Index
- Trial 002: 5%
- Trial 003 US subset: 10%
- Trial 003: 17%

PTB <35 Weeks
- Trial 002: 12%
- Trial 003 US subset: 18%
- Trial 003: 30%
Comparison Between Trials 003 and 002 – “Composite” Risk at Baseline

- “Composite” Risk Profile:
  - Black
  - History of >1 prior SPTB
  - Single or without a partner
  - Substance use during pregnancy
  - ≤12 years of education

% of Subjects who had at least one factor:

- Trial 003: 55% (943/1708)
- Trial 003 US subset: 79% (308/391)
- Trial 002: 92% (424/463)
FDA Subgroup Analyses

• By single factor (stratified Cochran–Mantel–Haenszel (CMH) and shrinkage estimation)
  – Region (U.S., non-U.S.)
  – Race (Black, non-black)
  – History of SPTB (1 previous SPTB, >1 previous SPTB)
• By “composite” risk at baseline (no factor, ≥1 factor, ≥2 factors)
FDA Subgroup Analysis – by Region (003)

- No evidence of treatment effect on coprimary endpoints in either regional subgroup

<table>
<thead>
<tr>
<th>Endpoint Subgroup</th>
<th>Make na</th>
<th>Placebo</th>
<th>Diff CMH</th>
<th>Diff SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Index (%)</td>
<td>5.4</td>
<td>5.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>US (252, 126)</td>
<td>7.1</td>
<td>9.5</td>
<td>-2.2</td>
<td>-0.2</td>
</tr>
<tr>
<td>Non_US (839, 434)</td>
<td>4.9</td>
<td>3.9</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>PTB&lt;35 Weeks (%)</td>
<td>11.0</td>
<td>11.5</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>US (256, 131)</td>
<td>15.6</td>
<td>17.6</td>
<td>-2.2</td>
<td>-0.8</td>
</tr>
<tr>
<td>Non_US (857, 443)</td>
<td>9.6</td>
<td>9.7</td>
<td>-0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>
FDA Subgroup Analysis – by Region (003)

- No evidence of treatment effect on secondary efficacy endpoints in either regional subgroup

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<thead>
<tr>
<th>Endpoint Subgroup</th>
<th>Makena</th>
<th>Placebo</th>
<th>Diff CMH</th>
<th>Diff SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB&lt;32 Weeks (%)</td>
<td>4.8</td>
<td>5.2</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>US (256, 131)</td>
<td>5.5</td>
<td>9.2</td>
<td>-3.9</td>
<td>-0.6</td>
</tr>
<tr>
<td>Non_US (860, 443)</td>
<td>4.7</td>
<td>4.1</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>PTB&lt;37 Weeks (%)</td>
<td>23.1</td>
<td>21.9</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>US (256, 131)</td>
<td>33.2</td>
<td>28.2</td>
<td>4.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Non_US (856, 441)</td>
<td>20.1</td>
<td>20.0</td>
<td>0.2</td>
<td>0.9</td>
</tr>
</tbody>
</table>
No evidence of treatment effect on coprimary endpoints in Black or non-Black subgroups

<table>
<thead>
<tr>
<th>Endpoint Subgroup</th>
<th>Makena</th>
<th>Placebo</th>
<th>Diff CMH</th>
<th>Diff SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Index (%)</td>
<td>5.4</td>
<td>5.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Black (69, 40)</td>
<td>8.7</td>
<td>7.5</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Non-Black (1022, 520)</td>
<td>5.2</td>
<td>5.0</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>PTB&lt;35 Weeks (%)</td>
<td>11.0</td>
<td>11.5</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>Black (72, 41)</td>
<td>23.6</td>
<td>19.5</td>
<td>3.0</td>
<td>-0.1</td>
</tr>
<tr>
<td>Non-Black (1041, 533)</td>
<td>10.1</td>
<td>10.9</td>
<td>-0.8</td>
<td>-0.7</td>
</tr>
</tbody>
</table>
No evidence of treatment effect on secondary endpoints in Black or non-Black subgroups

### Endpoint Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Makena</th>
<th>Placebo</th>
<th>Diff CMH</th>
<th>Diff SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB&lt;32 Weeks (%)</td>
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<tr>
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<td>11.1</td>
<td>9.8</td>
<td>0</td>
<td>-0.4</td>
</tr>
<tr>
<td>Non-Black (1044, 533)</td>
<td>4.4</td>
<td>4.9</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>PTB&lt;37 Weeks (%)</td>
<td>23.1</td>
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<td></td>
</tr>
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<td>Black (72, 41)</td>
<td>37.4</td>
<td>34.2</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Non-Black (1041, 533)</td>
<td>22.1</td>
<td>20.9</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>
FDA Subgroup Analysis – by History of SPTB (003)

- No evidence of treatment effect on coprimary endpoints in either subgroup defined by history of SPTB

<table>
<thead>
<tr>
<th>Endpoint Subgroup</th>
<th>Makena</th>
<th>Placebo</th>
<th>Diff CMH</th>
<th>Diff SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Index (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (933, 478)</td>
<td>5.4</td>
<td>5.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>&gt;1 (158, 80)</td>
<td>10.1</td>
<td>8.8</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>PTB&lt;35 Weeks (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (949, 491)</td>
<td>11.0</td>
<td>11.5</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>&gt;1 (164, 81)</td>
<td>25.6</td>
<td>18.5</td>
<td>7.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>
FDA Subgroup Analysis – by History of SPTB (003)

- No evidence of treatment effect on the secondary efficacy endpoints in either subgroup with history of SPTB

<table>
<thead>
<tr>
<th>Endpoint Subgroup</th>
<th>Makena</th>
<th>Placebo</th>
<th>Diff CMH</th>
<th>Diff SHR</th>
</tr>
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<tr>
<td>PTB&lt;32 Weeks (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (951, 491)</td>
<td>4.8</td>
<td>5.2</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>&gt;1 (165, 81)</td>
<td>10.3</td>
<td>6.2</td>
<td>4.3</td>
<td>0.1</td>
</tr>
<tr>
<td>PTB&lt;37 Weeks (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (948, 489)</td>
<td>23.1</td>
<td>21.9</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>&gt;1 (164, 81)</td>
<td>42.1</td>
<td>35.8</td>
<td>7.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>
No evidence of treatment effect in any risk groups defined using the 5 selected factors.
Concluding Remarks

• **Primary Analysis**
  – Makena did not demonstrate statistically significant treatment benefit vs. placebo on either gestational age at delivery or the neonatal composite index in Trial 003

• **Exploratory Analyses**
  – No evidence that Makena had a treatment effect on the efficacy endpoints vs. placebo in the subgroups
  – Although baseline risk factors can impact the overall probability of a PTB or the neonatal composite index, there is no evidence that they are effect modifiers to Makena’s treatment effect
Makena (hydroxyprogesterone caproate injection)  
New Drug Application 021945

Hydroxyprogesterone caproate (HPC) Utilization  
in the United States

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting  

October 29, 2019

Huei-Ting Tsai, Ph.D.  
Epidemiologist  
Division of Epidemiology II  
Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research  
Food and Drug Administration
We evaluated 1) HPC utilization and 2) possible reasons for HPC use in each of two separate analyses below:

1. In U.S outpatient settings
   • Patients, pregnant and non-pregnant
   • National estimates

2. During 2\textsuperscript{nd} or 3\textsuperscript{rd} trimesters in live-birth pregnancies
   • In Sentinel Distributed Database
   • Not national estimates
HPC Utilization in U.S. Outpatient Settings
Increased Number of Patients With HPC Prescriptions (2014-2018)

Estimated annual number of 15- to 44-year-old patients with dispensed prescriptions for injectable hydroxyprogesterone, from U.S. retail and mail order/specialty pharmacies, 2014 through 2018

Source: Symphony Health IDV® Integrated Dataverse. Data years 2014-2018. Extracted August 2019. Unique patient counts should not be added across time periods due to the possibility of double counting those patients who received multiple products within the same calendar year or over multiple periods in the study. Prescriptions for bulk powder forms of hydroxyprogesterone were not included.
Physician Survey for Diagnoses Associated With Injectable HPC Use Among 15- to 44-Year-Old Women

• Injectable HPC
  – Supervision of high risk pregnancy (50%)
    ➢ Of which 78% for supervision of pregnancy with history of preterm labor
  – History of preterm labor (20%)
  – Supervision of normal pregnancy (13%)
  – Preterm labor in current pregnancy (10%)

• Progesterone Products
  – Supervision of high risk pregnancy (14%); female infertility (40%)

Source: Syneos Health Research and Insights, TreatmentAnswers™ with Pain Panel. Data years 2013-2018. Extracted July 2019. Diagnosis data are not directly linked to dispensed prescriptions but obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity one day a month.
Limitations and Summary

• Limitations
  – Patient estimates obtained for retail and mail-order pharmacy settings, not hospital or clinics
  – Diagnoses related to HPC use were obtained from physician survey data
    ➢ Do not directly link to dispensed prescriptions
    ➢ Do not necessarily result in dispensed prescriptions

• Summary
  – Outpatient injectable HPC use increased from 2014 to 2018; use was low
  – HPC use was largely associated with history of preterm labor diagnosis
Utilization During 2nd or 3rd Trimesters in Pregnancy in Sentinel Distributed Database
Methods: Utilization in 2nd or 3rd Trimesters of Pregnancy

• Database: Sentinel Distributed Database
• Population: Live-birth pregnancies delivered Jan 2008-Apr 2019
• Medications of interest: HPC or progesterone
• Related obstetrical conditions (possible reasons for use):
  – Narrow definition:
    ➢ Preterm delivery in a prior pregnancy
    ➢ Preterm labor in a current pregnancy
    ➢ Cervical shortening in a current pregnancy
  – Broad definition:
    ➢ Same three obstetrical conditions above recorded in a prior or current pregnancy
Temporal Trend on Number of Pregnancies With HPC Use Per 1,000 Pregnancies

- **Total Live-Birth Pregnancies: 3,451,121**

![Graph showing temporal trend on number of pregnancies with HPC use per 1,000 pregnancies from 2008 to 2018.](image)

1 Data from 2019 was incomplete and excluded from the figure
### Injectable HPC Users:
Most Had a Related Obstetrical Diagnosis Code

<table>
<thead>
<tr>
<th>Related Obstetrical Conditions</th>
<th>Injectable HPC (N=16,535)</th>
<th>Progesterone (N=40,144)</th>
<th>Any HPC or Progesterone (N=61,615)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narrow Definition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Preterm delivery in a prior pregnancy</td>
<td>39%</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>2. Preterm labor in a current pregnancy</td>
<td>49%</td>
<td>45%</td>
<td>47%</td>
</tr>
<tr>
<td>3. Cervical shortening in a current pregnancy</td>
<td>20%</td>
<td>32%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Any of the conditions above</strong></td>
<td>73%</td>
<td>61%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Broad Definition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Preterm labor or delivery in a prior pregnancy</td>
<td>95%</td>
<td>37%</td>
<td>56%</td>
</tr>
<tr>
<td>2. Preterm labor or delivery in a current pregnancy</td>
<td>54%</td>
<td>55%</td>
<td>56%</td>
</tr>
<tr>
<td>3. Cervical shortening in a past or current pregnancy</td>
<td>24%</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Any of the conditions above</strong></td>
<td>98%</td>
<td>75%</td>
<td>83%</td>
</tr>
</tbody>
</table>
Limitations and Summary of Sentinel Analysis

• Limitations
  – May not be generalizable to women without a commercial health plan
  – Unspecified timing between related obstetrical conditions and injectable HPC use
  – Inability to capture out of pocket payment

• Summary
  – Overall modest use of injectable HPC during 2\textsuperscript{nd} or 3\textsuperscript{rd} trimesters among pregnancies with a live birth
  – A high percentage (at least 73\%) of pregnancies using injectable HPC had a related obstetrical condition recorded before or during the current pregnancy.
Makena (hydroxyprogesterone caproate injection)  
New Drug Application 021945/Supplement 023  

Summary Remarks  
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting  
October 29, 2019  

Christina Chang, M.D., M.P.H.  
Clinical Team Leader  
Division of Bone, Reproductive and Urologic Products  
Office of New Drugs, Center for Drug Evaluation and Research  
Food and Drug Administration
Background

- Neonatal morbidity and mortality from preterm birth (PTB) is a significant public health concern.
- No drugs are approved to reduce the risk of neonatal mortality and morbidity due to prematurity.
- Progestogens have been used to reduce the risk of preterm birth.*

NDA 021945 Makena

• Received accelerated approval 2011 based on a single clinical trial

• Indication
  – To reduce the risk of preterm birth in pregnant women with a singleton pregnancy who have a history of spontaneous preterm birth

• Dosage & Administration
  – Administered at a dose of 250 mg once a week beginning between 16\(^0\) weeks and 20\(^6\) weeks gestation to week 37 of gestation or birth
Pre-Approval Data (Trial 002)

• Completed in 2002

• Double blind, randomized, placebo-controlled

• 463 U.S. women randomized to receive either HPC (n=310) or placebo (n= 153)

• Efficacy evaluated using a surrogate endpoint
  – Delivery at <37 weeks gestation
  – “Reasonably likely to predict a clinical benefit” in reducing adverse clinical outcomes, such as infant mortality/morbidity

• Makena reduced proportion of women who delivered prior to 37 weeks by 18% (37% Makena vs. 55% placebo)

• Possible safety signal of fetal loss
Design: Confirmatory Trial (Trial 003)

• Completed in 2018

• Double-blind, randomized, placebo-controlled, international trial

• Virtually identical design as Trial 002 except:
  – Gestational age surrogate endpoint
  – Adding clinical outcome

• Efficacy evaluated with two coprimary endpoints:
  – Delivery prior to 35 weeks gestation
  – Neonatal morbidity/mortality composite index*

*The neonatal morbidity/mortality composite index includes neonatal death, Grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.
Results: Confirmatory Trial (Trial 003)

- Total number of subjects randomized = 1708
  - Makena (n=1130) vs. placebo (n=578)
  - Total U.S. subjects randomized (n=391, 23%)

- No statistically significant treatment effect for either coprimary endpoints:
  - Proportion of women delivering <35 weeks (11% Makena vs. 12% placebo-vehicle, p=0.72)
  - Neonatal composite index (5.4% Makena vs. 5.2% placebo-vehicle, p = 0.84)

- Proportions of women delivering <32 weeks and <37 weeks were also not different between the Makena and placebo groups.
Results: Confirmatory Trial (Trial 003)

- No relevant differences in the treatment effect when analyzed by region (U.S. vs. non-U.S.) or subgroups (e.g., race, previous # of spontaneous PTB)

- In the U.S. subgroup:
  - Makena did not improve the neonatal outcome
  - Makena did not reduce the risk of delivery <35 weeks (16% Makena vs. 18% placebo)

- 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
Effectiveness Standard for Drug Approval

• All approved drugs, including those approved under accelerated approval, must meet the statutory standard of “substantial evidence” of effectiveness.

Evidence consisting of adequate and well-controlled investigations, including clinical investigations... to evaluate the effectiveness of the drug involved...*

*21 U.S.C. § 355(d), FD&C Act Section 505(d)
Trial 002 vs. Trial 003

Trial 002
• Assessed efficacy based on gestational age at delivery (surrogate)
• U.S. academic centers only
• ~60% blacks
• Unusually high PTB rate (55%) in placebo group
• Makena reduced proportion of PTB <37 weeks by 18%

Trial 003
• Assessed efficacy based on neonatal outcomes (clinical benefit) and gestational age at delivery (surrogate)
• International trial (but 23% from United States)
• Makena had no treatment effect for proportion of delivery <35 weeks, <32, or <37 weeks
• No difference in neonatal outcomes
Substantial Evidence of Effectiveness

Accelerated Approval
(surrogate endpoint)
Allows for earlier access to therapy
Less certainty that observed treatment effect translates into clinical benefit

Traditional Approval
(clinical endpoint or validated surrogate endpoint)
Directly measuring how a patient feels, functions, or survives (the outcome of interest)

Requires verification of clinical benefit

FDA Approval
Why the Discrepant Results?

• Trial 002 (with the surrogate endpoint only) falsely positive?
• Trial 003 falsely negative?
• Discrepant results between Trials 002 and 003 due to unknown factors?
Issue 1: Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness?

Yes

Accelerated Approval (surrogate endpoint)

No

Traditional Approval (clinical/validated surrogate endpoint)

Issue 1: Conflicting results on surrogate endpoint (GA of delivery)

No Approval
Issue 2: Accelerated Approval

Substantial Evidence of Effectiveness

- Yes
  - Accelerated Approval (surrogate endpoint)
    - Clinical Benefit Verified?
      - Yes
        - (full) Approval
      - No
        - Issue 2: Clinical benefit to neonate not verified
          - FDA can withdraw approval
  - Traditional Approval (clinical or validated surrogate endpoint)