Medical Policy and Program Review Council Meeting
Regulatory status of NDA 021945 Makena (hydroxyprogesterone caproate, HPC) (DBRUP)
January 15, 2020
MPPRC input sought on recommendations on the regulatory status of Makena to reduce the risk of recurrent preterm birth

Background

Clinical

Premature delivery, defined as birth prior to 37 weeks gestation occurs in about 10% of the 4 million births per year in the U.S. Although multiple risk factors are associated with spontaneous preterm birth (sPTB), the most important identifiable risk factor for *recurrent* PTB is a history of sPTB. The public health significance of preterm birth is the neonatal morbidity and mortality from prematurity.

No drugs are approved to reduce the risk of neonatal mortality and morbidity due to prematurity. Progestogens (progesterone and synthetic progestogens), or intramuscular injection, have been used to reduce a pregnant woman's risk of PTB. Currently, Makena (hydroxyprogesterone caproate (HPC) injection) is the only pharmacotherapy approved to reduce the risk of *recurrent* PTB (secondary prevention).

Regulatory

Based on the data from Trial 002, conducted by the Maternal Fetal Medicine Unit (MFMU) Network, for primary support of efficacy and safety, NDA 021945 sought approval of Makena for the prevention of recurrent PTB. In 2011, Makena was granted accelerated approval based on reduction in the risk of preterm birth prior to 37 weeks, a surrogate endpoint considered reasonably likely to predict clinical benefit to the neonate, with the requirement that the Applicant conduct a confirmatory efficacy and safety trial.

The confirmatory trial (Trial 003) was an international, randomized, double-blind, placebo-controlled study with coprimary efficacy endpoints of delivery <35 weeks gestation and a neonatal morbidity/mortality composite index (neonatal composite index). The inclusion of a clinical endpoint (the neonatal composite index) was to confirm that the surrogate endpoint (gestational age at delivery) did lead to direct clinical benefit to the neonate.

The trial did not demonstrate a statistically significant treatment effect for the coprimary endpoints of the proportion of women delivering prior to 35 weeks and the neonatal composite index. Also, no differences between Makena and placebo were seen in the secondary outcomes of delivery <32 or <37 weeks. Multiple subgroup analyses failed to reveal any relevant differences in the treatment effect for the different subgroups. Although several demographic and baseline characteristics (e.g., Black race, number of prior sPTB, low socioeconomic status, and lower education attainment) are thought to increase the risk of PTB, there was no evidence in Trial 003, or Trial 002, that they were treatment effect modifiers. There was no consistent

convincing evidence of treatment benefit within an identifiable subpopulation across the two trials.

Advisory committee meeting

An advisory committee meeting was convened in October 2019 to discuss the findings of Trials 002 and 003 and the implications on Makena's approval. The committee voted on three questions:

VOTE 1: Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal outcomes? Yes: 0; No: 16; Abstain: 0

VOTE 2: 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? Yes: 3; No: 13; Abstain: 0

VOTE 3: Should FDA-

- Pursue withdrawal of approval for Makena: 9
- Leave Makena on the market under accelerated approval and require a new confirmatory trial: 7
- Leave Makena on the market without requiring a new confirmatory trial: 0

Of note, in October 2019, Public Citizen submitted a Citizen Petition requesting that FDA remove Makena and all generic products containing hydroxyprogesterone caproate from the market due to lack of effectiveness.

The Division

The Division of Bone, Reproductive, and Urologic Products (DBRUP) agree that Trial 003 was a well-conducted trial and failed to demonstrate a clinical benefit of Makena for pre-term birth.

The Division sought MPPRC's input on two options; either withdraw the approval of Makena or keep Makena approved under subpart H while a new confirmatory trial is conducted. The Division recommends withdrawing the accelerated approval.

Discussion at the MPPRC meeting

Is there any pharmacological basis for this observation?

There is no good animal model for preterm birth. Historically, progesterone has been used to prevent miscarriage, which can be attributed, at least partially, to its anti-inflammatory properties. Although progesterone was used off-label for preterm birth, HPC was not commonly used until after the July 2003 publication of Trial 002 in the New England Journal of Medicine. In addition, after advances in ultrasound technology, particularly in the measurement of cervical lengths, the mainstream use of progesterone increased in the 2000s.

Is the timepoint of less than 35 weeks of pregnancy validated?

At this time, the Agency has not determined a certain gestational age at delivery to be a validated surrogate endpoint. Late preterm birth (34-36 weeks gestation) is not considered a validated surrogate endpoint, although early preterm birth (less than 34 weeks) is expected to be more a robust predictor of neonatal outcomes and could be considered for validation in the future.

Is there a certain gestational age for which the data are strong?
In general, an increase in gestational age has been associated with a decrease in neonatal morbidity and mortality, with benefits being relatively more clinically meaningful at earlier gestational age of delivery. The average prolongation of gestation in Trial 002 was 6 days (prolonging gestation on the average from about 35 ½ weeks to 36 ½ weeks gestation). Trial 002 showed compelling evidence for risk reduction in births < 37 weeks. Although statistically significant treatment benefit was also seen for earlier gestation ages (< 35 weeks, < 32 weeks), the upper end of the confidence interval for those treatment differences from placebo was close to zero.

Does the study capture endpoints such as duration of stay of the neonates in the hospital after birth?
The primary clinical endpoint—composite neonatal index—did not include the duration of stay as a component of the index. However, data collected under the secondary endpoints could be used to assess it.

Could the differences in population of Trial 002 and 003 account for the discordant outcomes between the two trials?
A greater proportion of patients in Trial 002 had certain risk factors for sPTB, such as being Black or having >1 prior sPTB, than the Trial 003 U.S. subgroup or Trial 003 overall. However, subgroup analysis did not show these risk factors to be effect modifiers. Therefore, differences in these factors between Trials 002 and 003 did not explain their discordant efficacy findings.

Applicant's take on the Trial 003 results
The Applicant believed that findings from Trial 002 and some positive trends in the Trial 003 U.S. subgroup provided substantial evidence of Makena's efficacy in U.S. women. The Applicant did not believe that data obtained from outside the U.S. in Trial 003 applied to U.S. women. However, the Division does not believe there is evidence related to a biological or pharmacological basis to expect a difference between U.S. and non-U.S. populations. Additionally, subgroup analysis did not show a treatment difference by region (U.S. vs. non-U.S).

Could the population of Trial 002 be the outlier?
The Council raised the possibility of the population of Trial 002 being the outlier, since the outcome of subgroup analysis on Trial 003 was very similar to the outcome of the overall population of Trial 003. However, there is no definitive way to verify this. The Division noted that the recurrent sPTB rate (55%) in the placebo arm in Trial 002 significantly deviated from expected recurrent rate of approximately 20-30%.

Did the citizen petition (CP) raise points not discussed in the AC meeting?
The Division responded that the CP provided no new data analysis or additional insight.

Could early versus late preterm birth explain the differences between Trial 002 and 003?
The understanding of PTB as a syndrome is very limited. However, the causes of early PTB (24 to 34 weeks of gestation) are presumably very different from the causes of late PTB (34 to 36 weeks of gestation). The mechanism of action of the drug is also not known. However, the drug is believed to have anti-inflammatory properties that might render better therapeutic effects in early PTB than in late PTB. However, the available data from Trials 002 and 003 do not provide support that the drug is more efficacious in preventing early preterm birth. Most preterm births in both trials were late preterm births.

Can socio-economic factors drive the outcome?
Socio-economic (SEC) factors such as poverty, education level, are associated with the risk of PTB. However, the composite index and subgroup analysis of Trial 003 data did not show that these factors modify the treatment effect.

Is HPC injection standard of care outside the U.S.?
It's unclear but it is not commonly used in the U.K.

Other issues

- Most women with a history of preterm birth do not experience a recurrence.
- There was no dose finding in these trials, so it's unclear whether the Makena dose is the appropriate dose.

Would a new confirmatory trial be useful?
Trial 003 was a well-thought-out, well-planned, and well-executed large study with compellingly negative data. Although the Council agreed that it would be helpful to uncover the reasons for the discrepancy between Trials 002 and 003, the unequivocal failure of this larger, well-conducted study lead to a conclusion that there is not substantial evidence of efficacy for use of this drug to prevent pre-term birth. The feasibility of completing a robust trial within a reasonable time frame is exceedingly low. The Council unanimously recommended withdrawal of the drug.

Focus on messaging
Given the context around Makena, the Council recommended focusing on transparent messaging. The Division should explain how the prior decision of approval was justified. Then carefully and clearly indicate that the confirmatory trial failed to show benefit. This can also be presented as a success of the accelerated approval process.

Perspective piece

The Council also recommended that the Division write a perspective piece in the relevant professional journal(s) to explain the basis of this decision.

Convening an expert panel
The Council recommended discussing the feasibility of convening an expert panel or a public workshop to discern the possibility of studying this drug further. The panel could discuss issues such as study design, relevant questions to be answered, appropriate population, endpoints, etc. The Council also suggested including a public health expert to provide input on the SES factors.

Recommendation: Given that the current data do not lend themselves to the design of another confirmatory trial, the Council unanimously agreed with the Division's recommendation of withdrawal. The Council recommended focusing on transparent messaging, writing a perspective piece, and convening a panel/workshop to discuss a path forward for drug development for preterm birth.

Attendees

Council Members

Peter Stein, OND
Jacqueline Corrigan-Curay, OMP
Janet Woodcock, CDER
Patrizia Cavazzoni, CDER
Steven Lemery, DO3
Christine Nguyen, DBRUP
Issam Zineh, OCP
Hylton Joffe, DBRUP
Bob Temple, CDER
Stella Grosser, OB
John Farley, OID
Judith Zander, OSE
Julie Beitz, ODEIII
Aliza Thompson, DCRP
Gerald Dal Pan, OSE
Lauren Wedlake, Project Manager
Kayla Holman, Project Manager

Attendees

Christina Chang, DBRUP
Maarika Kimbrell, OND Policy
Sylva Collins, OB
William Chong, OGD
Mary Dempsey, OGD
Iilun Murphy, OGD
Barbara Wesley, DBRUP
Audrey Gassman, DBRUP
Christine Hunt, OCC
Abby Brandel, OCC
Laura Lee Johnson, OB
Monika Deshpande, Medical Writer
Mark Levenson, OB
Barry Miller, OND
Michelle Weiner, ORP
Elizabeth Jungman, ORP
David Joy, ORP
Jeannie Roule, DBRUP
Taehyun Jung, OB
Clara Kim, OB
Jennifer Lawrence, DBRUP
Catherine Sewell, DBRUP
Nneka McNeal-Jackson, DBRUP
Kalesha Grayson, DBRUP
Jia Guo, OB
John Concato, OMP

Jim Smith, OND Policy
Mahboob Sobhan, OB
Eric Brodsky, OND
Ioanna (Yanna) Comstock, DBRUP
Mary Ross Southworth, DCRP
Edisa Gozun, OC
Victor Crentsil, OND/ODEIII
Mary Thanh Hai, OND/ODEII
Sofia Chaudhry, CBER
Adebola Ajao, OSE/DEPI
Leonard Sacks, OMP
Katherine Donigan, CDRH
Corinne Woods, OSE/DEPIII
David Money, OSE/DEPIII
Graham Thompson, OSP
Grail Sipes, OCD
Stefanie Kraus, ORP
Erin Conroy, OCC
Gerald Willet, DBRUP
Theresa Kehoe, DBRUP
Mat Soukup, OB
Gregory Levin, OTS/OB
Robert Berlin, OND
Mitra Ahadpour, OTS
Kerry Lee, OND
Amanda Turney, OEA/OMA
Sarah Connelly, OND
Lisa Soule, DGIEP
Mathilda Fienkeng, OMP
Raj Madabushi, OTS/OCP
Bryon Pearsall, OMP
Laura Zendel, OSE
Khushboo Sharma, OND
Miriam Dinatale, DPMH
Stephanie Omokaro, OMP
Sally Seymour, DPARP
Iris Masucci, OMP
Rita Ouellet-Hellstrom, OSE/DEPIII
Annmarie Trentacosti, OND
Janet Maynard, OCPP/OOPD
Lauren Choi, OND
Katherine Schumann, OND
Leila Lackey, OSP
Yodit Belew, DAVP
Kristiana Brugger, ORP
Susan Honig, OND
John Alexander, DPMH
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Paul Gouge, OMP
Jennifer Mercier, DBRUP
Mukesh Summan, DBRUP
Patricia Keegan, OHOP/DOPII
Lisa Kwok, OGD
Carlisha Gentles, OSE