Presentation at the FDA's October 17-19, 2022, Hearing on the Center for Drug Evaluation and Research's Proposal to Withdraw Approval of MAKENA (Hydroxyprogesterone Caproate Injection), New Drug Application 021945

Michael A. Carome, M.D.
Director, Public Citizen's Health Research Group
I have no financial conflicts of interest.

PUBLIC CITIZEN 50
People • Power • Progress YEARS

Introduction

Public Citizen strongly supports the Center for Drug Evaluations and Research's (CDER's) proposal to withdraw approval of the new drug application (NDA) for Makena (hydroxyprogesterone caproate injection) to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

We requested such action in our October 2019 citizen petition to the FDA because evidence derived from the FDA-mandated postmarket clinical trial for Makena failed to verify that the drug provides any clinical benefit. Moreover, the drug never should have been approved by the FDA because the single pivotal premarket trial that was relied on to establish efficacy was seriously flawed.

Presentation Overview

- Topic 1: Significant flaws and limitations of the premarket clinical trial supporting approval of Makena
- Topic 2: The failure of the postmarket trial of Makena — which was much larger and better designed than the premarket trial — to show any clinically meaningful benefit
- Topic 3: The risks of Makena

Presentation Overview

- **<u>Topic 1: Significant flaws and limitations of the premarket clinical trial supporting approval of Makena</u>**
- Topic 2: The failure of the postmarket trial of Makena — which was much larger and better designed than the premarket trial — to show any clinically meaningful benefit
- Topic 3: The risks of Makena

Summary of the Flawed Premarket Clinical Trial

- Makena's approval was based primarily on safety and efficacy data from a single clinical trial (hereinafter, "Trial 002").
- Investigators at 19 clinical centers in the U.S. randomly assigned 463 pregnant women who had a history of spontaneous preterm birth to receive either weekly injections of hydroxyprogesterone (310 subjects) or placebo (153 subjects) starting between 16 weeks and 20 weeks, 6 days of gestation and continuing until delivery or 36 weeks of gestation.
- The prespecified primary outcome was preterm delivery before 37 weeks of gestation.

Source: Meis et al, *N Engl J Med*, 348(24):2379-2385

Results of Trial 002

Table 5 Proportion of Subjects Delivering at < 37, < 35 and < 32 Weeks Gestational Age (ITT Population)

Delivery Outcome	Makena[1] (N=310) %	Control (N=153) %	Treatment difference and 95% Confidence Interval[2]
<37 weeks	37.1	54.9	-17.8% [-28.0%, -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

[1] Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18^4, 22^0, 34^3 and 36^4 weeks).

[2] Adjusted for interim analysis.

Source: FDA-approved product labeling for Makena, 2018

Initial Problems with Trial 002

- Unexpectedly high incidence of preterm delivery - *New England Journal of Medicine* editorial regarding Trial 002 noted the following:

  "The 54.9 percent incidence of preterm delivery in the placebo group is so much higher than the rates reported in other high-risk cohorts that it calls into question whether these women are representative of the U.S. population at large." (Source: Greene MF. *N Eng J Med*.2003; 348(24): 2453-2455)

- Mean number of previous preterm deliveries was statistically significantly higher in the subjects assigned to the placebo group than in those assigned to the hydroxyprogesterone group (1.6±0.9 versus 1.4±0.7, respectively; P=0.007). (Source: Meis et al, *N Eng J Med*.2003; 348(24): 2379-2385)
- The proportion of subjects who had more than one preterm delivery prior to enrollment in the trial also was higher in the placebo group than in the hydroxyprogesterone group (41.2% versus 27.7%, respectively). (Source: Meis et al, *N Eng J Med*.2003; 348(24): 2379-2385)

FDA Statistical Reviewer's Assessment of Initial NDA Submission in 2006

"From a statistical perspective, the level of evidence from [Trial 002] is not sufficient to support the effectiveness of [hydroxyprogesterone]... Without a second study, the generalizability of the study results to a larger population cannot be assessed" [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF pages 103-104

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 1: Inadequate Prespecified Primary Endpoint

"**[Trial 002] was not designed for drug approval.** FDA and the applicant did not have the usual meetings and discussions regarding the choice of endpoint needed to establish efficacy in a regulatory environment. As a result, **the primary endpoint for the study – Delivery <37 weeks [of] gestation – is not what the FDA would have advised**" [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 104

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 2: Significant likelihood of false-positive results

The FDA statistical reviewer emphasized that the upper bounds of the confidence intervals for differences in the rate of preterm delivery before 35 and 32 weeks of gestation between the hydroxyprogesterone and placebo groups were very close to zero.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 104

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 2: Significant likelihood of false-positive results

"Although the results are statistically significant for Delivery < 35 weeks [of] gestation and Delivery <32 weeks [of] gestation when accounting for interim analyses, **the confidence intervals for the treatment effects are not convincing when considering that only one study was submitted to support the claim of effectiveness for [hydroxyprogesterone]…**

"When two studies are submitted, the chance of both studies yielding a false positive result is 1/1600. In the case of a single study, the results must be less than a nominal p-value of 0.00125 to ensure the same false positive rate... Deliveries at times earlier than 37 weeks [of] gestation were not statistically significant at 0.001. **The results of the analyses of the 32 and 35 week endpoints suggest their false positive rates could be as great as 1/40**." [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF pages 104-105

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 3: One site enrolled a disproportionate number of subjects

Of 19 study sites in Trial 002, one site — the University of Alabama — enrolled 126 subjects, accounting for approximately 25% of total enrollment, which was about three times larger than the second largest study site, and 44% of enrollment of subjects at 18 weeks of gestation or earlier

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF pages 104-105

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 3: One site enrolled a disproportionate number of subjects

Table 3.5 Delivery <37 weeks, <35 weeks, <32 weeks: University of Alabama versus All Other Centers

	University of Alabama				All Other Centers Combined			
Endpoint	17P[a] (n=86) %	Placebo (n=40) %	p-value[b]	95% CI[c] around treatment difference	17P[a] (n=224) %	Placebo (n=113) %	p-value[b]	95% CI[c] around treatment difference
<37 weeks	26.7	45.0	.042	-37%, -0.8%	41.1	58.4	.003	-29%, -5%
<35 weeks	17.4	27.5	.194	-28%, 6%	22.8	31.9	.072	-20.0%, 1%
<32 weeks	10.5	25.0	.034	-32%, 0.04%	12.5	17.7	.197	-15%, 3%

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 91

FDA Statistical Reviewer's Assessment of Initial NDA

Problem 4: Apparent confounding of study site and gestational age at randomization

Additional analyses by the statistical reviewer further suggested apparent confounding of study site and gestational age at randomization.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 91

FDA Statistical Reviewer's Assessment of the 2008 Complete Response for the Makena NDA

[F]rom a statistical perspective, the effect of 17 α-hydroxyprogesterone…on preterm births has not been established by adequate and well-controlled clinical trials… Although [Trial 002] demonstrated statistically [significant] reductions in preterm deliveries, **it is my position that the level of evidence from this single study is not sufficient to support the effectiveness of 17 α-hydroxyprogesterone**. [Emphasis added]

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 49

FDA Statistical Reviewer's Assessment of the 2010 Complete Response for the Makena NDA

Since the FDA was contemplating approval of Makena under the accelerated approval pathway based on the reduction in preterm birth before 37 weeks of gestation seen in Trial 002, the same FDA statistical reviewer conducted additional analyses related to this endpoint, which revealed the following:

(1) The treatment effect at 37 weeks did not appear to be consistent among groups defined by gestational age at randomization.

(2) There was a lack of consistency of efficacy results among subgroups defined by race.

(3) There was a lack of consistency of safety results at 24 weeks of gestation among subgroups defined by race.

(4) The doubling of the treatment effect from <35 weeks to <37 weeks was likely due to the increased number of deliveries among non-black subjects randomized to placebo.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 7

FDA Statistical Reviewer's Assessment of the 2010 Complete Response for the Makena NDA

"From a statistical perspective, the information and data submitted by the Applicant do not provide convincing evidence regarding the effectiveness of 17 α-hydroxyprogesterone…for the prevention of preterm deliveries among women with a history of at least one spontaneous preterm delivery."

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf, PDF page 6

Presentation Overview

- Topic 1: Significant flaws and limitations of the premarket clinical trial supporting approval of Makena
- **Topic 2: The failure of the postmarket trial of Makena — which was much larger and better designed than the premarket trial — to show any clinically meaningful benefit**
- Topic 3: The risks of Makena

Summary of the Postmarket PROLONG Trial (Trial 003)

- The postmarket PROLONG trial was well-designed, well-executed, and appropriately powered, with 1,708 subjects having been randomized.
- It did not suffer from the multiple flaws and deficiencies seen in Trial 002.
- The trial's coprimary efficacy endpoints were delivery prior to 35 weeks of gestation and a neonatal morbidity/mortality composite index (neonatal composite index.

Source: https://www.fda.gov/media/132003/download, PDF page 9

Results of Trial 003

Table 7: Trial 003 Efficacy Results

Efficacy Endpoints	Makena (N=1130)	Placebo (N=578)	Difference (95% CI)*	P-value*
Neonatal composite index	5.4% (59/1091)	5.2% (29/560)	0.2% (-2.0, 2.5)	0.84
PTB <35^0 weeks (%)	11.0% (122/1113)	11.5% (66/574)	-0.6% (-3.8, 2.6)	0.72
PTB <32^0 weeks (%)	4.8% (54/1116)	5.2% (30/574)	-0.4% (-2.8, 1.7)	
PTB <37^0 weeks (%)	23.1% (257/1112)	21.9% (125/572)	1.3% (-3.0, 5.4)	

Abbreviations: N: number of randomized subjects, CI: confidence interval, PTB: preterm birth
*Difference, 95% CI and P-value were from CMH method stratified by gestational age at randomization
Source: FDA analysis

Advisory Committee Assessment of the Postmarket PROLONG Trial (Trial 003)

- At the October 29, 2019, meeting of the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee, when asked whether the findings from Trial 003 verified the clinical benefit of Makena on neonatal outcomes, the 16 voting member voted unanimously in the negative. When asked whether, based on the findings from Trial 002 and Trial 003, there was substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth, the committee voted 3 yes, 13 no.

Source: https://www.fda.gov/media/136107/download, PDF page 6

Presentation Overview

- Topic 1: Significant flaws and limitations of the premarket clinical trial supporting approval of Makena
- Topic 2: The failure of the postmarket trial of Makena — which was much larger and better designed than the premarket trial — to show any clinically meaningful benefit
- **Topic 3: The risks of Makena**

Conclusions

- Under the precautionary principle of public health, in the absence of evidence establishing that hydroxyprogesterone is effective for reducing the risk of preterm labor, it is unacceptable to continue to expose women and their fetuses to the known and potential risks of the drug.

Conclusions

- It is inconceivable that the FDA would have approved the Makena NDA if the efficacy data from the postmarket trial showing no benefit had been available prior to approval. The FDA itself stated that "[i]f these conflicting findings of Trials 002 and 003 were submitted at the same time in an NDA seeking approval for Makena, we would conclude that there is not substantial evidence of effectiveness of Makena for reducing the risk of recurrent [preterm birth]."
- Importantly, the proposal to withdraw approval of Makena was endorsed unanimously by CDER's Medical Policy and Program Review Council, the membership of which included the most senior and experienced leaders of the center.

Conclusions

- Makena should have been removed from the market soon after the results of the PROLONG trial were available. The yearslong delay in the FDA withdrawing approval of the NDA for Makena demonstrates fundamental deficiencies in the current regulatory oversight for drugs approved under the accelerated approval pathway.
- In closing, Public Citizen urges the FDA as soon as possible after the conclusion of this hearing to withdraw approval of the NDA for Makena and for the abbreviated new drug applications for all generic hydroxyprogesterone caproate injection products for which Makena was the reference listed drug. Failure to take such action would further erode FDA's credibility and public confidence in the agency's accelerated approval process.