Presentation at the Food and Drug Administration's Hearing on the Center for Drug Evaluation and Research's Proposal to Withdraw Approval of MAKENA (Hydroxyprogesterone Caproate Injection), New Drug Application 021945, Held by Covis Pharma Group/Covis Pharma GmbH

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group. I have no financial conflicts of interest.

Public Citizen strongly supports the Center for Drug Evaluations and Research's (CDER's) evidence-based 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 Food and Drug Administration (FDA) because evidence derived from the FDA-mandated postmarket clinical trial for Makena failed to verify that the drug provides any clinical benefit.[1] 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.

I will address three major topics. First, I will highlight the significant flaws and limitations of the premarket clinical trial supporting approval of Makena and explain why it failed to provide substantial evidence of effectiveness. Second, I will address 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. Finally, I will discuss the risks of Makena and argue that it is unacceptable to continue to expose pregnant women to these risks given the lack of evidence that the drug is effective.

Topic 1: Flawed premarket clinical trial

Makena's approval was based primarily on safety and efficacy data from a single clinical trial (hereafter, "Trial 002").[2] 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. Of note,

[1] Public Citizen. Citizen petition to the Food and Drug Administration to withdraw approval of Makena. October 8, 2019. https://www.citizen.org/wp-content/uploads/2493.pdf. Accessed September 6, 2022.
[2] Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Eng J Med.* 348(24):2379-2385.

enrollment in the trial was halted early after a second planned interim analysis found that the boundary for the test of significance for the primary outcome had been crossed.

Regarding the primary efficacy endpoint, preterm delivery prior to 37 weeks of gestation occurred in 37.1% of the subjects in the hydroxyprogesterone group compared with 54.9% of subjects in the placebo group , with a treatment difference of -17.8% (95% confidence interval: -28.0% to -7.4%) (see table below excepted from the FDA-approved product labeling).[3] Delivery prior to 35 weeks of gestation, occurred in 21.3% of women in the hydroxyprogesterone group versus 30.7% of women in the placebo group, with a treatment difference of -9.4% (95% confidence interval: -19.0% to -0.4%). Delivery prior to 32 weeks of gestation occurred in 11.9% of women in the hydroxyprogesterone group and 19.6% of women in the placebo group, with a treatment difference of -7.7% (95% confidence interval -16.1% to -0.3%.

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.

Trial 002 also provided absolutely no evidence that hydroxyprogesterone reduced fetal or neonatal morbidity or mortality.

Problems regarding the results of Trial 002 were readily apparent soon after they were published. For example, a *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.[4]

In addition, the 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).[5] Moreover, the proportion of subjects who had more than one preterm delivery prior to enrollment in the trial also was higher in the

[3] AMAG Pharmaceuticals, Inc. Label: hydroxyprogesterone caproate injection (MAKENA). February 2018.
[4] Greene MF. Progesterone and preterm delivery — déjà vu all over again. *N Eng J Med.* 2003;348(24):2453-2455.
[5] *Ibid*.

placebo group than in the hydroxyprogesterone group (41.2% versus 27.7%, respectively). These differences may have biased the trial's efficacy results in favor of the hydroxyprogesterone group.

During the initial review of the Makena NDA, which was submitted by Adeza Biomedical in 2006, the FDA statistical reviewer made the following overall conclusion:

> **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.[6]

The statistical reviewer enumerated numerous problems regarding the design, execution, and analysis of Trial 002 to support her conclusion that the trial was unsuitable for establishing the efficacy of hydroxyprogesterone for preventing preterm birth..

- *Problem 1: Inadequate prespecified primary endpoint*

The statistical reviewer explained that the prespecified primary outcome for the trial was not an appropriate endpoint to establish the efficacy of the drug and support its approval, noting the following:

> **[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.**[7] [Emphasis added]

On August 29, 2006, the FDA convened a meeting of its Advisory Committee for Reproductive Health Drugs to discuss the safety and efficacy of hydroxyprogesterone. A large majority of the committee (16 of 21 members) agreed with the FDA that a reduction in preterm birth before 37 weeks of gestation was *not* an adequate surrogate for a reduction in fetal and neonatal mortality or morbidity.[8] Nevertheless, the FDA based its eventual accelerated approval of the drug on this endpoint.

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[6] Food and Administration. Statistical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf. Accessed September 6, 2022. PDF pages 103-104.
[7] *Id*. PDF page 104.
[8] Food and Drug Administration. Summary minutes of the Advisory Committee for Reproductive Health Drugs. August 29, 2006. https://wayback.archive-it.org/7993/20170404053134/https://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4227M1.pdf. Accessed September 6, 2022. PDF page 5.

- *Problem 2: Significant likelihood of false-positive results based on appropriately adjusted analyses using the secondary endpoints of preterm delivery before 35 and 32 weeks of gestation*

The FDA statistical reviewer stated that the FDA had determined that the clinical significance of preterm birth with respect to neonatal mortality and morbidity is most pronounced prior to 32 weeks of gestation and therefore focused on this endpoint.[9] The fact that the study was stopped early made it more likely that any estimates of efficacy based on the endpoints of preterm delivery before 35 and 32 weeks of gestation overstated the drug's benefits.

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.[10]

The statistical reviewer concluded that the analyses of the data assessing the efficacy of hydroxyprogesterone based on preterm delivery before 35 and 32 weeks of gestation were not convincing:

> 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]**…
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> 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**.[11]
>
> [Emphasis added]

- *Problem 3: Potential lack of generalizability: One site enrolled a disproportionate number of subjects*

The statistical reviewer stated the following:

> [FDA] guidance on clinical evidence stresses the importance of a large multi-center study to help establish the credibility of a single study submission. The

[9] Food and Administration. Statistical review(s) of NDA 21945. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000StatR.pdf. Accessed September 6, 2022. PDF page 78.
[10] *Id*. PDF page 89.
[11] *Id*. PDF pages 104-105.

> guidance also notes the credibility of a single study is enhanced if no single center accounts for an unusually large proportion of the subjects and that no single center is disproportionately responsible for the observed results.[12]

However, 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.[13] The statistical reviewer's analyses that separated the data for the University of Alabama from the data for all other 18 study sites revealed that the disproportionately large representation of subjects from the University of Alabama influenced the significance of the overall results for delivery before 32 weeks of gestation (see table below excerpted from the FDA statistical review[14]):

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: Response to FDA Question 1, 10/6/06; p-values calculated by statistical reviewer

[a] Four 17P-treated patients were losses-to-follow-up. They are counted as deliveries at their gestational ages at time of last contact (18.6, 22.0, 34.4 and 36.6 weeks).
[b] Fisher's exact test, 2-sided
[c] The confidence intervals are adjusted for interim analyses.

The statistical reviewer noted the following:

> [T]he…finding that is notable is the result for delivery <32 weeks [of gestation] among all other centers combined, which is non-significant (p=.197). Moreover, the results for the University of Alabama are statistically significant for this

[12] *Id.* PDF page 90.
[13] *Ibid.*
[14] *Id.* PDF page 91.

> endpoint (p=0.034). **This may suggest that the University of Alabama may be responsible for the overall findings of this endpoint.**[15] [Emphasis added]

- *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.[16]

In April 2008, the sponsor (then Cytec Corporation) submitted a Complete Response for the Makena NDA in response to the FDA's October 2006 Approvable Letter. The same FDA statistical reviewer highlighted the fact that the Complete Response did not contain "any additional efficacy data" to obviate the concerns and deficiencies noted during the review of the first NDA submission [17] and again voiced the following comments indicating strong opposition to approval of the drug based on Trial 002 alone:

> [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...**[18] [Emphasis added]

- *Problem 5: Inconsistencies in treatment effect among groups defined by gestational age at randomization and by race*

In July 2010, the sponsor (then Hologic, Inc.) submitted a second Complete Response to the FDA. Since the FDA at this time 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:[19]

(1) The treatment effect at 37 weeks did not appear to be consistent among groups defined by gestational age at randomization. This finding may be confounded with race and study center.

(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.

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[15] *Ibid.*
[16] *Id.* PDF pages 104-105.
[17] *Id.* PDF page 59.
[18] *Id.* PDF page 49.
[19] *Id.* PDF page 7.

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

The FDA statistical reviewer reaffirmed her prior view that the data from Trial 002 failed to demonstrate the efficacy of the drug for the prevention of preterm delivery and concluded the following:

> 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.[20]

Topic 2: 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).[21]

Trial 003 did not demonstrate a treatment benefit of Makena on reducing the neonatal composite index or the rate of spontaneous preterm birth prior to 35 weeks gestation, nor was there evidence of a treatment benefit on the rate of spontaneous preterm birth prior to 37 weeks or 32 weeks of gestation (see Table below).[22]

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

Furthermore, the FDA concluded that the unplanned exploratory subgroup analyses conducted by the sponsor (stratified by geographic region and race) did "not provide convincing evidence

[20] *Id*. PDF page 6.
[21] Food and Drug Administration. FDA briefing document, NDA 021945, hydroxyprogesterone caproate injection (trade name Makena); Bone, Reproductive, and Urologic Drugs Advisory Committee meeting. October 29, 2019. https://www.fda.gov/media/132003/download. Accessed September 6, 2022. PDF page 9.
[22] *Id*. PDF page 9 and 32.

of efficacy over placebo in any subpopulation and there is no statistically significant interaction between Makena and any of these risk factors."[23]

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 members voted unanimously in the negative.[24] 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.[25]

A drug lacking substantial evidence of effectiveness does not meet the legal standard for approval and must not be allowed to be marketed.

Topic 3: Safety issues

Makena, like all drugs, can cause adverse effects. The FDA-approved product labeling for Makena provides warnings about thromboembolic disorders; allergic reactions, including urticaria, pruritus and angioedema; decreased glucose tolerance; fluid retention; depression; jaundice; and hypertension. Many of these adverse effects are seen with other progestins.[26] The fact that there were no significant differences between the treatment and placebo arms in Trials 002 and 003 for any major maternal safety outcomes is not surprising given the size of the trials and the expected frequency of adverse events due to hydroxyprogesterone.

The recent study by Murphy et al published in the *American Journal of Obstetrics and Gynecology* found an association between the risk of in utero exposure to hydroxyprogesterone and the risk of cancer in the offspring.[27] Despite its limitations, this study serves as a reminder that in utero exposure to the synthetic hormone hydroxyprogesterone may carry long-term risks for the offspring and that the long-term safety of such exposure to the offspring remains uncertain.

Conclusions

Many commenters have argued that Makena and its generic equivalents must remain on the market because they are the only FDA-approved treatments available for pregnant women at risk for recurrent preterm birth.[28] But the argument that having some drug treatment for a serious

[23] *Id*. PDF page 35.
[24] Food and Drug Administration. Summary Minutes of the of the Bone, Reproductive and Urologic Drugs Advisory Committee Meeting. October 29, 2019. https://www.fda.gov/media/136107/download. Accessed September 6, 2022. PDF page 6.
[25] *Id*. PDF page 7.
[26] AMAG Pharmaceuticals, Inc. Label: hydroxyprogesterone caproate injection (MAKENA). February 2018.
[27] Murphy CC, Cirillo PM, Krigbaum NY, Cohn BA. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. *Am J Obstet Gynecol*. 2022;226(1):132.e1-132.e14.
[28] For example, see: National Consumers League. National Consumers League statement urging FDA to make patient-centered decision on only available treatment option for pregnant mothers at risk for recurrent preterm birth. https://www.regulations.gov/comment/FDA-2020-N-2029-0002. Accessed August 30, 2022; HealthyWomen.

condition is better than no treatment is deeply flawed and dangerous, particularly for a treatment for which there is lack of evidence of effectiveness and clear evidence of potentially serious risks.

CDER's proposal to withdraw approval of the NDA for Makena is evidence-based, whereas the sponsor's arguments opposing such action are not.

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.

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]."[29]

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.[30]

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.

Statement from HealthyWomen CEO on proposal to withdrawal only FDA-approved treatment option for preterm birth. https://www.regulations.gov/comment/FDA-2020-N-2029-0003. Accessed August 30, 2022.

[29] Food and Drug Administration. Letter to AMAG Pharma USA, Inc., and holders of abbreviated new drug applications for hydroxyprogesterone for reducing the risk of preterm birth proposing to withdraw marketing approval; notice of opportunity for hearing. October 5, 2020. https://www.regulations.gov/document/FDA-2020-N-2029-0001. Accessed August 30, 2022.

[30] Food and Drug Administration. Medical Policy and Program Review Council meeting – Regulatory status of NDA 021945 Makena (hydroxyprogesterone caproate, HPC) (DBRUP). January 15, 2020. https://www.regulations.gov/document/FDA-2020-N-2029-0186. Accessed September 10, 2022.