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

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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 ≥ 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

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  - 15% if the product has had its marketing approval withdrawn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

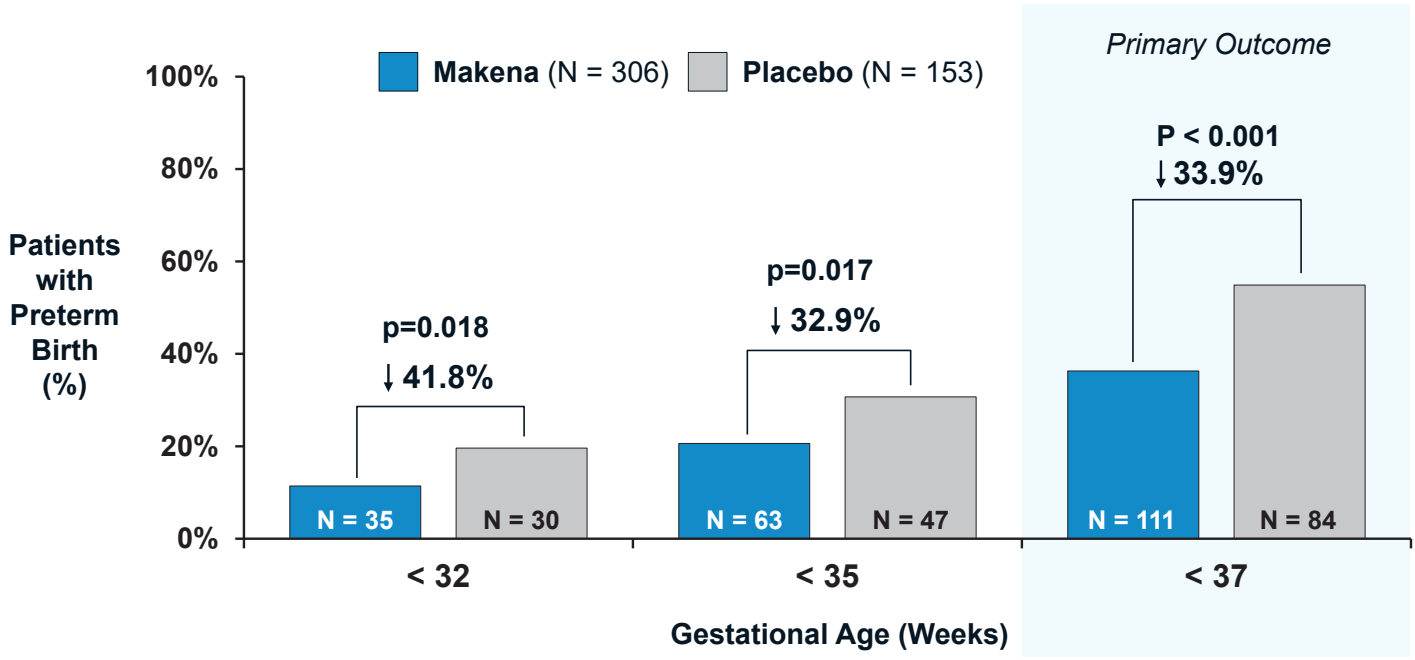
COVIS Position on Questions Presented

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



Meis et al., NEJM 2003

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

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

▲ **Higher risk** compared to Meis ▼ **Lower risk** compared to Meis

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Results in Higher-Risk Target Patient Population for Continuous Endpoint: Nominally Statistically Significant

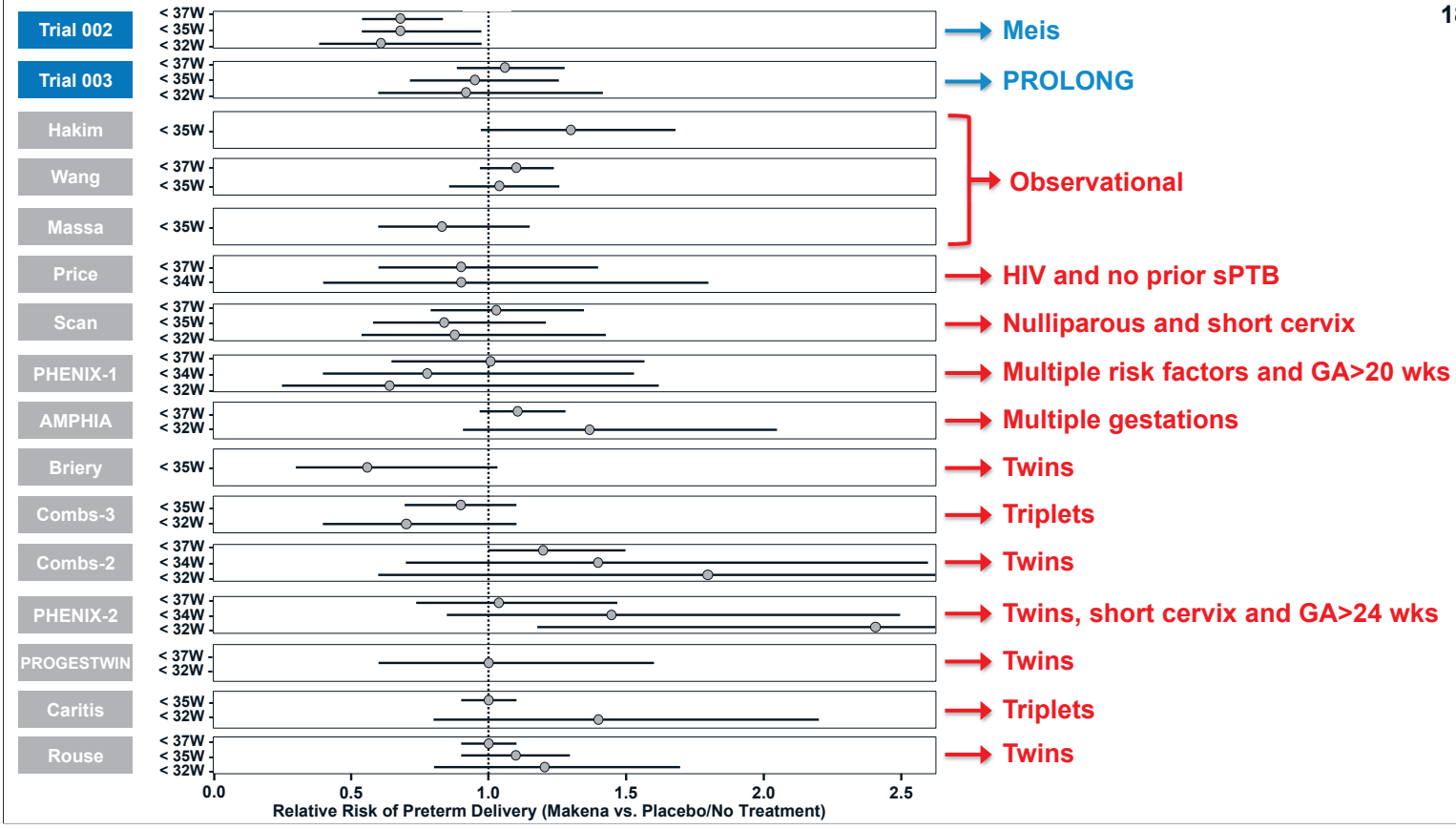
Study	N	Estimated Difference in Time from Randomization to Delivery (up to 35 weeks)[1]	95% CI
PROLONG-US	87	1.86	(0.18, 3.54)
Meis	164	1.33	(0.08, 2.59)

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

Study	N	Endpoint	Odds Ratio	95% CI
PROLONG-US	87	PTB < 37	0.69	(0.28, 1.73)
		PTB < 35	0.55	(0.19, 1.58)
		PTB < 32	0.36	(0.09, 1.44)
Meis	164	PTB < 37	0.24	(0.12, 0.48)
		PTB < 35	0.35	(0.18, 0.70)
		PTB < 32	0.33	(0.15, 0.70)

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

	Integrated Safety (Meis and PROLONG)	
	Makena N = 1130	**Placebo** N = 578
Admission for preterm labor	**16.4%**	**14.4%**
Preeclampsia or gestational hypertension	**5.2%**	**5.1%**
Nausea	**5.1%**	**4.5%**
Gestational diabetes	**3.6%**	**3.8%**
Headache	**5.0%**	**3.8%**
Injection site pruritus	**4.2%**	**3.8%**
Injection site swelling	**4.0%**	**1.9%**
Back pain	**3.8%**	**2.9%**
Vomiting	**3.6%**	**3.3%**
Urticaria	**3.0%**	**2.3%**

Sibai et al. Journal of Perinatology (2021)

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

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Covis respectfully requests that its proposed path forward receive serious consideration by the Panel and the Agency

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