Cross-Discipline Team Leader Review

Date	February 14, 2018
From	Christina Chang, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 021945/S-012
Applicant	AMAG Pharmaceuticals
Date of Submission	April 14, 2017
PDUFA Goal Date	February 14, 2018
Proprietary Name	Makena
Established or Proper Name	Hydroxyprogesterone caproate
Dosage Form(s)	Solution for Injection
Applicant Proposed Indication(s)/Population(s)	To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
Recommendation on Regulatory Action	**Approval**
Recommended Dosing Regimen(s)	Administer subcutaneously using auto-injector at a dose of 275 mg once weekly (every 7 days) in the back of either upper arm by a healthcare provider Administer intramuscularly at a dose of 250 mg (1 mL) once weekly (every 7 days) in the upper outer quadrant of the gluteus maximus by a healthcare provider Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation Continue administration once weekly until 37 weeks (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Preterm birth, defined as delivery before 37 weeks of gestation, is a leading cause of neonatal morbidity and mortality in the United States, affecting approximately 10% of pregnancies. Although the causes of preterm births are multifactorial and not well understood, the public health burden of preterm births is evident: preterm births account for approximately 70% of neonatal deaths, 36% of infant deaths, and 25-50% of cases of long-term neurologic impairment in children.[1] Thus, having effective treatment available to prevent preterm delivery in women who are at risk is of immense societal value. This consideration led the Agency to grant an accelerated approval to hydroxyprogesterone caproate (HPC, trade name Makena) intramuscular injection in 2011 for the indication of "reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth."

In this supplemental NDA, the Applicant seeks approval for a drug/device combination product, consisting of preservative-free Makena to be delivered subcutaneously (SC) by an auto-injector containing a syringe pre-filled with the drug. The Applicant has shown comparable systemic exposure between the proposed SC Makena auto-injector combination product and the approved IM formulation. Therefore, the auto-injector and IM products are expected to have comparable benefit with regard to prevention of preterm birth. Although some subjects had higher, transient, peak hydroxyprogesterone concentrations with the auto-injector compared to the IM formulation, published literature using doses up to 3.6-fold above that used in the SC auto-injector have not identified any safety concerns. Two clinical studies comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection were evaluated for safety. The most common adverse reactions reported with Makena auto-injector use was injection site pain. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects receiving intramuscular injection. In the second study, injection site pain occurred in 20/59 (34%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

I find the benefit/risk profile of the proposed product to be favorable and recommend this supplemental NDA be approved.

[1] American Congress of Obstetricians and Gynecologists, Practice Bulletin No. 171, October 2016. Management of preterm labor. Obstet Gynecol. 2016;128(4):931-3.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Preterm birth is one of the leading causes of perinatal morbidity and mortality. • The incidence of preterm birth (delivery before 37 weeks of pregnancy) remains high in the US despite advances in perinatal care. In 2014, the preterm birth rate in the US was 9.6%.[2] • Risk factors for preterm births include: a prior history of preterm delivery, having a short cervix, short intervals between pregnancies, history of uterine or cervical surgeries, chronic medical conditions (hypertension, diabetes, etc.), pregnancy complications (such as preeclampsia, placental abruption, or intrauterine growth restriction resulting in medically necessary early delivery), low pre-pregnancy weight, physical trauma, and substance use (including nicotine) during pregnancy	Safe and efficacious pharmacotherapies to reduce the risk for preterm birth are crucial to public health.
Current Treatment Options	• Makena IM injection • Compounded HPC products • Bed rest • Tocolytic agents • Cervical cerclage (a suture surgically placed in the cervix)	Makena intramuscular injection is the only FDA-approved pharmacotherapy to reduce the risk of recurrent preterm delivery. The other options listed have drawbacks and are subject to few rigorous, adequately controlled, clinical investigations. Specifically, from a product quality standpoint, the purity and potency of compounded HPC products cannot always be assured. Restricting the expectant mother's physical activities may not always be possible nor desirable given the increased risk for thromboembolic events (with pregnancy already being a hypercoagulable state). Additionally, tocolytics, such as magnesium sulfate,

[2] Births: Final Data for 2014. National Vital Statistics Reports. Vol. 64, No. 12, December 23, 2015.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		beta-mimetics, and non-steroidal anti-inflammatory drugs (e.g., indomethacin) are frequently used off-label to stop or slow uterine contractions; however, none has a clearly established benefit/risk profile when used in this setting. Finally, as to cervical cerclage, although reasonably effective, the procedure exposes the mother and fetus to potential surgical and anesthetic risks.
Benefit	• Makena IM injection received accelerated approval for the proposed indication. The confirmatory trial is ongoing. • Data submitted by the Applicant demonstrate that the systemic bioavailability following Makena SC injection via the auto-injector (275 mg/1.1 mL) is comparable to that achieved following the approved Makena IM injection (250 mg/1 mL). Therefore, these two products should lead to comparable benefit with regard to reduction in preterm birth.	The proposed auto-injector product adds a new treatment option for patients and providers and is expected to have the same efficacy as the IM formulation.
Risk and Risk Management	• Other than more frequent reports of injection site pain, the safety profile of Makena SC injection via auto-injector is comparable to that of Makena IM injection. • Some subjects had higher, transient, peak concentrations of hydroxyprogesterone with the auto-injector product compared to the approved IM product. However, published literature using hydroxyprogesterone doses up to 3.6-fold above that used in the SC auto-injector have not identified any safety concerns.	The proposed auto-injector product is associated with a greater incidence of injection site pain than the IM formulation. This risk can be mitigated with labeling. The higher, transient, peak concentration of hydroxyprogesterone in some subjects does not raise safety concerns.

2. Background

Hydroxyprogesterone caproate (HPC), a synthetic progestin, was originally approved in 1956 for a variety of gynecological indications, including amenorrhea and abnormal uterine bleeding.[3] In 2011, HPC for intramuscular (IM) injection was approved under Subpart H as Makena to "reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. An important limitation of use states that "It is not intended for use in women with multiple gestations or other risk factors for preterm birth." Makena is currently available at a concentration of 250 mg/mL in a 5 mL multi-dose vial or a single-use 1 mL vial. The dosing regimen is 250 mg IM once weekly in the gluteus maximus. Treatment begins between 16 weeks 0 days and 20 weeks 6 days of gestation and continues once weekly until week 37 or delivery, whichever occurs first. Administration of the IM injection involves using a large, 21-gauge needle (1.5 inch in length) due to the high viscosity of the drug. Because Makena received a designation as an orphan-drug in 2005 for prevention of preterm birth in singleton pregnancies, it received seven years of marketing exclusivity, beginning on February 3, 2011. For a comprehensive regulatory history of the original NDA, refer to the summary memorandum by Dr. Lisa Soule (then clinical team leader), with concurrence from Dr. Scott Monroe (then Division Director), dated February 3, 2011.

In this supplemental application (sNDA), the Applicant proposes labeling revisions for dosing of preservative-free Makena (approved on February 19, 2016 under Supplement 7) for a subcutaneous (SC) injection, to be administered by healthcare providers, via a pre-filled auto-injector device, in the back of either upper arm. The Applicant believes the proposed change offers a benefit over the currently available IM injection because the auto-injector platform uses a smaller (27-gauge, 0.5 inch long) needle and less cumbersome administration for both the patients (no undressing necessary) and providers (no need to withdraw the solution from a vial and switch needle before injection, thus minimizing accidental needle sticks). No changes to the indication and target population are being proposed.

Prior to receiving the sNDA, the Division had several interactions with the Applicant relating to the drug/auto-injector device combination over the last two years. Key agreements reached with the Applicant are summarized in chronologic order below:

- Type C Guidance Meeting held on January 29, 2015; meeting minutes dated February 25, 2015:

[3] HPC, (proprietary name Delalutin) was approved under NDA 010347; additional indications were approved NDA 016911 in 1972. The NDA holder for Delalutin discontinued marketing in the 1990s; the Agency announced in 65 FR 55264, published on September 13, 2000, that the NDAs were withdrawn "without prejudice." In 75 FR 36419, published on June 25, 2010, the Agency announced its determination that Delalutin was not withdrawn from the market for reasons of safety or effectiveness.

  - Because Makena was already awarded seven years of orphan drug exclusivity at the initial 2011 approval, marketing approval for this combination product, if granted, will not result in additional orphan drug exclusivity unless the Applicant could demonstrate clinical superiority of the combination over any HPC products also approved by the FDA for the same indication.
- Written Responses dated December 22, 2015:
  - Unless confirmatory trials associated with the original Subpart H have been completed, approval of the new combination product would also be under Subpart H.
  - In addition to establishing bioequivalence (BE) between a single dose of the proposed SC administration and the approved IM administration, similar pharmacokinetic (PK) profiles (e.g., area under the curve, AUC, Cmax, and Tmax) should be demonstrated in the BE study. Whether multiple doses of the new SC administration have accumulation potential that can affect efficacy or safety profile of the drug should also be addressed.
  - (b) (4)
- Type C Guidance Meeting held on July 5, 2016; meeting minutes dated July 27, 2016:
  - The sNDA will need to establish a PK bridge between the to-be-marketed (TBM) product that will be given via an SC injection and the currently marketed reference product given via an IM injection.
  - The FDA recommended that the PK study be conducted in premenopausal women. Otherwise, the Applicant should discuss the clinical implications of the differences in PK profiles expected between pregnant and non-pregnant women and between SC and IM injections.
  - The Applicant should address whether multiple doses of the proposed SC injection have accumulation potential that can affect the efficacy or safety profile of the drug.
- Advice letter dated December 1, 2016 concerning the human factor validation study:
  - The FDA recommended that the healthcare provider user group in the validation study be composed entirely of untrained participants because in real-life scenarios, training may not always occur or be consistently provided to all providers when it does occur.
  - The FDA recommended that the users in the validation study include providers with experience administering both subcutaneous and intramuscular injections. No more than half of those participants should have previous experience injecting Makena intramuscularly using the current marketed vials and 21 gauge needles.

- Advice letter dated December 12, 2016 conveying FDA's comments on the clinical protocol AMAG-HPC-HPM-301, a Phase 3 trial to evaluate pain preference and patient assessment of injection pain when administering the proposed SC injection via auto-injector and the IM injection. The FDA noted multiple concerns, including:
  - An open-label study design, which limits interpretability of patient-reported outcome (PRO) data
  - Insufficient rationale to study postmenopausal women, for whom the proposed product would be inappropriate
  - Failure to account for the use of rescue analgesic and/or ice for injection pain
  - Insufficient justification for the proposed (b) (4) (b) (4)
  - Inadequate content validity of the PRO instrument chosen (Numeric Pain Rating Scale, NPRS) used to assess injection pain
- Advice letter dated February 10, 2017:
  - After reviewing the Applicant's development program for the autoinjector device, the FDA requested design specifications and verification data for the needle as well as the release specifications for the autoinjector, including dose accuracy and needle extension length.
- In a correspondence dated January 27, 2017, (b) (4) (b) (4)

3. Product Quality

This submission includes data to support the manufacture of the approved preservative-free formulation in prefilled syringes, and the manufacture and controls for prefilled syringe in an auto-injector device. The prefilled syringe in the autoinjector is a drug/device combination product.

Drug Product

Each Makena auto-injector contains a 1.1 mL prefilled syringe of HPC USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v, as vehicle) and benzyl benzoate USP (46% v/v, as solubilizing agent). The drug substance, HPC, is manufactured according to DMF (b) (4) which has been evaluated several times since the original NDA approval and is adequate. No changes have been made in the approved drug substance manufacturing and controls. Further, no change has been made to the quality of approved excipients in the product and no new impurities are identified.

Device

The device used in the clinical studies is identical to the to-be-marketed device. Review of the auto-injector device was overseen by the Center of Devices and Radiological Health (CDRH). In a review dated January 2, 2018, the CDRH review team (Lening Shen, Carolyn Dorgan, and Alan Stevens) found the information submitted regarding device design, input/output, validation and verification activities, to be acceptable. However, the team identified deficiencies relating to release specification, design transfer test methods, and some essential performance specifications and requested additional information from the Applicant. After reviewing responses provided by the Applicant, the CDRH team (Lening Shen, John McMichael, and Alan Stevens) concluded in a revised review, dated January 18, 2018, that these deficiencies were satisfactorily addressed.

Based on their review of the device constituent of this combination product, (b) (4) (b) (4) (b) (4) CDRH recommended approval of this sNDA.

Stability

Stability data are provided to six months at accelerated and long-term conditions for the drug product in the prefilled syringe, supporting an expiration date of 36 months. Stability data are also provided to three months for the prefilled syringe in the auto-injector and to support a device expiration date of 48 months. The microbiology reviewer, Nutan Mytle, has evaluated the manufacturing process of the drug product in the pre-filled syringe and recommended approval of this supplement. The microbiology review was incorporated into assessment of product quality.

Biocompatibility

The Applicant has described the materials used in the prefilled syringe and provided quality standards used to ensure biocompatibility. The proposed syringe and syringe components are all approved for use and are commonly found in CDRH-approved products. Review of the extractable/leachable testing performed for the drug product in contact with the syringe materials raised no safety concerns.

Manufacturing Facilities

Inspections of all facilities involved in manufacturing were carried out by the Office of Pharmaceutical Quality (OPQ)/Office of Process and Facilities (OPF) and Office of Compliance (OC). Deficiencies at one site – (b) (4) a sample stability storage facility – were placed on alert for an "Official Action Indicated" (OAI) status during the review. By month 9 in the review, the facility responded adequately to inspection issues raised by OPF. The OPF recommended the drug manufacturing sites for approval and provided the CDRH OC recommendation for approval of the device sites.

Environmental Assessment
The Applicant requested a categorical exclusion from the preparation of an environmental assessment. Their rationale was deemed acceptable and the request was granted.

Overall Product Quality Assessment
Following an integrated review of all information above, the product quality review team (Jean Salemme, Ph.D. and David Lewis, Ph.D.) recommended an overall approval action in a review dated January 18, 2018.

4. Nonclinical Pharmacology/Toxicology

There is no nonclinical information in this supplement. The nonclinical reviewer, Kimberly Hatfield, Ph.D., with concurrence from pharmacology/toxicology supervisor, Mukesh Summan, Ph.D., concluded in their January 17, 2018 review that no additional nonclinical studies are necessary and that from a nonclinical perspective, this supplement is approvable.

The pharmacology/toxicology team has labeling recommendations to bring Section 8 of labeling into compliance with the 2014 Pregnancy and Lactation Labeling Rule (PLLR). Refer to Section 12 of this review for additional details.

5. Clinical Pharmacology

The submission includes a multi-center, randomized, single-dose, comparative bioavailability (BA) study, AMAG-HPC-PK-010 (hereafter, PK-010), which was conducted in 120 healthy post-menopausal women. Subjects were randomized 1:1 (61 to 59) to either Makena SC injection via an auto-injector (275 mg preservative-free Makena in 1.1 mL) or Makena IM injection using a single use glass vial (250 mg preservative-free Makena in 1.0 mL).

Prior to conducting Study PK-010, the Applicant conducted four bioanalytical studies – Studies HPC-PK-007, HPC-PK-008, HPC-PK-008A, and HPC-PK-009 – to establish the appropriate SC dose that would provide similar HPC exposure to the 250 mg IM administration. Data from these four studies led the Applicant to hypothesize that a SC dose of 275 mg Makena auto-injector would likely achieve a similar HPC exposure to 250 mg IM Makena with respect to area under the curve (AUC).

Data from Study PK-010 showed that, except for a higher peak concentration at 24 hours, the geometric mean whole blood concentrations of HPC after the 1.1 mL (275 mg) SC injection in the upper arm were comparable to those after IM administration of 1 mL (250 mg) in the gluteus maximus in healthy post-menopausal women. As shown in Table 1., 90% confidence intervals (CIs) of the SC/IM least squares geometric means ratios (LSGMR) for three time periods of areas under the curves (AUC) were all within 80.00 to 125.00%. Specifically, $AUC_{(0\text{-}168\ hours)}$, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$ were 102.89%, 110.25%, and 113.51%, respectively. The LSGMR for C_{max} was 113.95%; however, the upper bound of the 90% CI (91.94-141.23%) was above 125%.

Table 1. Statistical Comparison of PK Parameters for HPC after SC Administration Using an Auto-injector and IM Administration – Primary PK Population

	Least Squares Geometric Means*		Least Squares Geometric Mean Ratio (%)			
Parameter	Test	Reference	Estimate	90% Confidence Interval		
SC (1.1 mL) vs. IM (1.0 mL)						
Cmax	7.88	6.91	113.95	91.94	→	141.23
AUC(0-168)	813.20	790.32	102.89	87.50	→	121.00
AUC(0-t)	2,313.45	2,098.42	110.25	100.90	→	120.46
AUC(inf)	2,468.97	2,175.21	113.51	103.38	→	124.62

Source: clinical pharmacology review, Table 2 on page 4.

To further investigate the out-of-bound C_{max}, the review team identified three outliers with high C_{max} following Makena SC administration. The team's assessment of the PK profile for these three subjects showed a single peak concentration that is "not consistent with the PK profile in other subjects, suggesting that the high C_{max} in these subjects may be an anomaly." The clinical pharmacology review team also conducted a separate BE assessment after excluding these three outliers from the SC treatment group and confirmed that BE was established between the two treatment groups for C_{max}, $AUC_{(0\text{-}168)}$, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$. The team's analysis is shown in Table 2 below.

Table 2. Statistical Comparison of PK Parameters for HPC after SC Auto-Injector and IM Administration – Primary PK Population Excluding Three Subjects with High Single Sampling Time C_{max}

Parameter	Least-Squares Geometric Means		Least-Squares Geometric Mean Ratio (%)	
	Test	Reference	Point Estimate	90% CI
C_{max} (ng/mL)	6.91 (N=42)	6.91 (N=45)	99.9	83.5-119.6
AUC(0-168) (h·ng/mL)	781.4 (N=42)	790.3 (N=45)	98.9	84.0-116.3
AUC(0-t) (h·ng/mL)	2289.3 (N=42)	2098.4 (N=45)	109.1	99.6-119.5
AUC(0-inf) (h·ng/mL)	2440.8 (N=36)	2175.2 (N=41)	112.2	101.9-123.6

Source: clinical pharmacology review, Table 3 on page 5.

Based on these assessments, the clinical pharmacology review team concluded that the two treatments resulted in comparable exposure, providing adequate support for the approval of this sNDA.

> *CDTL comment:*
> *The excursions in C_{max} in three (of 59) subjects who received subcutaneous Makena injections via auto-injector were unexpected. However, even with these excursions in C_{max}, (resulting in the upper bound of 90% CI of the least squares geometric means ratio being 141%), there are no safety concerns based on reassuring safety information from: 1) two clinical studies evaluating the auto-injector in this submission, and 2) published literature in which pregnant women at risk for preterm birth were given HPC at doses up to 3.6 times of that given by the proposed auto-injector product. Please refer to Section 8 of this memorandum for additional detail.*

It should be noted that Study PK-010 was conducted in healthy postmenopausal women rather than in the target population of pregnant women as recommended by the FDA, given potential differences in fat and muscle mass in the two groups. To justify the generalizability of PK data obtained to pregnant women, the Applicant stated their position that "there is no reason to believe that the comparison between SC and IM would be population-dependent." The Applicant further argued that "[w]ith the exception of cancer drugs, comparative BA studies are almost always done in healthy volunteers and not patients," consistent with the FDA's recommendations made in the January 29, 2015 meeting (meeting minutes dated February 25, 2015). The clinical pharmacology review team found the Applicant's rationale to be acceptable.

Additionally, the clinical pharmacology review team requested that the Office of Study Integrity and Surveillance (OSIS) conduct a bioanalytical site inspection. The Division of New Drug Bioequivalence Evaluation (DNDBE) within the OSIS recommended

accepting data without an on-site inspection in their memorandum issued on July 14, 2017. Therefore, there are no pending bioanalytical site inspection issues.

In a review dated January 22, 2018, the clinical pharmacology reviewer, Chongwoo Yu, Ph.D., with concurrence from his team leader Doanh Tran, Ph.D., concluded that "[a]dministration of HPC by SC injection of 1.1 ml (275 mg) via auto-injector to the arm results in comparable exposure to IM injection of 1 mL (250 mg) using a conventional needle and syringe to the gluteus maximus." The clinical pharmacology team recommended that the sNDA be approved, pending agreement on labeling.

6. Clinical Microbiology

Clinical microbiology review of the drug product is discussed under Section 3, Product Quality, of this memorandum.

7. Clinical/Statistical- Efficacy

No new efficacy data are submitted in the sNDA. As discussed in Section 5 Clinical Pharmacology, data from Study PK-010 were adequate to support a PK bridge to the FDA's previous findings of efficacy in the original NDA.

(b) (4)

Providers in Study 301 were asked to compare the auto-injector and the IM injection and to rate their satisfaction with respect to the ease of injection preparation and injection technique. Providers appear to have preferred the auto-injector platform over IM injection (100% responded that they were "completely" or "mostly" satisfied with the auto-injector vs. 81% with the IM injection). However, while these results appear reassuring, provider assessment was evaluated as a secondary outcome and this analysis had not been pre-specified. Thus, (b) (4) In a qualitative survey (the "Patient Preference Assessment

Study"), the Applicant sought feedback from 183 patients at risk for preterm birth on attributes of a hypothetical injection product (features of which were identical to those of the auto-injector) they felt to be essential. In addition to safety and effectiveness, the respondents indicated preference for shorter/narrower needles. Because the responses were derived from patient perception on a hypothetical product, results from this survey study might provide theoretical support at best for patient preference in the real-world setting. In light of the observation from Study 301 (discussed in Section 8 below) that subjects receiving the auto-injector product reported injection pain more frequently than those receiving the IM product, whether patients in the real world would indeed prefer the auto-injector product over the IM product is unknown.

8. Safety

The following sources of safety information provided by the Applicant contributed to support safety of the auto-injector product:

- Five single-dose, clinical pharmacology studies, focusing on findings from Study PK-010
- A multiple-dose, pain assessment trial (Study 301) comparing the proposed auto-injector product and approved IM injection
- A human factors validation study to evaluate the safe and effective use of the auto-injector device and its associated labeling
- Postmarketing safety information
- A literature review on the overall safety of HPC doses greater than 250 mg administered in pregnancy

In the auto-injector clinical program, 89 subjects received the to-be-marketed HPC drug product (275 mg/mL) administered subcutaneously to the back of the upper arm via the auto-injector, and another 17 received SC HPC injection via a standard syringe. As summarized in Table 3 below, the extent of exposure appears adequate.

Table 3. Number of Subjects Who Received At least One Dose of HPC 275 mg by Study

Study	PK-010	Study 301	PK-009	Total
N	59	30	17	106

Source: extracted from the Applicant's Summary of Clinical Safety, Table 2, page 15 of 55.

Clinical Pharmacology Studies

Four single-dose, Phase 1 pilot studies (HPC-PK-007, HPC-PK-008, HPC-PK-008A, HPC-PK-009) were conducted to assess relative bioavailability to establish the appropriate dose and location for the intended SC injection that would give similar HPC systemic exposures compared to the approved 1 mL IM injection of 250 mg/mL of Makena. Data from these pilot studies were used to support

the selection of the 275 mg/1.1 mL HPC dose for the pivotal PK study. There were also 43 subjects who received single HPC SC injections (administered via syringe, not the auto-injector) at doses greater than 275 mg (shown below in Table 4). No safety concerns arose from these pilot studies; injection pain was the most commonly reported adverse reactions (ranging from 12% in Study PK-009 to 41% in Study-PK-008).

Table 4. Number of Subjects Who Received At least One Dose of HPC Subcutaneous Injection ≥ 250 mg by Study

HPC Dose and Location	PK-007	PK-008	PK-009	PK-008A	Total
250 mg, upper arm	12	18			30
250 mg, anterior thigh		18			18
300 mg, upper arm			16		16
325 mg, upper arm				10	10
375 mg, anterior thigh		17			17
Total					91

Source: extracted from the Applicant's Summary of Clinical Safety, Table 2, page 15 of 55.

With 120 subjects participating, Study PK-010 provided the largest safety database in this submission. There were no serious adverse events (AEs), AEs of severe intensity, or deaths in the study. Subjects receiving the SC auto-injector reported more AEs and adverse drug reactions (54% and 46% subjects reporting, respectively) than those receiving the IM injections (38% and 25% subjects reporting, respectively). As expected, injection site pain was the most commonly reported adverse reaction, reported by 34% (20 of 59 subjects) in the auto-injector cohort as compared to 8% (5 of 61 subjects) in the IM injection cohort. Duration of injection site pain until resolution ranged from 3 minutes to 7 days for the auto-injector group and 1 minute to 2 days for the IM injection group. The second most commonly reported adverse reaction was headache; the reported rates were not appreciably different between the two treatment groups (14% in the auto-injector cohort vs. 13% in the IM manual injection cohort).

Pain Assessment Study (Study 301)

In this clinical trial, 30 postmenopausal women were enrolled in each of the two treatments – SC auto-injector weekly for 4 injections and IM manual injections weekly for 4 injections. There were no deaths. One serious AE was reported by a subject in the auto-injector group. She had a tibia fracture and was hospitalized for open reduction and internal fixation; the event was not considered

related to the study drug. As in Study PK-010, the most commonly reported adverse reactions were pain at injection site (10%, 3 of 30 subjects in the auto-injector group vs. 7%, 2 of 30 subjects in the IM injection group).

Human Factors Validation Studies

The Applicant conducted two human factors validation studies using the Makena auto-injector. Results of the first validation study, PD-RPT-0136 API-OBA_S2, were submitted on April 14, 2017. Subjects included in this study were 15 healthcare providers with and without prior experience with auto-injectors. Review by the Division of Medication Error Prevention and Analysis (DMEPA) identified a critical use error by one subject in interpreting the duration needed to hold the auto-injector at the injection site. DMEPA determined that the subject incorrectly interpreted the graphic "clock" display in the Instructions for Use (IFU). After receiving feedback from DMEPA, the Applicant revised the IFU and conducted a second validation study, PD-RPT-0163 API-OBA_S3B using 17 Makena naïve healthcare providers who had experience with subcutaneous and intramuscular injections; the study results were submitted on September 13, 2017. Following review, the DMEPA team (Walter Fava, R.Ph., M.S.Ed., Lolita White, Pharm.D., QuynhNhu Nguyen, M.S.) concluded in their January 31, 218 review that the revised IFU adequately mitigated user error concerns.

Postmarketing Safety

Periodic safety reports submitted to the Agency have been reviewed by the clinical reviewer, Barbara Wesley, M.D., M.P.H. Dr. Wesley has concluded that the types of adverse reactions seen since the original NDA approval have been consistent with those identified during the clinical program and are already reflected in labeling.

> *CDTL comment:*
> *I have also reviewed the periodic safety reports submitted from May 2011 through March 2017; I agree with Dr. Wesley's assessment.*

Literature Review

In the pivotal comparative bioavailability study (Study PK-010), the proposed auto-injector product (275 mg HCP in 1.1 mL) resulted in a greater Cmax at 24 hours as compared to the approved IM injection. To support the safety of the auto-injector product, the Applicant provided a summary of literature, reviewing published studies wherein HPC was administered at doses greater than 250 mg IM. The Applicant identified 21 publications (including 16 individual studies and 5 meta-analyses) that evaluated HPC used in pregnancy at doses ranging from 300 mg to 1500 mg weekly, and as a single dose up to 4000 mg. Acknowledging the heterogeneity among the publications (e.g., different population, doses, timing of HPC used during pregnancy), the Applicant concluded that, relative to controls (placebo or progesterone), the maternal, fetal, and neonatal outcomes in pregnancies exposed to HPC at doses

greater than 250 mg were not adversely impacted. After undertaking her own literature review of these articles, the clinical reviewer, Barbara Wesley, M.D., M.P.H., reached the same conclusion as the Applicant.

CDTL comment:
Among the 21 publications, five trials are most germane to this sNDA given similar study populations to that indicated for Makena. Findings from these five trials are relevant given the following factors: sample size (> 50 subjects administered HPC), dosing regimen (> 250 mg administered weekly or twice weekly), timing of treatment (second trimester through delivery, similar to Makena), and population enrolled (at risk for preterm birth). After reviewing these publications, I concur with Dr. Wesley's conclusion.

Table 5. Published Trials with Multiple Doses of HPC > 250 mg Administration

Publication	HPC Regimen	Route	Timing during Pregnancy	Study Design	Study Population	N Subjects Given HPC
Hauth[4]	1000 mg weekly	IM	Starting 16-20 weeks, until 37 weeks	R, DB, PC	Active-duty pregnant women in the military	80
Katz[5]	500 mg weekly	IM	Starting 10 weeks up to 33 weeks	Historical control	Women with first trimester bleeding	334
Rozenberg[6]	500 mg twice weekly	IM	2nd and 3rd trimester until 37 weeks	R, open-label	Singleton pregnancies with preterm labor and shortened cervix	94
Senat[7]	500 mg twice weekly	IM	2nd and 3rd trimester until 37 weeks	R, open-label	Twin pregnancies and shortened cervix	82
Winer[8]	500 mg weekly	IM	2nd and 3rd trimester until 36 weeks	R, open-label	Women with shortened cervix	51

R = randomized; DB = double-blind; PC = placebo-controlled; Source: extracted from the Applicant's White Paper, Module 5.3.5.4, Table 2, page 8 to 14

[4] Hauth JC, Gilstrap LC, Brekken AL, Hauth JM. The effect of 17 alpha- hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983;146(2):187-190.
[5] Katz Z, Lancet M, Skornik J, Chemke J, Mogilner BM, Klinberg M. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol. 1985;65(6):775-780.
[6] Rozenberg P, Chauveaud A, Deruelle P, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Am J Obstet Gynecol. 2012;206(3):206 e1-9.
[7] Senat MV, Porcher R, Winer N, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2013;208(3):194 e1-8.
[8] Winer N, Bretelle F, Senat MV, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2015;212(4):485 e481-485 e410.

Overall Assessment
The primary reviewer, Barbara Wesley, M.D., M.P.H., has reviewed the safety information submitted and recommended that the supplement be approved in a review dated February 7, 2018. I concur with Dr. Wesley's assessment.

9. Advisory Committee Meeting

No advisory committee meeting is held for this supplement because expert input from an advisory committee was not needed for this supplemental application.

10. Pediatrics

No pediatric studies are required. During the second review cycle for the original NDA, the Applicant requested a full waiver for pediatric studies because such studies would be impossible or highly impractical given the small number of children with the condition to study. On September 10, 2008, the Pediatric Review Committee (PeRC) agreed to a partial waiver for premenarchal females, and to extrapolate efficacy for postmenarchal females.

On February 11, 2011, Makena was granted orphan drug status for the indication currently approved.[9] Because this sNDA seeks the same indication, the Applicant is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

With respect to financial disclosures, the Applicant stipulated that among the 12 investigators who participated and enrolled subjects across the 6 clinical studies submitted in this application, none had any disclosable financial interests.

The Applicant stated that all clinical studies were conducted in conformance with 21 CFR 50 and 56, Good Clinical Practices (GCP), and Institutional Review Board (IRB) research policies and procedures. Audits conducted by the Office Scientific Investigations (OSI) were not considered necessary for any of the 6 clinical studies in this sNDA.

[9] Letter from Timothy R. Cote, M.D., M.P.H., Director, Office of Orphan Products Development, dated February 11, 2011.

12. Labeling

Prescribing Information (PI)

- The PI was updated to reflect the dosing regimen of the HPC auto-injector product in Section 2 Dosage and Administration.
- Instructions for Use (IFU) are to be incorporated into Section 2.2 of the PI, consistent with labeling for other products administered by healthcare providers.
- Section 8 of the proposed PI did not comply with the Pregnancy and Lactation Labeling Rule (PLLR), which was finalized in 2014. The Applicant agreed to update the PI to adhere to the PLLR content and format requirements and accepted all the edits in this section recommended by the FDA.
- Section 6 of the proposed PI should reflect the safety profile of the proposed auto-injector product as seen in the two clinical studies supporting approval. Injection site pain was the most commonly reported adverse reaction in the studies and the incidence of this reaction was greater in the auto-injector group than in the IM injection group. The Applicant agreed to state the incidences of injection site pain from both treatment groups.
- New pharmacokinetic information obtained from Study PK-010 was added to Section 12.3.
- Storage and handling for the auto-injector product was added to Section 16.

Other Labeling

- The Patient Packet Insert (PPI) was jointly reviewed by the Office of Prescription Drug Promotion (OPDP, Lynn Panholzer, Pharm.D.) and the Division of Medical Policy Programs (DMPP, Nyedra Booker, Pharm.D., M.P.H., Marcia Williams, Ph.D., LaShawn Griffiths, MSHS-PH, B.S.N., R.N.). OPDP and DMPP made numerous edits for format and ensured that the language in the PPI is consistent with the PI and consumer-friendly.
- The Instructions for Use (IFU) were jointly reviewed by OPDP and DMEPA. OPDP noted an inconsistency in the instructions for storage of the auto-injector ("Do not refrigerate" in the PI vs. "Do not refrigerate or freeze" in the IFU); the Applicant has resolved this discrepancy and updated the PI and the IFU consistently with the phrase "Do not refrigerate or freeze." Based on their review of the human factor validation study results that support appropriate use of the device, DMEPA deemed the proposed IFU to be acceptable from the medication errors perspective.
- Carton and container labeling was reviewed by both Product Quality reviewers and DMEPA; both found these elements to be satisfactory.

13. Postmarketing Recommendations

Makena's accelerated approval under subpart H was based on a surrogate endpoint – reduction of preterm birth at < 37 weeks of gestation, rather than reduction in maternal/neonatal morbidities. Two outstanding postmarketing requirements (PMRs) remain. Ongoing trials to assess clinical maternal (PMR 1722-1) and neonatal outcomes (PMR 1722-2) are expected to be completed in 2018 and 2020, respectively. No new postmarekting requirements are necessary at this time.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA Y CHANG
02/14/2018

HYLTON V JOFFE
02/14/2018
I concur with Dr. Chang's recommendations and with approval. This document serves as the decisional memorandum on this application.