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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	April 24, 2015
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	NDA 206333
Applicant Name	Kythera Biopharmaceuticals, Inc.
Date of Submission	May 13, 2014
PDUFA Goal Date	May 13, 2015
Proprietary Name / Established (USAN) Name	Kybella (deoxycholic acid)
Dosage Forms / Strength	Solution for injection, 10 mg/mL
Proposed Indication(s)	For improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.
Action:	Approval

Summary

The submental fat compartment of the neck is a discrete area within the preplatysmal fat. The submental fat compartment plays a role in the appearance of the youthful and aesthetic neck. Excess fat within the submental fat compartment can arise due to aging, lifestyle, or genetic predisposition, and is often refractory to improvement through diet and exercise. The condition can have a negative impact on an individual's self-perception and emotional well-being.

Currently available therapies for excess submental fat include aesthetic surgical procedures and targeted liposuction.

The subject of this NDA, Kybella (deoxycholic acid) is a first-in-class injectable drug product. Kybella is a synthetic form of endogenous deoxycholate (DC), a secondary bile acid. Endogenous DC solubilizes dietary fat, facilitating its absorption in the gut. Kybella injected into localized sub-cutaneous fat causes adipocyte lysis. This triggers a tissue response characterized by the attraction of macrophages to eliminate cellular debris and lipids, followed by the appearance of fibroblasts, thickening of fibrous septa and an increase in total collagen. Deoxycholic acid (DCA) has a molecular weight of approximately 392.6 g/mol.

This memo documents my concurrence with the Division of Dermatology and Dental Products' (DDDP) approval recommendation for Kybella (deoxycholic acid) injection for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

Dosing

Kybella is available in single patient use vials containing 20 mg of DCA (10 mg/mL in 2 mL vials). The recommended dose is up to 10 mL per single treatment, administered as 0.2 mL per injection site spaced one centimeter apart (approximately 50 injections per single treatment). Up to six single treatments may be administered at intervals no less than 4 weeks apart.

Because of the potential for an aesthetically undesirable outcome in patients with excessive skin laxity or prominent platysmal bands, the use of Kybella in such patients should be carefully considered. Similarly, because of alterations in the anatomy and landmarks, and because of the presence of scar tissue, Kybella should be administered with caution in patients who have had prior surgical or aesthetic treatment of the submental area.

Product labeling will detail proper injection technique to mitigate the risks of marginal mandibular nerve injury and skin ulceration.

Regulatory History

A pre-IND meeting was held July 3, 2006. IND 79726 was opened in November, 2007.

A guidance meeting was held on August 19, 2009 to discuss the development plan for DCA, including the primary endpoint(s), patient-reported outcome (PRO) instruments, and the use of an objective measure, i.e., imaging of submental fat thickness, to support the findings from the PROs.

An End of Phase 2 meeting was held on April 20, 2011, at which the applicant was asked to use improved standardization of the head and neck position when obtaining assessments by clinician and patient-reported measures, and to develop a PRO measure that included line drawings representing different degrees of submental convexity as response options. The applicant was also asked to provide data that justify that a 1-grade improvement in the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) and the Patient-Reported Submental Fat Rating Scale (PR-SMFRS) is clinically meaningful, and to establish a meaningful threshold for reduction of submental fat as assessed by MRI.

Multiple discussions were held with the applicant to establish and validate clinically meaningful clinician and patient assessments of the effects of DCA on submental fullness/convexity. The applicant and the Agency reached agreements on the three assessments of efficacy (clinician scale, patient scale, and MRI imaging).

The protocol for Trial 1 was submitted as a Special Protocol Assessment on November 4, 2011, and an agreement letter was issued on December 16, 2011. The Agency and the applicant reached agreement on the study design and one of the primary endpoints (2-grade reduction on both CR-SMFRS and PR-SMFRS), and the secondary endpoint of 10% reduction in submental fat (SMF) volume as assessed by MRI.

On November 19, 2012 and February 14, 2013, the applicant submitted an initial Pediatric Study Plan (PSP) and amended PSP, respectively, to address the Pediatric Research Equity Act (PREA). In a letter dated March 23, 2013, DDDP and the Pediatric Review Committee agreed that a full waiver of pediatric studies would be appropriate, pending a final decision to be made during the NDA review.

On November 13, 2013 a pre-NDA meeting was conducted with the applicant, and agreement was reached on the content and format of the NDA submission.

The NDA was submitted on May 13, 2014. The Agency issued a filing communication, dated July 10, 2014, identifying potential clinical, clinical pharmacology, statistical and product quality review issues.

Deoxycholic acid has also been filed for approval in this indication in Switzerland and Canada.

Product Quality Considerations

The Division of New Drug Quality Assessment II (DNDQA II)/Branch IV in the Office of New Drug Quality Assessment concluded that “the applicant of this NDA has submitted sufficient information to assure the identity, strength, purity and quality of the drug product.” Further, the drug substance specification was deemed adequate to assure the identity, strength, purity, and quality of the drug substance.

DNDQA II determined that “based on the stability data and the efforts made by the manufacturer to control the sterility and bioburden of the drug product it is concluded that there is low risk to the quality of the drug product with respect to the sterility and bioburden.”

DNDQA II also concluded that the container closure systems “are compatible and adequate to protect the drug product from light and moisture during the proposed shelf life.” An expiration dating period of 30 months for DCA drug product when stored at 25°C was recommended.

On May 13, 2014, DNDQA II concluded that the applicant’s claim for categorical exclusion from the requirement to submit an Environmental Assessment was acceptable. The calculated expected introduction concentration is below the 1 ppb threshold, and no extraordinary circumstances exist that may significantly affect the quality of the human environment.

The Division of Pharmaceutical Analysis (DPA) evaluated the identity, assay, and related substances for deoxycholic acid injection by high performance liquid chromatography (HPLC), and the assay, purity, and related substances in deoxycholic acid by HPLC. In a review dated September 25, 2014, DPA concluded that the methods are acceptable for control and regulatory purposes.

Final reports of manufacturing facility inspections were completed on February 13, 2015, and were found acceptable.

DNDQA II has determined that the applicant has provided adequate comparability protocols and a listing of proposed supplements to be submitted post-approval, and that the post-approval commitment for stability studies is adequate. No additional CMC post-marketing commitments (PMCs) have been recommended.

Microbiology Product Quality Considerations

Container closure and preservative effectiveness studies, the manufacturing process described in the application, and the validation studies described in the application were all deemed adequate to ensure the microbiological quality of the drug product. The drug product microbiological specifications are adequate. The stability program described in the application is adequate to ensure the microbiological quality of the drug product over its shelf life.

Non-clinical Considerations

The mechanism of action of DC has been described in the literature as a detergent that lyses and dissolves cell membranes.¹ This effect has been reported to occur in both fat and muscle tissue.² *In vitro* studies demonstrated that DC-mediated adipocyte toxicity is attenuated by exposure to protein-rich tissues. Thus, the cytolytic action of DC becomes preferential for adipose tissue when the injection technique itself limits the detergent's exposure to adipose tissue and avoids muscle tissue.

The nonclinical program was initiated using animal-derived deoxycholate (aDC). Based on concerns over the use of animal-derived material, the applicant developed a synthetic process for manufacturing DCA (sDCA). The applicant conducted a 4-week subcutaneous study in rats comparing the toxicity profile of aDC and sDCA, which demonstrated that the toxicity profiles were similar. An *in vitro* bridging pharmacology study, comparing the relative cytotoxicity of aDC to sDCA determined no pharmacologic difference in the cytolytic potential of aDC and sDCA.

Secondary pharmacology studies investigated the mechanism by which free fatty acids and triglycerides released from lysed adipocytes following DCA injection in rats are cleared, and demonstrated that the process is similar to the clearance of dietary fats in rats. A study was conducted to characterize the area of cell destruction following subcutaneous injection. The study demonstrated that subcutaneous injection of 0.5% and 1% DCA induced a brisk inflammatory response with concentration-related increases in apoptosis within 1 cm of the point of injection.

Safety pharmacology studies were conducted in rats and dogs. Single subcutaneous DCA doses of ≤ 250 mg/kg in rats and ≤ 100 mg/kg in dogs were systemically well tolerated. No meaningful cardiovascular or pulmonary effects were observed in beagle dogs, and no QT/QTc prolongation was observed. Sodium deoxycholate was considered to have a low probability of QT prolongation in hERG channel inhibition studies.

No effects on fertility were observed in male and female rats administered DCA up to 5 times the maximum recommended human dose (MRHD).

Embryo-fetal development studies conducted in New Zealand White rabbits with DCA caused fetal malformations in rabbits (absent intermediate lung lobe), in the presence of maternal toxicity (injection site ulceration), when given at doses two times the MRHD. The lack of a non-maternally toxic dose in the study design precluded the ability to isolate a potential drug effect from that associated with maternal toxicity; therefore, the malformations are considered drug effects (b) (4).

¹ Rotunda AM et al. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. *DermatolSurg.*2004;30:1001-1008.

No effects on prenatal and postnatal development were observed in rats.

The steroid receptor binding potential of a sDCA drug substance impurity was assessed. No significant binding potential to glucocorticoid, progesterone, adenosine, or estrogen receptors was observed *in vitro*.

Repeat dose toxicity studies in rats and dogs induced no significant systemic toxicity, although an increase in plasma DC levels was observed. There was no apparent accumulation or sex difference in systemic exposure to DC. Injection site toxicities (mild to severe dermal irritation) occurred in all dose groups tested; injection site irritation was minimal after the one month recovery period. There was no indication of pre-neoplastic hyperplasia at or adjacent to DCA injection sites.

Sodium deoxycholate was determined to be non-mutagenic in Ames testing; non-clastogenic in *in vitro* mammalian chromosomal aberration testing in human lymphocytes; and non-genotoxic in the *in vivo* rat erythrocyte micronucleus assay. A Quantitative Structure Activity Relationship (QSAR) assessment was conducted to evaluate the genotoxic and clastogenic potential of six DCA impurities and three DCA intermediates. The results were negative in the Ames assay, *in vitro* mammalian gene mutation assay, *in vitro* chromosomal aberration assay, and *in vivo* micronucleus assay. A QSAR assessment for potential genotoxic structural alerts was performed for several impurities and DC-related compounds; no structural alerts were raised and no sub-structures were correlated with mutagenicity. A chemical database query did not find structurally related compounds of the impurities. The non-clinical reviewer concluded that the evaluated impurities did not show evidence of genotoxicity.

Because Kybella is comparable to endogenous deoxycholate, and because the intended clinical treatment will not result in a significant increase in the natural lifetime exposure to deoxycholate, and because previous clinical and non-clinical data did not provide a basis for carcinogenic potential concerns, carcinogenicity studies were waived.

Clinical Pharmacology Considerations

The pharmacokinetic (PK) characteristics of Kybella were determined in subjects with submental fat administered the benzyl alcohol-preserved formulation (the U.S. formulation) or the preservative-free formulation (the EU formulation). The mean plasma exposures for the U.S. formulation as measured by AUC_{0-24} and C_{max} were approximately 1.6-fold greater and 3.2-fold greater, respectively, than the endogenous values at baseline. The median T_{max} was 18 minutes. Post-treatment DCA plasma levels returned to the endogenous range within 24 hours. No accumulation is expected with the proposed treatment frequency. Exogenous DCA joins the endogenous bile acid pool in the enterohepatic circulation and is excreted along with endogenous DCA.

The to-be-marketed formulation was used in the Phase 3 safety and efficacy trials, the thorough QT trial, and the maximal use PK trial.

The metabolic pathway of DCA has been previously studied and demonstrated that DCA was metabolized mainly by CYP3A4.² *In vitro* studies demonstrated that DCA had little or no direct inhibition on CYP450 enzymes at clinically relevant concentrations. Further, *in vitro* studies demonstrated that DCA is unlikely to induce CYP enzymes at clinically relevant concentrations. The potential for DCA to inhibit or induce human transporters was also assessed, and demonstrated that DCA does not inhibit or induce the following transporters: P-gp, BCRP, MRP4, MRP2, BSEP, OATP1B1, OATP2B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, NTCP, and ASBT.

A population PK analysis was used to evaluate the effects of sex and race on the PK of DCA; however, due to limited data on race, the influence of race on the PK of DCA could not be fully assessed. The population PK analysis did not identify a significant effect of sex on either apparent clearance or volume of distribution. No formal trial of the effect of hepatic impairment on the PK of Kybella was conducted. Because of the small dose administered and the intermittent dosing frequency, the clinical pharmacology reviewer concluded that the PK of Kybella injection is unlikely to be influenced by hepatic impairment. Effects of extrinsic factors, such as herbal products, smoking, and alcohol use on the PK of Kybella were not evaluated. Since Kybella is intended for sub-cutaneous use, food interactions in the gastrointestinal tract are not anticipated.

A thorough QT study was conducted with Kybella. The study was reviewed by the Interdisciplinary Review Team for QT studies who concluded that at the maximum therapeutic dose, Kybella does not prolong the QTc interval.

Efficacy

The efficacy of Kybella was assessed in two pivotal placebo-controlled phase 3 trials (Trials 1 and 2) conducted in the U.S. and Canada. Two additional placebo-controlled Phase 3 trials were conducted in Europe, although with different dose concentrations, injection volumes, number of injections, number of treatment sessions, and endpoints.

Trials 1 and 2 were conducted in 506 subjects and 516 subjects, respectively, ages 19 to 65 years with a history of stable body weight and with scores of 2 to 3 on both the CR-SMFRS and PR-SMFRS, equating to moderate to severe submental convexity, and moderate to large amount of chin fat, respectively. The co-primary endpoints were the proportion of subjects achieving at least a 1-grade improvement in both the CR-SMFRS and PR-SMFRS at 12 weeks post-treatment, and the proportion of subjects achieving at least a 2-grade improvement in both the CR-SMFRS and PR-SMFRS at 12 weeks post-treatment. The applicant included

² Bodin K et al. Novel pathways of bile acid metabolism involving CYP3A4. *Biochimica et Biophysica Acta*.2005;1687:84-93.

two secondary endpoints: 1) proportion of subjects who achieve at least a 10% reduction in SMF volume as assessed by MRI; and 2) the change from baseline to 12 weeks in the Patient-Reported Submental Fat Impact Scale (PR-SMFIS) total score, which assessed how unhappy, bothered, self-conscious, embarrassed, older, and overweight the subject feels due to chin fat. MRI assessments were conducted in a subset of subjects.

The mean age of enrolled subjects in Trial 1 was 49 years. The majority of subjects were female (83%) and Caucasian (88%). Of enrolled subjects, 87% were from the U.S. and 13% were from Canada. At baseline, 51% of subjects had moderate disease and 49% had severe disease as assessed by the CR-SMFRS, and 63% of subjects had a moderate amount of chin fat and 36% had a large amount of chin fat as assessed by the PR-SMFRS.

In Trial 1, 506 subjects were randomized 1:1 to receive Kybella (n=256) 0.2 mL per injection or placebo (n=250) dosed as one injection spaced every centimeter into the submental fat tissue (approximately 50 injections per single treatment) every four weeks up to a maximum of six treatments. Subjects were followed for up to 24 weeks following last administration of study treatment.

In Trial 1, the proportion of subjects achieving at least a 1-grade improvement in both the CR-SMFRS and PR-SMFRS at 12 weeks post-treatment was 70% for Kybella versus 18.6% for placebo; the proportion of subjects achieving at least a 2-grade improvement in both the CR-SMFRS and PR-SMFRS at 12 weeks post-treatment was 13.4% for Kybella versus <0.1% for placebo.

Table 1: Trial 1 – Proportion of subjects with 1-grade improvement and 2-grade improvement in CR-SMFRS and PR-SMFRS 12 weeks post treatment*

	Kybella (N=256) n (%)	Placebo (N=250) n (%)
1-grade improvement in CR-SMFRS and PR-SMFRS	179.3 [†] (70)	46.6 [†] (18.6)
2-grade improvement in CR-SMFRS and PR-SMFRS	34.3 [†] (13.4)	0.1 [†] (<0.1)

*Source: Adapted from Table 9 of the Statistical Review.

[†]Based on multiple imputation method for missing data

Subgroup analyses were conducted for gender, age, race, and country. No significant treatment differences were observed among these subgroups

Kybella also achieved a higher response rate than placebo on the key secondary endpoint of MRI responder, 42.5% and 4.5%, respectively, and change from baseline in total PR-SMFIS score at 12 weeks post-treatment, -3.61 and -1.10, respectively. FDA analyses of the MRI data treated missing data as failures.

The median age of enrolled subjects in Trial 2 was 48 years. The majority of subjects were female (86%) and Caucasian (86%). Of enrolled subjects, 88% were from the U.S. and 12% were from Canada. At baseline, 50% of subjects had moderate disease and 50% had severe disease as assessed by the CR-SMFRS, and 63% of subjects had a moderate amount of chin fat and 37% had a large amount of chin fat as assessed by the PR-SMFRS.

In Trial 2, 516 subjects were randomized 1:1 to receive Kybella (n=258) 0.2 mL per injection or placebo (n=258) dosed as one injection spaced every centimeter into the submental fat tissue (approximately 50 injections per single treatment) every four weeks up to a maximum of six treatments. Subjects were followed for up to 24 weeks following last administration of study treatment.

In Trial 2, the proportion of subjects achieving at least a 1-grade improvement in both the CR-SMFRS and PR-SMFRS at 12 weeks post-treatment was 66.5% for Kybella versus 22.2% for placebo; the proportion of subjects achieving at least a 2-grade improvement in both the CR-SMFRS and PR-SMFRS at 12 weeks post-treatment was 18.6% for Kybella versus 3% for placebo.

Table 2: Trial 2 – Proportion of subjects with 1-grade improvement and 2-grade improvement in CR-SMFRS and PR-SMFRS 12 weeks post treatment*

	Kybella (N=258) n (%)	Placebo (N=258) n (%)
1-grade improvement in CR-SMFRS and PR-SMFRS	171.6 [†] (66.5)	57.3 [†] (22.2)
2-grade improvement in CR-SMFRS and PR-SMFRS	48.0 [†] (18.6)	7.7 [†] (3.0)

*Source: Adapted from Table 9 of the Statistical Review.

[†]Based on multiple imputation method for missing data

Subgroup analyses were conducted for gender, age, race, and country. No significant treatment differences were observed among these subgroups.

Kybella also achieved a higher response rate than placebo on the key secondary endpoint of MRI responder, 33.6% and 4.5%, respectively, and change from baseline in total PR-SMFRS score at 12 weeks post-treatment, -3.44 and -1.46, respectively. FDA analyses of the MRI data treated missing data as failures.

In both trials, the mean CR-SMFRS and PR-SMFRS scores improved over the treatment period, with greater improvement noted in the Kybella arm relative to the placebo arm. The improvements in scores were similar on both instruments. The mean scores on both instruments remained relatively constant through 24 weeks post-treatment.

The Office of Scientific Investigations (OSI) conducted inspections of two clinical sites. OSI classified both sites as NAI; however, OSI noted that the unanticipated closure of the MRI facility responsible for imaging studies resulted in study subjects either not having baseline and end-of-study imaging done or for those in whom baseline imaging was done, the End of Study imaging was done well outside of the protocol-specified window. A separate efficacy analysis was conducted excluding these data, and the impact on the efficacy analysis was minimal.

Safety

In the Kybella development program, 1547 subjects were exposed to at least one dose of Kybella. A total of 1246 subjects were dosed at (2 mg/cm²; n=1048) or above (4 mg/cm² and 8 mg/cm²; n=135 and 63, respectively) the recommended dose, and received 4-6 treatments.

The proportion of subjects with at least one adverse event was 97% for Kybella-treated subjects and 90% for placebo-treated subjects. The most common adverse reactions across the phase 3 program were injection site reactions (edema, bruising, pain, numbness, erythema, induration, paresthesia, nodule formation, pruritus, and warmth), skin tightness, injection site nerve injury, oropharyngeal pain, and dysphagia.

Five deaths occurred in the Kybella clinical development program – three on Kybella and two on placebo. None appear to be treatment-related.

Serious adverse events (SAEs) were reported in 2% of Kybella-treated subjects and 3% of placebo-treated subjects. No SAE was considered to be treatment-related with the exception of a case of recovered mandibular nerve injury in a Kybella-treated subject.

In the phase 3 program, adverse events leading to discontinuation occurred in 7% of Kybella-treated subjects and 1% of placebo-treated subjects. The most frequent adverse events leading to discontinuation in Kybella-treated subjects were injection site reactions.

Adverse events of special interest included marginal mandibular nerve injury, dysphagia, skin ulceration, dysphonia, allergic events, hypertension, and pre-syncope/syncope.

Marginal mandibular nerve injuries were reported in 4% of Kybella-treated subjects and in less than 1% of placebo-treated subjects. All cases presented as an asymmetric smile and all were reported as completely recovered. The median duration of symptoms was 44 days, with a range of 1 to 298 days.

In the phase 3 program, dysphagia occurred in eleven subjects, ten Kybella-treated subjects and one placebo-treated subject. Two Kybella-treated subjects discontinued treatment because of dysphagia, one of whom had not recovered prior to discontinuation. The median duration of dysphagia was 3 days, with a range of 1 to 81 days.

Skin ulceration can occur from injections of Kybella that are too superficial (into the dermis). Skin ulceration occurred in two Kybella-treated subjects and in one placebo-treated subject. All skin ulceration cases resolved without sequelae.

In the phase 3 program, dysphonia developed in two Kybella-treated subjects and no placebo-treated subjects. Both subjects recovered - one in 5 days, and the other in 23 days.

There were four cases of drug hypersensitivity – 3 in Kybella-treated subjects, all of which were attributable to concomitant medications, and one in a placebo-treated subject, which was attributable to a spider bite. Injection site urticaria occurred in 4 Kybella-treated subjects and one placebo-treated subject. The time to onset varied between 1 and 40 days; all cases resolved (some with antihistamines), and none reoccurred upon additional treatment.

Hypertension was observed in 3% of Kybella-treated subjects versus 1% of placebo-treated subjects. Pre-syncope/syncope was observed in 1% of Kybella-treated subjects versus no placebo-treated subjects. These events were considered likely due to the injection administration and/or associated pain.

Safety follow-up from an open-label long term study in 165 subjects who received Kybella according to the same dosing regimen as subjects in the pivotal trials was provided and demonstrated no new adverse reactions.

Safety in subjects aged 65 to 75 years will be further assessed in the ongoing ATX-101-13-28 trial.

Pediatric Considerations

DDDP and PeRC concurred with the applicant's request for a waiver of pediatric studies in all subsets of the pediatric population (up to 18 years of age), because Kybella is not likely to be used in a substantial number of pediatric patients.

Tradename Review

The Division of Medication Error Prevention and Analysis, in consultation with the Office of Prescription Drug Promotion, has concluded that the applicant's proposed proprietary name "Kybella" is acceptable from both a promotional and safety perspective. In a letter dated April 10, 2015, FDA notified Kythera Biopharmaceuticals, Inc. that the proposed proprietary name was acceptable.

Advisory Committee

A meeting of the Dermatologic and Ophthalmologic Drugs Advisory Committee (DODAC) was held on March 9, 2015 to discuss the overall safety and efficacy of Kybella, as well as the robustness of its clinical development program. The committee unanimously (17-0) agreed that the available data support the approval of Kybella for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. Advisory Committee members applauded the interaction between the Agency and applicant in creating new clinician- and patient-reported endpoints. They expressed concern regarding the potential for off-label use of the product; however, agreed that this could be addressed through labeling and healthcare provider training, which the applicant has proposed to provide on a voluntary basis.

Consults

Center for Devices and Radiological Health (CDRH)

CDRH was consulted to review Kybella labeling as it pertains to injection technique and the avoidance of injury to the marginal mandibular nerve. In a consultative memo dated October 23, 2014, CDRH recommended revisions to the text and schematics in the proposed package insert as relates to proper injection technique.

Study Endpoints and Labeling Development (SEALD)

SEALD reviewed the applicant's CR-SMFRS, PR-SMFRS, and PR-SMFIS instruments. SEALD concluded that the evidence submitted by the applicant is sufficient to support the CR-SMFRS and PR-SMFRS in the context of a composite endpoint to measure the appearance of moderate to severe convexity or fullness associated with submental fat. SEALD further concluded that the PR-SMFIS total score is appropriate to support a claim in labeling as an assessment of the impact of treatment on how patients feel about their chin fat appearance, ^{(b) (4)}

Division of Pediatric and Maternal Health

The Division of Pediatric and Maternal Health (DPMH) searched for and reviewed relevant data pertaining to the effects of DCA exposure during pregnancy and lactation. DPMH concluded that there are no human data on the effects of synthetic DCA exposure during pregnancy, and none of the publications reviewed provided data sufficient to be included in Section 8.1 of product labeling. Similarly, there are no data to confirm or refute the presence of synthetic DCA or endogenous DCA in human milk. Appropriate edits were recommended for the Kybella labeling to make it compliant with the Pregnancy and Lactation Labeling Rule guidelines.

Division of Risk Management

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology provided a consultative review to determine if a risk evaluation and mitigation strategy (REMS) is needed for Kybella, a new molecular entity. DRISK concluded that “the benefit-risk profile for deoxycholic acid is acceptable and the risks can be mitigated through professional labeling.”

Postmarketing Requirements under 505(o)

Section 505(o)(3) of the Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

FDA determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA would not be sufficient to assess known serious risks associated with deoxycholic acid treatment including marginal mandibular nerve injury and dysphagia in subjects 65 to 75 years of age.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks in this sub-population.

Finally, FDA has determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks in this sub-population.

Therefore, the applicant will be required to complete and submit the following:

PMR 2897-1: A safety assessment of deoxycholic acid treatment in subjects aged 65 years and older. This assessment is to be performed in the ongoing ATX-101-12-28 trial population of subjects aged 65 to 75 years. To the extent possible, all subjects should be continued through the planned end of the trial (even if a full course of treatment is not administered).

Conclusions

Excess submental fat is an aesthetic condition that can have a negative impact on an individual’s self-perception and emotional well-being. There are currently no available non-surgical treatments. Kybella provides a non-surgical treatment option for individuals impacted by moderate to severe convexity or fullness associated with submental fat.

Treatment with Kybella injection demonstrated superiority to placebo in adult subjects with moderate to severe convexity or fullness associated with submental fat, as assessed by both clinician and patient reporting, and supported by MRI measurement.

The safety of Kybella has been adequately characterized to support approval. Physician and patient labeling will convey the known safety concerns associated with Kybella, in particular injury to the marginal mandibular branch of the facial nerve, as well as convey appropriate injection technique to mitigate the risk of this adverse reaction. Additionally, product labeling will carry a limitation of use, noting that the safety and effectiveness of Kybella for the treatment of subcutaneous fat in regions outside the submental area have not been established and is not recommended. The applicant has proposed to make training on proper injection technique mandatory for healthcare providers. While the Agency supports such an effort, we do not believe that the available data on the safety of the product compels us to impose this as a requirement under a REMS. Finally, the ongoing ATX-101-13-28 clinical trial will further assess the safety of the product in subjects aged 65 to 75 years.

DDDP has recommended approval of NDA 206333 for Kybella (deoxycholic acid) injection for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. I concur with DDDP's recommendation for approval, the PMR detailed in this memo, and the agreed upon labeling. Kybella represents a non-surgical option for individuals seeking treatment for this aesthetic condition.

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

/s/

AMY G EGAN
04/24/2015