CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206333Orig1s000

SUMMARY REVIEW

Decisional Memorandum to the File

Date:	April 3, 2015
From:	Kendall A. Marcus, M.D. Director, Division of Dermatology and Dental Products
Subject:	Summary and Recommendations
NDA/BLA #:	206,333 Kythera Pharmaceuticals
Submission Date **PDUFA Goal**	May 13, 2014 May 13, 2015
Proprietary / Generic (USAN) names	(b) (4) Deoxycholic acid for injection
Dosage forms / strength	Solution for injection, 10 mg/mL
Proposed Indication(s)	Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat

1. Introduction

ATX-101, the drug product under consideration in this NDA, contains the drug substance deoxycholic acid (DCA). DCA is a small, fully synthesized new molecular entity that is structurally identical to endogenous deoxycholic acid. DCA is a naturally occurring bile acid which functions to emulsify and solubilize dietary fat in the gut in order that the fat may be absorbed. DCA has a long history of use as a solubilizing excipient in other products. Examples include amphotericin for injection and various influenza vaccines.

Historically, DCA had been compounded with phosphatidyl choline (PC) and used off-label as an injectable treatment for reduction of unwanted subcutaneous fat for many years. These compounded agents were often not manufactured using good manufacturing practice and in 2010, FDA issued warning letters to six medical spas warning that they were making false and misleading claims about their PC/DCA products. Subsequent in vitro and in vivo studies demonstrated that only DCA, and not PC, disrupts the lipid bilayer of cell membranes leading to cell death; when injected into subcutaneous fat, this cytolytic action is the purported mechanism of action for this product.

The proposed indication for ATX-101 is improvement in the appearance of moderate to severe convexity or fullness associated with submental fat. Currently available therapies include surgical and non-surgical options such as neck lift, liposculpture, medical laser and cryolipolysis. If approved, ATX-101 will be the first drug approved for this indication. It may offer an alternative to other interventions in the properly selected patient.

The recommended dosing regimen is an area-adjusted dose of 2 mg/cm^2 delivered at a concentration of 10 mg/mL via 0.2 mL injections spaced 1-cm apart until all sites in the planned treatment area have been injected. Up to 100 mg or 10 mL may be injected in a

single treatment and up to 6 single treatments may be administered at intervals no less than 1-month apart.

Deoxycholic acid was evaluated in three Phase 2 studies, two supportive Phase 3 studies conducted in Europe and two pivotal placebo-controlled Phase 3 studies conducted in the U.S. and Canada. The Phase 2 studies and European Phase 3 studies evaluated dose levels of 0.1% up to 2%, various numbers of injections (24 to 50), and injection volumes (0.2 mL to 0.4 mL) in 4 to 6 treatment sessions four weeks apart.

2. CMC

Please refer to the reviews prepared by Hitesh Shroff, Ph.D. from the Office of New Drug Quality Assessment/DNDQA II/Branch IV and the review by Erika Pfeiler, Ph.D. from the [product quality microbiology] for full details.

The drug product is an injectable solution that contains 10 mg/mL of the active ingredient, deoxycholic acid, formulated in a sterile solution of sodium hydroxide, dibasic sodium phosphate, sodium chloride and water for injection (WFI), with benzyl alcohol as a preservative.

During the development program, the drug substance was manufactured via two different processes. Initially a sodium salt form was produced through the purification from bovine and ovine bile. Subsequently, the applicant was able to chemically synthesize free deoxycholic acid. The deoxycholate from both sources were found to be structurally identical in solution.

In summary, data submitted in the NDA and inspections conducted by FDA staff support the conclusion that the drug substance specification is deemed adequate to assure the strength, purity and quality of the drug substance.

Currently, no post-marketing requirements or commitments are recommended.

3. Nonclinical Pharmacology/Toxicology

Please refer to the review prepared by Jill Merrill, Ph.D., the Pharmacology/Toxicology reviewer for full details. The pharm/tox review team finds this NDA approvable.

Repeat-dose toxicity studies with biweekly subcutaneous infections of ATX-101 were conducted in rats and dogs. Systemic toxicity was not observed. The primary findings in all repeat-dose studies were confined to the injection site and were associated with cytolysis. Dermal signs were reversed or nearly reversed at the completion of the recovery periods.

ATX-101 was negative in the standard ICH battery of in vitro (Ames test and chromosomal aberration assay in human lymphocytes) and in vivo (rat erythrocyte micronucleus assay) genetic toxicology assays.

Deoxycholic acid at subcutaneous doses up to 50 mg/kg, administered weekly during the pre-mating and mating periods in males and females and through gestation day 7 in females, did not lead to changes in fertility or general reproductive parameters in rats.

Embryofetal development studies were performed in rats and rabbits using subcutaneous doses of deoxycholic acid at up to maternally toxic doses during the period of organogenesis. These studies revealed no evidence of fetal harm at up to 50 mg/kg in rats but missing intermediate lung lobe was noted in rabbits at all doses tested (≤ 30 mg/kg). These effects may be related to maternal toxicity which was also seen at all dose levels.

No effects on prenatal and postnatal development were observed in pregnant rats treated subcutaneously with up to 50 mg/kg ATX-101 three times weekly from gestation day 7 through postweaning.

4. Clinical Pharmacology

Please refer to the review completed by An-Chi Lu, M.S., Pharm.D., the clinical pharmacology reviewer from the Office of Clinical Pharmacology/DCP III for full details. The review team considers this NDA approvable from a clinical pharmacology perspective.

The systemic bioavailability of ATX-101 was evaluated in a clinical trial in which subjects were randomized 1:1 to receive either a BA-preserved formulation or the preservative free formulation. All study drug was administered as proposed for the final marketed product; as 50 injections into the submental fat (0.2 mL each for a total volume of 10 mL and total dose of 100 mg) spaced on a 1.0-cm grid in a single treatment session.

At baseline, the individual values of endogenous plasma concentrations varied across subjects and timepoints, with a range of below the lower limit of quantification to 1280 ng/mL. The average endogenous plasma concentration was 227 ng/mL over the 24-hour collection period. Following a single treatment session, the mean deoxycholic acid concentrations increased from pre-treatment values of about 200 ng/mL to nearly 1000 ng/mL at 5 minutes post-treatment; the mean post-treatment plasma DCA decreased gradually and, on average, returned to endogenous baseline levels by 24 hours post-treatment.

The drug-drug interaction potential of ATX-101 was assessed in *in vitro* inhibition and induction studies. The results indicated that ATX-101 is not likely to induce the activity of CYP1A, CYP2B6, and CYP3A or inhibit the activity of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. Similarly, ATX-101 was not found to be an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3. However, ATX-101 was shown to be an inhibitor of BSEP transporter, which was expected, since deoxycholic acid is an endogenous compound, and is a substrate for BSEP.

5. Clinical/Statistical

Please refer to the reviews completed by Milena Lolich, M.D., the clinical reviewer, and Kathleen Fritsch, Ph.D., the biostatistical reviewer for full details of the efficacy review. The review team considers this NDA approvable from an efficacy perspective.

Two randomized, blinded, placebo-controlled Phase 3 trials were conducted to demonstrate that deoxycholic acid 1% for injection is superior to placebo. Studies 22 and 23 enrolled subjects aged 18 to 65 with scores of 2-3 on the clinician and patient submental fat rating scales (moderate to severe submental convexity on the clinician-reported submental fat rating scale (CR-SMFRS) and moderate to large amount of chin fat on the patient-reported submental fat rating scale (PRSMRFS). Subjects were treated in up to 6 treatment sessions at 28-day intervals. Each treatment session involved up to 50 injections (0.2 mL each) spaced on a 1-cm grid. Subjects could stop treatment if they lacked sufficient tissue for injection or were satisfied with the reduction in submental fat.

The protocols defined two co-primary endpoints based on improvement on both the CR-SMFRS and the PR-SMFRS. The first co-primary endpoint was defined as at least a 1-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. The second coprimary endpoint was defined as at least a 2-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS. Both primary endpoints were required to demonstrate statistical significance.

The protocols also defined two secondary endpoints: MRI responder (at least 10% reduction in volume from baseline to 12 weeks post-treatment) and change from baseline to 12 weeks post-treatment in patient-reported submental fat impact score (PR-SMFIS) total score, which is an average of scores assessing how unhappy, bothered, self-conscious, embarrassed, older, and overweight the subject feels due to chin fat. MRI response was assessed in a subset of subjects. The primary and secondary endpoints were all statistically significant. Multiplicity for the two secondary endpoints was handled using Holm's method. The efficacy results are presented in Table 1:

Table 1 – Primary and Secondary Efficacy Endpoints in Studies 22 and 23 (ITT)*

	Study 22		Study 23	
	Deoxy. acid N=256	Placebo N=250	Deoxy. acid N=258	Placebo N=258
2-grades improvement CR-SMFRS / PR-SMFRS[a]	34.3/256 (13.4%)	0.1/250 (<0.1%)	48.0/258 (18.6%)	7.7/258 (3.0%)
	p<0.001		p<0.001	
1-grade improvement CR-SMFRS / PR-SMFRS[a]	179.3/256 (70.0%)	46.6/250 (18.6%)	171.6/258 (66.5%)	57.3/258 (22.2%)
	p<0.001		p<0.001	
≥ 10% reduction in MRI volume[b]	52.0/113 (46.0%)	5.9/111 (5.3%)	45.8/113 (40.5%)	5.8/112 (5.2%)
	p < 0.001		p < 0.001	
Change from baseline in PR-SMFIS [LSmeans (SE)][b]	-3.61 (0.143)	-1.10 (0.143)	-3.44 (0.158)	-1.46 (0.156)
	p<0.001		p<0.001	

*Reproduced from the primary statistical review of NDA 206,333 of Dr. Kathleen Fritsch

[a] Co-primary endpoints

[b] Multiplicity among the secondary endpoints was handled with Holm's method

Treatment effects were found to be consistent across gender, race, age and country subgroups. A separate Phase 3b clinical trial in subjects older than 65 years is currently ongoing.

6. Clinical/Safety

In the ATX-101 development program, 1547 trial subjects received at least one dose of ATX-101 during the conduct of 13 clinical trials. The number of subjects treated with ATX-101 was considered adequate to conduct a safety assessment. The primary safety assessment was based on two Phase 3 vehicle-controlled trials conducted in the United States and Canada and comprised of 1019 subjects (513 subjects randomized to ATX-101 and 506 subjects randomized to placebo).

Five deaths were reported during the clinical trials; none were considered related to ATX-101. Two percent of ATX-101 subjects and three percent of placebo subjects reported at least one serious adverse event (SAE). Only a single SAE of recovered mandibular nerve injury was considered related to ATX-101. About 7% of ATX-101 subjects and 1% of placebo subjects discontinued due to adverse events; the most common reasons for treatment discontinuation were injection site pain, anesthesia and edema.

No systemic toxicities that could be attributed to ATX-101 were observed. Hypertension was observed in 3% of ATX-101 treated subjects as compared to 1% of placebo-treated subjects. Pre-syncope/syncope was observed in 1% of ATX-101 subjects and was not reported in placebo-treated subjects. These events were considered to be most likely due to the injection administration and/or associated pain.

Adverse events considered related to ATX-101 were predominantly related to local injection effects. The four most frequently reported adverse reactions (in >50% of trial subjects) were pain, hematoma, anesthesia and edema. These events were primarily reported as mild to moderate in intensity. Adverse events reported more frequently in ATX-101 subjects as compared to placebo using the proposed dose for marketing are summarized in the following table:

Table 2 Adverse Reactions in Subjects Receiving 2 mg/cm^2 Dose

	ATX-101 (N=556)		Placebo (N=551)	
P	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Injection site hematoma	389	69.84	384	69.44
Injection site pain	379	68.04	173	31.28
Injection site anesthesia	367	65.89	33	5.97
Injection site edema	327	58.71	160	28.93
Injection site swelling	187	33.57	85	15.37
Injection site erythema	148	26.57	105	18.99
Injection site induration	134	24.06	18	3.25
Injection site pruritus	75	13.46	33	5.97
Injection site paresthesia	74	13.29	23	4.16
Injection site nodule	72	12.93	16	2.89
Headache	46	8.26	26	4.7
Skin tightness	24	4.31	6	1.08
Injection site warmth	22	3.95	8	1.45
Nerve injury	22	3.95	2	0.36
Oropharyngeal pain	16	2.87	8	1.45
Hypertension	15	2.69	8	1.45
Nausea	12	2.15	3	0.54
Injection site discomfort	11	1.97	0	0
Dysphagia	10	1.8	1	0.18
Injection site hemorrhage	10	1.8	14	2.53
Pain	10	1.8	7	1.27

Source: Clinical review of NDA 206,333 by Milena Lolic, M.D.

Several adverse events of concern were identified; motor nerve injury, dysphagia and skin ulceration.

The marginal mandibular branch of the facial nerve courses outside of the submental fat region but adjacent to the external border of the potential treatment area (within a 3-cm

radius circle centered at a point approximately 2 cm lateral to and 2 cm inferior to the oral commissure). To reduce the potential for motor nerve injury, which may present as an asymmetrical smile, the applicant advised investigators not to inject ATX-101 above the inferior aspect of the mandible or within a 3-cm radius above it. Marginal mandibular nerve injuries were reported in 4% of ATX-101 subjects and in less than 1% of placebo-treated subjects. All cases of nerve injury presented as an asymmetric smile and all were reported completely recovered. The median duration of symptoms was 42 days and ranged from a few days to over 180 days.

While injury to this nerve is among the primary concerns from this proposed treatment, the clinical team, with input from Agency otolaryngologists from CDRH, concluded that labeling is adequate to mitigate this risk. Detailed use instructions are recommended for product labeling.

Dysphagia, another adverse event of interest, was reported in the pivotal Phase 3 trials in ten ATX-101 subjects and one placebo subject. Two subjects reported this event as severe, however, the median duration of symptoms for dysphagia events was short, about three days. All but one event of dysphagia were reported in follow-up as resolved. Please see Dr. Milena Lolic's review for details regarding this unresolved event.

Skin ulceration, the third adverse event of special interest, occurred in only two ATX-101 subjects and in one placebo subject. All skin ulceration events resolved without sequelae.

7. Advisory Committee Meeting

A Dermatologic and Ophthalmologic Drugs Advisory Committee meeting was convened on March 9, 2015 to discuss the safety and efficacy results for this application. Committee members were asked to comment as to whether they considered that the overall safety and efficacy data presented to them supported approval of ATX-101 for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat.

There was general discussion regarding the demonstration of safety and efficacy of the product in clinical trials. The panel was informed about the process of clinician and patient-reported endpoints development and validation for this novel indication as well as the need for an objective outcome measure as a secondary endpoint (MRI in this case).

Some concern was raised during committee discussion about potential off-label use or misuse of the product. The Agency responded that they had no data evaluating use of the product in other areas, but at this time have no indication that off-label use presents increased risk to consumers relative to the proposed indication. To use the product in an area other than the area indicated at this time is considered a practice of medicine issue.

Ultimately, the committee unanimously agreed that based on the potential risks and benefits, the available data support approval of ATX-101 for this indication.

8. Risk Management

The review team, in collaboration with review team members from the Division of Risk Management, concluded that a Risk Evaluation and Mitigation Strategy is not necessary for this product at this time. Labeling is considered adequate to inform prescribers and patients of expected adverse events and risks. The applicant intends to distribute product only to those clinicians who have completed voluntary training. Pharmacovigilance by the applicant should be adequate to monitor for the occurrence of adverse reactions, with particular focus on injuries to the marginal mandibular branch of the facial nerve.

9. Summary of Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application. The Office of Compliance made an overall "Acceptable" recommendation for the facilities involved in this NDA. The Office of Scientific Investigators (OSI) Inspections are complete and clinical data was found to be acceptable for review.

10. Conclusions and Recommendations

10.1. Regulatory Action

I concur with FDA reviewers and the Advisory Committee that ATX-101 should be approved for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat. The committee voted unanimously that benefits outweigh the risks and that deoxycholic acid 1% for injection should receive marketing approval. I concur that the treatment effect is substantial, clinically meaningful and highly statistically significant.

Adverse reactions associated with deoxycholic acid 1% for injection appear to be almost entirely related to local effects. Pain, swelling, hematoma/bruising and anesthesia were reported by most trial subjects, although the events were generally only mild to moderate in severity. The special adverse events of interest, mandibular nerve injury, dysphagia and skin ulceration occurred uncommonly and were reported as resolved in follow-up in all cases but one. None of the events were considered life-threatening or led to hospitalization or disability. I concur the current risks associated with the use of ATX-101 can be addressed in professional labeling.

10.2. Postmarketing Trials

This application triggered PREA because it is a new chemical entity. The applicant requested and was granted a full waiver for all subsets of the pediatric population because the indication is typically age-related and the product would not be utilized in pediatric patients. Thus, no PREA PMRs were established for this NDA.

A clinical trial enrolling subjects over the age of 65 is currently ongoing. Submission of the final study report for this trial is the only post-marketing requirement for this NDA.

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

/s/

KENDALL A MARCUS
04/03/2015