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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 17, 2015
From	David L. Kettl, MD, FAAP
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 206333
Supplement#	Related IND 79726 0
Applicant	Kythera Biopharmaceuticals, Inc
Date of Submission	May 13, 2014
PDUFA Goal Date	May 13, 2015
Proprietary Name / Established (USAN) names	ATX 101 (deoxycholic acid) for injection
Dosage forms / Strength	Solution for injection
Proposed Indication(s)	Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults
Recommended:	<i>Approval</i>

1. Introduction

Kythera Biopharmaceuticals, Inc., submitted an original 505 (b)(1) application for ATX 101, a synthetic deoxycholic acid injectable drug product with a proposed indication for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

The proposed product is a new molecular entity (NME), and is described as a cytolytic injectable for the aesthetic indication of improving the contour of the submental area of the neck. This original NDA was reviewed under “the Program” for NME’s as authorized in PDUFA V/FDASIA.

Deoxycholic acid (DCA) occurs naturally in the gut, and is a bile acid which emulsifies and solubilizes dietary fat to aid in nutrient absorption. As a subcutaneous injection in the submental area of the anterior neck, DCA acts as a detergent that chemically lyses and then dissolves the lipid bilayer of cell membranes.

The applicant conducted two successful, adequate and well controlled Phase 3 clinical trials in which efficacy was demonstrated from screening to 12 weeks post-treatment compared to placebo.

Safety was substantiated on the analysis of the experience of the safety data from the clinical program of 13 clinical trials in which a total of 1547 subjects received at least 1 dose of ATX-101.

There are no outstanding review issues as of the date of this review beyond conclusion of labeling negotiations with the applicant and final agreement of a post marketing commitment.

A REMS program is neither proposed by the applicant nor recommended by the Agency review team for this application. Labeling is adequate to inform prescribers and patients of the known and expected adverse reactions and clinical risks.

Following presentations by the applicant and the Agency on March 9, 2015, the members of the DODAC Advisory Committee voted 17-0 in favor of an approval action for this application.

The primary clinical review, by Dr. Milena Lolic, concluded that ATX 101 is safe and effective for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. An approval action is recommended by the entire multidisciplinary review team pending completion of final labeling negotiations with the applicant. This CDTL review concurs with that recommendation to approve this application.

2. Background

ATX-101 is a cytolytic agent developed as a subcutaneous injection intended for the reduction of small areas of localized subcutaneous fat. The active ingredient in ATX-101, deoxycholic acid (DCA), is structurally identical to endogenous deoxycholate found in the bile of humans and other mammals.

Endogenous DCA is a secondary bile and serves to solubilize dietary fat, thereby aiding the absorption of fat in the gut. DCA is either absorbed in the gut where it rejoins the enterohepatic circulation or is excreted intact in the feces.

Consistent with its natural role in solubilizing dietary lipids, deoxycholic acid has been shown to disrupt the lipid bilayer of cell membranes leading to cell death. While this cytolytic action is not specific to fat cells, direct injection into the pre-platysmal fat layer in the neck is the purported mechanism of action for this product to achieve the desired indication.

The applicant also considered a development plan for the “treatment of patients with superficial lipomas”, but this IND ^{(b) (4)} was made inactive by the applicant on December 30, 2010.

Deoxycholic acid has been available for some time in unapproved drug products such as MesoDerm Cream, and others, with claimed effects to “help dissolve fat, smooth the skin and improve skin texture, reduces fat and diminishes cellulite.” Frequently paired with other acids, such as hyaluronic acid, none have been approved for any claim and when topically applied and have dubious treatment effects.

The applicant opened their IND in November, 2007. Deoxycholic acid was evaluated in three Phase 2 studies (Studies 3, 7, and 15), two supportive Phase 3 studies conducted in Europe (Studies 16 and 17), and two pivotal placebo-controlled Phase 3 studies conducted in the U.S. and Canada (Studies 22 and 23). 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.

For aesthetic indications, the Agency typically recommends both a clinician and patient outcome assessment. Multiple collaborative discussions were held with the applicant to establish and validate clinically meaningful clinician and patient assessments of the effects of DCA on the submental area following injections. Since the applicant pursued a novel indication, no precedent endpoints were available. In addition, the applicant pursued imaging of the submental area to provide substantiation of the action of DCA injections and to provide an objective assessment of the changes in submental fat. The applicant and the Agency reached agreements on the three assessments of efficacy (clinician scale, patient scale, and objective MRI imaging) and the phase 3 trials were conducted following special protocol assessment agreements.

3. CMC/Device

ATX-101 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.

ATX 101 is supplied in a clear colorless, sterile solution for subcutaneous administration. It is supplied in 2 ml USP Type 1 glass vial, sealed with [REDACTED] ^{(b)(4)} rubber stopper and sealed with [REDACTED] ^{(b)(4)} flip-top lid. Each carton contains 4 individual 2 ml vials. Each vial contains 20 mg of deoxycholic acid in 2 ml of solution. Each vial is a single patient use vial and should not be diluted.

None of the excipients in the ATX 101 drug product are novel. All excipients are commonly used in numerous parenteral pharmaceutical products that have been previously approved.

The ATX-101 drug substance was manufactured via two different processes during the development program. Initial manufacturing produced deoxycholate (DC) purified from bovine and ovine bile by a process which yielded the sodium salt form (sodium deoxycholate, [NaDCA]). Subsequently, DC was chemically synthesized yielding free deoxycholic acid (DCA). Deoxycholate from both sources (animal-derived and synthetic) was demonstrated to be structurally identical in solution

The CMC review by Dr. Hitesh Shroff concluded that the applicant submitted sufficient information in the application, and the drug substance specification is deemed adequate to assure the identity, strength, purity, and quality of the drug substance.

The product quality microbiology review by Erika Pfeiler, Ph.D. found no deficiencies with the product or carton/container information. The product is terminally sterilized ^{(b) (4)} and there are no outstanding issues related to product quality.

No post marketing requirements or commitments are recommended, and there are no outstanding CMC issues beyond agreement on labeling.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review by Dr. Jill Merrill concludes that there are no outstanding issues for this application, and no recommended post marketing studies should be required. Labeling changes for Sections 8, 12 and 13 of product labeling are proposed to be communicated the applicant. Of special note are recommendations obtained in consultation with the Division of Pediatric and Maternal Health – Maternal Health Team (DPMH-MHT) to review and revise sections of the ATX 101 labeling to bring it into compliance with the final Pregnancy and Lactation Labeling Rule. Pertinent findings from Dr. Merrill's review are noted below.

As noted above, the ATX-101 drug substance was manufactured via two different processes during the development program. Nonclinical toxicity and toxicokinetic bridging evaluations did not identify any important differences between the original and reformulated drug products. There are no DCA-related drug substance or drug product impurities which required nonclinical qualification

The applicant proposed a pharmacologic class of “adipocytolytic”, but the submitted data more appropriately support a class of “cytolytic”.

Repeat-dose studies of biweekly subcutaneous injections of ATX 101 at 50 mg/kg for up to 6 months in rats (5% at 1 mL/kg; 13 doses) and at 25 mg/kg for up to 9 months in dogs (5% at

0.5 mL/kg; 20 doses) demonstrated an absence of systemic signs of toxicity. The primary findings in all repeat-dose studies were confined to the injection site and were associated with the pharmacological effect of cytolysis. Dermal signs were reversed or nearly reversed at the completion of the recovery periods.

Secondary pharmacology studies were conducted to investigate the mechanism by which fat (free fatty acids and triglycerides) released from lysed adipocytes following subcutaneous DCA injection are processed in rats). The results from these studies indicate that lipid released from adipocytes after DCA treatment is processed in a similar manner as dietary fat in rats.

Sodium deoxycholate has been tested in the complete ICH battery for genetic toxicology. It is not mutagenic in the Ames test, not clastogenic in the in vitro mammalian chromosomal aberration test in human lymphocytes and not genotoxic in the in vivo rat erythrocyte micronucleus assay.

Carcinogenicity studies for ATX-101 were waived based on the conclusion that the drug substance is comparable to endogenous deoxycholate. The intended clinical treatment will not result in a significant increase in the natural lifetime exposure to deoxycholate, as supported by Phase 1 studies in which plasma levels of ATX-101 returned to baseline within 24 hours.

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.

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 post-weaning.

Dr. Merrill's review concludes that "ATX-101 is approvable for the treatment of improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults from a pharmacology/toxicology perspective." There are no outstanding issues related to the nonclinical review and no recommended post marketing commitments or requirements.

As an NME, this application also received secondary and tertiary concurrence reviews recommending approval from Dr. Barbara Hill and Dr. Abigail Jacobs.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review by Dr. An-Chi Lu concluded that the application was acceptable from a Clinical Pharmacology perspective, pending agreement on recommended labeling changes.

Systemic bioavailability was assessed in Trial ATX-101-12-32, a safety and pharmacokinetic trial to characterize the profile of the two final to-be-marketed formulations (one with benzyl alcohol [BA] to be marketed in the U.S. and one without benzyl alcohol to be marketed in the EU. A total of 24 subjects with presence of sufficient submental fat were randomized in a 1:1 ratio to receive the BA-preserved formulation or the preservative-free formulation; all study drug was administered 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 dosing session.

Dr. Lu reports that at baseline, the individual values of endogenous plasma concentrations varied across subjects and time points, with a range of below the lower limit of quantification (LOQ=25.6 ng/mL) to 1280 ng/mL. The average endogenous plasma concentration (AUC0-24/24) was 227 ng/mL over the 24-hour collection period. Following single treatment administration of ATX 101, the mean deoxycholic acid concentrations increased from pre-treatment values of approximately 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 mean Day 1 plasma exposures for the U.S. formulation as measured by AUC0-24 and Cmax were approximately 1.6-fold greater (7896 ng*hr/mL vs 4854 ng*hr/mL) and 3.2-fold greater (1024 ng/mL vs 324 ng/mL), respectively, than the endogenous values at Baseline. The median Tmax was 18 minutes.

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.

Dr. Moh Jee Ng from the Interdisciplinary Review Team for QT Studies concluded in the DCRP review that no significant QTc prolongation effect of ATX-101 (100 mg and 200 mg) was detected in the Thorough QTc Trial ATX-101-11-24.

The study population was too small to allow for any conclusion to be drawn regarding the influence of race on the PK of deoxycholic acid. A population pharmacokinetic analysis by Dr. Lu did not identify a significant effect of sex on either apparent clearance or volume of distribution, and she concluded that there is no statistically significant difference between deoxycholic acid PK parameters for males and females.

There is no approvability issue related to clinical pharmacology requirements, and no post marketing commitments or requirements are recommended in their reviews.

6. Clinical Microbiology

This section is not applicable to this application.

7. Clinical/Statistical- Efficacy

The clinical review by Dr. Milena Lolic and the biostatistics review by Dr. Kathleen Fritsch conclude that there is adequate evidence to determine that deoxycholic acid 1% for injection was superior to placebo in the treatment of submental fat in two adequate and controlled studies.

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 co-primary 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. The Agency provided the applicant agreement with regard to the use of the 2-grade improvement endpoint as a primary endpoint. While there has been discussion regarding the semantics of “composite” vs. “co-primary”, according to the protocol, both primary endpoints were required to demonstrate statistical significance.

Phase 3 pivotal protocols were reviewed under special protocol assessment. The Agency did not provide agreement regarding the ‘1-grade reduction’ endpoint. The clinical and biostatistics reviews both conclude that adequate evidence of efficacy has been demonstrated.

There were two, 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 Dr. Fritsch’s efficacy summary table:

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

^a Co-primary endpoints^b Multiplicity among the secondary endpoints was handled with Holm's method

Source: Agency Biostatistics review by Dr. Kathleen Fritsch

Treatment effects were generally consistent across gender, race, age, and country subgroups in Studies 22 and 23.

Efficacy was demonstrated to be clinically meaningful, statistically significant, and adequate for labeling.

At the EOP 2 meeting held on April 20, 2011, the applicant proposed to conduct a separate Phase 3b trial in subjects older than 65 and the Division agreed. This trial is ongoing. The rationale was that this aesthetic treatment will be mostly used by a younger population, therefore trials submitted for approval enrolled subjects 18-65 years. To ensure timely submission of the ongoing geriatric trial data, the following post-marketing requirement has been agreed to by the applicant:

“Complete the treatment and evaluation of subjects ages 65-75 years enrolled in the ongoing ATX-101-13-28 trial. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration).”

Final study report submission is anticipated in the third quarter of 2016.

8. Safety

The clinical review by Dr. Milena Lolic provides extensive examination of the safety data from the clinical program of 13 clinical trials in which a total of 1547 subjects received at least 1 dose of ATX-101.

The safety evaluation consisted of reported adverse events, active assessment of adverse events of special interest (treatment area edema, bruising, erythema, dyspigmentation, induration, numbness, pain, paresthesia, pruritus dysphasia, dysphonias, nerve injury and allergic reactions) vital signs, and laboratory tests, including liver function tests to address any issues with exogenously administered DCA for effects on the liver or digestive tract.

There were five deaths reported in the development program of ATX-101 due to: cholangiocarcinoma, heroin overdose, traffic accident, myocardial infarction, and pancreatic cancer, respectively. All deaths were judged by the applicant and the clinical team to be unrelated to the drug treatment. Dr. Lolic's review notes that it is likely that the cholangiocarcinoma existed prior to treatment. The MI case report notes that the subject died at day ^{(b) (6)} after treatment, and the pancreatic cancer case was from the placebo treatment group.

No systemic toxicities of clinical importance were observed. There were no clinically meaningful changes observed in vital signs or laboratory values that could be reasonably associated with ATX-101. However, there were 3% of ATX-101 treated subjects who had adverse reaction "hypertension" (placebo rate 1%) and 1% who had "pre-syncope/syncope" (placebo rate 0%) most likely due to injection administration itself and/or associated pain. A Thorough QT/QTC study was negative.

A total of 29 subjects (2%) in the all ATX-101 groups and 28 subjects (3%) in the placebo group reported at least 1 serious adverse event (SAE) during drug development. All but one case of recovered mandibular nerve injury were considered unrelated to the treatment.

The marginal mandibular nerve injuries occurred in the active arm at a 4% rate and dysphagia at 2%, and all cases but one (dysphagia) completely resolved and without any treatment. Placebo rates were <1% for both adverse reactions. While injury to this nerve is among the primary concerns from this proposed treatment, the clinical team, with consultative advice from Agency otolaryngologists from CDRH, concludes that labeling is adequate to mitigate this risk. Detailed use instructions are recommended for product labeling.

Most subjects (>87%) experienced at least one adverse event. Approximately 7% of deoxycholic acid subjects and 1% of placebo subjects discontinued due to adverse events.

The most common adverse reactions were injection site reactions. More than half of deoxycholic acid subjects experienced injection site hematomas, pain, edema, and anesthesia. More than 10% of deoxycholic acid subjects experienced injection site swelling, erythema, induration, paresthesia, pruritus, and nodule formation.

This CDTL review concurs with the conclusion of the review team that a positive risk-benefit determination for this product has been achieved for this application. Labeling will be sufficient to inform prescribers of potential safety concerns with use of the product. Special emphasis in labeling will be to provide anatomic detail and instruction technique guidance so that potential injuries to critical structures in the neck, including the marginal mandibular nerve, can be adequately mitigated.

9. Advisory Committee Meeting

A DODAC Advisory Committee meeting was held to discuss this application on March 9, 2015. Although there were no substantive review issues identified during the multidisciplinary Agency review that might affect approvability, a public forum discussion of the application was deemed appropriate since the proposed product was a new chemical entity and the proposed indication was novel as well.

There was general discussion regarding the demonstration of safety and efficacy of the product as well as the approach to determining reliable, reproducible, and clinically meaningful endpoints that could be transcribed into labeling which adequately informed prescribers. Panel members were drawn from dermatology, plastic surgery, otolaryngology, and biostatistics specialties.

Questions presented to the committee were:

1. VOTE: Do the efficacy and safety data provided to you today support the approval of deoxycholic acid injection for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat?
 - a. If not, what additional studies/analyses are needed?
2. DISCUSSION: Do the members of the committee have any comments on the approach which was developed for evaluation of safety and efficacy for this novel indication?

The members of the panel voted 17-0 in favor of supporting the approval of the application.

There was some concern during the panel discussion with potential off label use of the product for application sites beyond the neck area, but no data was available to inform this discussion. The Agency stated that it was beyond the scope of the application and labeling to further advise prescribers, and this would be a practice of medicine issue. Labeling will contain a limitation of use statement that “The safe and effective use of ATX-101 has not been established outside the submental area and is not recommended.”

The lay press noted after the meeting that “Various panel members praised Kythera and FDA for working together to develop a pair of assessment scales, providing both the clinician’s and the patient’s evaluation of the treatment’s efficacy, as well as an objective measure that determined submental fat reduction based on MRI scans.” (Joseph Haas, “The Pink Sheet Daily”).

10. Pediatrics

This application triggered PREA due to ATX 101 being a new chemical entity.

The applicant requested a waiver for all subsets of the pediatric population (up to 17 years of age), because the indication of non-surgical reduction of submental fat are typically age-related and would not be utilized in pediatric patients. The applicant submitted literature, incidence and prevalence data, and additional rationale to justify that the condition did not occur with frequency in pediatric subjects and few would avail themselves of such a therapy.

The PeRC agreed with the Division to grant a full waiver because product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in a substantial number of pediatric patients.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

GMP inspections are complete, and there are no outstanding issues impacting approval from the Office of Compliance. The Office of Compliance has made an overall “Acceptable” recommendation for the facilities involved in this NDA.

Two clinical sites were chosen for inspection by OSI. Dr. Bhatia’s clinical site was selected for inspection because of the relatively large enrollment and the above average efficacy demonstrated in the study. (b) (6)

Dr. Roy Blay concluded that the Bhatia study site appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

A Form FDA 483 was not issued at the conclusion of the Monheit clinical study site inspection; however, the unanticipated closing 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.

The final classification of both clinical study site inspections was No Action Indicated (NAI).

Separate efficacy analysis (courtesy of Dr. Fritsch) was conducted following the exclusion of data from this site 116 (with large number of out-of-window MRI readings). The impact of protocol-deviated data on efficacy analysis was minimal. Upon consideration of the concerns related to the Monheit site, the review team concluded that these findings did not impact the safety and efficacy conclusions for the application.

There are no outstanding regulatory issues that will impact the approval of this application.

12. Labeling

The applicant initially proposed the name “Kybella”, but was found to be unacceptable due to the proposed name “Carbella” in an unrelated application in another OND review division. The second proposed trade name of “(b) (4)” had been accepted by Office of Medication Error Prevention and Risk Management. Following a complete response action for the application that proposed Carbella, the applicant withdrew the name (b) (4) and re-submitted the proposed name Kybella, which is currently under review by OMEPRM/DMEPA.

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trials for the BLA as well as DMEPA, DRISK, and OPDP consultative reviews.

The most critical aspect of labeling was to develop instructions and graphics to inform prescribers regarding the proper injection techniques. Knowledge of relevant neuroanatomy in the region is among the most important aspects to mitigate risks related to marginal mandibular nerve injury. The review team was assisted by otolaryngologists and plastic surgeons with particular expertise in this area to craft appropriate labeling to inform and decrease these risks.

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”³ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirement include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X)

will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

Although the action for this application will take place in advance of the official required date for such labeling, consultation was obtained from the Division of Pediatric and Maternal Health – Maternal Health Team (DPMH-MHT) to review and revise sections of the ATX 101 labeling to bring it into compliance with the final Pregnancy and Lactation Labeling Rule. This label will be among the first to be approved with PLLR compliance.

The MHT review noted that there are no human data on the effects of DCA exposure during pregnancy. None of the publications reviewed provided data sufficient to be included in the Pregnancy (8.1). Likewise, there are no data to confirm or refute the presence of DCA or endogenous DCA in human milk and the edits proposed for the ATX 101 Lactation (8.2) labeling focused on making it compliant with the PLLR guidelines.

DPMH recommendations were communicated to the applicant for Section 8. Final applicant concurrence is pending at this time.

Labeling is adequate to communicate necessary safety information to prescribers. Final agreement on Agency proposed labeling, including carton/container labeling, is pending as of the date of this CDTL review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The conclusion of the clinical review, and that of the review team, and concurred by this CDTL review, is that safety and efficacy of ATX 101 has been adequately demonstrated by the clinical development program for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. An approval action is recommended pending successful completion of ongoing labeling negotiations.

- Risk Benefit Assessment

Efficacy has been adequately demonstrated by the applicant in two adequate and well controlled clinical trials. The safety findings are not unexpected given the nature of this proposed injectable treatment.

The benefits of ATX 101 outweigh the risks when used as recommended in the prescribing information, and this CDTL review concurs with the review team that this application should be approved. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond final agreement of draft labeling and terminology related to the post marketing commitment.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The review team, in consultation with Agency representatives from OSE, concluded that a REMS is neither required nor recommended for this product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks. Pharmacovigilance by the applicant should be adequate to monitor for the occurrence of adverse reactions, with particular focus injuries to the marginal mandibular branch of the facial nerve.

- Recommendation for other Postmarketing Requirements and Commitments

The only post marketing requirement relates to submission of the final study report for the ongoing trial for geriatric subjects aged 65-75 years of age:

“Complete the treatment and evaluation of subjects ages 65-75 years enrolled in the ongoing ATX-101-13-28 trial. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration).”

Trial Completion:	04/30/2016
Final Report Submission:	09/30/2016

The post-marketing requirement has been agreed to by the applicant.

- Recommended Comments to Applicant

There are no comments to be conveyed to the applicant beyond agreement of final labeling and agreement on the post marketing commitment. Labeling negotiations are ongoing with the

Cross Discipline Team Leader Review

applicant as of the date of this review, but there are only minor differences to be resolved as of the date of this CDTL review.

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/s/

DAVID L KETTL

03/17/2015