CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206333Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	206,333
Priority or Standard	Standard
Submit Date	May 13, 2014
Received Date	May 13, 2014
PDUFA Goal Date	May 13, 2015
Reviewer Name	Milena Lolic, M.D.,M.S.
Review Completion Date	January 20, 2015
Established Name	ATX-101
(Proposed)Trade Name	(b) (4)
Therapeutic Class	Cytolytic
Applicant	Kythera Biopharmaceuticals, Inc.
Formulation	Injectable solution, 10 mg/mL
Dosing Regimen	Up to 6 treatments (up to 50 injections, 0.2 mL each per treatment) one month apart
Indication	Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat
Intended Population	18-65 years

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that NDA 206,333, for ATX-101 be approved for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

Two adequate and controlled phase 3 trials demonstrated the efficacy and safety of ATX-101 for adult patients 18-65 years old with moderate to severe submental fat.

The recommended dosing regimen is up to 6 treatment sessions at (b) (4)-day intervals. Each treatment session involves up to 50 injections of 1% ATX-101 solution (0.2 mL each) spaced on a 1-cm grid (2mg/cm^2). The treatments are to be administered by healthcare professional in ambulatory setting.

1.2 Risk Benefit Assessment

The risk to benefit assessment for this application is based on the clinical trial results. The clinical program consisted of 13 clinical trials/studies in which 2424 subjects participated.

The drug substance, deoxycholic acid (DCA) is a small, fully synthesized new molecular entity that is structurally identical to endogenous deoxycholic acid. The drug product, ATX-101, is injectable 1% DCA. The pathophysiologic effect of the drug involves cytolytic effect on submental fat tissue. Clinical trials conducted under 'maximal use conditions' demonstrated that following single treatment with ATX-101 there was rapid, approximately threefold increase in maximal deoxycholic acid plasma concentrations followed by return to baseline levels within 24 hours.

Two adequate, placebo controlled phase 3 pivotal trials (ATX-101-11-22 and ATX-101-11-23, (thereafter referred to as trials 22 and 23) were conducted in the United States and Canada. Subject were 87% Caucasian, 85% female, and the mean age was 49.

The composite primary efficacy endpoint, defined as the proportion of subjects with at least a 2-grade improvement from screening to 12 weeks post-treatment on both, the clinician-reported submental fat rating scale (CR-SMFRS) and the patient-reported submental fat rating scale (PR-SMFRS) was achieved by 13% of subjects in trial 22 and 18% in trial 23. For placebo treated subjects rates were <1% and 3% for respective trials ($p \leq 0.001$).

There were two agreed upon secondary endpoints: a) proportion of subjects who achieve at least 10% reduction in submental volume from baseline to 12 weeks post-treatment as assessed by

MRI, and b) change from baseline to 12 weeks post-treatment in patient-reported submental fat impact score (PR-SMFIS). The analyses of secondary endpoints supported the primary endpoint.

In addition, the applicant submitted data on a composite endpoint that 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. There was no prior agreement regarding the '1-grade reduction' following SPA review due to Agency's concerns about the accuracy of the measurements from phase 2 trials. Based on the measurements improvements and improved data quality submitted in NDA, I recommend that 1-grade improvement be included in labeling to inform prescribers (1-grade responder rate was 70% vs. (b)(4)% in trial 22 and 67% vs.(b)(4)% in trial 23).

In two pivotal phase 3 clinical trials, safety assessment of 1019 subjects (513 randomized to ATX-101 and 506 subjects randomized to placebo) extended to 24 weeks following last treatment.

The most common adverse reactions in active arms were injection site edema/swelling (87%), injection site hematoma (72%), and injection site pain (70%). The vast majority of injection site reactions was described by the investigators as mild to moderate and was considered resolved by the end of the trial.

The marginal mandibular nerve injuries in the ATX-101 treatment arm occurred at the 4% rate and dysphagia at 2%. All cases (except one of dysphagia) completely resolved without any treatment.

A total of 1547 subjects received at least 1 dose of various DCA concentrations in 13 clinical trials during development. None of the 5 deaths and 74 serious adverse events (SAE) was considered to be related to the treatment. However, there was one case of mandibular nerve injury (from European trial) that was considered serious by the investigator- the outcome was reported as recovered. The safety review of supportive trials from phase 1 and 2 was comparable to pivotal trials.

In conclusion, benefits outweigh the risks for the recommended indication.

If approved, ATX -101 could offer first drug therapy for submental fullness due to localized fat deposits. ATX-101 may be a reasonable option for patients with submental fullness who do not wish to undergo more aggressive surgical treatment (e.g., liposuction), or who want more gradual resolution of submental fat and option to stop treatments when the desirable aesthetic outcome has been achieved. The adverse events associated with the drug product are within the scope of expected for given invasive treatment and can be adequately informed by labeling. The label also provides adequate information for instructions for use.

1.3 Recommendations for Postmarket Risk Management Activities

There are no recommendations for a specific postmarketing risk management plan beyond labeling. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting, comprise an adequate risk management plan for this application.

1.4 Recommendations for Postmarket Studies/Clinical Trials

It is my recommendation that the applicant submits data from the ongoing safety trial under protocol ATX-101-13-28 reflecting ATX-101 use in population 65-75 years within an appropriate timeline for submission.

2 Introduction and Regulatory Background

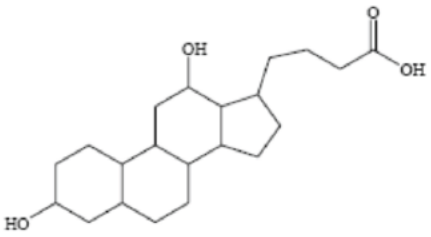
Aesthetic drug products are intended to produce change in visible physical attributes of the human body via effect on structure or function. Multiple drugs for aesthetic indications have been approved by FDA, e.g., minoxidil (1988) and finasteride (1997) for androgenetic alopecia, tretinoin (1995) and tazarotene (2000) for fine wrinkling, onabotulinum toxin (2002) for glabellar lines, bimatoprost (2008) for eyelash hypotrichosis, and polidocanol (2010) for spider veins of legs.

Submental fat (SMF), i.e., subcutaneous (SC) fat in the area below the chin, presents minimal morbidity however it may negatively affect the satisfaction and well-being of a proportion of the population (Schlessinger,2013; Rohrich,2006). Current treatment options for submental contouring include surgical resection and liposuction.

There are no approved drugs in the US for submental fat reduction.

2.1 Product Information

ATX-101 is 1% solution of deoxycholic acid (DCA). Deoxycholic acid ($C_{24}H_{39}NaO_4$) has a molecular weight of 414.6 Da. Its structural formula is:



The composition of ATX-101 is presented below:

Component	Quality Standard(s)	Percent of formula (w/v)	Amount per 2.0 mL	Function
Deoxycholic acid (DCA)	In-house	1.00%	20.00 mg	Drug substance
Sodium hydroxide	NF/PhEur	0.14%	2.86 mg	(b) (4)
Dibasic sodium phosphate	USP/PhEur	0.14%	2.84 mg	Buffer
Sodium chloride	USP/PhEur	0.44%	8.76 mg	(b) (4)
Benzyl alcohol	NF/PhEur	0.90%	18.00 mg	Preservative
Sodium hydroxide	NF/PhEur	q.s.	q.s.	pH adjustment
Hydrochloric acid	NF/PhEur	q.s.	q.s.	pH adjustment
Water for injection	USP/PhEur	to 100%	to 2.0 mL	(b) (4)

There are no novel excipients used in this product.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no approved drugs for the improvement of fullness in the submental area.

2.3 Availability of Proposed Active Ingredient in the United States

ATX-101 is a new molecular entity thus not available in the United States as an active ingredient and has not been marketed in any other country. Deoxycholic acid (CAS# 83-44-3) is included as an inactive ingredient in United States Food and Drug Administration (US FDA) approved drug products.

2.4 Important Safety Issues with Consideration to Related Drugs

There are no related drugs to ATX-101 as it belongs to a new therapeutic class of cytolytics.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant pre-submission regulatory activity for ATX-101 was notable for the following:

- Pre-IND Meeting July 3, 2006

- Guidance Meeting August 19, 2009
- End-of-Phase 2 Meeting April 20, 2011. Among others the following comments were conveyed:
    - Proposed 1-grade improvement might not be sufficient to garner an efficacy claim. The Agency did not agree that a 1 point change was a meaningful treatment benefit (from the perspective of the individual seeking SMF reduction) on the basis of the results from Study 15 where 1 grade improvement was observed in placebo treated subjects at the rate of 60% (by subjects).
    - CR-SMFRS and PR-SMFRS scales are both 5-point categorical over continuum scales where one grade improvement may be difficult to correlate clinically. For example, difference between higher end of grade 1 and lower end of grade 2 represents 1 point scale difference, but not necessarily a meaningful clinical difference. Setting the effect threshold to at least 2-grade reduction from the baseline measurement, would increase the probability that scale grade difference represents the true, meaningful difference in the treatment. This is particularly important, when the effect of the drug may not be robust, and when placebo effect is high.
    - The MRI threshold for success should be a static criterion rather than a result generated from the data within the trial itself. Sponsor was advised to propose and justify a clinically-meaningful minimum reduction from that of the corresponding baseline measurement as the threshold for the classification of a MRI responder. The threshold should be related to the success criteria based on CR-SMFRS and PR-SMFRS.
- SPA received on November 4, 2011 and the Agreement Letter sent on December 16, 2011. Among others, agreements were:
    - The primary endpoint "Composite 2-grade SMFRS response rate at Visit 9: proportion of subjects who simultaneously have at least a 2-grade improvement from baseline on the CR-SMFRS and PR-SMFRS at Visit 9"
    - The primary endpoint assessment at 12 weeks after the last treatment.
    - The secondary endpoint "MRI volume response rate at Visit 9: proportion of subjects who have at least a 10% reduction in SMF volume from baseline to Visit 9".

  Non-agreements were:
    - The second primary endpoint "Composite 1-grade SMFRS response rate at Visit 9: proportion of subjects who simultaneously have at least a one-grade improvement from baseline on the CR-SMFRS and PR-SMFRS at Visit 9". For a categorical scale imposed on a continuous variable, a two-grade change is needed to ensure clinical meaningfulness, especially in light of the impact of subject position on assessment of treatment effect and validation based on a narrow population.
    - The secondary efficacy endpoint "Improvement, from baseline to Visit 9, in the PR-SMFIS Total Scale Score," (b) (4)

(b) (4)

- Pre-NDA Meeting November 13, 2013

Comment: The content and format of this NDA is consistent with the prior agreements with the Division.

2.6 Other Relevant Background Information

Endogenous deoxycholic acid is a bile acid produced by the liver as one of several end- products of sterol metabolism. It functions as detergent to solubilize dietary lipids. In the United States pharmacological DCA has been used as a solubilizing agent in injectable formulations of amphotericin B. Deoxycholate has also been used as a detergent to solubilize phosphatidylcholine as part of a drug called Lipostabil lI (Nattermann-Aventis Pharma), which is used outside of the US for the treatment of fat emboli, dyslipidemia, alcohol-induced liver cirrhosis, and has found off-label use in the treatment of unwanted fat deposits for cosmetic purposes (Ablon 2004, Duncan 2005).

The applicant started development of ATX-101 as a nonsurgical treatment modality for lipomas (under IND (b) (4) opened in 2006) and unwanted submental fat (under IND 79,726 opened in 2007) for both, US and European markets. The lipoma development was later abandoned and IND (b) (4) was inactivated in 2010.

Throughout the clinical review, terms deoxycholic acid and ATX-101, reflect the same product and are used interchangeably.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and the compliance with local and FDA regulatory requirements. The protocol and Informed Consent Forms were reviewed by the Investigations Review Board (IRB) associated with the trial sites or by consulting central IRB. Written informed consents were obtained from subjects at the first (baseline) visit.

The Office of Scientific Investigators (OSI) was consulted to review the conduct of two pivotal clinical trials (22 and 23), and included the inspections of the site 116 (Dr. Gary Monheit from Birmingham, AL) and site 531 (Dr. Ashish Bhatia from Naperville, IL). The sites were selected

by the Division based on the financial disclosures of the investigators, and high numbers of enrolled subjects (14 and 16 subjects, respectively).

Site 116 had an issue with out-of-window MRI efficacy assessments attributed largely to the unexpected closure of the MRI facility. This issue was not reported as major protocol deviation by the applicant. A sensitivity analysis with excluded data from the site 116 (courtesy of Dr. Kathleen Fritsch, the Agency biostatistics reviewer) concluded minimal impact of that protocol deviation on the overall results.

OSI inspections of the trial sites have been completed. Per report, both investigators adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and Form FDA 483 was not issued to either site.

3.3 Financial Disclosures

In accordance with 21 CFR § 54.4(a)(3)(i)-(iv), applicant provided a list of the clinical investigators with a disclosable financial interest and/or arrangement who participated in clinical trials which support this NDA.

Table 1 Investigators with Disclosable Financial Interest

Covered Study	Role	Institution Name	Clinical Investigator Name	Address	Type of Financial Interest	Applicable Contract Period	Amount
Study 22	PI	(b) (6)			Consulting Payments	30Jun2011 to 30May2013	$46,500
Study 22 and 23	PI (Study 22); Sub-PI (Study 23)				Consulting Payments	30Jun2011 to 30Sep2013	$51,500*
Study 22	PI				Stock Options	19Oct2005 (awarded); 24Apr2013 (exercised)	$83,044
					Consulting Payments	05May2010 to 31Jan2014	$99,301
Studies 15 and 22	PI				Stock Options (1,890 @$7.80/each)	02Nov2011 (awarded; not exercised to date)	Estimated at approx. $75,000
					Consulting Payments	29Oct2010 to 20Dec2013	$54,562
Study 23	PI				Consulting Payments	31Mar2013 to 20Dec2013	$29,000

*Includes $20,000 in payments to (b) (6) This institution had two other investigators (b) (6) (b) (6) who participated in one of the abovementioned studies but did not exceed $25,000.

Source: Applicant's Table 6 from section 1.3.4

Comment: The disclosed financial interests/arrangements, did not affect the approvability of the application. See 9.4 Clinical Investigator Financial Disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

ATX-101 is formulated as a sterile, isotonic, clear, colorless, injectable, 1% solution. The product is preserved by benzyl alcohol, buffered by phosphate, and pH-adjusted to pH 8.3. All excipients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products for systemic administration.

The solution is contained in a 2 mL fill, Type I, glass vial with a rubber stopper and an (b) (4) overseal with flip-top lid. The compatibility, suitability, functionality, and safety of the in-use container closure system with the drug product have been established.

ATX-101 is supplied in a single packaging configuration consisting of four individual 2 mL vials held in a (b) (4) (b) (4) and placed in a folding paper carton box.

Stability data support the proposed expiration period of 30 months when stored at 20-25 ºC (68-77 ºF).

Microbial limits testing showed that the applicant has presented adequate information to mitigate risks outlined in the initial product quality microbiology risk assessment.

The Office of Compliance final acceptability for the manufacturing facilities has not been made at the time of this review completion.

In the Executive Summary of NDA 206,333 the CMC reviewer Hitesh Shroff Ph.D., concluded:

"The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. However, a final "Acceptable" recommendation from Office of Compliance for the manufacturing facilities has ***not*** been made."

4.2 Clinical Microbiology

There were no clinical microbiology data in this submission, as the indication does not involve clinical microbiology claims.

4.3 Preclinical Pharmacology/Toxicology

The applicant proposes "adypocytolitic" pharmacology class for ATX-101 based on the results of pre-clinical and clinical studies conducted during ATX-101 development for lipoma and submental fat reduction. However, DCA as a detergent dissolves not only intracellular fat but also any cell membrane (due to membrane's phospholipid structure) as noted in several publications (Rotunda 2004, Sculler-Petrovic 2008). Pharmacology/Toxicology review Jill Merrill, Ph.D., proposed that pharmacology class be broadened to "cytolytic" citing a publication from Thuangtong from 2010 in which the author states: "Our results suggest that adipocytes are not intrinsically more sensitive to DCA than other cells. Rather, we suggest that fat may lack enough DC (deoxycholate) binding proteins to protect it from the detergent effects of DC after intra-adipose injection."

Comment: I agree that ATX-101 exhibits cytolytic rather than adipocytolytic properties. While injection technique into adipose tissue makes the treatment more specific for adipocytes due to the site of injection, the drug itself may be damaging to other surrounding tissues and that should be reflected in the pharmacology class.

There was a change in the manufacturing process of the drug substance during the development program. Appropriate nonclinical bridging studies have been performed to bridge the animal-derived sodium salt form [sodium deoxycholate, (NaDCA)] with synthetic DCA (Study #IXB00080) and to evaluate vehicle reformulations [vehicle changes to phosphate buffered saline (PBS) with and without 0.9% benzyl alcohol (study # 20001032)]. No important differences were identified between the original and reformulated drug products.

All appropriate nonclinical studies were conducted and reviewed by Pharmacology/Toxicology review Jill Merrill, Ph.D.

Presented below is the summary of nonclinical studies:

- Repeat dose toxicology studies were conducted in rats for up to 6 months (($\leq$50 mg/kg, S.C. biweekly) and dogs for up to 9 months (($\leq$25 mg/kg S.C. weekly). Studies demonstrated injection site reactions and no systemic toxicity. The injection site reactions recovered by the end of the 1 month recovery period.
- In genetic toxicology studies DCA was negative in *in vitro* chromosome aberration test, and an *in vivo* micronucleus test. Chromosome aberrations observed at cytotoxic concentrations were deemed biologically not relevant and a result of cytotoxicity by toxicology reviewer.
- Carcinogenicity studies were waived based on the structural comparability of ATX-101 to endogenous deoxycholate.
- Reproductive toxicology studies include fertility study in rats, embryofetal development studies in rats and rabbits (up to maternally toxic doses during the period of organogenesis), and pre- and post-natal development study in rats.
    - No treatment related effects on fertility were noted in rats dosed weekly with 50 mg/kg, S.C.
    - There was no observed fetal harm in rats dosed at up to 50 mg/kg.

  - An increase in the incidence of missing intermediate lung lobes was noted in offspring of the all treated rabbits groups. The presence of maternal toxicity in all treated rabbits prevented further differentiation of this finding as well as NOAEL determination. Dr. Merrill concluded that: "…although the study design was deficient, potentially drug-related embryofetal malformations were noted in rabbits and are considered to be drug related," and recommended (b) (4)
  - No treatment related effects on pre- and post-natal development were noted in pregnant rats treated subcutaneously with up to 50 mg/kg ATX-101 three times weekly.

- Safety pharmacology studies have been conducted to evaluate the effects of ATX-101 on the cardiovascular system (hERG assay and in vivo oral dog study) and CNS (in vivo single I.V. rat study). As for CV system, DCA was classified as low-potency HERG-channel blocker and its administration did not elicit any cardiovascular effects in dogs at the single I.V. dose up to 20 mg/kg. In CNS study, at high doses (10mg/kg) two animals exhibited decrease motor activity and hyperpnea that resolved after 24 hours. The NOAEL for CNS effects was determined to be 5 mg/kg.

Pharmacology/Toxicology reviewer recommended approval for this NDA from a pharmacological/toxicological perspective without nonclinical postmarketing requirements.

Comment: I agree with Dr. Merrill that, based on nonclinical data, there are no significant safety concerns for ATX-101 at the proposed clinical dose. I also agree with her recommendation that product should be labeled as (b) (4)

4.4 Clinical Pharmacology

There were five Pharmacologic studies done with ATX-101 during development program ((b) (4) ATX-101-11-24, (b) (4), and ATX-101-12-32). Two of these studies were conducted with to-be-marketed formulation and those are: ATX-101-11-24 [(Thorough QT/QTc safety and PK trial-reviewed in section 7.4.5 Special Safety Studies/Clinical Trials], and ATX-101-12-32 that will be summarized in this section.

4.4.1 Mechanism of Action

ATX-101 is a cytolytic drug, which, when injected into tissue, dissolves cellular fat and disrupts the cell membrane causing lysis. More discussion on mechanism of action is provided in section 4.3.

4.4.2 Pharmacodynamics

In Study ATX-101-11-24 ATX-101 did not exhibit potential to prolong QT (section 7.4.5.)

4.4.3 Pharmacokinetics

In study ATX-101-12-32 (thereafter referred as study 32), a total of 24 subjects were randomized in a 1:1 ratio to receive a single 100 mg dose (2 mg/cm^2) of ATX-101 formulated either with (b) (4), US formulation) or without (b) (4) EU formulation) the preservative benzyl alcohol. Study drug was administered as 50 injections into the SMF area (0.2 mL each) spaced on a 1-cm grid. Serial blood samples were collected at pre-treatment, and at 5 minutes, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after the final injection of study drug. Subjects were enrolled under controlled dietary conditions to permit more accurate measurement. PK parameters were summarized at Baseline (Day -1) and Post-dose (Day 1) for each formulation group.

Considering only data from US formulation, the baseline mean C_{max} plasma concentration of endogenous deoxycholic acid was 324 ng/mL demonstrating high variability across subjects and nine sampling times. After single S.C. administration of ATX-101 the mean C_{max} tripled to 1024 ng/mL. ATX-101 had a rapid absorption with mean T_{max} of 0.3 hours. Mean half- life was approximately 9 hours and plasma concentrations of ATX-101 returned to baseline by 24 hours.

Summary statistics for deoxycholic acid plasma PK parameters are presented in Table 2.

Table 2 Mean Pharmacokinetic Parameters after Single Dose of ATX-101

PK Parameter	Baseline (Day -1) BLOQ = 25.6 ng/mL[a]		Postdose (Day 1) BLOQ = 25.6 ng/mL[a]		Baseline-Adjusted BLOQ = 25.6 ng/mL[a]	
	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12
AUC_{0-24}[b] (ng•hr/mL)	4854 ± 2339	6045 ± 3277	7896 ± 2269	10421 ±4676	3042 ± 1217	4376 ±3476
C_{max}[c] (ng/mL)	324 ± 182	441 ± 293	1024 ± 304	1036 ± 254	822 ± 263	784 ± 230
t_{max}[d] (hr)	12.0 (0, 24.0)	8.0 (0, 24.0)	0.3 (0.1, 1.1)	0.1 (0.1, 16.0)	NC	NC
$t_{1/2}$[e] (hr)	NC	NC	9.3 (8.4, 10.0)	8.5 (8.1, 9.0)	NC	NC

Abbreviations: ATX-101 = deoxycholic acid injection; AUC_{0-24} = area under the plasma concentration versus time curve (from time 0 to 24 hours); BA=benzyl alcohol; BLOQ = below the lower limit of quantitation; C_{max} = maximum observed plasma concentration; DCA = deoxycholic acid; N = number of subjects; NC = not calculated; PK = pharmacokinetic; SC = subcutaneous; SD = standard deviation; $t_{1/2}$ = half-life associated with terminal phase of the concentration-time profile; t_{max} = time to observed maximum concentration

[a] BLOQ = 25.6 ng/mL: values below 25.6 ng/mL set to 0 in summary statistics
[b] Presented as mean ± SD and is the area under the concentration-time curve from time zero to 24 hours
[c] Presented as mean ± SD and is the maximum observed plasma concentration
[d] Presented as median (minimum, maximum) and is the time at which C_{max} was observed
[e] Presented as mean (minimum, maximum)

Source: Applicant's Table 6 from Section 2.7.2

The applicant did not assess the PK of ATX-101 after repeated doses as no accumulation is expected with administration in monthly intervals.

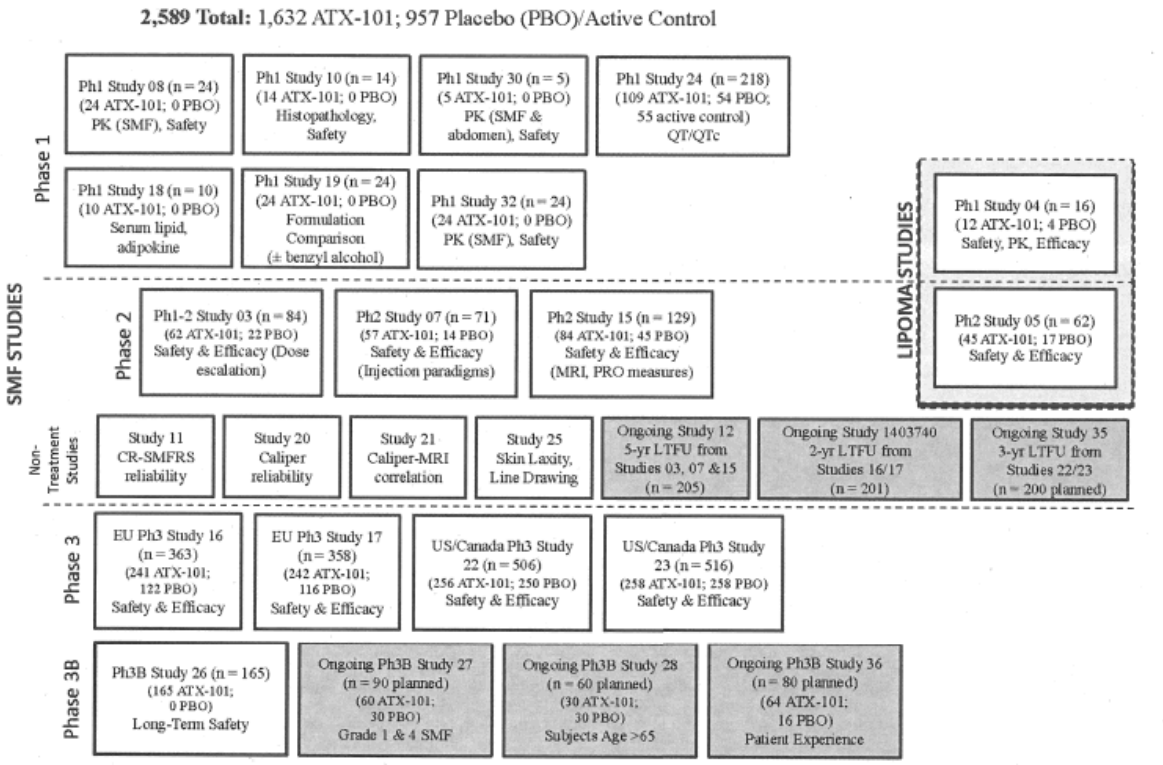
ATX-101 follows endogenous deoxycholic acid excretion path mainly through intestinal system.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

During the ATX-101 development, 25 studies were done in SMF program and 2 in lipoma program. In regard to SMF studies, seven phase 1 studies, three phase 2 studies and four phase 3 studies have been completed. One long term study has also been completed (study 26) and three other long term studies (studies 12, 35 and 1403740) were ongoing at the time of NDA submission. Additional three 3b studies were ongoing (27, 28, and 36) as well.

Figure 1 ATX-101 Clinical Program



ATX-101 = deoxycholic acid injection; CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; EU = European Union; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PBO = placebo; Ph = phase; PK = pharmacokinetic; PRO = patient-reported outcomes; SMF = submental fat; US = United States
Note: Shaded boxes represent ongoing studies

Source: Applicant's Figure 1, Section 2.5

A total of five ATX-101 formulations were used in the clinical trials. The to-be-marketed formulation in the US (b) (4) was used in the safety and PK trial (Trial 32), TQT trial (Trial 24), and two US/Canada pivotal phase 3 trials (Trials 22 and 23).

5.2 Review Strategy

A brief summary of the protocol for pivotal trials will be presented is this section.

Efficacy evaluation for ATX-101 based on intent-to-treat (ITT) population from US phase 3 trials is presented in section 6.1.4 Analysis of Primary Endpoint(s).
Relevant Phase 2 efficacy data is presented in section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Safety evaluation is presented in section7.3 Major Safety Results.

Safety evaluation was primarily based on the pivotal trials. Raw datasets were reviewed in conjunction with the applicant's clinical study reports (CSRs) and the Integrated Summary of Safety (ISS). The data from other individual selected trials as well as pooled data from all clinical trials were used as supporting evidence.

Full review of the pharmacokinetic trial was deferred to Clinical Pharmacology. The key review points from maximal use PK study are presented in section 7.2.5 Metabolic, Clearance, and Interaction Workup.

A summary of thorough TQT study is provided in the section 7.4.5 Special Safety Studies/Clinical Trials .

5.3 Discussion of Individual Studies/Clinical Trials

Identical phase 3 protocols ATX-101-11-22 (22) and ATX-101-11-23 (23) were submitted under IND 79, 726. A Special Protocol Assessment (SPA) was received on 11/4/2011, and an agreement letter was issued on 12/16/2011. The Agency and applicant reached agreement on the study design and primary endpoints.

The protocols were amended 4 times: in February 2012 (sponsor extended length of the trials from 15 months to 18 and rejected blinded assessor at the primary efficacy time point), in February 2013 (the MRI cohort enrollment was limited to the first 200 randomized subjects

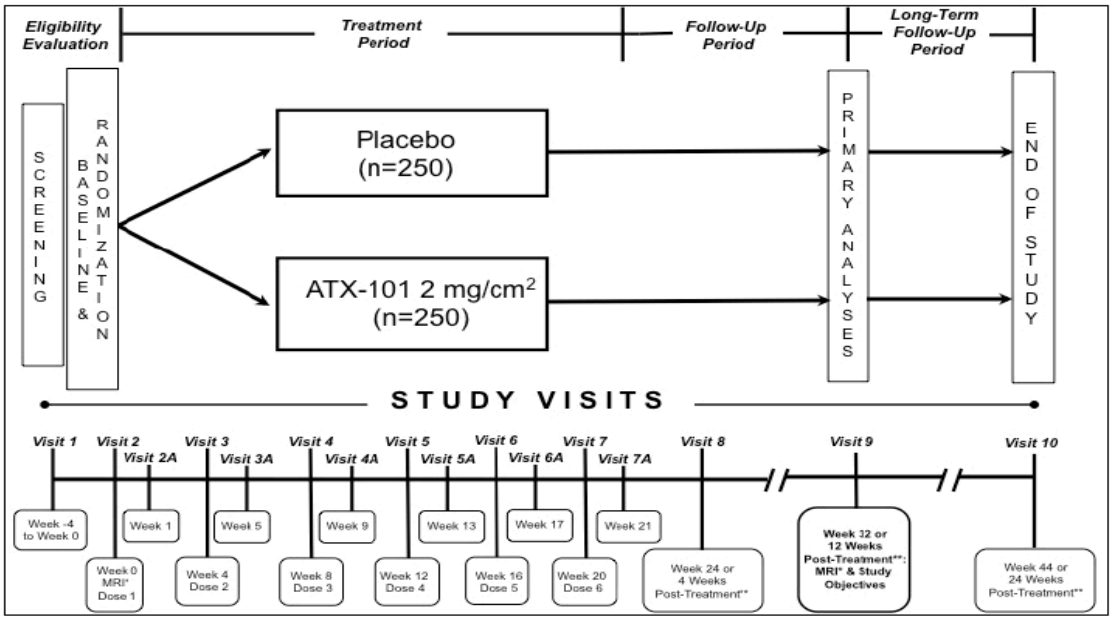
enrolled at the MRI clinical sites and changes to SAP), in May 20113 (change in the timing of the unblinded analysis), and in June 2014 (clarification and consistency of endpoints summarized at each post-baseline visit).

Trials were conducted from February 2012 to August 2013 at 70 sites in USA and Canada.

Trial design(s)

The design of the trials was identical: randomized, placebo controlled, double blind, two-arm parallel trial of approximately 44 weeks duration. Treatment period was for up to 24 weeks and primary efficacy assessment was 12 weeks post last treatment as presented in Figure 2 below:

Figure 2 Phase 3 Trial Design



MRI = magnetic resonance imaging
*Determination of MRI evaluability is required before randomization and again in association with Visit 9.
** Posttreatment, relative to the subject's last treatment session, irrespective of when that occurs.
Analyses were made after the last subject completed Visit 9. Sample sizes shown for each treatment group are based on planned, not actual, enrollment.

Source: Applicant's Figure 4, Section 5.3.5.3

Major inclusion criteria:

- Submental fat graded by the investigator as 2 or 3 using the CR-SMFRS and graded by the subject as 2 or 3 using the PR-SMFRS as determined on Visit 1 (within 28 days before randomization).
- Dissatisfaction with the submental area expressed by the subject as a rating of 0, 1, or 2 using the SSRS as determined on Visit 1 (within 28 days before randomization).

- Males and nonpregnant, nonlactating females 18 to 65 years of age, inclusive, on the day of randomization (Visit 2). Females of childbearing potential had a negative human chorionic gonadotropin (hCG) test result within 28 days before randomization and agreed to practice adequate contraception, in the judgment of the investigator, during the course of the study. Females of childbearing potential who were not sexually active were not required to practice contraception.
- History of stable body weight, in the judgment of the investigator, for at least 6 months before randomization.

Major exclusion criteria:

- History of any intervention to treat SMF (e.g., liposuction, surgery, or lipolytic agents).
- History of trauma associated with the chin or neck areas that in the judgment of the investigator may affect evaluation of safety or efficacy of treatment.
- A grade of 4 on the Submental Skin Laxity Grade (SMSLG) or other anatomical feature (e.g., predominant subplatysmal fat, loose skin in the neck or chin area, prominent platysmal bands), as assessed within 28 days before randomization, for which reduction in SMF may, in the judgment of the investigator, result in an aesthetically unacceptable outcome.
- Evidence of any cause of enlargement in the submental area (e.g., thyroid enlargement, cervical adenopathy) other than localized SMF.
- Body mass index (BMI) of > 40.0 kg/m2 as determined on Visit 1.
- History or current symptoms of dysphagia.
- A result on coagulation tests (prothrombin time, partial thromboplastin time) obtained within 28 days before randomization that indicates the presence of any clinically significant bleeding disorder (subjects being treated with antiplatelet therapy, anticoagulants and acetylsalicylic acid could be enrolled after 7-day washout period).
- Any medical condition (e.g., respiratory, cardiovascular, hepatic, neurological disease, or thyroid dysfunction) that would interfere with assessment of safety or efficacy or compromise the subject's ability to undergo study procedures or give informed consent.

Restrictions

- Subjects were required to maintain their existing dietary and exercise practices, refrain from starting any weight reduction program during the study, and forego any treatment or behavior that could affect the assessments of the submental area.

Treatment

The study drug was formulated as an injectable solution containing either deoxycholic acid at concentration of 10 mg/mL (1.0%) in preserved phosphate-buffered saline (PBS) with 0.9% (w/v) benzyl alcohol (lot #: PD11231 and PD12006) or placebo (PBS with 0.9% benzyl

alcohol (lot #: PD11232 and PD12007). Both ATX-101 and placebo formulations were clear liquid, and were packaged identically. Treatment arms/regimens were:

- ATX-101 1%: up to 50 injections, 0.2 mL each spaced on a 1-cm grid (2 mg/cm^2), in up to a maximum of 6 treatment sessions, or

- Placebo: up to 50 injections, 0.2 mL each, spaced on a 1-cm grid, in up to a maximum of 6 treatment sessions

At each treatment session, the investigator determined the number and locations of injections based on inspection and palpation of the area. Topical or local anesthesia (e.g., topical or injectable lidocaine preparations without epinephrine, ice) was permitted based on the investigator's judgment. Treatment was delivered via 30-gauge, 0.5-inch needle attached to a 1-mL syringe inserted transcutaneously directly into the submental fat tissue. Spacing of the injections was determined using a 1.0-cm grid. There was provision that upon needle withdrawal, the area could be gently massaged, pressure applied to each injection site as necessary to minimize bleeding; and an adhesive dressing could be applied.

Figure 3 Phase 3 Trial Schedule

	Eligibility Evaluation		Study Week													
	Screen	Baseline[a]	Treatment Period										Follow-up[b]			
Tests and Observations	Day -28 to -1	Week 0	1	4	5	8	9	12	13	16	17	20	21	24	32	44
Visit:	1	2	2A	3	3A	4	4A	5	5A	6	6A	7	7A	8	9	10
Informed Consent	X															
Medical History	X															
Physical Examination	X[c]														X	X
Vital Signs/Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests[d]	X			X		X		X		X		X		X	X	X
CR-SMFRS	X			X		X		X		X		X		X	X	X
PR-SMFRS	X			X		X		X		X		X		X	X	X
MRI[e]	X														X	
SMSLG	X									X				X	X	X
SSRS	X														X	X
Caliper Measurements		X												X	X	X
PR-SMFIS		X												X	X	X
Self-Ratings of Attractiveness		X													X	X
Subject Line-Drawing Assessment[f]	X			X		X		X		X		X		X	X	X
Standardized Photography[g]	X														X	X
Subject Global Questions															X	
Randomization		X														
Treatment Session		1		2		3		4		5		6				
Treatment Area Evaluation[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Final Visit																X

CR-SMFRS = Clinician-Reported Submental Fat Rating Scale; PR-SMFRS = Patient-Reported Submental Fat Rating Scale; MRI = magnetic resonance imaging; SMSLG = Submental Skin Laxity Grade; SSRS = Subject Self-Rating Scale; PR-SMFIS = Patient-Reported Submental Fat Impact Scale.

[a] All tests and observations (except treatment session, treatment area evaluation, concomitant medications, and adverse events) at the baseline visit were completed before randomization.

[b] Any subject who did not complete 6 treatment sessions was to undergo all tests and procedures outlined for Visit 8, 28 days (± 5 days) after receiving his or her last treatment session. Procedures outlined for Visits 9 and 10 were conducted 12 and 24 weeks (± 1 week), respectively, after the subject's last treatment session.

[c] Screening physical included documentation of Fitzpatrick Skin Type, height measurement, and body mass index determination.

[d] Subjects returning for Visit 2 must have had the screening laboratory test performed within 28 days before the visit. If the screening laboratory tests were performed more than 28 days before Visit 2, laboratory tests were redone and the Visit 2 date rescheduled. Coagulation and human chorionic gonadotropin (hCG) tests were done at screening (Visit 1) only.

[e] At selected centers, baseline MRI (performed during screening period) was conducted after subject qualifies on all screening criteria (approximately 200 subjects). Posttreatment period MRIs were completed 12 weeks (± 1 week) after the subject's last treatment session. Instructions regarding acquisition and interpretation of MRIs are contained in Appendix 16.1.13.
[f] Each subject was given 10 line drawings (2 representatives for each of the 5 SMF scores). Subjects were asked to select the drawing that best represented their profile at the present time. Subject line drawing assessment procedures are described in the Protocol (Appendix 16.1.1).
[g] Standardized photography, for documentation purposes only, was performed at any time during the screening period but should have been done after eligibility was determined (based on nonlaboratory screening evaluation) but before the first dose of study drug. Appendix 16.2.9 includes photography procedure details.
[h] At each visit the treatment area was evaluated for clinical tests and observations, adverse events, to determine the area to be injected (on visits when study drug was administered), or for treatment effects depending on the protocol requirements at each visit.
[i] Documentation of preexisting medical conditions and concurrent medications.

Source: Applicant's Original protocol Section 16.1.1.1 pg.11

Efficacy

Primary end-points:

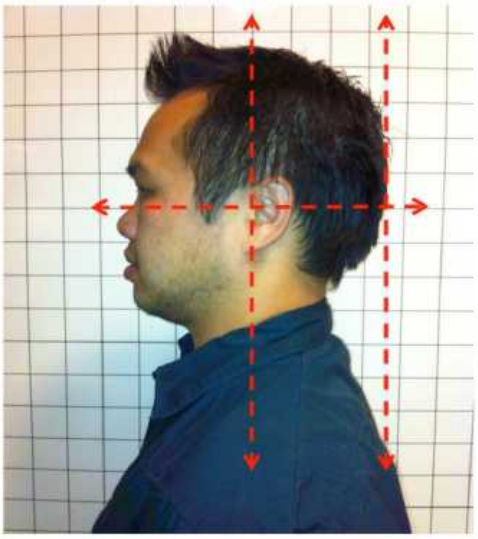
- Composite 2-grade SMFRS response rate at Visit 9: proportion of subjects who simultaneously have at least a 2-grade improvement from baseline on the CR-SMFRS and PR-SMFRS at Visit 9
- Composite 1-grade SMFRS response rate at Visit 9: proportion of subjects who simultaneously have at least a 1-grade improvement from baseline on the Clinician-Reported Submental Fat Rating Scale **(**CR-SMFRS) and Patient-Reported Submental Fat Rating Scale (PR-SMFRS) at Visit 9

Table 3 Clinician-Reported Submental Fat Rating Scale **(**CR-SMFRS)

Score	Submental Fat Description
0	Absent Submental Convexity: No localized submental fat evident.
1	Mild Submental Convexity: Minimal, localized submental fat.
2	Moderate Submental Convexity: Prominent, localized submental fat.
3	Severe Submental Convexity: Marked, localized submental fat.
4	Extreme Submental Convexity.

The CR-SMFRS score was based on the investigator's clinical evaluation of the subject, including palpation of the chin and neck area; anterior, oblique, and profile views of the chin and neck; as well as observation of pronation, supination, and lateral movement of the head. Each investigational center was provided with the CR-SMFRS book containing representative photographs for each score. The score was determined using the definitions in the rating scale and representative photographs associated with each score. To maintain a consistent posture from which the scores were made, the final determination of the score was made while the subject's head was in the Frankfort plane posture. Each site had a 2-inch by 2-inch grid poster that was placed on the wall, with the horizontal lines parallel to the floor, in the area where the assessments were conducted. Subject's positioning for CR-SMFRS is presented below:

Figure 4 Subject's Positioning for CR-SMFRS Assessment



Source: Applicant's photography from Original protocol Section 16.1.1.1 pg.64

The PR-SMFRS score was based on the subject's own evaluation using the scoring system presented below:

Table 4 Patient-Reported Submental Fat Rating Scale (PR-SMFRS)

*Please look in the mirror at **the area under your chin** to help you answer the following question: How much fat do you have under your chin right now?*	
Mark ☒ in 1 box below	
☐	No chin fat at all
☐	A slight amount of chin fat
☐	A moderate amount of chin fat
☐	A large amount of chin fat
☐	A very large amount of chin fat

Secondary endpoints:

- MRI volume response rate at Visit 9: proportion of subjects who have at least a 10% reduction in SMF volume from baseline to Visit 9 (MRI's were evaluated in approximately 200 subjects at selected centers).

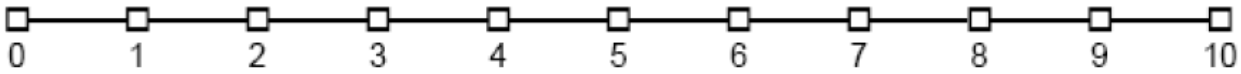
  MRI of the chin/neck area was performed similarly to standard, non-contrast, high field (1.5 Tesla) clinical MR examination. Instructions for imaging included reproducible subject positioning, anatomical coverage, and image parameter settings. All images were subject to centralized independent and blinded review of image data.

- Improvement, from baseline to Visit 9, in the Patient-Reported Submental Fat Impact Scale (PR-SMFIS) overall score. The scale that was developed for this assessment is presented below:

Table 9 Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

Please look in the mirror at the area under your chin to help you answer the following questions:
How happy are you with the appearance of your chin fat?
How bothered are you by the appearance of your chin fat?
How self-conscious are you about the appearance of your chin fat?
How embarrassed are you about the appearance of your chin fat?
How much older do you look because of your chin fat?
How much overweight do you look because of your chin fat?

The answers were recorded on 11-point horizontal scale going from Not at all (0) to Extremely (10)



Other endpoints

- Improvement in other measures of SMF including: measurements of thickness of SMF using MRI and calipers, Submental Skin Laxity Grade, and Subject Global Questions

- Changes in CR-SMFRS, PR-SMFRS, PR-SMFIS, and other measures at alternate time points during the study

Statistical analysis plan

Data analysis was performed on the following populations:

- Intent-to –treat (ITT) population

All subjects who were randomized.

- Safety population (SP)

All subjects who were randomized, and received at least one confirmed dose of investigational product.

- Intent-to –treat (ITT-MRI) population

All randomized subjects in the MRI cohort.

The treatment group differences for the primary efficacy endpoint were compared using the Cochran-Mantel- Haenszel (CMH) test stratified by analysis center. Multiplicity for the two secondary endpoints was handled using Holm's method.

Efficacy analyses were performed for the ITT population following the imputations for missing data. Three sensitivity analyses were planned: 1) assuming that all subjects having missing data had received ATX-101; subjects who were treated with ATX-101 and had complete data will be used to generate the imputed values, 2) assuming that all subjects having missing data had received placebo; subjects who were treated with placebo and had complete data will be used to generate the imputed values, and 3) LOCF.

The trial would be successful if both primary null hypotheses were rejected in favor of the two-tailed alternative at the 0.05 level of significance and the response rates were higher for the ATX-101 treatment group than the placebo group.

Safety assessment

- incidence of all adverse events
- adverse events of special interest (including, but not limited to evaluation of injection site edema, bruising, erythema, dyspigmentation , induration, numbness, pain, paresthesia, pruritus and further on dysphasia, dysphonia, nerve injury and allergic reactions). These events were spontaneously reported or may have been solicited by investigators
- changes from baseline in clinical laboratory test results (CMP, lipid profile, CBC, UA, coagulation, thyroid tests)
- changes from baseline in vital signs and weight measurements

- MRI results were evaluated in a priori-defined subset of subjects to determine whether any undiagnosed abnormality was evident.

6 Review of Efficacy

Efficacy Summary

To demonstrate the efficacy of ATX-101, the applicant submitted data from two randomized, double-blind, placebo-controlled phase 3 trials (22 and 23). The population consisted of all randomized subjects 18-65 years who had baseline submental fullness graded moderate to severe 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 (PR-SMRFS).

The treatment was applied in up to 6 sessions, approximately one month apart. Single treatment session consisted of up to 50 injections, 0.2 mL each, administered transcutaneously directly into submental fat using a 1 cm spacer grid for injection distribution.

The primary endpoint defined success as at least a 2-grade improvement from screening on both the CR-SMFRS and the PR-SMFRS assessed at 12 weeks post-treatment. The protocols also defined a co-primary endpoint as at least a 1-grade improvement from screening to 12 weeks post-treatment on both the CR-SMFRS and the PR-SMFRS.

Two secondary endpoints a) MRI responder defined as at least 10% reduction in submental fat volume and b) change from baseline in patient-reported submental fat impact score (PR-SMFIS), were assessed at the same time point (12 weeks post-treatment).

Success at the primary endpoint was achieved by 13% of subjects treated with ATX-101 in trial 22 and by 17% in trial 23. For vehicle-treated subjects rates were < 1% and 3% for respective trials ($p<0.001$).

As per SPA letter and based on the results from Study 15, the analysis of the second co-primary proposed endpoint (at least a 1-grade improvement on both the CR-SMFRS and the PR-SMFRS) was not an agreed-upon endpoint. However, in the NDA, the applicant submitted completed PRO dossier that included important measurement improvements. As a result, increased consistency in efficacy results was observed and therefore, the addition of 1 point improvement in conjunction with 2 point improvement is justified in labeling.

At least a 1-grade improvement from screening to 12 weeks post-treatment on both, the CR-SMFRS and the PR-SMFRS was demonstrated in 70% subjects treated with ATX-101 v. 17% in trial 22 and in 66% v. 22% subject in trial 23 ($p<0.001$).

Statistical superiority of the two pre-specified secondary endpoints was achieved in both trials.

In summary, this reviewer concludes that efficacy of ATX-101 was demonstrated in improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults when injected for up to 6 treatment sessions.

6.1 Indication

The applicant proposes that ATX-101, receive the following indication: improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. Final agreement on labeling is pending at the time of closure of this review.

6.1.1 Methods

The primary population for the efficacy analysis of pivotal trials 22 and 23 was the intent to treat (ITT) population and included all randomized subjects with dispensed study drug (1022). MRI-ITT population consists of ITT subset of subjects who underwent MRI imaging (449).

Table 5 Analysis sets

	ATX-101		**Placebo**	
	Trial 22	Trial 23	Trial 22	Trial 23
	N		N	
Randomized	256	258	250	258
Safety population set	256	257**	249*	257***
ITT analysis set	256	258	250	258
MRI-ITT set	113	113	111	112

*Subject 131-014-randomized to placebo, did not receive any treatment
**Subject 524-025-randomized to ATX-101, did not receive any treatment
***Subject 537-006-randomized to placebo, did not receive any treatment
Source: Reviewer's analysis

6.1.2 Demographics

There were no notable differences in demographic characteristics between either arms or trials (Table 6) or in baseline condition characteristics (Table 7).

Table 6 Baseline Demographics-ITT population

	Trial 22		Trial 23	
	ATX-101	**Placebo**	**ATX-101**	**Placebo**
ITT Subjects	256	250	258	258
Age (mean)	50	49	48	48
Female	213 (83%)	208 (83%)	221 (86%)	224 (87%)
Male	43 (17%)	42(17%)	37 (14%)	34 (13%)
Race				
White	218 (85%)	227 (91%)	222 (86%)	222 (86%)
Black	24 (9%)	13 (5%)	24 (9%)	21 (8%)
Asian	7 (3%)	5 (2%)	4 (2%)	5 (2%)
Other	5 (2%)	3 (1%)	5 (2%)	8 (3%)

Source: Reviewer analysis

Table 7 Baseline Characteristics in Respect to SMF

	Trial 22		Trial 23	
	ATX-101 N=256	Placebo N=250	ATX-101 N=258	Placebo N=258
CR-SMFRS				
Moderate	130 (51%)	130 (52%)	127 (49%)	132 (51%)
Severe	126 (49%)	120 (48%)	131 (51%)	126 (48%)
PR-SMFRS				
Moderate	164 (64%)	157 (63%)	163 (63%)	161 (62%)
Large	92 (36%)	92 (37%)	95 (37%)	97 (38%)
Very large	--	1 (<1%)	--	--
SMF Volume (MRI)	N=113	N=110	N=113	N=113
Mean (SD)	7012.2 (1523.8)	7047.1 (1529.5)	7186.6 (1763.6)	7042.8 (1769.4)

Source: Agency Statistical review

Most of the subjects underwent total of 6 treatments, followed by 1 treatment as presented in Table 8:

Table 8 Number of Treatments Completed

Number of treatments	Trial 22		Trial 23	
	ATX-101 N=256	Placebo N=250	ATX-101 N=258	Placebo N=258
6	164 (64%)	213 (85%)	140 (54%)	199 (77%)
5	21 (8%)	7 (3%)	19 (7%)	12 (5%)
4	17 (7%)	6 (2%)	31 (12%)	15 (6%)
3	11(4%)	8 (3%)	22 (9%)	8 (3%)
2	14 (5%)	11 (4%)	15 (6%)	10 (4%)
1	29 (11%)	4 (2%)	30 (12%)	13 (5%)
0	0	1 (<1%)	1 (<1%)	1 (<1%)

Source: Agency Statistical review

Considering only the subjects who received six ATX-101 treatments, the average number of injections per treatment declined from 32 at session 1 to 22 at session 6.

6.1.3 Subject Disposition

Higher proportions of subjects on ATX-101 discontinued the trials before the efficacy timepoint than those on placebo (10% vs. 6% and 16% vs. 11% for the two studies). The most common reasons for discontinuation were "withdrawal of consent due to subject convenience" and "lost to follow-up." There remained adequate numbers of subjects who completed the planned treatments to demonstrate efficacy despite the dropouts summarized in the Table 9 below:

Table 9 Disposition of Subjects-ITT population

	Trial 22		Trial 23	
	ATX-101	Placebo	ATX-101	Placebo
Subjects randomized	256	250	258	258
Not dispensed treatment	0	1	1	1
Subjects completing 12-week post-treatment visit (primary efficacy timepoint)	230 (90%)	234 (94%)	218 (84%)	230 (89%)
Reason for trial discontinuation prior to the 12-week post-treatment visit				
Withdrawal of consent due to convenience	18 (7%)	7 (3%)	15 (6%)	14 (5%)
Administrative decision	0	2(1%)	0	0
Non-compliance	1(<1%)	0	1(<1%)	0

	Trial 22		Trial 23	
	ATX-101	Placebo	ATX-101	Placebo
Subjects randomized	256	250	258	258
Adverse event	2 (1%)	2 (1%)	6 (2%)	3 (1%)
Lost to Follow-up	5 (2%)	5 (2%)	16 (6%)	11 (4%)
Other	0	0	2 (1%)	0
Reason for treatment discontinuation				
Insufficient SMF	33 (13%)	5 (2%)	44 (17%)	12 (5%)
Subject satisfaction with SMF reduction	9 (4%)	2 (1%)	12 (5%)	1 (<1%)
Withdrawal of consent for further treatments due to discomfort with procedure	4 (2%)	0	11 (4%)	2 (1%)
Withdrawal of consent for further treatments due to subject convenience	14 (5%)	6 (2%)	13 (5%)	16 (6%)
Adverse event	19 (7%)	3 (1%)	17 (7%)	3 (1%)
Administrative decision	5 (2%)	4 (2%)	9 (3%)	3 (1%)
Lost to Follow-up	5 (2%)	5 (2%)	12 (5%)	5 (2%)
Other	3 (1%)	12 (5%)	1 (<1%)	16 (6%)

Source: Agency Statistical review

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints were:

- Composite 2-grade response rate: proportion of subjects who simultaneously have at least a 2-grade improvement from baseline on the CR-SMFRS and PR-SMFRS at 12 weeks after the last treatment
- Composite 1-grade response rate: proportion of subjects who simultaneously have at least a 1-grade improvement from baseline on the CR-SMFRS and PR-SMFRS at 12 weeks after the last treatment

Efficacy of ATX-101versus placebo was demonstrated in both trials ($p \leq 0.001$).

Table 10 Primary Endpoint Analysis

	Trial 22		Trial 23	
	ATX- 101 N=256	Placebo N=250	ATX-101 N=258	Placebo N=258
2-grades improvement CR-SMFRS / PR-SMFRS*	34.3/256 (13.4%)	0.1/250 (<0.1%)	48.0/258 (18.6%)	7.7/258 (3.0%)
1-grade improvement CR-SMFRS / PR-SMFRS*	179.3/256 (70.0%)	46.6/250 (18.6%)	171.6/258 (66.5%)	57.3/258 (22.2%)

* Co-primary endpoints
Source: statistical review

Comment: The efficacy discussion will focus on 1 grade improvement that was not part of SPA agreement.

Although there are still some reservations about overall SMF rating using scales not tested across all grades, most of the concerns that existed prior to NDA submission have been adequately addressed:

1. *Applicant incorporated Agency's advice about standardized subject's positioning for clinician assessment minimalizing potential inter- investigators' differences in SMF assessment due to posture and positioning of the subjects.*
2. *To help with the self-assessment, subjects were given a guide tool in the form of standardized line drawings representing each grade.*

Additional reasons for reconsideration of 1 grade improvement as a co-primary endpoint are:

1. *In her consult, Agency SEALD reviewer Sarrit Kovacs, PhD commented that, as documented in the completed PRO dossier, scales were adequate to discern 1 point grade difference:*

   > *"The applicant provided anchor-based and distribution-based analyses derived from the phase trials to support the use of a 1-grade composite SMFRS responder definition as clinically meaningful. The applicant's argument for and evidence supporting the inclusion of a 1-grade improvement in labeling appears adequate.*

2. *Further reassurance is provided in totality and reproducibility of success results across supportive trials and two secondary endpoints (one being a biomarker capturing 10% reduction difference).*

It is my recommendation that one point grade improvement be accepted as valid efficacy endpoint and be included in labeling. However, it may be considered a valid endpoint only in conjunction with 2 grade improvement data for the purpose of labeling and advertising. The rationale comes from the clause in in the protocol, were both co-primary endpoints (starting

with 2 grade improvement) were required to demonstrate statistical significance for trial to be a success.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoint (s)

- MRI volume response rate: proportion of subjects at the selected centers who have at least a 10% reduction in SMF volume
- Improvement in the Patient-Reported Submental Fat Impact Scale (PR-SMFIS) overall score

Table 11 Secondary Endpoint Analysis

	Study 22		Study 23	
	ATX-101 N=256	Placebo N=250	ATX-101 N=258	Placebo N=258
>10% reduction in MRI volume	52/113 46%	6/111 5%	46/113 41%	6/112 5%
Change from baseline in the sum score PR-SMFIS [mean (SD)]	-3.6	-1.1	-3.4	-1.5

Source: Agency Statistical review

The applicant reported that the baseline MRIs of 59 subjects who did not return for the post-treatment MRI were not originally read. In the supplementary report those results were read and Agency statistical reviewer Kathleen Fritsch, Ph.D. conducted sensitivity analysis using the updated database treating missing subjects as failure. The MRI responder endpoint remained statistically significant under Holm's method in both analyses.

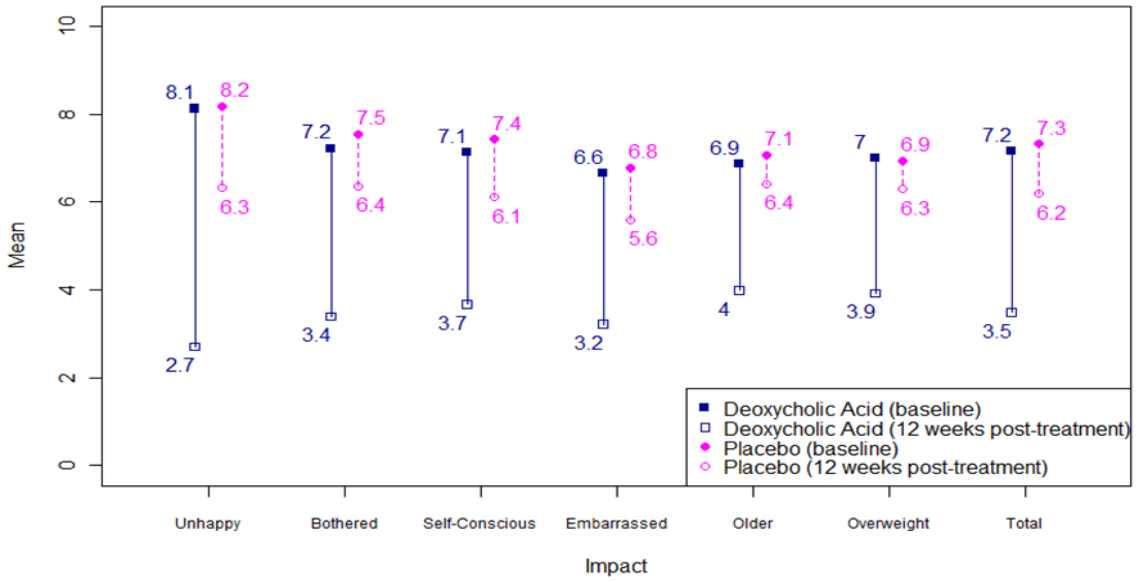
Separate efficacy analysis (courtesy of Dr. Fritsch) was conducted following the exclusion of data from the site 116 (with large number of out-of-window MRI readings):

	Trial 22	
≥ 10% reduction in volume	Deoxycholic acid N=113	Placebo N=111
Full database	52/113 (46.0%)	6/111 (5.3%)
Excluding Monheit Center (#116)	49/109 (45.0%)	6/106 (5.5%)
Monheit Center (#116)	3/4 (75.0%)	0/5 (0%)

The impact of protocol-deviated data on efficacy analysis was minimal.

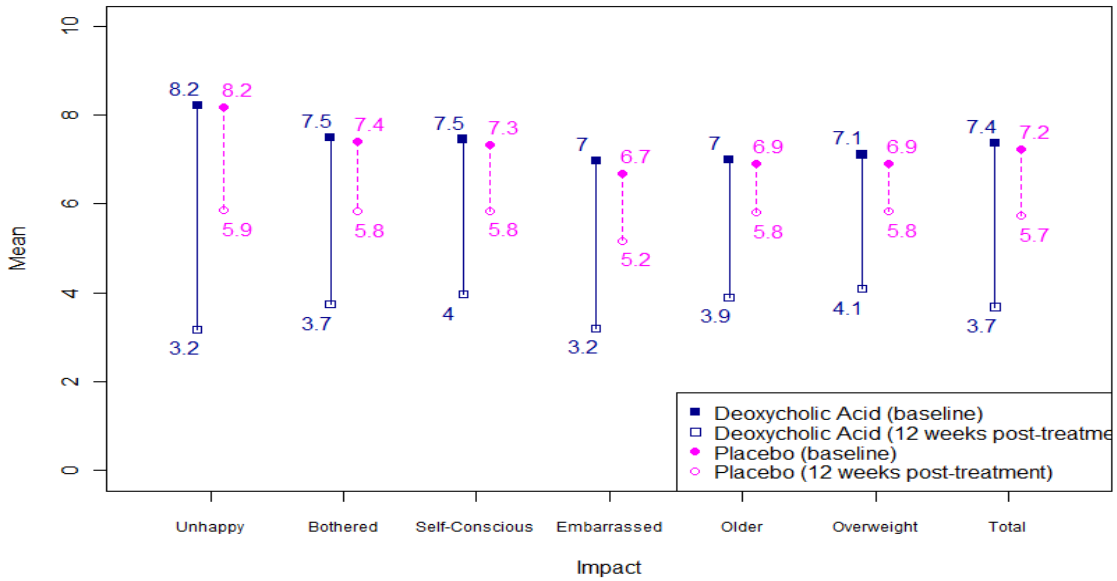
The other secondary endpoint was change from baseline in the patient-reported submental fat impact score (PR-SMFIS). The scores on each element were averaged to get the total score followed by the mean change ANCOVA analysis. Results are presented in Figures 5 and 6.

Figure 5 Baseline and 12 Weeks Post-Treatment Means on the PR-SMFIS (Trial 22)



Source: Agency Statistical review

Figure 6 Baseline and 12 Weeks Post-Treatment Means on the PR-SMFIS (Trial 23)



Source: Agency Statistical review

Comment: The PR-SMFIS scale was deemed adequate to support an efficacy claim per SEALD consult dated 1/9/2015. More specifically (electronically copied from the review by Sarrit Kovacs, PhD):

> *"The PR-SMFIS, which has been included as a secondary endpoint in phase 3 studies was developed in alignment with the PRO Guidance and the instrument's measurement properties are adequate. There is some concern that certain individual items in the PRSMFIS (e.g., "how much older do you look because of your chin fat" and "how much overweight do you look because of your chin fat") may be misleading if taken out of context. The drug is specifically for the treatment of fullness associated with submental fat in adults,* (b) (4) *. However, the total PR-SMFIS score does not appear to be misleading given that all six items' change scores from baseline showed improvement with a similar magnitude of change. We conclude that the PR-SMFIS total score is appropriate for inclusion in labeling as an assessment of impact of treatment on how patients feel about their chin fat appearance.* (b) (4) *."*

The mean change in PR-SMFIS for both trials was statistically significant.

In conclusion, both secondary endpoints are supportive of primary endpoints ($p<0.001$). The proposed language for this section of the labeling is:

The proportion of ATX-101-treated subjects who had at least a 10% reduction in SMF volume using MRI was greater than for the proportion of placebo-treated subjects. (b) (4) *and self-perceived visual attributes showed greater improvement in the ATX-101 group than in the placebo group.*

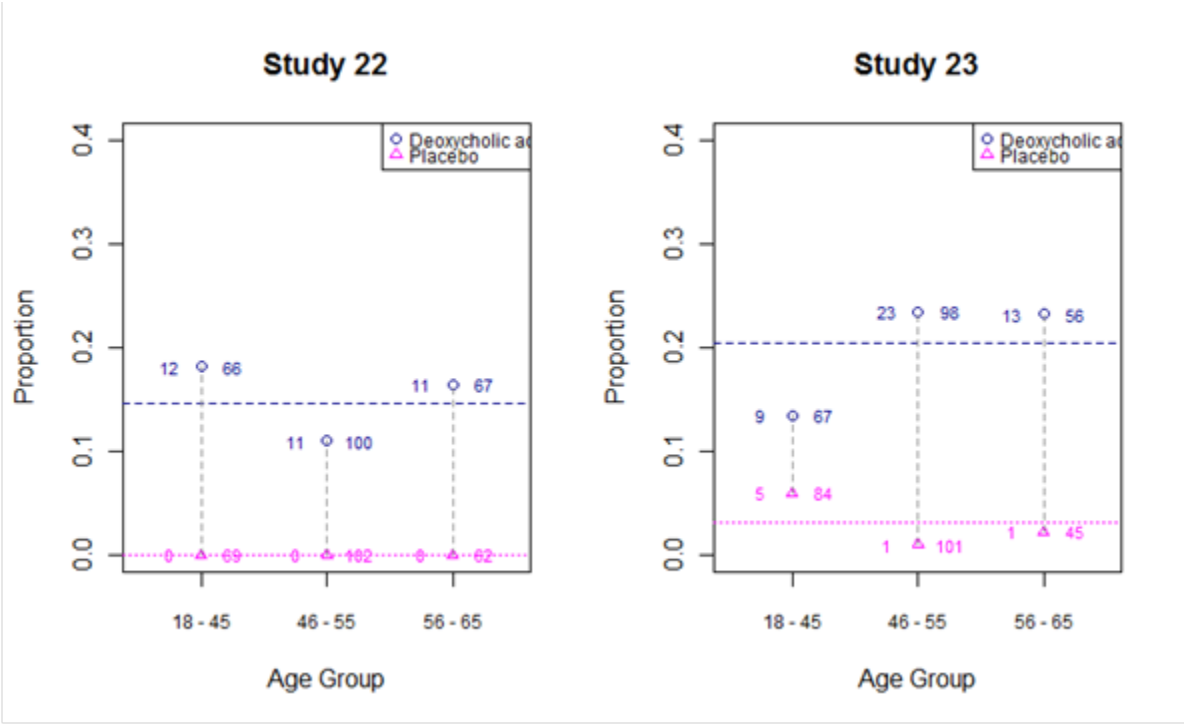
6.1.6 Other Endpoints

No other endpoints were analyzed given that the protocol did not include plans to adjust for the Type I error.

6.1.7 Subpopulations

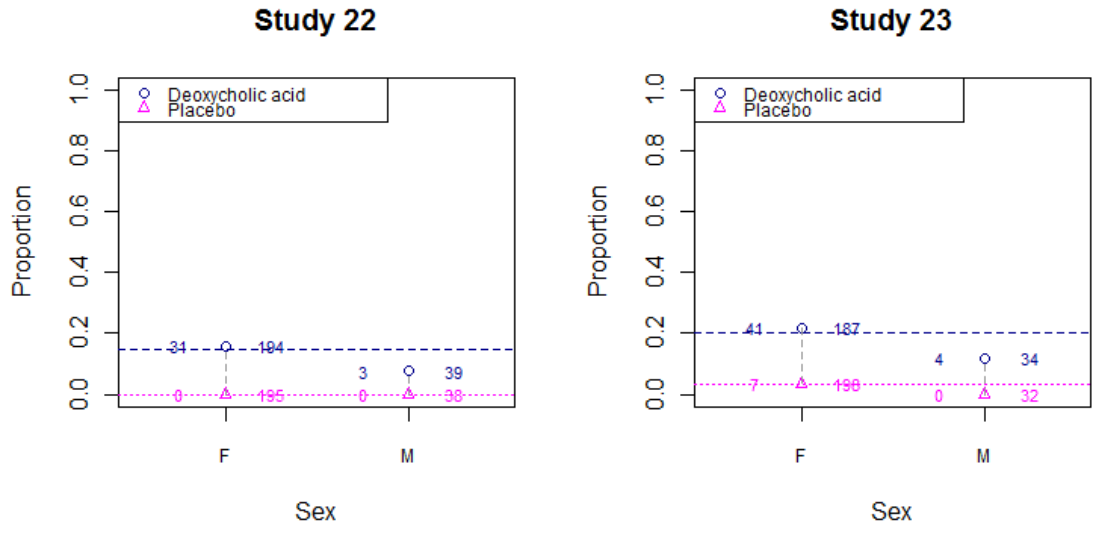
Results were generally consistent across subgroup analyses of gender, age, and race (see Figures 7-9).

Figure 7 At Least 2 Grades Composite Reduction by Age



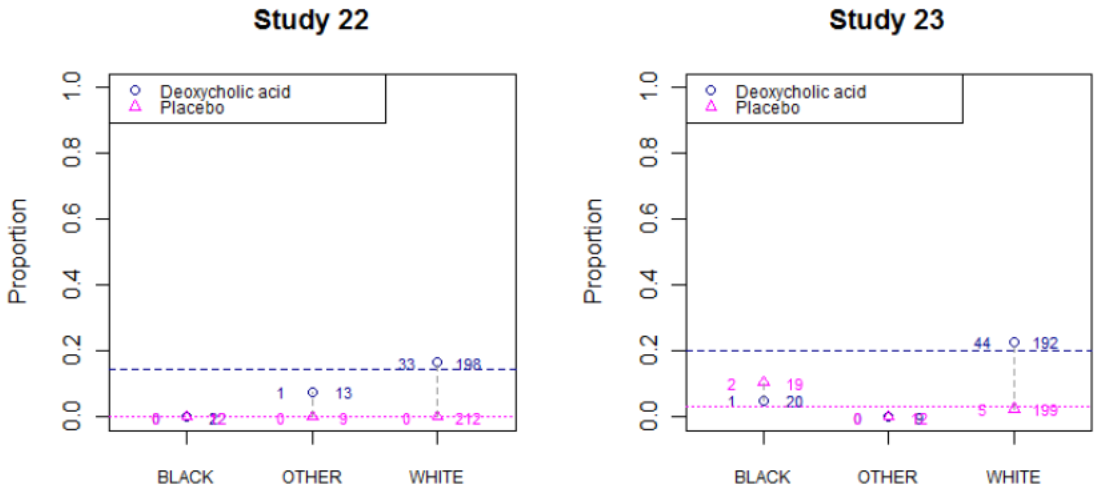
Source: Agency Statistical review

Figure 8 At Least 2 Grades Composite Reduction by Gender



Source: Agency Statistical review

Figure 9 At Least 2 Grades Composite Reduction by Race



Source: Agency Statistical review

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Clinically relevant dosing information originated from three phase 2 trial (trials 3, 7, and 15) where deoxycholic acid was evaluated in concentrations from 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.

Table 12 Phase 2 Trials Relevant to Dosing Recommendation

Trial number	Trial 3 (N=85)	Trial 7 (N=57)	Trial15 (N=129)
Doses	0.5%, 1%, 2%, placebo	0.1%, placebo	0.5%, 1%, placebo
Injection Pattern	up to 24 injections of 0.2 mL each	-up to 48 injections of 0.2 mL each on a 0.7 cm grid -up to 24 injections of 0.2 mL each on a 1 cm grid -up to 24 injections of 0.4 mL each on a 1 cm grid	up to 50 injections of 0.2 mL each on a 1 cm grid
Treatment regimen	up to 4 treatments every 4 weeks	up to 4 treatments every 4 weeks	up to 6 treatments every 4 weeks
Treatment	0.5% : 21	-48 inj/0.2 mL/0.7 cm:	0.5%: 41

arms and sample size	1%: 20 2%: 22 Placebo: 22	0.1% -18; placebo - 3 -24 inj/0.2 mL/1 cm: 0.1% - 12; placebo - 3 -24 inj/0.4 mL/ 1 cm: 0.1% - 18; placebo - 3	1%: 43 Placebo: 45

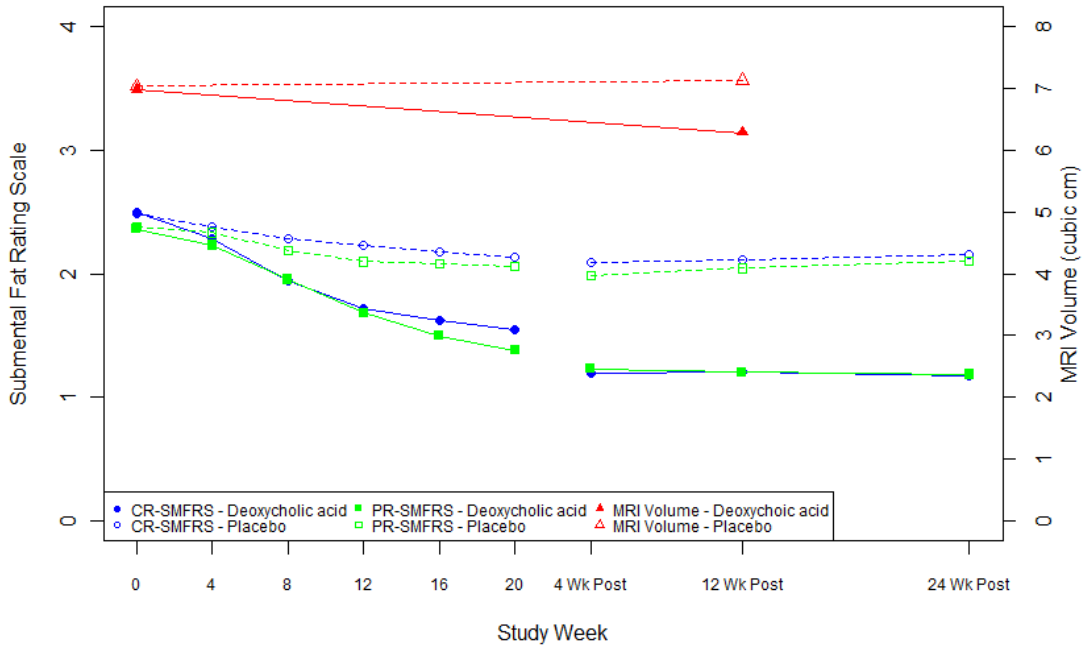
Source: Adopted from Agency Statistical review

Comment: Higher concentration (2% in trial 3), higher volume per injection (0.4 mL), or reduced spacing (0.7 cm) in trial 7 did not provide additional efficacy over 1% given as 0.2 mL per injection on 1 cm grid as judged by not fully developed endpoints. That finding coupled with safety evaluation led to appropriate dosing selection.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

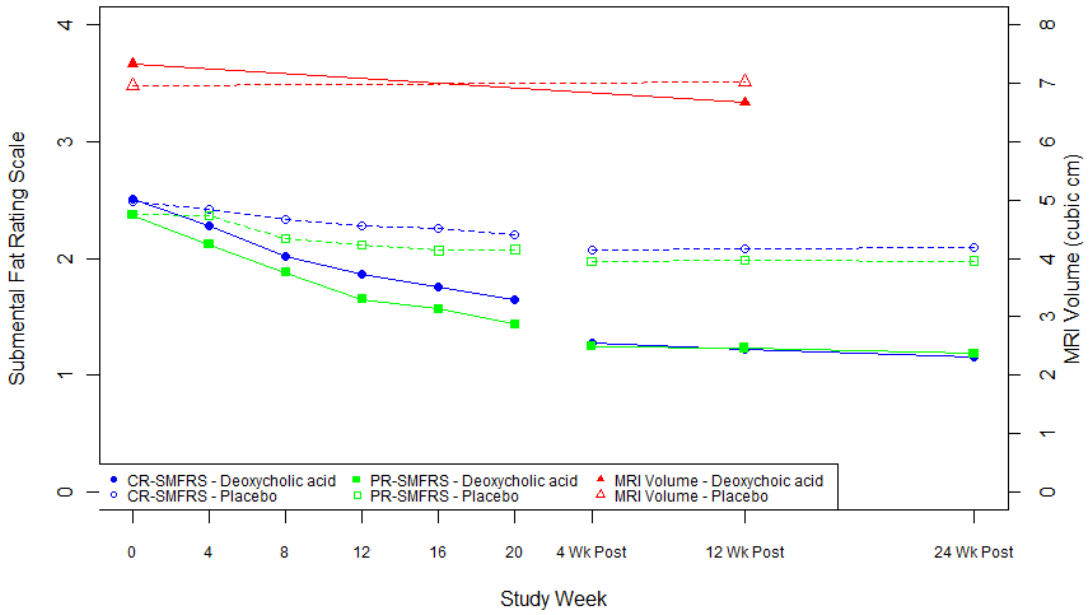
The primary and secondary endpoints were analyzed 12 weeks post last treatment. In agreement with Division recommendation, non-treatment follow-up was continued for additional 12 weeks in blinded fashion to provide for assessment of persistence of efficacy. The results of efficacy over time are presented in Figure 10 and 11 for each individual trial.

Figure 10 Mean CR-SMFRS, PR-SMFRS, and MRI Volume over Time (Trial 22)



Source: Agency Statistical review

Figure 11 Mean CR-SMFRS, PR-SMFRS, and MRI Volume over Time (Trial 23)



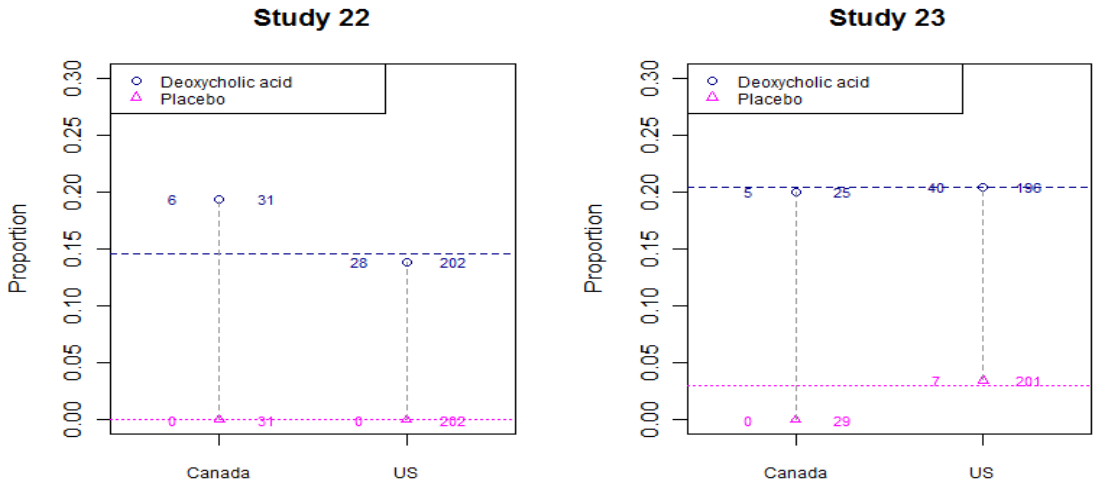
Source:Agency Statistical review

Comment: The achieved improvement remained relatively constant through 24 weeks post-treatment.

6.1.10 Additional Efficacy Issues/Analyses

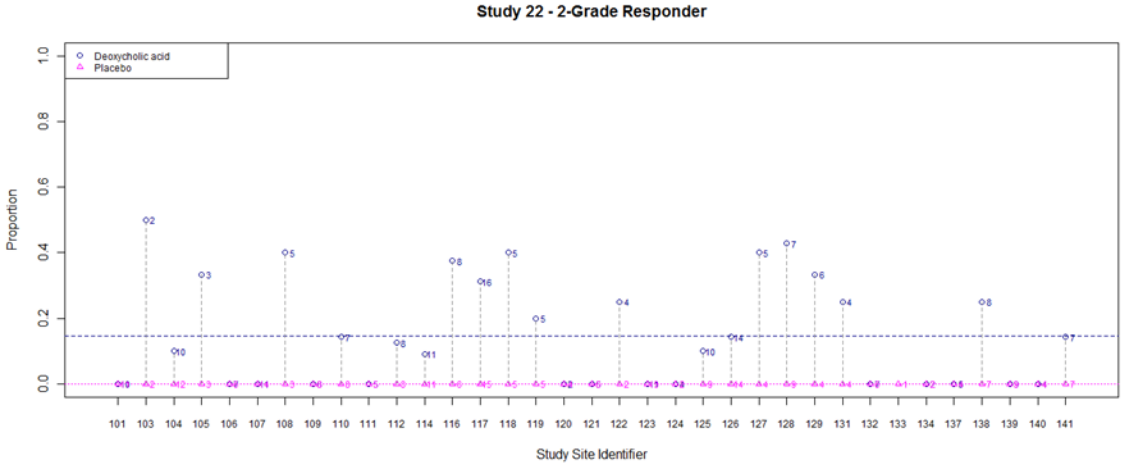
Most of the subjects were from US sites. Efficacy rates expressed as "at least 2 grade composite reduction" did not differ significantly by study site country and by site are presented in Figures 12-14.

Figure 12 At Least 2 Grades Composite Reduction by Country



Source: Agerncy Statistical review

Figure 13 At Least 2 Grades Composite Reduction by Site (Trial 22)



Source:Agency Statistical review

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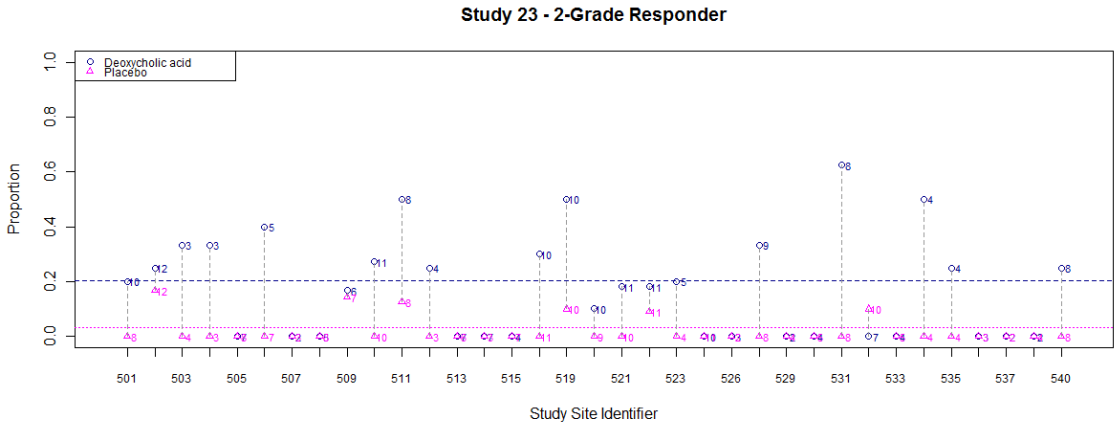
Figure 14 At Least 2 Grades Composite Reduction by Site (Trail 23)



Source: Agency Statistical review

Comment: No clinically relevant efficacy difference is notable in comparison of sites.

7 Review of Safety

Safety Summary

The clinical program used for safety assessment consists of 13 clinical trials in which a total of 1547 subjects received at least 1 dose of ATX-101.

There were five deaths reported in the development of ATX-101 due to: cholangiocarcinoma, heroin overdose, traffic accident, myocardial infarction, and pancreatic cancer, respectively. All deaths were judged by the applicant and this reviewer to be unrelated to the drug treatment.

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

Safety assessment was based primarily on two adequate phase 3 vehicle-controlled trials conducted in the United States and Canada and comprised of 1019 subjects (513 randomized to ATX-101 and 506 subjects randomized to placebo).

The safety assessments from phase 1 and phase 2 clinical trials demonstrated results that were similar to those from phase 3 trials.

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, dysphonia, nerve injury and allergic reactions) vital signs, and laboratory tests, including liver function tests.

The number of subjects and exposure to the drug were adequate to assess safety issues and define language appropriate for labeling.

The drop-out rates from the safety population was about 14% for active and 11% was placebo arm.

The most common adverse reactions in the active arm were injection site edema/swelling (87%), injection site hematoma (72%), and injection site pain (70%). Vast majority of injection site reactions were reported by the applicant as "mild to moderate" in intensity. For the most part, application site reactions resolved without specific treatment.

The marginal mandibular nerve injuries occurred in 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.

No systemic toxicities of clinical importance have been identified. 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.

7.1 Methods

The safety population includes all subjects in SMF studies who received at least 1 dose of study drug (ATX-101, placebo, or active control).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety analysis population comprised 2424 subjects (1547 ATX-101; 877 placebo) for the all SMF trials, 2019 subjects (1196 ATX-101; 823 PBO) for the randomized, controlled trials, and 1019 subjects (513 ATX-101; 506 PBO) for the US pivotal trials.

Table 13 Studies Used to Evaluate Safety

STUDY	Randomized (N=2739)	Safety population (N=2424)
ATX-101-06-03	85	84
ATX-101-07-07	73	71
[redacted]		(b) (4)
ATX-101-09-15	129	129
ATX-101-10-16	463	362
ATX-101-10-17	472	354
ATX-101-10-19	24	24
ATX-101-11-22	506	505
ATX-101-11-23	516	514
ATX-101-11-24	163	163
ATX-101-11-26	255	165
[redacted]		(b) (4)
ATX-101-12-32	24	24

Source: Reviewer's analysis

Comment: The number of exposed subject is adequate to conduct safety analysis.

In regard to Phase 3 trials (ATX-101-22 and ATX-101-23) that had 1019 subjects in safety population, reviewer's and applicant's per arm distribution slightly differs due to 2 subjects who received both, active and placebo treatments as follows:

- *Subject ATX-101-11-22-124-009 -randomized to placebo , received 1 dose of ATX-101 and 5 doses of placebo*
- *Subject ATX-101-11-23-533-006-randomized to placebo, received 1 dose of ATX-101 and 3 doses of placebo*

Applicant included these subjects in active arm (therefore ATX-101 arm had 515 subjects and placebo arm 504 subjects), however, it is my preference to count them according to the randomization, therefore, safety population for phase 3 trials presented in this review comprise 513 subject in ATX-101 arm and 506 in placebo arm.

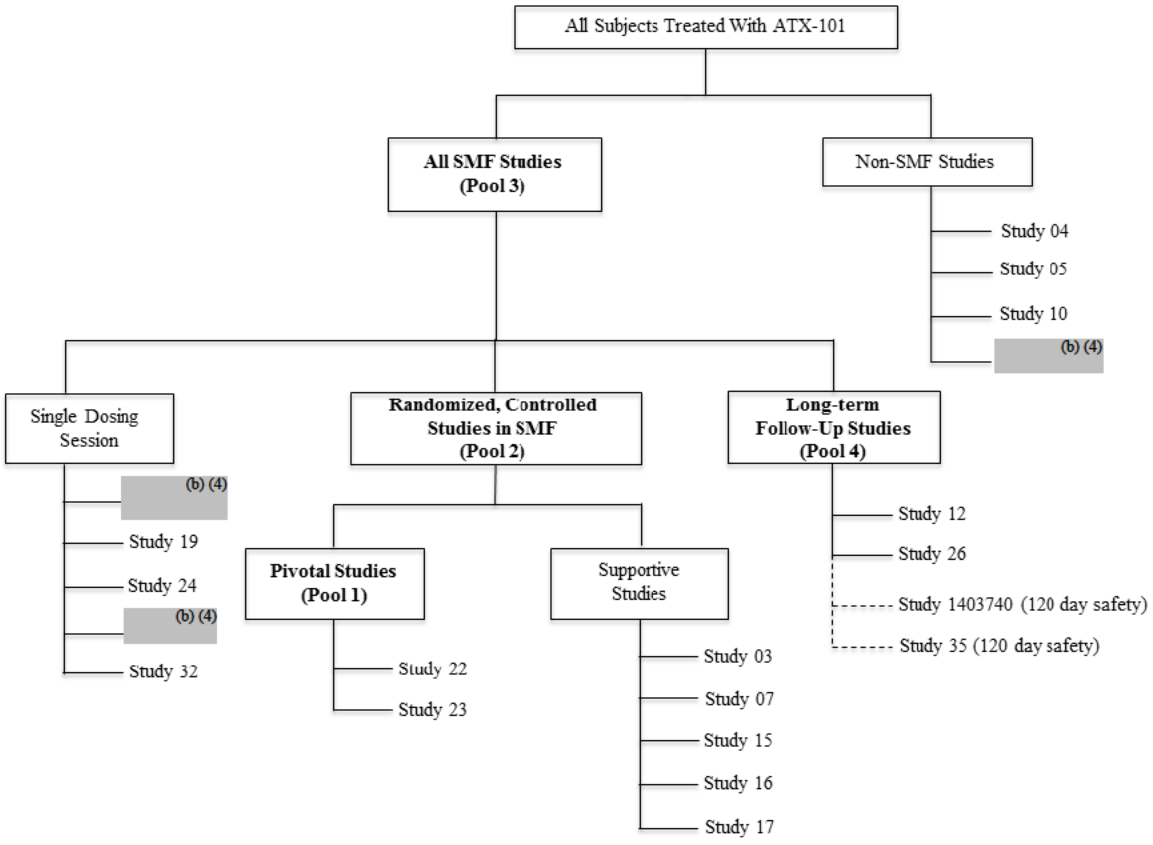
7.1.2 Categorization of Adverse Events

The coding of adverse events using MedDRA classification Version 14.1 terminology appeared adequate and allowed for accurate estimation of adverse event risks.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of the data was provided by the applicant. However, safety population pooled data was incorrectly flagged representing randomized rather than safety populations, thus adjustment was done by the reviewer.

Figure 15 Data Polling Schematic



ATX-101 = deoxycholic acid injection; SMF = submental fat
The 4 non-SMF studies (Studies 04, 05, 10, and (b) (4) are not part of any analysis pooling group but are included in the figure for completeness. For Study 1403740, only tables, figures, and listings are included in the New Drug Application; data from Study 1403740 will be pooled with the All SMF Studies and the Long-term Follow-up Studies in the 120-day safety update. Interim data from Study 35 will be pooled with the All SMF Studies and the Long-term Follow-up Studies in the 120-day safety update.
Source: Applicant's Figure 1 Section 2.7.4

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The number of individuals exposed to ATX-101 exceeds 1500. The majority of the subjects (1246) were dosed at or above the recommended dose (expressed as area-adjusted dose) and for the most part they received 4-6 treatments. One long term trial has been completed.

7.2.2 Explorations for Dose Response

Pooled data from all SMF trials

Applicant has conducted adequate dose exploration studies to describe safety of ATX-101. Due to wide variety of ATX-101 concentrations and dosing paradigms explored during ATX-101 development, and to allow for easier dosing comparisons, all safety data will be presented using area-adjusted dosing.

The break down for ATX-101 dosed subjects is: 301 subjects were dosed with 1 mg/cm^2, 1048 with 2 mg/cm^2 (intended marketing administration), 135 with 4 mg/cm^2 and 63 with 8 mg/cm^2. All placebo arms are grouped together (877 subjects). The proportion of subjects with reported AEs (cut off >2% for active) in each dosing group is presented in Table 14.

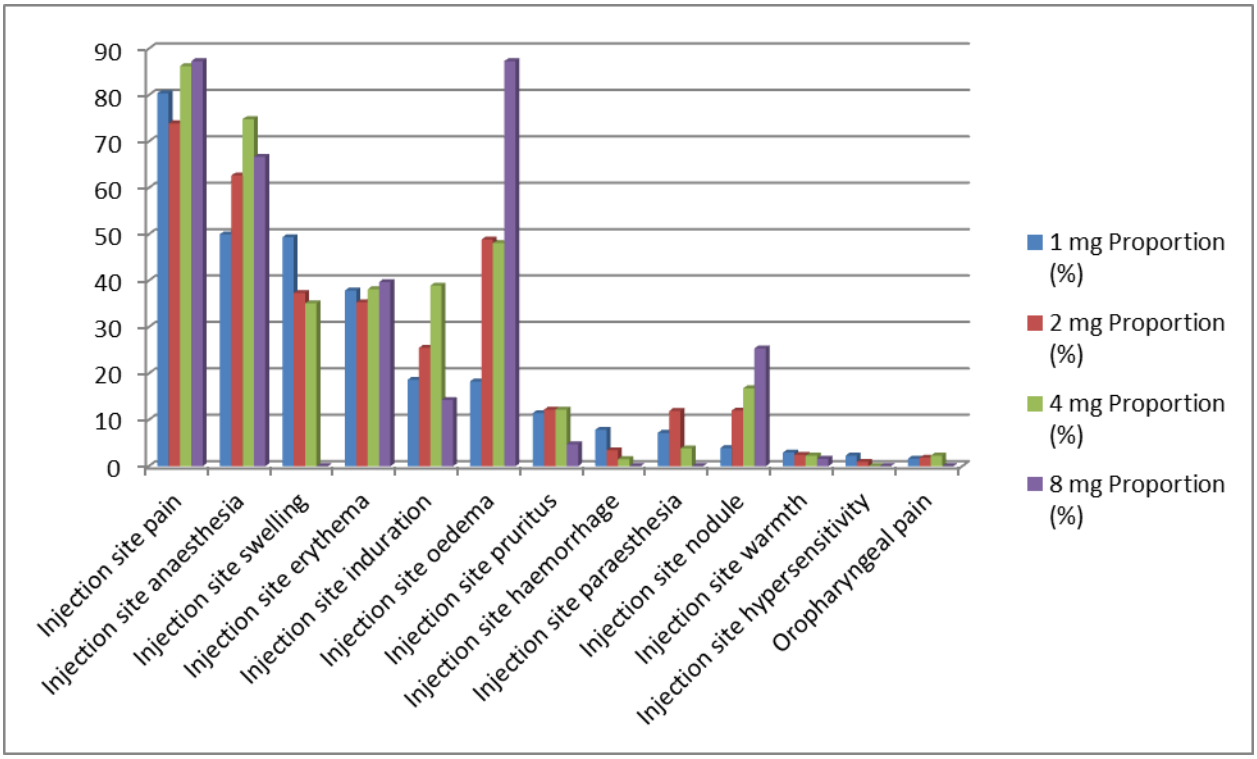
Table 14 Safety Dose Exploration for all SMF Trials

	1 mg	*2 mg*	*4 mg*	*8 mg*	*Placebo*
PT	*Proportion (%)*	*Proportion (%)*	*Proportion (%)*	*Proportion (%)*	*Proportion (%)*
Injection site pain	80.39	73.9	86.26	87.3	31.18
Injection site haematoma	55.88	65.05	51.15	36.51	58.5
Injection site anaesthesia	50	62.67	74.81	66.67	5.78
Injection site swelling	49.35	37.33	35.11	0	17.23
Injection site erythema	37.91	35.33	38.17	39.68	19.27
Injection site induration	18.63	25.52	38.93	14.29	3.29
Injection site oedema	18.3	48.86	48.09	87.3	22.34
Injection site pruritus	11.44	12.19	12.21	4.76	4.08
Headache	9.8	8.76	15.27	9.52	7.03
Nasopharyngitis	8.17	5.81	3.05	0	6.8
Injection site haemorrhage	7.84	3.43	1.53	0	3.63
Injection site paraesthesia	7.19	11.9	3.82	0	2.83
Injection site nodule	3.92	12	16.79	25.4	2.27
Back pain	2.94	1.24	0	0	1.7
Injection site warmth	2.94	2.48	2.29	1.59	1.25
Diarrhoea	2.61	1.81	0.76	0	1.13
Bronchitis	2.29	1.43	0	0	1.7
Injection site hypersensitivity	2.29	0.95	0	0	0.23
Abdominal pain	1.96	0.57	0	0	0.57
Nausea	1.96	2.29	3.05	0	0.45
Fatigue	1.63	0.95	0.76	0	0.68
Migraine	1.63	0.76	0.76	0	1.02
Oropharyngeal pain	1.63	1.81	2.29	0	1.36
Upper respiratory tract infection	1.63	2.1	0	0	3.74

Source: Reviewer's analysis

Same distribution data are presented in graphic form for ease of the comparison:

Figure 16 Safety Dose Exploration



Source: Reviewer's analysis

Comment: For the most part, higher proportion of subjects in higher dosing groups (4 and 8 mg) experienced AEs, particularly those that are associated with the treatment area. Therefore, from the safety perspective 2 mg/cm ^{2} dosing was appropriately selected.

Out of 1048 subjects dosed with ATX-101 at 2 mg/cm^2, 165 subjects were dosed in open-label design study and 51 in single-dose studies. All the others participated in randomized controlled trials and those are explored further below.

Pooled data from all randomized controlled trials (RCT)

In all RCT (trials 3,7,15,16,17,22 and 23) 832 subjects were dosed at 2mg/cm^2 v. 823 dosed with placebo. It should be noted that there are some important dosing differences among trials:

a) number of injection differs: up to 24 per session for trials 3 and 7 and up to 50 for the other trials
b) number of treatments differs: for trials 3,7,16 and 17 it was up to 4, and for 15, 22 and 23 up to 6 treatments.

Table 15 Adverse Reactions in RCT with ATX-101 Dosed at 2 mg/cm^2

	ATX-101 2 mg/cm2 (N = 832)			Placebo (N = 823)		
PT	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Injection site pain	1937	612	73.56	606	265	32.2
Injection site hematoma	1275	539	64.78	1363	508	61.73
Injection site anesthesia	825	518	62.26	77	47	5.71
Injection site edema	1124	367	44.11	455	180	21.87
Injection site swelling	921	332	39.9	379	152	18.47
Injection site erythema	589	253	30.41	393	164	19.93
Injection site induration	391	206	24.76	49	29	3.52
Injection site nodule	122	94	11.3	26	17	2.07
Injection site pruritus	127	91	10.94	55	36	4.37
Injection site paresthesia	119	90	10.82	30	25	3.04
Headache	89	68	8.17	96	58	7.05
Injection site hemorrhage	74	36	4.33	77	32	3.89
Injection site warmth	43	24	2.88	18	11	1.34
Skin tightness	36	24	2.88	6	6	0.73
Nerve injury	25	22	2.64	2	2	0.24
Hypertension	20	19	2.28	8	8	0.97
Nausea	20	18	2.16	3	3	0.36
Oropharyngeal pain	19	17	2.04	16	12	1.46
Injection site discomfort	16	13	1.56	1	1	0.12
Injection site discoloration	14	12	1.44	2	2	0.24
Dysphagia	11	11	1.32	2	2	0.24
Dizziness	11	10	1.2	8	6	0.73
Fatigue	10	10	1.2	6	6	0.73
Injection site hypersensitivity	13	10	1.2	3	2	0.24
Pain	12	10	1.2	8	8	0.97

Source: Reviewer's analysis

Comment: Overall, the proportion of subjects with the most common reactions remains within range observed in population from all SMF trials.

Pooled data from RCT with proposed dosing regimen

Therefore, 556 subjects from controlled trials were dosed with ATX-101 according to the proposed regimen. Adverse events from those pooled studies (15, 22, and 23) are presented below:

Table 16 Adverse Reactions in Pooled Trials 15, 22, and 23

	ATX-101 (N=556)		Placebo (N=551)	
PT	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: Reviewer's analysis

Comment: As expected, somewhat higher percentages of the most frequent AEs are noted in comparison to the data from all RTC. The reason is likely higher number of treatments (up to six for all three trials). It should be noted that trial 15 differs from trials 22 and 23 in the fact that different formulation was used (b) (4)

7.2.3 Special Animal and/or In Vitro Testing

In vitro data suggest that ATX-101 has a low potential for metabolic drug-drug interactions. In accordance with the FDA Guidance on Drug Interaction Studies from 2012, clinical drug-drug

interaction studies with ATX-101 were not needed.

Histologic evaluation of the drug activity was explored in study ATX-101-08-10 where ATX-101 was administered in abdominal fat tissue of healthy subjects who were scheduled to undergo elective abdominoplasty and included H&E and Masson's trichrome staining of the treated tissue. The applicant concluded that ATX-101 administration resulted in adipocytolysis (Day 1), inflammatory response and small vessel damage (Day 7), and septal fibrosis (Day 28). Higher ATX-101 concentrations (2% and 4%) resulted in arterial damage of larger vessels, hemorrhage, lipid lake formation, and necrosis.

7.2.4 Routine Clinical Testing

The schedule of clinical safety assessments for each of the trials consisted of vital signs, general physical examination, routine laboratory testing, and monitoring for AE (local and systemic). The methods and tests used as well as the frequency of testing were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Deoxycholic acid from ATX-101 joins the metabolic pathway of endogenous DCA; therefore no formal studies were conducted to assess its clearance and interactions. See Section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no approved similar drugs in the same drug class.

7.3 Major Safety Results

7.3.1 Deaths

There were five deaths in ATX-101 program. The deaths were due to:

- Cholangiocarcinoma -Subject 05-008 from trial 7, was a 47-year-old white man with PMH of seasonal allergies, hypertension, spinal decompression treatment, hiatus hernia and skin cancer. He was administered 2 mg/cm^2 ATX-101 with a total injected volume of 6.2 mL on May 6, 2008. On June 28, 2008, he was diagnosed with cholangiocarcinoma. The subject died (b) (6)

Comment: Subject's screening LFTs were elevated（AST at 128 IU/L, ALT at 291 and alkaline phosphatase at164). In June 2008 he developed symptoms of obstructive jaundice (pruritus, dark urine, and pale stool) with abdominal pain. It is likely that subject had undiagnosed malignancy at the screening visit which then rapidly progressed. I agree with the assessment that event was not related to the drug based on the initial laboratory values and short drug-exposure time.

- Heroin overdose- Subject 523-009, from trial 23 was a 24-year-old white man with PMH significant for bipolar disorder, alcohol and drug abuse, and suicidal ideation. He received 6 doses of placebo (last one on November 14, 2012). The subject was found dead in his home on (b) (6). The results of the autopsy confirmed heroin toxicity.

- Traffic accident- Subject 529-002, from a trial 23 was a 48-year-old man with PMH of seasonal allergy and obesity. He was administered a single dose of 2 mg/cm2 ATX-101 on July 3, 2012. (b) (6) subject had died on impact in a head-on car collision.

- Myocardial infarction - Subject 14-005, from trial 26 was a 60-year-old man who underwent his first and only treatment on October 19, 2011 with 25 injections (5 mL) of 1% ATX-101. On his follow up visit on December 20, 2011 the subject was not satisfied with the results of treatment and declined further study treatment. He died suddenly on (b) (6) from presumable myocardial infarction.

- Pancreatic cancer- Subject 301-009 from trial 12 was a 63 years old man with PMH of hypercholesterolemia, hypertension, CAD, and seasonal allergy. He was enrolled in predecessor trial 15 and received 6 placebo treatments (from December 28, 2009 until May 19, 2010). The subject's last LTFU study visit occurred on September 12, 2011. He died from pancreatic cancer on (b) (6), however, the applicant was notified about his death on November 19, 2013 therefore the case was not included in the original NDA submission but in 120-safety data update.

Comment: I agree with the investigators' assessments that none of these fatal events were related to study drug, and none require inclusion in labeling.

7.3.2 Nonfatal Serious Adverse Events

An overview of SAEs in the all SMF studies revealed 58 subjects with 75 SAEs: 29 subjects (2%) in the all ATX-101 groups and 28 subjects (3%) in the placebo group reported at least 1 SAE. One subject who developed metrorrhagia (23-501-041) did not have assigned treatment arm.

In regard to SAEs that were reported in active arms, there were no SAEs in subjects dosed at 8 and 4mg/cm^2, and only 2 subjects dosed with ATX-101 at 1 mg had SAEs (depression and endometriosis, respectively). All other subjects who developed SAEs received 2 mg/cm^2 are presented in Table 17.

Table 17 Serious Adverse Events in Subjects Dosed ATX-101 at 2mg/cm^2

	ATX-101 (N = 1048)			*Placebo(N = 877)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Injection site nerve damage	3	1	0.1	0	0	0
Diverticulitis	1	1	0.1	2	2	0.23
Osteoarthritis	1	1	0.1	2	2	0.23
Cardiac arrest	1	1	0.1	1	1	0.11
Gastrooesophageal reflux disease	1	1	0.1	1	1	0.11
Abdominal abscess	1	1	0.1	0	0	0
Abdominal adhesions	1	1	0.1	0	0	0
Abortion spontaneous	1	1	0.1	0	0	0
Anxiety	1	1	0.1	0	0	0
Appendicitis perforated	1	1	0.1	0	0	0
Arteriosclerosis	1	1	0.1	0	0	0
Bile duct cancer	1	1	0.1	0	0	0
Breast cancer recurrent	1	1	0.1	0	0	0
Cardiac death	1	1	0.1	0	0	0
Cervical polyp	1	1	0.1	0	0	0
Colitis microscopic	1	1	0.1	0	0	0
Colon cancer	1	1	0.1	0	0	0
Concussion	1	1	0.1	0	0	0
Contusion	1	1	0.1	0	0	0
Cystocele	1	1	0.1	0	0	0
Gastric cancer	1	1	0.1	0	0	0
Head injury	1	1	0.1	0	0	0
Infectious peritonitis	1	1	0.1	0	0	0
Intervertebral disc operation	1	1	0.1	0	0	0
Intracranial hypotension	1	1	0.1	0	0	0
Meningismus	1	1	0.1	0	0	0
Ovarian cancer	1	1	0.1	0	0	0
Rectocele	1	1	0.1	0	0	0
Respiratory failure	1	1	0.1	0	0	0
Road traffic accident	1	1	0.1	0	0	0
Skull fracture	1	1	0.1	0	0	0
Spinal column stenosis	1	1	0.1	0	0	0
Stent placement	1	1	0.1	0	0	0
Thyroid cancer	1	1	0.1	0	0	0

Urinary tract infection	1	1	0.1	0	0	0
Uterine cancer	1	1	0.1	0	0	0
Uterine leiomyoma	1	1	0.1	0	0	0
Uterine prolapse	1	1	0.1	0	0	0

Source: Reviewer's analysis

Comment: Most of the serious adverse events occurred in only one subject, and association with drug treatment seems unlikely. The only SAEs that occurred in 2 subjects were in placebo arm (diverticulitis, osteoarthritis, and breast cancer).
Five SAEs occurred in 4 subjects in the long-term follow up studies: diverticulitis, anxiety, cervical polyp, and (in the same subject) arteriosclerosis and stent placement.

Only 1 subject (ATX-101-10-17-307-002) had an event considered related to study drug (three episodes of nerve injury were continuous of the same event reported several times due to changes in intensity and reported outcome). Case presentation:

> *This 44-year-old female was enrolled in trial 114253 (EU trial) and received 32 injections of ATX-101 (2mg/cm^2) on 5/09 /2011. The same day subject's mouth dropped on the right side of the face with moderate intensity. Study drug was permanently discontinued. The event became mild in intensity on June 14, 2011 and resolved on July 2, 2011. No treatment for the event was reported. The subject completed the trial on October 22, 2011. The investigator reported that the alteration of the smile of the subject could be due to damage of the mentalis muscle or supplying nerve of the right side.*
>
> *Important concomitant medications received during the study included Botulinum toxin A 50-65 units (frequency not reported) for cosmetic treatment of upper face.*

Mandibular nerve injuries were reported in other trials but never as SAEs. Perhaps, perceived serious determination is a result of limited personal experience with neck/chin injuries (PI is an ophthalmologist) and/or concomitant botulinum toxin use. Labeling will address proper injection techniques to minimize the potential of injury to this nerve.

In order to review possible clustering of serious events analysis by System Organ Class (SOC) was done and revealed the following:

Table 18 SAEs by System Organ Class

	ATX-101 (N = 1048)			*Placebo (N = 877)*		
SOC	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	8	7	0.67	4	4	0.46
Infections and infestations	5	4	0.38	7	7	0.8

Gastrointestinal disorders	3	3	0.29	5	4	0.46
General disorders and administration site conditions	4	2	0.19	0	0	0
Injury, poisoning and procedural complications	5	2	0.19	2	2	0.23
Musculoskeletal and connective tissue disorders	2	2	0.19	3	3	0.34
Nervous system disorders	2	2	0.19	2	2	0.23
Reproductive system and breast disorders	4	2	0.19	1	1	0.11
Surgical and medical procedures	2	2	0.19	3	3	0.34

Source: Reviewer's analysis

Comment: As expected, more SAEs were reported in active arm in General disorders and administration site conditions class. Also, somewhat higher proportion of subjects in active arm had neoplasms (benign and malignant, combined). This finding was explored further.

The following table summarizes all cases of malignant neoplasms that occurred in development program (therefore across all dosing groups). Overall 8/1547 in active and 5/877 subjects developed malignancies during the studies (0.52 % v.0.57%).

Table 19 Malignancy Occurrences in All SMF Studies

PT	Subject ID	Remark
Received 2 mg ATX-101		
Bile duct cancer	ATX-101-07-07-005-008	
Breast cancer recurrent	ATX-101-11-23-532-011	
Gastric cancer	ATX-101-10-16-512-022	
Ovarian cancer	ATX-101-11-23-502-001	Same subject
Uterine cancer	ATX-101-11-23-502-001	
Thyroid cancer	ATX-101-11-26-004-009	LTFU
Colon cancer	ATX-101-11-26-013-005	
Basal cell	ATX-101-11-26-002-001	
Squamous cell	ATX-101-11-26-008-008	
Received placebo		
Non-Hodgkin lymphoma	ATX-101-16-509-007	
Breast cancer	ATX-101-11-22-104-017	
Multiple myeloma	ATX-101-11-22-108-011	
Breast cancer	ATX-101-11-23-521-023	
Pancreatic cancer	ATX-101-08-12-301-00	LTFU

Source: Reviewer's analysis

Comment: The proportions and type of cancers do not raise safety concern. It is reassuring that DCA is short-lived in the circulation, and is naturally produced in the liver; therefore its impact on potential neoplasm development would be rather negligible. All cancer cases were assessed as "not related" per investigators.

Overall, the type and frequency of SAEs do not raise safety concerns or implications for labeling.

7.3.3 Dropouts and/or Discontinuations

The impact of trial or treatment discontinuations should be assessed in the context of elective procedure.

Table 20 Dropouts and Discontinuations in All SMF Studies

Reason for discontinuation	1mg (N=301)	2mg (N=1048)	4mg (N=135)	8 mg (N=63)	All ATX (N=1547)	Placebo (N=877)	Total (N=2424)
Administrative decision	0	0	0	0	0	3 (3%)	3
Adverse Event	6 (2%)	16 (2%)	0	0	22 (1%)	6 (1%)	28 (1%)
Death	0	3	0	0	3	2	5
Lost to Follow-up	10 (3%)	47 (5%)	2(1%)	0	59 (4%)	31 (4%)	90 (4%)
Other	4 (1%)	19 (2%)	3 (2%)	0	26 (2%)	5 (1%)	31 (1%)
Subject Non-compliance	0	2	0	0	2	1	3
Withdrawal of consent	9 (3%)	61 (6%)	4 (2%)	0	74 (5%)	38 (4%)	112 (5%)

Source: Reviewer's analysis

Comment: The proportion of subjects who discontinued trials for any of the listed reasons was comparable between ATX 101 and placebo. It does not appear to be dose related correlation between different ATX 101 concentrations and discontinuations.

Considering pivotal trials, more subjects in active arm discontinued the trials (73/513, 14%) than in placebo arm (55/506, 11%) as presented below:

Table 21 Dropouts and Discontinuations in Pivotal Trials

Reason for discontinuation	ATX (N=513)	Placebo (N=506)	Total (N=1019)
Administrative decision	0	3 (1%)	3 (<1%)
Adverse Event	7 (1%)	4 (1%)	11 (1%)
Death	1 (<1%)	1(<1%)	2(<1%)
Lost to Follow-up	27 (5%)	21 (4%)	48 (5%)
Other	1(<1%)	0	1(<1%)
Subject Non-compliance	2(<1%)	1(<1%)	3(<1%)
Withdrawal of consent	35 (7%)	25 (5%)	60 (6%)

Source: Reviewer's analysis

Comment: All subjects in active arm who discontinued also reported injection site reactions while that was the case with 50% of those in placebo arm.

Table 22 Treatment Discontinuations in All SMF Studies

Reason for discontinuation	1mg (N=301)	2mg (N=1048)	4mg (N=135)	8 mg (N=63)	All ATX (N=1547)	Placebo (N=877)	Total (N=2424)
Administrative decision	0	14 (1%)	0	0	14 (1%)	7 (1%)	21(1%)
Adverse Event	15 (5%)	75 (7%)	0	0	90 (6%)	8 (1%)	98(4%)
Death	0	3(<1%)	0	0	3 (<1%)	0	2(<1%)
Early therapeutic success	10 (<1%)	19 (2%)	0		29 (2%)	1(<1%)	30 (1%)
Insufficient SMF into which injections may safely be given	1	92 (9%)	0	0	93 (6%)	17 (2%)	110 (5%)
Lost to Follow-up	3	25 (2%)	0	0	28 (2%)	12 (1%)	40 (2%)
Other	4	9 (1%)	0	0	13(1%)	32 (4%)	45 (2%)
Pregnancy	0	1(<1%)	0	0	1(<1%)	1(<1%)	2((<1%)
Subject satisfaction with SMF reduction	0	50 (0.5%)	0	0	50 (3%)	3(<1%)	53(2%)
Withdrawal by subject	14(5%)	17 (2%)	0	0	28 (2%)	18 (2%)	46 (2%)
Withdrawal of consent for further treatments due to discomfort with procedure (Not an AE)	0	15(1%)	0	0	15(1%)	2(<1%)	17 (1%)
Withdrawal of consent for further treatments due to subject convenience	0	30 (3%)	0	0	30 (2%)	20(2%)	50 (2%)

Source: Reviewer's analysis

Comment: Adverse events caused higher number of subjects who received active to discontinue the treatment.

Table 23 Treatment Discontinuations in Pivotal Trials

Reason for treatment discontinuation	ATX-101 (N=513)	Placebo (N=506)	Total (N=1019)
Administrative decision	14 (3%)	7 (1%)	21(2%)
Adverse Event	36 (7%)	6 (1%)	42 (4%)
Death	1 (<1%)	0	1
Insufficient SMF into which injections may safely be given	77 (15%)	17 (3%)	94(9%)
Lost to Follow-up	16 (3%)	10 (2%)	26 (3%)
Other	3 (1%)	28 (6%)	31 (3%)
Pregnancy	0	1 (<1%)	1(<1%)
Subject satisfaction with SMF reduction	21(4%)	3 (<1%)	24 (2%)
Withdrawal of consent for further treatments due to discomfort with procedure (Not an AE)	15 (3%)	2(<1%)	17 (2%)
Withdrawal of consent for further treatments due to subject convenience	27 (5%)	20 (4%)	47 (5%)

Source: Reviewer's analysis

Analysis of the AEs leading to discontinuations of the treatment revealed that all 36 subjects from ATX-101 arm who discontinued treatment due to AE discontinued due to injection site reactions while that was the case with 50% of subjects receiving placebo. Therefore accounting for subjects who discontinue the treatment "due to discomfort with procedure' final AEs treatment related discontinuations are 51 (10%) for active and 5 (1%) for placebo arm.

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

In pivotal trials, at least one adverse event was reported by 97% of ATX-101 treated subjects and 90% of placebo treated subjects and 96% (492/513) of active and 81% (411/506) of placebo-treated subjects reported administration site reactions (by HLGT). Those events comprise the top 10 most frequent AEs presented by PT in Table 24:

Table 24 Adverse Events in the Pooled Studies 22 and 23*

	ATX-101 (N = 513)			*Placebo (N = 506)*		
PT	*Events*	*N*	*(%)*	*Events*	*N*	*(%)*
Injection site hematoma	942	368	71.73	1040	353	69.76

Injection site pain	1101	356	69.4	357	160	31.62
Injection site anesthesia	525	341	66.47	43	29	5.73
Injection site edema	985	311	60.62	365	147	29.05
Injection site swelling	512	170	33.14	218	80	15.81
Injection site erythema	296	136	26.51	192	91	17.98
Injection site induration	246	120	23.39	15	13	2.57
Injection site paresthesia	98	70	13.65	24	20	3.95
Injection site nodule	92	68	13.26	23	14	2.77
Injection site pruritus	90	64	12.48	45	30	5.93
Headache	45	41	7.99	29	20	3.95
Skin tightness	36	24	4.68	6	6	1.19
Injection site warmth	41	22	4.29	15	8	1.58
Nerve injury	25	22	4.29	2	2	0.4
Oropharyngeal pain	17	15	2.92	9	7	1.38
Urinary tract infection	14	14	2.73	9	7	1.38
Hypertension	14	13	2.53	7	7	1.38
Nausea	14	12	2.34	3	3	0.59
Dysphagia	10	10	1.95	1	1	0.2

*Adverse events that occurred in ≥ 2% of ATX-101 treated subjects and at greater incidence than placebo
Source: reviewer's analysis

Comment: The majority of the AEs that occurred in >2% of subjects were at or near the site of injection. Considering cytolytic mode of action of ATX-101 these are representing ARs.

As for headache, hypertension, and nausea, the disparity in number of subjects between active and placebo arm is suggestive of adverse reaction. The reasonable argument for higher active arm rates may be their connection to post-procedural ARs (e.g. pain, swelling). Therefore, I recommend that all three be included in labeling.

In respect to nerve injuries, 2/22 subjects in active and one in placebo arm had distant nerve involvements, far from the injection sites. These are likely not related to the treatment.

It is my recommendation that the Section 6.1 Clinical Trials experience contains the following table (adverse reaction listed in descending frequency order):

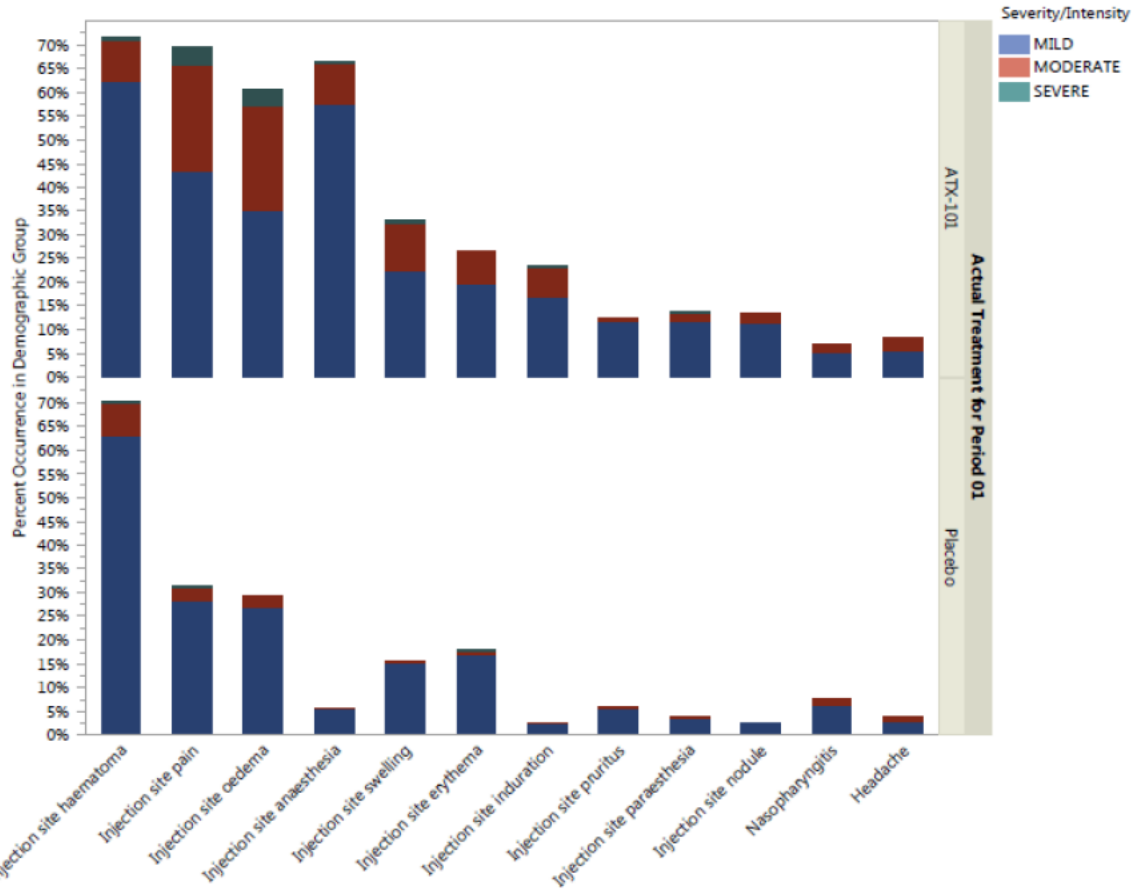
Adverse Reaction in the Pooled Studies 22 and 23*

Preferred term	ATX-101 (N=513) n (%)	Placebo (N=506) n(%)
Injection site edema/swelling	448 (87%)	218 (43%)
Injection site hematoma	368 (72%)	353 (70%)
Injection site pain	356 (70%)	160 (32%)
Injection site numbness	341 (66%)	29 (6%)
Injection site erythema	136 (27%)	91 (18%)
Injection site induration	120 (23%)	13 (3%)
Injection site paresthesia	70 (14%)	20 (4%)
Injection site nodule	60 (13%)	14 (3%)
Injection site pruritus	64 (12%)	30 (6%)
Headache	41 (8%)	20 (4%)
Skin tightness	24 (5%)	6 (1%)
Injection site warmth	22 (4%)	8 (2%)
Injection site nerve injury	20 (4 %)	1 (<1%)
Oropharyngeal pain	15 (3%)	7 (1%)
Hypertension	13 (3%)	7 (1%)
Nausea	12 (2%)	3 (1%)
Dysphagia	10 (2%)	1 (<1%)

*Adverse reactions that occurred in ≥ 2% of ATX-101 treated subjects and at greater incidence than placebo

Per protocol, all AEs were graded by intensity. The breakdown of the most frequent AEs according to the intensity is presented in Figure 17:

Figure 17 Adverse Events by Severity



Source: Reviewer's analysis

Severity of the adverse reactions was analyzed separately and presented in Table 25:

Table 25 Severe ARs Occurring in ≥2 Subjects Receiving ATX-101

	ATX-101 (N = 513)			Placebo (N = 506)		
PT	Events	N	(%)	Events	N	(%)
Injection site pain	24	20	3.9	1	1	0.2
Injection site edema	19	17	3.31	0	0	0
Injection site swelling	4	4	0.78	1	1	0.2
Injection site hematoma	4	4	0.78	1	1	0.2
Dysphagia	2	2	0.39	0	0	0

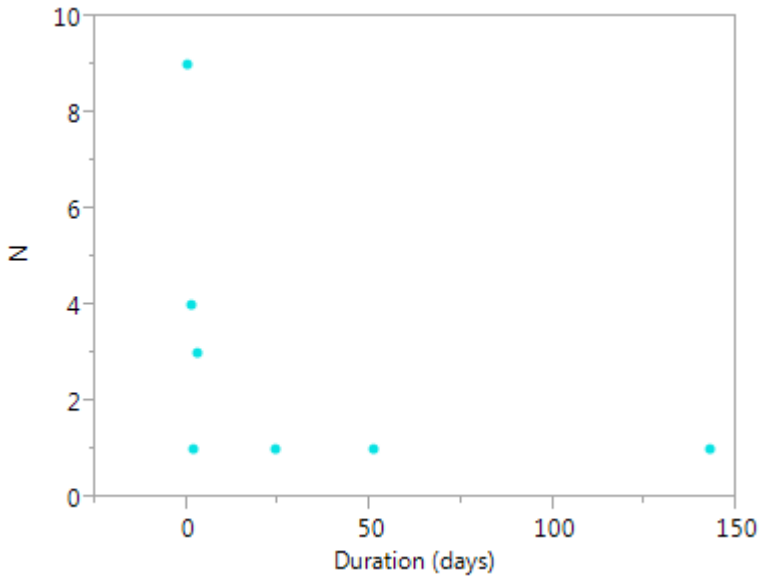
Source: Reviewer's analysis

Comment: It should be noted that pain and dysphagia grading relied on the subject's assessment. The outcome of all severe reactions was reported as "recovered."

Specific attention was drawn to severe pain. For the most subjects verbatim terminology was "pain" but one subject reported "burning" and three subjects reported "stinging." Drug was withdrawn for two subjects and interrupted for one subject due to this AR. Severe pain was reported after an average of 6 ml (30 injections) of ATX-101. Almost half of the all subjects who experienced severe pain (9/20) received their treatments at three sites perhaps pointing at the injection technique as the culprit.

In terms of the duration, the severe pain lasted from less than one day to 144 days. For the most subjects (17) pain lasted up to 3 days .Interestingly, the subject who experienced the longest duration of severe pain, completed the treatment with 6 sessions and with no change in dosing (ATX-101-11-22-124-006).

Figure 18 Duration of Severe Pain in Subjects Receiving ATX-101



Source: Reviewer's analysis

Comment: It is my recommendation that occurrence of severe reactions be included in labeling as follows:

The most commonly reported severe adverse reactions were injection site pain (b) (4) *and injection site edema/swelling* (b) (4).

Nerve Injuries

Listed below are only those nerve injuries that occurred near or at the treatment area:

Table 26 Nerve Injuries in the Treatment Area

Preferred Term	Subject ID	Duration (days)
Nerve injury	ATX-101-11-22-106-010	61
Nerve injury	ATX-101-11-22-112-006	39
Nerve injury	ATX-101-11-22-112-007	298
Nerve injury	ATX-101-11-22-120-011	6
Nerve injury	ATX-101-11-22-121-012	1
Nerve injury	ATX-101-11-22-123-024	82
Nerve injury	ATX-101-11-22-125-017	31
Nerve injury	ATX-101-11-22-126-011	26
Nerve injury	ATX-101-11-22-132-014	11
Nerve injury	ATX-101-11-22-137-010	114
Nerve injury	ATX-101-11-23-502-005	38
Nerve injury	ATX-101-11-23-505-010	46
Nerve injury	ATX-101-11-23-505-021	52
Nerve injury	ATX-101-11-23-515-016	49
Nerve injury*	ATX-101-11-23-517-014	85
Nerve injury	ATX-101-11-23-528-009	25
Nerve injury	ATX-101-11-23-528-012	61
Nerve injury	ATX-101-11-23-537-009	23
Nerve injury	ATX-101-11-23-540-007	44
Nerve injury	ATX-101-11-23-540-010	60
Nerve injury	ATX-101-11-23-515-015 (Placebo)	54

*Severe injury
Source: Reviewer's analysis

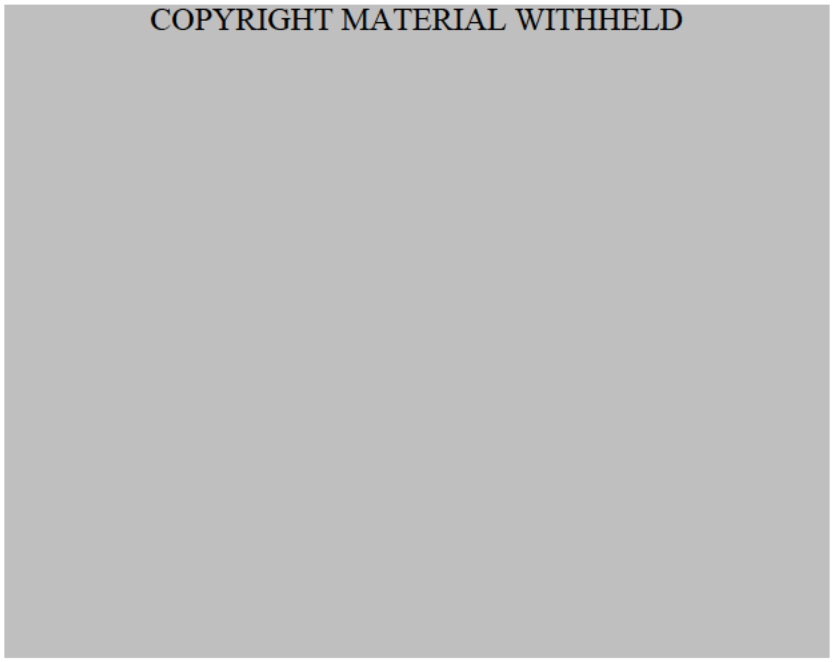
Comment: All but one AR was in the active arm and all but one was assessed by PI as "mild or moderate" in severity. All listed nerve injuries resolved completely and without treatment by their respective duration time.

In the interest of clarifying the anatomical point of injury, the complete subjects' listing from US trials with verbatim terminology is included below:

SUBJID	SITEID	ARM	AETERM	Duration	Severity	AREL	dosing	Outcome
106-010	106	2 mg/cm2	Rt marginal mandibular neuropraxia	61	Mild	Related	Dose Not Changed	Recovered/Resolved
112-006	112	2 mg/cm2	Left Depressor Labii Weakness	39	Mild	Related	Dose Not Changed	Recovered/Resolved
112-007	112	2 mg/cm2	Right Depressor labii paresis	70	Mild	Related	Dose Not Changed	Recovered/Resolved
112-007	112	2 mg/cm2	Rt. depressor labii paresis	37	Mild	Related	Dose Not Changed	Recovered/Resolved
112-007	112	2 mg/cm2	Residual Right Depressor Labii weakness	298	Mild	Related	Dose Not Changed	Recovered/Resolved
120-011	120	2 mg/cm2	RIGHT DEPRESSOR ANGULI ORIS PARESIS	6	Moderate	Related	Dose Not Changed	Recovered/Resolved
121-012	121	2 mg/cm2	temporary neuropraxia lower lip	1	Mild	Related	Dose Not Changed	Recovered/Resolved
123-024	123	2 mg/cm2	Neuropraxis Left depressor Labii	82	Mild	Related	Dose Not Changed	Recovered/Resolved
125-017	125	2 mg/cm2	mild facial palsy left chin	31	Mild	Related	Dose Not Changed	Recovered/Resolved
126-011	126	2 mg/cm2	Transient marginal-mandibular palsy	26	Mild	Related	Dose Not Changed	Recovered/Resolved
132-014	132	2 mg/cm2	Asymmetrical look in sub mental area	11	Mild	Related	Dose Not Changed	Recovered/Resolved
137-010	137	2 mg/cm2	Lower lip asymmerty	114	Moderate	Not Relate	Dose Not Changed	Recovered/Resolved
137-010	137	2 mg/cm2	Weakness on lower lip depressor	114	Moderate	Not Relate	Dose Not Changed	Recovered/Resolved
502-005	502	2 mg/cm2	Right Lower lip depressor muscle affected	38	Mild	Related	Dose Not Changed	Recovered/Resolved
505-010	505	2 mg/cm2	Left lower lip palsy	46	Mild	Related	Dose Not Changed	Recovered/Resolved
505-021	505	2 mg/cm2	Muscle palsy left lower lip	52	Moderate	Related	Dose Not Changed	Recovered/Resolved
515-015	515	Placebo	Assymetry Left lower lip	54	Mild	Related	Dose Not Changed	Recovered/Resolved
515-016	515	2 mg/cm2	Asymmetry lower lip, left corner. anguli oris muscle injury.	49	Mild	Related	Dose Interrupted	Recovered/Resolved
517-014	517	2 mg/cm2	Diffusion to left Depressor Anguli oris	85	Severe	Related	Dose Interrupted	Recovered/Resolved
528-009	528	2 mg/cm2	weakness right side lower lip	25	Mild	Related	Dose Interrupted	Recovered/Resolved
528-012	528	2 mg/cm2	WEAKNESS RT LOWER LIP	61	Moderate	Related	Dose Not Changed	Recovered/Resolved
537-009	537	2 mg/cm2	Weakness of left marginal mandibular branch of facial nerve	23	Mild	Related	Dose Not Changed	Recovered/Resolved
540-007	540	2 mg/cm2	Asymmetrical Smile(right depressor labii paresis)	44	Mild	Related	Dose Interrupted	Recovered/Resolved
540-010	540	2 mg/cm2	Asymmetrical Smile(left depressor Labii inferioris paresis	60	Mild	Related	Dose Not Changed	Recovered/Resolved

Considering investigator's description, it appears that local nerve injuries were due to the damage of the marginal mandibular nerve.

Figure 19 Mandibular Nerve (V3) Branches



Source: Adapted from http://intranet.tdmu.edu.ua

Comment: The Marginal mandibular nerve and its branches bear an important relationship with the inferior border of the mandible which is part the treatment area. To mitigate the risk of this

injury, and following the consultation with Dr. Khan (from CDRH), the following language is proposed for the Section 2.3 of the labeling:

2.3 Injection Technique

The safe and effective use of ATX-101™ depends on the use of the correct number and locations for injections, proper needle placement, and administration techniques.

Health care professionals administering ATX-101™ must understand the relevant submental anatomy and associated neuromuscular structures in the area involved and any alterations to the anatomy due to prior surgical or aesthetic procedures *[see Warnings and Precautions (5)]*.

Avoid injections near the area of the marginal mandibular nerve

Needle placement with respect to mandible is very important as it reduces the potential for injury of the marginal mandibular (b) (4) nerve (which may present as an asymmetrical smile).

- To avoid injury to the marginal mandibular nerve (b) (4) 1-1.5 cm below the (b) (4) inferior border (b) (4) (from angle of mandible to mentum).
- Do not inject above the inferior border of the mandible

Avoid platysma (b) (4)

Palpate the submental area to ensure sufficient SMF and to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) (b) (4)

Injecting into the treatment area

Outline the planned treatment area with a surgical pen and apply a 1 cm injection grid to mark the injection sites

Do not inject ATX-101 outside the defined parameters *[see Warnings and Precautions (5.15.2)]*.

- Using a large bore needle, draw 1 mL of ATX-101™ into a sterile 1 mL syringe and expel any air bubbles in the syringe barrel.
- Using a 30 gauge (or smaller) 0.5-inch needle, inject 0.2 mL of ATX-101™ into the pre-platysmal fat next to each of the marked injection sites by advancing the needle perpendicular to the skin.
- Injections which are too superficial (into the dermis) may result in skin ulceration.
- Avoid injecting into the post-platysmal fat by injecting ATX-101 into fat tissue at the depth of approximately mid-way into the subcutaneous fat layer.
- If at any time resistance is met as the needle is inserted, indicating the possibility of contact with fascial or nonfat tissue, the needle must be withdrawn to an appropriate depth before the injection is administered.
- Avoid injecting into other tissues such as the muscle, salivary glands, and lymph nodes.

- Upon needle withdrawal, pressure may be applied to each injection site as necessary to minimize bleeding; an adhesive dressing may be applied. (b) (4)

Dysphagia

Dysphagia adverse reaction was observed in early trials and therefore was added to the safety assessment of the events associated with the treatment area. Table 27 summarizes all the dysphagia cases from pivotal trials.

Table 27 Analysis of Dysphagia AEs

Preferred Term	Subject ID	Duration (days)	Outcome/treatment
Dysphagia	ATX-101-11-22-109-023	32	not recovered/not resolved/drug withdrawn
Dysphagia	ATX-101-11-22-110-016	3	recovered/resolved
Dysphagia	ATX-101-11-22-118-009	3	recovered/resolved
Dysphagia	ATX-101-11-22-141-025	5	recovered/resolved
Dysphagia	ATX-101-11-23-506-008	1	recovered/resolved
Dysphagia*	ATX-101-11-23-514-002	81	recovered/discontinued
Dysphagia	ATX-101-11-23-521-014	4	recovered/resolved
Dysphagia	ATX-101-11-23-523-007	1	recovered/resolved
Dysphagia	ATX-101-11-23-524-032	3	recovered/resolved
Dysphagia*	ATX-101-11-23-528-016	2	recovered/resolved
Dysphagia	ATX-101-11-23-530-010 (Placebo)	1	recovered/resolved

*severe dysphagia
Source: Reviewer's analysis

Comment: Total of 11 subject experienced dysphagia, and all but one were in active group. Two subjects discontinued the treatment because of it and one of them did not recover prior to discontinuation. Most of the time dysphagia duration was short (1-3 days).

I recommend that (b) (4)

The table below summarizes all the cases of dysphagia in ATX-101 development program grouped by the treatment received.

Table 28 Dysphagia ARs in ATX-101 Development Program

Preferred Term	Subject ID	Dose (mg/cm^2)
Dysphagia	ATX-101-09-15-004-003	1 mg
Dysphagia	ATX-101-10-16-505-005	1 mg
Dysphagia	ATX-101-10-16-104-009	2 mg
Dysphagia	ATX-101-11-22-109-023	2 mg
Dysphagia	ATX-101-11-22-110-016	2 mg
Dysphagia	ATX-101-11-22-118-009	2 mg
Dysphagia	ATX-101-11-22-141-025	2 mg
Dysphagia	ATX-101-11-23-506-008	2 mg
Dysphagia	ATX-101-11-23-514-002	2 mg
Dysphagia	ATX-101-11-23-521-014	2 mg
Dysphagia	ATX-101-11-23-523-007	2 mg
Dysphagia	ATX-101-11-23-524-032	2 mg
Dysphagia	ATX-101-11-23-528-016	2 mg
Dysphagia	ATX-101-11-26-003-003	2 mg
Dysphagia	ATX-101-07-07-011-009	>2 mg
Dysphagia	ATX-101-07-07-012-005	>2 mg
Dysphagia	(b) (4) -001-019	>2 mg
Dysphagia	(b) (4) -001-024	>2 mg
Dysphagia	ATX-101-10-17-307-015	placebo
Dysphagia	ATX-101-11-23-530-010	placebo

Source: Reviewer's analysis

Dysphonia

Dysphonia developed rarely, but never in placebo treated subjects. In pivotal trials there were two cases:

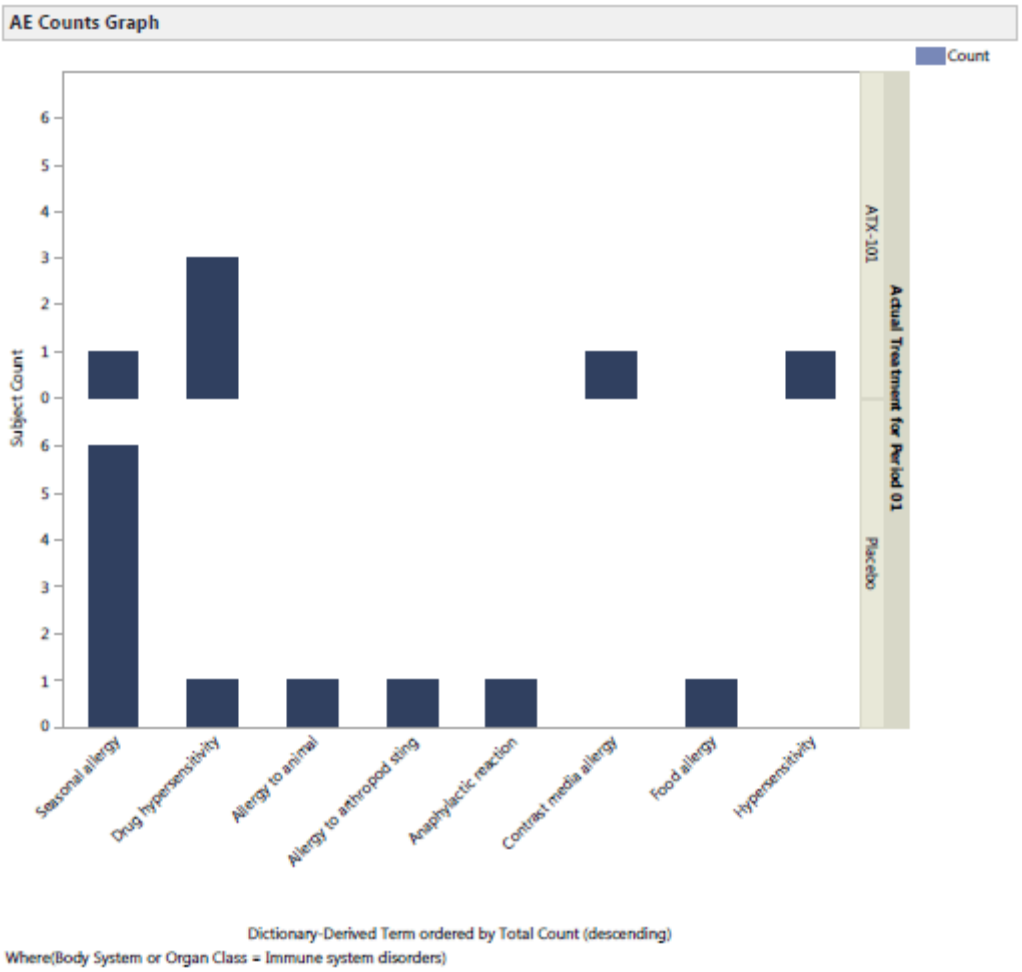
- subject ATX-101-11-22-109-023 who discontinued with unresolved dysphonia/dysphagia of 23 days, and
- subject ATX-101-11-22-141-019 who had dysphonia for 5 days that resolved.

There was one more case reported in phase 3b open label trial: ATX-101-11-26-015-023 that resolved as well.

Allergic Events

The following graph summarizes all observe events in Immune System Disorders class from pivotal trials.

Figure 20 Adverse Events in Immune System Disorder Class



Source: Reviewer's analysis

Anaphylactic reaction in placebo treated subject developed after a spider bite. It should be noted that this was the only anaphylactic reaction reported in the whole ATX-101 development program.
All 4 cases of drug hypersensitivity (3 in active and one in placebo arm) were attributed to other concomitant drugs which are known to cause hypersensitivity. Additionally, there was one subject (22-106-027) in active arm that developed "hypersensitivity" 3 weeks after the last received dose classified by PI as possibly related. The event was described as "jabbing pains", therefore, in my clinical judgment; event does not fulfill the criteria for immunologic reaction. Subject recovered.

In the category of injection site reactions there were 4 subjects in active arm and one in placebo who had "injection site urticaria." The rash/hives developed at the injection site from 1- 40 days after the treatment, all resolved (some with antihistamines), and in all cases, the event did not reoccur following additional treatments.

Comment: The timeline and negative re-challenge do not fully support allergic reactions, however they were all described as "possibly" or "definitely" related by the investigators and (b) (4)

It is my recommendation that "injection site uriticaria" remains in the section 6.1 of the labeling in the list of Other adverse reactions associated with the use of ATX-101.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events that occurred in subjects dosed with 2 mg/cm ^{2} ATX 101 (N=1048) are presented in Table 29. Comparison to adverse events in placebo treated subjects (N=877) is included.

Table 29 Most Common Adverse Events with ATX-101 Dosed at 2mg/cm^2

Preferred Term	ATX-101 Number of Events	Placebo Number of Events	P-value
Injection site pain	2400	616	3E-80
Injection site induration	486	49	4E-47
Injection site edema	1556	472	6E-34
Injection site swelling	1081	379	8E-23
Injection site nodule	164	29	3E-17
Injection site erythema	942	399	5E-15
Injection site paresthesia	160	30	1E-14
Injection site pruritus	178	55	8E-11
Nerve injury	25	2	0.00011
Nausea	27	4	0.00081
Injection site discomfort	21	2	0.001
Injection site hematoma	1582	1371	0.005

Skin tightness	36	6	0.005
Injection site discoloration	15	2	0.016
Hot flush	8	0	0.018
Hypertension	25	8	0.02
Dysphagia	12	2	0.028
Contusion	6	0	0.035
Ligament sprain	8	1	0.045
Hypercholesterolemia	11	2	0.046

Source: Reviewer's analysis

Comment: Adverse events are ranked in descending order according to the p-value. The trials which provided the data for this analysis were not powered for safety analysis; therefore p-values are not representative of statistical significance but rather of order of ranking.

7.4.2 Laboratory Findings

Overall, the number of subjects whose abnormal laboratory values were reported as adverse events was ≤ 1% and did not significantly differ between arms.

Table 30 Laboratory Tests Reported as Adverse Events

	2 mg/cm2 (N = 513)			*Placebo (N = 506)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
White blood cell count increased	8	6	1.17	5	5	0.99
Hypothyroidism	6	6	1.17	4	4	0.79
Thyroxine decreased	5	5	0.97	5	4	0.79
Blood alkaline phosphatase increased	5	5	0.97	4	3	0.59
Blood thyroid stimulating hormone increased	4	4	0.78	3	3	0.59
Proteinuria	5	4	0.78	2	2	0.4
Blood cholesterol increased	5	4	0.78	1	1	0.2
Hypertriglyceridaemia	5	4	0.78	1	1	0.2
Blood urea increased	3	3	0.58	3	2	0.4
Haematocrit decreased	3	3	0.58	3	2	0.4
Neutrophil count decreased	4	3	0.58	2	2	0.4
Red blood cell count decreased	3	3	0.58	2	2	0.4
White blood cell count decreased	4	3	0.58	2	2	0.4
Blood calcium increased	3	3	0.58	0	0	0

Source: Reviewer's analysis

Table 31 Laboratory Tests Reported as Out-of- Normal Range

		Actual Treatment for Period 01				
		Placebo		ATX-101		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Investigations	Blood glucose increased	18	3.6%	18	3.5%	36
	Tri-iodothyronine decreased	14	2.8%	16	3.1%	30
	Protein urine	14	2.8%	11	2.1%	25
	Blood triglycerides increased	13	2.6%	8	1.6%	21
	Alanine aminotransferase increased	11	2.2%	6	1.2%	17
	White blood cell count increased	5	1.0%	6	1.2%	11

Source: Reviewer's analysis

Comment: No clinically meaningful difference was observed between treatment arms in regard to out-of normal range laboratory tests.

Separate analysis was conducted for liver function tests. The ATX-101 is short-lived in the systemic circulation and, therefore it is not expected that its temporary increase will cause liver damage. 19 subjects (12 in ATX-101 arm and 7 in placebo arm) have no record or are missing measurements of all four liver lab tests.

Total of 12 subjects in active arm (2.4%) and 10 subjects in placebo arm (2%) had at least one LFT's elevated ≥ 3 x ULN. None of the events was considered serious or severe or prompted study treatment change by the investigators..

Table 32 All Subjects with Elevated Liver Function Tests (ALT, AST, ALP, and bilirubin)

ALT Counts and Percents

	Actual Treatment for Period 01			
	ATX-101		Placebo	
ALT Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects
Missing Test Result	4	0.8%	4	0.8%
Less than 2x ULN	471	93.6%	457	92.0%
Between 2x and 5x ULN	25	5.0%	34	6.8%
Between 5x and 10x ULN	3	0.6%	2	0.4%
All	503	100.0%	497	100.0%

AST Counts and Percents

	Actual Treatment for Period 01			
	ATX-101		Placebo	
AST Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects
Missing Test Result	4	0.8%	4	0.8%
Less than 2x ULN	483	96.0%	477	96.0%
Between 2x and 5x ULN	14	2.8%	14	2.8%
Between 5x and 10x ULN	1	0.2%	2	0.4%
Between 10x and 20x ULN	1	0.2%	0	0.0%
All	503	100.0%	497	100.0%

ALP Counts and Percents

	Actual Treatment for Period 01			
	ATX-101		Placebo	
ALP Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects
Missing Test Result	4	0.8%	4	0.8%
Less than 2x ULN	498	99.0%	491	98.8%
Between 2x and 5x ULN	1	0.2%	2	0.4%
All	503	100.0%	497	100.0%

BILI Counts and Percents

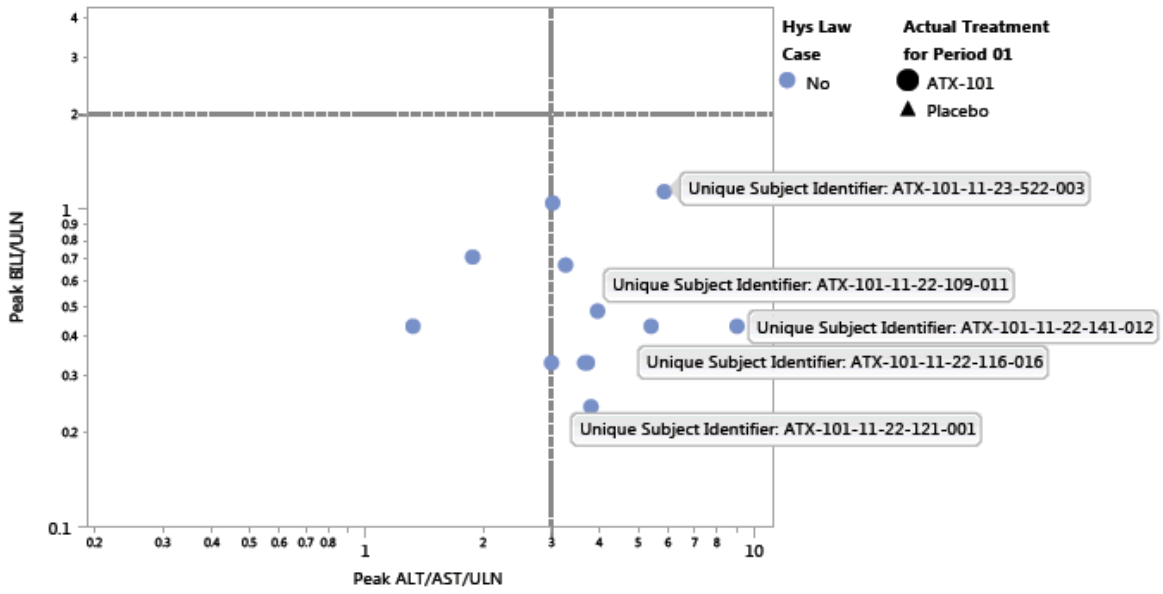
	Actual Treatment for Period 01			
	ATX-101		Placebo	
BILI Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects
Missing Test Result	8	1.6%	5	1.0%
Less than 2x ULN	494	98.2%	491	98.8%
Between 2x and 5x ULN	1	0.2%	1	0.2%
All	503	100.0%	497	100.0%

Source: Reviewer's analysis

Comment: Transient elevation of one or more LFT's is not uncommon finding in random laboratory testing, therefore only potentially clinically relevant enzyme elevations were analyzed further.

All subjects in active arm with either ALT or AST elevated ≥ 3 x ULN are presented below:

Figure 21 Subjects with ≥ 3 x ULN Elevated ALT/AST Receiving ATX-101



Source: Reviewer's analysis

Comment: One subject (22-141-012) had LFTs elevated >10 x ULN from the blood sample collected on visit 12 (ALT 306, AST 349, alkaline phosphatase 348). Same day repeat tests were significantly lower (ALT 106, AST 53, alkaline 187) therefore, it is likely that 10 x ULN was laboratory error.

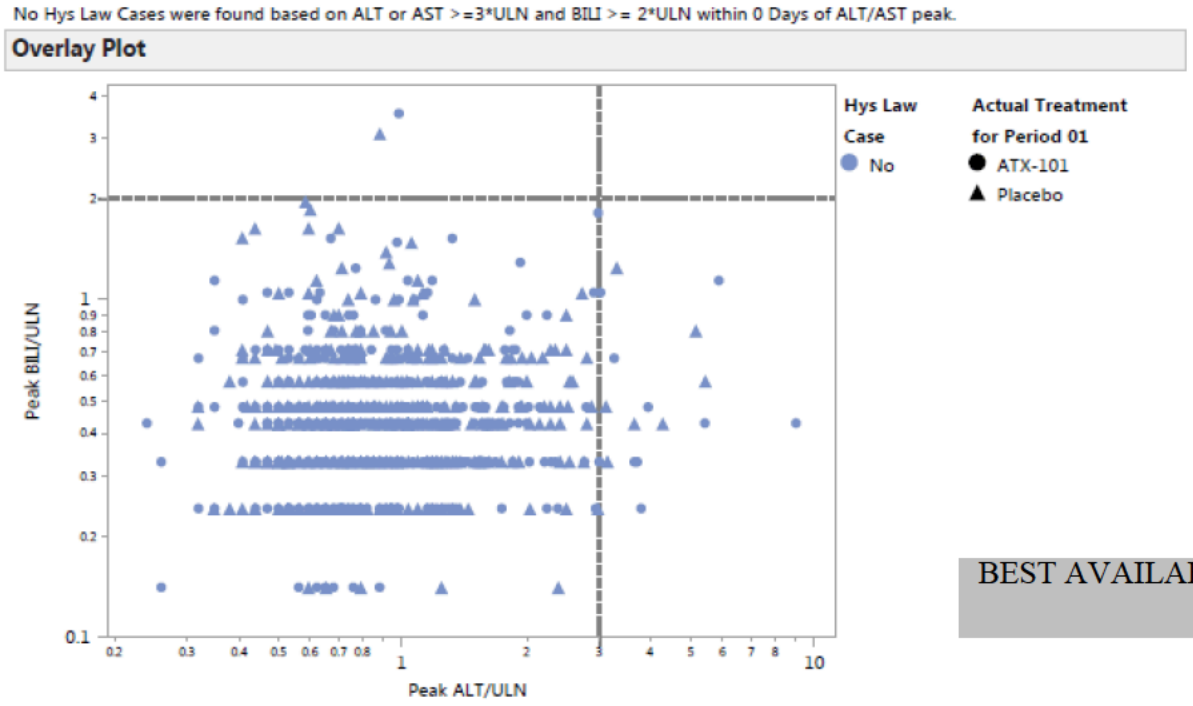
Second highest values were recorded on the last visit for subject 22-522-003 (ALT 199) approximately 5 months after the last ATX-101 injection making the causality unlikely. In the case of subject 22-109-011 baseline ALT/AST values were 2xULN similarly to subject 121-001. Both subjects had high BMI (33 and 35 respectively) raising the possibility of undiagnosed non-alcoholic fatty liver seen frequently in obese, middle aged patients.

As for subject 22-116-016, one time elevated ATL 184/AST 151 were noted on the last day of dosing. Labs were not repeated the same day, however all other subsequent values were normal.

All the subjects' reports were reviewed in detail and this review did not raise safety concern about ATX-101 causing elevated LFTs or any other signs of effects on the liver.

The following figure represents screening within pivotal trials for liver damage as defined in Hy's Law. There were no cases detected.

Figure 22 Screening for Hy's Law



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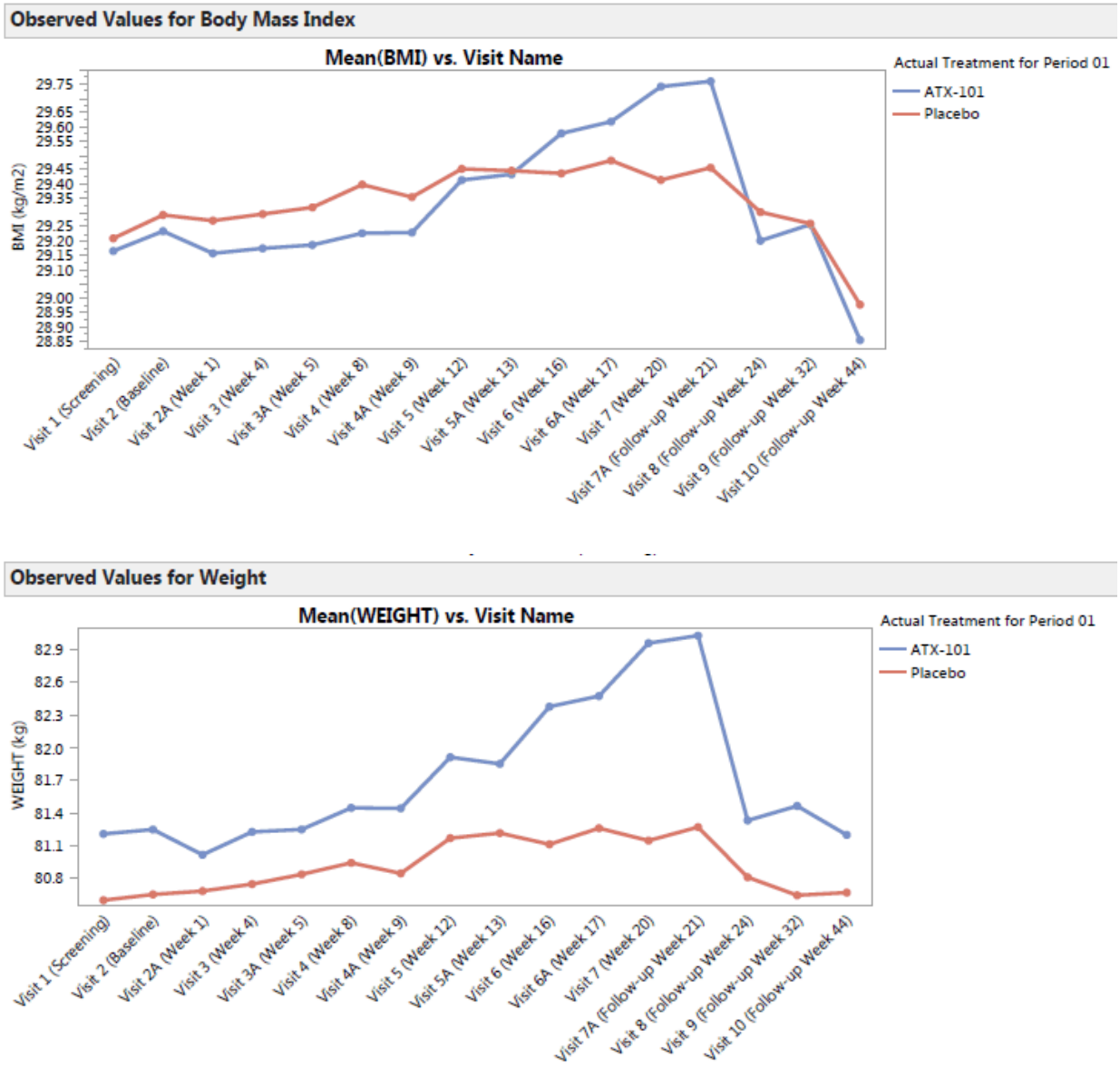
Source: Reviewer's analysis

Conclusion: No signal was detected in ATX-101 ability to cause liver damage.

7.4.3 Vital Signs.

In addition to the mean changes in vital signs, the grouped graphs below include change in mean BMI and weight during the pivotal trials.

Figure 23 Mean BMI and Weight Change during the Trials 22 and 23



Source: Reviewer's analysis

Comment: There was slight increase in overall weight (1.5 kg) and consequently BMI (0.5) for subjects in active arm. Subjects were instructed not to commence dieting during the trial in order to limit cofounding effects of weight loss with anticipated submental fat reduction. It is reassuring that interpretation of submental fat reduction occurs in conjunction with either same or slighter higher BMI than at baseline.

Figure 24 Mean Systolic Blood Pressure and Pulse Change in Trails 22 and 23

Source: Reviewer's analysis

Comment: It does not appear that there were overall clinically meaningful differences in mean systolic pressure between active and placebo arms.

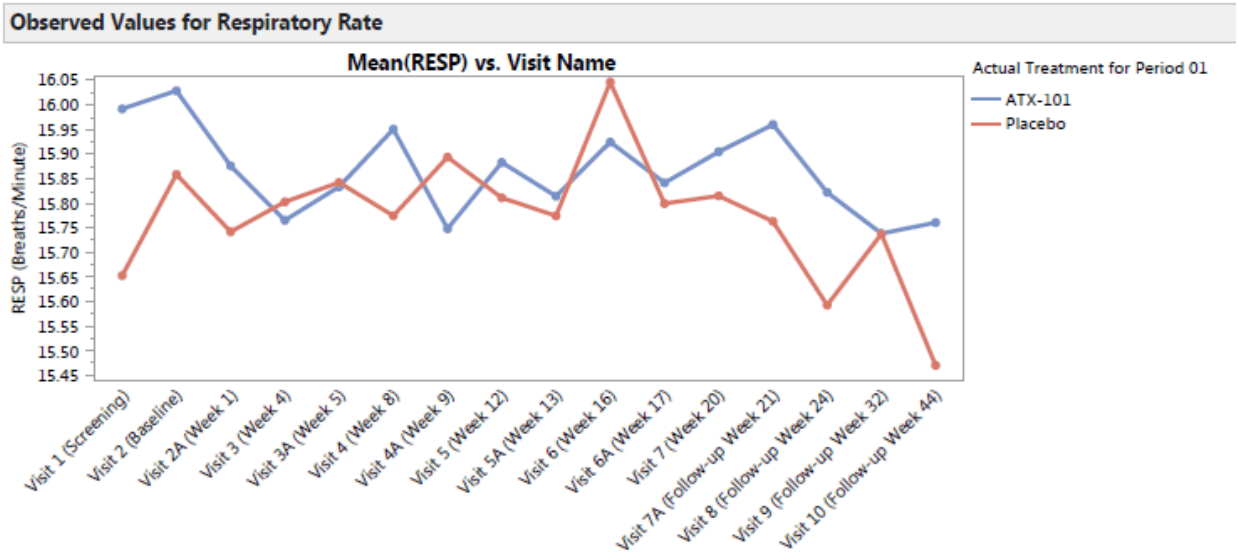
However, the individual blood pressure data from AE datasets revealed that higher number of ATX-101 treated subjects had HTN v. placebo treated.
On the opposite side of that spectrum, four subjects (all women) developed syncope. They received 1, 2, 5, and 6 treatments (respectively) and total volume of 0.8ml, 9ml, 13.8ml, and 18.4 ml of ATX-101. Day of AEs in relationship to the protocol ranged from study day 1 to study day 213.Treatment was discontinued in 2 cases due to the event and administrative decision in one. All subjects recovered without sequelae.

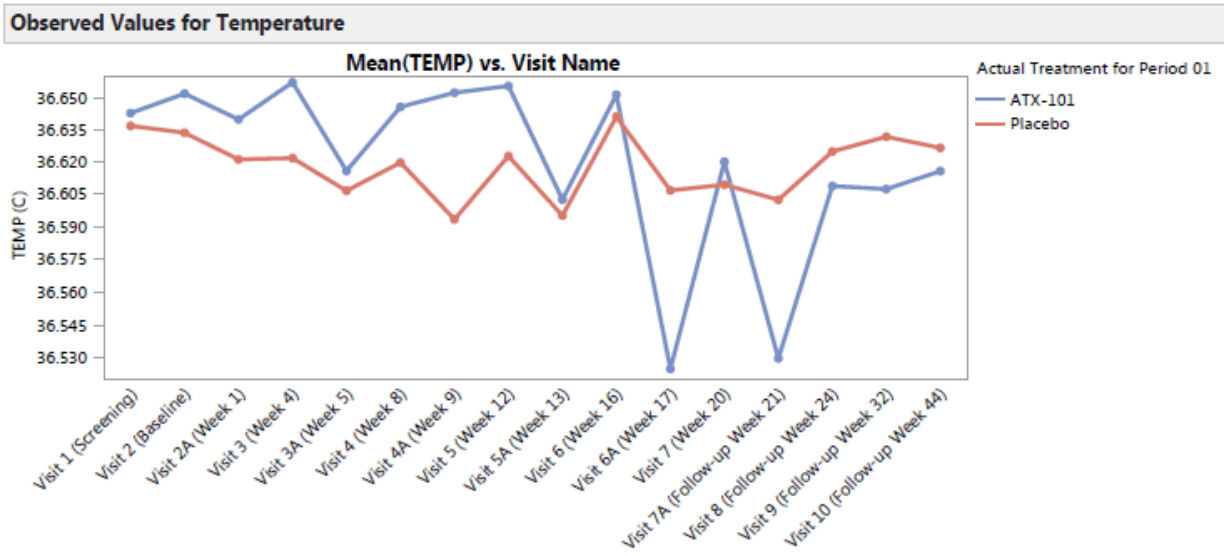
There were also 3 cases of pre-syncope (all in active arm) that resulted in treatments not being completed in two cases (due to withdrawal of consent and AE, respectively). The reported term for all three AEs was vasovagal event.

It does not appear to be dose-relationship for these events thus it is likely that (pre) syncopies are neurogenic in etiology (due to injections/pain). It is reassuring that one subject in TQT study who received ATX-101, developed syncope during Holter monitoring which did not correlate to any significant cardiac rhythm changes.

In addition to hypertension, I recommend that possibility of developing pre/syncope be included in labeling due to the observed combined frequency (1.4 % for active v. 0% for placebo) and plausible causality to injection administration.

Figure 25 Mean Respiratory Rate and Temperature Change in Trials 22 and 23





Source: Reviewer's analysis

7.4.4 Electrocardiograms (ECGs)

There were 5 studies in which 12-lead ECG was included in safety assessment: 4, 8, 18, 19, and 32. None of the studies found clinically meaningful effect of ATX-101 on ECG parameters.

7.4.5 Special Safety Studies/Clinical Trials

TQT study was conducted under protocol ATX- 101-11-24 titled A Four-Arm, Parallel Design, Randomized, Double-Blinded, Placebo, and Active Controlled Study for the Evaluation of the Effect of Therapeutic and Supratherapeutic Single-Dose ATX-101 on the QT/QTc Intervals in Healthy Volunteers.

A total of 218 healthy men and women between 18 and 65 years of age were randomized in 1:1:1:1 ratio into one of the following four treatment groups:

Regimen	Treatment	Administration
A	ATX-101 1.0%	25 x 0.4 mL subcutaneous injections of ATX-101 1.0% (100 mg total) into submental fat
B	ATX-101 2.0%	25 x 0.4 mL subcutaneous injections of ATX-101 2.0% (200 mg total) into submental fat
C	Moxifloxacin[a]	Single oral 400 mg moxifloxacin dose
D	ATX-101 Placebo	25 x 0.4 mL subcutaneous injections of phosphate-buffered saline containing 0.9% (w/v) benzyl alcohol into submental fat

*Administered in open-label fashion; all other treatments administered in double-blind fashion.

All injections (ATX-101 100 mg, ATX-101 200 mg, and placebo) were administered in a single session. Each subject received 25 injections (0.4 mL each for a total volume of 10 mL) into the submental fat spaced on a 1.0-cm grid within 5 minutes. Moxifloxacin was administered as a single oral dose. Continuous 12-lead ECGs were recorded using an ambulatory Holter monitor throughout the confinement period.

The QT team assessed the dosing as well as the timing of ECG/PK assessments as adequate to capture potential effects at Tmax and delayed effects over 24 hours.

The point estimates and the 90% CIs corresponding to the largest upper bounds for ATX-101 (100 mg and 200 mg) and the largest lower bound for Moxifloxacin is summarized below (Table 1 from interdisciplinary QT review copied electronically):

Treatment	Time	ΔΔQTcF (ms)	90% CI (ms)
ATX-101 100 mg	24 hr	2.2	(-0.8, 5.1)
ATX-101 200 mg	15 min	2.0	(-0.3, 4.2)
Moxifloxacin 400 mg	3 hr	13.2	(11.0, 15.5)

- Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 10.2 ms

The QT team concluded that:

"The supratherapeutic dose (200 mg) produces mean Cmax values 30% higher than the mean Cmax for the therapeutic dose (100 mg). At these concentrations there are no detectable prolongations of the QT-interval."

Safety assessment revealed that 1subject in ATX-101 100 mg group and 1 subject in moxifloxacin group experienced syncope during the study; however, none of these subjects had clinically significant abnormalities detected in their ECGs prior or during the syncope episode.

Comment: No significant QTc prolongation effect of ATX-101 (100 mg and 200 mg) was detected in this TQT study. It should be noted that the mean Cmax from the supratherapeutic dose of 200 mg was 961±244 ng/mL, and is lower than the mean Cmax from the 100 mg dose used in the PK trial (1024±304 ng/mL in Trial 32). One explanation could be different dosing regimen (25 injections 0.4 ml each v. 50 injections 0.2 ml each, respectively).

7.4.6 Immunogenicity

This drug is small molecule and not expected to induce systemic immunogenicity.

7.5 Other Safety Explorations

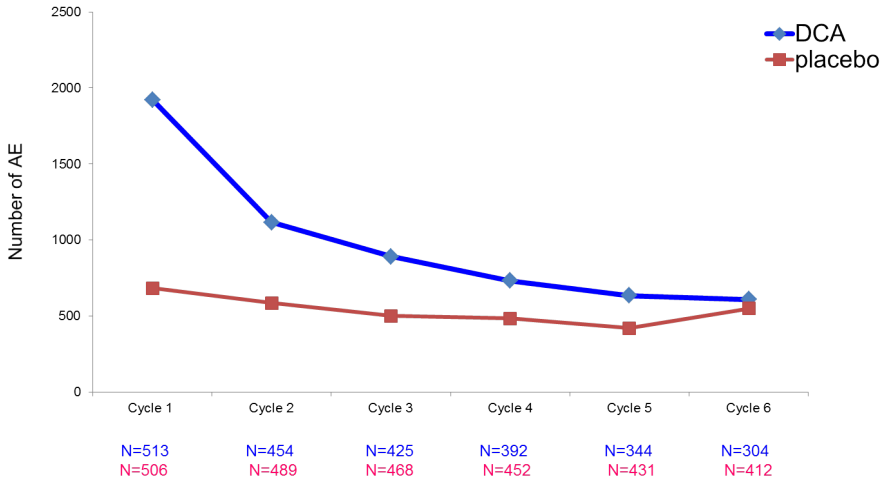
7.5.1 Dose Dependency for Adverse Events

As previously stated vast majority of the adverse events was mild-to-moderate in intensity. Exploration of the severe pain and edema in relationship to the volume of ATX-101 (number of injections) was conducted by reviewer and showed that both AEs occurred when subjects received on average 6.2 ml of ATX-101 (30 injections). For comparison, the mean number of injections for all ATX-101 treated subjects was 27 (median 27).

7.5.2 Time Dependency for Adverse Events

The total number of adverse events trended down from Cycle 1 to Cycle 6 (Figure 26). It should be noted that total number of subjects who reported AEs in the treatment area also declined Considering that treatment related AEs were also the most common AEs, one explanation for declining number of AEs over time may be that, as the treatment progressed, reduced volume of fat tissue was available for injecting.

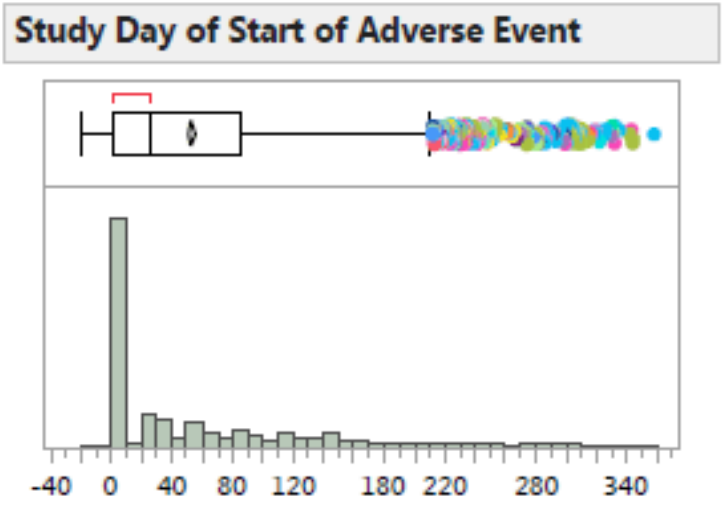
Figure 26 Time Dependency for Adverse Events



Source: Reviewer's analysis

Most of the AEs occurred at the Study day 1, following first injection administration.

Figure 27 Adverse Reactions by Study Day



Source: Reviewer's analysis

The duration of the common adverse reactions is presented below:

Table 33 Most Frequent Adverse Reactions with ≥ 30 Days Duration

	ATX-101 (N = 513)			Placebo (N = 506)		
Preferred Term	**Events**	**N**	**(%)**	**Events**	**N**	**(%)**
Injection site anesthesia	241	213	42	2	2	0.4
Injection site pain	96	80	16	9	7	1
Injection site induration	82	67	13	0	0	0
Injection site edema	63	54	11	4	4	0.8
Injection site swelling	49	43	8	3	3	0.6
Injection site nodule	37	32	6	4	3	0.6
Injection site paresthesia	20	20	4	0	0	0
Injection site hematoma	18	16	3	8	8	2
Injection site pruritus	14	14	3	2	2	0.4
Nerve injury	17	14	3	2	2	0.4

Source: Reviewer's analysis

Table 34 Most Frequent Adverse Reactions with > 6 Month Duration

	ATX-101 (N = 513)			Placebo (N = 506)		
Preferred Term	**Events**	**N**	**(%)**	**Events**	**N**	**(%)**
Injection site anesthesia	31	31	6	0	0	0
Injection site induration	8	8	2	0	0	0
Injection site pain	7	7	1	0	0	0
Injection site nodule	5	5	2	0	0	0
Injection site paresthesia	3	3	0.6	0	0	0
Injection site pruritus	3	3	0.6	0	0	0
Skin tightness	3	3	0.6	0	0	0

Source: Reviewer's analysis

Comment: The longest duration of AR was Injection site anesthesia (numbness) that started after Cycle 1 and lasted 349 days (subject ATX-101-11-23-517-007).

The table below presents all subjects in active arm that had unresolved adverse reactions in the treatment area at the end-of-study:

Table 35 Unresolved ARs at the Treatment Area

Subject	AE Term	Duration (days)	Severity	Causality
ATX-101-11-22-106-024	Edema	27	Mild	Related
ATX-101-11-22-107-026	Wrinkling of the submental skin	253	Mild	Related
ATX-101-11-22-116-020	Skin sensitive to touch in treatment area	241	Mild	Related
ATX-101-11-22-129-013	Hyperpigmented atrophic linear scar	130	Moderate	Related
ATX-101-11-22-139-025	Hair Loss	189	Mild	Related
ATX-101-11-22-139-025	Hypopigmented macules	330	Mild	Related
ATX-101-11-23-517-008	Induration on left side of neck	187	Mild	Related
ATX-101-11-23-520-003	Lymphadenopathy; left side of neck	85	Mild	Not Related
ATX-101-11-23-524-002	Numbness	8	Moderate	Related
ATX-101-11-23-533-011	Numbness	103	Mild	Related

Source: Reviewer's analysis

Comment: As judged from the duration, these single events (except for "numbness") obviously do not represent events that are definitely unresolved, but rather the outcome as recorded at the last subject's visit.

LONG TERM STUDIES

An open label long term study 26 was conducted in 165 subjects from eighteen centers in USA who received ATX-101 according to the same dosing regimen as the subjects from pivotal trials. Inclusion criteria were slightly different allowing older population as well as population with extreme submental fullness (grade 4) to participate. Although, the upper age of subjects was not limited, only 5 subjects were ≥ 65 years. Similarly, there were only 13 subjects who had grade 4 baseline submental fullness.

Discontinuations, serious, severe, and most frequent adverse events from this study are captured in previous analyses that include all subjects in development program who were dosed at 2 mg/cm^2.

The main objective of the study was to allow for the safety follow up 12 months after the last administered dose, and 131 subjects (79.4%) attended long-term follow-up Visit 12 (12 months after last treatment). Summarized below are only adverse events in at least 2 subjects that lasted ≥180 days:

	ATX 101 (N = 165)		
PT	Events	Number of subjects	Proportion (%)
Blood triglycerides increased	6	6	3.64
Hypercholesterolaemia	3	3	1.82
Blood glucose increased	2	2	1.21
Gastrooesophageal reflux disease	2	2	1.21
Hypertension	2	2	1.21
Injection site anaesthesia	2	2	1.21
Migraine	2	2	1.21
Type 2 diabetes mellitus	2	2	1.21

Source: Reviewer's analysis

Comment: There were no new or unexpected ARs in the long term study that could be reasonably attributed to ATX-101.

Additional long term study 12 was designed to follow subjects from studies 3, 7, and 15 for 5 years. Out of 203 enrolled subjects, 23 subjects have completed 5 year follow up (as of database freeze April 12, 2014), and 152 subjects are ongoing.

7.5.3 Drug-Demographic Interactions

In submission dated July 25, 2014, the applicant submitted an acceptable rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.

Table 36 Demographics -Safety Population in Phase 3 Trials

Characteristics	ATX 101 (N=513)	Placebo (N=506)	Total (N=1019)
Gender			
Female	433 (84%)	430 (85%)	863 (85%)
Male	80 (16%)	76 (15%)	156 (15%)
Age (mean)	49	49	49
BMI (mean)	29	29	29
Race			
White	439 (86%)	447 (88%)	886 (87%)
African American	48 (9%)	34 (7%)	82 (8%)
Asian	11 (2%)	10 (2%)	21 (2%)
Other	15 (3%)	15 (3%)	30 (3%)

Source: Reviewer's analysis

AGE

Overall, 22/2424 subjects were ≥65 years of age in development program. Of those, 15 were treated with 2mg/cm^2, 6 with placebo and 1 with 1 mg/cm.^{2} Considering only pivotal trials, 9 subjects >=65 years of age were treated with ATX-101 and 5 with placebo.

Age groups in pivotal trials

Age groups	ATX-101	Placebo
19-30	24	22
31-50	246	248
51-64	234	231
>=65	9	5

Comment: The number of subjects ≥65 years is not sufficient to meaningfully assess potential differences between this and other age groups. Ongoing phase 3b study ATX-101-13-28 entitled "A Multicenter, Double-blind, Placebo-controlled Safety Study of ATX-101 (Deoxycholic Acid Injection) for the Reduction of Localized Subcutaneous Fat in the Submental Area in Subjects 65 to 75 Years of Age" is designed to address drug effects in population older than 65 years.

GENDER

Most subjects in the pivotal trials were women, therefore the distribution of AEs in women is similar to the combined populations.

Table 37 Most Frequent AEs in Women

	ATX-101(N = 433)			Placebo (N = 430)		
PT	Events	N	(%)	Events	N	(%)
Injection site pain	956	305	70.44	332	143	33.26
Injection site anesthesia	410	281	64.9	40	27	6.28
Injection site edema	827	258	59.58	325	125	29.07
Injection site swelling	421	145	33.49	192	71	16.51
Injection site erythema	269	123	28.41	170	80	18.6
Injection site induration	228	108	24.94	13	11	2.56
Injection site paresthesia	84	63	14.55	15	14	3.26
Injection site nodule	85	62	14.32	22	13	3.02
Injection site pruritus	84	59	13.63	40	26	6.05
Headache	40	36	8.31	28	19	4.42
Injection site nerve injury	25	20	4.62	1	1	0.47
Injection site warmth	37	20	4.62	14	7	1.63

Skin tightness	28	19	4.39	6	6	1.4
Blood glucose increased	19	15	3.46	20	13	3.02
Oropharyngeal pain	17	15	3.46	8	6	1.4
Urinary tract infection	13	13	3	9	7	1.63
Hypertension	13	12	2.77	5	5	1.16
Nausea	14	12	2.77	3	3	0.7
Dysphagia	10	10	2.31	1	1	0.23
Diarrhea	10	9	2.08	6	5	1.16
Injection site discomfort	11	9	2.08	0	0	0

Source: Reviewer's analysis

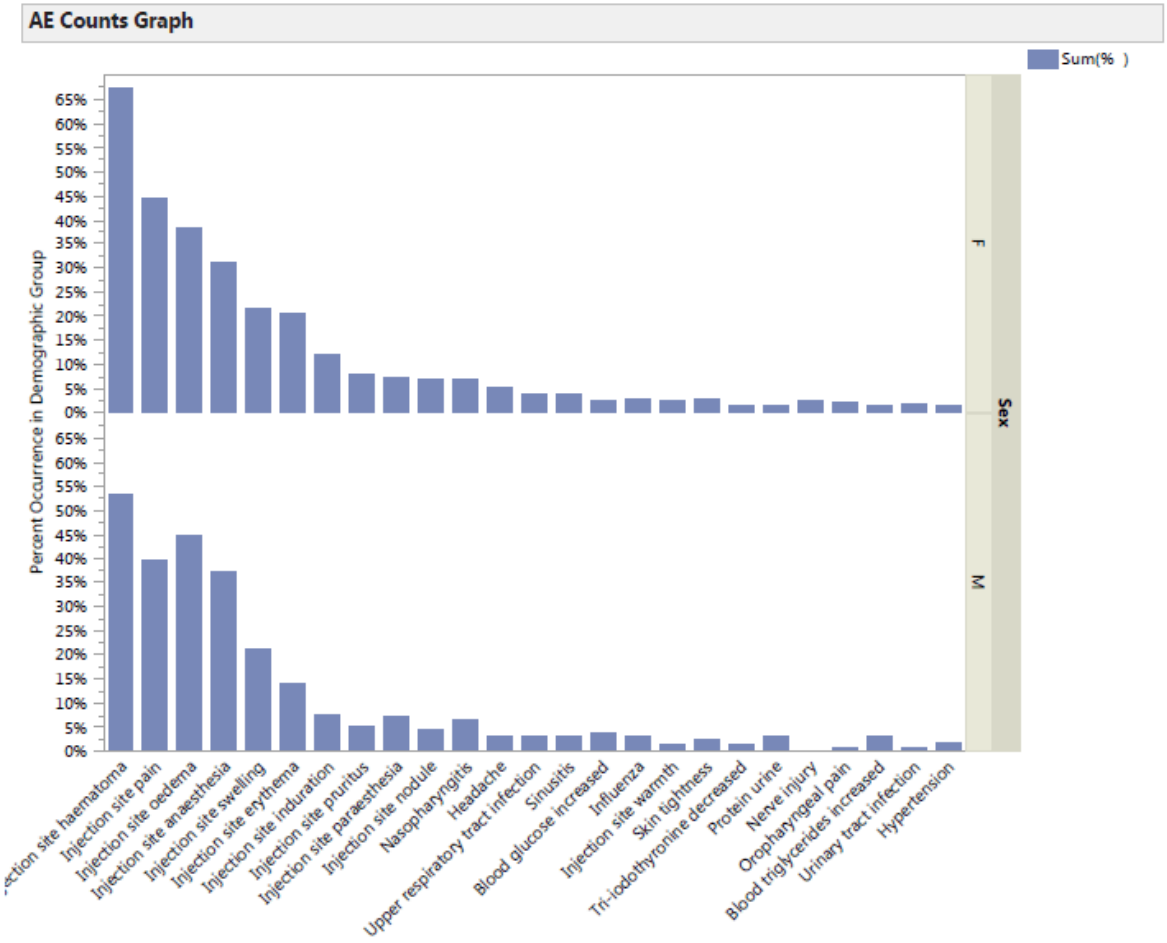
Table 38 Most Frequent AEs in Men

	ATX-101 (N = 80)			Placebo (N = 76)		
PT	Events	N	(%)	Events	N	(%)
Injection site anesthesia	115	60	75	3	2	2.63
Injection site hematoma	149	54	67.5	63	32	42.11
Injection site edema	158	53	66.25	40	22	28.95
Injection site pain	145	51	63.75	25	17	22.37
Injection site swelling	91	25	31.25	26	9	11.84
Injection site erythema	27	13	16.25	22	11	14.47
Injection site induration	18	12	15	2	2	2.63
Injection site paresthesia	14	7	8.75	9	6	7.89
Injection site nodule	7	6	7.5	1	1	1.32
Headache	5	5	6.25	1	1	1.32
Injection site pruritus	6	5	6.25	5	4	5.26
Skin tightness	8	5	6.25	0	0	0
Lymphadenopathy	4	4	5	1	1	1.32
Protein urine	4	4	5	2	2	2.63
Influenza	3	3	3.75	2	2	2.63
Injection site hemorrhage	5	3	3.75	0	0	0
Blood bilirubin increased	2	2	2.5	0	0	0
Blood urea increased	2	2	2.5	2	1	1.32
Glucose urine	3	2	2.5	0	0	0
Injection site warmth	4	2	2.5	1	1	1.32
Neck pain	2	2	2.5	0	0	0

Source: Reviewer's analysis

Comment: Overall, the incidence of AEs was similar between genders with exception of nerve injuries and dysphagia which occurred exclusively in women. Direct comparison between genders is presented below:

Figure 28 Adverse Events-Gender Comparison



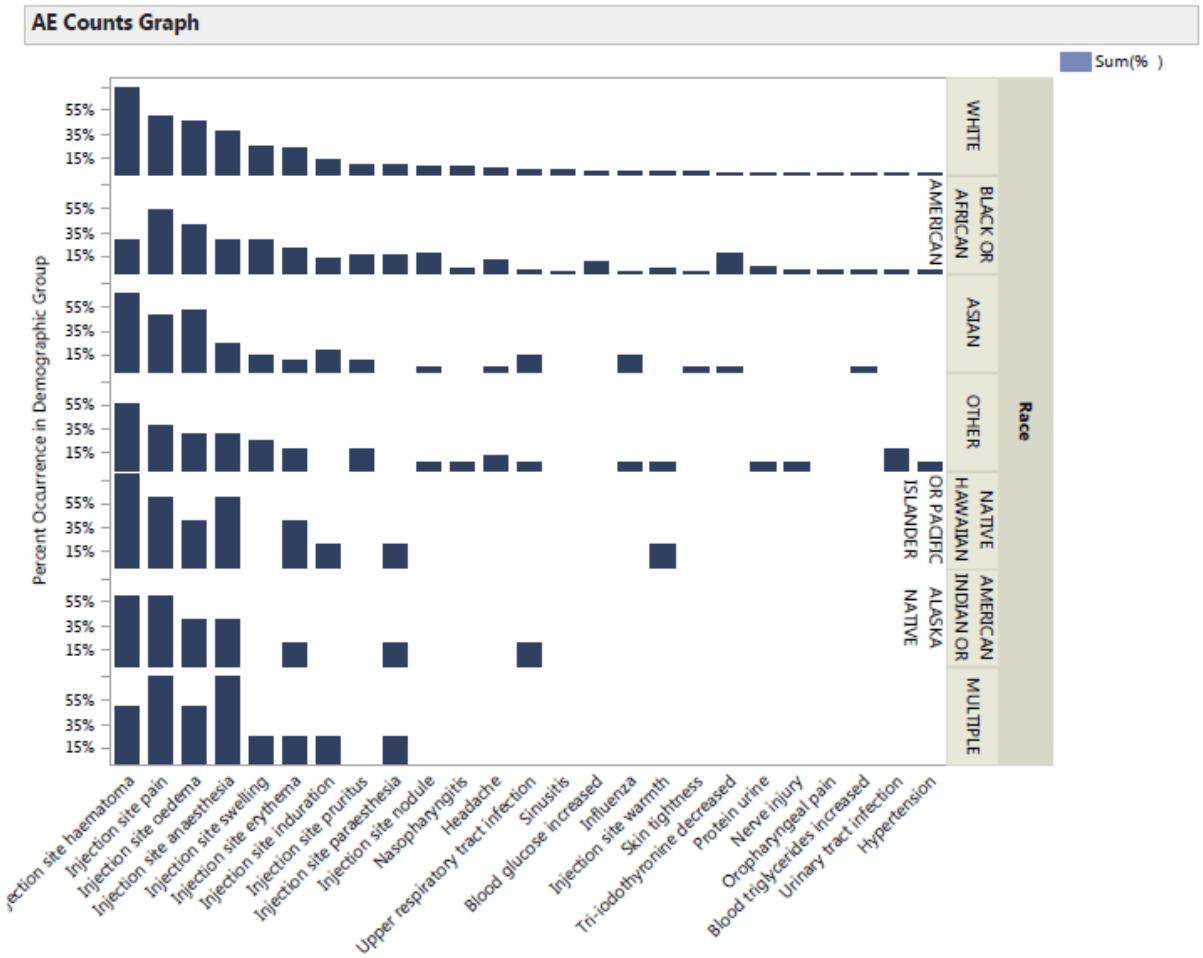
Source: Reviewer's analysis

Comment: The gender differences are influenced by disparity between women and men (5:1) and are not likely to be of clinical significance with exception of nerve injuries and dysphagia. (b) (4)

RACE

Majority of subjects were White followed by African-American. All racial groups are presented in Figure 29 for visual comparative purpose:

Figure 29 Adverse Events -Racial Comparison



Source: Reviewer's analysis

Comment: With the exception of injection site hematoma, there was no observable difference in the incidence of AEs between the two most represented race groups. Other races are presented as well, however the number of subject in each of them is too small for meaningful comparisons.

7.5.4 Drug-Disease Interactions

Not explored.

7.5.5 Drug-Drug Interactions

Not explored in clinical trials. *In vitro* inhibition and induction studies indicated that ATX-101 is not likely to induce the activity of P450 enzymes at the concentrations found in human after administration at the proposed doses of up to 100 mg.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Non-clinical carcinogenicity studies were waived. No formal clinical trials in human carcinogenicity were neither recommended nor conducted.

7.6.2 Human Reproduction and Pregnancy Data

There were two subjects who reported pregnancies while receiving the treatment:

- Subject 306-007, 39 years old, who received ATX-101 (10 mg/mL) in Study 16 had a spontaneous abortion (miscarriage) approximately 7 weeks after her last treatment. The subject discontinued from the study. Subject has a PMH significant for congenital uterine anomaly, salpingectomy, and 4 previous miscarriages.
- Subject 532-029, who received PBO in Study 23, reported pregnancy 18 days after her last treatment. The subject delivered a healthy child.

There were two pregnancies that occurred after the treatments were completed:

- Subject 7305-018, who received PBO in Study 17, became pregnant soon after completing her last study treatment and subsequently gave birth to a healthy child.
- Subject 0426/0149, who received ATX-101 (200 mg) in Study 24, had a positive pregnancy test at the end of study. The subject elected to terminate the pregnancy.

Comment: Although, these cases do not raise safety concern, ATX-101 is (b) (4) *according to preclinical data, and the conclusion of the Agency nonclinical review by Dr. Merrill.*

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant requested a full waiver of pediatric studies (up to 18 years of age), because the indication of non-surgical reduction of submental fat is unlikely to be used in a substantial number of all pediatric age groups.

The request for full waiver was presented to Pediatric Review Committee (PeRC) on December 3, 2014. The Committee agreed with the Division's recommendation that a waiver for pediatric population less than 18 years of age be granted.

Comment: The sponsor conducted a review of the literature confirming no case of submental fat reduction in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is minimal risk of abuse for ATX-101 given that drug is administered by a health care provider in the office setting. Accidental administration of excessive doses/volumes of ATX-101 may lead to increased local adverse reactions.

7.7 Additional Submissions

The 120 day safety update was submitted on September 5, 2014. In addition to updated data on long term no-treatment follow up-studies 12, 1403740, and 35, safety summary was provided for ongoing studies 27, 28, and 36. There were no new safety signals that could be reasonably attributed to ATX-101.

8 Postmarket Experience

Not applicable; ATX-101 is not currently marketed in any country.

9 Appendices

9.1 Literature Review/References

Ablon G, Rotunda AM. Treatment of lower eyelid fat pads using phosphatidylcholine: clinical trial and review. *Dermatol Surg*. 2004;30(3):422-427

Duncan DI, Hasengschwandtner F. Lipodissolve for subcutaneous fat reduction and skin retraction. *Aesthetic Surg J*. 2005;25(5):530-543.

Schlessinger J, Weiss SR, Jewell M, et al. Perceptions and practices in submental fat treatment: a survey of physicians and patients. *Skinmed*. 2013;11(1):27-31.

Schuller-Petrovic S, Wolkart G, Hofler G, Neuhold N, Freisinger F, Brunner F. 2008. Tissue-toxic effects of phosphatidylcholine/deoxycholate after subcutaneous injection for fat dissolution in rats and a human volunteer. Dermatol Surg 34:529-543.

Rohrich RJ, Rios JL, Smith PD, Gutowski KA. Neck rejuvenation revisited. *Plast Reconstr Surg*. 2006;118(5):1251-1263.

Rotunda AM, Suzuki H, Moy RL, Kolodney MS. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. *Dermatol Surg*. 2004;30(7):1001-1008.

Thuangtong R, Bentow JJ, Knopp K, Mahmood NA, David NE, Kolodney MS. Tissueselective effects of injected deoxycholate. *Dermatol Surg*. 2010;36(6):899-908.

Thuangtong R, Bentow JJ, et al. Tissue-Selective Effects of Injected Deoxycholate. *Dermatol Surg*. 2010;36: 899-908.

9.2 Labeling Recommendations

On December 12, 2014, the proposed name (b) (4) was found conditionally acceptable by Office of Medication Error Prevention and Risk Management; however, the applicant withdrew the name (b) (4) and re-submitted the proposed name Kybella, which is currently under review.

Labeling recommendations are under negotiations with the applicant. Key clinical recommendations that differ from the applicant's proposal have been incorporated though-out the Review. Agreed upon labeling will be attached to the Approval letter.

9.3 Advisory Committee Meeting

This NDA was presented to the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) on March 9, 2015 for discussion and recommendations. Committee members were asked to comment on the overall safety and efficacy data presented in support of approval of ATX-101 for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

Committee unanimously agreed that available data support approval of ATX-101 for this indication. Please see the transcript for details of the committee discussion.

9.4 Clinical Investigator Financial Disclosure

Application Number: 206,333

Submission Date: 05/13/2014

Applicant: Kythere Biopharmaceuticals, Inc.

Product: ATX-101

Reviewer: Milena Lolic, MD, MS

Date of Review: 12/20/2014

Covered Clinical Study: ATX-101-11-22 and ATX-101-11-23

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 143		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

These arrangements do not raise the questions about the integrity of the data due to randomized, blinded design of the trials, stringent composite endpoints, and minimal contribution of individual investigators to overall trial data. The analysis of efficacy according to the investigative site did not show any significant outliers. Statistical analysis excluding data from clinical investigator with the largest financial arrangement did not significantly influence the final outcome.

The disclosed financial interests/arrangements, do not affect the approvability of the application.

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

/s/

MILENA M LOLIC
03/12/2015

DAVID L KETTL
03/15/2015

CLINICAL FILING CHECKLIST FOR NDA

NDA Number: 206333 **Applicant: Kythera Biopharmaceuticals, Inc** **Stamp Date: 5/13/2014**

Drug Name: ATX-101 **NDA Type: standard**

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? • Study Number: ATX-101-03 Study Title: Phase 1-2, Multicenter, Randomized, Placebo-controlled, Parallel-group Study of the Safety and Efficacy of ATX-101 (Sodium Deoxycholate for Injection) for the Reduction of Subcutaneous Fat in the Submental Area Size: 85 subjects Arms:4 • Study Number: ATX-101-07-07	X			

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
	Study Title: Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of the Safety and Efficacy of ATX-101 (Sodium Deoxycholate for Injection) Given by Three Dosing Paradigms for the Reduction of Localized Subcutaneous Fat in the Submental Area Size:74 Arms:3 • Study Number: ATX-101-09-15 Sudy Title: Multicenter, Randomized, Double-blind, Placebo-controlled Study of ATX-101 (sodium deoxycholate injection) versus Placebo for the Reduction of Localized Subcutaneous Fat in the Submental Area (SMF) Using Magnetic Resonance Imaging (MRI) and a Battery of Clinician and Subject-reported Measurements Size: 129 Arms: 3				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? • Pivotal Study #1 ATX-101-11-22 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ATX-101 (Sodium Deoxycholate Injection) Versus Placebo for the Reduction of Localized Subcutaneous Fat in the Submental Area • Pivotal Study #2 ATX-101-11-22 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ATX-101 (Sodium Deoxycholate Injection) Versus Placebo for the Reduction of Localized Subcutaneous Fat in the Submental Area	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Study ATX-101-11-24

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	This is NME
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
	available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	Division requested CRF for deaths, serious adverse events, and adverse dropouts only.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Per *Guidance for Industry- Expedited Programs for Serious Conditions – Drugs and Biologics* dated May 2014 Priority Review Designation is intended for NDA submitted for an approval of drug that treats a serious condition. A serious disease or condition is defined in 21 CFR 312.300(b)(1) as follows:

> . . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Moderate to severe convexity or fullness associated with submental fat in adults does not represent a serious disease or condition, therefore a Priority Review can not be granted for this NDA.

2. Submit a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.

Milena Lolic, MD, MS — June 18, 2014

Reviewing Medical Officer — Date

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

/s/

MILENA M LOLIC
06/25/2014

DAVID L KETTL
06/26/2014