CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206333Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206333	Submission Date(s): 5/13/2014
Brand Name	To be determined
Generic Name	Deoxycholic acid injection, 10 mg/mL
Primary Reviewer	An-Chi Lu, M.S., Pharm.D.
Pharmacometric Team Leader	Jeffry Florian, Ph.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Kythera
Submission Type	Original NDA
Formulation; Strength(s)	Injectable solution, 10 mg/mL
Indication	For the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults

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1 Executive Summary

This application is for ATX-101 (deoxycholic acid) injection, 10 mg/mL. ATX-101 is a new molecular entity (NME). The Sponsor has submitted this NDA via 505(b)(1) regulatory pathway, and the proposed indication for ATX-101 is for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults. Up to six single treatments may be administered at intervals no less than 4-weeks apart.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 206333 acceptable from a Clinical Pharmacology perspective, pending agreement on recommended labeling changes.

1.2 Phase IV Commitments/Requirements

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Systemic bioavailability:

Trial 32 was a safety and pharmacokinetic trial to characterize the pharmacokinetic profile of the 2 final to-be-marketed formulations (one with benzyl alcohol [BA] as U.S. formulation and one without BA as EU formulation) of ATX-101 after subcutaneous (SC) administration into the submental fat using the maximum proposed dosing regimen that is intended for labeling. A total of 24 subjects with presence of sufficient submental fat were randomized in a 1:1 ratio to receive the BA-preserved formulation or the preservative-free formulation; all study drug was administered as 50 injections into the submental fat (0.2 mL each for a total volume of 10 mL and total dose of 100 mg) spaced on a 1.0-cm grid in a single dosing session.

At baseline, the individual values of endogenous plasma concentrations varied across subjects and timepoints, with a range of below the lower limit of quantification (LOQ=25.6 ng/mL) to 1280 ng/mL. The average endogenous plasma concentration ($AUC_{0-24}/24$) was 227 ng/mL over the 24-hour collection period.

Following single treatment SC administration of ATX-101, the mean deoxycholic acid concentrations increased from pre-treatment values of approximately 200 ng/mL to nearly 1000 ng/mL at 5 minutes post-treatment; the mean post-treatment plasma DCA decreased gradually and, on average, returned to endogenous baseline levels by 24 hours post-treatment. The mean Day 1 plasma exposures for the U.S. formulation as measured by AUC_{0-24} and C_{max} were approximately 1.6-fold greater (7896 ng*hr/mL vs 4854 ng*hr/mL) and 3.2-fold greater (1024 ng/mL vs 324 ng/mL), respectively, than the endogenous values at Baseline. The median T_{max} was 18 minutes.

Effects on QT interval:
From the review of Interdisciplinary Review Team for QT Studies Consultation, Dr.Moh Jee Ng has concluded that no significant QTc prolongation effect of ATX-101 (100 mg and 200 mg) was detected in the Thorough QTc Trial ATX-101-11-24. For the supratherapeutic dose group of 200 mg, ATX-101 2.0% was administered as 25 x 0.4 ml into submental fat. The mean C_{max} from the supratherapeutic dose of 200 mg was 961±244 ng/mL, and is lower than the mean C_{max} from the 100 mg dose used in the PK trial (1024±304 ng/mL in Trial 32). By assessing the QTcF change from placebo and baseline adjusted vs deoxycholic acid concentration profile, it appears that the QTcF change is not affected by deoxycholic acid concentration at the range approximately up to 1200 ng/mL. Therefore, even though the C_{max} of the supratherapeutic dose obtained in this TQT trial is lower than that from the maximal use PK trial, ATX-101 does not have the potential for TQT prolongation up to the systemic concentration of 1200 ng/mL.

Drug-Drug Interaction:
The drug-drug interaction potential of ATX-101 was assessed in *in vitro* inhibition and induction studies. The results indicated that ATX-101 is not likely to induce the activity of CYP1A, CYP2B6, and CYP3A or inhibit the activity of CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. The [I]/Ki ratio based on mean C_{max} from Trial 32 is <0.052. In addition, ATX-101 is shown to be an inhibitor of BSEP transporter, which is anticipated since deoxycholic acid is an endogenous compound, and is a substrate for BSEP. Otherwise, ATX-101 is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3.

Pediatrics:
The applicant requested a waiver of pediatric data in all subsets of the pediatric population (up to 18 years of age), because the indication of non-surgical reduction of submental fat are typically age-related and for growth and development reasons should not be recommended in pediatric patients. The Division of Dermatology and Dental Products (DDDP) concludes that this full waiver is acceptable.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for ATX-101, 10 mg/mL?

ATX-101(deoxycholic acid) injection, 10 mg/mL is proposed for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults.

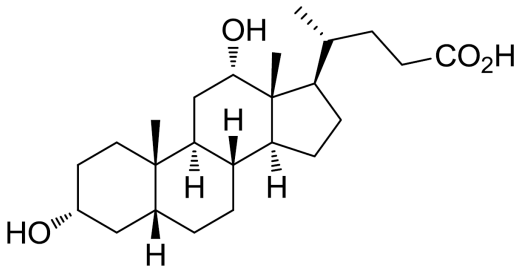
2.1.2 What is submental fat?

Submental area is the area under the chin. The submental fat is usually presented as a double chin. Current treatment options for submental contouring include traditional aesthetic surgical procedures performed under general anesthesia, as well as targeted liposuction, which may be performed under general or local anesthesia.

2.1.3 What are the highlights of the physicochemical properties of ATX-101, 10 mg/mL?

Chemically, ATX-101 (deoxycholic acid) is (4R)-4-(3R,5R,8R,9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoic acid. Deoxycholic acid has a molecular weight of 392.57 g/mol, and is a white to off-white crystalline powder with a melting range of 172° to 175°C.

The molecular formula of deoxycholic acid is $C_{24}H_{40}O_4$. The structural formula is as follows:



Formulation properties:
ATX-101 is an injectable solution that contains 10 mg/mL of the active ingredient, deoxycholic acid, formulated in a sterile solution of sodium hydroxide, dibasic sodium phosphate, sodium chloride and water for injection (WFI), with benzyl alcohol as a preservative. The formulation is adjusted to pH 8.3 with hydrochloric acid and has a tonicity compatible with that of biological tissues and fluids with an osmolality of 270-330 mOsm/kg. For details of product composition see section 2.5.2.

Dosage and Route of Administration:
Inject a dose of 0.2 mL into each injection site, 1 cm apart, repeating the process using multiple vials and syringes if necessary, until all sites in the planned treatment area have been injected. In treating patients with ATX-101, the maximum dose should not exceed 100 mg (10 mL or 50 injections) in a single treatment. Standard post-treatment methods of managing localized pain, swelling and bruising should be considered (e.g., ice, compression, etc.).

Mechanism of Action:
ATX-101 is a cytolytic drug, which when injected into tissue, physically disrupts the cell membrane causing lysis.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical trials used to support ATX-101, 10 mg/mL?

The applicant has sponsored the following 17 clinical trials in support of the development of ATX-101, 10 mg/mL:

Clinical Pharmacology Trials:

(b) (4)

ATX-101-12-32 (Trial 32): Maximal use Pharmacokinetic (PK) trial of ATX-101 in 24 subjects to receive a single 100 mg dose (2 mg/cm^2) of ATX-101 formulated either with (b) (4) or without (b) (4) the preservative benzyl alcohol.

ATX-101-11-24 (Trial 24): Thorough QT/QTc safety and PK trial of ATX-101(100 mg and 200 mg). A total of 109 subjects received ATX-101. This reviewer has reviewed the PK portion of the result. The Interdisciplinary Review Team reviewed the QT prolongation potential of ATX-101 in this trial.

Phase II trials:

ATX-101-06-03 (Trial 03): randomized, double-blind, placebo-controlled, parallel group trial of ATX-101 (n=84).

ATX-101-07-05 (Trial 05): randomized, double-blind, placebo-controlled, parallel group trial of ATX-101 (n=62).

ATX-101-07-07 (Trial 07): double-blind, placebo-controlled, parallel group trial of ATX-101 (n=71).

ATX-101-09-15 (Trial 15): double-blind, placebo-controlled, parallel group trial of ATX-101 (n=129).

Phase III trials:

ATX- 101-10-22 (Trial 22): randomized, double-blind, placebo-controlled, parallel group trial of ATX-101 (n=505) at up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%) for up to 6 treatment sessions every 4 weeks.

ATX- 101-10-23 (Trial 23): randomized, double-blind, placebo-controlled, parallel group trial of ATX-101 (n=514) at up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%) for up to 6 treatment sessions every 4 weeks.

ATX-101-10-16 (Trial 16): supportive Phase 3 trial as European formulation was used in the trial.

ATX- 101-10-17 (Trial 17): supportive Phase 3 trial as European formulation was used in the trial.

2.2.2 How was the dose/duration selected for ATX-101, 10 mg/mL?

The proposed ATX-101 clinical dose of 2 mg/cm^2 for pivotal clinical trials and commercialization, which is delivered at a concentration of 10 mg/mL in 0.2-mL injections spaced on a 1-cm grid, was chosen based on safety and efficacy results from Phase 2 trials 03, 07, and 15. These trials evaluated the product strength, volume per injection, and injection spacing. In Trial 03, the administered doses included 1 mg/cm^2 at a concentration of 5 mg/mL, 2 mg/cm^2 at 10 mg/mL, and 4 mg/cm^2 at 20 mg/mL. The doses were up to 24 injections of 0.2 mL spaced on a 1-cm grid. The results suggested that 5 mg/mL and 10 mg/mL concentrations were effective. In Trial 07, this trial was to evaluate the injection volume and grid distance. The subjects received 10 mg/mL up to 48 injections of 0.2 mL spaced on a 0.7-cm grid, or up to 24 injections of 0.2 mL spaced on a 1-cm grid, or up to 24 injections of 0.4 mL spaced on a 1-cm grid. The result showed that both the 0.2 mL/0.7 cm and 0.2 mL/1.0 cm treatment groups responded better than the 0.4 ml/1.0 cm and pooled placebo groups over time. Thus the 0.2 mL dose administered on a 1.0 cm grid was chosen for further development. In Trial 15, the administered doses included 1 mg/cm^2 at 5 mg/mL and 2 mg/cm^2 at 10 mg/mL up to 50 injections of 0.2 mL spaced on a 1-cm grid. It was concluded that ATX-101 10 mg/mL showed better efficacy than 5 mg/mL.

Across these trials, 10 mg/mL ATX-101 provided better efficacy results compared to 5 mg/mL ATX-101 across multiple efficacy parameters and had a similar safety profile. Higher local doses, achieved via increased concentration (20 mg/mL) (Trial 03), higher volume per injection (0.4 mL), or reduced spacing (0.7 cm) (Trial 07) did not appear to provide additional efficacy and resulted in a less desirable adverse event (AE) profile (more prolonged AEs).

2.2.3 What trials have been conducted for bioavailability evaluation of the drug product? What is the systemic bioavailability of ATX-101, 10 mg/mL?

The systemic exposure of ATX-101, 10 mg/mL was evaluated in Trial 32. Trial 32 was a safety and pharmacokinetic trial to characterize the pharmacokinetic profile of the 2 final to-be-marketed formulations (with and without benzyl alcohol [BA]) of ATX-101 after subcutaneous (SC) administration into the submental fat using the maximum proposed dosing regimen that is intended for labeling.

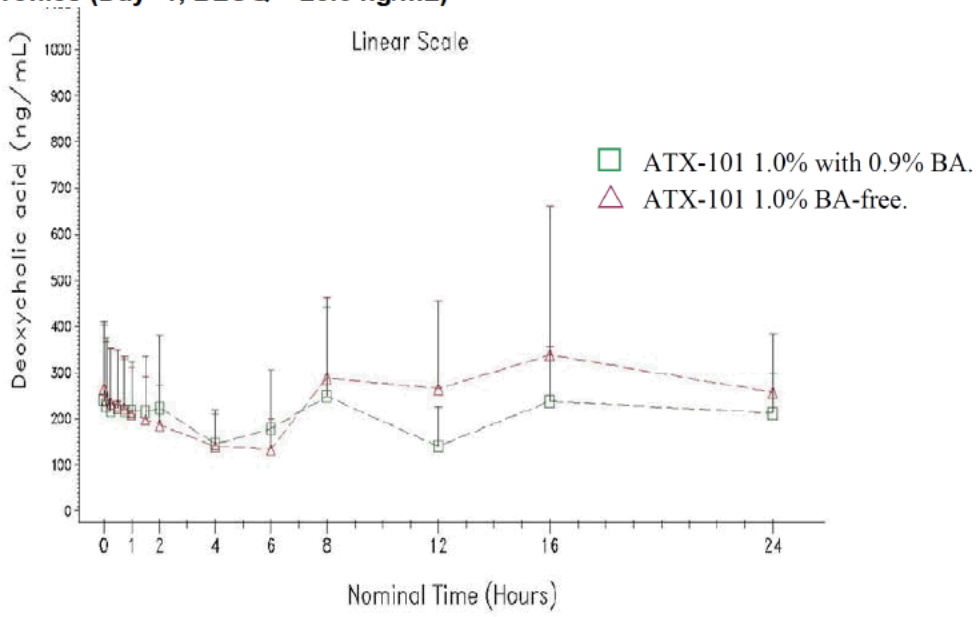
A total of 24 subjects with presence of sufficient submental fat were randomized in a 1:1 ratio to receive the BA-preserved formulation or the preservative-free formulation; all study drug was administered as 50 injections into the submental fat (0.2 mL each for a total volume of 10 mL and total dose of 100 mg) spaced on a 1.0-cm grid in a single dosing session.

Since deoxycholic acid is an endogenous substance, serial blood samples were collected on Day -1 (at approximately the same timepoints as the planned collection timepoints following study drug administration on Day 1) and Day 1 under controlled dietary conditions to permit a more accurate evaluation of the pharmacokinetic (PK) profile of deoxycholic acid from ATX-101. 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.

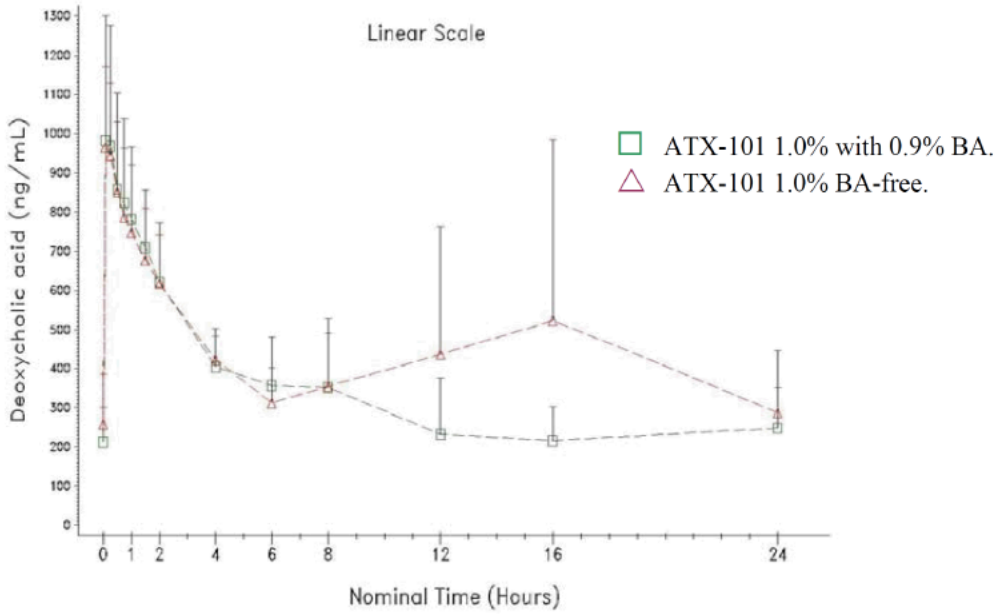
For the baseline endogenous plasma concentrations of deoxycholic acid, the individual values varied across subjects and timepoints, with a range of below the lower limit of quantification (LOQ=25.6 ng/mL) to 1280 ng/mL. The average endogenous plasma concentration (AUC_{0-24}/24 [5453/24]) was 227 ng/mL over the 24-hour collection period. The mean baseline deoxycholic acid plasma concentration-time profile for each of the two formulations is illustrated in Figure 1.

Figure 1: Mean (SD) Baseline Deoxycholic Acid Plasma Concentration-Time Profiles (Day -1, BLOQ = 25.6 ng/mL)



Following SC administration of ATX-101, the mean deoxycholic acid concentrations increased from pre-treatment values of approximately 200 ng/mL to nearly 1000 ng/mL at 5 minutes post-treatment; the mean post-treatment plasma DCA decreased gradually and, on average, returned to endogenous baseline levels by 24 hours post-treatment. The mean post-treatment deoxycholic acid plasma concentration-time profile for each of the two formulations is illustrated in Figure 2.

Figure 2: Mean (SD) Post-treatment Deoxycholic Acid Plasma Concentration-Time Profiles (Day 1, BLOQ = 25.6 ng/mL)



All 24 subjects had concentrations above the LOQ, except one subject in the BA-preserved formulation group who had one unreportable value at 1 hour post-treatment. The sponsor did not assess the PK of ATX-101 after repeated doses as no accumulation is expected with administration every 4 weeks. The mean Day 1 plasma exposures for the U.S. formulation as measured by $AUC_{0\text{-}24}$ and C_{max} were approximately 1.6-fold greater (7896 ng*hr/mL vs 4854 ng*hr/mL) and 3.2-fold greater (1024 ng/mL vs 324 ng/mL), respectively, than the endogenous values at Baseline. The median T_{max} was 18 minutes. With the LLOQ of 25.6 ng/mL, the pharmacokinetic parameters are presented below in Table 1.

Table 1: Mean (SD) Deoxycholic Acid Pharmacokinetic Parameters following Single-Treatment Subcutaneous Administration of ATX-101 (Day 1)

	BLOQ = 25.6 ng/mL[a]			Baseline-Adjusted BLOQ = 25.6 ng/mL[b]		
	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	Overall N = 24	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	Overall N = 24
Parameter						
AUC_{0-24}[c] (ng*hr/mL)	7896 (2269)	10421 (4676)	9159 (3819)	3042 (1217)	4376 (3476)	3709 (2636)
AUC_{0-inf}[d] (ng*hr/mL)	7443 (762)	7501 (1774)	7465 (1110)	NC	NC	NC
AUC_{last} (ng*hr/mL)	7915 (2272)	10421 (4675)	9168 (3816)	NC	NC	NC
C_{max}[e] (ng/mL)	1024 (304)	1036 (254)	1030 (274)	822 (263)	784 (230)	803 (242)
t_{max} (hr)[f]	0.3 (0.1, 1.1)	0.1 (0.1, 16.0)	0.1 (0.1, 16.0)	NC	NC	NC
$t_{1/2}$ (hr)[c,g]	9.3 (0.66)	8.5 (0.46)	9.0 (0.70)	NC	NC	NC

Source: Table 14.2.3.

[a]Summary statistics using the 2 BLOQ values (<50 ng/mL [historical] and <25.6 ng/mL [new]) resulted in identical PK parameters on Day 1; therefore, only results derived from the BLOQ of 25.6 ng/mL are presented in the above table and discussed throughout the clinical study report for Day 1.
[b]Baseline-adjusted PK parameters were determined using BLOQ of 25.6 ng/mL only.
[c]AUC_{0-24}: presented as mean (SD) and is the area under the concentration-time curve from time zero to 24 hours postdose.
[d]For AUC_{0-inf} and $t_{1/2}$, N = 5 for BA-preserved formulation, N = 3 for preservative-free formulation, and N = 8 for both formulations at both BLOQ levels. Subjects with invalid AUC_{0-inf} and $t_{1/2}$ values were previously identified in Table 11-f and Appendix 16.2.6.2. AUC_{0-inf} values were only available for a limited number of subjects (n=3 or 5); mean estimates for AUC_{0-inf} were lower than AUC_{last} (n=12), and no reliable interpretations can be drawn from the AUC_{0-inf} data.
[e]$C_{max:}$ presented as mean (SD) and is the maximum observed plasma concentration.
[f]t_{max}: presented as median (range) and is the time at which C_{max} was observed.
[g]$t_{1/2}$: terminal elimination half-life, calculated using 3 to 12 decreasing time points in the terminal phase of the concentration-time profile.
NC=not calculated.

2.2.4 What is the metabolic pathway for ATX-101?

No *in vitro* reaction phenotyping studies were conducted for ATX-101 by the Sponsor because information on DCA metabolism in the liver and its biotransformation pathway was reported in the literature[1].

The bile acid homeostasis is maintained by feedback regulation and feed-forward regulation. The feedback regulation is by cholesterol 7a-hydroxylase (CYP7A1), which catalyzes the rate-limiting step in bile acid biosynthesis. The feed-forward regulation is by increasing the genes that are responsible for detoxifying the bile acids by Phase I and Phase II metabolism. Bodin et al[1] conducted a study by using Human liver microsomes

[1] Bodin K, et al. Novel pathways of bile acid metabolism involving CYP3A4. Biochimica et Biophysica Acta 1687 (2005) 84–93

(HG 93) and human recombinant CYP3A4 expressed in insect cells (Supersomesk) with DCA concentration ranging from 25 to 250 μM. When incubated with recombinant CYP3A4, DCA metabolized to two products, identified as 12α-hydroxy-3-oxo-5β-cholanoic acid (3-dehydro-DCA) and 1 β, 3α, 12α-trihydroxy-5β-cholanoic acid (1β-hydroxy-DCA). When human liver microsomes and DCA were incubated with TAO (triacetyloleandomycin, a CYP3A4 inhibitor), the formation of 1 β -hydroxy-DCA was decreased, suggesting CYP3A4 is a major catalyst in human liver. In patients treated with carbamazepine (CYP3A4 inducer), the urinary concentrations of DCA were approximately the same compared to healthy volunteers, while the urinary concentrations of 1β-hydroxy-DCA were significantly increased. In summary, the study showed that DCA was metabolized mainly by CYP3A4 to 1β-hydroxy-DCA and 3-dehydro-DCA.

2.2.5 Does ATX-101, 10 mg/mL prolong QT intervals?

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

In the Thorough QTc Trial 24, a total of 218 men and women between the ages of 18 and 65 years of age (inclusive) who had not used tobacco or nicotine- containing products for at least 3 months prior to the study were to be enrolled and randomized, in a 1:1:1:1 ratio, into 1 of the 4 treatments groups below:

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

[a]Administered in open-label fashion; all other treatments administered in double-blind fashion.

The serial PK blood samples were collected at the following time points:

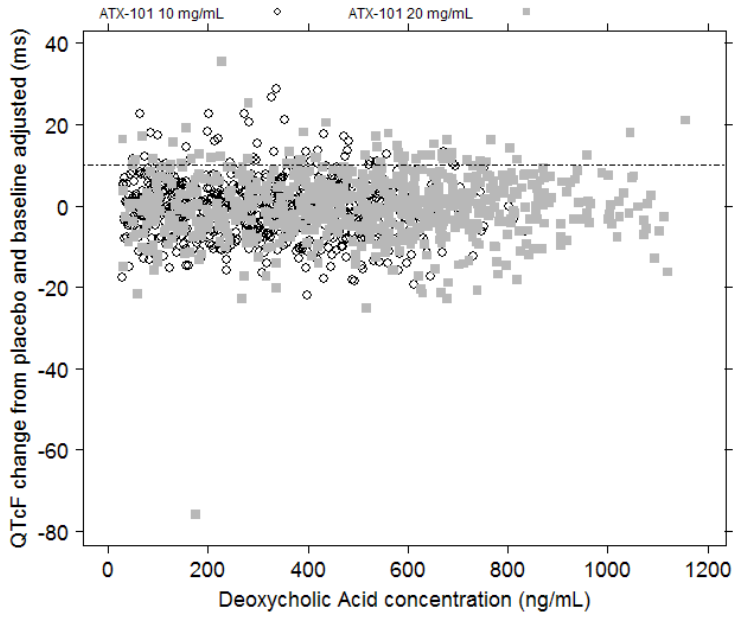
Day -1: At approximately the same times as the planned dose on Day 1: predose (0 hr), 0.083[a], 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 5, 6 [b], 8, 12 [b], 16 and 24 [c] hours.

Day 1: Predose (0 [c] hr [within 30 minutes prior to dosing]), 0.083[a], 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 5, 6 [b], 8, 12 [b], 16 and 24 hours.

[a]Per email clarification (Appendix 16.1.1.8), due to the multiple study procedures planned at 5 minutes postdose, 5-minute PK blood samples were allowed to be collected at 11 minutes postdose, and this delay in collection was not considered a protocol deviation.
[b]Collected prior to consumption of a standardized meal or snack.
[c]Day -1 24-hour postdose sample and Day 1 predose sample were the same blood samples.

For the PK results, the mean C_{max} from the supratherapeutic dose of 200 mg was 961±244 ng/mL, and is lower than the mean C_{max} from the 100 mg dose used in the PK trial (1024±304 ng/mL in Trial 32). By looking at the QTcF change from placebo and baseline adjusted vs deoxycholic acid concentration profile (Figure 3), it appears that the QTcF change is not affected by deoxycholic acid concentration at the range approximately up to 1200 ng/mL. Therefore, even though the C_{max} of the supratherapeutic dose obtained in this TQT trial is lower than that from the maximal use PK trial, ATX-101 does not have the potential for TQT prolongation up to the systemic concentration of 1200 ng/mL.

Figure 3: ΔΔ QTcF vs. Deoxycholic Acid Concentration



2.3 Intrinsic Factors

2.3.1 What is the systemic drug exposure in pediatrics?

The applicant requested a waiver of pediatric data in all subsets of the pediatric population (up to 18 years of age), because the indication of non-surgical reduction of submental fat are typically age-related and for growth and development reasons should not be recommended in pediatric patients. The Division of Dermatology and Dental Products (DDDP) concludes that this full waiver is acceptable.

2.3.2 How does the PK of ATX-101 differ in different sex and race?

A population pharmacokinetic analysis was used to evaluate the effects of sex and race on the PK of deoxycholic acid. Due to the data limitation on race [the majority of the subjects were white (117), black or African American (23), American Indian or Alaskan Native (4), Hispanic or Latino (11), Asian (2) and multiple and others (15)], the influence of race on the PK of deoxycholic acid cannot be fully assessed. As for the effects from sex, the population pharmacokinetic analysis did not identify a significant effect of sex on

either apparent clearance or volume of distribution. In addition, this reviewer conducted a statistical analysis of individual predicted CL and V based on sex, and the results showed that there is no statistically significant difference between deoxycholic acid PK parameters for males and females.

2.4 Extrinsic Factors

2.4.1 What is the effect of ATX-101 on the PK of other drugs?

In the *in vitro* inhibition study 13772, the ability of ATX-101 to inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 was evaluated in pooled human liver microsomes (HLM) using eight (8) CYP isoform specific marker substrate reactions at the concentration of 0.23, 0.94, 3.75, 15, 60, and 100 μM. Incubation mixtures containing HLM, test article, and each marker substrate in 50 mM potassium phosphate buffer (pH 7.4) were pre-warmed and reactions were initiated by the addition of NADPH. The final incubation mixture (ca. 100 μL) contained 0.1 mg/mL HLM, 4 mM $MgCl_2$, 1 mM EDTA, 1 mM NADPH, each marker substrate, and varying concentrations of test article or a selective inhibitor as positive control.

The result showed that DCA had no or little direct and time-dependent inhibitions on the tested CYP isozymes. The maximal DCA-related inhibition observed for CYPs under both direct and time-dependent inhibition conditions was less than 50% at 100 μM, which would result in a IC_{50} >100μM and Ki >50μM, assuming competitive inhibition. The [I]/Ki ratio based on mean C_{max} from Trial 32 is <0.052. Therefore, it is unlikely for ATX-101 to inhibit CYP enzymes at the concentrations found in human after administration at the proposed doses of up to 100 mg.

In the *in vitro* induction study, 100000544, the potential of ATX-101 to induce CYP1A, CYP2B6, and CYP3A enzymes at 1, 10, and 100 μM was assessed *in vitro* by enzymatic activity in primary cultured human hepatocytes from 3 donors. ATX-101 caused little or no change in the CYP activities examined with the change less than 40% of the positive control, except for CYP1A, where the induction by 1 and 10 μM ATX-101 equates to 31% to 43% of induction relative to the positive control omeprazole (in 1 of 3 lots of hepatocytes), whereas it was 15% relative to the positive control for 100 μM. There was no dose-response relationship, and other samples were all below 40% of the positive control. Therefore, it is unlikely for ATX-101 to induce CYP enzymes at the concentrations found in human after administration at the proposed doses.

2.4.2 Is ATX-101 an inhibitor and/or an inducer of transporter processes?

<u>P-gp and BCRP inhibition:</u>

The evaluation of DCA as an inhibitor of the Human BSEP, MRP2, MRP4, BCRP and MDR1 (P-gp) efflux transporters was done using the vesicular transport inhibition assays. The [I]/Ki values were all below 0.1, except for BSEP, where [I]/Ki was 0.12. Since deoxycholic acid is an endogenous compound, and is a substrate for BSEP, it is anticipated that DCA is an inhibitor of BSEP.

OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 inhibition:
The evaluation of DCA as an inhibitor of the Human OATP1B1 (OATP2/OATP-C), OATP1B3(OATP8), OATP2B1 (OATP-B), OCT1, OCT2, OAT1, OAT3, NTCP and ASBT uptake transporters was done using the uptake transporter inhibition assay. The [I]/Ki ratios based on mean C_{max} from Trial 32 were all below 0.1, except for OATP1B1 (0.14), OATP1B3 (0.11), and NTCP (1.11). However, the calculated R-values for OATP1B1, OATP1B3, and NTCP were all less than 1.25. Therefore, the potential for DCA to inhibit OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 is small.

2.4.3 What other extrinsic factors (food, herbal products, smoking, alcohol use) influence the PK of ATX-101, 10 mg/mL?

Effects of extrinsic factors, such as herbal products, smoking, and alcohol use on the PK of deoxycholic acid were not evaluated. Since ATX-101 is intended to be used subcutaneously, food interactions at GI tracts are not anticipated.

2.5 General Biopharmaceutics

2.5.1 Is the to-be-marketed formulation identical to the one used in Phase 3 efficacy and safety trials?

The to-be-marketed formulation was used in the Phase 3 safety and efficacy trials (Trial 22 and 23), the Thorough QTc trial (Trial 24), and the maximal use PK trial (Trial 32). Including the to-be-marketed formulation, a total of five ATX-101 formulations were used in the clinical trials. One of the formulations is used for the market in Europe (without Benzyl alcohol as preservative compared to US formulation).

2.5.2 What is the final product composition?

Table 2 shows the components and composition of ATX-101, 10 mg/mL.

Table 2: Composition of ATX-101, 10 mg/mL

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)

q.s. = Quantity sufficient

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess drug concentrations?

Maximal Use PK Trial 32 and Thorough QTc Trial 24

Deoxycholic acid concentration in human plasma with K_2EDTA as anticoagulant was determined by liquid chromatography tandem mass spectrometry (LC-MS/MS).

In summary, the method involved the extraction of deoxycholic acid and the added deoxycholic acid-d4 (IS), using protein precipitation. This supernatant was then subjected to reverse phase high performance liquid chromatography on a Betasil C18 column and detection of the analytes by tandem mass spectroscopy using the Sciex API3000 and API4000 LC-MS/MS systems.

2.6.2 Were the bioanalytical methods adequately validated?

Trial 24 and 32

The method for measuring deoxycholic acid concentrations in human plasma (containing K2 EDTA as anticoagulant) by LC-MS/MS was validated at (b) (4).

The standard curve range was from 15.0 to 3000 ng/mL above endogenous levels. The endogenous level of deoxycholic acid was measured by standard addition. The endogenous deoxycholic acid in the blank plasma pool used for this validation was determined to be 10.6 ng/mL. Inter-assay (between batch) precision and accuracy and intra-assay (within batch) precision and accuracy were assessed in three batches by analyzing 6 replicates each of QCs fortified at five separate concentrations (LLOQ, low, mid-1, mid-2, and high). The sponsor did not perform evaluation of extraction recovery and the sponsor noted that it was due to the fact that protein precipitation/dilution is a dilution technique and not an extraction technique. A summary of precision and accuracy results is shown in Table 3.

Table 3: Precision and Accuracy Results of Deoxycholic acid Assay in Human Plasma Validation in Trial 24 and 32

Standard Curve Range	15.0 to 3000 ng/mL above endogenous levels
Lower Limit of Quantitation (LLOQ)	15 ng/mL above endogenous level
Intra-assay Accuracy	15 ng/mL-3000 ng/mL: 104.0-109.8% 15 ng/mL (LLOQ): 101.1-107.9%
Inter-assay Accuracy	15 ng/mL-3000 ng/mL: 105.3-108.3% 15 ng/mL (LLOQ): 105.4%
Intra-assay Precision Range	15 ng/mL-3000 ng/mL: 1.3-3.5% 15 ng/mL (LLOQ): 2.5-6.1%
Inter-assay Precision Range	15 ng/mL-3000 ng/mL: 1.8-2.6% 15 ng/mL (LLOQ): 5.0%

3 Detailed Labeling Recommendations

The following changes are recommended for sections 5.1 and 12 of the label. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

(b) (4)

12.2 Pharmacodynamics

(b) (4)

Cardiac Electrophysiology

At therapeutic doses, ATX-101 does not prolong the QTc interval. (b) (4)

12.3 Pharmacokinetics

Endogenous deoxycholic acid plasma levels are highly variable within and between individuals; most of this natural bile component is sequestered in the enterohepatic circulation loop. (b) (4)

Absorption and Distribution

Deoxycholic acid from **ATX-101**™ is rapidly absorbed following subcutaneous injection. After dosing with the maximum recommended single treatment with **ATX-101**™ (100 mg), maximum plasma concentrations (mean C_{max}) were observed with a median Tmax of 18 minutes (b) (4) after injection. The (b) (4) mean (±SD) C_{max} value was 1024±304 ng/mL and was (b) (4) 3.2-fold higher than average C_{max} values observed during a 24-hour baseline endogenous period in the absence of **ATX-101**™. After maximum recommended single treatment dose (100 mg), (b) (4) mean (±SD) deoxycholic acid exposure (AUC_{0-24}) was 7896 ± 10421 ng.hr/mL and (b) (4) was 1.6-fold higher over endogenous exposure. (b) (4) AUC_{0-24} (b) (4)

(b) (4). Post-treatment deoxycholic acid plasma levels returned to the endogenous range within 24 hours. No accumulation is expected with the proposed treatment frequency.

(b) (4) Deoxycholic acid is extensively bound to proteins in plasma (98%).

Metabolism and Excretion
Endogenous deoxycholic acid is a product of cholesterol metabolism and is excreted intact in feces. Deoxycholic acid is not metabolized to any significant extent under normal conditions. Deoxycholic acid from **ATX-101**™ joins the endogenous bile acid pool in the enterohepatic circulation and is excreted along with the endogenous deoxycholic acid.

In Vitro Assessment of Drug Interactions
Results from *in vitro* studies indicate that deoxycholic acid does not inhibit human cytochrome P450 (CYP) enzymes at clinically relevant concentrations. (b) (4)
(b) (4) Deoxycholic acid does not inhibit (b) (4) the following transporters at herapeutic concentrations: P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3. (b) (4)

Specific Populations
(b) (4)

Hepatic Impairment
ATX-101™ has not been studied in subjects with hepatic impairment. Considering the intermittent dose frequency, the small dose administered that represents approximately 3% of the total bile acid pool, and the highly variable endogenous deoxycholic acid levels, the pharmacokinetics of deoxycholic acid following **ATX-101**™ injection is unlikely to be influenced by hepatic impairment.

Pharmacokinetic Effects of Gender (b) (4)
Deoxycholic acid pharmacokinetics were not influenced by gende (b) (4)

4 Appendix

4.1 Individual Trial Reviews

PK Trial ATX-101-12-32 (Trial 32)

Title: Phase 1, Open-Label, Randomized, Safety and Pharmacokinetic Study of Two Final Formulations of ATX-101 (Sodium Deoxycholate Injection) Following Subcutaneous Injections in the Submental Fat

Trial Initiation/Completion Dates: 7/11/2012-7/26/2012

Objectives: To evaluate the safety and tolerability of ATX-101 injections and to characterize the pharmacokinetic profile of the 2 final to-be-marketed formulations (with and without benzyl alcohol [BA]) of ATX-101 after subcutaneous (SC) administration into the submental fat using the maximum proposed dosing regimen that is intended for labeling.

Trial Center: Comprehensive Clinical Development NW, Inc., Tacoma, WA

Design of Trial:
Trial Population Demographics: Twenty-four adult subjects with presence of sufficient submental fat.
Age range: 20-63 years; **Race:** Caucasian (79%), African American (17%), Other (4%); **Gender:** 13 Male (54%), 11 Female (46%).

Diagnosis and Main criteria for inclusion:
- Males or nonpregnant, nonlactating females aged 18 to 65 years, inclusive, on the date of ATX-101 dosing
- Presence of sufficient submental fat into which 50 SC injections of ATX-101 spaced on a 1.0-cm grid could have been safely administered based on the investigator's judgment.

Investigational Products:

Product	Dose	Mode of Administration	Lot Number
ATX-101 (1.0%) with benzyl alcohol	100 mg	50 SC injections (0.2 mL each)	PD12007
ATX-101 (1.0%) without benzyl alcohol	100 mg	50 SC injections (0.2 mL each)	PD10091

Trial Design:
This was a single-center, open-label study in which 24 subjects were randomized in a 1:1 ratio to receive the BA-preserved formulation or the preservative-free formulation; all

study drug was administered as 50 injections into the submental fat (0.2 mL each for a total volume of 10 mL and total dose of 100 mg) spaced on a 1.0-cm grid in a single dosing session. Both formulations were to be administered under the same dietary conditions (fasting conditions [at least 12 hours pre-treatment until 6 hours post-treatment]), and standardized meals and snacks were served throughout study confinement. The total daily nutritional composition was approximately 50% carbohydrate, 35% fat, and 15% protein.
The daily caloric intake per subject did not exceed 2800 kcal. The table below (Table 4) shows the sampling requirements for Day -1 to Day 2.

Table 4: Sampling requirements

Collection Time[a]	Window (Relative to Collection Time)	Fasting/Standardized Meal[b]
Pre-Dose	Within 0.5 Hours Prior to Dosing	Fasting
5 minutes	+/- 1 min	Fasting
0.25 hours	+/- 7 min	Fasting
0.5 hours	+/- 10 min	Fasting
0.75 hours	+/- 10 min	Fasting
1 hour	+/- 10 min	Fasting
1.5 hours	+/- 10 min	Fasting
2 hours	+/- 10 min	Fasting
4 hours	+/- 10 min	Fasting
6 hours	+/- 10 min	Fasting/Lunch
8 hours	+/- 10 min	Fasting
12 hours	+/- 30 min	Fasting/Light Snack
16 hours	+/- 30 min	Fasting
24 hours	+/- 30 min	Fasting

[a] PK sample collection times on Day -1 and Day 1 should be time matched to occur at approximately the same time of day.
[b] The standardized meal is given after the blood sample is obtained at each specified collection time (i.e. 6h and 12h post-dose). Dinner will be provided 9 hours post-dose.

Since deoxycholic acid is an endogenous substance, serial blood samples were collected on Day -1 (at approximately the same timepoints as the planned collection timepoints following study drug administration on Day 1) and Day 1 under controlled dietary conditions to permit a more accurate evaluation of the pharmacokinetic (PK) profile of deoxycholic acid from ATX-101. 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. A final follow-up visit occurred on Day 8 (± 2 days).

Reviewer's comments:
In the clinical pharmacology review dated 5/2/2012 under IND 79726, it was noted that "Protocol ATX-101-12-32 has been reviewed. From a clinical pharmacology perspective the design of the study is acceptable."

Key Exclusion Criteria:
History of any intervention to treat submental fat; botulinum toxin injections in the neck/chin area, or treatment with radio frequency, laser procedures, chemical peels, or dermal fillers in the neck/chin area within 6 or 12 months before dosing, respectively; body mass index >40.0 at the Screening Visit; use of tobacco or nicotine-containing products within 3 months prior to dosing; use of investigational compounds or oral anticoagulants within 30 days prior to dosing, or agents with anticoagulative effects within 7 days before dosing; history of sensitivity to any components of the study material; and history of drug or alcohol abuse within 2 years before dosing.

Analytical Methods:
See Question-Based-Review section 2.6.1.

Analytical Method Validation:

Table 5: Deoxycholic acid in Human Plasma:

Assay Method	liquid chromatography tandem mass spectrometry (LC-MS/MS)
Analytical Site	(b) (4)
Compound	Deoxycholic acid in human plasma
Standard Curve Range	15.0 to 3000 ng/mL above endogenous levels
Lower Limit of Quantitation (LLOQ)	15 ng/mL above endogenous level
Intra-assay Accuracy	15 ng/mL-3000 ng/mL: 104.0-109.8% 15 ng/mL (LLOQ): 101.1-107.9%
Inter-assay Accuracy	15 ng/mL-3000 ng/mL: 105.3-108.3% 15 ng/mL (LLOQ): 105.4%
Intra-assay Precision Range	15 ng/mL-3000 ng/mL: 1.3-3.5% 15 ng/mL (LLOQ): 2.5-6.1%
Inter-assay Precision Range	15 ng/mL-3000 ng/mL: 1.8-2.6% 15 ng/mL (LLOQ): 5.0%
Freeze-Thaw Stability	4 cycles
Bench-Top Stability	7 hours
Processed Stability	Processed samples were stable at room temperature and when refrigerated stored in glass vials on the autosampler over a period of 3 days 2 hours.
Long Term Stability	244 days (-20°C) *The maximum period of storage between first sample collection on 7/12/2012 and last day of analysis on 8/2/2012 was 21 days. The samples were stored at or below -20°C.*
Dilution Integrity	Up to 5-fold
Matrix Effect	QC pools were spiked with deoxycholic acid-d4 (internal standard) at 75 ng/mL to six different lots of plasma. The %CV of the mean surrogate response across the 6 lots was 2.5%.
Reviewer's comments	***Method acceptable***

Pharmacokinetic Analysis:

- AUC_{0-24}: Area under the plasma concentration-time curve (AUC) from time 0 to 24 hours post-treatment (AUC_{0-24}), calculated using the linear trapezoidal rule (Day -1 and Day 1).
- AUC_{last}: AUC curve from time 0 to time of the last quantifiable concentration (last), calculated using the linear trapezoidal rule (Day 1 only).
- AUC_{0-inf}: AUC from time 0 to infinity, calculated as AUClast + Clast/λz, where C_{last} is the last quantifiable concentration and λz is the terminal elimination rate constant (Day 1 only).
- C_{max}: Maximum observed plasma concentration (Day -1 and Day 1).
- T_{max}: Time to reach C_{max} (Day -1 and Day 1).

- $t_{½}$: Half-life associated with terminal phase of the concentration-time profile, calculated by linear regression of at least 3 declining concentration time points in the terminal phase, calculated as ln(2)/ λz (Day 1 only).

In addition, baseline-adjusted values for C_{max} and AUC_{0-24} were also determined using the lower limit of quantitation of 25.6 ng/mL as follows:

- AUC_{0-24}_adj: Post-treatment deoxycholic acid plasma AUC_{0-24}– Baseline deoxycholic acid plasma AUC_{0-24}
- C_{max}_adj: Post-treatment deoxycholic acid plasma C_{max} – Baseline deoxycholic acid plasma C_{avg}, where Baseline C_{avg} = Baseline AUC_{0-24}/24.

Mean plasma concentrations were summarized separately using 2 different lower limits of quantitation (BLOQ). One was the historical BLOQ of 50 ng/mL used in previous clinical trials, and the other was a newer BLOQ determined from the validated assay performed by (b) (4) for this trial. The (b) (4) assay was validated for a concentration range of 15.0 ng/mL to 3000 ng/mL above the endogenous level. Since the endogenous concentration of deoxycholic acid in the blank plasma sample used to prepare standards was 10.6 ng/mL, the validated analytical range (including the endogenous concentration) was 25.6 ng/mL to 3010 ng/mL for this trial.
For parameter estimation, plasma concentrations that were less than the BLOQ were considered to be halfway between the BLOQ and zero for the 50 ng/mL BLOQ (ie, 25 ng/mL, for consistency with historical analyses), and were considered as zero for the 25.6 ng/mL BLOQ for summarization at each timepoint.

Pharmacokinetic Results:
A total of 24 subjects were enrolled and treated in the trial, and all 24 subjects completed the trial. Among the 24 subjects, the individual baseline endogenous plasma concentrations of deoxycholic acid varied across subjects and timepoints, with a range of below the lower limit of quantification (LOQ=25.6 ng/mL) to 1280 ng/mL. 12 out 12 subjects in BA-preserved formulation group had deoxycholic acid concentrations above LOQ, and 1 out of 12 subjects in preservative-free formulation group had BLQ concentrations at 6, 8, and 12 hours. The average endogenous plasma concentration (AUC_{0-24}/24 [5453/24]) was 227 ng/mL over the 24-hour collection period. Figure 4 is the mean baseline deoxycholic acid plasma concentration-time profile for each of the two formulations.

Following SC administration of ATX-101, the mean deoxycholic acid concentrations increased from pre-treatment values of approximately 200 ng/mL to nearly 1000 ng/mL at 5 minutes post-treatment; the mean post-treatment plasma DCA decreased gradually and, on average, returned to endogenous baseline levels by 24 hours post-treatment (Figure 5). All 24 subjects had concentrations above the LOQ, except one subject in the BA-preserved formulation group had one unreportable value at 1 hour post-treatment. For the cohort of ATX-101 with 0,9% BA (US formulation), the mean Day 1 plasma exposures as measured by AUC_{0-24} and C_{max} were approximately 1.6-fold greater (7896 ng*hr/mL vs 4854 ng*hr/mL) and 3.2-fold greater (1024 ng/mL vs 324 ng/mL), respectively, than the endogenous values at Baseline. The median T_{max} was 18 minutes.

Figure 4: Mean (SD) Baseline Deoxycholic Acid Plasma Concentration-Time Profiles (Day -1, BLOQ = 25.6 ng/mL)

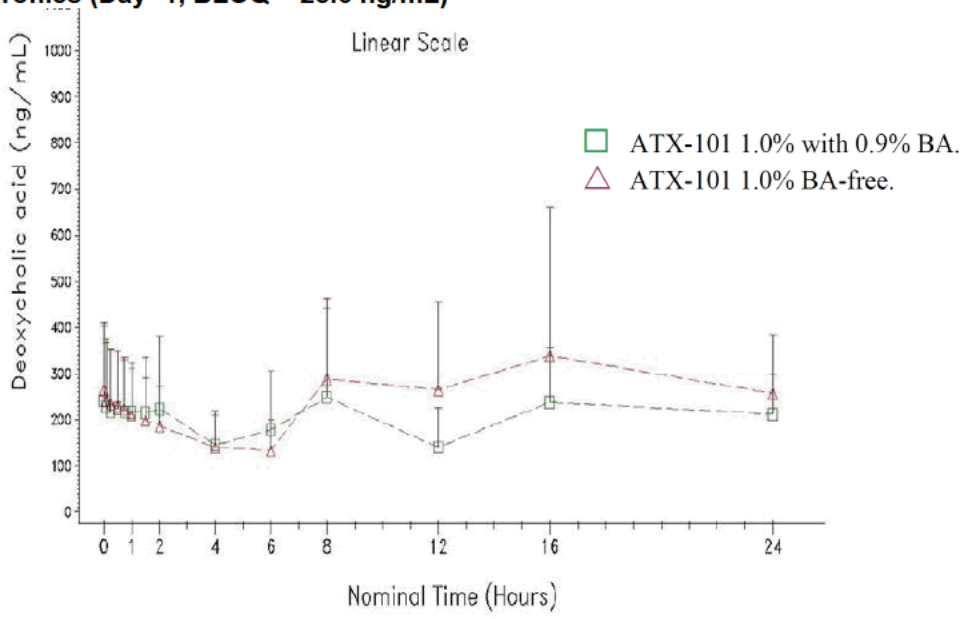
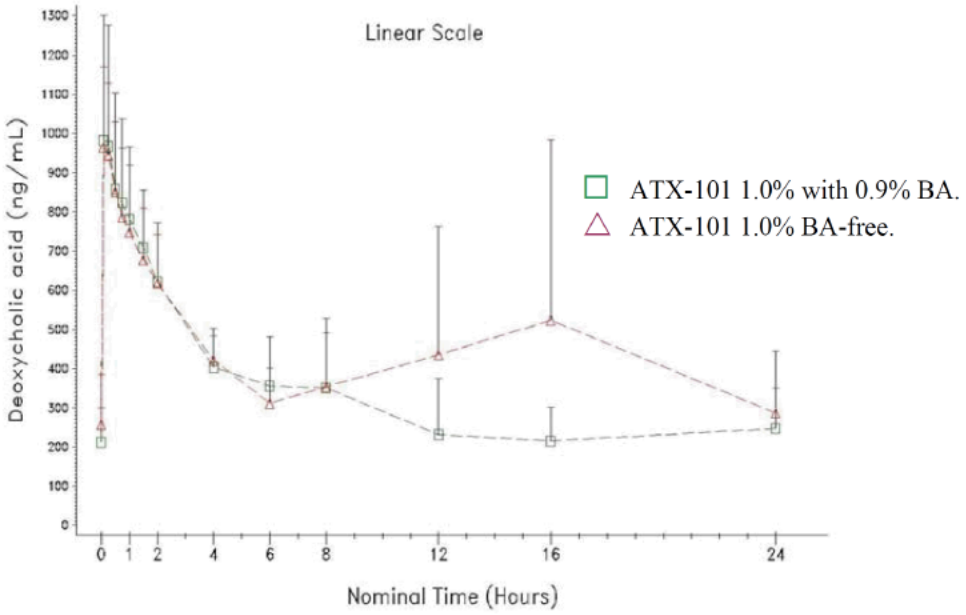


Figure 5: Mean (SD) Post-treatment Deoxycholic Acid Plasma Concentration-Time Profiles (Day 1, BLOQ = 25.6 ng/mL)



Reviewer's comments:
At baseline, the plasma concentration of deoxycholic acid increased slightly at 8 hours (lunch was at 6 hours) and 16 hours, and decreased at 24 hours. At Day 1 (post-treatment), the increase of plasma concentration was not apparent for the US formulation. For EU formulation, it started to increase at 8 hours, and continued to increase until 16 hours, and then decreased at 24 hours. This increase of concentration did not present in every subject, and the increase at 16 hours is probably due to the light snack provided at 12 hours.

With the LLOQ of 25.6 ng/mL, the pharmacokinetic parameters are shown in Table 6 (at baseline) and Table 7 (post-treatment). The sponsor reported that the post-treatment $AUC_{0\text{-}inf}$ and $t_{1/2}$ were only valid for 5 subjects in the BA-preserved formulation and 3 subjects in the preservative-free formulation group. The reasons for the non-reportable values include 1). AUC % extrapolation prediction was more than 20% and 2). Lambda z was not able to be calculated.

At baseline, there was high variability in C_{max}, $AUC_{0\text{-}24}$, and T_{max} among all enrolled 24 subjects. The mean (±SD) endogenous $AUC_{0\text{-}24}$ and endogenous C_{max} were 5450 ± 2850 ng*hr/mL and 383 ± 246 ng/mL, respectively. After administration of ATX-101, for the BA-preserved formulation, the range of $AUC_{0\text{-}24}$ and C_{max} values were 5394 to 12832 ng*hr/mL and 688 to 1530 ng/mL, respectively. For the preservative-free formulation, the range of $AUC_{0\text{-}24}$ and C_{max} values were 5239 to 21660 ng*hr/mL and 658 ng/mL to 1510 ng/mL, respectively.

Following ATX-101 dosing on Day 1, both formulations were rapidly absorbed, with median T_{max} values of 0.3 hours for the BA-preserved formulation and 0.1 hours for the preservative-free formulation. The mean Day 1 plasma exposures as measured by $AUC_{0\text{-}24}$ and C_{max} were approximately 1.5-fold greater (9159 ng*hr/mL vs 5450 ng*hr/mL) and 3-fold greater (1030 ng/mL vs 383 ng/mL), respectively, than the endogenous values at Baseline.

For the baseline-adjusted PK parameters, $AUC_{0\text{-}24}$ was 3042±1217 ng*hr/mL and 4376±3476 ng*hr/mL for BA and BA-free formulation, respectively. C_{max} was 822±263 ng/mL and 784±230 ng/mL for BA and BA-free formulation, respectively.

Table 6: Mean (SD) Endogenous Deoxycholic Acid Pharmacokinetic Parameters at Baseline (Day -1)

	BLOQ = 50.0 ng/mL[a]			BLOQ = 25.6 ng/mL[b]		
	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	Overall N = 24	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	Overall N = 24
$AUC_{0\text{-}24}$[c] (ng*hr/mL)	4846 (2352)	6060 (3255)	5453 (2846)	4854 (2339)	6045 (3277)	5450 (2850)
C_{max}[d] (ng/mL)	324 (182)	441 (293)	383 (246)	324 (182)	441 (293)	383 (246)
t_{max}[e] (hr)	12.0 (0-24.0)	8.0 (0-24.0)	8.0 (0-24.0)	12.0 (0-24.0)	8.0 (0-24.0)	8.0 (0-24.0)

Source: Table 14.2.2.

[a]BLOQ values (<50 ng/mL, historical) set to 25 ng/mL for the calculation of summary statistics.
[b]BLOQ values (<25.6 ng/mL, new) set to 0 ng/mL for the calculation of summary statistics.
[c]$AUC_{0\text{-}24}$: presented as mean (SD) and is the area under the concentration-time curve from time zero to 24 hours.
[d]C_{max}: presented as mean (SD) and is the maximum observed plasma concentration.
[e]t_{max}: presented as median (range) and is the time at which C_{max} was observed.

Table 7: Mean (SD) Deoxycholic Acid Pharmacokinetic Parameters following Single-Treatment Subcutaneous Administration of ATX-101 (Day 1)

	BLOQ = 25.6 ng/mL[a]			Baseline-Adjusted BLOQ = 25.6 ng/mL[b]		
	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	Overall N = 24	ATX-101 with 0.9% BA N = 12	ATX-101 BA-Free N = 12	Overall N = 24
Parameter						
AUC_{0-24}[c] (ng*hr/mL)	7896 (2269)	10421 (4676)	9159 (3819)	3042 (1217)	4376 (3476)	3709 (2636)
AUC_{0-inf}[d] (ng*hr/mL)	7443 (762)	7501 (1774)	7465 (1110)	NC	NC	NC
AUC_{last} (ng*hr/mL)	7915 (2272)	10421 (4675)	9168 (3816)	NC	NC	NC
C_{max}[e] (ng/mL)	1024 (304)	1036 (254)	1030 (274)	822 (263)	784 (230)	803 (242)
t_{max} (hr)[f]	0.3 (0.1, 1.1)	0.1 (0.1, 16.0)	0.1 (0.1, 16.0)	NC	NC	NC
$t_{1/2}$ (hr)[c,g]	9.3 (0.66)	8.5 (0.46)	9.0 (0.70)	NC	NC	NC

Source: Table 14.2.3.

[a]Summary statistics using the 2 BLOQ values (<50 ng/mL [historical] and <25.6 ng/mL [new]) resulted in identical PK parameters on Day 1; therefore, only results derived from the BLOQ of 25.6 ng/mL are presented in the above table and discussed throughout the clinical study report for Day 1.
[b]Baseline-adjusted PK parameters were determined using BLOQ of 25.6 ng/mL only.
[c]AUC_{0-24}: presented as mean (SD) and is the area under the concentration-time curve from time zero to 24 hours postdose.
[d]For AUC_{0-inf} and $t_{1/2}$, N = 5 for BA-preserved formulation, N = 3 for preservative-free formulation, and N = 8 for both formulations at both BLOQ levels. Subjects with invalid AUC_{0-inf} and $t_{1/2}$ values were previously identified in Table 11-f and Appendix 16.2.6.2. AUC_{0-inf} values were only available for a limited number of subjects (n=3 or 5); mean estimates for AUC_{0-inf} were lower than AUC_{last} (n=12), and no reliable interpretations can be drawn from the AUC_{0-inf} data.
[e]$C_{max:}$ presented as mean (SD) and is the maximum observed plasma concentration.
[f]t_{max}: presented as median (range) and is the time at which C_{max} was observed.
[g]$t_{1/2}$: terminal elimination half-life, calculated using 3 to 12 decreasing time points in the terminal phase of the concentration-time profile.
NC=not calculated.

An exploratory statistical analysis was performed for bioequivalence analysis although this trial was not powered. The result showed that the formulations were considered equivalent in terms of C_{max} (ie, the geometric mean ratio was near 1.0 and 90% CIs were within 0.8 and 1.25). However, the BA-preserved formulation resulted in a 21% lower exposure than the preservative-free formulation (based on the geometric mean ratio of AUC_{0-24}) and cannot be considered equivalent based on 90% CI analysis. The results are shown in Table 8.

Table 8: Statistical Comparisons of Pharmacokinetic Parameters

Pharmacokinetic Parameter (unit)		Geometric Mean Ratio (ATX-101 with 0.9% BA/ ATX-101 BA-Free)	90% CI
BLOQ=50 ng/mL[a]	AUC_{0-24} (hr*ng/mL)	0.79	(0.62, 1.00)
	C_{max} (ng/mL)	0.98	(0.81, 1.17)
BLOQ=25.6 ng/mL[b]	AUC_{0-24} (hr*ng/mL)	0.79	(0.62, 1.00)
	C_{max} (ng/mL)	0.98	(0.81, 1.17)
Baseline-adjusted BLOQ=25.6 ng/mL[b]	AUC_{0-24} (hr*ng/mL)	0.79	(0.54, 1.14)
	C_{max} (ng/mL)	1.04	(0.85, 1.27)

Source: Table 14.2.4.

[a]BLOQ values (<50 ng/mL, historical) set to 25 ng/mL for the calculation of summary statistics.
[b]BLOQ values (<25.6 ng/mL, new) set to 0 ng/mL for the calculation of summary statistics.

Reviewer's comments:
It is not clear the reason of causing the two formulations to be non-equivalent based on 90% CI analysis of AUC_{0-24}. *The possible reasons include the high variability of deoxycholic acid, small sample size, and the addition of benzyl alcohol. Conclusion cannot be made on the bioequivalence of the two formulations based on this trial.*

Summary of Safety:
According to the sponsor, injection site reactions were the most commonly observed adverse events (including oedema, pain, erythema, anaesthesia, haematoma, and hyperthermia [coded as reaction]). There were no deaths, SAEs, or adverse events leading to study discontinuation were reported.

Reviewer's comments: For further information on drug safety, please see review by Medical Officer Dr. Milena Lolic.

Demographic:

	ATX-101 1.0% with 0.9% BA 100 mg N = 12	ATX-101 1.0% BA-Free 100 mg N = 12	All Subjects N = 24
Gender (n,%)			
Female	7 (58.3%)	4 (33.3%)	11 (45.8%)
Male	5 (41.7%)	8 (66.7%)	13 (54.2%)
Race (n,%)			
Black/ African American	2 (16.7%)	2 (16.7%)	4 (16.7%)
White	9 (75.0%)	10 (83.3%)	19 (79.2%)
Other	1 (8.3%)	0	1 (4.2%)
Ethnicity (n,%)			
Hispanic/Latino	1 (8.3%)	1 (8.3%)	2 (8.3%)
Not Hispanic/Latino	11 (91.7%)	11 (91.7%)	22 (91.7%)
Age (yr)			
Mean (SD)	43.7 (12.57)	40.8 (14.26)	42.2 (13.23)
Range	20 – 59	20 – 63	20 – 63
Median	46.0	38.5	44.5
Body mass index (kg/m^2)			
Mean (SD)	32.40 (3.293)	34.05 (3.485)	33.18 (3.414)

Source: Table 14.1.2.

Applicant's Conclusion:
The baseline endogenous deoxycholic acid plasma exposures showed high variability between subjects and over time, with a range of 10-fold in AUC_{0-24} (1419 ng*hr/mL to 13504 ng*hr/mL) and 15-fold in C_{max} (87 ng/mL to 1280 ng/mL). Following a single treatment of ATX-101, both of the BA-preserved and the preservative-free formulations were rapidly absorbed with a Tmax of 0.3 hours for BA-preserved formulation and 0.1 hour for prefervative-free formulation. On average, deoxycholic acid plasma concentrations returned to endogenous Baseline levels by 24 hours post-treatment.

The deoxycholic acid plasma exposures after the single treatment of ATX-101 showed moderate variability, with a 2.4-fold range in AUC_{0-24} (5394 ng*hr/mL to 12832 ng*hr/mL) and a 2.2-fold range in C_{max} values (688 ng/mL to 1530 ng/mL) for the BA-preserved formulation, and a 4.1-fold range in AUC_{0-24} (5239 ng*hr/mL to 21660 ng*hr/mL) and a 2.4-fold range in C_{max} values (628 ng/mL to 1510 ng/mL) for the preservative-free formulation. Mean deoxycholic acid AUC_{0-24} values following ATX-101 administration were approximately 1.5-fold to 2-fold greater than the endogenous values at Baseline (eg, Day -1 to Day 1 mean AUC increased from 4854 ng*hr/mL to 7896 ng*hr/mL in the BA-preserved group and from 6045 ng*hr/mL to 10421 ng*hr/mL in the preservative-free group).

Reviewer's Comments:
The applicant's conclusion is acceptable.

Trial No. ATX-101-11-24

Title: A Four-Arm, Parallel-Design, Randomized, Double-Blinded, Placebo- and Active-Controlled Study for the Evaluation of the Effect of Maximum Therapeutic and Supratherapeutic Single-Dose ATX-101 on the QT/QTc Intervals in Healthy Volunteers

Trial Initiation/Completion Dates: 10/19/2012-2/17/2013

Objectives:

Primary objectives:

- The primary objective was to assess the effect of maximum therapeutic and supratherapeutic doses of ATX-101 on cardiac repolarization (QT interval corrected with Fridericia's formula [QTcF]) compared to placebo in healthy adult subjects.

Secondary objectives:

- Assess the effect of maximum and supratherapeutic doses of ATX-101 compared to placebo on the QT interval corrected for individuals (QTcI) (if deemed necessary), "Holter Bin" analysis (if necessary), QRS interval, PR interval, heart rate, categorical changes in intervals (QTc, QRS, PR, and heart rate), changes in ST and T-wave morphology, appearance of abnormal U waves, and overall electrocardiogram (ECG) characterization (normal/abnormal) in healthy adult subjects.
- Evaluate the pharmacokinetic (PK) profiles of ATX-101 (at 2 dose levels) and moxifloxacin (as needed).
- Evaluate the relationship between changes in QTcF and ATX-101 plasma concentrations.
- Evaluate the appearance of specific arrhythmias: Torsade de Pointes (TdP), ventricular tachycardia/fibrillation, atrial fibrillation/flutter, supraventricular tachycardia, etc., including the correlation of ECG findings with clinical adverse events (events that could signal pro-arrhythmia: syncope, palpitations, dizziness, tachycardia, etc.).

Trial Center:
Comprehensive Clinical Development NW, Inc., Tacoma, WA

Supply of drugs:
ATX-101 (1.0%) with 0.9% benzyl alcohol: Lot number PD12007
ATX-101 (2.0%) with 0.9% benzyl alcohol: Lot number PD12142
Placebo (phosphate-buffered saline with 0.9% benzyl alcohol): Lot number PD12006
Moxifloxacin: Lot number 54027TW

Design of Trial:

This was a single-center, randomized, double-blind, 4-arm, parallel-group, placebo- and active-controlled study evaluating the potential of ATX-101 to prolong cardiac repolarization in healthy adult subjects. Approximately 220 men and women between the ages of 18 and 65 years of age (inclusive) who had not used tobacco or nicotine-containing products for at least 3 months prior to the study were to be enrolled into the trial. The Body Mass Index (BMI) is in the range of 20-38 kg/m^2. Subjects were required to fast overnight for at least 12 hours before dosing and for at least 6 hours thereafter. Subjects were randomized, in a 1:1:1:1 ratio, into 1 of the 4 treatments groups below in Table 9:

Table 9: Study Drug Treatments

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

[a]Administered in open-label fashion; all other treatments administered in double-blind fashion.

The ATX-101 active treatment and ATX-101 placebo were administered as 25 injections (0.4 mL each for a total volume of 10 mL) into the submental fat spaced on a 1.0-cm grid in a single 5-minute dosing session. The moxifloxacin was administered as a single oral 400 mg dose. The serial PK blood samples were collected at the following time points:

Day -1: At approximately the same times as the planned dose on Day 1: predose (0 hr), 0.083[a], 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 5, 6 [b], 8, 12 [b], 16 and 24 [c] hours.

Day 1: Predose (0 [c] hr [within 30 minutes prior to dosing]), 0.083[a], 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 5, 6 [b], 8, 12 [b], 16 and 24 hours.

[a]Per email clarification (Appendix 16.1.1.8), due to the multiple study procedures planned at 5 minutes postdose, 5-minute PK blood samples were allowed to be collected at 11 minutes postdose, and this delay in collection was not considered a protocol deviation.
[b]Collected prior to consumption of a standardized meal or snack.
[c]Day -1 24-hour postdose sample and Day 1 predose sample were the same blood samples.

A total of 218 subjects (54 or 55 subjects per treatment group) were enrolled into the trial, and 217 subjects completed the trial. Subject 078, who received ATX-101 placebo, withdrew consent after completing study procedures through the 6-hour ECG extraction.

This trial is reviewed by the medical reviewer, Dr. Melina Lolic, and the Interdisciplinary Review Team for QT Studies (IRT-QT). This reviewer will discuss only the PK results in this trial.

Analytical Methods:
See Question-Based-Review Section 2.6.1.

Analytical Method Validation:
See Table 5

Pharmacokinetic Results:
The endogenous baseline levels of deoxycholic acid on Day -1 are presented in Figure 6. The endogenous deoxycholic acid had large between-subject variability, and the mean plasma concentrations for all subjects ranged from approximately 95 ng/mL to 151 ng/mL for the 100 mg ATX-101 group and 94.8 ng/mL to 252 ng/mL for the 200 mg ATX-101 group across the 24 hours. The sponsor noted that a few subjects had a large increase from Baseline concentrations at approximately 16 hours post-treatment, and although the reason is not known, the increase of concentrations may be related to a late evening snack, offered to subjects at the 12-hour time point.

Following subcutaneous administration of ATX-101 on Day 1, total deoxycholic acid concentrations increased rapidly to reach mean concentrations of 695 ng/mL for all subjects in the 100 mg group and 879 ng/mL for all subjects in the 200 mg group at 5 minutes post-treatment. Afterwards, total plasma concentrations declined and returned to average endogenous levels by 6 hours post-treatment (245 ng/mL) for the 100 mg group and 12 hours post-treatment for the 200 mg group (289 ng/mL). As similar with the endogenous baseline levels, a few subjects did have an increase from pre-treatment deoxycholic acid concentrations at approximately the 16-hour time point, and may be related to a late evening snake at the 12-hour time point. The total deoxycholic acid plasma concentration-time profiles on Day 1 are illustrated in Figure 7.

Figure 6: Mean (+SD) Endogenous Deoxycholic Acid Plasma Concentration-Time Profiles on Day -1 (All Subjects)

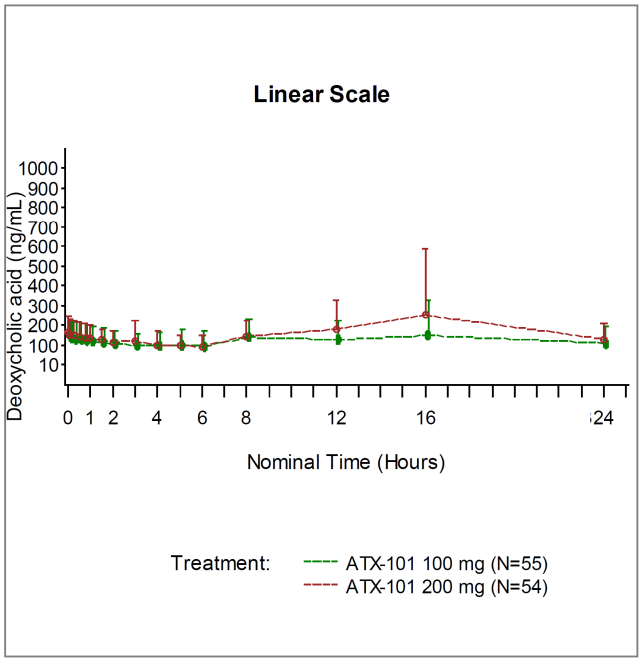
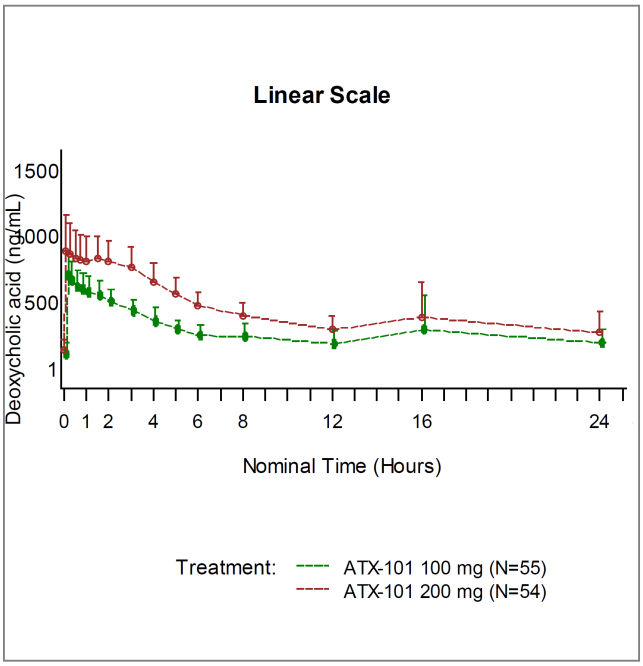


Figure 7: Mean (+SD) Total Deoxycholic Acid Plasma Concentration-Time Profiles on Day 1 (All Subjects)



For the endogenous deoxycholic acid PK parameters (Table 10), the variability in plasma exposures was high with the range in individual values approximately 100-fold for AUC_{0-24} (86.2 ng*hr/mL to 8710 ng*hr/mL) for the 100 mg group, and 8.5-fold for the 200 mg group (1420 ng*hr/mL to 12000 ng*hr/mL). It was noted that there was an outlier in the 100 mg dose group who had very low endogenous deoxycholic acid plasma exposures (AUC_{0-24}=86.2 ng*hr/mL). After excluding this outlying subject, the range of AUC_{0-24} would decrease to 13-fold (646.7 ng*hr/mL to 8710 ng*hr/mL). For C_{max}, there was a 30-fold range for the 100 mg group (27.7 ng/mL to 828 ng/mL) and a 24-fold range for the 200 mg group (70.0 ng/mL to 1700 ng/mL). Table 10 is the summary of endogenous deoxycholic acid PK parameters.

Following ATX-101 dosing on Day 1 (Table 11), both doses were rapidly absorbed, with median t_{max} values of 0.183 hours for the 100 mg dose and 0.475 hours for the 200 mg dose. Some subjects had an increase at approximately 16-24 hours post-treatment, and it may relate to a late evening snack offered at the 12-hour time point. For the 100 mg dose, the range in individual AUC_{0-24} values was from 3020 ng*hr/mL to 12800 ng*hr/mL and the range in individual C_{max} values was approximately 3.8-fold (from 418 ng/mL to 1600 ng/mL). For the 200 mg dose, the range in individual AUC_{0-24} values was from 6960 ng*hr/mL to 18200 ng*hr/mL and the C_{max} range was approximately 3.2-fold (from 496 ng/mL to 1550 ng/mL). The mean C_{max} was 733±195 ng/mL for 100 mg and 961±244 ng/mL for 200 mg, respectively, and the mean AUC_{0-24} was 6650±2250 hr*ng/mL for 100 mg and 10300±2470 hr*ng/mL for 200 mg, respectively. Increases in deoxycholic acid plasma exposures were less than proportional to the dose, with $AUC_{0-24\ adj}$ and $C_{max\ adj}$ following the 200 mg dose approximately 1.7-fold and 1.3-fold, respectively, greater than those following the 100 mg dose.

Table 10: Summary of Endogenous Deoxycholic Acid Pharmacokinetic Parameters at Baseline (Day -1)

	Day -1; PK Parameters									
	ATX -101 100 mg					ATX -101 200 mg				
	AUC_{0-24} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	C_{max} (ng/mL)	C_{avg} (ng/mL)	t_{max} (hr)	AUC_{0-24} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	C_{max} (ng/mL)	C_{avg} (ng/mL)	t_{max} (hr)
All Subjects										
N	49	53	53	49	53	51	54	54	51	54
Mean	3270	3030	248	136	ND	3990	3820	324	166	ND
SD	1740	1870	175	72.6	ND	2500	2520	311	104	ND
%CV	53.3	61.5	70.7	53.3	ND	62.7	66.0	96.2	62.7	ND
Median	3160	2620	217	131	8.00	3100	3020	236	129	12.0
Min	86.2	22.1	27.7	3.59	0.00	1420	596	70.0	59.1	0.00
Max	8710	8710	828	363	24	12000	12000	1700	500	24.0

[a]Since 75% of the subjects within each treatment group did not have available data, summary statistics were not determined for $t_{1/2}$.
[b]C_{avg}=(Baseline AUC_{0-24})/24.
ND=not determined.

Table 11: Mean (%CV) Total Deoxycholic Acid Plasma Pharmacokinetic Parameters on Day 1

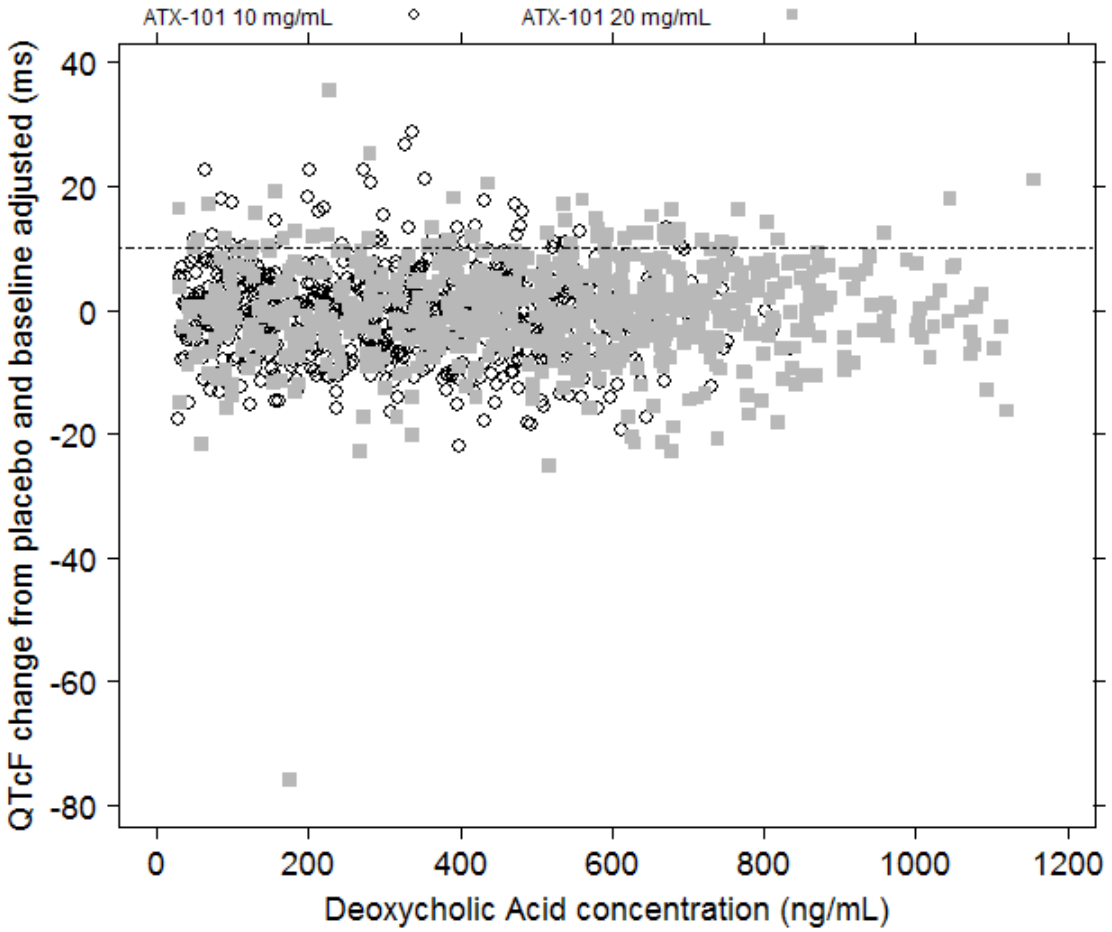
	ATX-101 100 mg						ATX-101 200 mg					
	All Subjects		Men		Women		All Subjects		Men		Women	
Parameter	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
AUC_{0-24}[a]	54	6650 (34%)	28	7000 (32%)	26	6270 (36%)	54	10300 (24%)	33	9700 (20%)	21	11200 (26%)
$AUC_{0-24\ adj}$[b]	48	3740 (45%)	26	4090 (44%)	22	3330 (46%)	51	6370 (32%)	32	6470 (26%)	19	6200 (41%)
AUC_{last}[c]	55	6710 (34%)	29	7080 (31%)	26	6290 (36%)	54	10300 (24%)	33	9720 (20%)	21	11200 (26%)
C_{max}[d] (ng/mL)	55	733 (27%)	29	757 (23%)	26	707 (31%)	54	961 (25%)	33	966 (24%)	21	954 (28%)
$C_{max\ adj}$[e] (ng/mL)	49	613 (29%)	27	628 (24%)	22	593 (36%)	51	802 (28%)	32	839 (26%)	19	741 (30%)
t_{max}[e] (hr)	55	0.18 (0.18, 16.2)	29	0.18 (0.18, 16.2)	26	0.20 (0.18, 16.2)	54	0.48 (0.08, 24.1)	33	0.18 (0.08, 16.1)	21	0.87 (0.18, 24.1)

Source: Table 14.2.3.
NOTE: Units for AUC are ng*hr/mL. Since 75% of the subjects within each treatment group did not have available data, summary statistics were not determined for AUC_{0-inf}, $t_{1/2}$, or λ_z.
[a]AUC_{0-24}: area under the plasma concentration-time curve from time zero to 24 hours.
[b]$AUC_{0-24\ adj}$: postdose deoxycholic acid AUC_{0-24} – Baseline deoxycholic acid AUC_{0-24}.
[c]AUC_{last}: area under the concentration-time curve from time zero to last quantifiable concentration.
[d]C_{max}: maximum observed concentration.
[e]$C_{max\ adj}$: postdose deoxycholic acid plasma C_{max} – Baseline deoxycholic acid plasma C_{avg}, where Baseline C_{avg} = Baseline AUC_{0-24}/24
[f]t_{max}: time of C_{max}; median (range) presented.

TQT results:

According to the review by QT-IRT reviewer Dr. Moh Jee Ng, No significant QTc prolongation effect of ATX-101 (100 mg and 200 mg) was detected in this TQT trial. (See review in DARRTS dated 1/7/2014).

Figure 8: ΔΔ QTcF vs. Deoxycholic Acid Concentration



Reviewer's comments:
Following one treatment of subcutaneous injection of ATX-101at 200 mg to submental area, the mean C_{max} *was 961±244 ng/mL. Compared to the* C_{max} *of 1024±304 ng/mL in the maximal use PK trial 32 of one dose of 100 mg, the* C_{max} *obtained from supratherapeutic dose of this TQT trial was lower than the* C_{max} *from therapeutic dose of the maximal use PK trial. By looking at the QTcF change from placebo and baseline adjusted vs deoxycholic acid concentration profile (Figure 8), it appears that the QTcF change is not affected by deoxycholic acid concentration at the range approximately up to 1200 ng/mL. Therefore, even though the* C_{max} *of the supratherapeutic dose obtained in this TQT trial is lower than that from the maximal use PK trial, ATX-101 does not have the potential for TQT prolongation up to the systemic concentration of 1200 ng/mL.*

Population Pharmacokinetic Analysis KYTH-01-13

Title: A Population Pharmacokinetic Analysis of Deoxycholic Acid (DCA) Before and After ATX-101 Administration in Healthy Subjects

Summary:

A population PK analysis was conducted using plasma concentration-time data from 172 adult subjects who received ATX-101 (93 males and 79 females) in 5 Phase 1 clinical Trials (Trials (b) (4) 24, (b) (4) and 32) (Table 12). Within these 5 trials, the subjects ranged in age from 18 to 64 years (median = 36 years), body weight (WT) from 56 to 128 kg (median = 89 kg), body mass index (BMI) from 22 to 39 kg/m^2 (median = 31 kg/m^2), and serum creatinine (SCR) from 0.48 to 1.53 mg/dL (median = 0.84 mg/dL). The covariates evaluated included dose, demographics (age, sex, WT, BMI, and race), SCR as a measure of renal function, selected blood chemistry variables (albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin), and pre-treatment concentrations of DCA (BDCA). The listing and descriptive statistics of covariates evaluated is listed in Table 13.

Table 12: Summary of Trials and Data Included in the Population Pharmacokinetic Analysis

Study ID	Indication	Dose (s)	N	No. of Samples	No. of Profiles
(b) (4)					
ATX-101-11-24 (Study 24)	SMF	100 mg 200 mg	109	3228	109
(b) (4)					
ATX-101-12-32 (Study 32)	SMF	100 mg	24	627	24

Note: A full 24-hour pharmacokinetic profile was obtained before (b) (4) and after single SC administration of ATX-101.
mg = milligrams; N = number of subjects; SMF = submental fat

Table 13: Listing and Descriptive Statistics (Median and Range) of Covariates Evaluated in the Population Analysis

Covariate	Median (Range)
Studies	5
N (Male, Female)	172 (93,79)
Race (Whites, Non-white)[a]	(117,55)
Body Weight (kg)	89 (56-128)
Age (y)	36 (18-64)
BMI (kg/m^2)	30.5 (21.5-38.6)
Height (cm)	172 (149-198)
Baseline ALT (μ/L)	23 (8-152)
Baseline AST (μ/L)	21 (11-159)
Baseline Serum Creatinine (mg/dL)	0.84 (0.48-1.53)
Baseline Bilirubin (mg/dL)	0.60 (0.20-1.60)
Baseline Albumin (g/dL)	4.1 (3.1-4.9)
BDCA	147.5 (12.8-505.5)

BDCA = predose baseline endogenous deoxycholic acid concentration.

[a] The majority of the subjects were White (117), Black or African American (23), American Indian or Alaskan Native (4), Hispanic or Latino (11), Asian (2) and Multiple and Other (15)

A 1-compartment model with first-order absorption and elimination was chosen based on a combination of diagnostic plots, the structure that minimized theobjective value function using nonlinear mixed-effects modeling (NONMEM) software, and the precision of base model parameter estimates.

Assumptions:

- The absolute bioavailability after SC administration was assumed to be complete.
- A formulation effect, if any, was negligible as DCA is administered in an aqueous formulation.
- Food effect, if any, could not be accounted in the model as administration was subcutaneous.

For the base model, baseline endogenous DCA concentrations were modeled as a fixed parameter (BASE) with log-normal distribution and an exponential inter-individual variability(IIV) term. A combined additive and proportional residual error model was used. For the PK of DCA after ATX-101 administration, a 1-compartment open model with first-order absorption and elimination was chosen. The population DCA BASE was estimated at 139 ng/mL, CL was estimated at 32.5 L/h and V was estimated at 193 L. Estimates of IIV for DCA parameters were 28%, 38%, and 52% for CL, V, and BASE, respectively. The t½, calculated based on the population estimates of CL and V, was approximately 4.1 hours.

Covariate analysis identified significant effects of age on baseline DCA, dose on CL, and BMI, baseline DCA, study population, and dose on V. Incorporating these various covariates into the population model resulted in approximately 5%, 11%, and 25%

reductions in the interindividual variability in BASE, CL, and V, respectively. The final population PK model parameter estimates, including population values, RSE, IIV, and residual variability, are presented in Table 14. None of these covariates were deemed as clinically relevant and no dose adjustments are proposed based on BMI, age, or sex.

The final model for DCA PK and the covariates impacting IIV are as follows:

- CL (L/h) = 36.2* X
- V (L) = $152*1.41^{POPL}*(BMI/30.5)^{0.835}*(BDCA/147.5^{)-0.109}*Y$
- k_a (1/h) = 47.5
- BASE (ng/mL) = $141*(AGE/36)^{0.404}$

(Where X = 0.772 for the 200-mg dose and 1 for all other doses, Y = 1.765 for the 200-mg dose and 1 for all other doses.
BMI is BMI for subjects in kg/m^2 divided by the median BMI, POPL is study population (0 is used for SMF and 1 for abdominal administration), AGE is the age for subjects in years divided by the median age, and BDCA is the pre-treatment baseline level divided by the median value.)

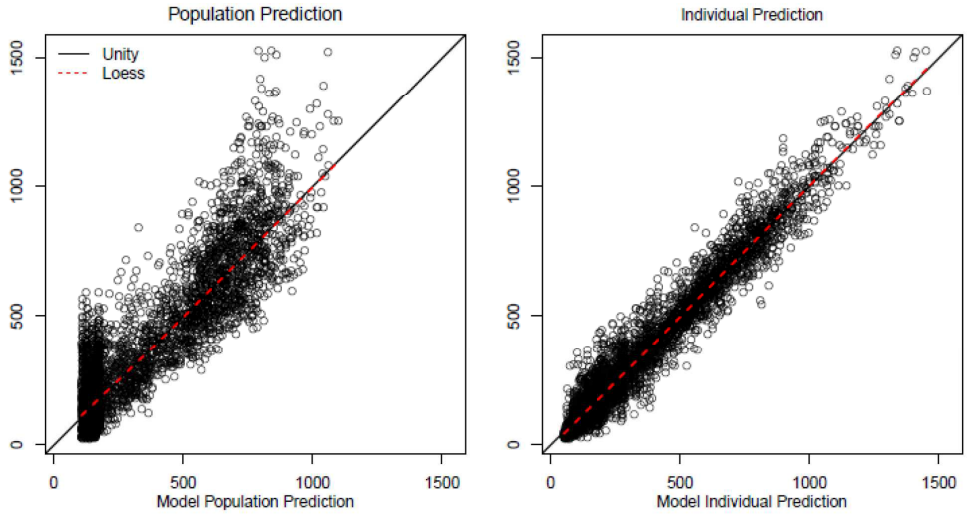
Table 14: Final Model Estimated Pharmacokinetic Parameters

Parameter	Median Value (%RSE)	Interindividual CV (%RSE)	% ETA Shrinkage
BASE (ng/mL)	141 (4.0%)	49.2% (10.9%)	4.3
Age on BASE	0.404 (29.7%)	NA	NA
CL (L/h)	36.2 (3.2%)	25.3% (18.3%)	14.4
Dose in CL	-0.228 (15.3%)	NA	NA
V (L)	152 (3.3%)	28.3% (11.4%)	4.2
BDCA in V	-0.109 (23.2%)	NA	NA
Population in V	1.41 (7.4%)	NA	NA
BMI in V2	0.835 (19.2%)	NA	NA
Dose in V	0.765 (10.6%)	NA	NA
ka (1/h)	47.5 (47.2%)	0 (Fixed)	100
Residual Error Parameters	**Estimate (%RSE)**		**% EPS Shrinkage**
Proportional (%)	9.5 (10.3%)		4.8
Additive	52.9 (4.9%)		4.8

NA = not applicable

The diagnostic plots show that the final model reasonably describes the central tendencies of the DCA plasma concentrations with no noticeable biases in the residual plots (Figure 9). A graphical display of the relationship between inter-individual estimates and covariate for those covariates included in the final model are shown for CL, V, and BASE in Figure 9, Figure 10, and Figure 11, respectively. In general, inclusion of the covariate reduced portions of association between the covariate and model parameter.

Figure 9: Observed vs. Individual and Population Predicted Plasma Concentration (ng/mL) from All Studies by Study: Final Model



Note: The black line is the unity line and the red line is the trend line.

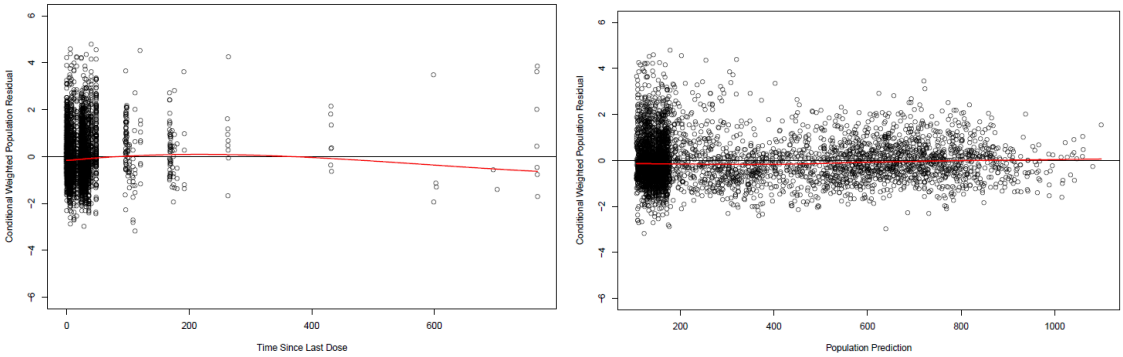


Figure 10: Interindividual Variability of CL vs Dose in the Base (left) and Final (right) Model

(A) ETA for CL (ETA1) on Dose (Base Model)

(B) ETA for CL (ETA1) on Dose (Final Model)

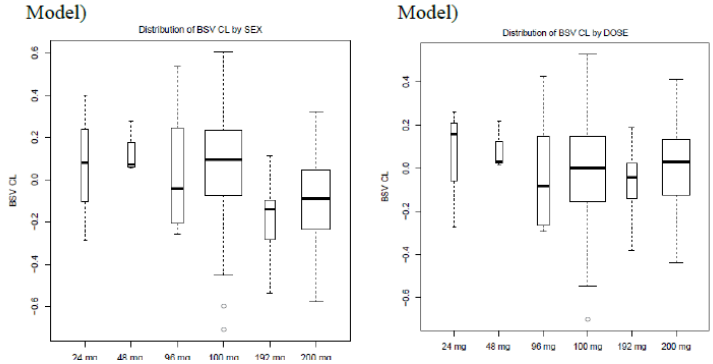
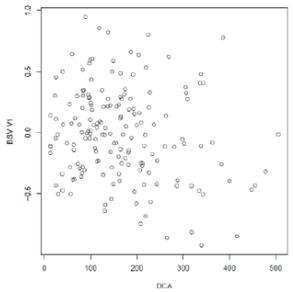
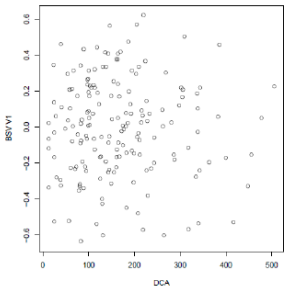


Figure 11: Interindividual Variability of V vs BDCA, BMI, Population, and Dose in the Base (left) and Final Model (right)

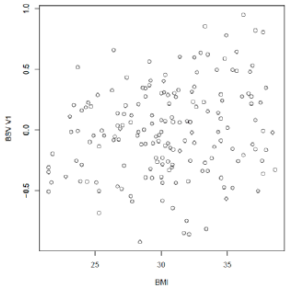
(A) ETA for V (ETA2) on BDCA (Base Model)



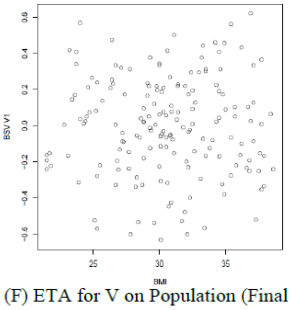
(B) ETA for V (ETA2) on BDCA (Final Model)



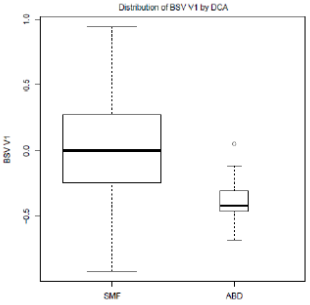
(C) ETA for V (ETA2) on BMI (Base Model)



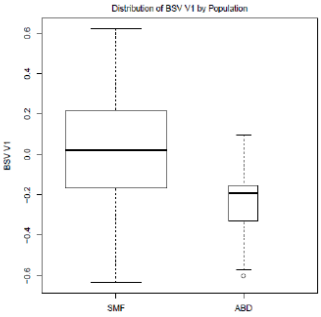
(D) ETA for V (ETA2) on BMI (Final Model)



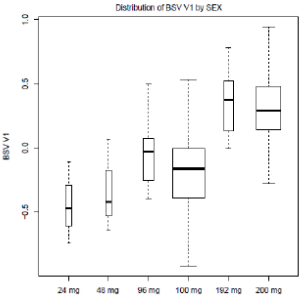
(E) ETA for V on Population (Base Model)



(F) ETA for V on Population (Final Model)



(G) ETA for V on Dose (Base Model)



(H) ETA for V on Dose (Final Model)

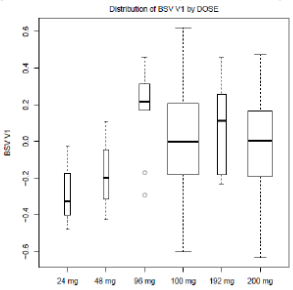
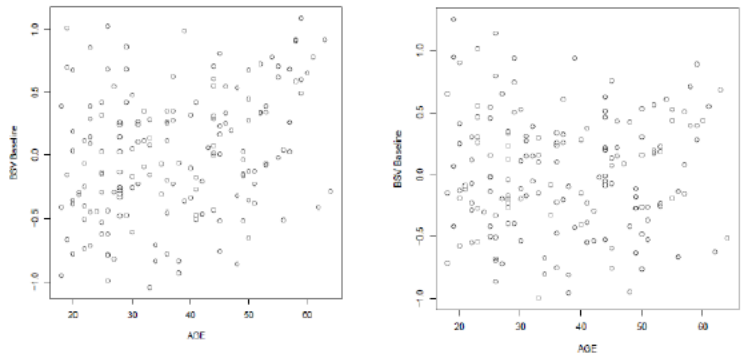


Figure 12: Interindividual Variability of BASE vs Age in the Base (left) and Final (right) Model

(A) ETA for BASE on Age (Base Model) (B) ETA for BASE on Age (Final Model)



Reviewer's comments:
The PK of deoxycholic acid shows non-linearity by observing the distribution of volume by dose. The sponsor's proposed labeling under 12.3 reads " (b) (4) [redacted] .
Moreover, under the pharmacokinetic effects of gender (b) (4) *, the sponsor proposed the statement that "deoxycholic acid pharmacokinetics were not influenced by gender* (b) (4) [redacted] *On the other hand, this reviewer conducted a statistical analysis on the individual predicted parameter estimates from final model to determine if gender has any influence on clearance or volume of distribution. The results showed that the p-values for clearance and volume of distribution were not significantly different between males and females (p-value of 0.14 and 0.22 for CL and V, respectively). The mean±SD of CL and V predicted parameters for each sex from the final model and the point estimates of Male/Female ratio are listed in* Table 15.
Altogether, the available data supports that, there is no statistically significant difference between PK parameters of deoxycholic acid in males and females

Table 15: The Mean±SD of Clearance (CL) and Volume of Distribution (V) Estimated from Final Model of Each Sex and the Point Estimates of Male/Female Ratio

	Female	Male	Point Estimate of Male/Female Ratio
CL (L/h)	35.6±9.1	38.2±7.4	1.1
V (L)	170.2±48.2	158.6±43.2	0.9

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/s/

AN-CHI LU
12/16/2014

JEFFRY FLORIAN
12/16/2014

DOANH C TRAN
12/16/2014

EDWARD D BASHAW
12/16/2014

CLINICAL PHARMACOLOGY REVIEW

NDA:	206333
Submission Date:	5/13/2014
Brand Name:	Kybella
Generic Name:	Deoxycholic acid injection, 10 mg/mL
Dosage Form:	Injectable
Dosage Strength:	10 mg/mL
Submission Type:	New submission
Indication:	For the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults
Sponsor:	Kythera
Primary Reviewer:	An-Chi Lu, M.S., Pharm.D.
Secondary Reviewer:	Doanh Tran, Ph.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Dermatology and Dental Product

Addendum to Clinical Pharmacology Filing Memorandum:
This addendum is to the clinical pharmacology filing memorandum dated 6/30/2014 in DARRTS. A scoping meeting was held on 7/3/2014, and it was recommended that the population pharmacokinetic analysis does not warrant a detailed review. Therefore the 2 comments for the sponsor were revised into 1 comment as follows:

Comments for Sponsor:

(b) (4)

(b) (4)

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/s/

AN-CHI LU
07/08/2014

DOANH C TRAN
07/08/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 206333 **Applicant: Kythera** **Stamp Date: 5/13/2014**

Drug Name: Kybella (Deoxycholic acid) injection, 10 mg/mL **NDA/BLA Type: Original NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			In vitro reaction phenotyping studies were not conducted as the sponsor stated that deoxycholic acid metabolism in the liver and its biotransformation pathway were reported in the literature. No in vivo drug-drug interaction information was provided. In vitro inhibition/induction information was provided. CYP enzymes tested for induction were CYP1A, CYP2B6, and CYP3A, and the enzymes tested for inhibition were CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.
Criteria for Assessing Quality of an NDA					
	Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X			
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			X	
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The applicant requested a waiver of pediatric data in all subsets of the pediatric population (up to 18 years of age).
10	Did the applicant submit all the pediatric exclusivity			X	

	data, as described in the WR?				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
17	Was the translation from another language important or needed for publication?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

See end of filing memorandum.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			In vitro reaction phenotyping studies were not conducted as the sponsor stated that deoxycholic acid metabolism in the liver and its biotransformation pathway were reported in the literature. No in vivo drug-drug interaction information was provided. In vitro inhibition/induction information was provided. CYP enzymes tested for induction were CYP1A, CYP2B6, and CYP3A, and the enzymes tested for inhibition were CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks	X			

	work leading to appropriate sections, reports, and appendices?				
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**206333**	**Brand Name**	**Kybella**
OCP Division	**Division of Clinical Pharmacology 3**	**Generic Name**	**Deoxycholic acid injection, 10 mg/mL**
Medical Division	**Division of Dermatology and Dental Product**	**Drug Class**	**Bile acid**
OCP Primary Reviewer	**An-Chi Lu, M.S., Pharm.D.**	**Indication(s)**	**For the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults**
OCP Secondary Reviewer	**Doanh Tran, R.Ph., Ph.D**	**Dosage Form**	**Injectable solution**
		Dosing Regimen	**Inject a dose of 0.2 mL into each injection site, 1 cm apart, (b) (4) until all sites in the planned treatment area have been injected. The maximum dose should not exceed 100 mg (10 mL or 50 injections) in a single treatment. Treatments should not be administered at intervals of less than 4 weeks.**
Date of Submission	**5/13/2014**	**Route of Administration**	**Subcutaneous injection**
Estimated Due Date of OCP Review	**12/12/2014**	**Sponsor**	**Kythera**
PDUFA Due Date	**5/13/2015**	**Priority Classification**	**Standard**
Division Due Date	**12/12/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				(b) (4)
single dose:	X	3		ATX-101-12-32
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	3		100000544 (induction) 13772 (inhibition) TRP01-022213
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	2		(b) (4) ATX-101-11-24
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:		1		KYTH-01-13
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		3		Alme et al, 1977 Bodin et al, 2005. Zollner et al, 2007.
Total Number of Studies		12		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Systemic exposure of deoxycholic acid** **Does TQT trial adequately capture max use conditions?** **Does the population PK analysis support the claim in the label?** **What are the DDI potentials for Kybella?**	

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

Filing Memorandum

Clinical Pharmacology Review

NDA: 206333
Compound: Deoxycholic acid injection, 10 mg/mL
Sponsor: Kythera

Date: 6/25/2014
Reviewer: An-Chi Lu

Background:
Kythera Biopharmaceuticals is submitting a New Drug Application (NDA 206333) for Deoxycholic acid injection, 10 mg/mL under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and under the provisions of Title 21CFR§314.50. This application is subject to "The Program" under PDUFA V agreement.

The proposed new drug product, Kybella (Deoxycholic acid injection), 10 mg/mL, is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. The proposed clinical dose is 2 mg/cm^2, which is delivered at a concentration of 10 mg/mL in 0.2-mL injections spaced on a 1-cm grid. The maximum dose should not exceed 100 mg (10 mL or 50 injections) in a single treatment. Treatments should not be administered at intervals of less than 4 weeks. The number of treatment sessions needed to achieve a satisfactory response depends on the individual patient. In clinical trials up to 6 treatments were allowed.

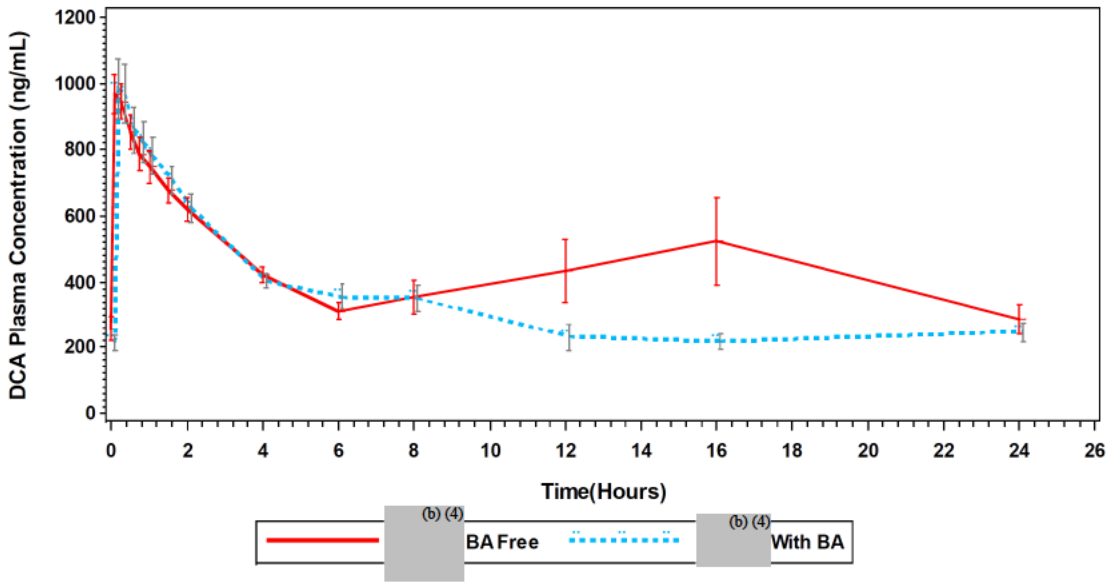
Clinical development program:
The clinical development program for deoxycholic acid injection included a total of 17 clinical trials. Two of these trials were for treatment of superficial lipomas, two were for treatment of abdominal fat, one for subjects undergoing abdominoplasty, and the rest were for the treatment of submental fat. Four Phase 3 safety and efficacy trials (2 US/Canada and 2 European) and one open-label treatment and long-term follow-up trial were completed. Three Phase 3B trials are ongoing.

A total of 5 clinical pharmacology single-dose trials in which ATX-101 was administered subcutaneously (SC) in a single dosing session to the fat tissue in the SMF or the abdominal areas were conducted (Table 1 in Appendix). A population PK analysis was conducted using data from a total of 172 subjects who participated in the 5 Phase 1 studies (Studies (b) (4) 24, (b) (4) and 32) and received ATX-101.

PK Trial ATX-101-12-32 (Trial 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. The result showed that DCA baseline has a mean level of 227 ng/mL with high variability across subjects and

sampling times. ATX-101 measured as DCA had a rapid absorption and returned to baseline by 24 hours (Figure 1). The PK parameters are shown in Table 1. The sponsor did not assess the PK of ATX-101 after repeated doses.

Figure 1: Mean (SE) Plasma DCA Concentration-Time Profiles After Single SC Dose of ATX-101 at 100 mg to the Submental Area



Abbreviations: ATX-101 = deoxycholic acid injection; BA = benzyl alcohol; DCA = deoxycholic acid; PBS = phosphate-buffered saline; SE = standard error
Source: Plotted per subject data (Study 32)

Table 1: Plasma DCA Pharmacokinetic Parameters (Mean ± SD) After Single SC Dose of ATX-101 (100 mg)

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: Appendix 16.2.6.2, Table 14.2.2, and Table 14.2.3 (Study 32)

Thorough QTc Trial, Trial ATX-101-11-24 (Trial 24)
In Trial 24, 100 mg ATX-101 (10 mg/mL) and 200 mg ATX-101 (20 mg/mL) were used to assess the potential for QT prolongation.

The sponsor stated that neither the 100 mg nor the supratherapeutic dose of 200 mg showed to prolong cardiac repolarization in healthy male and female subjects. 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). The appropriateness of study design will be considered during NDA review.

Population PK Analysis (KYTH-01-13):
A population PK analysis was conducted using plasma concentration-time data from 172 adult subjects who received ATX-101 (93 males and 79 females) in 5 Phase 1 clinical Trials (Trials (b) (4) 24, (b) (4) and 32).

Dose Selection:
Dose selection for pivotal clinical trials and commercialization was chosen based on safety and efficacy results from collective data of Phase 2-3 trials that evaluated different concentrations, volumes, and injection spacings of ATX-101, and different maximum numbers of treatment sessions.

Specific population:
Pediatrics:
The applicant requested a waiver of pediatric data in all subsets of the pediatric population (up to 18 years of age), because the indication of non-surgical reduction of submental fat are typically age-related and for growth and development reasons should not be recommended in pediatric patients.

Clinical vs. to-be-marketed formulation:
A total of five ATX-101 formulations were used in the clinical trials. The to-be-marketed formulation (b) (4) in the US 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).

Bioanalysis:
(b) (4).
The Agency has identified that for bioanalytical studies conducted (b) (4) during 3/1/2008 to 8/31/2009, the sponsor needs to perform an independent third-party data integrity audit using the Bioanalytical Electronic Raw Data Audit Plan for the Agency to accept studies for submission. Trial (b) (4) was analyzed (b) (4) during this time, and there was no independent third-party data integrity audit taken place.

Method validation:
For all PK trials (Trials (b) (4) 24, (b) (4) and 32), deoxycholic acid concentrations in human plasma (containing K_2 EDTA as anticoagulant) were determined using high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS).
Trials (b) (4) (b) (4)

(b) (4)

Trials 24 and 32 (by (b) (4))
The long term stability of deoxycholic acid in human plasma stored at -20°C was reported to be 244 days. For Trial 24, the maximum period of storage between first sample collection on 10/18/2012 and last day of analysis on 2/8/2013 was 123 days. For Trial 32, the maximum period of storage between first sample collection on 7/12/2012 and last day of analysis on 8/2/2012 was 21 days. The method validation report (VKYRA1200P1) and bioanalytical reports for Trials 24 and 32 are available for review.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 206333 is fileable.

Comments for sponsor:
1. (b) (4)

(b) (4)

2. For the final data set in the population PK analysis (KYTH-01-13), include a column indicating which formulation was used for each subject.

Appendix

Table 2: PK/PD Trials with ATX-101

Trial	Indication	Dose(s)	N	Type of Trial
[redacted] (b) (4)				
ATX-101-11-24 (Trial 24)	SMF	100 mg 200 mg	218 (109 subjects received ATX-101)	A safety thorough QT trial
[redacted] (b) (4)				
ATX-101-12-32 (Trial 32)	SMF	100 mg	24	safety and PK trial of 2 different to-be-marketed formulations

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/s/

AN-CHI LU
06/30/2014

DOANH C TRAN
06/30/2014