# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** 

# 206333Orig1s000

# **PHARMACOLOGY REVIEW(S)**

#### Pharmacology/Toxicology Supervisory Memorandum

NDA number:	206333
Supporting document:	1
CDER Stamp Date:	May 13, 2014
Type of submission:	Original NDA; 505(b)(1)
Applicant:	Kythera Biopharmaceuticals Inc.
Supervisor name:	Barbara Hill, PhD
Review Division:	Dermatology and Dental Products
Date:	December 16, 2014
Product:	<sup>(b) (4)</sup> (deoxycholic acid) injection
Pharmacologic class:	Cytolytic
Indication:	Improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults

#### General comments:

- I concur with the overall assessment and conclusions contained in Dr. Jill Merrill's • Pharmacology/Toxicology review for this drug product.
- I concur that there are no nonclinical approval issues for this drug product and that • this NDA is approvable from a Pharmacology/Toxicology perspective.
- I concur that there are no nonclinical Post-Marketing Requirements recommended • for this NDA.
- I concur with the recommended nonclinical labeling changes proposed by Dr. Merrill • <sup>(b) (4)</sup> injection contained in section 1.3.3 of her review which include: for
  - 0
  - Pharmacologic Class designation of "cytolytic" (<sup>b) (4)</sup> designation for this drug product 0
  - The revisions proposed for Section 8.1 of the label
  - The revisions proposed for Section 12.1 of the label
  - The revisions proposed for Section 13.1 of the label

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/s/

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BARBARA A HILL 12/16/2014

#### DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

#### PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206333
Supporting document/s:	SDN 1
Applicant's letter date:	05-13-2014
CDER stamp date:	05-13-2014
Product:	<sup>(b) (4)</sup> (deoxycholic acid) injection, 10 mg/mL
Indication:	For improvement in the appearance of moderate
	to severe convexity or fullness associated with
	submental fat in adults
Applicant:	Kythera Biopharmaceuticals Inc.
Review Division:	DDDP
Reviewer:	Jill C Merrill, PhD
Supervisor/Team Leader:	Barbara A Hill, PhD
Acting Division Director:	Tatianna Oussova, MD
Project Manager:	Matthew White

#### Template Version: September 1, 2010

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# **1** Executive Summary

#### 1.1 Introduction

Kythera Biopharmaceuticals Inc, is developing ATX-101 (deoxycholic acid injection) for subcutaneous (SC) administration. ATX-101 is a cytolytic agent intended for the clinical reduction of small areas of localized subcutaneous fat. The active ingredient in ATX-101, deoxycholic acid (DCA), is structurally identical to endogenous deoxycholate found in the bile of humans and other mammals. Endogenous DCA is a secondary bile acid formed from cholate by bacterial action (*i.e.*, partial dehydroxylation) and serves to solubilize dietary fat, thereby aiding in its absorption in the gut. It does not undergo subsequent degradative modification to other catabolites. It is either absorbed in the gut where it rejoins the enterohepatic circulation or is excreted intact in the feces.

Consistent with its natural role in solubilizing dietary lipids, deoxycholic acid has been shown to disrupt the lipid bilayer of cell membranes leading to cell death. Sequestration of deoxycholate by endogenous serum albumin or similar proteins may limit the damage to surrounding non-adipose tissues.

#### 1.2 Brief Discussion of Nonclinical Findings

The ATX-101 drug substance was manufactured via two different processes during the nonclinical development program. Initial manufacturing produced deoxycholate (DC) purified from bovine and ovine bile by a process which yielded the sodium salt form (sodium deoxycholate, [NaDCA]). Subsequently, DC was chemically synthesized yielding free deoxycholic acid (DCA). Deoxycholate from both sources (animal-derived and synthetic) was demonstrated to be structurally identical in solution (see Figure 1 in Section 2.1, taken directly from the submission). The majority of the nonclinical program was completed using ATX-101 containing NaDCA in 0.9% benzyl alcohol (BA) and sterile water for injection (SWFI). Subsequently repeat-dose (28-day) studies were conducted to bridge synthetic DCA with animal-derived NaDCA (study IXB00080) and to evaluate vehicle reformulations (vehicle changes to phosphate buffered saline (PBS) with and without BA; Study 20001032). Nonclinical toxicity and toxicokinetic bridging evaluations did not identify any important differences between the original and reformulated drug products.

Repeat-dose toxicity studies with biweekly subcutaneous injections of ATX-101 have been conducted in rats (≤50 mg/kg for up to 6 months) and dogs (≤25 mg/kg for up to 9 months). Systemic toxicity was not observed in either species. The primary findings in all repeat-dose studies were confined to the injection site and were associated with the pharmacological effect of cytolysis. Dermal signs were reversed or nearly reversed at the completion of the recovery periods.

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

Deoxycholic acid at subcutaneous doses up to 50 mg/kg, administered weekly during the pre-mating and mating periods in males and females and through gestation day 7 in females, did not lead to changes in fertility or general reproductive parameters in rats. Embryofetal development studies have been performed in rats and rabbits using subcutaneous doses of deoxycholic acid at up to maternally toxic doses during the period of organogenesis. Injection site irritation precluded daily dosing in both species. These studies revealed no evidence of fetal harm at up to 50 mg/kg in rats but missing intermediate lung lobe was noted in rabbits at all doses tested (≤ 30 mg/kg). These effects may be related to maternal toxicity which was also seen at all dose levels. No effects on prenatal and postnatal development were observed in pregnant rats treated subcutaneously with up to 50 mg/kg ATX-101 three times weekly from gestation day 7 through postweaning.

#### 1.3 Recommendations

#### 1.3.1 Approvability

ATX-101 is approvable from a pharmacology/toxicology perspective.

#### **1.3.2 Additional Non Clinical Recommendations**

None.

#### 1.3.3 Labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the <u>underlined</u> wording be inserted into and the <del>strikeout</del> wording be deleted from the ATX-101 label text. A clean copy of these revised labeling sections is provided in Appendix #1.

# HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

**ATX 101**<sup>TM</sup> <u>Tradename</u> is a <u>cytolytic drug</u> indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. (1)

#### FULL PRESCRIBING INFORMATION

#### 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy

(b) (4) (b) (4)

(b) (4)

(b) (4)

There are-Tradename in pregnant women.

Embryofetal development studies have been performed in rats and rabbits using subcutaneous doses of deoxycholic acid administered during the period of organogenesis. For the basis of comparing animal to human doses, the MRHD is 1.7 mg/kg (100 mg/60 kg). No evidence of fetal harm was observed in rats at up to the highest dose tested (50 mg/kg) which is 5-fold higher than the MRHD of Tradename based on a mg/m<sup>2</sup> comparison. However, missing intermediate lung lobe was noted in rabbits at all dose levels tested including the lowest dose (10 mg/kg) which is 2-fold higher than the MRHD of Tradename based on a mg/m<sup>2</sup> comparison. These effects may be related to maternal toxicity which was also seen at all dose levels tested.

#### CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

ATX 101 <sup>™</sup> Trade	ename is a 👘	<sup>(4)</sup> cytolytic drug, which when injected into	(b) (4)
	tissue physically	( <sup>b) (4)</sup> the cell membrane	(b) (4)
caus <sup>(b)</sup> ing	<sup>(b) (4)</sup> lysis,	(b) (4)	(b) (4)

#### NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Long term Sstudies in animals have not been performed to evaluate the carcinogenic potential of ATX 101<sup>TM</sup>

H

(b) (4) -		
(b) (4)		

ATX 101<sup>™</sup> <u>Tradename</u> was negative in a battery of in vitro (<u>Ames test</u> and chromosomal aberration assay <u>in human lymphocytes</u>) and in vivo (<u>rat erythrocyte</u> micronucleus assay) genetic toxicology assays.

(b) (4)

No effects on fertility were observed in male and female rats administered deoxycholic acid at subcutaneous doses up to 50 mg/kg (5 times the MRHD based on a mg/m<sup>2</sup> comparison) once weekly prior to and during the mating period and through gestation day 7 in female rats.

# 2 Drug Information

#### 2.1 Drug

CAS Registry Number: 83-44-3

Generic Name: deoxycholic acid

Code Name: ATX-101

Chemical Name:  $3\alpha$ ,  $12\alpha$ -dihydroxy- $5\beta$ -cholan-24-oic acid  $3\alpha$ ,  $12\alpha$ -dihydroxycholanic acid

Molecular Formula/Molecular Weight: C<sub>24</sub>H<sub>40</sub>O<sub>4</sub> / 392.57 g/mol

#### Structure:

# Figure 1:Structures for the Bovine/Ovine-derived Sodium Deoxycholate and<br/>Synthetically-Derived Deoxycholic Acid ([3α,12α-dihydroxy-5β-cholan-24-oic<br/>acid] chemical formula C24H40O4, molecular weight 392.57 g/Mol).



Pharmacologic Class: cytolytic

Reviewer's comment: Although the sponsor proposed "adipocytolytic" as the Pharmacologic Class this designation implies the drug's cytolytic action is specific for adipocytes. The sponsor's data supported a cytolytic effect, but not one specific for adipocytes. The designation of Pharmacologic Class as "cytolytic" has been determined in discussions with the Clinical Reviewer, Dr. Milena Lolic.

#### 2.2 Relevant INDs, NDAs, and MFs

IND 79726 (12-05-2007), reduction of localized subcutaneous fat IND <sup>(b) (4)</sup> treatment of patients with superficial lipomas

#### 2.3 Drug Formulation

Deoxycholic acid (DCA) is freely soluble (100 mg/mL - 1 g/mL) in solutions of alkali hydroxides or carbonates. The drug product contains 10 mg/mL of the active ingredient, DCA, formulated in a sterile solution of sodium hydroxide, dibasic sodium phosphate, sodium chloride and water for injection, with benzyl alcohol as a preservative (see Table 1, taken directly from the submission). The formulation is adjusted to pH 8.3 and has a tonicity compatible with that of biological tissues and fluids.

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	(6) (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	<b>q.s</b> .	q.s.	pH adjustment
Water for injection	USP/PhEur	to 100%	to 2.0 mL	(b) (4)

q.s. = Quantity sufficient; USP = United States Pharmacopeia; NF = National Formulary

The two most significant changes during the formulation development effort were inclusion of a phosphate buffer system <sup>(b) (4)</sup> and conversion from animal-derived sodium deoxycholate (NaDCA) drug substance to synthetic deoxycholic acid (DCA) drug substance <sup>(b) (4)</sup>

The bulk of the nonclinical program was conducted using ATX-101 containing NaDCA in a vehicle of 0.9% benzyl alcohol and sterile water for injection (BA /SWFI). However, the final to-be-marketed formulation contains DCA in a PBS vehicle with 0.9% BA. The toxicity profile and toxicokinetic-pharmacokinetic characteristics of the final DCA clinical formulation were assessed in a 28-day bridging study in rats (Study IXB00080). Nonclinical toxicity and toxicokinetic bridging evaluations did not identify any important differences between the original and reformulated drug products. This study was reviewed by Dr. Carmen Booker (IND <sup>(b) (4)</sup>, entered in DARRTS 4-29-2010) and summarized below (Section 6.2).

### 2.4 Comments on Novel Excipients

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

#### 2.5 Comments on Impurities/Degradants of Concern

There are no DCA-related drug substance or drug product impurities which require nonclinical qualification since the impurity acceptance criteria are below the qualification thresholds described in ICH Q3A(R2) for drug substance with a maximum daily dose of  $\leq 2 \text{ g/day} (0.15\% \text{ or } 1 \text{ mg} \text{ total daily intake (TDI)}, whichever is lower) and ICH Q3B(R2) for drug products with a maximum daily dose of <math>10 - 100 \text{ mg} (0.5\% \text{ or } 200 \text{ µg} \text{ TDI}, whichever is lower)$ . Therefore, nonclinical qualification is not required.

Nonetheless during the development of the synthetic manufacturing process in silico studies were conducted to evaluate the genotoxic potential for potential impurities of the drug substance. These studies are further discussed in Section 7.

The sponsor has conducted studies for extractables/leachables from the container/closure system using various analytical techniques. Of these, only HPLC/DAD/MS detected unknown peaks in the drug product. Of the four unknown peaks detected, one impurity (retention time [RT] <sup>(b)(4)</sup> minutes) was shown to be present at a concentration of <sup>(b)(4)</sup>  $\mu$ g/mL in samples stored for 12 months under accelerated conditions (40°C/75% RH). For each use of ATX-101 (10 mL x <sup>(b)(4)</sup>  $\mu$ g/mL) the amount of this unknown impurity would be equal to <sup>(b)(4)</sup>  $\mu$ g/dose. ATX-101 is not intended for daily use and dosing instructions limit use of the drug to not more than once in 30 days, making the average daily dose of the unidentified leachable <sup>(b)(4)</sup>  $\mu$ g/day ( <sup>(b)</sup><sub>(4)</sub>  $\mu$ g/dose x 1 /30 dose/day = <sup>(b)(4)</sup>  $\mu$ g/day). This value is considered acceptable for this unknown

#### 2.6 Proposed Clinical Population and Dosing Regimen

ATX-101 is intended to be administered as a 2 mg/cm<sup>2</sup> dose in 0.2 mL injections, spaced 1 cm apart. The maximum intended dose in a treatment session is 100 mg (*i.e.*, 10 mL; 50 injections). ATX-101 may be given in up to 6 treatment sessions, at intervals at least 4 weeks apart.

#### 2.7 Regulatory Background

Pre-NDA meeting: 11/13/13 Clinical SPA agreement: 12/16/11 EoP2 meeting: 4/20/11

# 3 Studies Submitted

#### 3.1 Studies Reviewed

#### **Pharmacology**

In vitro pharmacology: Study of DCA129 (study # 100000645)

Deoxycholic acid diffusion study to determine safe injection distance in pigs (ATX-101-0027)

Determination of the  $LD_{50}$  of sodium deoxycholate (NaDC) for five developmentally distinct cell types in vitro (Report 003)

The effects of tissue pre-incubation on deoxycholate-mediated cytolytic activity (Report 004)

The effects of collagen exposure on sodium deoxycholate-mediated loss of cell viability (Report 005)

The effects of albumin exposure on sodium deoxycholate-mediated cytolytic-activity (Report 006)

The effects of tissue pre-incubation on deoxycholate (DC)-mediated cytotoxicity (Report 007)

Cytotoxicity of deoxycholate (DC) towards multiple cell lines in vitro (Report 008)

The effects of albumin exposure on deoxycholate (DC)-mediated cell lysis (Report 009)

Investigating deoxycholate (DC) dose response in vivo (Experimental Report 0014)

Comparison of deoxycholate (DC)-mediated adipolysis in vivo when DC is solubilized in either of two vehicles (Report 0015)

Comparison of vehicle-mediated adipolysis in vivo (Report 0016)

#### **Pharmacokinetics**

Tissue distribution of [<sup>3</sup>H]deoxycholic acid sodium salt following subcutaneous administration to Sprague-Dawley rats (study # IXB00011)

A pharmacokinetic study of the baseline levels of endogenous deoxycholic acid in rats (non-GLP; study number IXB00042)

Deoxycholic acid: Evaluation of human cytochrome P450 inhibition in human liver microsomes (XBL 13772)

In vitro interaction studies of deoxycholic acid with human BSEP, MRP2, MRP4, MDR1 and BCRP efflux transporters, and with human OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, OATP2B1, NTCP and ASBT uptake transporters (TRP01-022213)

#### 3.2 Studies Not Reviewed

The following studies have been previously reviewed. Summaries are provided in the corresponding section of this document. For further details consult reviews listed in Section 3.3.

#### **Pharmacokinetics**

Excretion mass balance and quantitative whole-body autoradiography for a single subcutaneous fat pad injection of [<sup>14</sup>C]-triolein following deoxycholate pretreatment in Sprague Dawley rats (Study number ATX101-0023)

Metabolite profiling of [<sup>14</sup>C]-triolein in plasma, urine, and feces of female Sprague Dawley rats following a single subcutaneous fat pad injection of [<sup>14</sup>C]-triolein (Study Number ATX101-024)

Discovery tissue distribution study by micro-autoradiography for a single subcutaneous fat pad injection of [<sup>14</sup>C]-triolein following deoxycholate pretreatment in Sprague Dawley rats (Study number ATX101-026)

ADME Tox study of deoxycholic acid (non-GLP; study # 100000544)

#### Safety Pharmacology

Report 26734 Effect of deoxycholic acid on hERG tail currents recorded from stably transfected CHO cells

Report IXB00008 Acute intravenous central nervous system (CNS) safety pharmacology study of deoxycholic acid sodium salt in rats.

Report IXB00007 A cardiovascular and respiratory safety pharmacology study of deoxycholic acid sodium salt administered by subcutaneous injection to telemetered Beagle dogs.

Report IXB00009. A bioavailability study of deoxycholic acid sodium salt administered by the intravenous or subcutaneous route to rats.

Report IXB00010. A bioavailability study of deoxycholic acid sodium salt administered by the intravenous or subcutaneous route to dogs.

#### General toxicology

Comparing the relative in vitro cytotoxicity of the commercial formulation of synthetic deoxycholic acid (sDCA) to the phase IIb formulation of animal derived sodium deoxycholate (aDC) (Study # 0026)

Expert opinion on injection site pathology from laboratory animals given subcutaneous injections of deoxycholic acid sodium salt (Study number 955-001)

#### Repeat dose toxicology

A 4-Week Subcutaneous Injection Study of 3 Dose Formulations of Deoxycholic Acid Administered to Sprague Dawley Rats, with a 4-Week Recovery Period. Study Number IXB00080.

A 4-Week Comparative Toxicity Study of 2 Deoxycholic Acid Sodium Salt Formulations Administered via Subcutaneous Injection to Sprague-Dawley Rats, with a 4-Week Recovery Period. Study Number 20001032.

A 41-Week Repeat Dose Cycle Toxicity Study of 3 Subcutaneously Administered Deoxycholic Acid Sodium Salt to Beagle Dogs, with a 4-Week Recovery Period. (Study # IXB00076)

#### Genetic Toxicology

Report 960827 Deoxycholic acid, sodium salt: Bacterial mutation test

Report 960828 Deoxycholic acid, sodium salt: Chromosome aberration test

Report 960829 Deoxycholic acid, sodium salt: rat micronucleus test

Report 964300 DCA129: Bacterial reverse mutation test in *Salmonella typhimurium* and *Escherichia coli* 

Report 964442 Deoxycholic acid (DCA) with impurities : Bacterial reverse mutation test in Salmonella

typhimurium and Escherichia coli

Report 964443 Deoxycholic acid (DCA) with impurities

In vitro mammalian chromosome aberration test in human peripheral blood lymphocytes

Theoretical genotoxicity assessment of several impurities of deoxycholic acid (TOXT2082921)

Structure-based assessment of potentially mutagenic impurities (study # TOXT101079-8)

Computational assessment and evaluation of potential genotoxicity of 6 DCA impurities using MC4PC (study # 11414-21371)

Computational assessment and evaluation of potential genotoxicity of 3 DCA synthetic process intermediates using MC4PC (study # 11426-21378)

#### Reproductive toxicology

Subcutaneous fertility and general reproduction toxicity study of deoxycholic acid sodium in rats (study # IXB00024)

Subcutaneous dosage-range developmental toxicity study of deoxycholic acid sodium salt in rats (study # IXB00020)

Subcutaneous dosage-range developmental toxicity study of deoxycholic acid sodium salt in rabbits (study # IXB00021)

Subcutaneous developmental toxicity study of deoxycholic acid sodium in rats (study # IXB00022)

Developmental toxicity study of subcutaneously administered deoxycholic acid sodium salt in rabbits (study # IXB00023)

Developmental and Perinatal/Postnatal Reproduction Toxicity Study of Subcutaneously Administered Deoxycholic Acid Sodium Salt (DCO) in Rats, Including a Postnatal Behavioral/Functional Evaluation. (Study # IXB00025)

The following studies have not been previously reviewed and are not reviewed under this NDA:

Analytical method validation for deoxycholic acid sodium slat (DCO) in a phosphate buffered saline dosing formulation and determination of formulation stability (study # 0020001159)

Method validation to support analysis of sodium deoxycholate dose formulations for Aestherx, Inc. (Study # IXB00012AX)

Validation of a high performance liquid chromatographic-mass spectrometric method for the analysis of sodium deoxycholate in K<sub>2</sub>EDTA rat plasma (IXB00013LX)

Long-term matrix stability assessment of deoxycholic acid in K<sub>2</sub>EDTA rat plasma (IXB00014SX)

Validation of a high performance liquid chromatographic-mass spectrometric method for the analysis of deoxycholic acid in K<sub>2</sub>EDTA dog plasma (IXB00015LX)

Long-term matrix stability assessment of deoxycholic acid in K<sub>2</sub>EDTA dog plasma (IXB00016SX)

Formulation sample analysis for	(b) (4)
(Study 960827)	

Partial validation of a high performance liquid chromatographic-mass spectrometric method for the analysis of deoxycholic acid in K<sub>2</sub>EDTA rabbit plasma (IXB00039LX)

Long-term matrix stability assessment of deoxycholic acid in K<sub>2</sub>EDTA rabbit plasma (IXB00040SX)

Physical appearance, stability and homogeneity assessment in nonclinical formulations of deoxycholic acid sodium salt in 0.9% benzyl alcohol (IXB00071AX)

Verification of stability and homogeneity of deoxycholic acid sodium salt (DCO) and deoxycholic acid (SYN-DCO) in a phosphate buffered saline vehicle (IXB00082DX)

#### 3.3 Previous Reviews Referenced

IND 79726, Dr. Barbara Hill, entered in DARRTS 04-02-2013 IND 79726, Dr. Barbara Hill, entered in DARRTS 03-15-2012 IND 79726 Dr. Carmen Booker, entered in DARRTS 03-04-2011 IND 79726 Dr. Carmen Booker, entered in DARRTS 06-17-2010 IND 79726 Dr. Carmen Booker, entered in DARRTS 04-29-2010 IND <sup>(b)(4)</sup>, Dr. Carmen Booker, entered in DARRTS 7-14-2009 IND 79726, Dr. Carmen Booker, entered in DARRTS 2-12-2009 IND <sup>(b)(4)</sup>, Dr. Carmen Booker, entered in DARRTS 11-29-2006

# 4 Pharmacology

### 4.1 **Primary Pharmacology**

Rotunda et al (2004) proposed that deoxycholate acts as a detergent that lyses and dissolves cell membranes. This proposed mechanism of action has been subsequently confirmed by other researchers (Duncan et al, 2009). Since biologic membranes are composed of the same bilipid structure, it is not surprising that deoxycholate was cytolytic to all cell types tested in vitro (Report 008) without an intrinsic fat cell sensitivity (Report 003). Rotunda et al (2004) report that deoxycholate causes architectural disruption in both fat and muscle tissue when using an ex vivo porcine model.

In vitro exposure to various protein-rich tissues attenuates sodium deoxycholatemediated adipocyte lysis (Report 004, Report 005, Report 006, Report 007). DCmediated adipocyte toxicity was dose-dependently attenuated with increasing bovine serum albumin (BSA) concentrations and abolished at 4% BSA, the highest concentration tested (Report 009). Thus DC's nonspecific cytolytic action only becomes "preferential" for adipose tissue when the injection technique itself limits the detergent's exposure to adipose tissue and avoids muscle tissue (Thuangtong et al, 2010, Schuller-Petrovic et al, 2008).

Using eight male genetically obese Zucker rats the sponsor investigated the effects of different concentrations of DC on adipose tissue viability (Experimental Report 0014). Caudal lateral fat pads were chosen as the injection site, with two fat pads per animal treated with either DC (1%, 0.5%, 0.25%, 0.1%) or vehicle. Each fat pad was injected with 2.5 mL and a total of three fat pads were injected per test solution (n=3). Twenty-

four hours post-injection rats were terminated and the injected fat pads were resected from the animal. The area of necrosis was determined by visual inspection of photographed fat pads and each image was spatially calibrated using quantitation software.

Both gross observation of the treated fat pads as well as surface area quantitation demonstrated that 1% DC caused more necrosis than the lower concentrations. The next highest concentration used, 0.5% DC, was approximately 2.5-fold less potent than 1% DC. Both the 0.25% and 0.1% DC sample solutions caused minimal fat necrosis, similar to that of the vehicle. DC adipolytic activity was similar when solubilized in either benzyl alcohol or phosphate-buffered vehicles (Report 0015) and neither vehicle showed appreciable activity in the absence of DC (Report 0016).

Reviewer's comment: The supporting nonclinical program was initiated under IND <sup>(b)(4)</sup> using animal-derived deoxycholate (aDC). Based on concerns for use of animalderived material, the sponsor developed a synthetic process for manufacturing DCA (sDCA). The sponsor conducted a 4-week subcutaneous study in rats comparing the toxicity profile of aDC and sDCA at a dose of 50 mg/kg administered once weekly (Study # IXB00080). The toxicity profiles of aDC and sDCA were similar in this study which indicated no safety concerns for use of sDCA in clinical studies from a Pharmacology/Toxicology perspective.

An in vitro bridging pharmacology study (Study # 0026), conducted to compare the relative cytotoxicity of animal-derived sodium deoxycholate (aDC) to synthetic deoxycholic acid (sDCA) determined no pharmacologic difference in the cytolytic potential of aDC and sDCA. The  $LC_{50}$  for both samples was ~ 0.05% DC. Further details are in the IND reviews.

#### 4.2 Secondary Pharmacology

Secondary pharmacology studies were conducted to investigate the mechanism by which fat (free fatty acids and triglycerides) released from lysed adipocytes following subcutaneous DCA injection are processed in rats (ATX101-0023, ATX101-024, ATX101-026). The results from these studies indicate that lipid released from adipocytes after DCA treatment is processed in a similar manner as dietary fat in rats. Further details are in the IND reviews.

To characterize the area of cell destruction following subcutaneous injection, a single male Yorkshire pig was administered placebo (vehicle; 0.9% benzyl alcohol in PBS, pH 8.2), and DCA (ATX-101 <sup>(b)(4)</sup>) at concentrations of 0.5% and 1.0% to 16 pre-marked dorsal sites, each measuring 36 cm<sup>2</sup> (ATX-101-0027). Injections were administered to a depth of 0.5 cm in order to mimic the intended clinical administration. Tissue samples were collected at each injection site 48 hours post-dosing to ensure peak apoptosis. Following fixation in 10% neutral buffered formalin each sample was divided in half and stained for histologic evaluation (hematoxylin and eosin [H&E] staining) or left unstained for terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) analysis. The extent and severity of effects (*e.g.* cytolysis, inflammation) and cell death

(apoptosis) were determined by histologic evaluation using H&E staining and TUNEL assay, respectively.

Reviewer's comment: Apoptosis results in condensation of the nucleus and shrinkage of the cell contents. Chromosomal fragmentation, cytoplasmic blebbing, and apoptotic bodies without inflammation of the surrounding tissue are characteristically observed during apoptosis.

The study findings indicate that subcutaneous injection of 0.5% and 1% DCA induced a brisk inflammation with concentration-related increases in TUNEL staining of adipocytes within 1 cm of the point of injection. The most inflammation and the largest number of TUNEL-positive adipocyte nuclei were observed within 1 cm of the site of injection of 1% DCA (0.2 mL/injection site and 0.4 mL/injection site).

In a 30-patient study Odo et al (2007) showed adipocyte lysis with inflammation and phagocytosis by macrophages. Schuller-Petrovic et al (2008) concurred and noted dose-dependent fibroplasia in histological specimens, as well as muscle loss and necrotic changes in the walls of small blood vessels.

#### 4.3 Safety Pharmacology

#### Neurological effects

Single intravenous doses of 1, 5, and 10 mg/kg sodium deoxycholate were administered to male and female Sprague Dawley rats to evaluate central nervous system effects (Report IXB00008). Signs of injection site irritation were observed in the mid- and high-dose groups. Immediately after dosing, one high dose male had decreased motor activity, continuous whole body tremors and hyperpnea. After 15 minutes, he was observed with a purple tail, discolored urine, coldness to the touch, and decreased body temperature. Immediately after dosing one high dose female had decreased motor activity, loss of righting reflex and hyperpnea. After 15 minutes, she was observed with ptosis (both eyes), lacrimation (both eyes), coldness to the touch, decreased motor activity, a purple tail and a decrease in body temperature. After 24 hours the only effect still present in both rats was discoloration of the tail. The NOAEL for local signs of irritation was determined to be 1.0 mg/kg. The NOAEL for CNS effects was determined to be 5.0 mg/kg.

#### Cardiovascular and pulmonary effects

Conscious, telemetered beagle dogs were subcutaneously injected with sodium deoxycholate (5, 10, and 20 mg/kg) to evaluate hemodynamic and respiratory parameters and monitored for 24 hours (Report IXB00007). Arterial blood pressure, respiratory rate, core body temperature and arterial blood gasses were unaffected. High dose animals had a slight increase in heart rate approximately 2.5 hours post-dose; however, the change was not statistically significant. Thus all electrocardiograms were considered normal and no QT/QTc prolongation was observed.

Sodium deoxycholate has been tested for the potential to inhibit the repolarizing current in the cardiac action potential in Chinese hamster ovary cells transfected with hERG (human Ether-a-go-go-Related Gene; Report 26734). Cells were exposed to increasing concentrations and although a loss in current was observed, the effect was independent of deoxycholate concentration and irreversible. The effects did not fit the classical hERG channel inhibitor profile and were concluded to be due to membrane perturbation. Thus sodium deoxycholate was considered to have a low probability of QT prolongation. Further details are in the IND reviews.

Nonclinical evaluations of renal, autonomic nervous system or gastrointestinal system effects were not conducted.

# 5 Pharmacokinetics/ADME/Toxicokinetics

#### 5.1 PK/ADME

#### **Bioavailability**

The sponsor has conducted bioavailability studies in rats and dogs. A summary of the information from these studies is provided below. Further details are in the IND reviews.

A bioavailability study conducted in rats (Report IXB00009) demonstrated that mean concentration-time profiles for plasma DCA were qualitatively similar following intravenous or subcutaneous administration. Mean concentrations declined in a multiphasic manner from  $C_{max}$ , which was observed at time zero following intravenous dosing and at 0.25 hours after subcutaneous dosing.  $C_{max}$  was 4.8-fold higher for males than females after intravenous administration, but was comparable for males and females after subcutaneous administration. AUC<sub>last</sub> was higher for males than for females for both routes by approximately 55% and 111%, respectively. AUC<sub>last</sub> data for the two routes of administration indicated essentially quantitative subcutaneous bioavailability, with estimates of 130% for males and 97% for females.

A bioavailability study conducted in dogs (Report IXB00010) demonstrated that mean concentration-time profiles for plasma DCA were qualitatively similar following intravenous or subcutaneous administration, but the profiles differed 4 hours post-dose. For intravenous dosing, mean concentrations declined in a multi-phasic manner from  $C_{max}$ , which was observed at time zero, through 4 hours post-dose, then increased substantially at 8 hours and remained near that level through 18 hours ( $t_{last}$ ). After subcutaneous dosing,  $C_{max}$  was reached at a median time of 0.5 hours post-dose for males and females, indicating rapid absorption. Mean concentrations declined from  $C_{max}$  through the remainder of the time-course. Mean  $C_{max}$  was comparable for males and females after both routes of administration. The intravenous  $C_{max}$  values were approximately 3-fold greater than the respective subcutaneous values. Mean AUC<sub>last</sub> was comparable for males and females and females for each route, after excluding results of one

female dosed subcutaneously. Mean AUC<sub>last</sub> values from subcutaneous and intravenous administration were roughly equivalent when normalized for dose.

#### Absorption and Distribution

The tissue distribution of total radioactivity was investigated following SC injection of 10 mg/kg [<sup>3</sup>H]-deoxycholic acid (12[<sup>3</sup>H]-DC) at a volume of 1 mL/kg to male Sprague Dawley rats (Study IXB00011).

Rapid systemic absorption was shown by a  $C_{max}$  of 3420 ng equiv/g in plasma at the first sampling time (0.25 hr postdose). The majority of tissues exhibited  $C_{max}$  values at 0.5 hr.

Concentration-time profiles for plasma and tissues were generally characterized by an initial decline, followed by attainment of an apparent plateau level by 24 h postdose, suggesting some level of retention of [<sup>3</sup>H]deoxycholic acid-derived radioactivity.

[<sup>3</sup>H]Deoxycholic acid-derived radioactivity showed the highest affinity for small intestine and liver, suggesting participation in enterohepatic circulation along with naturally occurring bile acids. Affinity for other tissues was generally much lower.

#### Pharmacokinetic Drug Interactions

The potential for direct and time dependent inhibition and induction of human cytochrome P450 (CYP) enzymes by DCA was evaluated (Study # 100000544) and previously reviewed (IND 79726 entered in DARRTS 4-2-2013). Based on the results of these in vitro studies, the sponsor believes the potential of CYP enzyme inhibition and induction by subcutaneous DCA administration would not be clinically significant and drug-drug interaction studies are not warranted.

The inhibitory potential of DCA against seven major human CYP isozymes (*i.e.*, CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4), was assessed using pooled human liver microsomes (XBL-13772). Little or no inhibitory effects were observed under the experimental conditions. In accordance with FDA Guidance for Industry (Drug Interaction Studies – study design, data analysis, implications for dosing and labeling recommendations) and based on these in vitro results, the sponsor believes in vivo drug-drug interaction studies are not warranted. In vitro inhibition studies with selected efflux and uptake drug transporters also suggest that ATX-101 has little or no potential for clinically meaningful drug interactions at the maximum intended clinical dose (100 mg; TRP01-022213). However, the Clinical Pharmacology reviewer will determine the clinical significance of these in vitro results.

<u>Other</u>

The sponsor conducted a study to determine the effect of feed consumption on baseline levels of endogenous deoxycholic acid in rats (IXB00042). Assessments on the bioavailability of exogenously administered deoxycholic acid based on plasma deoxycholate levels need to consider the fed/fasted status of the animals as endogenous deoxycholate varies accordingly. Further details are in the IND reviews.

#### 5.2 Toxicokinetics

Refer to Repeat Dose Toxicity studies in Section 6.2.

# 6 General Toxicology

#### 6.1 Single-Dose Toxicity

Single subcutaneous ATX-101 doses of ≤250 mg/kg in rats (Studies IXB00001, IXB00002, IXB00032) and ≤100 mg/kg in dogs (Studies IXB00003, IXB00035) were systemically well tolerated. Local effects were associated with pharmacologically-mediated cytolysis. A maximum ATX-101 dose of 50 mg/kg was identified for repeat-dose administration in both species.

### 6.2 Repeat-Dose Toxicity

The sponsor conducted a 4-week subcutaneous toxicity study in rats (5/sex/group) with the bovine DCA in 0.9% benzyl alcohol vehicle, bovine DCA in PBS-based vehicle and synthetic DCA in PBS-based vehicle; each at a dose of 50 mg/kg (Study # IXB00080). Rats were dosed once weekly for 4 weeks followed by a 4-week recovery period. Similar toxicities were observed amongst all the groups, except for the PBS-based vehicle control. No new toxicities were observed in the synthetic DCA group. Toxicities observed were limited to the injection site.

This new data demonstrates that the synthetic DCA appears to have the same safety profile as the bovine DCA. Therefore the sponsor's switch to synthetic DCA does not raise any new pharmacology/toxicology safety concerns. Further details are in the IND reviews.

The sponsor conducted a 4-week comparative toxicity study of ATX-101 using two different vehicles (Study 20001032). Vehicle 1 contained sodium phosphate monobasic monohydrate, benzyl alcohol, sodium chloride and sterile water for injection. Vehicle 2 contained sodium phosphate dibasic anhydrous, sodium chloride and sterile water for injection. Both groups of animals (5/sex/group) received 50 mg/kg ATX-101 via subcutaneous injection weekly for four weeks. Six additional male rats in each group were included for toxicokinetic analysis. Clinical signs were limited to localized injection site irritation. Body weight and feed consumption were unaffected. No differences in dermal responses were observed between the two groups. Toxicokinetic data indicated

that the exposure from each of the formulations was similar. No accumulation of ATX-101 was noted after repeated administration. Further details are in the IND reviews.

Repeat-dose toxicity studies of up to 6 months duration in rats and 9 months duration in dogs have been conducted with ATX-101. The study of the longest duration in each species is summarized below. Further details are in the IND reviews .

Twice monthly subcutaneous doses of 0 (vehicle: 0.9% benzyl alcohol in sterile water), 5, 10, and 50 mg/kg ATX-101 were administered to Sprague Dawley rats (10/sex/group) for 6 months (IXB00052). A 1 month recovery group was included in this study. No significant systemic toxicity was noted in this study. The systemic NOAEL was 50 mg/kg, the highest dose tested in this study. A local NOAEL was not identified in this study due to mild to severe dermal irritation noted at the injection sites in all dose groups. Injection site irritation was minimal after the 1 month recovery period.

An increase in plasma DC levels with increased ATX-101 dose was noted in this study. There was no apparent accumulation or sex difference in systemic exposure to DC noted in this study. A summary of the toxicokinetic data from this study is provided in the following table (copied from NDA submission).

Doses (mg/kg) [conc.]	Day	Sex	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	t <sub>last</sub> (hr)	AUC <sub>0-72</sub> (ng·hr/mL)
0	1	М	346	72	72	10944
[vehicle]		F	106	72	72	3588
	180	М	152	2	72	4708
		F	176	72	72	7199
5	1	М	811	1	72	10168
[0.5%]		F	471	1	72	4345
	180	М	734	1	72	6374
		F	454	1	72	6699
10	1	М	1380	1	72	13402
[1%]		F	863	1	72	5634
	180	М	1167 1		72	17510
		F	944 1 7		72	11284
50	1	М	4170 <sup>a</sup>	2	72	32899
[5%]		F	2150 <sup>a</sup>	2	72	21013
	180	М	4633 <sup>a</sup>	2	72	36000
		F	2953 <sup>a</sup>	2	72	25983

<sup>a</sup> Statistically significantly greater than control group ( $p \le 0.01$ )

Weekly subcutaneous doses of 0 (vehicle: 0.9% benzyl alcohol in sterile water), 10, 25, and 50 mg/kg ATX-101 were administered to Beagle dogs (3/sex/group) for 9 months. A 1 month recovery group was included in this study. The systemic NOAEL was 25 mg/kg due to the possible renal lipid embolus observed in the 50 mg/kg group. A local NOAEL was not identified in this study due to dermal toxicity observed in all dose groups. Dermal toxicities included swelling, erythema, edema and ulceration at the treatment site. The injection site reactions had recovered by the end of the 1 month recovery period.

Toxicokinetic data showed variable endogenous plasma DC concentrations in predose samples and in control groups, ranging from below the limit of quantitation (<5.00 ng/ml) to 676 ng/ml. An increase in plasma DC levels with increased ATX-101 dose was noted in males, but not females. There was no apparent accumulation or sex difference in systemic exposure to DC noted in this study. A summary of the toxicokinetic data from this study is provided in the following table (copied from NDA submission). The

Doses (mg/kg) [conc.]	Day	Sex	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	t <sub>last</sub> (hr)	AUC <sub>0-24</sub> (ng·hr/mL)
0	1	М	133	8	24	1334
(Untreated control)		F	260	8	24	1884
	271	М	29.2	282		
		F	470	12	24	3389
0	1	М	1116	8	24	5973
(Vehicle Control)		F	248	8	24	1580
	271	М	215	8	24	1325
		F	99	8	24	918
10	1	М	939	0.5	24	4765
[2%]		F	4388	0.5	24	25918
	271	М	723	0.5	24	5469
		F	1608	0.5 24		10475
25	1	М	1740	0.5	24	12248
[5%]		F	1510	0.5	24	10394
	271	М	1087	4	24	13348
		F	1360	2	24	15162
50	1	М	2096	0.5	24	17845
[10%]		F	1706	0.5	24	15152
	271	М	1692	8	24	24936
		F	1920	8	24	26105

toxicokinetic data are very unreliable due to the enormous differences in the endogenous levels of DC (i.e., between the untreated control and vehicle control levels).

A comprehensive histopathology review showed that tissue reactions to subcutaneous ATX-101 administration were consistent between the key toxicology species, rat and dog, and those observed in local tolerance studies in minipigs (955-001). Effects increased in incidence and severity with dose and frequency of injection and were consistent with local irritation reactions. In addition, there was no indication of pre-neoplastic hyperplasia at or adjacent to the ATX-101 injection sites in any toxicity study with treatment durations of up to 6 months in rats and 9 months in dogs. Further details are in the IND reviews.

# 7 Genetic Toxicology

Sodium deoxycholate has been tested in the complete ICH battery for genetic toxicology. It is not mutagenic in the Ames test (Report 960827), not clastogenic in the

in vitro mammalian chromosomal aberration test in human lymphocytes (Report 960828) and not genotoxic in the in vivo rat erythrocyte micronucleus assay (Report 960829). Further details are in the IND reviews.

Late in the development of the synthetic DCA manufacturing process in vitro genotoxicity studies were initiated for impurities which were considered to have the potential to exceed qualification threshold limits as well as for the API starting material, <sup>(b)(4)</sup>. <sup>(b)(4)</sup> (study # 964300) and DCA spiked with elevated levels of <sup>(b)(4)</sup> (study # 964442) did not show any evidence of mutagenicity in any bacterial strain in the Ames assay. An in vitro chromosomal aberration assay of the same impurity-spiked DCA mixture was conducted in human peripheral lymphocytes and evaluated for potential clastogenicity (study # 964443). Chromosomal aberrations were observed in the 21-hour treatment in the absence of S9, but only at concentrations which produced cytotoxicity (*i.e.*, RMI of 50%, Table 1, taken directly from the study report).

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	Final										I	ncid	lenta	al .
	Conc.	_	RMI	No. Cells	%	N	<u>o</u> . of	Abe	rra	tions	Ob	serv	atio	ns 🕆
Treatment	(µg/mL)	MI	(%)	Examined	Aberrant	<u>b</u>	e	B	E	other	(g	G	P	<u>C)</u>
4 hours treatm	ent in the a	bsence	e of S9	(0S9)										
Vehicle	-	8.3	100	200	1.0	2	0	0	0	0	0	0	0	0
Test Item	31.3	8.4	102	200	1.0	1	0	1	0	0	0	0	0	0
	62.5	8.4	101	200	1.0	1	0	1	0	0	0	0	1	0
	125	6.6	80	200	3.0	6	0	0	0	0	1	0	0	0
	250	2.8	34	191					Ν	/A				
MMC	0.10	7.5	91	200	13.0**	20	2	8	0	0	2	0	_0_	0
4 hours treatm	ent in the p	resenc	e of S9	) (+S9)										
Vehicle	-	7.7	100	200	1.0	2	0	1	0	0	0	0	0	0
Test Item	31.3	8.5	111	200	0.5	1	0	0	0	0	0	0	1	1
	62.5	6.7	87	200	2.0	2	1	3	0	0	0	0	2	1
	125	6.4	83	200	2.0	3	0	1	0	0	0	0	0	0
	250	3.4	44	86					Ν	/A				
CP	6.0	6.8	89	200	26.5**	45	15	15	0	0	5	0	0	0
21 hours treat	ment in the d	absen	ce of S	9 (0S9)										
Vehicle	-	6.5	100	200	0.5	1	0	0	0	0	1	0	0	0
Test Item	31.3	5.1	79	200	1.5	2	0	3	0	0	0	0	0	0
	62.5	5.2	80	200	1.5	4	0	0	0	0	0	0	1	2
	125	3.2	50	200	6.5**	18	0	1	0	0	1	0	0	0
MMC	0.05	5.5	85	200	10.5**	17	2	8	0	0	0	0	0	0
MI, RMI	Mitotic Ind	lex, Re	lative N	Aitotic Index	(vehicle =	100%	6).							
b, e, g	Chromatid	break,	exchan	ige, gap.										
B, E, G	Chromosor	me bre	ak, excl	iange, gap.										
other	Includes pu	ulveriz	ed chro	mosomes and	l cells with	> 8 a	aberr	ations	5.					
Р	Polyploidy	and en	ndoredu	plication.										
С	Centromer	ic disr	uption.											
t	g, G, P and	l C are	exclude	ed from the ca	alculation o	f%	aberr	ant c	ells.					
N/A	Not assessable (insufficient cells available due to toxicity).													

#### Table 1 Results and Statistical Analysis - Initial Test

Results of statistical analysis using one-tailed Fisher's exact test

 $\label{eq:planet} \begin{array}{ll} * & p \leq 0.01 \mbox{ (significant)}. \\ ** & p \leq 0.001 \mbox{ (highly significant)}. \end{array}$ 

 $Otherwise, \qquad p > 0.01 \ (not \ significant).$ 

A supplemental test at concentrations ranging from 65 to 200  $\mu$ g/mL was conducted (see Table 2, taken directly from the study report). The supplemental test yielded similar results, with chromosomal aberrations being observed for DCA plus impurities, but only in the presence of cytotoxicity. Further details are in the reviews.

#### Final Report

Page 29 Test Facility Study No. 964443

				•										
	Final Conc.		RMI	No. Cells	%	No	). of	Abe	rra	tions	] Ob	inció serv	lent: atio	al ns †
Treatment	(µg/mL)	MI	(%)	Examined	Aberrant	b	e	В	Ε	other	(g	G	Р	<b>C</b> )
21 hours treat	nent in the	absend	ce of S	9 (0S9) – Su	pplementa	l Tes	t							
Vehicle	-	8.5	100	200	0.0	0	0	0	0	0	0	0	0	0
Test Item	65.5	5.3	62	200	1.5	3	0	0	0	0	0	0	0	1
	81.9	5.5	65	200	0.0	0	0	0	0	0	0	0	1	0
	102	5.0	58	200	6.0**	12	0	1	0	0	3	0	0	0
	128	5.9	69	200	7.5**	12	0	4	0	0	1	0	0	0
	160	4.7	55	200	7.0**	22	0	3	0	0	2	0	0	2
	200	4.1	49	200	7.5**	13	0	2	0	0	1	0	0	1
MMC	0.05	6.2	73	200	9.5**	10	2	10	0	0	2	0	0	0

#### Table 2 Results and Statistical Analysis - Supplemental Test

For explanatory footnotes, please see Table 1.

Reviewer's comment: Chromosome aberrations observed at cytotoxic concentrations are difficult to interpret. DNA double strand breaks are precursors to chromosome aberrations (Galloway, 2000), but they are also known to be associated with cytotoxic conditions and produced by compounds not otherwise known to be genotoxic. Using the explanatory footnotes provided for Table 1, the aberrations noted in Table 2 are further defined as chromatid breaks (b) and chromosome breaks (B). Given that chromosome aberrations were not observed in the absence of cytotoxicity (Table 1), this isolated genotoxic finding is considered biologically nonrelevant and is regarded as a secondary effect of cytotoxicity.

A QSAR assessment was conducted to evaluate the genotoxic and clastogenic potential of 6 DCA impurities (study # 11414-21371) and the 3 DCA synthetic process intermediates (study # 11426-21378) employing the MC4PC (MultiCase for Personal Computers) software with modules built for genetic toxicity. The results indicated that the 6 impurities and the 3 synthetic process intermediates were negative in the Ames assay, in vitro mammalian gene mutation assay, in vitro chromosomal aberration assay and in vivo micronucleus assay assessment by the MC4PC software analysis. Currently, a negative in the QSAR assessment for the Ames assay is all that is needed for impurity genotoxicity assessment. Further details are in IND reviews.

A QSAR assessment for potential genotoxic structural alerts was performed for several impurities and DC-related compounds (Study # TOXT2082921) using the Deductive Estimation of Risk from Existing Knowledge (DEREK) rule-based expert system and MultiCase QSAR AZ2 module. No structural alerts were raised in DEREK and no substructures were correlated with mutagenicity in MultiCase. A Vitic (Lhasa Limited) chemical database query produced no results for structurally related compounds of the

impurities. Based on these results, it is concluded that the evaluated impurities did not show evidence of genotoxicity. Further details are in the IND reviews.

The sponsor performed an additional structure activity relationship assessment of 20 potential or actual DCA impurities using computer-based genotoxicity prediction systems and the VITIC database (study # TOXT101079-8). All 20 impurities were considered to be Cramer Class 5, defined as having sufficient evidence for absence of mutagenicity or without predicted mutagenicity. Based on these results it is concluded that the evaluated impurities did not show evidence of genotoxicity and specification limits should be derived as for normal impurities (*i.e.*, as per ICH Q3A(R2), and ICH Q3B(R2).

# 8 Carcinogenicity

Carcinogenicity studies for ATX-101 have been waived (IND 79726, review entered in DARRTS 4-2-2009) based on the Agency's review of the sponsor's request. ATX-101 is comparable to endogenous deoxycholate. The intended clinical treatment will not result in a significant increase in the natural lifetime exposure to deoxycholate, as supported by Phase 1 studies in which plasma levels of ATX-101 returned to baseline within 24 hours. Previous clinical and nonclinical data do not provide a basis for carcinogenic potential concerns. No significant toxicities have been observed in nonclinical studies, and genotoxicity studies were negative.

# 9 Reproductive and Developmental Toxicology

#### 9.1 Fertility and Early Embryonic Development

Deoxycholic acid at subcutaneous doses up to 50 mg/kg, administered weekly during the pre-mating and mating periods in males and females and through gestation day 7 in females, does not lead to changes in fertility or general reproductive parameters in rats (IXB00024). Further details are in the IND reviews.

### 9.2 Embryonic Fetal Development

*Reviewer's comment: In the embryofetal development studies summarized below DCA was solubilized in a vehicle containing 0.9% benzyl alcohol in sterile water for injection.* 

The sponsor has conducted a subcutaneous embryofetal development study in pregnant Sprague Dawley rats (5, 10, 50 mg/kg; 20 females/group, study # IXB00022). Dose selection was based on a subcutaneous dose range finding study conducted in pregnant rats (study # IXB00020). The irritating nature of DCA precluded daily dosing and rats were divided into two subsets. Group one was injected on gestation day (GD) 7, 9, and 11; group two was injected on GD 13, 15, and 17. The rats were injected once on each of three dorsal skin sites. Parameters and endpoints evaluated included viability, clinical observations, body weight, feed consumption, skin observations, necropsy, C-section observations, fetal (external, soft tissue and skeletal) examination,

fetal body weights, and terminal maternal body weights. Pregnancy occurred in 18-20 dams in each subset. Injection related adverse dermal effects were noted in all drug treated rats, but not in vehicle treated controls. No treatment-related effects were observed in the fetuses. The NOAEL for malformations is 50 mg/kg. Further details are in the IND reviews.

The sponsor has conducted a subcutaneous embryofetal development study in pregnant New Zealand White rabbits (10, 20, 30 mg/kg; 20 females/group, study # IXB00023). Dose selection was based on a subcutaneous dose range finding study conducted in pregnant rabbits (study # IXB00021). Due to the irritating nature of DCA rabbits did not tolerate daily dosing at the same site. Therefore, rabbits were dosed on GD 7, 9, 11, 13, 15, 17, and 19 using alternating sites. Parameters and endpoints evaluated included viability, clinical observations, body weight, feed consumption, skin observations, necropsy, C-section observations, soft tissue and skeletal alterations, fetal body weights and terminal maternal body weights. One low dose doe was terminated early due to severe ulceration at an injection site. Pregnancy occurred in 19-20 does in each subset with no treatment-related effects observed at necropsy. An increase in the incidence of missing intermediate lung lobes was noted in offspring of the high dose group. The sponsor attributes this increase to stress, stating it is a common alteration in rabbits. At the time of the initial review, the Agency considered it treatment-related; thus the NOAEL for developmental effects was determined to be 20 mg/kg. Further details are available in the IND review.

Plasma DC levels were quantifiable in all rabbits predose (LLOQ 40 ng/ml). Subcutaenous ATX-101 injection did not produce dose related increases in plasma DC levels at doses up to 30 mg/kg and there was no apparent dose related increase relative to baseline measurements or vehicle control animals. These observations are consistent with the known high endogenous level of DC in rabbits (Hagey et al., 1998).

Reviewer's comment: In the NDA submission the sponsor's proposed label identifies this drug product as <sup>(b)(4)</sup> which may be inconsistent with a possible drug-related developmental effect. Thus the embryofetal data for study # IXB00023 will be independently reviewed below based on the new information provided in the NDA submission.

Review of Table 12 (taken directly from the study report) indicates absent intermediate lung lobe was observed in all treated groups. The malformation was noted in 2, 1, and 4 litters treated with 10, 20 and 30 mg/kg, respectively, but was absent in the control group. A developmental NOAEL could not be determined for this study.

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PROTOCOL IXB00023: DEVELOPMENTAL TOXICITY STUDY OF SUBCUTANEOUSLY ADMINISTERED DEOXYCHOLIC ACID SODIUM SALT IN RABBITS

Jill C Merrill

NDA 206333

TABLE 12 (PAGE 2): FETAL :	SOFT TISSUE ALT	ERATION	IS - CAESAREAN-	DELIVERE	D LIVE FET	JSES (DAY 29	OF GESTATI	ON) - SUMMAR	Y
DOSE GROUP DOSE (MG/KG/DOSE) a		0 (VI	I HICLE)		II 10	I	II 20		IV 30
LITTERS EVALUATED FETUSES EVALUATED LIVE	N N N	1 14 14	9 15 15	1	19 49 49	1	20 64 64		19 155 155
VESSELS: INNOMINATE ARTER LITTER INCIDENCE FETAL INCIDENCE	( ABSENT N(%) N(%)	0 ( 0 (	0.0) 0.0)	0(0(	0.0)	0 ( 0 (	0.0) 0.0)	1 ( 1 (	5.3) 0.6)d
VESSELS: RIGHT SUBCLAVIAN LITTER INCIDENCE FETAL INCIDENCE	ARISES TO THE N(%) N(%)	LEFT 0 ( 0 (	0.0) 0.0)	0(0(	0.0)	0 ( 0 (	0.0) 0.0)	1 ( 1 (	5.3) 0.6)d
VESSELS: RIGHT SUBCLAVIAN LITTER INCIDENCE FETAL INCIDENCE	ARTERY PASSES N(%) N(%)	DORSAL 0 ( 0 (	TO THE TRACHEA 0.0) 0.0)	AND ESC 0( 0(	0.0) 0.0)	0(0(	0.0) 0.0)	1 ( 1 (	5.3) 0.6)d
LUNGS: INTERMEDIATE LOBE / LITTER INCIDENCE FETAL INCIDENCE	AB SENT N (%) N (%)	0 ( 0 (	0.0) 0.0)	2 ( 2 (	10.5) 1.3)	1( 1(	5.0) 0.6)	4 ( 11 (	21.0) 7.1)**b

Treatment with the drug substance caused ulceration at the treatment sites (Table 1, partially reproduced from the study report) in all treated groups and led to early termination of a low dose doe on day 15 of gestation due to a severe ulceration. Does treated with the vehicle only did not have injection site ulceration. A nonmaternally toxic dose was not included in the study design to isolate a potential drug effect from that associated with maternal toxicity. Therefore, the malformations observed at all dose levels are considered drug effects.

Reference ID: 3673206

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NDA 206333

PROTOCOL IXB00023: DEVELOPMENTAL TOXICITY STUDY OF SUBCUTANEOUSLY ADMINISTERED DEOXYCHOLIC ACID SODIUM SALT IN RABBITS

TABLE 1 (PAGE 1): DERMAL GRADING AND CLINICAL OBSERVATIONS - SUMMARY

DOSE GROUP DOSE (MG/KG/DOSE) a	I 0 (VEHICLE)	II 10	111 20	IV 30
MAXIMUM POSSIBLE INCIDENCE	460/ 20	452/ 20	460/ 20	460/20
UNSCHEDULED SACRIFICE	0	1b	0	0
DERMAL GRADING OBSERVATIONS:				
SKIN OBSERVATION: APPEARED NORMAL	210/ 20	88/ 19	107/ 19	101/ 20
SCAB: SITES A THROUGH G	8/ 4	117/ 19**	87/ 17**	130/ 18**
EDEMA: GRADE 1 GRADE 2	13/ 4 0/ 0	69/ 14** 19/ 7**b	72/ 17** 19/ 6**	70/ 16** 26/ 6**
DISCOLORATION: SITES A THROUGH G c	12/ 5	59/ 15**b	39/ 18**	218/ 15**
ULCERATION: SITES A THROUGH G	0/ 0	85/ 17b**	33/ 10*	66/ 13**
ERYTHEMA: GRADE 1 GRADE 2	51/ 13 12/ 4	108/17b 15/5b	121/ 18 11/ 3	93/ 12 27/ 5
HYPOPIGMENTATION	0/ 0	0/ 0	0/ 0	1/ 1
FLAKING: GRADE 1 GRADE 2	0/ 0 1/ 1	2/ 2 0/ 0	3/ 2 0/ 0	0/ 0 0/ 0

STATISTICAL ANALYSES OF CLINICAL OBSERVATION DATA WERE RESTRICTED TO THE NUMBER OF RABBITS WITH OBSERVATIONS. MAXIMUM POSSIBLE INCIDENCE - (DAYS x RABBITS)/NUMBER OF RABBITS EXAMINED PER GROUP ON DAYS 7 THROUGH 29 OF PRESUMED GESTATION N/N - TOTAL NUMBER OF OBSERVATIONS/NUMBER OF RABBITS WITH OBSERVATION a. Dosing occurred on days 7, 9, 11, 13, 15, 17 and 19 of presumed gestation. b. Doe 4322 was sacrificed on day 15 of gestation as per veterinary recommendation due to a severe separated ulceration. c. Purple, red, blue, black, white, brown and/or yellow.

\* Significantly different from the vehicle group value (p≤0.05).

\*\* Significantly different from the vehicle group value (p≤0.01).

Thus the nonclinical findings are consistent with a

(b) (4 classification.

#### 9.3 Prenatal and Postnatal Development

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

#### 10 Special Toxicology Studies

(b) (4) The steroid receptor binding potential of a synthetic DCA drug substance impurity, was assessed in vitro using specific agonist radioligands (Study # 100000645). Four steroid nuclear receptors were evaluated (*i.e.*, glucocorticoid, progesterone, adenosine, estrogen) using human (b) (4) did not exhibit significant cytosolic cells or human recombinant Sf9 cells. binding potential to any of these receptors in vitro at a concentration of 10  $\mu$ M.

#### Integrated Summary and Safety Evaluation 11

Repeat-dose studies of biweekly subcutaneous injections of ATX-101 at 50 mg/kg for up to 6 months in rats (5% at 1 mL/kg; 13 doses) and at 25 mg/kg for up to 9 months in dogs (5% at 0.5 mL/kg; 20 doses) demonstrated an absence of systemic signs of toxicity. At the completion of the dosing periods gross observations of thickening and

discoloration at the injection site with subcutaneous gelatinous material were noted in both species. The incidence and severity of these gross findings were both dose-related and temporally related to time post-injection, but did not correlate with treatment duration (4-weeks to 6-months [rats] or 9-months [dogs]).

From a risk assessment perspective, injection site inflammation and fibrosis were not prominent at 5 mg/kg in rats and dogs when ATX-101 was administered every other week. Fibrosis was present at 10 mg/kg in dogs when ATX-101 was administered every other week, but was much less severe than that seen in the higher dose groups after 41 weeks. There was no evidence of local injection site pre-neoplastic lesions or malignancies. Based on the collective nonclinical data, an ATX-101 NOEL for local injection site reactions following repeat-dose administration was identified as 0.5% administered at a volume of 1 mL/kg in both species. In rats, a NOAEL of 1% at 1 mL/kg was identified. A NOAEL for dogs of 1% at 1 mL/kg and 2% administered at a volume of 0.5 mL/kg was established. These data demonstrate that the maximum intended clinical administration of ATX-101 given at 1% in a volume of 0.2 mL/injection (0.003 mL/kg/injection [60 kg human]; up to 50 injections [0.17 mL/kg]) presents only a minimal risk of adverse local reactions.

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

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

Embryofetal development studies have been performed in rats and rabbits using subcutaneous doses of deoxycholic acid at up to maternally toxic doses during the period of organogenesis. Injection site irritation precluded daily dosing in both species. In rats the developmental NOAEL was 50 mg/kg, the highest dose tested. In rabbits fetal malformations in all treated groups precluded determination of a developmental NOAEL. The presence of maternal toxicity in all treated rabbits prevents isolating a potential drug effect on development toxicity from that also associated with maternal toxicity. Although the study design was deficient, potentially drug-related embryofetal malformations were noted in rabbits and are considered to be drug related.

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

ATX-101 is approvable for the treatment of improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults from a pharmacology/toxicology perspective.

(b) (4)

# 11 Appendix/Attachments

Appendix #1 Recommended label and supportive information

# HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

Tradename is a cytolytic drug indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults. *(1)* 

#### FULL PRESCRIBING INFORMATION

#### 8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy

(b) (4)

There are no adequate and well-controlled studies of Tradename in pregnant women.

(b) (4)

Embryofetal development studies have been performed in rats and rabbits using subcutaneous doses of deoxycholic acid administered during the period of organogenesis. For the basis of comparing animal to human doses, the MRHD is 1.7 mg/kg (100 mg/60 kg). No evidence of fetal harm was observed in rats at up to the highest dose tested (50 mg/kg) which is 5-fold higher than the MRHD of Tradename based on a mg/m<sup>2</sup> comparison. However, missing intermediate lung lobe was noted in rabbits at all dose levels tested including the lowest dose (10 mg/kg) which is 2-fold higher than the MRHD of Tradename based on a mg/m<sup>2</sup> comparison. These effects may be related to maternal toxicity which was also seen at all dose levels tested.

#### CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

Tradename is a cytolytic drug, which when injected into tissue physically <sup>(b) (4)</sup> the cell membrane causing lysis.

#### NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate the carcinogenic potential of Tradename.

Tradename was negative in a battery of in vitro (Ames test and chromosomal aberration assay in human lymphocytes) and in vivo (rat erythrocyte micronucleus assay) genetic toxicology assays.

No effects on fertility were observed in male and female rats administered deoxycholic acid at subcutaneous doses up to 50 mg/kg (5 times the MRHD based on mg/m<sup>2</sup> comparison) once weekly prior to and during the mating period and through gestation day 7 in female rats.

#### Appendix #2- References

Duncan D, Rubin JP, Golitz L, Badylak S, Kesel L, Freund J, Duncan D. 2009. Refinement of technique in injection lipolysis based on scientific studies and clinical evaluation. Clin Plast Surg 36(2):195-209.

Galloway SM. 2000. Cytotoxicity and chromosome aberrations in vitro: Experience in industry and the case for an upper limit on toxicity in the aberration assay. Environmental Mol Mutagen 35:191-201.

Hagey LR, Schteingart CD, Rossi SS, Ton-Nu NT, Hofmann AF. 1998. An N-acyl gylcyltaurine conjugate of deoxycholic acid in biliary bile acids of the rabbit. J. Lipid Research 39(11):2119-2124.

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

Rotunda AM, Ablon G, Kolodney MS. 2005. Lipomas treated with subcutaneous deoxycholate injections. J Am Acad Dermatol 53, 973-978.

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

Thuangtong R, Bentow JJ, Knopp K, Mahmood NA, David NE, Kolodney MS. 2010. Tissue-selective effects of injected deoxycholate. Dermatol Surg 36:899-908.

Yagima Odo ME, Cuce LC, Odo LM, Natrielli A. 2007. Action of sodium deoxycholate on subcutaneous adipose human tissue: local and systemic effects. Dermatol Surg 33(2):178-189.

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/s/

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JILL C MERRILL 12/15/2014

BARBARA A HILL 12/16/2014

Comments on NDA 206333 deoxycholic acid

From A. Jacobs , AD

Date 11/3/14

1. I concur that there are no pharm/tox approval issues

2. I concur that the appropriate (b) (4)

3. I conveyed a number of other comments to the reviewer and they will be addressed as appropriate.

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ABIGAIL C JACOBS 11/03/2014

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

**NDA Number: 206333** 

**Applicant:** Kythera Biopharmaceuticals, Inc.

Stamp Date: 05/13/2014

**Drug Name:** ATX-101<sup>™</sup> (deoxycholic acid)

NDA Type: original

On **<u>initial</u>** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Y		Formatted to allow substantive review.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Y		Indexed and paginated to allow substantive review.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	Y		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	Y		Carcinogenicity studies were waived (IND 79726, SDN 8, entered in DARRTS 04-02-2009).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	Y		There was a change in the manufacturing process of the drug substance during the development program. Appropriate nonclinical bridging studies have been done to bridge synthetic DCA with nonclinical studies done with animal-derived NaDC (Study #IXB00080) and to evaluate vehicle reformulations (study # 20001032).
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	Y		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	Y		Stated on page 4, Nonclinical Overview.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Y		

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	Y		Dose multiples are incorrect.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Y		Impurity issues have been addressed.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

# IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_\_Yes\_\_\_\_

Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

None.

Jill Merrill	06-25-2014
Reviewing Pharmacologist	Date
Barbara Hill	see sign-off date
Team Leader/Supervisor	Date

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/s/

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JILL C MERRILL 06/25/2014

BARBARA A HILL 06/25/2014