![Australian Government - Department of Health - Therapeutic Goods Administration]

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Deoxycholic acid

Proprietary Product Name: Belkyra

Sponsor: Allergan Australia Pty Ltd

April 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.

- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.

- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.

- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
AUC_{0-24}	Area under the plasma concentration time curve from time 0 to 24 hours
BA	Benzyl alcohol
BIQLI	Body Image Quality of Life Inventory
BMI	Body mass index
BPM	Beats per minute
CL	Clearance
C_{max}	Maximum plasma concentration
CR-SMFRS	Clinician-Reported Submental Fat Rating Scale
DAE	Discontinuation due to adverse event
DAS-24	Derriford Appearance Scale short form
ECG	Electrocardiogram
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
Ka	First order absorption
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IWRS	Interactive web response system

Abbreviation	Meaning
LOCF	last observation carried forward
LS Mean	Least squares mean
mITT	Modified Intent-to-Treat population
MRI	Magnetic resonance imaging
PR-SMFIS	Patient-Reported Submental Fat Impact Scale
PR-SMFRS	Patient-Reported Submental Fat Rating Scale
QTc	QT-interval corrected
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SLRS	Skin Laxity Rating Scale
SMFRS	Refers to both CR-SMFRS and PR-SMFRS
SMFIS	Submental Fat Impact Scale
SMFIS TSS	Submental Fat Impact Scale Total Scale Score
SSRS	Subject Self-Rating Scale
TEAE	Treatment-emergent adverse event
V_d	Volume of distribution
SGI	Subject Global Impression of Improvement

1.   Introduction

This is a full submission to register a new chemical entity.

Deoxycholic acid is a small, fully synthetised, new active ingredient that is structurally identical to endogenous deoxycholic acid. The product itself is 1% deoxycholic acid. It reduces submental fat by causing cytolysis of fat cells.

The proposed indication is:

> ...for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

Comment: This submission was originally submitted with proposed proprietary product name Kybella and changed to Belkyra after the Round 2 evaluation. This was later amended to Belkyra as requested by the sponsor. Further details of name and sponsor changes are given in the AusPAR that accompanies this document.

1.1.   Dose form and strength

The submission proposes registration of the following dosage forms and strengths: deoxycholic acid 10 mg/mL, ready to use solution for injection in a 2 mL type I glass vial with stopper and fliptop lid.

1.2.   Dosage and administration

A brief overview of the dosage and the proposed method of administration is outlined here specific reference to submental anatomy. For further information please see the approved product information (PI) available from the TGA website.

1.2.1.   Dosage

2 mg (0.2 mL) of drug product is injected at each injection site, 1 cm apart with up to 50 injections per treatment session Treatments can be repeated up to 6 times, with at least 4 weeks between treatments. The maximum dose of 100 mg (10 mL or 50 injections) Belkyra should not be exceeded in one treatment session. The number of treatment sessions needed to achieve a satisfactory response depends on the individual patient.

1.2.2.   Administration

Safe and effective use of Belkyra depends upon selection of appropriate patients, use of the correct number of and locations for injections, and proper needle placement and administration techniques. Health professionals administering Belkyra must understand the relevant submental anatomy and associated neuromuscular structures in the area involved and any alterations to the anatomy due to prior surgical or aesthetic procedures.

The needle is inserted perpendicularly to the skin for injections with Belkyra. Careful consideration should be given to use of Belkyra in patients with excessive skin laxity, prominent platysmal bands or other conditions for which reduction of submental fat may result in an aesthetically undesirable outcome.

1.2.2.1.   *Avoid injections near the area of the marginal mandibular nerve (see Precautions in PI; Attachment 1).*

Needle placement with respect to the mandible is very important as it reduces the potential for injury to the marginal mandibular nerve, a motor branch of the facial nerve. Injury to the nerve presents as an asymmetrical smile due to paresis of lip depressor muscles *(see Precautions).*

To avoid injury to the marginal mandibular nerve:

- Do not inject above the inferior border of the mandible.

- Do not inject within a region defined by a 1-1.5 cm line below the inferior border (from the angle of the mandible to the mentum).

- Inject Belkyra only within the target submental fat treatment area (see Figures 1 and 3).

Figure 1: Avoid the Marginal Mandibular Nerve Area
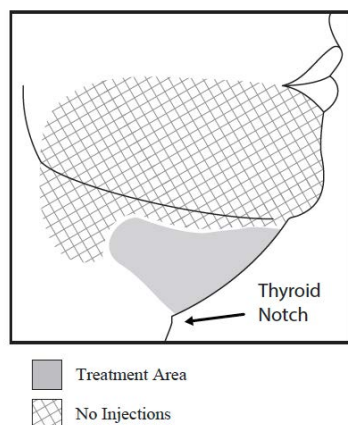
1.2.2.2. *Avoid injection into the platysma*

Prior to each treatment session, palpate the submental area **to ensure sufficient submental fat** and to identify subcutaneous fat between the dermis and platysma (pre-platysmal fat) within the target treatment area (Figure 2). The number of injections and the number of treatments should be tailored to the individual patient's submental fat distribution and treatment goals.

Figure 2: Sagittal View of Platysma Area
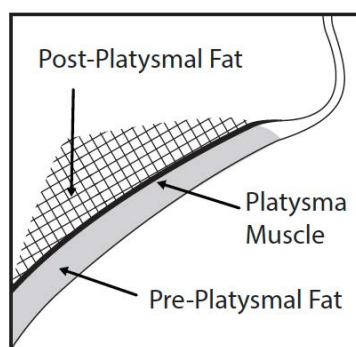
1.2.2.3. *Injecting into the treatment area*

Use of ice/cold packs, topical and/or injectable local anaesthesia (e.g., lidocaine) may enhance patient comfort.

Outline the planned treatment area with a surgical pen and apply a 1 cm injection grid to mark the injection sites (Figures 2 and 3).

Figure 3: Treatment Area and Injection Pattern

Treatment Area

Injection Pattern
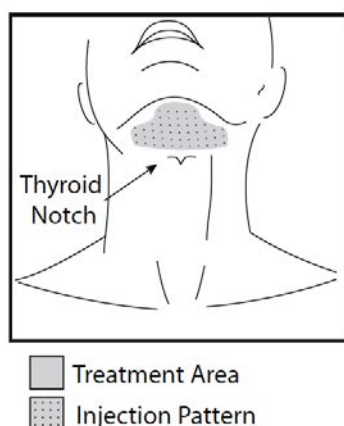
1.2.2.4. *Do not inject belkyra outside the defined parameters (see Precautions; Attachment 1).*

- Using a large bore needle, draw 1 mL of Belkyra into a sterile 1 mL syringe and expel any air bubbles in the syringe barrel.

- Have the patient tense the platysma. Pinch the submental fat and, using a 30 gauge (or smaller) 0.5 inch needle, inject 0.2 mL of Belkyra into the pre-platysmal fat (see Figure 2) next to each of the marked injection sites by advancing the needle perpendicular to the skin.

- Injections that are too superficial (into the dermis) may result in skin ulceration. Do not withdraw the needle from the subcutaneous fat during injection as this could increase the risk of intradermal exposure and potential skin ulceration.

- Avoid injecting into the post-platysmal fat by injecting Belkyra into fat tissue at the depth of approximately mid-way into the subcutaneous fat layer (Figure 2).

- If at any time resistance is met as the needle is inserted, indicating the possibility of contact with fascial or non-fat tissue, the needle must be withdrawn to an appropriate depth before the injection is administered.

- Avoid injecting into other tissues such as the muscle, salivary glands and lymph nodes.

- Upon needle withdrawal, pressure may be applied to each injection site as necessary to minimise bleeding; an adhesive dressing may be applied.

Prior to each treatment session, the patient's submental area is inspected to ensure sufficient submental fat (noting that reduction in submental has been observed as early as a single treatment session). 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.

2. Clinical rationale

Belkyra (deoxycholic acid) has been developed as a 'potential first-in-class, adipocytolic, submental-contouring, injectable drug' for the treatment of undesired submental fat, hence, it has been developed as a cosmetic treatment for submental fat that presents as 'an unappealing submental profile, convexity or fullness that negatively affects the satisfaction and well-being of a substantial proportion of the population'. Currently available treatments for this condition are limited and include surgical procedures performed under general anaesthetic and targeted liposuction. These currently available treatments can be associated with significant morbidity and may have a suboptimal outcome.

Submental fat is a common condition and is not related to any co-morbidity. It is more common with aging and occurs in both men and women. Not all subjects with submental adiposity are bothered by the condition, as the sponsor reports that '34% of those with marked submental fat reported being bothered by their submental fat' hence the morbidity associated with the condition is psychosocial.

2.1. Guidance

The sponsor has had extensive correspondence with regulatory agencies, including the TGA, FDA (Food and Drug Administration (United States)) and EU authorities. The sponsor has used this correspondence to clarify the data requirements for the application and also whether the addition of preservative to the vials would be acceptable. While the FDA was accepting of the addition of benzyl alcohol (BA) as a preservative, several of the European agencies and the TGA considered that there would be issues with regard to reuse and safety. The TGA stated that 'the company would need to provide a robust clinical and scientific justification for inclusion of BA in the formulation'. The sponsor was also advised that two pivotal efficacy studies would be required in support of efficacy. There was also regulatory advice on using questionnaires to assess psychological impact.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The data represented a full clinical development program for the indication of submental fat. The submission contained the following clinical information:

- Five clinical pharmacology studies, including three that provided pharmacokinetic data (Study 08, Study 30 and Study 32) and two that provided both pharmacokinetic and pharmacodynamic data (Study 18 and Study 24)

- One population pharmacokinetic analysis (Study KYTH-01-13)

- Two pivotal efficacy and safety studies using the formulation intended for Marketing in Australia (Study 22 and Study 23)

- Three dose-finding studies (Study 03, Study 07 and Study 15)

- Five supportive studies, including two other efficacy and safety studies using an alternative formulation (Study 16 and Study 17); one open label, long term follow-up study (Study 26); and two long term follow-up studies (Study 12 and Study 1403740)

- Four studies evaluable only for safety (Study 04, Study 05, Study 10 and Study 19)

- Four studies designed to validate efficacy and safety outcome measures (Study 11, Study 20, Study 21 and Study 25)

- An Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS).

3.2. Paediatric data

The submission did not include paediatric data.

The sponsor has been granted a waiver for a Paediatric Investigation Plan in the EU on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients. The sponsor has also been granted a waiver by the FDA on the grounds that firstly the drug product does not represent a meaningful

therapeutic benefit over existing treatments for paediatric patients and secondly the drug product is not likely to be used in a substantial number of paediatric patients.

3.3. Good clinical practice

The clinical studies presented in the submission are stated to have been conducted according to Good Clinical Practice (GCP) guidelines and appear to have been conducted according to GCP.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The following table (Table 1) summarises the studies relating to each pharmacokinetic topic. None of these studies had deficiencies that excluded their results from consideration.

Table 1: Summary of studies providing pharmacokinetic data

Pharmacokinetic topic	Subtopic	Study ID
Pharmacokinetics in healthy adults	General pharmacokinetics (Single dose)	Study 08
		Study 30
		Study 32
		Study 18
		Study 24
Population pharmacokinetic analyses	Target population	Study KYTH-01-13

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries supplied in the clinical dossier. Deoxycholic acid is an endogenous secondary bile acid that serves to emulsify and solubilize dietary fat, thereby aiding in its breakdown and absorption within the gut. The active moiety in the drug product is deoxycholate which has been provided either as the free acid or as the sodium salt, sodium deoxycholate.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanisms of absorption

Deoxycholic acid was administered subcutaneously. In Study 30 when comparing least square means, there was similar exposure to deoxycholic acid when administered into the submental fat compared with abdominal wall fat. However, the geometric mean for maximum plasma

concentration (C_{max}) was lower with abdominal wall administration: geometric mean ratio (95% CI) 62.24% (50.65% to 76.49%). Overall exposure was similar for the two routes of administration: the area under the plasma concentration time curve from time 0 to 24 hours (AUC_{0-24}) geometric mean ratio (95% CI) 90.25% (69.84% to 116.63%).

4.2.2.2. Bioavailability

Absolute bioavailability

Absolute subcutaneously administered bioavailability was not determined in humans because absolute bioavailability was 100% in Sprague-Dawley rats and Beagle dogs. The site of administration is also the site of action. The sponsor argues that systemic exposure is not expected to be related to efficacy or toxicity.

Bioavailability relative to an oral solution or micronised suspension

Belkyra is not intended for oral administration.

Bioequivalence of clinical trial and market formulations

The formulation used in the pivotal clinical trials is the same as that intended for marketing in Australia.

Bioequivalence of different dosage forms and strengths

In Study 32 the BA containing and BA free formulations were not bioequivalent. At a dose level of 100 mg administered into submental fat, mean baseline adjusted AUC_{0-24} was 3042 (standard deviation (SD) = 1217) ng hr/mL for BA-containing and 4376 (3476) ng hr/mL for BA-free: geometric mean ratio (95% CI) BA/BA-free 0.79 (0.54 to 1.14). Mean (SD) baseline adjusted C_{max} was 822 (263) ng/mL for BA-containing and 784 (230) ng/mL for BA-free: geometric mean ratio (95% CI) BA/BA-free 1.04 (0.85 to 1.27). However, the study was not optimally designed for demonstrating bioequivalence as it was not a crossover study and the two study groups were different in gender and weight profiles.

The overall exposure to deoxycholic acid, at a 100 mg dose administered subcutaneously, was similar to submental fat when administered abdominally.

Dose proportionality

In the dose range 24 mg to 198 mg, administered by injection into submental fat, C_{max} increased less than proportional to dose and the area under the plasma concentration time curve (AUC) increased in proportion to dose.

Bioavailability during multiple-dosing

Belkyra is intended for 4 weekly administration and the Evaluator does not predict any carry over effect from previous doses.

4.2.3. Distribution

4.2.3.1. Volume of distribution

In the population pharmacokinetic study the typical value for baseline deoxycholic acid concentration was 149 ng/mL, clearance (CL) was 32.5 L/h and the volume of distribution (V_d) was 193 L. The half-life of deoxycholic acid was estimated to be approximately 4.1 hours.

4.2.3.2. Plasma protein binding

In vitro studies indicate deoxycholic acid is > 90% protein bound.

4.2.4. Metabolism

Deoxycholic acid is an endogenous compound and is utilised as a bile salt. There is extensive enterohepatic circulation of deoxycholic acid.

4.2.5. Excretion

4.2.5.1. Routes and mechanisms of excretion

At doses up to 198 mg, injected into submental fat, deoxycholic acid concentrations returned to baseline within 24 hours of administration. Similar profiles were observed with 100 mg.

4.2.5.2. Mass balance studies

Mass balance studies were not performed.

4.2.5.3. Renal clearance

Very little bile acid is excreted in the urine due to highly efficient tubular reabsorption.

4.2.6. Intra- and inter-individual variability of pharmacokinetics

The population pharmacokinetic study (Study KYTH-01-13) estimated the typical value for baseline deoxycholic acid concentration as 141 ng/mL, CL as 36.2 L/h and V_d as 152 L. Inter-individual variability (IIV) was 25.3% for CL, 28.3% for V_d and 49.2% for baseline deoxycholic acid concentration. This indicates considerable variability in the pharmacodynamics of deoxycholic acid, particularly with baseline deoxycholic acid concentrations. In the covariate analysis, dose had a significant effect on CL; body mass index (BMI), dose, baseline deoxycholic acid concentration and study population (submental fat versus abdomen) had a significant effect on V_d; and age had a significant effect on baseline deoxycholic acid concentration.

For a more in-depth overview of the population pharmacokinetics relevant to this submission, please see section 4.3 below.

4.2.7. Pharmacokinetics in the target population

The target population is similar to the volunteers used in the pharmacokinetic studies.

4.2.8. Pharmacokinetics in other special populations

4.2.8.1. Pharmacokinetics in subjects with impaired hepatic function

There were no data on pharm

acokinetics in subjects with impaired hepatic function.

4.2.8.2. Pharmacokinetics in subjects with impaired renal function

There were no data on pharmacokinetics in subjects with impaired renal function.

4.2.8.3. Pharmacokinetics according to age

There were few subjects aged > 65 in the development program. There were no data on pharmacokinetics in this population.

4.2.8.4. Pharmacokinetics related to genetic factors

There were no data on pharmacokinetics related to genetic factors.

4.2.9. Pharmacokinetic interactions

4.2.9.1. Pharmacokinetic interactions demonstrated in human studies

No pharmacokinetic interactions were explored in the development program.

4.2.10. Clinical implications of *in vitro* findings

There were no clinical issues raised by the in vitro data.

4.3. Population pharmacokinetics

4.3.1. Objectives

- Characterise the baseline endogenous levels of deoxycholic acid in healthy subjects.

- Characterise the pharmacokinetics of deoxycholic acid after SC administration to the submental fat area in healthy subjects

- Evaluate the effect of various covariates including demographics, clinical laboratory parameters, and renal function on deoxycholic acid pharmacokinetics

- Simulate the systemic exposure after single deoxycholic administration at 50 mg and upon repeated administration at a 100-mg dose every 4 weeks for 6 dosing sessions.

4.3.2. Data

Pharmacokinetic data were obtained from Studies 08, 18, 24, 30 and 32.

There were 172 health subjects included in the study. Following exclusion of 161 missing concentrations and 57 outliers there were 4717 plasma deoxycholic acid concentrations.

The dose range was 24 to 200 mg.

Plasma samples were obtained over 24 hour intervals before and after deoxycholic acid administration. There were 93 males and 79 females. The range for age was 18 to 64 years, for weight was 56 to 128 kg, for BMI was 22 to 39 kg/m^2 and for serum creatinine was 0.48 to 1.53 mg/dL.

4.3.3. Methods

The modelling was performed using NONMEM version 7, Intel® Visual Fortran Compiler Professional Edition 11.1 and NMTRAN in a Windows 7 environment. Plots were generated using S-PLUS, Windows Excel 2007 and R software. The estimation method was FOCE with INTERACTION.

The structural model included a model for baseline endogenous deoxycholic acid. This was highly variable but did not exhibit any diurnal pattern. Hence the form of this model was a constant parameter with inter-individual and intra-individual variability terms. The structural model explored one and two compartment models. The absorption was modelled as first order or zero order. Inter-individual error was modelled as exponential with a diagonal variance matrix. Residual variability was modelled as additive, proportional or combined additive and proportional. Hypothesis tests were performed using the likelihood ratio test: a decrease in the objective function of > 6.64 corresponding to a p-value of < 0.01. Diagnostic plots were used to evaluate goodness of fit.

The covariate model was developed by examining graphical relationship between empirical Bayes estimates of parameters and the covariates. The covariates tested for inclusion in the model were: weight, sex, race, BMI, selected blood chemistry variables, and serum creatinine as a marker of renal function. Correlations between variables were also explored using plots. Covariates were included in the model using a multiplicative relationship. Continuous covariates were centred on the median. Categorical covariates were entered into the model using binary indicator variables. A backward stepwise process was used to determine the final covariate model, with a level of significance of p < 0.005 (corresponding to an increase in objective function of 7.88) for being retained in the model.

Missing plasma concentrations (including concentrations < lower limit of quantification) were not imputed, and were excluded from the analysis. Potential outliers were identified visually and from a weighted residual > 5 and were excluded from the analysis. Missing covariate data were imputed using central values. This was only necessary for the height and weight for one subject.

The final model was evaluated using a visual predictive check and bootstrap resampling.

Simulations were performed for a 100 mg dose every 4 weeks for 6 doses and also for a 50 mg dose. The 172 subjects in the population pharmacokinetic analysis were used to supply the covariate profiles for the 100 simulated subjects (that is, a non-parametric approach was used to supply the covariate distributions).

4.3.4.   Results

The plots of deoxycholic acid compared to time were considered to represent best a one compartment model. The selected structural model was one-compartment, parameterised as CL, and V_d with first order absorption (ka). IIV could not be estimated for ka. The residual error was a combined additive and proportional model. The typical value for baseline deoxycholic acid concentration was 149 ng/mL, CL was 32.5 L/h and V_d was 193 L. IIV was 28% for CL, 38% for V_d and 52% for baseline deoxycholic acid concentration. The half-life of deoxycholic acid was estimated to be approximately 4.1 hours. The diagnostic plots indicated an acceptable fit for the model to the data.

On univariate analysis dose and baseline deoxycholic acid concentration had a significant effect on CL; BMI, dose, baseline deoxycholic acid concentration and study population (submental versus abdominal fat) had a significant effect on V_d; age had a significant effect on baseline deoxycholic acid concentration. The backward elimination excluded only the effect of baseline deoxycholic acid concentration on CL.

The final model estimated the typical value for baseline deoxycholic acid concentration as 141 ng/mL, CL as 36.2 L/h and V_d as 152 IIV was 25.3% for CL, 28.3% for V_d and 49.2% for baseline deoxycholic acid concentration. The bootstrap estimates were near-identical to the model estimates The visual predictive checks indicated an acceptable predictive ability for the model, hence the model was suitable for simulating the 50 mg and 100 mg dose profiles.

The simulation of the 100 mg dose level administered six times with 4 week dosing intervals predicts no accumulation of deoxycholic acid by the 6th dose.

4.3.5.   Evaluator's comments on the population pharmacokinetic study

The modelling process was conducted and reported in accordance with the guideline CHMP/EWP/185990/06.[1] The base structural model was supported by the goodness of fit plots. The covariate model was developed using all the available covariate data. The covariate model building process was rigorous. The final model was supported by the goodness of fit plots and the visual predictive checks. The model was suitable for the simulation of the 100 mg and 50 mg dose levels. The simulations were also performed with 50 mg.

The modelling and simulation process supports the Sponsor's claims with regard systemic exposure to deoxycholic acid. Deoxycholic acid concentrations return to baseline by 24 hours post-dose and accumulation is unlikely.

4.4.   Evaluator's overall conclusions on pharmacokinetics

The sponsor has adequately characterised the pharmacokinetics of deoxycholic acid. Following subcutaneous administration to submental fat of doses up to 200 mg there was increased exposure to deoxycholic acid for 24 hours. There was considerable variability in baseline deoxycholic acid concentrations. There was greater systemic exposure to deoxycholic acid with the BA free formulation.

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1 CHMP/EWP/185990/06: Committee for Medicinal Products for Human Use/Efficacy Working Parky; Guideline on Reporting the Results of population Pharmacokinetic Analyses

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 below provides a summary of the studies providing pharmacodynamic data.

Table 2: Summary of studies providing pharmacodynamic data

Pharmacodynamic topic	Subtopic	Study ID
Primary Pharmacology	Effect on adipokines	Study 18
Secondary Pharmacology	Effect on QTc	Study 24

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

Deoxycholic acid is adipocytolytic and emulsifies lipids. These effects occur at the site of injection.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

In Study 18 following subcutaneous injection of deoxycholic acid 100 mg into subcutaneous abdominal fat, there were no significant changes in cholesterol, total triglycerides, 1,2- and 1,3-diacylglycerols, free fatty acids, C-reactive protein, interleukins 6, 1α and 1β, interferon-gamma, tumour necrosis factor-alpha, apolipoprotein-B, adiponectin, insulin, leptin or resistin.

5.2.2.2. Secondary pharmacodynamic effects

In Study 24 doses of 100 mg and 200 mg deoxycholic acid administered into submental fat there was no effect on QTc (corrected QT interval) or other electrocardiogram (ECG) parameters over a 24 hour period. Two subjects in the 100 mg group had a heart rate > 100 beats per minute (BPM) and an increase in heart rate > 20 BPM: one subject at 5 minutes post-dose (from 84 to 105.7 BPM), and one at 12 and 16 hours post-dose (from 83.3 to 103.7 BPM and 79 to 100.7 BPM, respectively).

5.2.2.3. Time course of pharmacodynamic effects

Time course of effect is addressed in Section 7: Clinical efficacy.

5.2.3. Relationship between drug concentration and pharmacodynamic effects

Concentration and dose-effect are addressed in Section 6: Dosage selection for the pivotal studies.

5.2.4. Genetic-, gender- and age-related differences in pharmacodynamic response

Genetic, gender and age-related differences in pharmacodynamic response were not addressed in the development program.

5.2.5. Pharmacodynamic interactions

Pharmacodynamic interactions were not addressed in the development program.

5.3. Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic data indicated that deoxycholic acid did not have an adverse effect on lipid profiles or lipid metabolism. There was no indication of an adverse effect on QTc interval.

6. Dosage selection for the pivotal studies

6.1. Dosage finding studies

Studies 03, 07 and 15 were dosage finding studies evaluated as part of this submission.

6.1.1. Study 03

6.1.1.1. Study overview

Study 03 was a multicentre, randomised, double blind, placebo controlled, parallel group safety and efficacy study for the reduction of subcutaneous fat in the submental area. The study was conducted at six centres: one in the UK, three in Australia, and two in Canada from August 2007 to October 2008. The study included males or non-pregnant, non-lactating females who were aged 25 to 65 years, inclusive; with submental fat that was considered undesirable by the subject and graded by the investigator as 2 or 3 using the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS);[2] a history of maintenance of a stable body weight, for at least 6 months; and medically able to undergo the administration of study material as determined by clinical and laboratory evaluations obtained within 28 days before randomisation.

6.1.1.2. Study treatments

The 4 study treatment groups were: deoxycholic acid 24 mg (1 mg/cm^2, 5 mg/mL (0.5%)); deoxycholic acid 48 mg (2 mg/cm^2, 10 mg/mL (1.0%)); deoxycholic acid 96 mg (4 mg/cm^2, 20 mg/mL (2.0%)) and placebo.

There were up to 24 x 0.2 mL injections given 1 cm apart, administered subcutaneously into submental fat. The formulation contained BA.

6.1.1.3. Efficacy outcomes and variables

The primary efficacy outcome measure was the change in submental rating scale over 16 weeks. Secondary efficacy outcome measures included subject satisfaction with appearance, global improvement rating, skin laxity (measured using a 4 point scale: 1 = no laxity; 2 = minimal laxity; 3 = moderate laxity; 4 = very lax) and cervicomental angle (measured using a profile view photograph and a goniometer to determine the angle).

The safety outcome measures were: adverse events (AE), clinical laboratory tests, vital signs and weight.

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2 The CR-SMFRS is 5-grade clinician-reported scoring system based on the appearance of submental convexity. Grade 0 = absent submental convexity, no localised submental fat evident; Grade 1 = mild submental convexity, minimal localised submental fat; Grade 2 = moderate submental convexity, prominent localised submental fat; Grade 3 = severe submental convexity, marked localised submental fat; Grade 4 = extreme submental convexity. See Tables 3, 4 and 5 for an overview of validity.

6.1.1.4.   *Participant flow and baseline data*

There were 84 subjects included in the study, 20 in the 1 mg/cm^2 group, 20 in the 2 mg/cm^2 group, 22 in the 4 mg/cm^2 group, and 22 in the placebo group. There were 73 (85.9%) subjects who completed the study. The study groups were similar in demographic characteristics and submental fat severity. There were 56 (66.7%) females, 28 (33.3%) males, and the age range was 25 to 61 years.

6.1.1.5.   *Results for the efficacy outcomes*

The three deoxycholic acid treatment groups had similar effect sizes: mean (SD) change from baseline in submental rating scale was -0.9 (0.70) for 1 mg/cm^2, -0.8 (0.60) for 2 mg/cm^2, -0.7 (0.75) for 4 mg/cm^2, and -0.5 (0.6) for placebo. The proportion of subjects with a 1 unit improvement in submental fat was similar for all active treatment groups at each post-baseline visit. Mean (SD) change from baseline in subject satisfaction with appearance was 3.8 (1.85) for 1 mg/cm^2, 3.3 (1.78) for 2 mg/cm^2, 3.5 (1.42) for 4 mg/cm^2, and 1.9 (2.29) for placebo. In all three active treatment groups relative to placebo subject global improvement rating improved to a similar extent. There was a slight increase in skin laxity in the 1 mg/cm^2 group and the 2 mg/cm^2 group at Week 12, but not at any other time-point. The mean (SD) change in cervicomental angle to Week 16 was -0.7 (3.45) in the 1 mg/cm^2 group, 2.3 (13.67) in the 2 mg/cm^2, 6.9 (10.67) in the 4 mg/cm^2 and -2.3 (9.71) in the placebo group.

6.1.2.   **Study 07**

6.1.2.1.   *Study overview*

Study 07 was a multicentre, randomised, double blind, placebo controlled, parallel group efficacy and safety study. The study was conducted at seven centres (two in Australia, four in Canada and one in the UK) from April to December 2008. The study had the same inclusion and exclusion criteria as Study 03 (see study above).

6.1.2.2.   *Study treatments*

The study treatments were: deoxycholic acid 96 mg (4 mg/cm^2, 10 mg/mL (1.0%)), up to 48 x 0.2 mL injections given 0.7 cm apart; deoxycholic acid 48 mg (2 mg/cm^2, 10 mg/mL (1.0%)) up to 24 x 0.2 mL injections given 1.0 cm apart; deoxycholic acid 96 mg (4 mg/cm^2, 10 mg/mL (1.0%)) up to 24 x 0.4 mL injections given 1.0 cm apart and placebo. The treatments were administered as subcutaneous injections in submental fat. There were up to 4 treatment sessions 4 weeks apart.

6.1.2.3.   *Efficacy outcomes and variables*

The outcome measures were the same as for Study 03 (see above) with the exception that the cervicomental angle was not used as an outcome measure.

6.1.2.4.   *Participant flow and baseline data*

The study enrolled 71 healthy subjects with submental fat: 24 in the 0.2 mL/0.7 cm grid group; 13 in the 0.2 mL/1.0 cm grid group; 20 in the 0.4 mL/1.0 cm grid group; and 14 in the placebo group. There were 11 (15.1%) subjects who prematurely discontinued and 62 (84.9%) who completed the study. There were 55 (77.5%) females, 16 (22.5%) males and the age range was 27 to 64 years. Submental fat severity was greater in the placebo group.

6.1.2.5.   *Results for the efficacy outcomes*

The improvement in submental rating scale at Week 16 was greatest in the 48 mg group with the change in submental rating scale (SD); p-value compared to placebo): -1.0 (0.58; p = 0.005) for the 0.2 mL/0.7 cm grid group; -1.2 (0.63; p = 0.001) for the 0.2 mL/1.0 cm grid; -0.8 (0.72; p = 0.069) for the 0.4 mL/1.0 cm grid; and -0.4 (0.50) for the placebo group.

The Subject Satisfaction with Appearance rating scale had similar results: change (SD; p-value compared to placebo) 3.5 (1.47; p = 0.001) for the 0.2 mL/0.7 cm grid group; 4.3 (1.34; p = 0.001) for the 0.2 mL/1.0 cm grid; 2.8 (2.20; p = 0.122) for the 0.4 mL/1.0 cm grid; and 1.8 (1.72) for the placebo group.

The Subject Global improvement rating was significantly better (compared with placebo) for the 0.2 mL/0.7 cm grid group (p = 0.008) but not for the 0.2 mL/1.0 cm grid (p = 0.172) or the 0.4 mL/1.0 cm grid (p = 0.252).

The responder analysis was similar for all three treatments at Week 24. The mean (SD) change in cervicomental angle was -5.0 (9.85) for the 0.2 mL/0.7 cm grid group; -1.5 (7.84) for the 0.2 mL/1.0 cm grid; -1.5 (10.40) for the 0.4 mL/1.0 cm grid; and -2.7 (7.80) for the placebo group.

6.1.3.   Study 15

6.1.3.1.   *Study overview*

Study 15 was a multicentre, randomised, double blind, placebo controlled, parallel group safety and efficacy study. The study was conducted at ten centres in the US from December 2009 to December 2010. The study included subjects who were grade 2 or 3 on the CR-SMFRS; indicated dissatisfaction with the submental area, as defined as rating of 0, 1, 2, or 3 on the Subject Self-Rating Scale (SSRS);[3] male or non-pregnant, non-lactating females between 18 and 65 years of age; normal result on coagulation tests; history of stable body weight in the judgment of the investigator for at least 6 months before randomisation; and medically able to undergo the administration of study material as determined by the absence of clinically significant results from the clinical and laboratory tests obtained within 28 days of randomisation.

6.1.3.2.   *Study treatments*

The study treatments were: deoxycholic acid (BA formulation) up to 50 mg (1 mg/cm^{2}, 5 mg/mL (0.5%)); deoxycholic acid (BA formulation) up to 100 mg (2 mg/cm^{2}, 10 mg/mL (1.0%)); and placebo. Subjects were treated with up to 50 x 0.2 mL injections in a 1.0 cm grid for up to 6 treatment sessions, separated by 4 weeks between treatments.

6.1.3.3.   *Efficacy outcomes and variables*

The study endpoints were:

- Changes from baseline at Visits 6, 8, 9 and at intermediate time points for the following endpoints:

    - CR-SMFRS (treated as a continuous variable)

    - CR-SMFRS (responder analyses)

    - volume and thickness of submental fat measured using magnetic resonance imaging (MRI) (absolute and percent change).

- Change from baseline at Visits 6 and 9 for the following endpoints:

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3 The SSRS is a 7-point patient reported scoring system of the appearance of the submental fat region. Patients were asked at baseline: 'Considering your appearance in association with your face and chin, how satisfied do you feel with your appearance at the present time?' and at post-baseline: Post-baseline: Considering your appearance in association with your face and chin, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment? A score of 0 = extremely dissatisfied; a score of 6 = extremely satisfied.

- Patient Reported Submental Fat Rating Scale (PR-SMFRS) (treated as a continuous variable) [4]
- PR-SMFRS (responder analyses)
- Patient Reported Submental Fat Impact Scale (PR-SMFIS) (by item and overall); [5] other subject-reported questions (when collected at baseline)
- composite CR-SMFRS and PR-SMFRS responder analyses.

- Change from baseline at Visit 9 for the following endpoints:
  - Skin Laxity Rating Scale (SLRS) [6]
  - SSRS (change from screening treated as a continuous variable)
  - SSRS (change from screening responder analysis)
  - Self-Ratings of Attractiveness (each of six questions)
  - Derriford Appearance Scale 24 (DAS-24)
  - Body Image Quality of Life Inventory (BIQLI). [7, 8]

- Data collected only at 12 weeks following the last treatment were:
  - Subject global questions (3 questions)
  - post-treatment questions (2 questions);
  - association in change of MRI measurements and change in CR-SMFRS and
  - the relationship of change in MRI measurements and caliper measurements at the end of the study.

In addition to the efficacy endpoints, the psychometric performance of three newly developed measures of submental fat size and submental fat impacts were evaluated, including the single item CR-SMFRS, the single item PR-SMFRS, and the six item PR-SMFIS.

6.1.3.4. Participant flow and baseline data

The subjects included 129 healthy subjects with submental fat: 41 in the 1 mg/cm^2 group; 43 in the 2 mg/cm^2 group; and 45 in the placebo group. Of these 26 (20.2%) subjects discontinued and 103 (79.8%) completed. The modified intent-to-treat (mITT) analysis included 40 (97.6%) subjects in the 1 mg/cm^2 group; 42 (97.7%) in the 2 mg/cm^2 group; and 45 (100%) in the placebo group. There were 92 (71.3%) females, 37 (28.7%) males and the age range was 24 to 65 years. Median (range) BMI was 30.5 (19.5 to 48.8) kg/m^2. The treatment groups were similar in demographic characteristics. There were fewer subjects with CR-SMFRS grade 3 in the 2 mg/cm^2 group.

6.1.3.5. Results for the efficacy outcomes

The change in CR-SMFRS score from baseline to 12 weeks post-treatment was greater in the 2 mg/cm^2 group than placebo (least squares mean (LS Mean) difference (95% CI) -0.5

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4 PR-SMFRS is a patient reported scoring system using a 5-point scale assessing the appearance of the submental area. The patient to look at the chin area in a mirror and rate the appearance of the submental area. A score of 0 = no chin fat present; score of 4 = a very large amount of chin fat. See Tables 3, 4 and 5 for an overview of validity.

5 PR-SMFIS is a patient reported scoring system assessing the impact of submental fat on patient self-perceptions related to visual and emotional attributes.

6 SLRS is a clinician reported scoring system using a 4-point scale assessing skin laxity. A score of 0 = no skin laxity; score of 4 = very lax.

7 DAS24 is a patient reported 24 item scale used in the assessment of distress and difficulties experienced in living with problems of appearance.

8 BIQLI is a patient reported scale assessing the impact of body image on wellbeing.

(-0.77 to -0.16); p = 0.003 but there was no significant difference for the 1 mg/cm^2 group, LS Mean difference (95% CI) -0.3 (-0.61 to -0.00); p = 0.052. There was cumulative improvement after each treatment session with maximum effect 4 weeks after the 6th treatment. The percentage of subjects with a 1-grade improvement 12 weeks after the last treatment was 31.1% for placebo and 57.5% and 64.3% for 1 mg/cm^2 and 2 mg/cm^2 groups respectively.

The change in PR-SMFRS score from baseline to 12 weeks post-treatment was also greater in the 2 mg/cm^2 group than placebo (LS Mean difference (95% CI) -0.6 (-0.91 to -0.30); p < 0.001) but there was no significant difference for the 1 mg/cm^2 group: LS Mean difference (95 %CI) -0.2 (-0.55 to 0.06); p = 0.117. The percentage of subjects with a 1-grade improvement in PR-SMFRS score 12 weeks after the last treatment was 60.0% for placebo and 70.0% and 78.6% for 1 mg/cm^2 and 2 mg/cm^2 groups respectively.

The change in SSRS score from baseline to 12 weeks post-treatment was also greater in the both deoxycholic acid treatment groups than the placebo group: LS Mean difference (95% CI) 1.3 (0.46 to 2.05); p = 0.002 for the 1 mg/cm^2 group; LS Mean difference (95% CI) 2.0 (1.22 to 2.81); p < 0.001 for the 2 mg/cm^2 group.

The change in PR-SMFIS score from baseline to 12 weeks post-treatment was also greater in the both deoxycholic acid treatment groups than the placebo group: LS Mean difference (95% CI) -1.4 (-2.44 to -0.46); p = 0.005 for the 1 mg/cm^2 group; LS Mean difference (95% CI) -2.5 (-3.48 to -1.48); p < 0.001 for the 2 mg/cm^2 group. The individual components of the PR-SMFIS score all supported the overall score.

The change in submental fat volume by MRI from baseline to 12 weeks post-treatment was greater in the both deoxycholic acid treatment groups than placebo, LS Mean difference (95% CI) -296 mm^3 (-578 mm^3 to -13.5 mm^3); p = 0.040 for the 1 mg/cm^2 group, LS Mean difference (95% CI) -398 mm^3 (-678 mm^3 to -118 mm^3); p = 0.006 for the 2 mg/cm^2 group.

The change as a percentage in submental fat volume by MRI from baseline to 12 weeks post-treatment compared to placebo was, LS Mean difference (95% CI), -4.3% (-8.13% to -0.41%); p = 0.030 for the 1 mg/cm^2 group and LS Mean difference (95% CI) -5.8% (-9.67% to -2.00%); p = 0.003 for the 2 mg/cm^2 group.

The number (percentage) of subjects with ≥ 10% reduction in submental fat volume was 11 (27.5%) in the 1 mg/cm^2 group, 19 (45.2%) in the 2 mg/cm^2 group and three (6.7%) in the placebo group. The change in submental fat thickness by MRI from baseline to 12 weeks post-treatment compared to placebo was: LS Mean difference (95% CI), -1.5 mm (-2.32 mm to -0.69 mm); p < 0.001 for the 1 mg/cm^2 group and LS Mean difference (95% CI) -1.7 mm (-2.46 mm to -0.85 mm); p < 0.001 for the 2 mg/cm^2 group.

The percentage change in submental fat thickness by MRI from baseline to 12 weeks post-treatment compared to placebo was, LS Mean difference (95% CI), -9.2% (-14.1% to -4.25%); p < 0.001 for the 1 mg/cm^2 group and LS Mean difference (95% CI) -11% (-15.5% to -5.73%); p < 0.001 for the 2 mg/cm^2 group.

The number (percentage) of subjects with CR-SMFRS and PR-SMFRS scores of 0 or 1 at 12 weeks after final treatment was 9 (22.5%) in the 1 mg/cm^2 group, 19 (45.2%) in the 2 mg/cm^2 group and 6 (13.3%) in the placebo group.

The number (percentage) of subjects with at least 1 grade improvement in CR-SMFRS and PR-SMFRS scores of 0 or 1 at 12 weeks after final treatment was 18 (45.0%) in the 1 mg/cm^2 group, 24 (57.1%) in the 2 mg/cm^2 group and ten (22.2%) in the placebo group.

Improvement in skin laxity at 12 weeks after final treatment was 29% in the 1 mg/cm^2 group, 25% in the 2 mg/cm^2 group and 7% in the placebo group.

There was no significant difference between the groups in the change from baseline for self-ratings of overall appearance 12 weeks after last treatment: mean (SD) 0.7 (1.36) points for 1 mg/cm^2, 0.9 (1.16) points for 2 mg/cm^2, and 0.5 (1.10) points for placebo.

For the following questions, all asked 12 weeks after the last treatment:

- 'Since the start of this study, how would you rate the fat under your chin right now?' there were 33 (82.5%) responders for 1 mg/cm^2, 36 (85.7%) for 2 mg/cm^2 and 23 (51.1%) for placebo.

- 'Since the start of this study, how would you rate the definition between your chin and neck right now?' there were 33 (82.5%) responders for 1 mg/cm^2, 36 (85.7%) for 2 mg/cm^2 and 20 (44.4%) for placebo.

- 'How satisfied are you with the treatment you received in this study?' there were 33 (82.5%) responders for 1 mg/cm^2, 36 (85.7) for 2 mg/cm^2 and 20 (44.4) for placebo.

- 'How well defined is the line between your chin and neck?' the change from baseline to 12 weeks post-treatment compared to placebo was, LS Mean difference (95% CI), 0.2 (-0.21 to 0.58); $p = 0.355$ for the 1 mg/cm^2 group, LS Mean difference (95% CI) 0.8 (0.37 to 1.14); $p < 0.001$ for the 2 mg/cm^2 group.

- 'How would you rate the fat under your chin right now?' the change from baseline to 12 weeks post-treatment compared to placebo was, LS Mean difference (95% CI), -0.4 (-0.72 to -0.03); $p = 0.036$ for the 1 mg/cm^2 group, LS Mean difference (95% CI) -0.5 (-0.88 to -0.20); $p = 0.002$ for the 2 mg/cm^2 group.

There was no significant difference in overall DAS score or BIQLI score between the treatments although there were some differences in individual components.

6.2. Evaluator's overall conclusions on dose selection

The results of Study 03 and Study 07 were confusing and although indicating treatment effect for deoxycholic acid did not indicate any dose effect; however, Study 15 was useful in indicating better efficacy for the 2 mg/cm^2 group. This study was also useful in developing the outcome measures used in the subsequent pivotal studies. Overall, the dose finding studies supported taking the following dose regimen through to the pivotal studies: deoxycholic acid (BA formulation) up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%) every 4 weeks.

7. Clinical efficacy

7.1. Pivotal efficacy studies

7.1.1. Study 22

7.1.1.1. Study design, objectives, locations and dates

Study 22 was a multicentre, randomised, double blind, placebo controlled, parallel group safety and efficacy study. The study was conducted at 35 centres in the US and Canada from February 2012 to August 2013.

Inclusion and exclusion criteria

The inclusion criteria included:

- Submental fat graded by the investigator as 2 or 3 using the CR-SMFRS and graded by the subject as 2 or 3 using the PR-SMFRS

- Dissatisfaction with the submental area expressed by the subject as a rating of 0, 1 or 2 using the SSRS

- Males and non-pregnant, non-lactating females 18 to 65 years of age

- History of stable body weight, in the judgment of the investigator, for at least 6 months before randomisation

- Agreement to forego any treatment or behaviour (such as unshaven facial hair) during the subject's participation in the study that may affect the assessments of the submental area

- Medically able to undergo the administration of study drug determined by clinical and laboratory tests obtained within 28 days before randomisation for which the investigator identified no clinically significant abnormality.

The exclusion criteria included:

- History of any intervention to treat submental fat (such as liposuction, surgery, or lipolytic agents)

- History of trauma associated with the chin or neck areas that in the judgment of the investigator may affect evaluation of safety or efficacy of treatment

- A grade of 4 on the Submental Skin Laxity Grade (SMSLG) or other anatomical feature (such as predominant subplatysmal fat, loose skin in the neck or chin area or prominent platysmal bands), as assessed within 28 days before randomization, for which reduction in submental fat may, in the judgment of the investigator, result in an aesthetically unacceptable outcome.

- Evidence of any cause of enlargement in the submental area (such as thyroid enlargement or cervical adenopathy) other than localised submental fat

- A BMI of > 40.0 kg/m^2.

- History or current symptoms of dysphagia.

- A result on coagulation tests (prothrombin time and partial thromboplastin time) obtained within 28 days before randomisation that indicates the presence of any clinically significant bleeding disorder

- Any medical condition (including respiratory, cardiovascular, hepatic, neurological disease or thyroid dysfunction) that would interfere with assessment of safety or efficacy or compromise the subject's ability to undergo study procedures or give informed consent.

- Treatment with radio frequency, laser procedures, chemical peels, or dermal fillers in the neck or chin area within 12 months before randomisation

- Treatment with botulinum toxin injections in the neck or chin area within 6 months before randomisation

- History of sensitivity to any components of the study drug. History of sensitivity to topical or local anaesthetics (such as lidocaine, benzocaine, procaine).

- For centres selected to conduct MRI evaluations, any subject with the presence of any condition that would render a subject unsuitable for MRI evaluation (such as claustrophobia), or metals in the body that would interfere with MRI acquisition (for example, non-removable metal appliances in the mouth such as silver or gold caps, pacemakers or metal joints).

Study treatments

The two study treatments were:

1. Deoxycholic acid (BA containing formulation) up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%); up to 50 x 0.2 mL injections using a 1.0 cm grid and a placebo

2. Placebo

The treatments were administered as subcutaneous injections in submental fat. There were up to 6 treatment sessions every 4 weeks.

7.1.1.2. *Efficacy variables and outcomes*

Primary efficacy outcomes

The primary efficacy outcome measures were composite scores:

*   Composite 1-grade SMFRS (subjects with simultaneous CR-1 (subject who has at least a 1-grade reduction from baseline in the CR-SMFRS assessment) and PR-1 (subject who has at least a 1-grade reduction from baseline in the PR-SMFRS assessment)) response (SMFRS-1) rate 12 weeks after last treatment

*   Composite 2-grade SMFRS (subjects with simultaneous CR-2 (subject who has at least a 2-grade reduction from baseline in the CR-SMFRS assessment) and PR-2 (subject who has at least a 2-grade reduction from baseline in the PR-SMFRS assessment)) response (SMFRS-2) rate at 12 weeks after last treatment.

The CR-SMFRS was validated in a separate study and demonstrated excellent intra- and inter-rater reliability with PR-SMFRS validated and found to have substantial intra-rater reliability. [information redacted]

Secondary efficacy outcomes

*   MRI responder (≥ 10% reduction in submental fat volume from baseline) status 12 weeks after last treatment

*   Improvement in PR-SMFIS Total Scale Score (TSS) from baseline 12 weeks after last treatment.

Other efficacy outcomes

*   SMFRS-1 response status at Visits 6 (Week 16), 8 (4 weeks after last treatment) and 10 (24 weeks after last treatment)

*   CR-1 response status at Visits 6, 8, 9 and 10.

*   PR-1 response status at Visits 6, 8, 9 and 10

*   SMFRS-2 response status at Visits 6, 8 and 10

*   CR-2 response status at Visits 6, 8, 9 and 10

*   PR-2 response status at Visits 6, 8, 9, and 10

*   CR-SMFRS change from baseline at Visits 3 (Week 4), 4 (Week 8), 5 (Week 12), 6, 7 (Week 20), 8, 9 and 10

*   PR-SMFRS change from baseline at Visits 3, 4, 5, 6, 7, 8, 9 and 10

*   MRI volume, percentage change from baseline at Visit 9

*   MRI thickness and percentage change from baseline at Visit 9

*   PR-SMFIS TSS change from baseline at Visits 6, 8 and 10

- PR-SMFIS individual item scores change from baseline at Visits 6, 8, 9 and 10

- SSRS responder status at Visits 9 and 10

- SSRS change from baseline at Visits 9 and 10

- Self-Ratings of Attractiveness, change from baseline at Visits 9 and 10

- Thickness of submental fat using callipers, percentage change from baseline at Visits 6, 8, 9 and 10

- Subject assessment of submental fat using standardised line-drawing representations of submental convexity, change from baseline at Visits 3, 4, 5, 6, 7, 8, 9 and 10

- Subject Global Questions responder status at Visit 9.

The caliper method was validated in a separate study and demonstrated excellent intra- and inter-rater reliability. The caliper method had high correlation with MRI measures of submental fat and with CR-SMFRS grading. [information redacted]

One additional parameter is summarised with the efficacy data: SMSLG response status at Visits 6, 8, 9 and 10 (SMSLG was also analysed as a safety outcome measure). The SMSLG was validated in a separate study and had excellent inter- and intra-rater reliability. See Table 4 above for an overview.

The safety outcome measures were: treatment emergent adverse events (TEAE), clinical laboratory test results, vital signs and weight.

7.1.1.3. Randomisation and blinding methods

Subjects were randomised to treatment in a 1:1 ratio, within centre, by Interactive web response system (IWRS). Active treatment and placebo were identical.

7.1.1.4. Analysis populations

The intent-to-treat (ITT) population included all subjects randomised to treatment and was used for all the efficacy analyses except for the MRI outcomes. The ITT-MRI population included all randomised subjects who participated in the MRI cohort.

The safety population included all randomised subjects who received at least one injection of study drug.

7.1.1.5. Sample size

The sample size calculation was based on the results from Study 15. Assuming a 10% dropout rate, 250 subjects in each treatment group would be required to obtain 93% power to detect a treatment difference at a level of significance of 0.05 for detecting a composite 2-grade response in SMFRS.

7.1.1.6. Statistical methods

Hypothesis tests were performed for dichotomous variables using the Cochran-Mantel-Haenszel test, and for continuous variables using analysis of variance (ANOVA) models. Covariate effects were examined using exact conditional logistic regression. Where missing values were imputed, the earliest post-baseline value was used.

7.1.1.7. Participant flow

A total of 740 subjects were screened, and 505 subjects were randomised: 257 to the 2 mg/cm^2 group and 250 to placebo. A total of 206 (80.5%) subjects in the 2 mg/cm^2 group and 200 (88.0%) in the placebo group completed the study. The most common reason for discontinuing was insufficient submental fat to treat: 33 (12.9%) in the 2 mg/cm^2 group and five (2.0%) in the placebo group. Discomfort with procedure was an uncommon reason for discontinuing: four subjects in the 2 mg/cm^2 group and none in the placebo group.

7.1.1.8.   Major protocol violations/deviations

There were no protocol deviations that resulted in exclusion from the ITT population.

7.1.1.9.   Baseline data

There were 421 (83.2%) females, 85 (16.8%) males and the age range was 19 to 65 years. The study population was predominantly White with 445 (87.9%) subjects. The study population was predominantly overweight with only 76 (15.0%) subjects with BMI ≤ 25 kg/m^2. The study groups were similar in demographic characteristics.

7.1.1.10.   Results for the primary efficacy outcome

There was greater efficacy for deoxycholic acid for both primary efficacy outcome measures:

- For composite 1-grade SMFRS response, there were 179 (70.0%) subjects in the 2 mg/cm^2 group and 47 (18.6%) in the placebo; risk ratio (95% CI) 3.702 (2.808 to 4.880); p < 0.001

- For composite 2-grade SMFRS response, there were 34 (13.4%) in the 2 mg/cm^2 group and none in the placebo group; risk ratio (95% CI) inestimable because of no members of the placebo group were composite 2-grade responders; p < 0.001.

There were no subgroup or covariate effects on efficacy.

7.1.1.11.   Results for other efficacy outcomes

Results for the secondary efficacy outcomes

- MRI response occurred for 48 (51.10%) subjects in the 2 mg/cm^2 group and five (5.1%) in the placebo group; risk ratio (95% CI) 9.208 (3.945 to 21.492); p < 0.001

- The mean (SD) change from baseline in PR-SMFIS total scale score was -3.56 (2.793) in the 2 mg/cm^2 group and -1.16 (2.064) in the placebo group; p < 0.001.

Results for other efficacy outcome measures

- SMFRS-1 response status at Visits 6 (Week 16), 8 (4 weeks after last treatment) and 10 (24 weeks after last treatment) was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- CR-1 response status at Visits 6, 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- PR-1 response status at Visits 6, 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- SMFRS-2 response status at Visits 8 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- CR-2 response status at Visits 6, 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- PR-2 response status at Visits 6, 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- CR-SMFRS change from baseline at Visits 4, 5, 6, 7, 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- PR-SMFRS change from baseline at Visits 4, 5, 6, 7, 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0.001

- MRI volume, percentage change from baseline at Visit 9 was: LS mean (95% CI) -10.3 mm^3 (-12.0 mm^3 to -8.6 mm^3) for the 2 mg/cm^2 group and 1.7 mm^3 (0.0 mm^3 to 3.4 mm^3) for the placebo group, LS mean (95% CI) difference -12.0 mm^3 (-14.4 mm^3 to -9.6 mm^3); p < 0.001

- MRI thickness, percentage change from baseline at Visit 9 was, LS mean (95% CI) -18.4% (-20.7% to -16.0%) for the 2 mg/cm^2 and 0.9% (-1.4% to 3.2%) for the placebo group, LS mean (95% CI), difference -19.3% (-22.6% to -15.9%); p < 0.001

- PR-SMFIS TSS change from baseline at Visits 6, 8 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0 .001

- PR-SMFIS individual item scores change from baseline at Visits 6, 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p < 0 .001

- SSRS responder status at Visit 9 occurred for 192 (82.8%) subjects in the 2 mg/cm^2 group and 72 (31.0%) in the placebo group, risk ratio (95% CI) 2.654 (2.172 to 3.242); p < 0.001. SSRS responder status at Visits 10 occurred for 184 (81.1%) subjects in the 2 mg/cm^2 group and 62 (27.3%) in the placebo group, risk ratio (95% CI) 2.960 (2.375 to 3.690); p < 0.001

- SSRS change from baseline at Visit 9 was LS mean (95% CI) 3.4 (3.2 to 3.6) for the 2 mg/cm^2 and 1.5 (1.3 to 1.6) for the placebo group, LS mean (95% CI) difference 1.9 (1.6 to 2.2); p < 0.001. SSRS change from baseline at Visit 10 was, LS mean (95% CI) 3.3 (3.1 to 3.5) for the 2 mg/cm^2 and 1.3 (1.1 to 1.5) for the placebo group, LS mean (95% CI) difference 2.0 (1.7 to 2.3); p < 0.001

- Self-Ratings of Attractiveness, changes from baseline at Visits 9 were improved for overall appearance, chin/neck, nose and entire face, but not significantly for eyes and mouth

- Thickness of submental fat using callipers, percentage change from baseline at Visits 8, 9 and 10 was greater in the 2 mg/cm^2 group than the placebo group; p< 0 .001

- Subject assessment of submental fat using standardised line-drawing representations of submental convexity, change from baseline at Visits 4, 5, 6, 7, 8, 9 and 10 improved in the 2 mg/cm^2 group compared to the placebo group; p < 0 .001

- Subject Global Questions responder status at Visit 9 improved in the 2 mg/cm^2 group compared to placebo group; p < 0 .001

For the one additional parameter summarised with the efficacy data (SMSLG response status at Visits 10 (and other visits)) results were similar for the two treatment groups.

7.1.2.   Study 23

7.1.2.1.   *Study design, objectives, locations and dates*

Study 23 was a multicentre, randomised, double blind, placebo controlled, parallel group safety and efficacy study. The study was conducted at 35 centres in the US and Canada from March 2012 to August 2013. The study was identical in design to Study 22 (discussed above).

Inclusion and exclusion criteria

As per Study 22.

Study treatments

As per Study 22.

Efficacy variables and outcomes

As per Study 22.

Randomisation and blinding methods

As per Study 22.

Analysis populations

As per Study 22.

Sample size

As per Study 22.

Statistical methods

As per Study 22.

7.1.2.2. Participant flow

A total of 818 subjects were screened and 516 subjects were randomised: 258 to the 2 mg/cm^2 group and 258 to the placebo group. A total of 195 (75.6%) subjects in the 2 mg/cm^2 group and 212 (82.2%) in the placebo group completed the study. The most common reason for discontinuing was insufficient submental fat to treat: 44 (17.1%) in the 2 mg/cm^2 group and 12 (4.7%) in the placebo group. Discomfort with procedure was an uncommon reason for discontinuing: 11 (9.2%) subjects in the 2 mg/cm^2 group and two (3.4%) in the placebo.

7.1.2.3. Major protocol violations/deviations

There were no protocol violations that resulted in exclusion from analysis.

7.1.2.4. Baseline data

There were 445 (86.2%) females, 71 (13.8%) males and the age range was 19 to 65 years. The study population was predominantly White: 444 (86.0%) subjects overall. The study population was predominantly overweight with only 92 (17.8%) subjects with BMI < 25 kg/m^2. The study groups were similar in demographic characteristics.

7.1.2.5. Results for the primary efficacy outcome

There was greater efficacy for deoxycholic acid for both primary efficacy outcome measures:

- For composite 1-grade SMFRS responders, there were 171 (66.5%) in the 2 mg/cm^2 group and 57 (22.2%) in the placebo group; risk ratio (95% CI) 2.983 (2.311 to 3.849); p < 0.001

- For composite 2-grade SMFRS responders, there were 48 (18.6%) in the 2 mg/cm^2 group and 8 (3.0%) in the placebo group; risk ratio (95% CI) 6.271 (2.908 to 13.520); p < 0.001.

There were no subgroup or covariate effects on efficacy.

7.1.2.6. Results for other efficacy outcomes

Results for secondary efficacy outcomes

- MRI response occurred for 45 (40.2%) subjects in the 2 mg/cm^2 group and 6 (5.2%) in the placebo group; risk ratio (95% CI) 7.838 (3.299 to 18.622); p < 0.001

- The mean (SD) change from baseline in PR-SMFIS total scale score was -3.48 (2.692) in the 2 mg/cm^2 group and -1.42 (2.453) in the placebo group; p < 0.001

Results for other the additional efficacy outcome measures

- SMFRS-1 response status at Visits 6 (Week 16), 8 (4 weeks after last treatment), and 10 (24 weeks after last treatment) was greater in the 2 mg/cm^2 group than the placebo; p < 0.001.

- CR-1 response status at Visits 6, 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- PR-1 response status at Visits 6, 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- SMFRS-2 response status at Visits 8, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- CR-2 response status at Visits 6, 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- PR-2 response status at Visits 6, 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- CR-SMFRS change from baseline at Visits 3 (Week 4), (Week 8), 5 (Week 12), 6, 7 (Week 20), 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- PR-SMFRS change from baseline at Visits 3, 4, 5, 6, 7, 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- MRI volume, percentage change from baseline at Visit 9 was, LS mean (95% CI) -8.9 (10.6 to -7.1) mm^3 for the 2 mg/cm^2 and 0.8 (-0.9 to 2.5) mm^3 for the placebo, LS mean (95% CI) difference -9.6 (-12.1 to -7.2) mm^3, p < 0.001.

- MRI thickness, percentage change from baseline at Visit 9 was, LS mean (95% CI) -8.5% (-11.0 to -6.1%) for the 2 mg/cm^2 and 1.3% (-1.1 to 3.6%) for the placebo, LS mean (95% CI) difference -9.8% (-13.2 to -6.5%) p < 0.001.

- PR-SMFIS TSS change from baseline at Visits 6, 8, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- PR-SMFIS individual item scores change from baseline at Visits 6, 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- SSRS responder status at Visit 9 occurred for 163 (75.1%) subjects in the 2 mg/cm^2 group and 83 (36.2%) in the placebo, risk ratio (95% CI) 2.094 (1.726 to 2.539) p < 0.001. SSRS responder status at Visits 10 occurred for 165 (77.1%) subjects in the 2 mg/cm^2 group and 86 (38.4%) in the placebo, risk ratio (95% CI) 2.051 (1.711 to 2.459) p < 0.001.

- SSRS change from baseline at Visit 9 was, LS mean (95% CI) 3.3 (3.1 to 3.5) for the 2 mg/cm^2 and 1.6 (1.4 to 1.8) for the placebo, LS mean (95% CI) difference 1.7 (1.4 to 2.0) p < 0.001. SSRS change from baseline at Visit 10 was, LS mean (95% CI) 3.3 (3.1 to 3.5) for the 2 mg/cm^2 and 1.7 (1.5 to 2.0) for the placebo, LS mean (95% CI) difference 1.5 (1.2 to 1.8) p < 0.001.

- Self-Ratings of Attractiveness, change from baseline at Visits 9 were improved for overall appearance, chin/neck, and entire face, but not significantly for eyes, nose and mouth.

- Thickness of submental fat using calipers, percentage change from baseline at Visits 8, 9, and 10 was greater in the 2 mg/cm^2 group than the placebo, p < 0.001.

- Subject assessment of submental fat using standardised line-drawing representations of submental convexity, change from baseline at Visits 4, 5, 6, 7, 8, 9, and 10 improved in the 2 mg/cm^2 group compared to the placebo, p < 0.001).

- Subject Global Questions responder status at Visit 9 improved in the 2 mg/cm^2 group compared to placebo, p < 0.001.

For the one additional parameter summarized with the efficacy data:

- SMSLG response status at Visits 10, and other visits, was similar for the two treatment groups.

7.2. Other efficacy studies

7.2.1. Study 16

7.2.1.1. Study design

Study 16 was a multicentre, randomised, double blind, three-arm placebo controlled, parallel group safety and efficacy study. The study was conducted at 28 centres in the European Union (Belgium, France, Germany, Spain and the UK) from December 2010 to January 2012. The study included healthy subjects with submental fat with submental fat graded by the investigator as 2 or 3 using the CR-SMFRS; dissatisfaction with the submental area expressed by the subject as a rating of 0, 1, or 2 using the SSRS; males and non-pregnant, non-lactating females 18 to 65 years of age; with a history of stable body weight; and medically able to undergo the administration of study drug determined by clinical and laboratory tests. The study excluded subjects with BMI > 30 kg/m².

7.2.1.2. Study treatments

The three study treatment groups were:

1. Deoxycholic acid (BA free formulation) up to 50 mg, 1 mg/cm², 5 mg/mL (0.5%), up to 50 x 0.2 mL injections using a 1.0 cm grid

2. Deoxycholic acid (BA free formulation), up to 100 mg, 2 mg/cm², 10 mg/mL (1.0%), up to 50 x 0.2 mL injections, 1.0 cm grid

3. Placebo.

Subjects were randomised in 1:1:1 ratio. The treatments were administered as subcutaneous injections in submental fat. There were up to 4 treatment sessions every 4 weeks, with follow-up for 12 weeks post-treatment.

7.2.1.3. Efficacy variables and outcomes

There were two co-primary efficacy outcome measures, the proportion of subjects with:

• A 1-point reduction in CR-SMFRS (responders)

• SSRS ≥ 4 response.

The secondary outcome measures were calliper measurements, SSRS, PR-SMFIS, self-ratings of attractiveness, modified DAS-24, BIQLI, PR-SMFRS, subject reported questions, post-treatment questions and Subject Global Questions. The safety outcome measures were: TEAEs, laboratory tests, and vital signs.

7.2.1.4. Baseline data

There were 362 subjects randomised: 119 in the 1 mg/cm² group, 121 in the 2 mg/cm² group, 122 in the placebo. A total of 107 (89.2%) subjects in the 1 mg/cm² group, 110 (90.9%) in the 2 mg/cm² group and 112 (91.8%) in the placebo completed the study. There were 277 (76.5%) females, 85 (23.5%) males, the age range was 19 to 64 years, BMI range was 18.1 to 29.9 kg/m² and 343 (94.8%) were White. The treatment groups were similar in demographic characteristics.

7.2.1.5. Results for the efficacy outcomes

Primary efficacy outcomes

For the co-primary efficacy outcome measures both deoxycholic acid regimens were superior to placebo and although not statistically significant, the 2 mg/cm² regimen was superior to the 1 mg/cm². For CR-SMFRS subjects there were 71 (59.2%) responders in the 1 mg/cm² group, 79 (65.3%) in the 2 mg/cm² and 28 (23.0%) in the placebo group. For SSRS (score ≥ 4) subjects

there were 64 (53.3%) responders in the 1 mg/cm^2 group, 80 (66.1%) in the 2 mg/cm^2, and 35 (28.7%) in the placebo group.

Secondary efficacy outcomes

For CR-SMFRS the LS mean (95% CI) change from baseline to 12 weeks after last treatment, relative to placebo was: -0.51 (-0.68 to -0.35) for the 1 mg/cm^2 group; $p < 0.001$ and -0.67 (-0.84 to -0.50); $p < 0.001$ in the 2 mg/cm^2 group

For SSRS the LS mean (95% CI) change from baseline to 12 weeks after last treatment, relative to placebo was: 1.04 (0.61 to 1.47) for the 1 mg/cm^2 group; $p < 0.001$ and 1.41 (0.99 to 1.84); $p < 0.001$ in the 2 mg/cm^2 group

For submental fat thickness measured by calliper, the LS mean (95% CI) change from baseline to 12 weeks after last treatment, relative to placebo was: -1.68 mm (-2.50 mm to -0.87 mm) for the 1 mg/cm^2 group; $p < 0.001$ and -1.97 mm (-2.79 mm to -1.15 mm) in the 2 mg/cm^2 group; $p < 0.001$

For PR-SMFRS there were 69 (67.0%) subjects that improved in the 1 mg/cm^2 group, 78 (73.6%) in the 2 mg/cm^2 group and 35 (32.4%) in the placebo group (deoxycholic acid versus placebo comparison, $p < 0.001$)

All PR-SMFIS Scores were significantly better in the deoxycholic acid treatment groups compared to placebo

For self-ratings in attractiveness there was significant improvement in chin/neck for both treatment groups

For modified DAS-24 there were significant findings for the following questions:

- 'How distressed do you get when you see yourself in the mirror/window?' for the 2 mg/cm^2 group relative to placebo ($p = 0.029$)

- 'I am self-conscious of my chin' between both the 1 mg/cm^2 group ($p = 0.14$) and 2 mg/cm^2 group ($p < 0.001$), relative to placebo

- 'How hurt do you feel?' for both the 1 mg/cm^2 group ($p = 0.032$) and the 2 mg/cm2 group ($p = 0.012$), relative to placebo

- 'My self-consciousness makes me irritable at home' for the 2 mg/cm^2 group, relative to placebo ($p = 0.013$)

- 'I adopt certain gestures, e.g., folding my arms in front of other people, covering my mouth with my hand' for both the 1 mg/cm^2 group ($p = 0.002$) and the 2 mg/cm^2 group ($p < 0.001$), relative to placebo

- 'How distressed do you get when going to social events?' for both the for both the 1 mg/cm^2 group ($p = 0.019$) and the 2 mg/cm^2 group ($p = 0.042$), relative to placebo

- 'How distressed do you get when other people make remarks about your chin?' for the 2 mg/cm^2 group ($p < 0.001$), relative to placebo

For the BIQLI there were significant findings for the following questions:

- 'My basic feelings about myself - feelings of personal adequacy and self-worth' for both the 1 mg/cm^2 group ($p = 0.033$) and the 2 mg/cm^2 group ($p = 0.011$), relative to placebo

- 'My interactions with people of the other sex' for both the 1 mg/cm^2 group ($p = 0.019$) and the 2 mg/cm^2 group ($p = 0.003$), relative to placebo

- 'My experiences when I meet new people' for both the 1 mg/cm^2 group ($p = 0.039$) and the 2 mg/cm^2 group ($p < 0.001$), relative to placebo

- 'My experiences at work or at school' for the 2 mg/cm^2 group (p = 0.025), relative to placebo

- 'My satisfaction with my life in general' for the 2 mg/cm^2 group (p = 0.028), relative to placebo

- 'How happy I feel in my everyday life' for the 2 mg/cm^2 group (p = 0.038), relative to placebo.

There was a worsening in skin laxity for 9 (8.5%) subjects in the 1 mg/cm^2 group, 13 (11.8%) in the 2 mg/cm^2 group and 12 (10.7%) in the placebo group.

There were improvements in the self-reported questions for both deoxycholic acid groups relative to placebo.

7.2.2.   Study 17

7.2.2.1.   *Study design*

Study 17 was a multicentre, randomised, double blind, three-arm placebo controlled, parallel group safety and efficacy study. The study was conducted at 29 centres in the European Union (Belgium, France, Germany North-East, Germany South-West, Italy, Spain and the UK) from January 2011 2010 to February 2012. The study was identical in design to Study 16 (see preceding study above).

7.2.2.2.   *Baseline data*

There were 360 subjects randomised: 121 in the 1 mg/cm^2 group, 122 in the 2 mg/cm^2 group, 117 in the placebo group. A total of 111 (91.7%) subjects in the 1 mg/cm^2 group, 112 (91.8%) in the 2 mg/cm^2 group and 103 (88.0%) in the placebo group completed the study. There were 255 (72.0%) females, 99 (28.0%) males, the age range was 19 to 65 years, BMI range was 18.6 to 30.0 kg/m^2, and 329 (92.9%) were White. The treatment groups were similar in demographic characteristics.

7.2.2.3.   *Results for the efficacy outcomes*

Primary efficacy outcomes

The co-primary efficacy outcome measures for both deoxycholic acid regimens were superior to placebo and similar to each other in efficacy:

- For CR-SMFRS there were 70 (58.3%) responders in the 1 mg/cm^2 group, 76 (62.3%) in the 2 mg/cm^2 and 40 (34.5%) in the placebo group.

- For SSRS (scores > 4) there were 82 (68.3%) responders in the 1 mg/cm^2 group, 79 (64.8%) in the 2 mg/cm^2 group and 34 (29.3%) in the placebo group.

Secondary efficacy outcomes

- For CR-SMFRS the LS mean (95% CI) change from baseline to 12 weeks after last treatment relative to placebo was -0.35 (-0.51 to -0.19) for the 1 mg/cm^2 group; p <0.001 and -0.40 (-0.56 to -0.24) in the 2 mg/cm^2; p < 0.001.

- For SSRS the LS mean (95% CI) change from baseline to 12 weeks after last treatment relative to placebo was 1.36 (0.97 to 1.75) for the 1 mg/cm^2 group; p <0.001 and 1.26 (0.87 to 1.65) in the 2 mg/cm^2 group; p < 0.001.

- For submental fat thickness, measured by calliper the LS mean (95% CI) change from baseline to 12 weeks after last treatment relative to placebo was -0.80 mm (-1.72 mm to 0.13 mm) for the 1 mg/cm^2 group; p = 0.090 and -1.89 mm (-1.89 mm to -0.05 mm) in the 2 mg/cm^2 group; p = 0.040.

- For PR-SMFRS there were 72 (64.9%) subjects that improved in the 1 mg/cm^2 group (p = 0.009 versus placebo); 74 (67.3%) in the 2 mg/cm^2 (p < 0.001 versus placebo) and 45 (44.1%) in the placebo group.

- All PR-SMFIS Scores were significantly better in the deoxycholic acid treatment groups compared to those of the placebo group.

- For self-ratings in attractiveness there was significant improvement in chin/neck for both treatment groups.

- For modified DAS-24 there were significant findings for the following questions:

  – 'How confident do you feel' between the 2 mg/cm^2 group relative to placebo; p = 0.018

  – 'How feminine/masculine do you feel?' between the 2 mg/cm^2 group relative to placebo; p = 0.042

  – 'I am self-conscious of my chin' between the 2 mg/cm^2 group relative to placebo; p = 0.045

  – 'How distressed do you get by shopping in department stores/supermarkets?' between the 2 mg/cm^2 group relative to placebo; p = 0.042

  – 'How rejected do you feel?' between the 1 mg/cm^2 group relative to placebo; p = 0.028

  – 'I close into my shell' between the 1 mg/cm^2 group relative to placebo; p = 0.009

  – 'How distressed are you by being unable to wear your favourite clothes?' between the 1 mg/cm^2 group relative to placebo; p = 0.046

  – 'I avoid going out of the house' between the 1 mg/cm^2 group relative to placebo; p = 0.006

- For the BIQLI there were significant findings for the following question: 'My ability to control what and how much I eat' between the 2 mg/cm^2 group relative to placebo; p = 0.024.

- There was a worsening in skin laxity for 10 (9.0%) subjects in the 1 mg/cm^2 group, 8 (7.1%) in the 2 mg/cm^2 group and 6 (5.9%) in the placebo group.

- There were improvements in the self-reported questions for both deoxycholic acid groups relative to placebo.

7.2.3. Study 26

Study 26 was an open label, multicentre, safety and efficacy study with follow-up for 12 months. The study was conducted at 18 centres in the US from August 2011 to June 2013. The study included healthy subjects with submental fat.

The study treatment was deoxycholic acid (BA formulation) up to 100 mg, 2 mg/cm^2, 10 mg/mL (1.0%), up to 50 x 0.2 mL injections, 1.0 cm grid. There were up to 6 treatment sessions every 4 weeks administered as subcutaneous injections in submental fat.

The efficacy outcome measures were CR-SMFRS, PR-SMFRS, self-ratings of attractiveness, SSRS, Subject Global Questions, calliper measurements, and SMSLG. The safety outcome measures were adverse events (AE), laboratory test results, and physical examinations.

The study included 165 subjects, 136 (82.4%) completed treatment, 144 (87.3%) attended the 12 week follow-up, and 131 (79.4%) attended the 12 month follow-up. There were 128 (77.6%) females, 37 (22.4%) males, the age range was 19 to 68 years, the BMI range was 19.3 to 39.1 kg/m2, and 129 (78.2%) were White.

CR-SMFRS decreased to the 6th treatment and was maintained for up to 12 months. PR-SMFRS decreased to the 6th treatment and was maintained for up to 12 months. PR-SMFIS improved to

the 6th treatment and was maintained for up to 12 months. For SSRS the mean (SD) change from baseline to 12 weeks post treatment was 3.6 (1.49) and from 12 weeks to 12 months post-treatment was 0.1 (1.28).

Self-ratings of attractiveness for chin improved by 12 weeks post treatment and the improvement was maintained for up to 12 months. There was a mean decrease of 30% in submental fat thickness as measured by calliper which was maintained to Month 12 post treatment. Skin laxity improved with treatment and the improvement was maintained to 12 months post-treatment.

7.2.4. Study 12

Study 12 was a multicentre long term follow-up of subjects who completed Study 03, Study 07 and Study 15. The study was conducted at 20 centres in the US, UK, Australia and Canada from February 2009 to July 2013, and was ongoing at the time of submission.

The study included healthy subjects who completed Study 03, Study 07 or Study 15. There were no study drugs administered during the study. The study included 203 subjects, of whom 138 had received active treatment. There were 22 (10.8%) subjects that discontinued, of whom 15 (7.4%) were lost to follow-up. There were 153 (75.4%) females, 50 (24.6%) males, the age range was 26 to 65 years, and 185 (91.1%) were White.

CR-1 response was reported in 66 (91.7%) subjects at 24 months, 41 (80.4%) at 36 months and 29 (87.9%) at 48 months. PR-1 response was reported in 32 (84.2%) subjects at 12 months and 28 (90.3%) at 36 months. There was no significant change from maintenance baseline (start of study) to Month 24 in PR-SMFIS. SSRS response was reported in 72 (84.7%) subjects at 24 months, 44 (78.6%) at 36 months and 26 (74.3%) at 48 months. The LS mean (95% CI) percentage change from maintenance baseline in calliper measurement was -9.9% (-15.4% to -4.5%) in the deoxycholic acid group and -4.5% (-10.9% to 1.9%) in the placebo group. Changes in Subject Global Impression of Improvement (SGI) were maintained to 48 months. Skin laxity, measured by SLRS, was similar for deoxycholic acid and placebo to 48 months.

7.2.5. Study 1403740

Study 1403740 was a multicentre long term follow-up of German subjects who had completed Study 16 or Study 17. The study was conducted at 18 centres in Germany from February 2012 to December 2013. The study included healthy subjects who had completed Study 16 or Study 17.

There was no active treatment administered during the study. Follow-up was for 2 years after completion of the lead-in study. The study included 201 subjects, 135 of whom had received deoxycholic acid. One subject in the placebo group did not complete. All 135 active treatment subjects completed and were included in the analysis. There were 152 (75.6%) females, 49 (24.4%) males, the age range was 20 to 65 years and all were White.

At 24 months, CR-1 was maintained in 36 (90.0%) of subjects treated with 5 mg/mL, 47 (87.0%) treated with 10 mg/mL and 20 (90.9%) treated with placebo. At 24 months, PR-1 was maintained in 31 (51.7%) of subjects treated with 5 mg/mL, 48 (64.0%) treated with 10 mg/mL and 23 (34.8%) treated with placebo. There was no significant change to Month 24 in PR-SMFIS. At 24 months, SSRS response was maintained in 27 (62.8%) of subjects treated with 5 mg/mL, 39 (81.3%) treated with 10 mg/mL and 20 (80.0%) treated with placebo. The mean (SD) change in calliper thickness from study baseline to 24 months was -0.8 mm (3.22) for 5 mg/mL, -0.7 mm (2.81) for 10 mg/mL and -0.6 mm (2.79) for placebo. Change in SGI scores was similar for the three treatment groups. Worsening in skin laxity occurred for 13 (21.7%) subjects in the 5 mg/mL group, 14 (18.7%) in the 10 mg/mL and 10 (15.2%) in the placebo group.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

The pooled analysis of the Pivotal studies found the mean percentage change in MRI volume of submental fat at Visit 9 was -8.87% in the 2 mg/cm^2 groups and 1.51% in the placebo groups. The mean percentage change in calliper thickness of submental fat at Visit 9 was -19.9% in the 2 mg/cm^2 groups and -7.3% in the placebo groups. The ISE performed subgroup analyses by age group, gender, race, baseline severity, and baseline skin laxity and did not demonstrate any subgroup effects on treatment.

7.4. Evaluator's conclusions on clinical efficacy

The pivotal studies demonstrated that deoxycholic acid was superior to placebo in reducing submental fat. In Study 22, using the dosing regimen proposed by the sponsor, there was a statistically and clinically significant decrease in submental fat. There was improvement in the severity of submental fat using severity scales: 179 (70.0%) in the 2 mg/cm^2 group and 47 (18.6%) in the placebo had a composite 1-grade improvement in submental fat; 34 (13.4%) in the 2 mg/cm^2 group and none in the placebo had a composite 2-grade improvement in submental fat. There were 48 (51.10%) subjects in the 2 mg/cm^2 group and five (5.1%) in the placebo group with a ≥ 10% reduction in MRI determined submental fat volume from baseline. The LS mean (95% CI) change in submental fat thickness as measured by MRI was -18.4% (20.7% to -16.0%) for the 2 mg/cm^2 group and 0.9% (-1.4% to 3.2%) for the placebo group. The change in submental fat thickness measured by callipers was -25% in the 2 mg/cm^2 group and -7.5% in the placebo group. However there was no resulting increase in skin laxity.

In Study 23 for composite 1-grade SMFRS responders there were 171 (66.5%) in the 2 mg/cm^2 group and 57 (22.2%) in the placebo group and for composite 2-grade SMFRS responder there were 48 (18.6%) in the 2 mg/cm^2 group and eight (3.0%) in the placebo group. There were 45 (40.2%) subjects in the 2 mg/cm^2 group and six (5.2%) in the placebo group with a ≥ 10% reduction in MRI determined submental fat volume from baseline. The LS mean (95% CI) change in submental thickness measured by MRI, was -8.5% (-11.0% to -6.1%) for the 2 mg/cm^2 and 1.3% (-1.1% to 3.6%) for the placebo group. The change in submental thickness measured by callipers was -22% in the 2 mg/cm^2 group and -8% in the placebo group. There was no resulting increase in skin laxity.

The pooled analysis of the pivotal studies found the mean percentage change in MRI volume of submental fat at Visit 9 was -8.87% in the 2 mg/cm^2 groups and 1.51% in the placebo groups. The mean percentage change in calliper thickness of submental fat at Visit 9 was -19.9% in the 2 mg/cm^2 groups and -7.3% in the placebo groups.

The studies performed using the BA free formulation (Study 16 and Study 17) also supported the choice of a 2 mg/cm^2 dosing regimen over the 1 mg/cm^2 dosage regimen. Although performed with a different formulation and fewer treatment sessions, these studies also supported efficacy.

The long-term follow-up studies demonstrated maintenance of effect for up to 4 years: Study 26 for 1 year; Study 12 for 4 years and Study 1403740 for 2 years.

The pivotal studies were conducted in a population similar to that identified in the product information document. There were few subjects older than 65 years and these patients may be considered unsuitable for this treatment. The study population was generally healthy but had a higher BMI than the general population. There were no subgroup characteristics that influenced efficacy.

The studies were appropriately designed. The outcome measures were developed and validated by the sponsor. These measures were appropriate for demonstrating efficacy, however the

necessity for the sponsor to develop definitions and measures in order to perform the studies reflects that the indication has not been identified as a disease. The studies were appropriately powered and the statistical tests were appropriate.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies safety data were collected for adverse events (AE), laboratory tests and vital signs.

8.1.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as the primary outcome.

8.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data for AEs, laboratory tests and vital signs.

8.1.4. Other studies evaluable for safety only

8.1.4.1. Study 10

Study 10 was a multicentre, open label study to obtain abdominal wall tissue for histopathology. The study was conducted at two centres in the US from November 2008 to March 2009. The doses used were:

1. 180 mg in 1, 2, 4 and 8 mg/cm^2 patches; 0.2 mL or 0.4 mL injections, 1.0 cm apart

2. 232 mg in 1, 2, 4 and 8 mg/cm^2 patches; 0.2 mL or 0.4 mL injections, 0.7 cm or 1.0 cm apart.

The treatments were administered into the abdominal wall by subcutaneous injection. There were 14 subjects included in the study. The histological changes were confined to the fat pannus. The observed histological changes included adipocyte necrosis, acute inflammation and small vessel damage. There was destruction of neutrophils. The histological changes were more marked at higher doses. At Day 28 post-dose there was adipocyte necrosis, lipid lakes, septal fibrosis, and lobular atrophy. Septae were often thickened by dense fibrous connective tissue. There were four TEAEs in one subject: erythema, irritation and vesicles at the injection site. There were no deaths, serious adverse events (SAE) or discontinuations due to adverse events (DAE).

8.1.4.2. Study 19

Study 19 was a multicentre, double blind, randomised, within subject bilateral paired comparison (BA containing versus BA free formulations) single dose study of safety and comfort. The study was conducted at two sites in the US from September to October 2010. The study included healthy subjects with submental fat. The study treatments were deoxycholic acid as both a BA-containing and BA-free formulation, 2 mg/cm^2, 10 mg/mL (1.0%).

The treatments were administered as a single treatment, with a total dose of 36 mg, one formulation to each side, and randomly allocated. The outcome measures were pain comparison score, Visual Analog Pain rating scale (VAS), AEs, laboratory tests, and vital signs. The study included 24 subjects of whom 19 (79.2%) were female and 5 (20.8%) were male, with an age range of 26 to 62 years. The results for pain and TEAEs are discussed under Section: Injection site pain and Section: Treatment-related adverse events respectively. There were no deaths, SAEs or DAEs.

8.1.4.3.   Study 04

Study 04 was a randomised, double blind, placebo controlled, sequential dose, escalation, parallel group safety and efficacy study of deoxycholic acid in subjects with superficial lipomas. The study was conducted at a single centre in the US from January to November 2007. The study treatment was deoxycholic acid 5 mg/mL (0.5%), 10 mg/mL (1.0%), 20 mg/mL (2.0%), 40 mg/mL (4.0%) and placebo. The treatments were administered as two injections into superficial lipomas 28 days apart. None of the subjects had complete clearance of any of the lipomas or at least 75% decrease in size of the lipoma. None of the subjects reported good or excellent response at end of study. All of the subjects reported injection site AEs. In the 12 active treatment subjects there was erythema in 12, induration in 11, pain in 11, and bruising in 10. There were no deaths, SAEs or DAEs. One subject reported elevated transaminases.

8.1.4.4.   Study 05

Study 05 was a multicentre, randomised, double blind, placebo controlled, parallel group safety, efficacy and long term follow up in subjects with superficial lipoma. The study was conducted at six centres in the US from November 2007 to August 2008. The study treatments were deoxycholic acid 10 mg/mL (1.0%), 20 mg/mL (2.0%), or 40 mg/mL (4.0%) and placebo. Treatments were administered as four injections into lipomas 28 days apart. The study included 61 subjects. Although there was some reduction in size, none of the subjects in the 1.0% or 2.0% treatment groups and only one (7.1%) in the 4.0% group had complete clearance. Two (13.3%) in the 1.0%, one (6.7%) in the 2.0%, two (14.3%) in the 4.0% and two (11.8%) in the placebo group had ≥ 75% clearance. TEAEs were reported in 12 (80.0%) subjects in the 1.0%, 13 (86.7%) in the 2.0%, 14 (93.3%) in the 4.0% and 12 (70.6%) in the placebo groups. There were no deaths. SAEs were reported in one (6.7%) subject in the 1.0%, none in the 2.0%, one (6.7%) in the 4.0% and none in the placebo groups. DAE was reported in one (6.7%) in the 1.0%, none in the 2.0%, three (20.0%) in the 4.0% and none in the placebo groups.

8.1.5.   Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.2.   Patient exposure

The sponsor states in the ISS submitted for evaluation that 1,549 subjects have been treated with Belkyra for the indication of submental fat. There were 1050 subjects treated with the dose proposed for marketing, 2 mg/cm^2. There were 424 subjects exposed to six doses of 2 mg/cm^2. There were 1172 females and 377 males; 16 subjects were aged ≥ 65 years and none aged < 18 years. There were 1334 White, 22 Asian, 98 Black and 95 subjects of other race groups. There were 301 subjects exposed to 1 mg/cm^2, 1050 to 2 mg/cm^2 and 198 to > 2 mg/cm^2. Exposure was limited to up to 6 consecutive treatment sessions with approximately 4-week treatment free intervals. Two subjects were exposed during pregnancy.

For the studies submitted for evaluation, patient exposure was as follows:

- In Study 08 there were 24 subjects exposed to submental deoxycholic acid, at doses ranging from 24 mg to 198 mg, and concentrations ranging from 0.5% to 4.0%.

- In Study 30 there were 5 subjects exposed to deoxycholic acid 100 mg by subcutaneous injection as a single dose.

- In Study 32 there were 12 subjects exposed to 100 mg deoxycholic acid in BA-containing formulation, and 12 exposed to the BA-free formulation by subcutaneous injection as a single dose.

- In Study 18 ten subjects were treated with deoxycholic acid 100 mg administered into abdominal wall fat.

- In Study 24 there were 55 subjects were exposed to 100 mg deoxycholic acid administered into submental fat and 54 subjects were exposed to 200 mg.

- In Study 03 there were 20 subjects exposed to 24 mg (1 mg/cm^2), 20 to 48 mg (2 mg/cm^2), and 22 to 96 mg (4 mg/cm^2) for up to 4 doses.

- In Study 07 there were 24 subjects exposed to 4 mg/cm^2, 0.2 mL/0.7 cm grid; 13 to 2 mg/cm^2, 0.2 mL/1.0 cm grid; and 20 to 4 mg/cm^2, 0.4 mL/1.0 cm grid.

- In Study 15 there were 41 subjects exposed to 1 mg/cm^2, with 33 (80.5%) exposed for the full 6 treatments, and 43 exposed to 2 mg/cm^2, with 28 (65.1%) exposed to the full 6 treatments.

- In Study 22 there were 256 subjects exposed to 2 mg/cm^2 with 164 (64.1%) exposed to all six treatment episodes.

- In Study 23 there were 258 subjects exposed to 2 mg/cm^2 with 140 (54.3%) exposed to all six treatment episodes.

- In Study 16 (using BA free formulations) there were 119 subjects exposed to 1 mg/cm^2 with 89 (74.8%) exposed to all four treatment episodes and 121 subjects exposed to 2 mg/cm^2 with 87 (71.9%) exposed to all four treatment episodes.

- In Study 17 (using BA free formulations) there were 118 subjects exposed to 1 mg/cm^2 with 102 (86.4%) exposed to all four treatment episodes and 122 subjects exposed to 2 mg/cm^2 with 90 (73.8%) exposed to all four treatment episodes.

- In Study 26 there were 165 subjects exposed to 2 mg/cm^2 with 92 (55.8%) receiving all 6 treatments. There was follow-up for 12 months post-treatment.

- In Study 12 there were 138 subjects treated with deoxycholic acid for submental fat who had completed Study 03, Study 07 and Study 15 and who were followed up for up to 48 months.

- In Study 1403740 there were 135 subjects treated with deoxycholic acid for submental fat who had completed Study 16 or Study 17 followed up for 24 months.

- In Study 10 there were 14 subjects exposed to either one or two administrations to the abdominal wall of either 180 or 232 mg.

8.3. Adverse events

8.3.1.   All adverse events (irrespective of relationship to study treatment)

8.3.1.1.   Pivotal studies

Study 22

There were 2604 TEAEs reported in 249 (96.9%) subjects in the 2 mg/cm^2 group and 1350 in 216 (87.1%) in the placebo group. The most common TEAEs were administration site related. Injection site anaesthesia was reported in 172 (66.9%) subjects in the 2 mg/cm^2 group and 11 (4.4%) in the placebo group. Injection site pain was reported in 168 (65.4%) subjects in the 2 mg/cm^2 group and 58 (23.4%) in the placebo group. Injection site oedema was reported in 136 (52.9%) subjects in the 2 mg/cm^2 group and 54 (21.8%) in the placebo group. Injection site induration was reported in 47 (18.3%) subjects in the 2 mg/cm^2 group and 4 (1.6%) in the placebo group. Nerve injury was reported in 10 subjects in the 2 mg/cm^2 group and none in the placebo group. All episodes resolved.

Study 23

There were 2934 TEAEs reported in 252 (97.7%) subjects in the 2 mg/cm^2 group and 1806 in 236 (92.2%) in the placebo group. The most common TEAEs were administration site related. Injection site anaesthesia was reported in 169 (65.5%) subjects in the 2 mg/cm^2 group and 18 (7.0%) in the placebo group. Injection site pain was reported in 190 (73.6%) subjects in the 2 mg/cm^2 group and 100 (39.1%) in the placebo group. Injection site oedema was reported in 175 (67.8%) subjects in the 2 mg/cm^2 group and 93 (36.3%) in the placebo group. Injection site induration was reported in 78 (28.3%) subjects in the 2 mg/cm^2 group and 9 (3.5%) in the placebo group. Nerve injury was reported in 11 subjects in the 2 mg/cm^2 group and two in the placebo group. All episodes resolved.

8.3.1.2. Other studies

Study 08

Study 08 investigated the effects of deoxycholic acid concentrations of 0.5%, 1%, 2%, and 4%; injection volumes of 0.2 mL and 0.4 mL, and grid sizes of 0.7 cm and 1 cm. There were fewer TEAEs in the 0.5% group but the other groups had a similar frequency of TEAEs. The most commonly reported TEAEs were at the administration site with pain in 22 (91.7%) subjects, anaesthesia in 21 (87.5%), erythema in 21 (87.5%), bruising in 18 (75%), induration in 16 (66.7%), oedema in 13 (54.2%), irritation in 8 (33.3%), pruritus in 8 (33.3%) and nodule in 3 (12.5%). These TEAEs were less frequent with the 0.5% concentration.

Study 30

There were 38 TEAEs overall, 22 with submental fat administration and 16 with abdominal administration. Injection site pain occurred in five subjects for both administrations.

Study 32

All 24 subjects reported TEAEs. The TEAEs were mostly at the administration site. All subjects reported injection site oedema and pain. Erythema, anaesthesia and haematoma were common in both treatment groups (both BA-containing and BA-free formulations). The intensity and recovery of administration site TEAEs was similar for the two treatment groups.

Study 18

There were 41 TEAEs in 10 (100%) subjects of which 40 were considered to be treatment related. All subjects reported administration site pain and haematoma.

Study 24

There were 183 TEAEs in 54 (98.2%) subjects in the 100 mg deoxycholic acid group, 193 TEAEs in 53 (98.1%) subjects in the 200 mg group, 13 TEAEs in 10 (18.2%) subjects in the moxifloxacin group and 62 TEAEs in 33 (61.1%) subjects in the placebo group. The excess in TEAEs in the deoxycholic acid group was due to a much greater incidence of administration site TEAEs.

Study 03

TEAEs were reported in 20 (100%) subjects in the 24 mg (1 mg/cm^2) group, 19 (95.0%) in the 48 mg (2 mg/cm^2) group, 22 (100%) in the 96 mg (4 mg/cm^2) group and 21 (95.5%) in the placebo group. The TEAEs were predominantly administration site related. Administration site pain occurred at a similar frequency for all four treatments but was more severe in the higher dose deoxycholic acid group. Oedema, bruising, anaesthesia, induration, nodule, and erythema were more common with deoxycholic acid, but not related to dose.

Study 07

TEAEs were reported in all subjects in the study. The most commonly reported TEAEs were administration site related. Pain, anaesthesia and induration were more common with

deoxycholic acid than placebo and most common in the 0.2 mL/1.0 cm group. Pain intensity VAS scores were similar for all four treatments.

Study 15

TEAEs were reported in 40 (97.6%) subjects in the 1 mg/cm^2 group, 41 (95.3%) subjects in the 2 mg/cm^2 group and 44 (97.8%) subjects in the placebo group. The TEAEs were predominantly administration site related. Injection site anaesthesia was more common with deoxycholic acid and reported in 26 (63.4%) subjects in the 1 mg/cm^2 group, 26 (60.5%) subjects in the 2 mg/cm^2 group and four (8.9%) subjects in the placebo group. Induration was more common with deoxycholic acid with 11 (28.8%) subjects in the 1 mg/cm^2 group, 14 (32.6%) subjects in the 2 mg/cm^2 group and five (11.1%) subjects in the placebo group. Injection site pain was more common with deoxycholic acid, reported in 29 (70.7%) subjects in the 1 mg/cm^2 group, 23 (53.5%) subjects in the 2 mg/cm^2 group and 13 (28.9%) subjects in the placebo group. Pruritus and swelling were also more common with deoxycholic acid.

Study 16

Study 16 used BA free formulations and TEAEs were reported in 114 (95.8%) subjects in the 1 mg/cm^2 group, 116 (95.9%) subjects in the 2 mg/cm^2 group and 89 (73.0%) subjects in the placebo group. The most frequently reported TEAEs were administration site related, and these occurred at similar frequency in the 1 mg/cm^2 and 2 mg/cm^2 groups (112 (94.1%) and 115 (95.0%) subjects respectively) and lesser frequency in the placebo group (71 (58.2%) subjects).

Study 17

Study 17 used BA free formulations and TEAEs were reported in 117 (99.2%) subjects in the 1 mg/cm^2 group, 121 (99.2%) subjects in the 2 mg/cm^2 group and 90 (78.9%) subjects in the placebo group. The most frequently reported TEAEs were administration site related, and these occurred at similar frequency in the 1 mg/cm^2 and 2 mg/cm^2 groups (116 (98.3%) and 121 (99.2%) subjects respectively) and lesser frequency in the placebo group (80 (70.2%) subjects).

Study 26

At a dose of 2 mg/cm^2 there were 2030 TEAEs in 160 (97.0%) subjects. The TEAEs occurring in > 10% subjects were all administration site related.

Study 19

There were 163 TEAEs in 24 (100%) subjects. Of the TEAEs 158 (96.9%) were administration site related of which pain (n = 67), erythema (n = 26), swelling (n = 22), oedema (n = 16), anaesthesia (n = 10), haematoma (n = 9), paraesthesia (n = 6), and injection site reaction (n = 2) were reported TEAEs.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. *Pivotal studies*

Study 22

There were 2113 treatment related TEAEs reported in 236 (91.8%) subjects in the 2 mg/cm^2 group and 836 in 182 (73.4%) in the placebo group. These AEs were predominantly administration site related.

Study 23

There were 2436 treatment related TEAEs reported in 251 (97.3%) subjects in the 2 mg/cm^2 group and 1259 in 208 (81.3%) in the placebo group. These AEs were predominantly administration site related.

8.3.2.2. Other studies

Study 24

Treatment related TEAEs were reported in in 54 (98.2%) subjects in the 100 mg deoxycholic acid, 53 (98.1%) in the 200 mg, three (5.5%) in the moxifloxacin and 27 (50.0%) in the placebo groups respectively.

Study 03

Treatment related TEAEs were reported in 20 (100%) subjects in the 24 mg (1 mg/cm^2), 19 (95.0%) in the 48 mg (2 mg/cm^2), 21 (95.5%) in the 96 mg (4 mg/cm^2) and 20 (90.9%) in the placebo group respectively.

Study 07

Treatment area associated TEAEs were reported in all subjects in the study.

Study 15

Treatment area associated TEAEs were reported in 40 (97.6%) subjects in the 1 mg/cm^2, 39 (90.7%) in the 2 mg/cm^2 group and 42 (93.3%) in the placebo group respectively. Treatment study material associated TEAEs were reported in 40 (97.6%) subjects in the 1 mg/cm^2, 39 (90.7%) in the 2 mg/cm^2 and 40 (88.9%) in the placebo group respectively.

Study 16

Study 16 used BA free formulations. Treatment related TEAEs were reported in 108 (90.8%) subjects in the 1 mg/cm^2 group, 115 (95.0%) in the 2 mg/cm^2 group and 62 (50.8%) in the placebo group.

Study 17

Study 17 used BA free formulations, treatment related TEAEs were reported in 116 (98.3%) subjects in the 1 mg/cm^2 group, 120 (98.4%) in the 2 mg/cm^2 group and 69 (60.5%) in the placebo group. Five subjects had injection site nerve damage, one of which had not completely resolved by the end of the study.

Study 26

At a dose of 2 mg/cm^2 there were 1803 treatment area associate TEAEs in 158 (95.8%) subjects. Five subjects were reported with injection site ulcers/erosion, and two subjects were reported with injection site nerve injuries.

Study 12

Study 12 was a long term follow-up study of subjects that had completed Study 03, Study 07 or Study 15. There were 14 treatment related TEAEs in 12 (8.7%) subjects. All were administration site related. There were five (3.6%) subjects with injection site induration, three (2.2%) with injection site alopecia, two (1.4%) with injection site nodule and two (1.4%) with injection site pruritus.

Study 1403740

TEAEs associated with the treatment area were reported in five (8.3%) subjects in the 5 mg/mL group, seven (9.3%) in the 10 mg/mL and none in the placebo group. In the 5 mg/mL group there was worsening of a benign parathyroid tumour that was not considered to be related to study drug and an injection site abscess. In the 10 mg/mL group four subjects had injection site nodules.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies

Study 22

There were no deaths. There were 10 SAEs reported in six (2.3%) subjects in the 2 mg/cm^2 group and 15 SAEs in 12 (4.8%) subjects in the placebo group. There was no apparent pattern to the SAEs.

Study 23

There were two deaths, one in the 2 mg/cm^2 group (motor vehicle accident) and one in the placebo group (heroin toxicity). There were 11 SAEs reported in 7 (2.7%) subjects in the 2 mg/cm^2 group (ovarian/uterine cancer; uterine prolapse/cystocele/rectocele/ uterine leiomyoma; gastro-oesophageal reflux; intervertebral disc operation; motor vehicle accident; recurrent breast cancer; urinary tract infection) and 10 SAEs in 10 (3.9%) subjects in the placebo group (menometrorrhagia; acute congestive heart failure; pancreatitis; vaginal repair; transient ischaemic attack; breast cancer; heroin toxicity; diverticulitis; influenza; macrophage infiltrate of spinal cord; hip surgery). There was no apparent pattern to the SAEs.

8.3.3.2. Other studies

Study 03

In Study 03 there were no deaths or SAEs.

Study 08

In Study 08 there were no deaths or SAEs.

Study 18

In Study 18 there were no deaths or SAEs.

Study 30

In Study 30 there were no deaths or SAEs.

Study 32

In Study 32 there were no deaths or SAEs.

Study 07

There was one death reported in the study in a subject in the 0.2 mL/1.0 cm grid group. The same subject had two SAEs reported, bile duct cancer and cardiac arrest. The subject had elevated AST and ALT at screening and was considered to be enrolled in error.

Study 15

There were no deaths. One (2.3%) subject in the 2 mg/cm^2 group reported a SAE of intracranial hypotension considered to be unrelated to study treatment.

Study 16

Study 16 used BA free formulations. There were no deaths. SAEs were reported in one (0.8%) subject in the 1 mg/cm^2 group (depression), three (2.5%) subjects in the 2 mg/cm^2 group (abdominal adhesions; gastric cancer; spontaneous abortion) and two (1.6%) subjects in the placebo group (chronic tonsillitis/ sleep apnoea; non-Hodgkin's lymphoma).

Study 17

Study 17 used BA free formulations. There were no deaths. SAEs were reported in one (0.8%) subject in the 1 mg/cm^2 group, two (1.6%) subjects in the 2 mg/cm^2 group and four (3.5%)

subjects in the placebo group One subject in the 2 mg/cm^2 group had injection site nerve damage recorded as a SAE.

Study 26

At a dose of 2 mg/cm^2 there was one death (cardiac death 163 days after last treatment). There were eight SAEs reported in seven (4.2%) subjects (cardiac death; severe thyroid cancer; severe colon cancer; severe anxiety attack; severe diverticulitis; moderate arteriosclerosis/ stent replacement; mild cervical polyp).

Study 1403740

There were no deaths. SAEs were reported in three (5.0%) subjects in the 5 mg/mL group (worsening of parathyroid tumour; bacterial enterocolitis; vestibular neuronitis), two (2.7%) subjects in the 10 mg/mL (worsening of hyperthyroidism; limb injury) and one (1.5%) subject in the placebo group (fractured radius).

8.3.4. Discontinuation due to adverse events

8.3.4.1. *Pivotal studies*

Study 22

DAE was reported for six (2.3%) subjects in the 2 mg/cm^2 group and one (0.4%) subject in the placebo group. There were 19 (7.4%) subjects in the 2 mg/cm^2 group and three (1.2%) in the placebo group who did not receive all 6 treatments because of TEAEs.

Study 23

DAE was reported for 6 (2.3%) subjects in the 2 mg/cm^2 group (injection site pain; injection site numbness/pain/swelling; injection site anaesthesia; injection site numbness/induration/pruritus/erythema/oedema/paraesthesias/dysphagia; motor vehicle accident; injection site oedema/pain) and 3 (1.2%) subjects in the placebo group (acute congestive heart failure; heroin toxicity; macrophage infiltrate of spinal cord).

8.3.4.2. *Other studies*

Study 03

In Study 03 there were no DAEs.

Study 08

In Study 08 there were no DAEs.

Study 18

In Study 18 there were no DAEs.

Study 30

In Study 30 there were no DAEs.

Study 32

In Study 32 there were no DAEs.

Study 07

There were 3 subjects with DAEs, 2 in the 0.2 mL/0.7 cm group (injection site induration; dysphagia) and one in the 0.2 mL/1.0 cm (bile duct cancer and cardiac arrest/death).

Study 15

DAEs occurred in 2 (4.9%) subjects in the 1 mg/cm^2 group (drooping/weakness right side of mouth; mild rash), two (4.7%) subjects in the 2 mg/cm^2 group (injection site

haematoma/swelling/pain/induration; intracranial hypotension) and no subjects in the placebo group.

Study 16

Study 16 used BA free formulations. Withdrawal from study drug was reported for 9 (7.6%) subjects in the 1 mg/cm^2 group, 10 (8.3%) subjects in the 2 mg/cm^2 group and one subject (0.8%) in the placebo group. DAEs were reported for 2 (1.7%) subjects in the 1 mg/cm^2 group, 2 subjects (1.7%) in the 2 mg/cm^2 group and one subject (0.8%) in the placebo group.

Study 17

Study 17 used BA free formulations. Withdrawal from study drug was reported in six (5.1%) subjects in the 1 mg/cm^2 group, 14 (11.5%) subjects in the 2 mg/cm^2 group and one (0.9%) subject in the placebo group. DAEs were reported in two (1.7%) subjects in the 1 mg/cm^2 group (injection site pain for both), none in the 2 mg/cm^2 group and one (0.9%) subject in the placebo group (syncope).

Study 26

At a dose of 2 mg/cm^2 there were seven TEAEs leading to DAE in six (3.6%) subjects.

8.4.   Laboratory tests

8.4.1.   Liver function

8.4.1.1.   Pivotal studies

Study 22

In Study 22, elevated alanine transaminase (ALT) was reported in one (0.4%) subject in the 2 mg/cm^2 group and none in the placebo group. Elevated aspartate transaminase (AST) was reported in one (0.4%) subject in the 2 mg/cm^2 group and none in the placebo group.

Study 23

In Study 23, elevated ALT was reported in one (0.4%) subject in the 2 mg/cm^2 group and 2 (0.8%) subjects in the placebo group. Elevated AST was reported in no subjects in the 2 mg/cm^2 group and 2 (0.8%) subjects in the placebo group.

8.4.1.2.   Other studies

In Study 32, Study 18 and Study 03 there were no clinically significant abnormalities in liver function.

Study 07

One subject in the 0.2 mL/0.7 cm group had mild elevation of ALT (< 3 x upper limit of normal) peaking at Week 16.

Study 15

One (2.3%) subject in the 2 mg/cm^2 group had elevation of ALT as a TEAE.

Study 26

At a dose of 2 mg/cm^2 two subjects had elevated ALT and AST reported as TEAEs.

8.4.2.   Kidney function

8.4.2.1.   Pivotal studies

Study 22

In Study 22 no abnormalities in renal function were reported as TEAEs.

Study 23

In Study 23 no abnormalities in renal function were reported as TEAEs.

8.4.2.2. Other studies

In Study 32 and Study 18, there were no clinically significant abnormalities in renal function.

Study 16

In Study 16 which used BA free formulations, one (0.8%) subject in the 2 mg/cm^2 group had elevation of creatinine reported as a TEAE.

Study 26

In Study 26, at a dose of 2 mg/cm^2 2 subjects had elevated serum creatinine and one subject had decreased glomerular filtration rate (GFR) reported as a TEAE.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

Study 22

In Study 22, elevated serum triglycerides were reported in one (0.4%) subjects in the 2 mg/cm^2 group and one (0.4%) subject in the placebo group. Decreased tri-iodothyronine was reported in 5 (1.9%) subjects in the 2 mg/cm^2 group and 4 (1.6%) in the placebo group.

Study 23

In Study 23, elevated serum triglycerides were reported in one (0.4%) subject in the 2 mg/cm^2 group and 4 (1.6%) subjects in the placebo group. Decreased tri-iodothyronine was reported in 3 (1.2%) subjects in the 2 mg/cm^2 group and 4 (1.6%) in the placebo group.

8.4.3.2. Other studies

Study 08

In Study 08, mean serum triglyceride concentrations were increased in the 198 mg dose level cohort at 364 mg/dL on Day 2 and 380 mg/dL on Day 3 (normal range 37 to 288 mg/dL). One subject in the 198 mg cohort had elevated triglycerides pre-study (510 mg/dL) and had a maximum of 837 mg/dL during the study.

Study 03

In Study 03, one subject in the 4 mg/cm^2 group had elevated serum triglycerides (maximum concentration 10.2 mmol/L, reference range 0 to 2.3 mmol/L).

Study 15

In Study 15, at 12 weeks after the last treatment (Week 32), the median (min, max) increases in triglycerides was 11.0 (-172 to 554) mg/dL in the 1 mg/cm^2 group, 21.0 (-162 to 339) mg/dL, in the 2 mg/cm^2 group, and 3.5 (-290 to 133) mg/dL in the placebo group. One (2.3%) subject in the 2 mg/cm^2 group and one (2.2%) subject in the placebo group had elevation of blood triglycerides as a TEAE.

Study 07

In Study 07, one subject in the 0.2 mL/0.7 cm group had elevation of thyroid stimulating hormone (TSH) at baseline that peaked at Week 12.

Study 15

One (2.3%) subject in the 2 mg/cm^2 group had decreased TSH as a TEAE and one subject in the 1 mg/cm^2 group and one (2.3%) subject in the 2 mg/cm^2 group had elevation of TSH as a TEAE.

Study 16

In Study 16 which used BA free formulations, hypertriglyceridaemia was reported as a TEAE in one (0.8%) subject in the 1 mg/cm^2 group, two (1.7%) in the 2 mg/cm^2 group and one (0.8%) in the placebo group. Hypercholesterolaemia was reported as a TEAE in one (0.8%) subject in the 1 mg/cm^2 group, one (0.8%) in the 2 mg/cm^2 group and one (0.8%) in the placebo group.

Study 17

In Study 17 which used BA free formulations, increased blood cholesterol was reported as a TEAE in one subject in the 2 mg/cm^2 group. Increased serum lipids were reported as a TEAE in one subject in the 1 mg/cm^2 group.

Study 26

In Study 26, at a dose of 2 mg/cm^2, 11 (6.7%) subjects had elevated serum triglycerides and 5 (3.0%) had elevated cholesterol reported as TEAEs.

8.4.4. Haematology

8.4.4.1. Pivotal studies

Study 22

In Study 22, no abnormalities in haematology were reported as TEAEs.

Study 23

In Study 23, decreased haemoglobin was reported in one (0.4%) subject in the 2 mg/cm^2 group.

8.4.4.2. Other studies

In Study 32, Study 18 and Study 03, there were no clinically significant abnormalities in haematology.

Study 07

In Study 07, one subject in the 0.4 mL/1.0 cm group had anaemia and neutropenia at Week 16 that resolved by Week 24.

Study 17

In Study 17 which used BA free formulations, increased platelet count was reported as a TEAE in one subject in the 2 mg/cm^2 group.

8.4.5. Vital signs

8.4.5.1. Pivotal studies

Study 22

In Study 22 there were no differences in vital signs between the treatment groups.

Study 23

In Study 23 there were no differences in vital signs between the treatment groups.

8.4.5.2. Other studies

In Study 16 and Study 17, which used BA free formulations, there were no differences between the study groups in vital signs.

Study 32

In Study 32, one subject in the BA-containing group experienced transient tachycardia 7 hours post-dose. For all subjects, there were no clinically significant abnormalities on Holter monitor recordings or 12-lead ECG.

8.4.5.3. *Injection site pain*

Study 08

Injection site pain was greatest in the 198 mg cohort and was greatest in intensity at 60 minutes post administration. The VAS scores (on a 100 mm scale with 100 mm being the most severe) ranged from 44 to 77 mm at that time point. The VAS scores at 60 minutes for the other cohorts ranged from 1 to 68 mm. At 48 hours the VAS scores ranged from 0 to 46 mm and at 72 hours, 0 to 24 mm.

Study 19

Using the pain comparison scale there was greater pain with the BA free formulation than with the BA containing formulation from the time of treatment to 4 hours post-treatment (see Figure 4, below). For VAS scores of pain there was greater pain in the BA free side than in the BA containing side from time of treatment to 60 minutes post-treatment (See Figure 4 below).

Figure 4: Pain Comparison Scale results at treatment and post-treatment
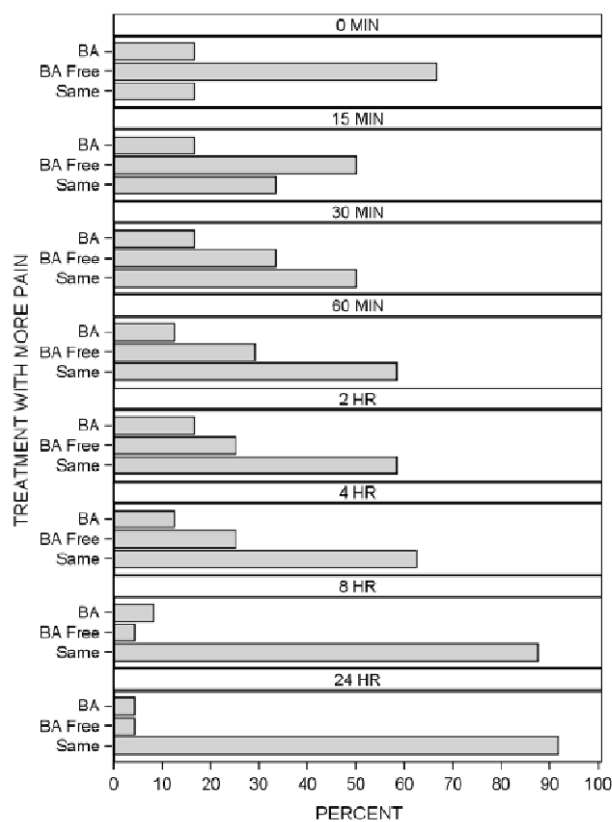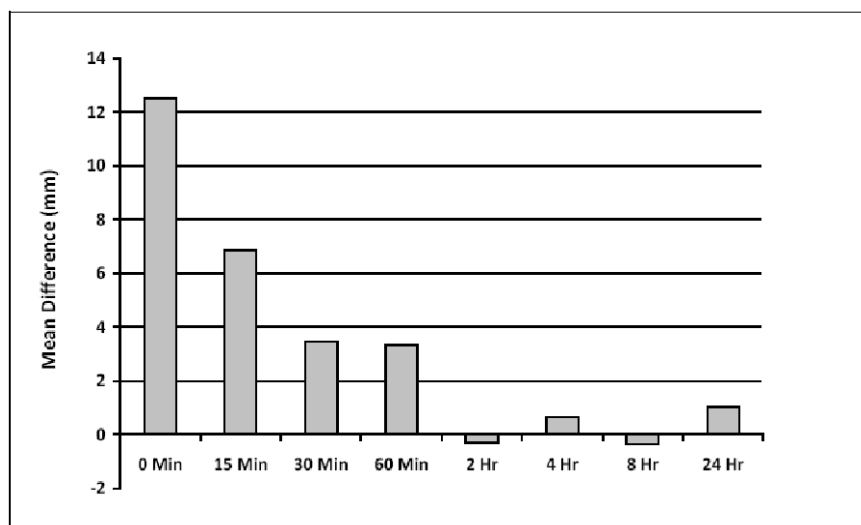
Figure 5: Mean difference in VAS Scores (BA-free formulation minus BA-formulation) at treatment and post-treatment

8.5. Post-marketing experience

8.5.1. Post-Marketing Data

There were no post-marketing data included in the submission.

8.6. Risk management plan

8.6.1. Summary of safety concerns:

The sponsor has identified the following Important Identified Risks:

- Injection site nerve injury
- Injection site skin ulceration.

The sponsor has identified the following Important Potential Risks:

- Use in patients or for conditions or with doses not yet studied.

The sponsor has identified the following missing information:

- None.

The sponsor proposes to monitor these safety issues using 'routine pharmacovigilance and monitoring of adverse drug reactions (ADR) from the Marketing Authorisation Holder's (MAH) database'. The sponsor also intends to address the Important Identified Risks by giving detailed dosing and administration information in the product information and by conducting a Healthcare Professional (HCP) training program.

8.6.2. Evaluator's comments on the risk management plan

The Risk Management Plan (RMP) does not identify as important missing information safety in patients either < 18 years of age or > 65 years of age. These populations were not represented in the clinical trials and may be at risk of more severe local effects due to the effects of growth or aging.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Nerve injury

In the ISS nerve injury was reported in 19 (3.7%) subjects treated with deoxycholic acid and one (0.2%) treated with placebo. In Study 22 nerve injury was reported in 10 subjects in the 2 mg/cm^2 group and none in the placebo group. All episodes resolved. In Study 23 nerve injury was reported in 11 subjects in the 2 mg/cm^2 group and two in the placebo. All episodes resolved.

8.7.2. Dysphagia

In the ISS dysphagia was reported in 10 (1.9%) subjects treated with deoxycholic acid and one (0.2%) treated with placebo.

8.7.3. Liver toxicity

Liver toxicity was not identified as a safety issue in the data.

8.7.4. Haematological toxicity

Haematological toxicity was not identified as a safety issue in the data.

8.7.5. Serious skin reactions

Serious skin reactions were not identified as a safety issue in the data. In the ISS urticaria was reported in five (1.0%) subjects treated with deoxycholic acid and three (0.6%) treated with placebo.

8.7.6. Cardiovascular safety

Cardiovascular safety was not identified as a safety issue in the data.

8.7.7. Unwanted immunological events

Unwanted immunological events were not identified as a safety issue in the data.

8.8. Other safety issues

8.8.1. Safety in special populations

Patients < 18 years and > 65 years of age were under-represented in the development program. These special populations could be at risk of more severe reactions due to the effects of either growth or ageing.

8.8.2. Safety related to drug-drug interactions and other interactions

Interactions were not identified as a safety issue in the data.

8.9. Evaluator's overall conclusions on clinical safety

- Virtually all subjects treated with deoxycholic acid reported TEAEs and these were predominantly administration site related and can therefore be considered as treatment associated. In the pivotal studies around 70% of subjects reported administration site pain, 65% reported injection site anaesthesia and more than 50% reported injection site oedema. Approximately 4% reported nerve injury, which subsequently resolved.

- In the supportive studies the frequency of administration site reactions was not related to concentration however the intensity of administration site pain increased with increasing concentration.

- The frequency and intensity of administration site reactions were similar for BA containing and BA free formulations.

- There were few long term adverse effects in the long-term follow-up studies.

- There were four deaths in the development program none of which were attributed to treatment.

- There were few SAEs. There was no pattern for the SAEs that might suggest any treatment effect.

- DAE was uncommon but most of the DAEs were administration site related. Most subjects appear to have willing to continue with treatment in spite of the very high rate of administration site TEAEs. The completion rate for studies using the 2 mg/cm² dose level was 86.5%.

- Laboratory test abnormalities were evenly distributed between deoxycholic acid and placebo. Vital signs were not abnormal in the deoxycholic acid groups relative to placebo.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Deoxycholic acid, using the dosing regimen proposed for marketing by the sponsor, reduces the amount of submental fat. This was demonstrated by the sponsor using multiple outcome measures. The pivotal studies demonstrated that deoxycholic acid was superior to placebo in reducing submental fat.

In Study 22, using the dosing regimen proposed by the sponsor there was a statistically and clinically significant decrease in submental fat. There was improvement in the severity of submental fat using severity scales: 179 (70.0%) in the 2 mg/cm² group and 47 (18.6%) in the placebo had a composite 1-grade improvement in submental fat; 34 (13.4%) in the 2 mg/cm² group and none in the placebo had a composite 2-grade improvement in submental fat. There were 48 (51.10%) subjects in the 2 mg/cm² group and five (5.1%) in the placebo group with a ≥ 10% reduction in MRI determined submental volume from baseline. The LS mean (95% CI) change in submental fat thickness measured by MRI was -18.4% (-20.7% to -16.0%) for the 2 mg/cm² group and 0.9% (-1.4% to 3.2%) for the placebo group. The change in submental thickness measured by callipers was -25% in the 2 mg/cm² group and -7.5% in the placebo. There was no resulting increase in skin laxity.

In Study 23 for composite 1-grade SMFRS responder there were 171 (66.5%) in the 2 mg/cm² group and 57 (22.2%) in the placebo group and for composite 2-grade SMFRS responder there were 48 (18.6%) in the 2 mg/cm² group and eight (3.0) in the placebo group. There were 45 (40.2%) subjects in the 2 mg/cm² group and six (5.2%) in the placebo with a ≥ 10% reduction in MRI determined submental fat volume from baseline. The LS mean (95% CI) change in submental fat thickness measured by MRI was -8.5% (-11.0% to -6.1%) for the 2 mg/cm² and 1.3% (-1.1% to 3.6%) for the placebo group. The change in submental fat thickness, measured by callipers, was -22% in the 2 mg/cm² group and -8% in the placebo group. There was no resulting increase in skin laxity.

There was no apparent difference in efficacy between BA containing and BA free formulations.

The measured change in the objective measures of the amount of submental fat was less than would be expected from the changes in rating scales. The pooled analysis of the Pivotal studies found the mean percentage change in MRI volume of submental fat at Visit 9 was -8.87% in the 2 mg/cm² groups and 1.51% in the placebo groups. The mean percentage change in submental thickness measured by callipers at Visit 9 was -19.9% in the 2 mg/cm² groups and -7.3% in the placebo groups.

There were limited efficacy data in subjects aged >65 years and in non-White populations.

9.2.   First round assessment of risks

Deoxycholic acid in the proposed usage has a favourable safety profile. There were few deaths or SAEs and, apart from some local reactions, these were not attributable to the treatment. The treatment is clearly a painful process but most subjects appear to have been willing to continue with treatment in spite of the very high rate of administration site TEAEs. The completion rate for studies using the 2 mg/cm^2 dose level was 86.5%.

Virtually all subjects treated with deoxycholic acid reported TEAEs and these were predominantly administration site related and can therefore be considered to be treatment associated. In the pivotal studies around 70% of subjects reported administration site pain, 65% reported injection site anaesthesia and more than 50% reported injection site oedema. Approximately 4% reported nerve injury, which subsequently resolved.

In the supportive studies the frequency of administration site reactions was not related to concentration however the intensity of administration site pain increased with increasing concentration.

The frequency and intensity of administration site reactions were similar for BA containing and BA free formulations.

There were few long term adverse effects in the long-term follow-up studies.

There were limited safety data in subjects aged over 65 years and in non-White populations.

9.3.   First round assessment of benefit-risk balance

The benefit-risk balance of deoxycholic acid, given the proposed usage, is favourable.

In the opinion of the evaluator, submental fat is not a disease and deoxycholic acid in the proposed usage is a cosmetic treatment. The sponsor has not demonstrated that submental fat causes sufficient distress to result in physical or psychological harm. In the context of a cosmetic treatment however, the sponsor has demonstrated that deoxycholic acid is efficacious and has an acceptable tolerability for the subjects undergoing treatment. The sponsor has also defined an appropriate treatment regimen.

10. First round recommendation regarding authorisation

Deoxycholic acid (Belkyra) 10 mg/mL, solution for injection, glass vial, should be approved for the proposed indication:

> *Belkyra (deoxycholic acid) injection is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.*

11. Clinical questions

11.1.   Additional expert input

The evaluator does not have a recommendation for additional expert input.

11.2. Clinical questions

11.2.1. Pharmacokinetics

The evaluator does not have any questions relating to pharmacokinetics.

11.2.2. Pharmacodynamics

The evaluator does not have any questions relating to pharmacodynamics.

11.2.3. Efficacy

Q1. Does the sponsor intend to obtain further efficacy data in patients aged > 65 years?

Q2. Does the sponsor intend to obtain further efficacy data in populations other than Caucasian?

11.2.4. Safety

Q3. Does the sponsor intend to obtain further safety data in patients aged > 65 years?

Q4. Does the sponsor intend to obtain further safety data in populations other than Caucasian?

Q5. Does the sponsor intend to conduct extended long term follow-up studies to monitor the effects of aging in patients who have received deoxycholic acid for submental fat?

12. Second round evaluation of clinical data submitted in response to questions

The sponsor, in response to recommendations proposes to market a different formulation of deoxycholic acid. The sponsor now proposes to market a benzyl alcohol (BA) free formulation. The sponsor also proposes to change the name of the product from Kybella to Belkyra.

The pharmacokinetic data indicate a slightly higher systemic exposure to deoxycholic acid with the BA free formulation. In the opinion of the evaluator, this would not be expected to result in any decrease in efficacy or increase in adverse effects. The efficacy data demonstrate similar efficacy for the BA free formulation compared to the BA formulation. The Safety data indicated a similar safety profile for the BA free and BA containing formulations.

12.1. Efficacy

12.1.1. Question 1

- Does the sponsor intend to obtain further efficacy data in patients aged > 65 years?

12.1.1.1. Sponsor's response

The sponsor intends to examine efficacy in patients aged > 65 years in an ongoing study: Study 28; A multicentre, double-blind, placebo-controlled safety study of Belkyra (deoxycholic acid injection) for the reduction of localised subcutaneous fat in the submental area in subjects 65 to 75 years of age. The study includes 55 subjects in an active treatment group and 55 in a placebo group.

12.1.1.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.1.2. Question 2

- Does the Sponsor intend to obtain further efficacy data in populations other than Caucasian

12.1.2.1. Sponsor's response

The sponsor believes that pivotal Phase III Studies 22 and 23 provided sufficient data from non-Caucasian subjects to confirm that Belkyra is effective for these patients. A total of 133 non-Caucasian subjects (82 Black or African American, 21 Asian and 30 other) were enrolled in Studies 22 and 23 combined, 74 of whom were randomised to Belkyra and 59 of whom were randomized to placebo. The sponsor also plans to conduct a post-marketing study in the US that may include non-Caucasian subjects. The sponsor also claims that the lack of a subgroup effect indicates similar efficacy in the non-Caucasian population.

12.1.2.2. Clinical evaluator's comment

The Sponsor's response is not satisfactory. In the opinion of the Evaluator there are insufficient data to demonstrate efficacy in non-Caucasian populations.

As stated in the first-round assessment 'There were limited efficacy data in subjects aged > 65 years and in non-Caucasian populations.' The studies were not powered to be able to demonstrate efficacy in the subgroup analysis hence, given the small sample size of the study population that was non- Caucasian, it is not surprising that no subgroup effects were demonstrated. In the opinion of the clinical evaluator, it would be of importance in the Australian context to also demonstrate efficacy in the Asian population.

12.2. Safety

12.2.1. Question 3

- Does the sponsor intend to obtain further safety data in patients aged >65 years?

12.2.1.1. Sponsor's response

The sponsor intends to examine safety in patients aged > 65 years in an ongoing study: Study 28, A multicentre, double-blind, placebo-controlled safety study of Belkyra (deoxycholic acid injection) for the reduction of localised subcutaneous fat in the submental area in subjects 65 to 75 years of age. The study includes 55 subjects in an active treatment group and 55 in a placebo group.

12.2.1.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.2.2. Question 4

- Does the sponsor intend to obtain further safety data in populations other than Caucasian?

12.2.2.1. Sponsor's response

The sponsor has responded that in the development program, there did not appear to be any differences in the adverse effect profile on the basis of ethnicity.

12.2.2.2. Clinical evaluator's comment

The sponsor's response is not satisfactory. Only 21 Asian subjects were enrolled in the pivotal studies. This is an insufficient sample size to determine whether there may be differences in the adverse event profile in this subpopulation. The sponsor should be encouraged to provide post-marketing data that examines the effect of ethnicity on the adverse event profile.

12.2.3. Question 5

- Does the sponsor intend to conduct extended long term follow-up studies to monitor the effects of aging in patients who have received deoxycholic acid for submental fat?

12.2.3.1. Sponsor's response

No further extended long-term follow-up studies are planned to specifically monitor the effects of aging in patients who have received deoxycholic acid for submental fat.

12.2.3.2. Clinical evaluator's comments

The sponsor's response is not satisfactory. The effects of deoxycholic acid upon submental fat may be modified by aging. Such effects would only be determined by long term follow-up studies. The sponsor should be encouraged to perform long-term follow-up studies such as registry based studies.

12.3. Additional clinical information submitted for second round evaluation

The sponsor, in response to recommendations from the TGA and comments from the microbiology evaluator, proposes to market a different formulation of deoxycholic acid. The sponsor now proposes to market a BA free formulation. The sponsor also proposes to change the name of the product from Kybella to Belkyra.

The pharmacokinetic data indicate a slightly higher systemic exposure to deoxycholic acid with the BA free formulation (see Table 6 below). In the opinion of the evaluator, this would not be expected to result in any decrease in efficacy or increase in adverse effects. The efficacy data demonstrate similar efficacy for the BA free formulation compared to the BA formulation (as detailed in the evaluation of efficacy). The safety data indicated a similar safety profile for the BA free and BA containing formulations (as detailed in the evaluation of safety).

Table 6: Pharmacokinetic parameters of deoxycholic acid obtained before and after single SC dose administration

	Baseline (Day -1)		Postdose (Day 1)		Baseline-Adjusted	
	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} [a] (ng*h/mL)	4854 (2339)	6045 (3277)	7896 (2269)	10421 (4676)	3042 (1217)	4376 (3476)
C_{max} [a] (ng/mL)	324 (182)	441 (293)	1024 (304)	1036 (254)	822 (263)	784 (230)
t_{max} [b] (h)	12.0 (0, 24.0)	8.0 (0, 24.0)	0.3 (0.1, 1.1)	0.1 (0.1, 16.0)	NC	NC

[a] Presented as mean (± SD)
[b] Presented as median (minimum, maximum)
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; N= number of subjects; NC = Not calculated; SC = subcutaneous; SD = standard deviation; t_{max} = time to maximum observed concentration
Note: BLOQ = 25.6 ng/mL; values below 25.6 ng/mL were set to 0 in summary statistics analysis
Source: Table 6, Section 2.7.2

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Belkyra in the proposed usage are unchanged from those identified in the first round assessment of benefits.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Belkyra in the proposed usage are unchanged from those identified in the first round assessment of benefits.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of deoxycholic acid (Belkyra) given the proposed usage, is favourable.

In the opinion of the Evaluator, submental fat is not a disease and deoxycholic acid in the proposed usage is a cosmetic treatment. The sponsor has not demonstrated that submental fat causes sufficient distress to result in physical or psychological harm. In the context of a cosmetic treatment however, the sponsor has demonstrated that deoxycholic acid is efficacious and has an acceptable tolerability for the subjects undergoing treatment. The sponsor has also defined an appropriate treatment regimen.

14. Second round recommendation regarding authorisation

Deoxycholic acid (Belkyra) 10 mg/mL, solution for injection, glass vial, should be approved for the proposed indication:

> *Belkyra (deoxycholic acid) injection is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.*

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