Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Diltiazem hydrochloride

Proprietary Product Name: Ano-Cream

Sponsor: AFT Pharmaceuticals Pty Ltd

First round CER: September 2015

Second round CER: February 2016

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.
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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

Abbreviations	Meaning
AE	adverse event
AF	anal fissure
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrio-ventricular
BP	blood pressure
BUN	blood urea nitrogen
cf.	compared with
CI	confidence interval
CL/F	apparent plasma clearance
Cmax	maximum drug concentration
Cmin	minimum drug concentration
DTZ	diltiazem hydrochloride
DTZ 2%	diltiazem hydrochloride 2% w/w cream
DTZ 4%	diltiazem hydrochloride 4% w/w cream
ECG	electrocardiogram
FDA	US Food and Drug Administration
Ftop/Foral	relative bioavailability based on the ratio of the dose-adjusted AUC for topical administration to the AUC for oral administration
GCP	good clinical practice
GTN	glyceryl trinitrate
h	hour/s
HCl	hydrochloride

HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
IVRS	interactive voice response system
kel	elimination rate constant
LLOQ	lower limit of quantitation
LLQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRP	maximum resting pressure
n	number
N/A	not applicable
NO	nitric oxide
NRS	numerical rating scale
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamics
PGI-I	patient's global impression of improvement
PI	product information
PK	pharmacokinetics
PLA	placebo
PopPK	population PK analysis
PP	per protocol
PR	pulse rate
PT	preferred term
QoL	quality of life
RIPT	repeated insult patch test

SAE	serious adverse event
SAP	statistical analysis plan
SF-36	Short Form 36
SIS	skin irritation score
SLS	sodium lauryl sulphate
SOC	system organ class
t1/2	elimination half-life
TEAE	treatment emergent adverse events
TID	three-times daily
Tmax	time after dosing at which the maximal concentration is achieved
VAS	visual analogue scale

1. Introduction

This is a submission to extend the indication for diltiazem hydrochloride. The submission was originally for the trade name "Anoheal", later renamed to "Ano-Cream".

1.1. Drug class and therapeutic indication

Diltiazem hydrochloride is an inhibitor of L-type calcium channels. It inhibits calcium influx into myocardial cells, vascular smooth muscle and smooth muscle in the GI tract. Diltiazem is marketed under several brand names for the treatment of hypertension, angina and various cardiac rhythm disorders.

The proposed new indication is:

> *Anoheal 2% w/w cream is indicated in adults for the relief of pain associated with chronic anal fissure.*

1.2. Dosage forms and strengths

The submission proposes registration of the following dosage form and strength:

> *ANOHEAL cream in a 30g aluminium tube containing diltiazem cream 2% w/w. A nominal dose of 450 mg cream contains diltiazem hydrochloride 20 mg/g delivering 8.5 mg diltiazem hydrochloride per application.*

1.3. Dosage and administration

Diltiazem hydrochloride 8.5 mg TID given topically to the anal canal via a nominal application of 450 mg diltiazem 2% cream.

1.4. Other proposed changes to the PI

Not applicable.

2. Clinical rationale

Anal fissures occur in otherwise healthy subjects irrespective of race, age and gender with a life-time incidence of approximately 11% (Lock, 1977). Acute anal fissures may occur after the passage of an abnormally large or hard stool and a low fibre intake in Western diets is often implicated. Anal fissures are linear ulcers in the epithelium of the anal canal, occurring most commonly in the posterior midline. The diagnosis is made by direct visualisation and endoscopy is not usually required. Anal fissures typically cause bleeding and pain during defaecation which may last for two hours or more. Most acute anal fissures heal spontaneously but some become chronic. In patients with chronic anal fissure, pain after defaecation is persistent and associated with resting anal hypertonia and poor spontaneous relaxation as measured by ambulatory manometry. Higher anal sphincter pressures are associated with lower anorectal blood flow, and ischaemic ulceration in the posterior segment is widely assumed to be the cause of persistent fissures. In patients who fail to respond to conservative or medical therapy, surgeries such as sphincterotomy can restore normal blood flow. Surgery provides healing and symptomatic relief in 90-95% of subjects; however, surgery is commonly associated with mild to moderate faecal incontinence.

Medical therapies designed to reduce anal sphincter tone and reduce ischaemia have been widely used in the last 20 years (Carpeti, 1998). However, randomised, controlled trials of numerous therapies have largely failed to demonstrate improved AF healing rates compared with placebo. In a systematic review of nine medical therapies, treatments including GTN, nifedipine, botulinum

toxin, hydrocortisone, and diltiazem were considered only marginally superior to placebo (Nelson, 2004). An updated review conducted on behalf of the Cochrane Collaboration in 2012 reached the same conclusion with no evidence for the value of diltiazem compared with placebo (Nelson, 2012). GTN was found to be marginally but significantly better than placebo in healing anal fissure (48.9% vs. 35.5%, p<0.0009). Botox and calcium channel blockers had similar efficacy to GTN with fewer adverse events but the studies were mostly small and poorly controlled and the benefits were not statistically significant. A systematic review of seven randomised controlled trials showed comparable efficacy for GTN and topical diltiazem with a lower incidence of headache in diltiazem subjects (Sajid, 2013). However, randomised, controlled trials conducted to date have not shown an efficacy benefit for topical diltiazem compared with placebo for AF healing. Despite this failure to demonstrate AF healing, the sponsors have conducted a clinical trial program to assess the value of topical DTZ 2% cream for relief of pain with or following defaecation in subjects with chronic AF.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Two clinical pharmacology studies, both studies provided pharmacokinetic and pharmacodynamic data.
- No population pharmacokinetic analyses.
- One pivotal efficacy/safety study DAF09.
- Four other efficacy/safety studies, DAF-0001, 99-CFAIII, VEN307-DERM-001, VEN307-DERM-002.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

All studies were conducted according to the principles of ICH GCP.

4. Pharmacokinetics

Summaries of the pharmacokinetic studies are presented. Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PKs in target population – Patients with AF§	General PK	VEN307-PK-001	Single- and multiple-dose PK parameters for topical DTZ and single-dose PK parameters for oral DTZ in subjects with AF. Evaluate pain using NRS.
		SC00802	Systemic absorption following topically applied DTZ at a range of doses in patients with AF. Effects of topical DTZ on the pulse rate, blood pressure and ECG readings.

* Indicates the primary aim of the study.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

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

4.1. Summary of pharmacokinetics

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

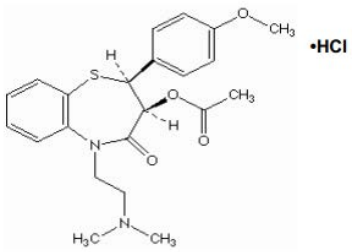
Plasma concentration analysis: DTZ, O-desacetyldiltiazem, and N-desmethyldiltiazem was quantified in lithium heparinised human plasma samples using a validated LC-MS/MS method which had a quantifiable range of 0.100-50.0 ng/mL.

4.1.1. Physicochemical characteristics of the active substance

- Chemical name: Diltiazem HCl
- Empirical formula: $C_{22}H_{26}N_2O_4S.HCl$
- Molecular weight: 450.98
- CAS Registry Number: 33286-22-5

Structural formula is shown in Figure 1.

Figure 1: Structural formula.



ANOHEAL cream contains 20 mg/g diltiazem hydrochloride equivalent to 18.38 mg diltiazem base. Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is freely soluble in water, methanol, and chloroform.

4.1.2. Pharmacokinetics in the target population

No dedicated PK trials examined the PKs of DTZ cream in healthy subjects; therefore, the following discussion will focus on the two PK/PD studies (VEN307-PK-001 and SC00802) undertaken in the target population (i.e. patients with anal fissure). Of these two studies, only Study VEN307-PK001

examined the PKs of DTZ following administration of the formulation proposed for commercialisation.

4.1.2.1. Absorption

Sites and mechanisms of absorption

ANOHEAL 2% w/w cream is topically administered to the perianal area. Following administration of the formulation proposed for marketing, at a dose of approximately 8.5 mg DTZ, the median Tmax (range) occurred at 4.04 h (1.00-24.0 h).

4.1.2.2. Bioavailability

Absolute bioavailability

No clinical studies contained in this submission examined the absolute bioavailability of ANOHEAL cream. However, Study VEN307-PK-001 compared the PKs of DTZ following a single perianal application of ANOHEAL cream (a dose of approximately 8.5 mg) and following a single oral tablet dose of 120 mg DTZ. The Cmax values following administration of the cream and tablet were 0.796 ng/mL and 130 ng/mL, respectively, and the corresponding $AUC_{0\text{-}inf}$ values were 20 ng.h/mL and 943 ng.h/mL, respectively. The $t_{1/2}$ and CL/F values for ANOHEAL cream were 21.2 h and 763 L/h, respectively and for the DTZ tablet were 7.75 h and 150 L/h, respectively. Therefore, based on the ratio of the dose-adjusted AUC for a single topical administration to the AUC for single oral administration, the relative bioavailability of DTZ following a single topical administration was approximately 30%.

Bioavailability relative to an oral solution or micronised suspension

Not applicable.

Bioequivalence of clinical trial and market formulations

No clinical studies directly compared the PKs of the cream formulation proposed for commercialisation and used in Study VEN307-PK-001 with the formulation used in Study SC00802 or the other formulations described in the "Formulation Development" section of this report. However, the skin permeability of the proposed commercial formulation (#3/78/4/D3), together with a similar formulation without propylene glycol (BD26/15), and a non-aqueous formulation (3/65) was measured in two *in vitro* studies (AX205 and AX562) using samples of human breast skin obtained following reconstruction/cosmetic surgery. In these studies epidermal preparations were mounted to form a barrier between the two chambers of a diffusion cell. The DTZ test formulation was then applied to the outer surface of the stratum corneum and the concentration of DTZ in the receptor chamber was measured at various time points. The results indicated that the proposed commercial formulation had the best permeability and that the aqueous-based formulation without propylene glycol had better permeability than the non-aqueous formulation. A third *in vitro* study (S05/01/02), which utilised a similar methodology to that described above, compared the proposed commercial DTZ formulation (3/78/4/D3) to another aqueous formulation (DA16) at the proposed dosage strength of 2% w/w. As in the previous *in vitro* studies, the proposed commercial formulation demonstrated higher skin permeability than the other aqueous formulation at the three time points measured.

Bioequivalence of different dosage forms and strengths

Only a single dosage strength is proposed for marketing (i.e. 2% w/w cream).

Bioequivalence to relevant registered products

Not applicable.

Influence of food

Not applicable.

Dose proportionality

No dedicated PK/PD studies examined dose proportionality following application of the formulation proposed for marketing. However, Study SC00802, which utilised a formulation that contained minor differences in the amounts of propylene glycol and liquid paraffin and also contained povidone, examined the PKs of DTZ following a single application of 2%, 4% or 8% w/w cream to patients with AF. Following administration of the 2%, 4% and 8% w/w cream, the mean Cmax values for DTZ were 1.8, 2.68 and 4.68 ng/mL, respectively, and the mean $AUC_{0\text{-}inf}$ values were 41.7, 48.9 and 227.1 ng.h/mL, respectively. Median Tmax ranged from 5.00 to 6.50 h. Therefore, following the administration of the 3 dosage strengths of DTZ cream used in this study, DTZ exposure increased dose dependently; however, the increase was not dose proportional.

Bioavailability during multiple-dosing

Study VEN307-PK-001, also compared the PKs of DTZ following a single application of ANOHEAL 2% w/w cream and following application of ANOHEAL cream three times daily (TID) for three days and a single morning application on the 4th day in patients with AF. Following TID doses steady-state was approached by the 4th day of dosing (Cmin = 1.02 ng/mL). Steady-state mean Cmax and $AUC_{0\text{-}8h}$ values for DTZ were 1.49 ng/mL (cf. 0.80 ng/mL following a single application) and 10.0 ng.h/mL (cf. 20.0 ng.h/mL), respectively; median Tmax occurred at 4.79 h (cf. 6.00 h) and mean $t_{1/2}$ was 25.0 h (cf. 31.2 h). DTZ clearance (CL/F) was also higher following multiple doses of cream (CL/F: 1339 L/h; SD: 1080) than following a single application (763 L/h; 767). In addition, this study calculated the relative bioavailability (F_{top}/F_{oral}) of DTZ following TID topical dosing based on the ratio of the dose-adjusted AUC for topical administration ($AUC_{0\text{-}8h}$) to the AUC for oral administration ($AUC_{0\text{-}inf}$). The mean of the resultant F_{top}/F_{oral} values was 0.148 ± 0.071, and the median value was 0.152 (range 0.036-0.286) indicating that the systemic bioavailability of DTZ following topical administration of 2% DTZ cream was approximately 15% of that for oral DTZ.

> *Comment: No explanation is provided for the increase in CL/F following multiple topical administrations of DTZ compared to a single topical application in Study VEN307-PK-001. One can only assume that it relates to the high variability associated with these values, which is to be expected given the difficulty in providing uniform doses via topical application.*

Effect of administration timing

No studies examined the effect of administration timing.

4.1.2.3. Distribution

No clinical studies examined the distribution of DTZ following perianal application and the following information is taken from the proposed PI:

> *The pharmacokinetic properties of orally administered diltiazem hydrochloride are well-established. Diltiazem is lipophilic and has a large volume of distribution. Diltiazem is plasma protein bound to the extent of 70-80%.*

4.1.2.4. Metabolism

Interconversion between enantiomers

Not applicable.

Sites of metabolism and mechanisms / enzyme systems involved

No clinical studies examined the sites of DTZ metabolism and mechanisms involved following perianal application. The proposed PI states the following regarding the metabolism of DTZ:

> *Diltiazem is metabolised extensively in the liver. The principal metabolites are N-desmethyldiltiazem and O-desacetyldiltiazem*

Non-renal clearance

See above.

Metabolites identified in humans

The following information is taken from the proposed PI:

> *The principal metabolites of DTZ, N-desmethyldiltiazem and O-desacetyldiltiazem, are estimated to have 20% and 25-50%, respectively, of the vasodilator activity of the parent compound.*

Pharmacokinetics of metabolites

Study VEN307-PK-001 examined the PKs of the principle metabolites of DTZ following a single perianal application of ANOHEAL or 3 days TID dosing with the cream in patients with AF.

N-desmethyldiltiazem

The mean Cmax and $AUC_{0\text{-}inf}$ values for N-desmethyldiltiazem following a single dose of DTZ 2% w/w cream were 0.0520 ng/mL and 6.83 ng.h/mL, respectively, and the median Tmax and mean $t_{1/2}$ values were 5.98 h and 21.1 h, respectively. Following TID doses of DTZ cream, steady state was approached by the 4th day (Cmin = 0.147 ng/mL). Mean DTZ Cmax and $AUC_{0\text{-}8h}$ values were 0.254 ng/mL and 1.64 ng.h/mL, respectively, and median Tmax and mean $t_{1/2}$ values were 5.98 h and 31.3 h, respectively. Based on the AUC values for N-desmethyldiltiazem following topical dosing of DTZ TID or a single oral dose of DTZ, the systemic bioavailability of N-desmethyldiltiazem following topical administration was approximately 5% of that resulting from oral DTZ.

O-desacetyldiltiazem

The mean Cmax and $AUC_{0\text{-}inf}$ values for O-desacetyldiltiazem following a single dose of DTZ 2% w/w cream were 0.0125 ng/mL and 0.064 ng.h/mL, respectively, and the median Tmax was 3.98 h. Following TID doses of DTZ cream, steady state was approached by the 4th day (Cmin = 0.133 ng/mL). Mean DTZ Cmax and $AUC_{0\text{-}8h}$ values were 0.195 ng/mL and 1.35 ng.h/mL, respectively, and median Tmax and mean $t_{1/2}$ values were 4.06 h and 32.0 h, respectively. Based on the AUC values for O-desacetyldiltiazem following topical dosing of DTZ TID or a single oral dose of DTZ, the systemic bioavailability of O-desacetyldiltiazem following topical administration was approximately 23% of that resulting from oral DTZ.

Consequences of genetic polymorphism

Not examined.

4.1.2.5. Excretion

The excretion of DTZ following perianal administration has not been studied. The following statement regarding elimination is taken from the proposed PI:

> *Following oral administration, it is eliminated principally as metabolites via the kidneys with an average elimination half-life of 6-8 hours. The apparent elimination half-life for topically applied diltiazem hydrochloride may be considerably longer since plasma levels are influenced by continuing transcutaneous flux from the site of application.*

In addition, Study VEN307-PK-001 provided estimates of the mean elimination constants for DTZ and its two principal metabolites (N-desmethyldiltiazem and O-desacetyldiltiazem), following TID application with ANOHEAL cream, of 0.0315/h, 0.0252/h and 0.0239/h, respectively.

4.1.2.6. Intra- and inter-individual variability of pharmacokinetics

No PopPK studies examined the intra- or inter-subject variability associated with the PKs of DTZ following perianal application. However the standard deviations associated with the DTZ PKs parameters derived in Study VEN307-PK-001 were high. For instance, following a single topical application of 2% w/w cream the Cmax and AUC values were 0.80 ng/mL and 20.0 ng/mL, respectively, whereas, the associated %SD values were ± 106% and ± 58%, respectively. By contrast, the %SD values associated with the Cmax and AUC of DTZ following a single oral dose were lower and represented variations of ±51% and ±41%, respectively. This increased variability

seen following doses of ANOHEAL cream may in part result from difficulty in providing uniform doses to all patients following topical application of the cream.

4.1.3. Pharmacokinetics in the target population

Please see preceding sections.

4.1.4. Pharmacokinetics in other special populations

No studies examined the PKs of DTZ in special populations following perianal administration of ANOHEAL cream. The proposed PI states the following regarding orally administered DTZ:

> *Renal impairment is reported to have no significant impact on the pharmacokinetics of orally administered diltiazem.*
>
> *Hepatic impairment may result in reduced oxidative metabolism and, hence, raised plasma levels of diltiazem.*
>
> *Diltiazem is present in breast milk following oral administration. For this reason, use of ANOHEAL is contraindicated during lactation.*

4.1.5. Pharmacokinetic interactions

4.1.5.1. Pharmacokinetic interactions demonstrated in human studies

No studies examined DDIs following perianal administration of ANOHEAL cream. The proposed PI states the following regarding orally administered DTZ:

> *It [sic: DTZ] does not appear to be altered by digoxin, hydrochlorothiazide, propranolol, salicylic acid, or warfarin. However, diltiazem may affect blood levels of carbamazepine, ciclosporin, theophylline, and phenytoin.*

4.1.5.2. Clinical implications of in vitro findings

No studies.

4.2. Evaluator's overall conclusions on pharmacokinetics

- ANOHEAL 2% w/w cream is topically administered to the perianal area. Following administration of the formulation proposed for marketing, at a dose of approximately 8.5 mg DTZ, the median Tmax (range) occurred at 4.04 h (1.00-24.0 h).
- The relative bioavailability of a single, topical, perianal administration of ANOHEAL cream compared to a single oral dose of DTZ was 30%.
- *In vitro* studies indicated that the proposed commercial formulation of DTZ cream demonstrated higher skin permeability than the other aqueous formulations and a non-aqueous formulation tested.
- A study, which utilised a slightly different formulation of DTZ cream to the one proposed for marketing, indicated that DTZ exposure increased dose dependently; however, the increase in exposure was not dose proportional. The systemic bioavailability of DTZ following topical administration was approximately 15% of that for a single oral dose of DTZ.
- Steady-state DTZ exposure was approached following 4 days of topical dosing TID with ANOHEAL cream.
- Diltiazem is metabolised extensively in the liver. The principal metabolites are N-desmethyldiltiazem and O-desacetyldiltiazem.
- The systemic bioavailability of N-desmethyldiltiazem following topical administration was approximately 5% of that resulting from oral DTZ, whereas the systemic bioavailability of O-desacetyldiltiazem following topical administration was approximately 23% of that resulting from oral DTZ.

- Following TID application with ANOHEAL cream, the mean elimination constants for DTZ and its two principal metabolites (N-desmethyldiltiazem and O-desacetyldiltiazem), was 0.0315/h, 0.0252/h and 0.0239/h, respectively.
- As expected the SD values associated with the DTZ PKs parameters following topical administration were relatively higher than those associated with DTZ PKs following a single oral dose.

4.2.1. Limitations of PK studies

- No dedicated PK trials examined the PKs of DTZ cream in healthy subjects.
- No clinical studies contained in this submission examined the absolute bioavailability of ANOHEAL cream.
- No clinical studies directly compared the PKs of the cream formulation proposed for commercialisation and the other formulations described in the Formulation Development section of this report.
- No dedicated PK/PD studies examined dose proportionality following application of the formulation proposed for marketing.
- No clinical studies examined the distribution of DTZ following perianal application.
- No clinical studies examined the sites of DTZ metabolism and mechanisms involved following perianal application.
- No PopPK studies examined the intra- or inter-subject variability associated with the PKs of DTZ following perianal application.
- No studies examined the PKs of DTZ in special populations following perianal administration of ANOHEAL cream.
- No studies examined DDIs following perianal administration of ANOHEAL cream.
- The proposed PI section regarding Pharmacokinetics does not specifically state that no clinical trials have examined the absolute bioavailability, distribution, metabolism and the PKs of ANOHEAL cream in special populations (such as patients with hepatic or renal impairment) following perianal application of DTZ cream.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

All of the PK/PD studies that contain a PD component have been previously summarised above.

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

Diltiazem is an inhibitor of L-type calcium channels. It inhibits the inward movement of calcium into myocardial cells and smooth muscle cells of the vasculature and gastrointestinal tract. It causes relaxation of smooth muscle, including that of the internal anal sphincter.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Study VEN307-PK-001 evaluated the worst anal pain associated with or following defecation and overall daily AF-related pain using an 11-point numerical rating scale (NRS), in which a score of 0 corresponded to no pain and a score of 10 corresponded to the worst pain imaginable, following topical administration of single or multiple doses (TID) of the DTZ formulation proposed for marketing (2% w/w cream) or a single oral dose of 120 mg DTZ. Anal pain associated with or following defaecation and overall daily anal fissure-related pain decreased during the course of the study. Relative to baseline, the mean NRS score for worst defaecation-related pain decreased by 0.7±1.86 on Day 3 (following the single topical dose of DTZ on Day 1), by 2.2±3.70 on Day 8 (following the administration of multiple topical doses of DTZ on Days 4, 5, 6, and 7), and by 4.0±3.22 on Day 17 (at the end of the study, after the single oral dose of DTZ on Day 14). Relative to baseline, the mean NRS score for overall daily anal fissure-related pain was decreased by 0.0±2.41 on Day 3 (following the single topical dose of DTZ on Day 1), by 1.4±3.32 on Day 8 (following the administration of multiple topical doses of DTZ on Days 4, 5, 6, and 7) and by 1.7±2.71 on Day 17 (at the end of the study, after the single oral dose of DTZ on Day 14).

> *Comment: As Study VEN307-PK-001 did not examine the effect on worst anal pain associated with or following defecation and overall daily AF-related pain following perianal application of a placebo control cream, the true effect of ANOHEAL cream on NRS in this study is difficult to determine.*

5.2.2.2. Secondary pharmacodynamic effects

Study SC00802 examined the effects of topical DTZ at doses of 2% to 8% w/w on the pulse rate (PR), blood pressure (BP) and ECG readings using a modified form of the DTZ formulation proposed for marketing in patients with AF. Although the patients' BP and PR results following treatment with DTZ were not subjected to formal statistical analyses, the sponsor states that the BP and PR taken around the time of the Cmax of DTZ and its two metabolites (2 h, 4 h and 8 h, respectively) were no different than those seen pre-dose. However, the data indicates that the average BP at these time points were lower than those seen pre-dose following all 3 doses on Day 1 and after treatment with the 8% DTZ cream on Day 4. For instance, following a single topical application of 8% w/w DTZ cream, the average BP values at 2 h, 4 h and 8 h post dosing were 123/75, 116/74 and 119/69 mmHg, respectively, compared to a pre-dose BP of 132/80 mmHg. Following TID dosing with 2% w/w cream, the average BP values at 2 h, 4 h and 8 h post dosing were 114/71, 117/67 and 117/71 mmHg, respectively, compared to a pre-dose BP of 122/73 mmHg.

5.2.3. Time course of pharmacodynamic effects

The reduction in worst defaecation-related pain and overall daily anal fissure-related pain following topical application of DTZ 2% w/w cream increased following multiple doses compared to a single dose (see section on Primary PD effects above).

5.2.4. Relationship between drug concentration and pharmacodynamic effects

Given the high variability associated with the PK parameters derived in Study **VEN307-PK-001,** it is difficult to determine whether a relationship exist between the pain relieving effects of DTZ 2% w/w cream and drug concentration.

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

Not examined.

5.2.6. Pharmacodynamic interactions

Not examined.

5.3. Evaluator's overall conclusions on pharmacodynamics

- Diltiazem is an inhibitor of L-type calcium channels, which induces smooth muscle relaxation, including that of the internal anal sphincter.
- Relative to baseline, the mean NRS score for worst defaecation-related pain decreased by 0.7±1.86 on Day 3 following the single topical dose of DTZ 2% w/w cream, by 2.2±3.70 following the administration of multiple topical doses of DTZ cream and by 4.0±3.22 after a single oral dose of DTZ.
- Relative to baseline, the mean NRS score for overall daily anal fissure-related pain was decreased by 0.0±2.41 following the single topical dose of DTZ, by 1.4±3.32 following the administration of multiple topical doses of DTZ, and by 1.7±2.71 after a single oral dose of DTZ.
- Worst defaecation-related pain and overall daily anal fissure-related pain was lowest following a single oral dose of DTZ.
- Topical application of both single and multiple doses of DTZ cream appeared to have no effect on PR.
- The average BP values at 2 h, 4 h and 8 h post-dosing were reduced following either a single dose or multiple TID doses of 8% w/w DTZ cream
- The reduction in worst defaecation-related pain and overall daily anal fissure-related pain following topical application of DTZ 2% w/w cream increased following multiple doses compared to a single dose.

Limitations of the PD studies

- Due to the nature of the data provided no relationship between drug concentration and PD effects could be determined.
- No studies examined genetic, gender or age related differences in PD response following perianal application of DTZ cream.
- No studies examined PD interactions following perianal application of DTZ cream.

6. Dosage selection for the pivotal studies

No formal dose ranging studies were submitted. However, two doses of DTZ cream (DTZ 2% and 4%) were included in the treatment arms of the pivotal study DAF09.

7. Clinical efficacy

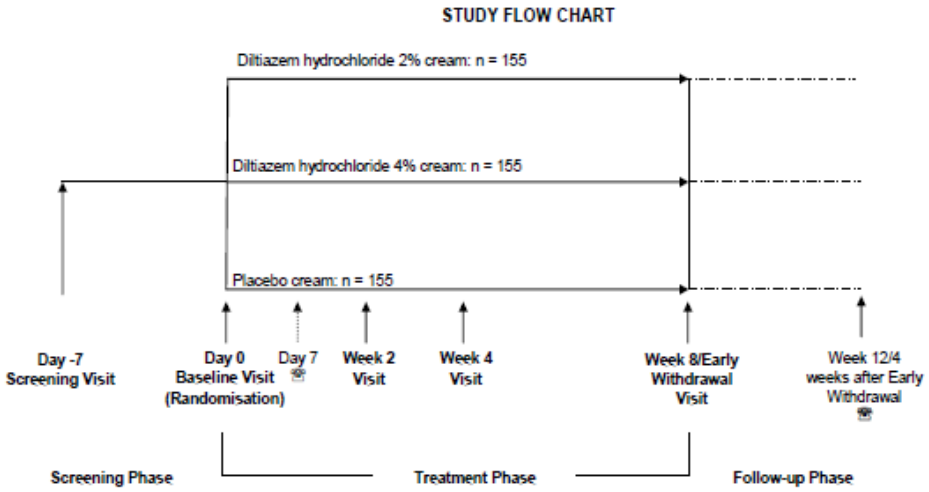
7.1. Pivotal efficacy study DAF09

7.1.1. Study design, objectives

This was a randomised, double-blind, placebo-controlled, Phase 3 study of the safety and efficacy of two doses of DTZ cream in subjects with anal fissure (AF) and AF-related pain. It was sponsored by S.L.A. Pharma (UK) and conducted in six European countries (Bulgaria, Germany, Lithuania, Romania, Spain, and the UK) between October 2010 and March 2012. The primary endpoint was the efficacy of DTZ 2% cream in reducing worst pain associated with AF. The most important secondary endpoint was the percentage of subjects achieving AF healing. The study design is summarised in Figure 2, below. A total of 465 subjects were planned with 155 subjects in each treatment arm. After a one week screening period, eligible subjects were randomised 1:1:1 to receive DTZ 4% w/w cream, DTZ 2% w/w cream or placebo cream containing vehicle only. The subjects were further stratified according to failure on previous topical GTN therapy. Topical study

treatment was applied TID for up to 8 weeks and clinic visits were scheduled at Weeks 2, 4, and 8 weeks. A final telephone assessment of AEs was performed at Week 12, four weeks after the treatment period was completed.

Figure 2: DAF09 study design.



Laxatives and stool softeners were permitted during the screening and treatment periods, and fibre supplements were permitted at levels used at the baseline visit. Subjects used IVRS and paper daily diaries to report the number of bowel movements, anal pain and bowel symptoms, worst anal pain associated with or following defaecation, and to report overall AF-related pain. The use of laxatives and analgesics, and the number of study cream applications were also recorded. At each visit, subjects underwent visual examination of their AF to assess healing and Skin Irritation Scores (SIS). Pain was recorded using a numerical rating scale (NRS) and the Patient's Global Impression of Improvement scale (PGI-I). Quality of life was assessed using a Short Form 36 (SF-36). Subjects with complete healing at Weeks 2 and 4 were asked to continue treatment until the Week 8 visit. Subjects who withdrew from the study underwent an early withdrawal visit and a final safety evaluation four weeks later. A subject could be withdrawn following a major protocol deviation, at subject request, or at the discretion of the investigator. PK samples for plasma diltiazem and its metabolites were taken from 25% of subjects at Weeks 2, 4, and 8 for analysis at a central laboratory (Quest Diagnostics, UK). No protocol amendments were made after commencement of study recruitment.

7.1.2. Inclusion and exclusion criteria

The main inclusion criteria were: male or female subjects aged ≥18 years; subjects with an AF history of at least four weeks prior to screening; AF pain experienced at least twice weekly with an average of ≥3 on an 11-point NRS; an average of ≥4 on NRS for worst AF pain during the most recent three days; clinical evidence of a circumscribed AF with indurated edges; willingness to stop all other topical anal preparations during the course of the study; willingness and ability to use the IVRS diary.

The main exclusion criteria were: subjects with acute AF defined as present for less than four weeks prior to screening; more than one AF; subjects with any prior surgical intervention for AF; botulinum injection in the previous 3 months; use of topical GTN for >1 week in the previous four weeks; AF associated with traumatic or other medical conditions; subjects with cardiovascular conditions including bradycardia, reduced LV function or heart block; known hypersensitivity to diltiazem; subjects who had previously used topical DTZ or other calcium channel blockers; subjects taking protocol defined prohibited medications; history of GI disorders and procedures, including inflammatory bowel disease, chronic faecal incompetence, chronic constipation with straining at stool, anal abscess, previous pelvic radiotherapy, and fixed anal stenosis/fibrosis; malignancy within the previous 5 years; a history of clinically significant medical or psychiatric disorders, including HIV infection; clinically significant laboratory or ECG abnormalities at

screening; subjects with planned elective treatments for other conditions; women of childbearing potential unless using adequate contraception; pregnancy and lactation.

7.1.3. Study treatments

The study treatments were either:

- DTZ 4% w/w cream applied TID for 8 weeks (a nominal DTZ 51 mg daily dose).
- DTZ 2% w/w cream applied TID for 8 weeks (a nominal DTZ 25.5 mg daily dose).
- Matching placebo cream for 8 weeks.

Two 30g tubes of study medication were provided to each subject at baseline. Subjects were requested to apply 2.5cm of cream (measured by a guide) at 8-hourly intervals, at least one hour before defaecation if possible. The cream was digitally massaged in and around the anus. Subjects were advised not to defaecate, shower or bathe within an hour of application; however, the cream was not to be re-applied if this was not possible.

At Week 4, the two tubes of study cream were returned and weighed to assess compliance. A further two tubes of medication were supplied for the remainder of the study. Compliance was considered adequate if 60-100% by weight of the study medication was used, and if dosing was recorded on ≥80% of days by IVRS.

7.1.4. Efficacy variables and outcomes

The primary efficacy outcome was the efficacy of DTZ 2% cream in reducing worst pain associated with AF.
The main efficacy variables and outcomes were:

- Changes in AF pain measured by NRS, a widely accepted, validated 11-point rating scale for chronic pain with 0 = no pain and 10 = worst imaginable pain.
- Time course of AF pain reduction over an eight week treatment period.
- AF healing rates.
- Global changes in the AF condition measured by PGI-I.
- Changes in QoL measured by SF-36.
- Determination of optimum DTZ dose.

Other efficacy outcomes included:

- The level of analgesic use.
- The effect of DTZ on medical and surgical rescue interventions.

7.1.5. Randomisation and blinding methods

Randomisation was conducted by IVRS and identical study medication tubes were provided according to the randomisation schedule. The investigators and subjects remained blind to the study treatment and PK data were not released until database lock.

7.1.6. Analysis populations

The primary analysis was performed on the ITT population which included all randomised subjects who received at least one dose of study medication. The PP analysis was performed on all subjects in the ITT population who did not meet of entry criteria or have other major protocol deviations.

7.1.7. Sample size

The sample size was based on estimates of variability derived from previous studies. A sample size of 155 subjects in each group was estimated to have 90% power to detect a treatment difference of 1 NRS unit with SD of 2.7 using a 5% 2-sided significance level.

> *Comment: It is unclear on what basis the sample size assumptions for NRS were made, in particular the selection of a treatment difference of I NRS unit. It is not stated if this was or was not considered a minimum clinically meaningful treatment difference compared with placebo.*

1.1.1.1 Statistical methods

The primary efficacy analysis was performed on the ITT population with the PP population used as a sensitivity analysis. No interim analyses were performed. Statistical analyses were performed using SAS Version 9.3. Comparisons of demographic and baseline characteristics were performed using t-tests, Fisher's Exact test, or Cochran-Mantel-Haenszel tests, as appropriate. Only 11 subjects had previously failed GTN therapy so history of GTN failure was not included in the final analysis. The primary analysis was based on average changes from baseline for worst anal pain experienced with or following defaecation using ANCOVA. The analyses determined the effects of DTZ on AF-related pain. The null hypothesis was tested with the type 1 error protected by a hierarchical structure testing the superiority of DTZ 4% cream vs placebo, followed by testing the superiority of DTZ 2% cream vs placebo. Treatment differences were estimated, as appropriate, using 1-sided (97.5%) or 2-sided (95%) CIs. Responder analysis curves for average daily overall AF-related pain were analysed using the log-rank test with time to response displayed using Kaplan-Meier plots. Multiplicity was controlled by the hierarchical testing structure. Subjects with missing data had their baseline observation carried forward, and subjects with a missing assessment at Week 4 were considered to be non-responders. Subjects with other missing data had their worst previous AF-related pain scores carried forward. Missing values for healing of AF were assigned as not healed. The proportion of subjects with complete healing of AF were analysed using a logistic regression model.

> *Comment: It is not clear why 97.5% CIs rather than conventional methodologies were used to correct for multiplicity (see Clinical Questions).*

7.1.8. Participant flow

A total of 520 subjects were screened, 465 subjects were randomised, and 440 subjects completed the study. A total of 148, 147, and 145 subjects completed the study in the DTZ 4%, DTZ 2%, and placebo groups, respectively. A total of 8, 7, and 10 subjects withdrew from the respective groups, most commonly due to withdrawal of consent.

7.1.9. Major protocol violations/deviations

Major protocol deviations occurred in 2, 1, and 1 subjects in the DTZ 4%, DTZ 2%, and placebo groups, respectively. Most major deviations resulted from failure to meet the inclusion criterion NRS ≥4 for worst AF pain at screening.

7.1.10. Baseline data

The majority of subjects were female (56.6%) and White (99.8%) with a mean age of 41.7 years and a mean body weight of 75.8 kg. Most AFs were posterior (76.6%) and all had indurated edges. The mean baseline NRS scores for AF pain in the ITT population were comparable in each treatment group (6.40 DTZ 4%, 6.21 DTZ 2%, and 6.38 placebo). At screening, approximately 15% of subjects had concurrent haemorrhoids and 12.5% of subjects were using topical treatments. Overall, 56.3% of subjects were taking at least one non-analgesic concomitant medication, mainly oral contraceptives (25.8%). During the study treatment period, laxatives and stool softeners were used by 15.4%, 21.4%, and 25.2% of the DTZ 4%, DTZ 2%, and placebo groups, respectively. During the study treatment period, analgesics were taken by 51.9%, 49.4%, and 53.5% of the respective groups. Compliance with study medication ranged from 88.7% to 89.8% during Weeks 1-4, and from 83% to 85.1% during Weeks 5-8.

> *Comment: Compared with the placebo group, somewhat fewer subjects in the DTZ 2% group used laxatives, stool softeners and analgesics throughout the study. This minor imbalance may have occurred by chance or represent treatment cause and effect. This cannot be determined as these concurrent interventions were not controlled in the study design.*

7.1.11. Results for the primary efficacy outcome

In the ITT population, the average NRS score for worst anal pain with or following defaecation at Week 4 decreased over the treatment period in each treatment group. At Week 4, the adjusted mean changes (+/- SD) from baseline were -2.64 (0.15), -2.63 (0.15), and -2.20 (0.15) in the DTZ 4%, DTZ 2%, and placebo groups, respectively. The adjusted differences from placebo were -0.44 (97.5% CI: <-0.06, p=0.011) in the DTZ 4% group, and -0.43 (97.5% CI: <-0.06, p=0.012) in the DTZ 2% group. A range of sensitivity analyses allowing for missing data confirmed the conclusions of the primary analysis. At Week 8, there were further reductions in NRS scores in each treatment group. The adjusted mean changes (+/- SE) from baseline were -3.69 (0.16), -3.65 (0.16), and -3.03 (0.15) in the DTZ 4%, DTZ 2%, and placebo groups, respectively. The adjusted differences from placebo were -0.65 (97.5% CI: <-0.25, p=0.0008) in the DTZ 4% group, and -0.62 (97.5% CI: <-0.21, p=0.002) in the DTZ 2% group.

7.1.12. Results for other efficacy outcomes

There were no meaningful differences between treatment groups in the time course of AF pain response. At Week 8, complete AF healing in the ITT population was recorded in 32.7%, 31.2%, and 23.9% of the DTZ 4%, DTZ 2%, and placebo groups, respectively. The difference from placebo was statistically significant for the DTZ 4% group (p=0.018) but not for the DTZ 2% group (based on 97.5% CIs with a significance limit of p<0.025). At Week 4 and Week 8 in the ITT population, there were modest improvements in PGI-I scores in each treatment group (data not shown). Compared with placebo, a small but statistically significant benefit (p=0.008) was observed in the DTZ 2% group but not in the DTZ 4% group. With the exception of small benefits in the pain and physical functioning domains, there were no meaningful improvements in SF-36 scores in either DTZ group compared with placebo (data not shown). No meaningful differences between groups were observed in the number of days per week on which analgesics were required. During the treatment period, no rescue medication or surgical intervention was required in any subject.

Overall, plasma concentrations were low without evidence of accumulation of diltiazem or its metabolites in both DTZ groups. Plasma concentrations ranged from undetectable to 15.2 ng/mL in the DTZ 4% group, and from undetectable to 12.6 ng/mL in the DTZ 2% group. Higher mean concentrations were observed in the DTZ 4% group compared with the DTZ 2% group.

> *Comment: This randomised, placebo-controlled, double-blind study was appropriately designed and conducted. The study subjects were representative of the general population with uncomplicated chronic AF. Compliance with study drug and procedures was generally good and daily IVRS diary entry ensured accurate recording of symptoms.*

VAS is a validated and widely used pain rating scale used over 4- 8 week observation periods in most previous AF studies. NRS is also a validated and widely used alternative measure of pain relief: it was adopted in this study to allow IVRS diary reporting. However, pain is subjective with significant inter- and intra-subject variability confounded by a high placebo response. Healing is a more objective endpoint and pain relief without healing is a therapeutic failure which usually results in the need for surgery. As such, it is difficult to accept the sponsor's view that pain relief is as important as healing in the management of AF (see Clinical Questions).

The primary endpoint of the study was met with DTZ 4% and DTZ 2% proving superior to placebo for changes in AF pain associated with or following defaecation. In the DTZ 2% group, the adjusted differences from placebo in NRS scores were -0.43 at Week 4, and -0.62 at Week 8. Both differences were statistically significant but not clinically meaningful. The sponsor has offered no opinion on what treatment differences measured by NRS are accepted as clinically significant. This should be provided with support from the literature or expert bodies (see Clinical Questions). It would also be useful to have a responder analysis of the percentage of subjects achieving the accepted clinically meaningful NRS treatment difference.

Although diltiazem causes immediate relaxation of increased anal sphincter tone, increasing pain relief was observed only gradually and progressively over the eight week treatment period in the DTZ and placebo groups. During the same period, AF healing was observed in 32.7% of the DTZ 4% group and 31.2% of the DTZ 2% group compared with 23.9% in the placebo group. The treatment benefit was not statistically significant for the DTZ 2% group. However, based on these data, it is plausible that the small benefit for pain relief was associated not with decreased anal sphincter tone but with improved healing rates (see Clinical Questions). This may have occurred by chance or represent a marginal but true increase in healing rates for DTZ 4% and 2% compared with placebo.

Compared with placebo, previous studies have failed to demonstrate a benefit in terms of AF healing with topical DTZ 2% cream. Presumably, this was the reason for selecting pain relief as the primary outcome for this study. Systematic literature reviews of treatments for AF have demonstrated little or no benefit for any medical treatment with the possible exception of GTN. In DAF09, the difference in pain relief in favour of DTZ 2% was statistically significant compared with placebo but it was of minimal clinical significance and possibly related to healing. Dose response relationships were not formally tested but pain relief was no better with the DTZ 4% formulation. In the absence of literature or supporting studies assessing pain as a primary endpoint, a second pivotal study is required to more accurately assess and confirm the possibly chance findings reported in DAF09.

7.2. Other Studies

7.2.1. Study DAF001

7.2.1.1. Methodology

This was a Phase 2, randomised, double-blind, placebo controlled study comparing topical diltiazem and placebo in the management of chronic anal fissure. It was conducted at two sites in the UK between May 2000 and February 2002. The primary objectives were to compare AF healing rates, and relapse rates after healing. Secondary objectives were AF pain measured by VAS, resting anorectal pressure measured by manometry, and recurrence rates during the follow-up period. Eligible subjects had posterior AF with indurated edges present for more than 2 months. Subjects were excluded if they had previous medical or surgical treatment for AF in the previous year. The study was powered to detect a 30% treatment difference in the primary endpoint and a total of 104 subjects were planned. Subjects were randomised to receive either DTZ 2% cream (2.5 cm, diltiazem 20 mg nominal daily dose) or matching placebo applied 12 hourly for 8 weeks. Open label DTZ 2% cream was offered for a further 8 week period in subjects who did have AF healing during the double-blind treatment period. AF healing rates in the ITT population were analysed using

Fisher's Exact Test, and VAS and rectal pressures were measured by ANCOVA. A post-treatment follow-up visit was scheduled at 4 months with telephone follow-up at 6 and 12 months.

7.2.1.2. Results

The study was stopped after 62 subjects (31 in each group) had been recruited due to unspecified stability problems with the study formulation. One patient in each treatment group had AF healing by Week 4. At Week 8, AF healing had occurred in 10% of the DTZ 2% group compared with 19% in the placebo group. The adjusted treatment difference was -9.7% (95% CI: -27.2, 7.9, p=0.47). A further 22% of subjects had AF healing during the eight week open-label treatment period. In the DTZ 2% group, mean VAS scores fell from 55.4 mm at baseline to 34.7 mm at Week 4, and 31.9 mm at Week 8. In the placebo group, mean VAS scores fell from 57.2 mm at baseline to 36.7 mm at Week 4, and 40.5 mm at Week 8. The adjusted treatment difference -1.32 mm at Week 4 (95% CI: -17.6, 15.0, p=0.87), and -5.44 mm at Week 8 (95% CI: -22.2, 11.3, p=0.52). Reductions in mean resting sphincter pressure from baseline were seen in both treatment groups. However, the adjusted treatment difference was small (0.52 mm Hg at week 8.).

> *Comment: This study was terminated prematurely due to unspecified stability issues with the study drug formulation. As the integrity of the study formulation was uncertain, the study results have no value and should be discounted in the overall evaluation of both safety and efficacy.*

7.2.2. Study 99CFAIII

7.2.2.1. Methodology

This was a Phase 2, randomised, double-blind, active comparator study of 0.2% GTN and DTZ 2% in subjects with chronic AF. It was conducted at two centres in the UK between January 2000 and January 2001. The primary objective was to compare AF healing rates, and the main secondary objective was AF pain relief measured by VAS. Eligible subjects had chronic AF with sentinel tags and visible muscle at the base of the fissure with pain present for at least three months. Subjects were excluded if they had previous medical or surgical treatment for AF in the previous year. The study was powered to detect a 40% treatment difference in the incidence of side effects and a total of 62 subjects were planned. Subjects were randomised to receive either DTZ 2% cream (2.5 cm, diltiazem 20 mg nominal daily dose), or GTN 0.2% cream (2.5 cm, GTN 2 mg nominal daily dose) matching placebo applied in and around the anus 12 hourly for 6 weeks. Subjects were screened and randomised with further visits at Weeks 3, 6, and 8. If a subject's fissure was not healed at Week 6, a further two weeks treatment was offered. AF healing rates in the ITT population were analysed using the Cochran-Mantel-Haenszel test. A total of 60 subjects were randomised (31 DTZ, 29 GTN) and 43 subjects completed the study (71% DTZ, 72% GTN). Withdrawals were due most commonly to AEs or withdrawal of consent. In the DTZ and GTN groups, most patients were female (65% vs 52%) with mean ages of 45.6 and 40.7 years, respectively. Chronic AF had been present for a median duration of approximately one year in each group.

7.2.2.2. Results

At Week 8, healing occurred in 26% and 41% of the DTZ and GTN groups, respectively (p=0.21 for the treatment difference). In the DTZ group, pain measured by VAS fell from 62.8 mm at screening to 26.7 mm at Week 8. In the GTN group, VAS scores fell from 56.3 mm at screening to 10.6 mm Week 8 (p=0.36 for the treatment difference).

> *Comment: This randomised, double-blind study compared the efficacy and safety of DTZ and GTN creams over an eight week treatment period. The study was small and not powered to detect differences in efficacy between the two treatments. Although the differences were not statistically significant, there were clear trends in favour of GTN for AF healing and pain relief.*

7.3. Analyses performed across trials (pooled & meta analyses)

None submitted.

7.4. Evaluator's conclusions on clinical efficacy

Clinical efficacy was assessed in the single pivotal DAF09. The supportive Phase 2 study DAF001 has no value for reasons discussed. The supportive Phase 2 study 99CFAIII was not placebo controlled, and better healing rates and pain relief were reported in the GTN active comparator arm. Due to the lack of a placebo arm, these data can also be discounted for evaluation purposes.

The primary objective was achieved in the only pivotal Phase 3, randomised, double-blind, placebo-controlled study (DAF09) involving 440 subjects, with a statistically significant benefit for DTZ 2% in terms of AF pain relief assessed by NRS. However, the benefit for DTZ 2% in NRS scores was marginal (less than 0.43 NRS units on an eleven point scale) and not clinically meaningful. The sponsor argues that the treatment difference in favour of DTZ 2% cream was clinically meaningful, citing the internal consistency of secondary outcomes, supporting studies, and literature studies. These arguments are tenuous but, even if they are accepted, they would support statistical robustness and not clinical significance. A responder analysis based on an accepted clinically significant treatment difference would have been useful but this was not done.

There was a trend towards increased AF healing with topical DTZ 2% compared with placebo. However, as in previous studies, the treatment difference was modest and not statistically significant. Improved pain scores with DTZ 2% might have resulted from a chance occurrence of increased AF healing rather than pharmacological reductions in anal sphincter tone. Overall, the marginal outcomes of the single pivotal study could have occurred by chance despite comparable outcomes in the DTZ 4% group. Even if the observations reflect a true therapeutic effect, they should be confirmed with a second, adequately powered study, preferably with AF healing as the primary endpoint.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy study DAF09, the following safety data were collected:

- General adverse events (AEs) were elicited by asking a standard non-leading question. AEs were recorded via the daily IVRS and paper diaries. AEs were coded and reported using the MedDRA classification.
- With the exception of local AEs related to AF, no AEs of particular interest were identified.
- Standard laboratory tests were performed at local laboratories. Haematology and biochemistry testing was performed centrally by Quest Diagnostics, UK.

8.1.1.1. Pivotal studies that assessed safety as a primary outcome

None submitted.

8.1.1.2. Dose-response and non-pivotal efficacy studies

The non-pivotal efficacy study 99CFAIII provided additional safety data in subjects with AF. Data from DAF001 are reported for completeness but they are not evaluable for reasons discussed.

8.1.1.3. Other studies evaluable for safety only

Studies VEN307-DERM-001 and VEN307-DERM-002 provided assessments of local tolerability in healthy subjects.

8.2. Pivotal studies that assessed safety as a primary outcome

None submitted.

8.3. Other studies that assessed safety as a primary outcome

8.3.1. Study VEN307-DERM-001

8.3.1.1. Methodology

This was a Phase 1, randomised, controlled study to evaluate the sensitizing potential of diltiazem 2% cream in healthy subjects. It was conducted by TKL Research, New Jersey, between March 2013 and May 2013. The primary objective was to compare DTZ 2% cream and its vehicle for their potential to sensitize the skin by repeated topical applications. The repeated insult patch test (RIPT) is a standard methodology for assessment of cell-mediated dermal immune responses. A total of 10 patch (2 cm x 2 cm) applications were made over a period of approximately 6-8 weeks. All subjects had positive and negative control patches applied under occlusion to the left infrascapular area at randomly assigned, adjacent sites. DTX 2% cream and its vehicle were applied with 0.1% SLS[a] patches as the positive control, and 0.9% saline solution as the negative control. During a three week induction phase, DTZ 2% cream, vehicle, and control patches were applied three times weekly. Dermal reactions at the application sites were assessed using a visual scale for erythema, oedema, and other signs of skin irritation. The patches were removed and subjects had a 10-14 day rest period. They were then rechallenged with a 48 hour patch application at a naïve site on the right infrascapular area. After removal of the challenge patch, dermal sensitization was assessed at 30 minutes, 24, 48, and 72 hours. If a cutaneous reaction was observed, a repeat challenge was permitted at the discretion of the investigator.

A total of 230 healthy male and female subjects were enrolled and 201 subjects completed the study. The subjects were either White (80.9%), Black (18.3%), or Asian (0.9%). Most were female (70.9%) with a mean age of 43.7 years.

Withdrawal of consent was the most common reason for study discontinuation. No efficacy indices were measured. Sensitizing potential was reported as the number and percentage of subjects with a sensitization response. Local tolerability was assessed using a visual Skin Irritation Score (SIS). All AEs were listed by subject and coded according to MedDRA.

8.3.1.2. Results

During the challenge phase, no subjects had a dermal reaction graded ≥3 and none underwent rechallenge. Cumulative irritation scores were highest at the SLS positive control sites. Compared with SLS, irritation scores were significantly less in the DTZ 2% cream and vehicle cream groups ($p<0.0001$ for both comparisons). Irritation scores in the DTZ 2% cream, vehicle cream, and saline control groups were comparable with no statistically significant differences between groups. Five AEs leading to study withdrawal were reported in 4 (1.7%) subjects, most commonly headache in 3 (1.3%) subjects. None of the AEs were severe and there were no deaths or other SAEs.

> *Comment: This was a well conducted study of potential skin irritation using standard occlusive patch methodology in 230 healthy subjects. The validity of the methodology was confirmed with significant reactions to the SLS positive control patches. DTZ 2% cream and vehicle cream were well tolerated with irritation scores comparable to inert 0.9% saline solution. The study demonstrated a lack of skin irritancy and sensitizing potential with the DTZ 2% cream formulation. However, while the results are reassuring, infrascapular skin is not representative of breached anal mucosal surfaces. The CSR does not state if the active and vehicle cream formulations were identical to that proposed for marketing. This should be clarified (see Clinical Questions). The frequency of reported AEs was extremely low. Further explanation was not provided on how AE reports were elicited because AEs are typically*

[a] SLS is a known skin irritant commonly used as a positive control in skin irritation studies.

reported in the great majority of healthy subjects in extended placebo controlled studies (see Clinical Questions).

8.3.2. Study VEN307-DERM-002

8.3.2.1. Methodology

This was a Phase 1, randomised, controlled study to evaluate the potential for skin irritation with diltiazem 2% cream in healthy subjects. It was conducted by TKL Research, New Jersey, in April 2013. The primary objective was to compare DTZ 2% cream and its vehicle for their potential to sensitize the skin by repeated topical applications. The repeated insult patch test (RIPT) is a standard methodology for assessment of cell-mediated dermal immune responses as employed in study VEN307-DERM-001. A total of 21 patch (2 cm x 2 cm) applications were made over a period of 22 days. All subjects had positive and negative control patches applied under occlusion to the left infrascapular area at randomly assigned, adjacent sites. DTX 2% cream and its vehicle were applied with 0.1% SLS[b] patches as the positive control, and 0.9% saline solution as the negative control. During the study period, patches were removed 24 hours (+/- 1.5 hours) after application and assessments were made immediately after removal of each patch. Dermal reactions at the application sites were assessed using a visual scale for erythema, oedema, and other signs of skin irritation.

A total of 40 healthy male and female subjects were enrolled and 37 subjects completed the study. The subjects were either White (87.5%) or Black (12.5%). Most were female (80.0%) with a mean age of 45.5 years. Three subjects withdrew consent and discontinued the study. No efficacy indices were measured. Local tolerability was assessed using the visual Skin Irritation Score (SIS) as described for study VEN370-DERM-001. All AEs were listed by subject and coded according to MedDRA.

8.3.2.2. Results

No subjects had significant skin reactions at the DTZ 2% and vehicle cream sites. One subject had minor irritation at the saline site. As expected, cumulative irritation scores were highest at the SLS positive control sites. Compared with SLS, irritation scores were significantly less in the DTZ 2% cream and vehicle cream groups ($p<0.0001$ for both comparisons). No AEs or SAEs were reported.

Comment: This was a well conducted study of potential skin irritation using standard occlusive patch methodology in 40 healthy subjects. The validity of the methodology was confirmed with significant reactions to the SLS positive control patches, and minimal irritation at the negative control sites. DTZ 2% cream and vehicle cream were well tolerated and no irritation was reported. The study demonstrated a lack of skin irritancy with the DTZ 2% cream formulation. However, as noted in VEN307-DERM-001, infrascapular skin is not representative of breached anal mucosal surfaces. As in VEN307-DERM-001, the CSR does not state if the active and vehicle cream formulations were identical to that proposed for marketing. This should be clarified (see Clinical Questions). Remarkably, no AEs were reported. Further explanation was not provided on how AE reports were elicited because AEs are typically reported in the great majority of subjects in healthy subject studies (see Clinical Questions).

8.4. Patient exposure

In the pivotal study DAF09, mean exposure to DTZ 4% was 54.7 days in 156 subjects. Mean exposure to DTZ 2% was 55.3 days in 154 subjects.

[b] SLS is a known skin irritant commonly used as a positive control in skin irritation studies.

8.5. Adverse events

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

8.5.1.1. Pivotal study DAF09

AEs were reported in 70.5%, 70.1%, and 60.6% of the DTZ 4%, DTZ 2%, and placebo groups, respectively. The majority of AEs by SOC were gastrointestinal, reported in 65.4%, 59.1%, and 54.2% of the respective groups. Overall, the most common AEs were proctalgia (43.0%), anal pruritus (12.5%), and anorectal discomfort (11.6%). Compared with the placebo group, anal pruritus and anorectal discomfort were notably more common in the DTZ 2% group. Overall, headache was reported in 13.8% of subjects with no notable differences between groups. There were four reports of dizziness, all of mild severity (3 DTZ 4%, 1 DTZ 2%). Application site pain by SOC was reported in by only eight subjects (5 DTZ 4%, 2 DTZ 2%, 1 placebo). There was no evidence of skin irritation assessed by SIS[c] in any treatment group. There were no other notable safety signals.

8.5.1.2. Other studies

In study 99CFAIII, treatment emergent AEs were reported in 42% of the DTZ 2% group and 72% of the GTN group. AEs were of severe intensity in 28% of the DTZ 2% group and 9% of the GTN group. Headache was reported in 26% and 59% of the respective groups.

> *Comment: Only brief AE summaries were reported in the CSR. In particular, there was no record of local tolerance. While reporting was superficial, no major safety concerns were raised.*

In study DAF001, 42% of subjects in the DTZ 2% group compared with 29% in the placebo group reported treatment emergent AEs. Four of these events were severe (2 DTZ 2%, 2 placebo). The pattern of AEs in the DTZ 2% and placebo groups was comparable to study DAF09 and no unexpected events were reported. The AEs are presented for completeness but they are non-evaluable and not considered further for reasons noted.

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

8.5.2.1. Pivotal study DAF09

With the exception of GI disorders, there were few ADRs. Nearly all cases of proctalgia by PT were considered unrelated to treatment by the investigator, but nearly all cases of anorectal discomfort and anal pruritus were considered possibly or probably related to active treatment. Nearly all cases of headache were considered unrelated to treatment in all groups.

8.5.2.2. Other studies

In study 99CFAIII, AEs considered likely or definitely related to treatment were reported in 50% of the DTZ 2% group and 48% of the GTN group. No detailed analysis of ADRs was provided.

8.5.3. Deaths and other serious adverse events

8.5.3.1. Pivotal study DAF09

No deaths were reported. A single SAE (prolapsed haemorrhoids requiring surgery) occurred in the DTZ 2% group after the end of the treatment period. It was considered unrelated.

8.5.3.2. Other studies

No deaths were reported in study 99CFAIII. One SAE was reported, a case of collapse requiring hospitalisation. The event occurred two weeks after the treatment period and it was considered unrelated to study drug.

[c] A score of <1 indicates minimal or no evidence of irritation.

8.5.4. Discontinuation due to adverse events

8.5.4.1. Pivotal study DAF09

Four AEs led to withdrawal from the study, 2 (1.3%) in the DTZ 4% group, 1 (0.6%) in the DTZ 2% group, and 1 (0.6%) in the placebo group. The single event in the DTZ 2% group was severe anal eczema, considered possibly related to study treatment.

8.5.4.2. Other studies

In study 99CFAIII, three subjects discontinued due to AEs, all in the DTZ 2% group. Two subjects had perineal skin irritation (one severe), and one withdrew due the SAE of collapse.

8.6. Laboratory tests

8.6.1. Laboratory abnormalities

8.6.1.1. Pivotal study DAF09

There were no significant trends or clinically significant findings related to laboratory abnormalities.

8.6.1.2. Other studies

Laboratory safety evaluations were not performed in study 99CFAIII.

8.6.2. Electrocardiograph

8.6.2.1. Pivotal study DAF09

No significant treatment emergent ECG changes were reported.

8.6.2.2. Other studies

ECGs were not recorded in 99CFAIII.

8.6.3. Vital signs

8.6.3.1. Pivotal studies

There were no significant changes in blood pressure, heart rate, or ECG findings in the active treatment groups.

8.6.3.2. Other studies

In study 99CFAIII, there was a median decrease of 5 mm Hg for systolic blood pressure in the DTZ 2% group compared with no change in the GTN group. No other meaningful changes in vital signs were noted.

8.7. Post-marketing experience

Not applicable.

8.8. Safety issues with the potential for major regulatory impact

8.8.1. Liver toxicity

No issues identified.

8.8.2. Haematological toxicity

No issues identified.

8.8.3. Serious skin reactions

No issues identified. Rare cases of allergic skin reactions such as exanthematous pustulosis have been identified in the literature.

8.8.4. Cardiovascular safety

No issues identified.

8.8.5. Unwanted immunological events

No issues identified. Rare cases of hypersensitivity to diltiazem hydrochloride have been identified in the literature.

8.9. Other safety issues

8.9.1. Safety in special populations

Not addressed in the clinical trial program.

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

No clinical studies examined the potential DDIs following perianal application of ANOHEAL 2% w/w cream. Previous clinical trials have identified the potential for orally administered DTZ to interact with the following drugs: dantrolene, lithium, nitrate derivatives, theophylline, alpha-adrenoceptor antagonists, amiodarone, digoxin, beta-blockers and other anti-hypertensives, anti-arrythmic agents, carbamazepine and ciclosporin. However, given that the maximum plasma concentrations of DTZ following perianal administration of ANOHEAL cream are far lower than those achieved following oral dosing with DTZ, the likelihood of these interactions occurring would be expected to be considerably lower following administration of ANOHEAL cream than following oral DTZ administration.

8.9.3. Evaluator's overall conclusions on clinical safety

The recommended total daily dose of diltiazem hydrochloride delivered in DTZ 2% cream is approximately 25 mg, compared with the recommended oral dose range of 180-480 mg with 120 mg in elderly. Oral administration typically provides a therapeutic range of 50-200 ng/mL. This contrasts with a median plasma concentration of 1 ng/mL, and a maximum concentration of 12.6 ng/mL reported in the DTZ 2% arm of the pivotal study DAF09. The potential for systemic effects is very low but it can't be completely discounted in vulnerable groups such as the elderly, subjects with hepatic or renal impairment, and subjects with unsuspected cardiac conduction abnormalities. DTZ 2% is contraindicated for bradycardia, 2nd or 3rd degree HB, sick sinus and LVF. No significant vital sign or ECG changes were detected in study DAF09; however, abnormalities such as 2nd degree heart block may be silent and unsuspected. There is also a potential risk of drug interactions with a range of medications listed, notably with dantrolene. The frequency of headache was similar in the active and placebo treatment groups in keeping with low systemic exposure to diltiazem with DTZ 2% cream.

Pre-clinical studies of diltiazem hydrochloride have demonstrated a potential for embryo-lethality and teratogenicity. This is a significant concern as AF is more common in females, many of childbearing potential. All single contraceptive methods have a failure rate of at least 1% so this is a serious potential risk in subjects with an otherwise non-life threatening condition.

The most common adverse reactions to DTZ 2% cream are related to local tolerability at the application site. In study DAF09, proctalgia with an overall incidence of 43% was reported equally commonly in the active and placebo groups, suggesting a relationship to the underlying condition. The other events occurring more commonly in the active treatment groups compared with placebo were anal pruritus and anorectal discomfort. Anal pruritus was reported in 14.9% and 7.7% of the DTZ 2% and placebo groups, respectively, while anorectal discomfort was reported in 13.6% and 5.8% of each group, respectively. While symptomatic discomfort was more common in the active

groups in DAF09 compared with placebo, no significant skin irritation was reported in studies VEN307-DERM-001 and VEN307-DERM-002 in healthy subjects. No AEs related to local tolerance were reported in the healthy subjects although at least some would be expected (see Clinical Questions). Severe skin sensitivity reactions described with oral diltiazem have been reported in the literature but none were reported in the DTZ 2% cream studies presented.

In the pivotal study, the majority of subjects were White females with a mean age of 43 years. However, males were well represented and subjects up to the age of 84 years were studied. No formal subgroup analyses were performed and numbers would be low in each group. However, numerous literature studies have been conducted in all geographic areas and races without evidence of differences in the disorder or in diltiazem metabolism or tolerability.

Overall, DTZ 2% is well tolerated. Compared with placebo, only anal pruritus and anorectal discomfort have been identified as common adverse reactions. With isolated exceptions, such events are mild to moderate in severity and resolve once treatment is stopped.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefit of ANOHEAL in the proposed usage is:

- Statistically significant but marginal reduction in AF related pain. However, a treatment difference of <1 NRS unit on an eleven point scale cannot be considered clinically meaningful.

9.2. First round assessment of risks

The risks of ANOHEAL in the proposed usage are:

- Potential cardiac risks in subjects with undetected ECG abnormalities or borderline left ventricular function. Abnormalities such as second degree AV block may exist in otherwise asymptomatic subjects. The cardiac risk is low because systemic diltiazem exposure is markedly lower than that associated with oral administration. However, risk cannot be discounted in isolated elderly subjects, or those with unidentified significant hepatic or renal impairment.
- Drug interactions with medications outlined in the proposed PI. The risk is low as systemic exposure to diltiazem hydrochloride is low.
- Hypersensitivity to the active substance, its metabolites, or any of the excipients.
- Potential teratogenicity in the event of unplanned or unsuspected pregnancy. Women of childbearing potential, unless using adequate contraception, were excluded from study DAF0001. However, a pregnancy did occur during the study and some contraceptive failures must be expected in routine clinical practice.
- Anorectal discomfort, proctalgia, and anal pruritus are commonly observed. The symptoms are usually mild to moderate but significant local skin reactions may occur. Serious systemic skin sensitivity reactions including exanthematous pustulosis have also been reported in the literature.
- Administration site pain is reported in a small percentage of subjects.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of ANOHEAL, given the proposed usage, is unfavourable.

Compared with placebo, no clinically meaningful benefit in terms of pain relief has been demonstrated. The potential risks of ANOHEAL are generally mild to moderate, mostly related to local application site intolerance. However, severe or serious outcomes related to hypersensitivity reaction, allergic reactions or cardiac events may rarely occur.

10. First round recommendation regarding authorisation

Authorisation for ANOHEAL for the proposed usage is not recommended. Insufficient clinical efficacy has been demonstrated in the single pivotal study presented.

11. Clinical questions

11.1. Additional expert input

Not required.

11.2. Clinical questions

11.2.1. Pharmacokinetics

No questions at this time.

11.2.2. Pharmacodynamics

No questions at this time.

11.2.3. Efficacy

- Question 1: In the pivotal study DAF09, the NRS treatment difference for DTZ 2% compared with placebo at Week 4 was -0.43, notably less than the 1 unit difference adopted in the sample size calculation. Please state if the 1 unit NRS difference was or was not identified a priori as a clinically meaningful treatment difference for NRS.
- Question 2: Please give a justification for adopting 97.5% CIs rather than conventional testing methods to control for multiplicity in study DAF09.
- Question 3: In the DAF09 protocol introduction, it is stated that pain relief is as important as healing. Pain relief without healing provides temporary palliation but healing must be considered superior as it is by definition curative. Please outline the arguments provided by the MHRA and the Swedish authority in support of pain relief rather than healing as a primary efficacy outcome in the pivotal study DAF09.
- Question 4: In the Clinical Overview, the sponsor proposes that the statistically significant reductions in NRS scores in favour of DTZ 2% cream in study DAF09 are also clinically significant. However, the arguments rely largely on the internal consistency of secondary outcomes other than pain relief, and on studies in the literature, themselves nearly all marginal, inconsistent and unconvincing. The sponsor has provided a reference supporting the use of NRS for measuring treatment responses to AF pain (Dworkin, 2005). However, this reference is largely a general statement of value and there is no description of the validity, reliability and sensitivity of this method. Nor is an accepted definition of the clinically significance of changes in NRS scores provided. Please provide a primary reference for the NRS method and use it to justify the clinical significance of the marginal (but statistically significant) treatment benefit in favour of DTZ 2% cream. It would also be useful to provide a responder analysis based on the nominated clinically significant treatment difference in NRS score.

- Question 5: In DAF09, there were marginal benefits in terms of pain relief and healing (ignoring levels of statistical significance). Was pain relief associated with healing? What were the treatment emergent changes in pain scores in subjects who did/did not heal?
- Question 6: Have manometry studies of anal sphincter tone been conducted using the DTZ 2% cream formulation proposed for marketing? If so, what percentage reductions in pressure were achieved?

11.2.4. Safety

- Question 7: Please confirm that the cream formulations applied in studies DAF09, VEN307-DERM-001 and VEN307-DERM-002 are identical to the formulation proposed for marketing. Was propylene glycol a component in each study?
- Question 8: In the DTZ 2% group of DAF09, anal pruritus and anal discomfort were in 14.9% and 13.6% of subjects, respectively, compared with 7.7% and 5.8% in the placebo group, respectively. However, in study VEN307-DERM-001, only five AEs (arthralgia, dizziness, and headache) were reported in 202 healthy subjects, and no AEs were reported in VEN307-DERM-002. While ADRs are obviously less common, typically the majority of healthy subjects in any Phase 1 study report at least one AE in response to a standard non-leading question. Please explain how AEs were elicited, documented and assessed in the healthy subject studies.

12. Second round evaluation of clinical data submitted

12.1. Efficacy

- ***Question 1: In the pivotal study DAF09, the NRS treatment difference for DTZ 2% compared with placebo at Week 4 was -0.43, notably less than the 1 unit difference adopted in the sample size calculation. Please state if the 1 unit NRS difference was or was not identified a priori as a clinically meaningful treatment difference for NRS.***

12.1.1. Sponsor's response

The 1 unit NRS difference was not identified *a priori* as being clinically meaningful difference (sic). The yardstick used to measure a pain benefit, pretty much any benefit above and beyond placebo when dealing with a reasonable, real-world study sample size (as opposed to an infinite sample) was considered to be clinically meaningful. In the context of sample size calculation, the smallest possible measurement of benefit was selected, using the quantised 11 point NRS.

This was simply a sample size estimating exercise based on the premise that any statistically significant benefit when dealing with a reasonable and not vast sample of measure that, having no meaning in words, nevertheless would be considered among surgeons to be clinically valuable.

12.1.2. Evaluators' response

The sponsor's response is not satisfactory.

The 1 unit NRS treatment difference was selected arbitrarily, based on the premise that any statistically significant benefit for pain relief is, by definition, clinically meaningful. This is at odds with conventional thinking and the claim that this view would be supported among surgeons is un-substantiated.

The more conventional method would have been to select a pre-determined minimal clinically important difference (MCID). This should have been based on previous AF clinical trial data if possible, or failing that, comparable pain studies in other indications.

- ***Question 2: Please give a justification for adopting 97.5% CIs rather than conventional testing methods to control for multiplicity in study DAF09.***

12.1.3. Sponsor's response

The 97.5% CI approach is an accepted methodology based on ICH E9.

12.1.4. Evaluators' response

The sponsor's response is satisfactory.

- ***Question 3: In the DAF09 protocol introduction, it is stated that pain relief is as important as healing. Pain relief without healing provides temporary palliation but healing must be considered superior as it is by definition curative. Please outline the arguments provided by the MHRA and the Swedish authority in support of pain relief rather than healing as a primary efficacy outcome in the pivotal study DAF09.***

12.1.5. Sponsor's response

Pain relief was not proposed as an endpoint by the MPA and MHRA. However, they accepted pain relief as a worthwhile alternative if improved healing rates cannot be demonstrated,

12.1.6. Evaluators' response

The sponsor's response is satisfactory.

- ***Question 4: In the Clinical Overview, the sponsor proposes that the statistically significant reductions in NRS scores in favour of DTZ 2% cream in study DAF09 are also clinically significant. However, the arguments rely largely on the internal consistency of secondary outcomes other than pain relief, and on studies in the literature, themselves nearly all marginal, inconsistent and unconvincing. The sponsor has provided a reference supporting the use of NRS for measuring treatment responses to AF pain (Dworkin, 2005). However, this reference is largely a general statement of value and there is no description of the validity, reliability and sensitivity of this method. Nor is an accepted definition of the clinically significance of changes in NRS scores provided. Please provide a primary reference for the NRS method and use it to justify the clinical significance of the marginal (but statistically significant) treatment benefit in favour of DTZ 2% cream. It would also be useful to provide a responder analysis based on the nominated clinically significant treatment difference in NRS score.***

12.1.7. Sponsor's response

The sponsor's response is not satisfactory.

The sponsor has provided a lengthy response. In summary:

- The preferred management of AF has moved from early surgery to surgery used as a last resort when medical management has failed.
- There is really no other clinical avenue than initial medical therapy. The degree of effectiveness for it to be valuable, so long as there is at least some measurable effectiveness, is really by the way.
- An extensive literature is provided, in compliance with FDA draft guidance, to support the use of NRS.
- A study of changes in chronic pain intensity measured on an 11 point NRS is cited (Farrar, 2001). The authors conclude that on average a reduction of approximately two points or a reduction of approximately 30% from baseline represented a clinically important difference. Both of which were achieved in the 2% diltiazem group (reduction: 2.63: 42%).
- A responder analysis of the proportion of subjects achieving ≥1 point reduction in the average NRS for worst anal pain associated with or following defaecation (mixed imputation) is provided.

Table 2: Pain scores.

Intent-to-treat (ITT) analysis set	Week 4		Week 8	
Product	**Diltiazem 2% (n=154)**	**Placebo (n=155)**	**Diltiazem 2% (n=154)**	**Placebo (n=155)**
Pain score ≥ 1 point reduction				
Yes	120 (77.9%)	111 (71.6%)	141 (91.6%)	130 (83.9%)
No	34 (22.1%)	44 (28.4%)	13 (8.4%)	25 (16.1%)
Pairwise comparisons with placebo				
Odds ratio	1.399	N/A	2.086	N/A
97.5% CI for odds ratio	(> 0.835)	N/A	(> 1.024)	N/A
p-value	0.1013	N/A	0.0214	N/A

Percentages are based on the total number of subjects in each treatment group.
CI = Confidence interval, N/A = Not applicable.
Pairwise comparisons with placebo were made using a logistic regression model adjusted for treatment. One-sided tests were performed at the 2.5% level of significance.

A greater number of subjects in the diltiazem group compared with placebo at Week 4 and Week 8. The difference at Week 8 was statistically significant.

12.1.8. Evaluators' response

1. The importance of medical therapy as first line therapy for AF is accepted. However, the treatment must be effective.
2. The sponsor reiterates the view that any statistically significant benefit is clinically meaningful or valuable. However, specialist bodies such as the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [IMMPACT (www.immpact.org)] are concerned about the relevance of statistically significant but minor changes in clinical pain studies, and stress the importance of a pre-determined MCID (Miller, 2010). Their recommended thresholds for a minimal, moderate, and substantial improvements are 1 unit (or 10-20%), 2 units (or 30-36%), and 4 units (≥50%) NRS, respectively This view is based on observed correlations between NRS scores and verbal rating scales, e.g. patients who report moderate improvement in pain will typically record changes of 2 units NRS.
3. The value of NRS as a measurement tool has been justified.
4. The sponsor notes that patients in the diltiazem 2% group did achieve a mean reduction of at least 2 units (2.63 units or 42%), thus meeting the IMMPACT criteria. This argument is unacceptable as the mean difference compared with placebo was only -0.43 units.
5. The responder analysis in patients achieving ≥1 unit reduction is not convincing. The primary endpoint was mean NRS scores for worst anal pain at Week 4 in the ITT population. At Week 4 in the responder analysis, the odds ratio compared with placebo was 1.399 but this was not statistically significant (p=0.101).

- ***Question 5: In DAF09, there were marginal benefits in terms of pain relief and healing (ignoring levels of statistical significance). Was pain relief associated with healing? What were the treatment emergent changes in pain scores in subjects who did/did not heal?***

12.1.9. Sponsor's response

Pain relief occurred in all subjects regardless of the anal fissure healing or not healing. However, there was a greater reduction in pain scores in those subjects that had healed compared to those that had not healed. Again this is consistent with the claimed indication of pain relief.

Table 3: Pain scores.

Week	Average score of worst anal pain associated with or following defaecation	Diltiazem 2%		Placebo	
		Healed	Not Healed	Healed	Not Healed
4	N	7	147	3	152
	Adjusted mean change from baseline (SE)	-4.18	-2.44	-4.74	-2.09
8	N	48	106	37	118
	Adjusted mean change from baseline (SE)	-3.44	-2.24	-3.19	-1.89

N is the number of subjects with both baseline and post-baseline measurements.
SE = Standard error.
An ANCOVA model adjusted for treatment, centre (grouped) and baseline value was used.

12.1.10. Evaluators' response

The sponsor's response is satisfactory.

- ***Question 6: Have manometry studies of anal sphincter tone been conducted using the DTZ 2% cream formulation proposed for marketing? If so, what percentage reductions in pressure were achieved?***

12.1.11. Sponsor's response

Manometry studies have not been conducted using the proposed diltiazem 2% cream formulation. Studies of diltiazem gel in varying concentrations have been conducted in healthy volunteers as reported.

12.1.12. Evaluators' response

It is unfortunate that no manometry studies have been conducted using the cream formulation in either healthy subjects or AF patients.

12.2. Safety

- ***Question 7: Please confirm that the cream formulations applied in studies DAF09, VEN307-DERM-001 and VEN307-DERM-002 are identical to the formulation proposed for marketing. Was propylene glycol a component in each study?***

12.2.1. Sponsor's response

The cream formulations applied in studies DAF09, VEN307-DERM-001 and VEN307-DERM-002 are identical to the formulation proposed for marketing. Propylene glycol was a component in each study.

12.2.2. Evaluators' response

The sponsor's response is satisfactory.

- ***Question 8: In the DTZ 2% group of DAF09, anal pruritus and anal discomfort were reported in 14.9% and 13.6% of subjects, respectively, compared with 7.7% and 5.8% in the placebo group, respectively. However, in study VEN307-DERM-001, only five AEs (arthralgia, dizziness, and headache) were reported in 202 healthy subjects, and no AEs were reported in VEN307-DERM-002. While ADRs are obviously less common, typically the majority of healthy subjects in any Phase 1 study report at least one AE in response to a standard non-leading question. Please explain how AEs were elicited, documented and assessed in the healthy subject studies.***

12.2.3. Sponsor's response

In the healthy volunteer studies, AEs were elicited by asking a non-leading question and documenting in in the CRF as relevant followed by investigation by the medical monitor. Exposure was shorter than in study DAF09 so the considerable reduction in AEs is not unexpected.

12.2.4. Evaluators' response

The sponsor's response is implausible as the incidence of AEs is typically 40-60% in single dose healthy volunteer studies. Possibly only clinically significant AEs or ADRs were reported in the CSR.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

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

13.2. Second round assessment of risks

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

13.3. Second round assessment of benefit-risk balance

After consideration of the responses to clinical questions, the benefit-risk balance of ANOHEAL in the proposed usage are unchanged from those identified in the first round.

14. Second round recommendation regarding authorisation

Authorisation for ANOHEAL (renamed ANO-CREAM) for the proposed usage is not recommended.

Insufficient clinical efficacy has been demonstrated in the single pivotal study presented and the benefit/risk assessment remains negative. The sponsor proposes that any statistically significant improvement in pain control is clinically meaningful, however small it may be. This view is not supported by experts in the field who suggest that treatment differences of at least 1-2 NRS units may be considered clinically important. The mean treatment difference of <1 NRS unit in the pivotal study cannot be considered clinically meaningful and the sponsor has put forward no evidence to support the contrary view.

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