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RESULTS SUMMARY

TITLE:	Randomized multicenter, placebo-controlled, single blind study to assess the efficacy and tolerability of a combination of a cream containing ubidecarenone, dexpanthenol and chlorhexidine and a paste containing 2% diltiazem hydrochloride in the treatment of chronic anal fissure.
PROTOCOL CODE:	DIL-UBI-DEX-CLO II/2003/003/PT
DATA OF STUDY INITIATION (FPFV):	30/Jan/2009
DATE OF STUDY COMPLETION (LPLV):	24/Apr/2014
BACKGROUND:	Although the efficacy of diltiazem hydrochloride in the treatment of chronic anal fissure (CAF) is already reported in the literature, the effect of this treatment when administered concomitantly with ubidecarenone 4%, dexpanthenol 5% and chlorhexidine 0.5% (UDC) has not yet been established. This study aimed to understand the efficacy and safety of diltiazem hydrochloride applied concomitantly with a fixed experimental combination of UDC, compared to diltiazem hydrochloride 2% (DTZ 2%) + placebo of the UDC (PLC), in the treatment of CAF.
STUDY OBJECTIVES:	The main objective of this clinical trial is to assess the relative efficacy of the concomitant administration of UDC cream and DTZ 2% paste versus the administration of DTZ 2% paste + placebo of the UDC (PLC) after 8 weeks of CAF treatment. Secondary objectives include the comparison between the two treatment arms regarding: a) improvement of symptoms (pain) within 8 weeks of treatment; b) improvement of symptoms (pain) within 4 weeks of treatment; c) cure rate within 4 weeks of treatment; d) tolerability within 8 weeks of treatment; 2) CAF relapse rate during a 24 week follow up period.
STUDY DESIGN:	This was a multinational, phase II/III, randomized, parallel, placebo controlled single blind clinical trial, developed to assess the efficacy and tolerability of co-administration of DTZ 2% and UDC versus DTZ 2% and PLC in the treatment of CAF. Two periods were defined for this study: 1. Treatment period (8 weeks) – period where the study treatment was administered, comprised by 4 visits. The treatment ended after week 8 or before, if the patient reached clinical cure, defined by complete closure of anal fissure observed in the objective exam. A follow-up period was conducted if clinical cure was reached. If not, no follow-up period was carried out. 2. Follow-up period (24 weeks) – carried out exclusively in patients that reached clinical cure. Two (2) phone contacts (PC) were carried out during the follow-up period. If clinical cure was observed before V4 , treatment would be terminated right away and the patient would be included in the follow-up period before week 8. On the other hand, if clinical cure was not achieved during the treatment period, the patient would discontinue the study at the end of the treatment period and not included in the follow-up period.

	Two groups were defined for this study: Group I, treated with DTZ 2% + PLC and Group II, treated with DTZ 2% + UDC. In an initial phase (study part I), an inclusion of 30 patients in each group (60 overall) was planned. An interim analysis on the primary endpoint was planned to be performed after the 60th patient achieved 8 weeks of treatment. The difference between Group I and Group II was not significant but was higher than 10%. In consequence, recruitment continued until 240 patients were included.
STUDY POPULATION	Study part I – 60 patients (30 per group). Study part II – 180 patients (90 per group). Study population (overall) – 240 patients (120 per group). Recruitment lasted 6 months after inclusion of the first patient in each country and per each study part. For patient disposition please refer to Figure 1.
Number of groups:	Two (2) groups: • Group I: DTZ 2% + PLC. • Group II: DTZ 2% + UDC. The ratio of allocation between Treatment Groups I and II was 1:1.
Main Inclusion/Exclusion criteria	Inclusion criteria: 1. Patients aged 18 years or above. 2. Diagnosis of idiopathic CAF unresponsive to previous therapy. 3. Patients able to comply with the study protocol as per investigator criteria. 4. Signed and dated informed consent by the patient or his/her representative/witness (as per applicable law). 5. Absence of any exclusion criterion. Exclusion criteria: 1. Patients presenting with any of the clinical conditions mentioned below: a) Anal fissure lacking features for chronicity. b) Cured anal fissure. c) Infected CAF. d) Multiple fissures. e) Fissure with irregular margins. f) Fissure at locations other than the midline.

g) Fissure unassociated with sphincter spasm.

2. Patients with fecal incontinence rectocele, rectal prolapse or fibrotic anal stenosis.
3. Patients with prior anal surgery.
4. Patients treated with botulinum toxin less than 6 months prior to enrolment.
5. Patients with CAF secondary to other disorders such as chronic inflammatory bowel disease, intestinal tuberculosis, anal or peri-anal cancer, anal fistula, sexually transmitted diseases, anal or peri-anal sepsis.
6. Patients with malignant diseases and a life expectancy of less than 1 year or patients undergoing chemo- or radiotherapy less than 6 months prior to enrolment.
7. Patients with clinically significant cardiovascular disorder, namely New York Heart Association (NYHA) class III and IV heart failure, atrial fibrillation, atrioventricular block, or clinically significant bradycardia.
8. Patients with orthostatic (postural) hypotension.
9. Patients with respiratory insufficiency and need for long term oxygen therapy or home ventilation.
10. Patients with clinically significant renal failure.
11. Patients with known human immunodeficiency virus (HIV) infection.
12. Patients with known neuromuscular disease.
13. Pregnant or lactating patients.
14. Women of childbearing potential who are sexually active and who do not use an effective contraceptive method. The following are considered to be effective contraceptive methods: intra-uterine device, oral contraceptives, injected contraceptives, contraceptive implants and surgical sterilization of partner (vasectomy with negative sperm count and in a monogamous relationship). In case barrier methods were used, double protection methods (condoms, spermicidal diaphragm and similar) were deemed effective.

    a) The protocol version applied for the Czech Republic described differently “Women of childbearing potential who are sexually active and who do not use a highly effective contraceptive method with Pearl index < 1. The following are considered to be highly effective contraceptive methods: intra-uterine device (IUD), surgical sterilization of partner supposing that the partner is the sole partner during study; further established use of oral contraceptives, injected contraceptives, contraceptive implants and at the same time one barrier method (i.e. condom). The men should use condom in every time. The use of two barrier methods with spermicide can be also considered as effective.”

15. Patients with any changes in the previous 12 weeks to oral, sublingual or intra-muscular therapy with vasodilators (beta blockers, nitrates, calcium antagonists, phosphodiesterase 4 inhibitors) or muscle relaxants.
16. Patients who used an analgesic, anesthetic, cicatrizant, topical vasodilators, corticosteroid, vitamins A or E, or any other active

	substances that might be active in anal mucosa regeneration, less than 3 days before. 17. History of hypersensitivity or intolerance to any of the investigational medicinal products, or to their active substances or excipients, or to similar drugs. 18. Patients with clotting disorders. 19. Any known abnormal clinical or laboratory change that, as per the investigator, might interfere with the safety or efficacy assessment or any study procedure. 20. Patients who had participated in another clinical trial less than one month prior to enrolment or who are still involved in another trial.
INVESTIGATIONAL MEDICINAL PRODUCTS:	- Diltiazem hydrochloride 2% cutaneous paste. - Ubidecarenone 4%, Dexpanthenol 5% and Chlorhexidine 0.5% cutaneous cream. - Placebo of the UDC cutaneous cream. Group I was treated with the DTZ 2% cutaneous paste and the PLC cutaneous cream. – Comparator Group. Group II was treated with the DTZ 2% cutaneous paste and the UDC cutaneous cream. – Test Group.
Route of administration:	Cutaneous Use
EVALUATION CRITERIA: Efficacy:	Primary endpoint: • Proportion of patients for which CAF cure (defined as total closing of anal fissure observed in the physical examination) was observed during the 8 week treatment period. Secondary endpoints: • Symptomatic improvement assessed as variation in millimeters, using a visual analogue scale (VAS) for pain applied on the 8th week of treatment (V4). • Symptomatic improvement assessed as variation in millimeters, using a visual analogue scale (VAS) for pain applied on the 4th week of treatment (V3). • Proportion of patients for which cure of the CAF was observed until the 4th week of treatment (V2 and V3). Proportion of patients with relapsing disease during a 24-week follow up period after treatment withdrawal. (VF).

Safety:	Secondary endpoints: • Number of adverse events (AE) reported for each treatment arm during the total duration of the study. • Number of serious and/or unexpected adverse reactions reported for each treatment arm during the total duration of the study.
Statistical methodology	Efficacy analysis: Study part I (interim analysis): • Main efficacy endpoint analysis was performed through the comparison CAF cure rates between Group I and Group II in the intention to treat (ITT) population, until V4, through Chi-square ($\chi 2$) test. Study part II (final analysis): • Main efficacy endpoint analysis was performed through the comparison CAF cure rates between Group I and Group II, in the ITT and per protocol (PP) populations, until V4, through Fisher's exact test. • Secondary efficacy endpoints analyses included: o Comparison of CAF cure rates between Group I and Group II, in the ITT population, until V3, through the Fisher's exact test. o Comparison of changes in VAS for pain between V1 and V4 and between V1 and V3 between Group I and Group II, in the ITT population, through Mann-Whitney U Test (2-sided). o All results were considered significant at a total significance level below 0.05. Accordingly, a level of significance of 0.01 was adopted for the interim analysis and 0.0452 for the final analysis. Safety analysis: Adverse events were analyzed descriptively per group of treatment in the safety population. Comparisons between Group I and Group II were performed for incidence of adverse events, serious adverse events, unexpected adverse events, unexpected and/or serious adverse events and unexpected and serious adverse events throughout the study, through the Fisher's exact test.
STUDY POPULATION Final demographic and baseline characteristics	For the ITT population, subject's mean age was approximately 45 years (43.5 years for group I and 47.4 years for group II), with a mean weight of 78.3 kg (77.0 kg for group I and 79.5 kg for group II) and height of 167.5 cm (169.7 cm for group I and 165.3 cm for group II). Overall sample showed a slightly higher proportion of female patients (51.3%), with 45.5% in group I and 57.0% in group

	II.
STUDY RESULTS <u>Interim efficacy results (part I)</u>	Primary endpoint (ITT population): • A higher proportion of patients in Group II were cured within 8 weeks (60.0%), compared to Group I (40.7%). However, this difference was not statistically significant (p=0.267).
<u>Final efficacy results (part II)</u>	Primary efficacy endpoint analysis (ITT population): • A higher proportion of patients in Group II showed cured CAF within 8 weeks of treatment, compared with Group I, although this difference was not statistically significant (64.0% vs. 58.0%, respectively; p=0.413). Primary efficacy endpoint analysis (PP population): • A higher proportion of patients in Group II presented CAF cure within 8 weeks of treatment, compared with patients in Group I, although this difference was not statistically significant (68.8% vs. 64.9%, respectively; p=0.642). Secondary efficacy endpoints analysis (ITT population): • Median variations (V1 – V4) in pain VAS were higher, and therefore more favorable, in Group I, compared to Group II (49.00 vs. 46.50, respectively), although no statistically significant differences were found (p=0.873). • Median variations (V1 – V3) in pain VAS were higher, and therefore more favorable, in Group II, compared to Group I (41.50 vs. 37.50, respectively), although no statistically significant differences were found (p=0.900). • A higher proportion of patients within Group II showed cured CAF within 4 weeks of treatment, compared with Group I, although this difference was not statistically significant (15.8% vs. 12.5%, respectively; p=0.568). • A higher proportion of patients with relapse was seen in the DTZ 2% + UDC group (Group II), compared with Group I (19.7% vs. 12.5%), although this difference was statistically non-significant (p=0.351). Safety analysis (ITT population): • A statistically significant higher incidence of AEs was observed in Group II, compared to Group I (56.2% vs. 42.7%; p=0.039). • Group II reports higher incidence of SAEs compared to Group I, although no statistically significant changes were found (7.4% vs. 5.1%; p=0.596). • Group II reported higher incidence of unexpected AEs compared to Group I, although no statistically significant changes were found (36.4% vs. 31.6%; p=0.495). • Group II reported higher incidence of unexpected and/or serious SAEs, although no statistically significant changes were found (36.4% vs.

	32.5%; p=0.586). • Group II reported higher incidence of unexpected and serious SAEs compared to Group I, although no statistically significant changes were found (7.4% vs. 4.3%; p=0.411).
MAIN CONCLUSIONS	Based on the results obtained in this study, no statistically significant differences were shown between groups regarding CAF cure rates or pain VAS, throughout the treatment period, as well as relapse rates during the follow-up period. Regarding safety analysis, Group II showed a higher prevalence of adverse events than Group I ($p<0.05$). However, no statistically significant differences were found regarding the incidence of serious and/or unexpected adverse events. In summary, both treatment options seem to provide similar clinical benefit in patients with CAF, as well as a comparable safety profile.

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Figure 1. Patient Disposition