Clinical Study Report

1 Title Page

Study Title:

Multicentre, double-blind, randomised clinical trial to evaluate and compare the efficacy and safety of Hemorrane Plus (Hemorrane® + benzocaine) with Hemorrane® and with placebo in patients with uncomplicated haemorrhoids

Study medicinal product:	Hydrocortisone acetate + benzocaine
Indication:	Uncomplicated haemorrhoids
Protocol Number:	HEMP-0119/ES
EudraCT Number	2019-003024-20
Study Phase	Phase III
Date First Subject Entered (FP/FV)	30-March-2023
Date First Subject Randomised	30-March-2023
Date Last Subject Completed (LP/LV)	04-January-2024
Sponsor:	FAES FARMA, S.A. Avda. Autonomía, 10 48940 Leioa (Vizcaya) Spain. Phone: +34 94 481 83 00 Fax: +34 94 481 83 09
Report version	1.0
Report date	July 02, 2024

This clinical trial was conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki (Fortaleza, Brazil; October 2013), the Harmonized Tripartite Guidelines for Good Clinical Practice, and applicable regulatory requirements.

Signature Page – Sponsor Medical Officer

Study Title:
Multicentre, double-blind, randomised clinical trial to evaluate and compare the efficacy and safety of Hemorrane Plus (Hemorrane® + benzocaine) with Hemorrane® and with placebo in patients with uncomplicated haemorrhoids.

Inmaculada Gilaberte Director Clinical Research Representative of FAES Farma, S.A.	Date:	Signature:

2 Synopsis

Clinical Trial
Protocol Identification Protocol Number: HEMP-0119/ES EudraCT Number: 2019-003024-20
Phase of the Study Phase III
Sponsor FAES FARMA, S.A. Avda. Autonomía, 10 48940 Leioa (Vizcaya) Spain. Phone: +34 94 481 83 00 Fax: +34 94 481 83 09
Participating Investigators The list of participating investigators is shown in **Table 1**.
Participating Centres A total of 11 centres in Spain were involved in the study. The list of participating investigators is shown in **Table 1**.
Publications (references) Not applicable.
Studied period Start of data collection (first patient inclusion (FP/FV): 30-March-2023 End of data collection (last patient, last visit (LP/LV): 04-January-2024
Study Objectives Primary: To evaluate the efficacy on pain of Hemorrane Plus (Hemorrane® + benzocaine) versus placebo; as well as the speed of action on pain of Hemorrane Plus and Hemorrane®, in patients with uncomplicated haemorrhoids. Secondary: 1. To evaluate the efficacy on pain of Hemorrane® versus placebo. 2. To evaluate the non-inferiority on pain of Hemorrane Plus versus Hemorrane®. 3. To compare the efficacy of the three treatments to relieve itching.

4. To compare the efficacy of the three treatments on the relief of stinging/burning.
5. To assess the action of the three treatments on bleeding.
6. To compare the efficacy of the three treatments on local inflammation.
7. To compare the efficacy of the three treatments on quality of life.
8. To evaluate the safety and tolerability of the three treatments.

Methods/ Trial design

This was a randomised, double-blind, multicenter clinical study in subjects with uncomplicated haemorrhoids.

The study consisted of:

- Screening and randomization visit (Visit 1)
- A 7-day treatment period (Visit 1 to Visit 2)
- A 7-day (± 2) follow-up period (Visit 3)

Number of patients (planned and analysed)

The planned sample size was 195 subjects. A total of 21 subjects were screened for the trial and 21 subjects met the inclusion criteria and none of the exclusion criteria.

Twenty-one (21) subjects were randomized and 18 completed their participation on the clinical study.

Study population

Inclusion criteria

1. Over 18 years of age and of either sex.
2. Voluntary signing of informed consent.
3. Diagnosis of uncomplicated haemorrhoids: grade I or II non-thrombosed external, mixed, or internal haemorrhoids.
4. VAS of pain ≥ 5 points.
5. VAS of itching and stinging/burning ≥ 5 points (for each one).
6. Commitment to comply with the hygienic-dietary measures established for the general management of haemorrhoids.
7. Negative urine pregnancy test (women of childbearing potential, if applicable).
8. Patients with adequate understanding of the study and ability to perform the procedures independently.

Exclusion criteria

1. History of hypersensitivity to any of the active ingredients or components of the products under investigation, as well as hypersensitivity to other local anaesthetics derived from para-aminobenzoic acid (PABA), parabens or para-phenylenediamine (e.g. hair dyes, henna tattoos).

2. Use of topical antihemorrhoidal or other topical agents for the anorectal area since at least 48 hours before the start of the study (Visit 1, day 1).
3. Haemorrhoidal surgery planned between Visit 1 (day 1) and the follow-up visit Visit 3 (day 15±2).
4. Diagnosis of external thrombosed haemorrhoids or internal grade III or IV haemorrhoids.
5. Medical history of anaemia, and/or current diagnosis of cardiac or pulmonary disease, shock, sepsis, acidosis, or genetic predisposition (NADH-cytochrome B5 reductase deficiency, glucose-6-phosphate dehydrogenase deficiency, and haemoglobin M disease); that suppose a risk factor for methaemoglobinaemia.
6. Documented diagnosis of active tuberculosis.
7. Active bleeding of haemorrhoids.
8. Presence of pain, stinging/burning, itching, anorectal bleeding, or rectal bleeding for causes other than haemorrhoidal disease.
9. Presence of bacterial, viral, and/or fungal infections in the perianal area.
10. History of pancreatic pathology that may require bentiromide screening test.
11. Use of any of the prohibited concomitant medications (sulphonamides, cholinesterase inhibitors, ester or prilocaine-type local anaesthetics, sodium nitrite, neurotoxic insecticides (topical malathion), aminosalicylic acid, suxamethonium, antiarrhythmics, monoamine oxidase inhibitors, tricyclic antidepressants, and PABA derivatives) one week prior to the start of the study (Visit 1, Day 1), or throughout the study.
12. Use of any hair dye, including those containing paraphenylenediamine during the study, from Visit 1 (Day 1) until follow-up Visit 3 (Day 15 ± 2).
13. Any other circumstance considered by the investigator that hinders proper monitoring and/or appropriate evolution of the study treatment response.
14. Pregnant women or those planning an upcoming pregnancy or in breast-feeding period.
15. Women of childbearing potential who do not agree to take the pregnancy test and use valid contraceptive methods during the study and until the end of the use of the investigational treatment. The following are considered valid contraceptive methods: combined hormonal oral, intravaginal or transdermal contraceptives (oestrogen and progesterone), oral, injectable or implantable progesterone-based hormonal contraceptives, intrauterine device (IUD), hormone-releasing intrauterine device, bilateral tubal occlusion, vasectomized partner (as long as they are the only sexual partner of the participating patient and the success of the intervention has been medically confirmed), or sexual abstinence (abstaining from heterosexual intercourse during the treatment period). The investigator is responsible for determining whether the patient has an appropriate contraceptive method for their participation in the study.
16. Fertile men who do not commit to use condoms or haven't had a vasectomy (as long as the success of the intervention has been medically confirmed), or who do not practice abstinence (abstinence from heterosexual sexual relationships during the treatment period). The investigator is

responsible for determining whether the patient has an appropriate contraceptive method for their participation in the study.

17. Patients who have had active cancer in the last five years.
18. Patients who have received an investigational medicinal product (including vaccines) or who have used an invasive medical device in the last 30 days prior to the start of the screening phase or who are currently participating in another clinical trial.
19. Patients who have a family or professional relationship with any member of the research team participating in the clinical study.

Test medicinal product, dose and mode of administration, batch number
Hemorrane Plus ointment (hydrocortisone 10 mg/mL + benzocaine 30 mg/mL) rectal application twice daily. Clinical batch number: IF0026 (expiry date: March-2024)

Reference therapy, dose and mode of administration, batch number
Hemorrane® ointment (hydrocortisone 10 mg/mL) rectal application twice daily. Clinical batch number: IF0026 (expiry date: March 2024)
Placebo ointment, rectal application twice daily. Clinical batch number: IF0026 (expiry date: March 2024)

Duration of treatment

Seven days.

Criteria for evaluation

Efficacy

Primary efficacy endpoint:

Percentage of responders at T156h +30 min (day 7 hour 12 + 30min) compared to T0 (day 1 hour 0), for Hemorrane Plus (group 1) and placebo (Group 3); as well as the percentage of responders within 30 minutes after the application of Hemorrane Plus (Group 1) and Hemorrane® (Group 2). Responders are defined as those patients with a decrease of two or more points out of ten on the Visual Analogue Scale (VAS) for pain (assessed by the patient).

Secondary efficacy endpoints:

1. Percentage of responders at T156h +30 min (day 7 hour 12 + 30min) compared to T0 (day 1 hour 0), for Hemorrane® versus placebo.

2. Percentage of responders at T156h +30 min (day 7 hour 12 + 30min) compared to T0 (day 1 hour 0), for Hemorrane® Plus and Hemorrane®.

3. Change in the VAS for itching (assessed by the patient), at the established times, compared to the baseline value (T0), for the three treatments.

4. Change in the VAS for stinging/burning (assessed by the patient), at the established times, compared to the baseline value (T0), for the three treatments.

5. Assessment of the mean values of the bleeding episodes recorded (assessed by the investigator) at Visit 1 (Screening and baseline), and at Visit 2 (day 8+1), for the three treatments.

6. Change in the VAS of inflammation (assessed by the investigator) at Visit 2 (day 8+1), compared to baseline (T0), for the three treatments.

7. Change in the patient's quality of life measured with the EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire, at Visit 2 (day 8+1), compared to the baseline value at Visit 1 (day 1, T0), for the three treatments.

Secondary safety endpoints:

Safety assessments included incidence of adverse events (AEs), topical allergic reactions, description of local tolerability and satisfaction, clinically significant changes in laboratory parameters (haematology, biochemistry, and methaemoglobin) compared to baseline values and percentage of patients withdrawn for safety reasons during study treatment.

Statistical methods

Considering that the study was closed without reaching the planned sample size, the study endpoints could not be analysed as planned in the study protocol. Thus, all analyses were performed on the safety population, defined as all randomised patients who received at least one application of the study treatment and had a subsequent follow-up visit or safety assessment. A descriptive analysis was carried out to show the main characteristics of the sample and, in a descriptive way, some of the main evaluation measures. Hypothesis testing was not carried out since the statistical power estimated with 11% of the pre-specified total sample size was less than 10%.

Quantitative variables were described with central tendency and dispersion measures, while qualitative variables were described using absolute and relative frequencies.

Safety and tolerability variables were analysed descriptively using number (n) and percentage (%) for the description. Finally, these results were not expressed as percentages due to the small number of patients assigned to each treatment group.

Data was analysed using SAS ® software, Version 9.4 of the SAS System for Windows.

Analysis of the study objectives

As indicated in the Statistical Methods section, some of the study objectives could not be analysed as originally planned in the study protocol and the Statistical Analysis Plan (SAP) due to the short sample size recruited. Instead, all comparative objectives were analysed descriptively.
The percentage of responders was represented descriptively at day 1, hour 0+30 and day 7 hour 12+30. The remaining efficacy endpoints such as the VAS for itching, stinging/burning and inflammation, bleeding episodes and the EQ*5D-5L questionnaire, including the VAS for Health were equally analysed in a descriptive manner.

Efficacy results
While the data collected from the participants who were enrolled may provide some data, the study's inability to reach its target sample size limits the efficacy analysis and the results obtained.
Primary endpoint

The percentage of responders observed at T156h +30 min (day 7 hour 12 + 30min) compared to T0 (day 1 hour 0) was 85.7% (6 subjects) in Hemorrane Plus group, and 100% (3 subjects) in placebo group).

Regarding speed of action, the percentage of responders within 30 minutes after the application of treatment (day 1 hour 0 + 30 min) were 42.9% (3 subjects) in Hemorrane Plus group in contrast to 50% (5 subjects) in Hemorrane® group.

Secondary endpoints

Percentage of responders observed at T156h +30 min of Hemorrane Plus group was 85.7% (6 subjects) compared to a 100% of responders in each Hemorrane® (9 subjects) and placebo (3 subjects) group.

The mean (SD) VAS score for itching at baseline (day 1 hour 0) of the three groups was 5.3 (0.32), 6.1 (1.35) and 6.8 (1.26) in Hemorrane®, Hemorrane Plus and placebo groups respectively compared to a mean (SD) score at T156h +30 min (day 7 hour 12 + 30min) of 0.4 (1.01) in Hemorrane® group, 1.1 (1.77) in Hemorrane Plus group and 0.0 (0.00) in placebo group

The mean (SD) VAS score for stinging/burning at baseline (day 1 hour 0) of the three groups was 5.1 (0.32), 5.7 (0.95) and 6.8 (1.26) in Hemorrane, Hemorrane Plus and placebo groups respectively. At T156h +30 min (day 7 hour 12 + 30min), the mean (SD) VAS score was 0.6 (1.13) in Hemorrane® group, 1.1 (1.77) in Hemorrane Plus group and 0.0 (0.00) in placebo group.

The mean (SD) VAS score for inflammation assessed by the investigator at baseline (day 1 hour 0) was 4.1 (1.45), 4.3 (1.60) and 4.5 (1.00) in Hemorrane®, Hemorrane Plus and placebo groups respectively. At V2 (day 8), mean (SD) VAS scores for inflammation of 1.8 (2.28) in Hemorrane® group subjects, 2.1 (1.77) in Hemorrane Plus group subjects and 2.0 (2.00) in placebo groups group subjects were reported.

At day 1 and day 8, mean (SD) number of bleeding events was 3.7 (2.3) and 3.5 (3.5) in Hemorrane® group, 1.0 (0) and 1.0(-) in Hemorrane Plus group and 2.6 (2.2) and 2.3 (2.5) in Placebo group patients.

Regarding quality of life, the items of the EQ-5D-5L questionnaire remained with minimal changes from day 1 to day 8 of treatment in all three treatment groups, except for pain/discomfort, for which an improvement was observed in the Hemorrane® and Hemorrane Plus groups from day 1 to day 8 of the study. VAS Health score improved also for Hemorrane® and Hemorrane Plus groups from day 1 to day 8 of the study, while placebo group score remained stable.

Safety results

Thirteen (13) AEs were reported in 11 patients, with a major incidence in the Hemorrane® group (6 patients) followed by placebo (2 patients) and Hemorrane Plus (3 patients). The most frequent AEs were infections and infestations (all of them in Hemorrane group,), and no topical allergic reactions were recorded in any group.

Three (3) patients experienced related AEs, two (2) of them belonging to the Hemorrane group and one (1) in the Hemorrane Plus group (which was considered expected AE based on the safety information provided in the Investigator's Brochure (IB)).

One (1) patient (Hemorrane® group) reported a severe AE, considered a worsening of preexisting condition.

None of the patients were withdrawn due to AEs, even though one (1) patient was mistakenly reported as having been withdrawn due to an adverse event (by the investigator).

No serious adverse events or deaths were reported during the study.

There were no clinically significant changes in haematology, biochemistry or methaemoglobin analysis from baseline.

Conclusion

Poor participant recruitment has led to the premature closure of this trial. The population targeted for its inclusion in this study typically does not seek clinical treatment for their pathology unless complications arise. Furthermore, many of the patients who were purposed to participate in the study declined since they did not perceive any benefits from their participation in it.

Although the small sample size prevents us from drawing definitive conclusions about efficacy, the experimental drug demonstrated to be well-tolerated and safe in the administered subjects

Date of report

10 June 2024 (version 0.1)