Sponsor:

BIOKOSMES S.r.l.
Via dei Livelli 1
23842 Bosisio Parini, Lecco (Italy)

Coordinating Centre

Unități medicale:Specializare: Medicină de familie
Principal Investigator:
C.M.I. Dr. Sisu Lucia-Cristina

Protocol Title:

Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief of haemorrhoidal disease and anal irritation symptoms

Final report: OpBio/0123/MD
Version: 1.0 20250513

1. COVER

Clinical Investigation Plan Title	Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief of haemorrhoidal disease and anal irritation symptoms
Study Product	OpBio/0123/MD
ClinicalTrials.gov Identifier	NCT 06944951
Sponsor/Manufacturer	BIOKOSMES S.r.l. Via Besana 10, 20122 Milano, Italy
Clinical Research Organization	Solaris Healthcare SA Via Favre 3 6830 Chiasso
Study Geography and Site	Unități medicale Specializare: Medicină de familie Str.Eustatiu Stoenescu 200443 CRAIOVA C.I. C.M.I. Dr. Sisu Lucia-Cristina
Patient Population	The sample size for this study is 50 patients Actual study population: 50 patients
Document Version	Version 1.0
Date	20250513

This Final Report has been prepared in accordance with current regulatory standards (ISO 14155:2020, MDR 2017/745, ICH GCP)

BIOkosmes
SKIN CARE CONTRACT MANUFACTURER

Version History

Version	Summary of Changes	Details
1.0	Initial draft	

SIGNATURES

We, the undersigned, have read and approved this Clinical Investigation Report, and approve its contents:

C.M.I. Dr. Sisu Lucia-Cristina, Principal Investigator — Date 05/06/2025

Lodovico Braguti, Direttore Tecnico Biokosmes Srl — Date 27/05/2025

Donatella Mariani, Chief Executive Officer — Date 13/05/2025

Solaris Healthcare SA

Prof. Bruno Mario Cesana, statistician — Data 13/5/2025

Solaris Healthcare SA

2. TABLE OF CONTENT

Index of Figures

Index of Tables

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3. SUMMARY

Title	Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief of haemorrhoidal disease and anal irritation symptoms
Study Start Date	28th October 2024
Study Stop Date	27th January 2025
Sponsor	BIOKOSMES S.r.l. Via Besana 10, 20122 Milano, Italy
Product/medical device description	PROCTOeze® PLUS is a soft and light hydrophilic emulsion, adjuvant for the symptomatic relief of internal and external haemorrhoids and anal irritation. PROCTOeze® PLUS key ingredients are mainly paraffinum liquidum, petrolatum, dimethicone, and hydroxyethyl cellulose.
Intended use	PROCTOeze® PLUS creates a physical barrier that protects the peri-anal tissue, minimizing the possibility of bacterial colonization and contact with local and environmental agents, which may exacerbate haemorrhoid condition. It has a protective, lubricating and refreshing action and emollient properties, which help to prevent irritation and discomfort of the perianal area, providing relief from pain, burning, itching and other related complaints, contributing to the physiological restoration of the anal and perianal tissues. Its application leaves the treated area soft and moisturized, avoiding the onset of irritation and cracking of the skin. The lubricating action helps to facilitate bowel movement, thus minimising the trauma and pain sensation associated with defecation.
Dosage form and Route of Administration	PROCTOeze® PLUS is a soft and light hydrophilic emulsion it is applied, throughout the anal orifice and on the surrounding perianal area to relieve symptoms associated to hemorrhoids and anal irritation, when required up to three/four times per day. To prevent anal irritation and cracking of the skin, it is possible to apply PROCTOeze® PLUS once a day.
Regulatory Status	This product is a substance-based medical device, CE marked, Class IIb rule 21 according to the Regulation (EU) 2017/745
Study Design	Open, non-comparative, multicenters, prospective, interventional trial.
Study Geography and Site Numbers	Three centers in Craiova, Romania
Introduction	Haemorrhoids are present universally in healthy individuals as cushions surrounding the anastomoses between the superior rectal artery and the superior, middle, and inferior rectal veins. Nonetheless, the term “haemorrhoid” is commonly invoked to characterise the pathologic process of symptomatic haemorrhoid disease instead of the normal anatomic structure. Haemorrhoids play a significant physiologic role in protecting the anal sphincter muscles and augment closure of the anal canal during moments of increased abdominal pressure (e.g., coughing, sneezing) to prevent incontinence and contribute 15 to 20% of the resting anal canal pressure. Increases in abdominal pressure increase the pressure in the inferior vena cava that cause these vascular cushions to engorge and prevent leakage. PROCTOeze® PLUS, a soft and light hydrophilic emulsion able to provide symptomatic relief of haemorrhoids and anal irritation thanks to its formulation (s). Moreover, due to its formulation, the product contributes to the physiological restoration of anal and perianal tissues.

Study Rationale/Purpose	The Research Question of the present trial is the following: in a population of adult patients, men and women, suffering from symptomatic haemorrhoids, will the administration for 4 weeks of the IMD PROCTOeze® PLUS improve the haemorrhoidal symptomatology, giving results assessed at the end of the treatment by means of validated questionnaires?
Study Objective	This trial aims to evaluate the overall performance and safety of the MD PROCTOeze® PLUS in relieving symptomatology of haemorrhoidal disease and anal irritation in adult patients affected by Grade I-II (Goligher classification) haemorrhoids as assessed by the patient and the Investigator at the end of the treatment period. The primary objective is the assessment of performance by the improvement in the quality of life (QoL). Secondary objectives are the assessment of performance by validated scales completed by the Investigator and by the patient at the end of the treatment period. The safety of the MD will be evaluated through AE and ADE incidence assessed by Investigators and reported according to the current legislation.
Study Primary endpoints:	● The Short Health Scale for Haemorrhoidal Disease (SHSHD) (Annex 3 "Collected variables") (5,16,17) will be used to evaluate the QoL. The questionnaire will be administered by the Investigator to each patient during the study visit, at baseline and on day 30, in PAPI mode (Paper and Pen Interview)
Secondary endpoints:	● The Haemorrhoid Severity Score (HSS) (Annex 3 "Collected variables") (6), a physician-reported outcome, will be completed by Investigator at baseline and day 30, at the end of the treatment with the MD ● The Haemorrhoidal Disease Symptom Score (HDSS) (Annex 3 "Collected variables") (5,19) is a patient-reported outcome. The questionnaire will be administered by Investigator to each patient at baseline and on day 30, at the end of the treatment with the MD. ● Evaluation of AE, SAE, ADE, SADE, ASADE, USADE incidence assessed by Investigator and reported according to the current legislation for the whole study period. Device Deficiencies (DD) will be also evaluated.
Study Population	Adult patients affected by Grade I-II (Goligher classification) haemorrhoids that did not need hospitalization and treated as outpatients (the treatment will be self-administered at home).
Selection criteria	● Men and women ≥ 18 years old. ● Patients diagnosed with Grade I – II symptomatic haemorrhoids (according to Goligher classification) confirmed by clinical and anoscopic or proctoscopic examination performed within 3 months before baseline. ● Patients able to do self-administration at home of the MD, for 30 days, to treat symptoms of haemorrhoids and anal irritation. ● Patient free from the following treatments for haemorrhoids for at least 4 weeks: laser treatments for haemorrhoids, steroidal or non-steroidal anti-inflammatory drugs, analgesics, any anti-haemorrhoidal treatment, anticoagulants, and antiplatelet agents. ● Patients able to communicate adequately with the Investigator and understand the trial questionnaire. ● Patients able to understand and who can provide valid informed consent to the trial.
Study sites	Unități medicale Specializare: Medicină de familie Str.Eustatiu Stoenescu 200443 - CRAIOVA PI C.M.I. Dr. Sisu Lucia-Cristina PI C.M.I. Dr. Paulina Brezoi PI C.M.I. Dr. Sanda Petcu

Executive summary	This report summarizes the results of the post-marketing clinical investigation conducted in Romania to evaluate the efficacy and safety of PROCTOeze® PLUS in treating hemorrhoidal symptoms and anal irritation. This open-label, non-comparative, prospective study enrolled 50 patients (68% females and 32% males) with Grade I-II hemorrhoids. The primary endpoint was assessed using the Short Health Scale for Hemorrhoidal Disease (SHSHD) to evaluate quality of life, while secondary endpoints were measured via the Hemorrhoidal Disease Symptom Score (HDSS) and Hemorrhoid Severity Score (HSS). Statistically significant reductions ($P < 0.0001$) were observed for SHSHD, HDSS, and HSS scores from baseline to the end of treatment. Notably, a significant interaction was observed in the HSS between genders. The device demonstrated good tolerability and an acceptable safety profile
Sample Size Calculation and Statistical Methods	A total of 50 subjects was be enrolled. Simple size estimation was based on the primary endpoint. By employing a one-tailed Wilcoxon signed-rank test for matched pairs at a significant level of 2.5 % and a power of 80 % we derived a sample size of 50 evaluable patients to prove PROCTOeze® PLUS performance. Considering a possible screen failure rate of 10% we require 55 enrollable patients. In addition, 5 patients should account for a possible 10% moderate drop-out rate, so 60 patients should be screened for enrolment in the clinical investigation. Descriptive statistics (mean, standard deviation - SD- median, first and third quartile - Q1-Q3, min-max) have been calculated for quantitative variables. Absolute and percent frequencies have been calculated for qualitative variables. Comparison between gender on quantitative variables normally/symmetrically distributed have been carried out by means of the Student's t test. The change of the total of the SHSDH (primary objective of the study), on the total of the HSS and HDSS (secondary objectives of the study) between baseline and the end of the study has been assessed, according to the protocol, by means of the Wilcoxon signed-rank test. In addition, the change between Visit 1 and Visit 2 of SHSDH, HSS, and HDSS has been modeled between the two genders by means of the repeated measurement ANOVA with gender as a fixed factor between patients, time as a fixed factor within patients and their interaction. The detailed statistical tables and figures are included below.
Discussion	The findings of this PMCF study confirm that PROCTOeze® PLUS is effective and safe in relieving the symptoms of haemorrhoidal disease and anal irritation. The significant reduction in pain, itching, burning, and swelling highlights the product's efficacy, while the absence of adverse events demonstrates good tolerability. The statistical analyses demonstrate a significant improvement in quality of life and symptom relief. • The SHSHD score decreased markedly, indicating enhanced quality of life. • Both the HDSS and HSS scores showed significant reductions, confirming the device's efficacy in alleviating symptom severity. • The significant interaction in the HSS suggests a gender-related difference in response, which may require further study. • Overall, the safety data were reassuring, with no adverse events reported. The integrated tables and figures from the statistical analysis clearly support the robustness of these findings.

Results	**Demographics and Baseline Characteristics** • Number of Patients: 50 • Gender Distribution 68% female, 32% male • Mean Age Approximately 50 years (SD 13.90) with no significant difference between genders (see Table 1). **Outcome Assessments** SHSHD • Baseline: 14.04 (SD 7.79) • End-of-Treatment: 7.80 (SD 3.69) • Mean Reduction: 6.24 points (P < 0.0001) (See Table 5 and Figure 2 for detailed analysis.) HDSS • Baseline: 10.12 (SD 3.60) • End-of-Treatment: 7.20 (SD 2.47) • Mean Reduction: 2.92 points (P < 0.0001) (See Table 6 and Figure 3 for detailed analysis.) HSS • Baseline: 8.50 (SD 2.11) • End-of-Treatment: 6.48 (SD 2.17) • Mean Reduction: 2.02 points (P < 0.0001) • A significant Visit x Gender interaction was found (P = 0.0272). (See Table 7 and Figure 4 for detailed analysis.) **Device Usage** Patient diaries indicated a mean usage of approximately 34 cream applications over the 14-day monitoring period, with daily consumption remaining relatively consistent and a slight decrease observed in the later study days. **Safety** No serious adverse events (SAEs) were reported. No, AE was reported.
Conclusions	This post-marketing clinical investigation demonstrates that PROCTOeze® PLUS is effective in improving quality of life and reducing the symptoms associated with hemorrhoidal disease and anal irritation in adult patients with Grade I-II hemorrhoids. The significant reductions in SHSHD, HDSS, and HSS scores (all P < 0.0001), combined with an acceptable safety profile, support the continued clinical use of PROCTOeze® PLUS. Ongoing post-marketing surveillance is recommended to further confirm the long-term safety of the device.

Timing	Approval by National Bioethics Committee for Medicines and Medical Devices	18th October, 2024
	Start of enrolment (FPI)	8th November 2024
	End of enrolment (LPI)	17th December 2024
	End of treatment (LPO)	16th January 2025
	Final Report of trial	03th April 2025

4. PROTOCOL

Sponsor:

BIOKOSMES S.r.l.
Via dei Livelli 1
23842 Bosisio Parini, Lecco (Italy)

Unități medicale: ; Specializare: Medicină de familie
Coordinating Centre:

C.M.I. Dr. Sisu Lucia-Cristina
Principal Investigator:

Protocol Title:

Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief of haemorrhoidal disease and anal irritation symptoms

Protocol Code: OpBio/0123/MD
Version: 1.0 – 20241201

Type: PMCF

Register: www.ClinicalTrials.gov
Contract Research Organization:
Solaris Healthcare SA
Via Favre 3
CH 6830 Chiasso

PROTOCOL APPROVAL - SPONSOR

Sponsor

I declare that our company has sent all information related to the Investigational Medical Device to the CRO to elaborate the clinical investigation plan code OPBIO/0123/MD (Version: 1.0– 20231201).

Name:	Dr Lodovico Braguti
Date:	_____/_____/_____
Signature:	_____
Professional position:	CEO and Legal Representative
Company:	BIOKOSMES S.r.l. Via Besana 10, 20122 Milano (Italy) (Registered Office)

PROTOCOL APPROVAL

Site No. 01 –Principal Investigator

I have carefully read the protocol trial plan code OpBio/0123/MD (Version: 1.0 – 20231201) and, on behalf of the study staff and myself, I agree to maintain the procedures required by the BIOKOSMES S.r.l. and CRO, to conduct this trial in accordance with Good Clinical Practice, Declaration of Helsinki, local laws and regulations. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. I agree that BIOKOSMES S.r.l., its delegates, CRO, and National Competent Authorities have direct access to all study documentation. I agree to obtain written Informed Consent from all participating patients.

Name: **C.M.I. Dr. Sisu Lucia-Cristina**

Date: _____/_____/_____

Signature: _____

Professional position: **Medical Doctor**

Site: **Unități medicale Specializare: Medicină de familie Str.Eustatiu Stoenescu 200443**

CRAIOVA

EMERGENCY CONTACTS

Role	*Contact Name*	*Phone/fax/e-mail*
SPONSOR BIOKOSMES S.r.l.	Andrea Turconi Quality Assurance Director Diana Koprivec Clinical and Safety	Phone: +39 0313581085 e-mail: andrea.turconi@biokosmes.it Phone +41 79 220 10 94 diana.koprivec@kbcompany.ch
CRO SOLARIS Healthcare SA	Donatella Mariani Project Director and QPPV	Mobile: +41 79 844 2600 e-mail: pv@solarishc.ch

RESPONSIBILITIES

SPONSOR

BIOKOSMES S.r.l.
Via dei Livelli 1, 23842 Bosisio Parini, Lecco (Italy) (Headquarters)
Via Besana 10, 20122 Milano (Italy) (Registered Office)
Telephone: +39 0313581085
Fax +39 0313581082
e-mail: biokosmes@biokosmes.it

Represented by:

Dr Lodovico Braguti
Phone: + 39 0313581085
e-mail: biokosmes@biokosmes.it

CRO

Represented by:

Donatella Mariani
Phone +41 79 8442600
e-mail info@solarishc.ch

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CRO	Contract Research Organization
DB	Data Base
DD	Device Deficiency
DPS	Data Privacy Sheet
EC	Ethics Committee
CRF	Case Report Form
EMA	European Medicines Agency
FPI	First Patient In
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HDSS	Haemorrhoidal Disease Symptom Score
HSS	Haemorrhoid Severity Score
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IFU	Instructions For Use
IMD	Investigational Medical Device
ISF	Investigator Site File
LPI	Last Patient In
LPO	Last Patient Out
CRO	Contract Research Organization S.r.l.
PMCF	Post-marketing Clinical Follow-Up
QC	Quality Control
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SHS_{HD}	Short Health Scale for Haemorrhoidal Disease
SR	Study Report
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

SYNOPSIS

Title	**Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief of haemorrhoidal disease and anal irritation symptoms**
Protocol code	OpBio/0123/MD
Version	1.0 – 20241201
Registry	www.ClinicalTrials.gov
Type	Post-Marketing Clinical Follow-Up
MD class	Medical Device of Class IIb, according to the classification rules of Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (Rule 21).
Sponsor	BIOKOSMES S.r.l. Via Besana 10, 20122 Milano, Italy (Registered Office)
CRO	Solaris Healthcare SA Via Favre 3 6830 Chiasso The Sponsor authorised and delegated the CRO to perform: ● Support to define the rationale and research hypothesis. ● Protocol writing. ● CRF and work instructions preparation. ● ICF and other study documents preparation. ● Elaboration of study documents in the Romanian language. ● Preparation and updating of Trial Master File (TMF) and Investigator Study File (ISF). ● **Ethics Committees and Competent Authority issues and submissions in Romania.** ● Supporting the procedures for the financial agreement between the Sponsor and administrations of involved Centres in Romania. ● Monitoring ● Data Management. ● Safety Management. ● Statistical Analysis. ● Preparation of the Final Report.
Introduction and Rationale	Haemorrhoids are variceal dilatations of the anal and perianal venous plexus and often develop secondary to the persistently elevated venous pressure within the haemorrhoidal plexus (1,2). Haemorrhoids may be present in three classical positions: the right anterior, right posterior and left lateral areas of the anal canal. External haemorrhoids are

	covered with skin and internal haemorrhoids are covered with anal mucous membranes. Goligher introduced the most widely accepted classification (3,4). Most symptoms and signs that patients present with arise from internal haemorrhoids, derive from structural changes of the normal anatomic padding (enlarged internal haemorrhoids) and are generally associated with chronic straining either due to constipation, diarrhoea or prolonged periods trying to defecate. Symptoms are also common during pregnancy and childbirth. The acute clinical manifestation of the haemorrhoidal disease is commonly known as haemorrhoidal crisis and it is characterized by rectal bleeding, prolapse, pruritus (itching), pain, oedema, often thrombosis, and less frequently soiling or mucoid discharge (1,2). The most common sign is rectal bleeding that appears bright red for the high blood oxygen content within the arteriovenous anastomosis. The bleeding is usually described as red spotting on the toilet tissue or dripping in the toilet bowl at the end of defecation, separately from the stool. External haemorrhoids may be asymptomatic or associated with discomfort or with acute extreme pain in the event of a local thrombosis (formation of a clot). BIOKOSMES has developed the medical device PROCTOeze® PLUS, a soft and light hydrophilic emulsion, containing film-forming agents that help minimise the possibility of bacterial colonisation and contact with environmental dirt, which may exacerbate haemorrhoid condition. The ingredients responsible for the formation of the barrier are mainly paraffinum liquidum, petrolatum, dimethicone, and hydroxyethylcellulose. The film-forming (barrier) effect allows the retention of the product locally, at the rectal mucosa level, maintaining the emollient action, meanwhile the overall rheologic effect of the product facilitates the emptying of the rectal ampoule with a subsequent decrease of local discomfort. PROCTOeze® PLUS is registered as a Medical Device of Class IIb, rule 21 according to the Regulation (EU) 2017/745 and it is largely used in the clinical practice of thousands of medical doctors in Italy, Romania, Iceland, Bulgaria, Taiwan, and Israel. Following the actual medical device legislation, the manufacturer must routinely present to the Notified Body for each CE-registered medical device the results of clinical investigations performed post-marketing clinical follow-up (PMCF) activities. The present trial is planned to follow this requirement and it will be performed in Romania where the IMD PROCTOeze® PLUS is commercialised with the brand name PROCTINUM®. The Research Question of the present trial is the following: in a population of adult patients, men and women, suffering from symptomatic haemorrhoids, will the administration for 4 weeks of the IMD PROCTOeze® PLUS improve the haemorrhoidal symptomatology, giving favorable results assessed at the end of the treatment by means of validated questionnaires?
Objectives	This trial aims to evaluate the overall performance and safety of the MD PROCTOeze® PLUS in relieving symptomatology of haemorrhoidal disease and

	anal irritation in adult patients affected by Grade I-II (Goligher classification) haemorrhoids as assessed by the patient and the Investigator at the end of the treatment period. The primary objective is the assessment of performance by the improvement in the quality of life (QoL). Secondary objectives are the assessment of performance by validated scales completed by the Investigator and by the patient at the end of the treatment period. The safety of the MD will be evaluated through Adverse Events (AE) and Adverse Device Effect (ADE) incidence assessed by Investigators and reported according to the current legislation.
Outcomes	Primary outcome ● The Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) (5) will be used to evaluate the QoL. The questionnaire will be completed by the patient at baseline and day 30, at the end of the treatment with the MD. Secondary outcomes ● The Haemorrhoid Severity Score (HSS) (6), a physician-reported outcome, will be completed by Investigator at baseline and day 30, at the end of the treatment with the MD. ● The Haemorrhoidal Disease Symptom Score (HDSS) (5), a patient-reported outcome questionnaire, will be administered by Investigator to each patient at baseline and at day 30, at the end of the treatment with the MD. ● Evaluation of AE, SAE, ADE, SADE, ASADE, USADE incidence assessed by Investigator and reported according to the current legislation for the whole study period. DD will be also evaluated.
Design	Open, non-comparative, prospective, interventional trial.
Disease	Hemoroidal disease :Grade I – II symptomatic haemorrhoids (according to Goligher classification)
Population	Adult patients affected by Grade I-II (Goligher classification) haemorrhoids that did not need hospitalization and treated as outpatients (the treatment will be self-administered at home).
Inclusion criteria	● Men and women ≥ 18 years old. ● Patients diagnosed with Grade I – II symptomatic haemorrhoids (according to Goligher classification) confirmed by clinical and anoscopic or proctoscopic examination performed within 3 months before baseline. ● Patients able to do self-administration at home of the MD, for 30 days, to treat symptoms of haemorrhoids and anal irritation. ● Patient free from the following treatments for haemorrhoids for at least 4 weeks: laser treatments for haemorrhoids, steroidal or non-steroidal anti-inflammatory drugs, analgesics, any anti-haemorrhoidal treatment, anticoagulants, and antiplatelet agents.

	● Patients able to communicate adequately with the Investigator and understand the trial questionnaire. ● Patients able to understand and who can provide valid informed consent to the trial.
Exclusion criteria	● Inflammatory and infectious disease of the digestive tract (e.g., IBD – Inflammatory Bowel Disease). ● Frequent hemorraidal bleeding ● Severe, uncontrolled hypertension, renal failure, cirrhosis, colorectal cancer, anal fissure or fistula. ● Patients with known sensitivity to the tested medical device or its components. ● Patients with any other medical condition that, in the opinion of the Investigator, would compromise participation or be likely to lead to hospitalisation during the study. ● Participation in an interventional clinical study or administration of any investigational agents in the previous 30 days.
Countries	Romania.
Number of patients	The number of evaluable patients will be 50.
Sample size calculation	The Short Health Scale for Haemorrhoidal Disease (SHS_{HD}), the primary outcome of this clinical investigation, was used as the basis for the calculation of the required sample size. In a study published by Renato Pietroletti et al. (2022) (7), the researchers assessed the performance of a rectal ointment based on Zn-L-carnosine in the treatment of haemorrhoidal disease by using the SHS_{HD} following 4 weeks of treatment with the medical device. Their results showed an SHSHD mean ± SD score of 7.90 ± 4.17 before treatment and 4.05 ± 0.22 after 4 weeks of treatment with Proctilor® rectal ointment. Lacking the results of a similar emulsion (PROCTOeze® PLUS) we assumed a mean ± SD SHS_{HD} score of 6.20 ± 0.25 after 4 weeks of treatment for the haemorrhoidal disease, resulting in a moderate effect size of around 0.42. By employing a one-tailed Wilcoxon signed-rank test for matched pairs at a significant level of 2.5 % and a power of 80 % we derived a sample size of 50 evaluable patients to prove PROCTOeze® PLUS performance. Considering a possible screen failure rate of 10% we require 55 enrollable patients. In addition, 5 patients should account for a possible 10% moderate drop-out rate, so 60 patients should be screened for enrolment in the clinical investigation.
Medical device	PROCTOeze® PLUS is a soft and light hydrophilic emulsion, adjuvant for the symptomatic relief of internal and external haemorrhoids and anal irritation. PROCTOeze® PLUS creates a physical barrier that protects the peri-anal tissue, minimizing the possibility of bacterial colonization and contact with local and environmental agents, which may exacerbate haemorrhoid condition. It has a protective, lubricating and refreshing action and emollient properties, which help to prevent irritation and discomfort of the perianal area, providing relief

	from pain, burning, itching and other related complaints, contributing to the physiological restoration of the anal and perianal tissues. Its application leaves the treated area soft and moisturised, avoiding the onset of irritation and cracking of the skin. The lubricating action helps to facilitate bowel movement, thus minimising the trauma and pain sensation associated with defecation. PROCTOeze® PLUS key ingredients are mainly paraffinum liquidum, petrolatum, dimethicone, and hydroxyethylcellulose. All the patients will use the MD PROCTOeze® PLUS during the whole study according to Instruction for Use of the MD and to standard clinical practice.
Chronogram of visits	The study envisages the following visits and phone follow up per patient: ● Visit 1, day 0: Screening / Baseline visit. ● Visit 2, day 14 (± 2 days): ● Phone follow up, day 30 (± 1 day).
Study duration	The study will last 30 days for each patient.
Procedures	Visit 1 Screening / Baseline visit (day 0) • Informed consent / Eligibility Criteria • Demographics / Medical History / Physical examination and vital signs (including haemorrhoids evaluation and confirmation of diagnosis) • Concomitant treatments and medications assessment • Quality of life assessment by means of the Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) by patient • Haemorrhoid Severity Score (HSS) by Investigator • Haemorrhoidal Disease Symptom Score (HDSS) by patient • Diary supply • MD supply Visit 2 End of Study visit (day 14 ± 2 days) • Treatment adherence • Diary's maintenance • Physical examination and vital signs (including haemorrhoids evaluation) • Concomitant treatments and medications assessment • Quality of life assessment by means of the Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) by patient • Haemorrhoid Severity Score (HSS) by Investigator • Haemorrhoidal Disease Symptom Score (HDSS) by patient • Diary collection • MD collection • Safety assessment by AE / ADE / DD collection **Phone call (day 30 ± 1 day)** • Treatment adherence • Diary's maintenance • Safety assessment by AE / ADE / DD collection
Not allowed concomitant treatment or	Any drug or treatment mentioned in the eligibility criteria as not allowed will be forbidden during the study and its use will have to be avoided by patients, otherwise they are excluded from the participation: use of laser treatment,

medications	steroidal or non-steroidal anti-inflammatory drugs, analgesics, any anti-haemorrhoidal treatment (both drugs and dietary supplements), anticoagulants, and antiplatelet agents will be not allowed during the whole study. No restriction on treatments taken previously by patients for medical conditions not related to this study protocol will be envisaged. Patients will be advised to note any concomitant treatment or medications or any major modification to their diet and / or lifestyle in the diary.
Statistical analysis	Statistical analyses will be conducted on all patients who have successfully completed the study without a protocol deviation that is regarded as impacting the assessment of the key variables (as per protocol). The quality and completeness of the collected data will be evaluated preliminarily ~~compared~~ to data analysis. If a patient is missing information for one or more variables, even after the resolution of its query, the missing data will not be replaced. If a patient has been involved in violation of inclusion/exclusion criteria, the respective data will be excluded from the analysis. Quantitative variables (i.e., demographic) if normally distributed will be described through media, and standard deviation (SD); non-normally distributed variables will be described using median and range of interquartile. The Student's t-test and the Mann-Whitney U will be employed to perform comparative analysis in accordance with the distribution of these variables. Factorial variance analysis can also be used to evaluate any interactions between quantitative variables and linear progression models to relate possible confounding bias with independent variables. Categorical variables will be finally described using frequencies and percentages and comparative analysis will use the $\chi 2$ test. The overall type I error rate will be preserved at 5%. All tests will be two-sided. Data from unscheduled visits will not be included in the analysis.
GCP Statement, Guidelines and legislation	The protocol is developed in accordance with the following: ● International Standard ISO 14155:2020 (10). ● Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (11). ● ICH 6 Harmonized Tripartite guidelines for Good Clinical Practice (ICH GCP) requirements (12). ● Local legislation.

Timing	Submission to Competent Authority	January, 2024
	Approval by Competent Authority/EC	February, 2024
	Start of enrolment (FPI)	February, 2024
	End of enrolment (LPI)	September, 2024
	End of treatment (LPO)	October, 2024
	Final Report of trial	December, 2024

SCHEDULE OF ASSESSMENTS

Procedures	***Visit 1***	***Visit 2***	***Follow up call***
	Screening Baseline	***visit***	Follow up
	Day 0	***Day 14 (± 2)***	***Day 30 (± 1)***
Informed consent	X		
Inclusion Criteria	X		
Exclusion Criteria	X		
Demographics and Medical History	X		
Physical examination and Vital signs[1]	X	X	
Concomitant treatments and medications assessment	X	X	X
Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) (by patient)	X	X	
Haemorrhoid Severity Score (HSS) (by Investigator)	X	X	
Haemorrhoidal Disease Symptom Score (HDSS) (by patient)	X	X	
Compliance		X	X
Patient Diary supply	X		
Patient Diary collection		X	
MD supply	X		
MD collection		X	
AE / ADE / DD assessment	X	X	X

[1]Patients diagnosed with Grade I – II symptomatic haemorrhoids (according to Goligher classification) confirmed by clinical and anoscopic or proctoscopic examination performed within 3 months before baseline will be enrolled. Haemorrhoids evaluation, pulse, blood pressure (diastolic and systolic), weight / height and BMI (kg/m^2) will be collected.

1. GENERAL INFORMATION

1.1. TITLE

Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief from haemorrhoidal disease and anal irritation.

1.2. STUDY REGISTRATION

Following the WHO statement on public disclosure of clinical study results in https://www.who.int/ictrp/results/WHO_Statement_results_reporting_clinical_trials.pdf, before a clinical study is initiated, its details must be registered in a publicly available, free to access, searchable clinical study registry complying with WHO's international agreed standards. The final version of this clinical study protocol will be registered on www.clinicaltrials.gov.

1.3. PROTOCOL VERSION

Issue Date: 1.0 – 20231201.

1.5.2. Sponsor

Sponsor	BIOKOSMES S.r.l.
Contact Name	Andrea Turconi, QA
Address	Via Besana 10, 20122 Milano (Italy)
Phone	+39 0313581085
e-mail	andrea.turconi@biokosmes.it
Contact Name	Diana Koprivec, MD PhD Clinical and Safety Consultant for Biokosmes S.r.l.
Address	KB Company SAGL Via San Gottardo 80 CH-6900 Massagno Lugano
Phone	+41 79 2201094
e-mail	diana.koprivec@kbcompany.ch

1.5.3. Centres

Sites located in Romania (i.e., the clinical centres), with all the necessary equipment required by the protocol, were selected for the trial.

1.5.5. Principal Investigator Roles

- General coordination of the site.
- Collection and reporting data with respect to International Standard ISO 14155:202, Romanian legislation and GDPR.

1.5.6. CRO

BIOKOSMES S.r.l., as Sponsor of the trial, has designated Contract Research Organization to perform the following activities:

- Support to define the rationale and research hypothesis.
- Protocol writing.
- CRF and work instructions preparation.
- ICF and other study documents preparation.
- Elaboration of study documents in the Romanian language.
- Preparation and updating of Trial Master File (TMF) and Investigator Study File (ISF).
- Ethics Committees and Competent Authority issues and submissions in Romania.
- Supporting the procedures for the financial agreement between the Sponsor and administrations of involved Centres in Romania.
- Data Management.
- Safety Management.
- Statistical Analysis.
- Preparation of the Final Report.

The extent of the delegation has been specified in a contract between the involved parties. During the study period, the CRO should implement quality assurance and quality control procedures, but the Sponsor will have the right to supervise the implementation of the methods in order to ensure quality.

1.6. CURRENT LEGISLATION AND GUIDELINES

The protocol of the present trial is developed in accordance with the following:

- International Standard ISO 14155:2020 (10).
- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (11).
- ICH Harmonized Tripartite guidelines for Good Clinical Practice (ICH GCP) requirements (12).
- Local Romanian legislation.

1.7. TIMING

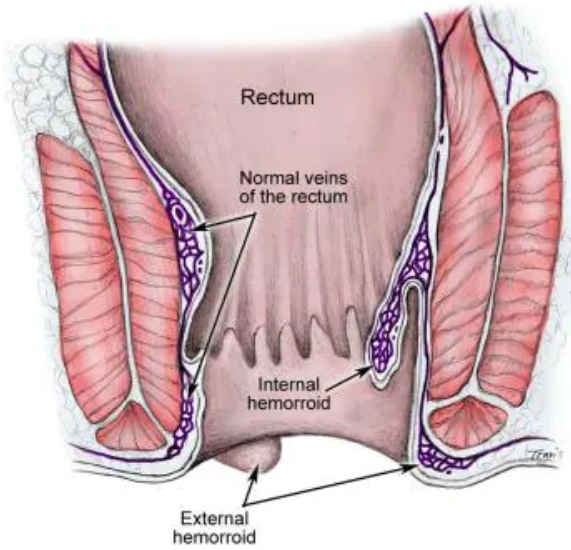
Timing	Submission to Competent Authority	January, 2024
	Approval by Competent Authority/EC	February, 2024
	Start of enrolment (FPI)	February, 2024
	End of enrolment (LPI)	September, 2024
	End of treatment (LPO)	October, 2024
	Final Report of trial	December, 2024

2. INTRODUCTION

2.1. BACKGROUND AND RATIONALE

Haemorrhoids are present universally in healthy individuals as cushions surrounding the anastomoses between the superior rectal artery and the superior, middle, and inferior rectal veins. Nonetheless, the term “haemorrhoid” is commonly invoked to characterise the pathologic process of symptomatic haemorrhoid disease instead of the normal anatomic structure. Haemorrhoids play a significant physiologic role in protecting the anal sphincter muscles and augment closure of the anal canal during moments of increased abdominal pressure (e.g., coughing, sneezing) to prevent incontinence and contribute 15 to 20% of the resting anal canal pressure. Increases in abdominal pressure increase the pressure in the inferior vena cava that cause these vascular cushions to engorge and prevent leakage.

Haemorrhoids are a very common anorectal condition defined as the symptomatic enlargement and distal displacement of the normal anal cushions. The abnormal dilatation and distortion of the vascular channel, together with destructive changes in the supporting connective tissue within the anal cushion, is a paramount finding of haemorrhoidal disease (13).



External haemorrhoids are located below the dentate line, internal haemorrhoids lie above the dentate line. Vascular outflows of internal haemorrhoids include the middle and superior rectal veins, which subsequently drain into the internal iliac vessels.

The most widely accepted classification for haemorrhoids was introduced by Goligher (3,4) (Annex 2).
The exact pathophysiology of symptomatic haemorrhoid disease is poorly understood. Currently, the theory of sliding anal canal lining, which proposes that haemorrhoids occur when the supporting tissues of the anal cushions deteriorate, is more widely accepted. Advancing age and activities such as strenuous lifting, straining with defecation, and prolonged sitting are thought to contribute to this process. Haemorrhoids is therefore the pathological term to describe the abnormal downward displacement of the anal cushions causing venous dilatation. On histopathological examination, changes seen in the anal cushions include abnormal venous dilatation, vascular thrombosis, degenerative process in the collagen fibres and fibroelastic tissues, and distortion and rupture of the anal subepithelial muscle (1,2).
The most common symptom is painless fresh rectal bleeding, but patients may also experience pruritus, swelling, prolapse, discharge, or soiling. For internal haemorrhoids, bleeding is the most commonly reported

symptom. The occurrence of bleeding is usually associated with defecation and is almost always painless (1,2).

The blood is bright red and coats the stool at the end of the defecation. Prolapsed internal haemorrhoids may accompany mild faecal incontinence, mucus discharge, sensation of perianal fullness, and irritation and pruritus of perianal skin. Pain is significantly less common with internal haemorrhoids than with external haemorrhoids, but can occur in the setting of prolapsed, strangulated internal haemorrhoids that develop gangrenous changes due to the associated ischemia. In contrast, external haemorrhoids are more likely to be associated with pain, due to activation of perianal innervations associated with thrombosis. Patients typically describe a painful perianal mass that is tender to palpation. This painful mass may be initially increasing in size and severity over time. Pruritis and “burning” can result from discharges or difficulty with hygiene (1,2).

The natural history of most cases of haemorrhoidal disease is self-limited. For a symptomatic haemorrhoidal disease that presents to the clinic or emergency room, treatments range from nonoperative medical interventions and office-based procedures to surgery.
One general guiding principle is that the least-invasive approaches should be considered first, except in cases of acute thrombosis. Specific choices of treatments depend on patients' age, severity of symptoms, and comorbidities (13). For symptomatic control, topical treatments containing various local anaesthetics, corticosteroids, or anti-inflammatory drugs are available. Notable topical drugs include 0.2% glyceryl trinitrate, which has been studied to relieve grade I or II haemorrhoids with high resting anal canal pressures but is associated with headaches in 43% of patients (14).
Pharmaceutical topical preparations containing steroids, anaesthetics, astringents, and/or antiseptics are often recommended for all grades of haemorrhoidal disease. However, no randomised studies support their use. Steroid-containing creams should not be used for prolonged periods because of their atrophic effects on skin and their efficacy remains unproven.
Except in the case of thrombosis, both internal and external haemorrhoids respond readily to conservative medical therapy.

BIOKOSMES has developed the medical device PROCTOeze® PLUS, a soft and light hydrophilic emulsion able to provide symptomatic relief of haemorrhoids and anal irritation thanks to its formulation (see in Annex 1 “Product composition” the composition of the product and the function of its components).
The product creates a physical barrier that protects the peri-anal tissue, minimising the possibility of bacterial colonisation and contact with environmental agents, which may exacerbate haemorrhoid conditions. The key ingredients responsible for the barrier film are the film-forming agents paraffinum liquidum, petrolatum, dimethicone and hydroxyethylcellulose.
The MD has a protective, lubricating and refreshing action; its emollient properties help to prevent irritation and discomfort of the perianal area, providing relief from pain, burning, itching and other haemorrhoidal-related complaints. Its application leaves the treated area soft and moisturised, avoiding the onset of irritation and cracking of the skin. The emollient and lubricating action helps to facilitate the emptying of the rectal ampoule with a subsequent decrease of local discomfort, minimising the trauma and pain associated with defecation. Moreover, due to its formulation, the product contributes to the physiological restoration of anal and perianal tissues.

PROCTOeze® PLUS is registered as a Medical Device of Class IIb, rule 21 according to the Regulation (EU) 2017/745 and it is largely used in the clinical practice of thousands of medical doctors in Italy, Romania, Iceland, Bulgaria, Taiwan, and Israel. Following the actual medical device legislation, the manufacturer must routinely present to the Notified Body, for each CE-registered medical device, the results of clinical investigations

performed as post-marketing clinical follow-up (PMCF) activities. The present trial is planned to follow this requirement and it will be performed in Romania where the IMD PROCTOeze® PLUS is commercialised with the brand name PROCTINUM®.

2.2. RESEARCH HYPOTHESIS

The Research Question of the present trial is the following: in a population of adult patients, men and women, suffering from symptomatic haemorrhoids, will the administration for 4 weeks of the IMD PROCTOeze® PLUS improve the haemorrhoidal symptomatology, giving results assessed at the end of the treatment by means of validated questionnaires?

2.3. STUDY OBJECTIVES

This trial aims to evaluate the overall performance and safety of the MD PROCTOeze® PLUS in relieving symptomatology of haemorrhoidal disease and anal irritation in adult patients affected by Grade I-II (Goligher classification) haemorrhoids as assessed by the patient and the Investigator at the end of the treatment period.

The primary objective is the assessment of performance by the improvement in the quality of life (QoL). Secondary objectives are the assessment of performance by validated scales completed by the Investigator and by the patient at the end of the treatment period.

The safety of the MD will be evaluated through AE and ADE incidence assessed by Investigators and reported according to the current legislation.

JUSTIFICATION FOR THE TRIAL

The protocol is based on what is already known on both the topic object of the study, i.e., the symptomatic treatment of haemorrhoids, and the investigational medical device, according to which is shortly summarized in section 2.1. MD PROCTOeze® PLUS is a specific adjuvant for the symptomatic relief of internal and external haemorrhoids and anal irritation. Due to its formulation, it contributes to the physiological restoration of the anal and perianal tissues.

The tool used in this research is a PMCF, a procedure which, through a scientific method of detection (one or more questionnaires to be submitted to a representative sample of patients related to the issue of the research), allows to collect, and subsequently analyse, the data needed to study the relationships between different variables.

3. PROCEDURES

3.1. DESIGN

Open, non-comparative, multicentre, prospective, interventional trial.

3.2. STUDY SETTING

Sites located in Romania (i.e., the clinical centres), will be involved

3.3. SELECTION OF POPULATION

The study population will include 50 evaluable patients, afferent at the study Centres. These patients will be asked for informed consent and verified for the inclusion and exclusion criteria.

3.3.1. Inclusion criteria

Patients will be eligible for inclusion if **ALL** the following criteria are respected:

- Men and women ≥ 18 years old.
- Patients diagnosed with Grade I – II symptomatic haemorrhoids (according to Goligher classification) confirmed by clinical and anoscopic or proctoscopic examination performed within 3 months before baseline.
- Patients able to do self-administration at home of the MD, for 30 days, to treat symptoms of haemorrhoids and anal irritation.
- Patient free from the following treatments for haemorrhoids for at least 4 weeks: laser treatments for haemorrhoids, steroidal or non-steroidal anti-inflammatory drugs, analgesics, any anti-haemorrhoidal treatment, anticoagulants, and antiplatelet agents.
- Patients able to communicate adequately with the Investigator and understand the questionnaire.
- Patients able to understand and who can provide valid informed consent to the trial.

3.3.2. Exclusion criteria

Patients fulfilling one or more of the following exclusion criteria will **NOT** be included in the study:

- Inflammatory and infectious disease of the digestive tract (e.g., IBD – Inflammatory Bowel Disease).
- Frequent hemorraidal bleeding
- Severe, uncontrolled hypertension, renal failure, cirrhosis, colorectal cancer, anal fissure or fistula.
- Patients with known sensitivity to the tested medical device or its components.
- Patients with any other medical condition that, in the opinion of the Investigator, would compromise participation or be likely to lead to hospitalisation during the study.
- Participation in an interventional clinical study or administration of any investigational agents in the previous 30 days. Patients considered smokers (≥10 cigarettes/day).
- Energy-restricted diet for weight loss.
- Pregnant woman, lactating woman, and woman of childbearing potential who is planning a pregnancy or is unwilling to use appropriate methods of contraception* during the study.
  *Methods of contraception: hormonal contraceptive, intrauterine device or intrauterine system, double barrier method (condom with spermicide/diaphragm or cervical cap with spermicide), surgical sterilization (vasectomy, tubal ligation, etc.).
- Patients unlikely to cooperate.
- Patients with any other medical condition that, in the opinion of the Investigator, would compromise participation or be likely to lead to hospitalisation during the study.
- Participation in an interventional clinical study or administration of any investigational agents in the previous 30 days.

3.3.3. Patient identification

Each patient enrolled will be identified by the patient number, a five digits code (e.g., 01.001), which will be the only identification element and will be used only for the purposes of this study. This code will consist of the Centre number (e.g., 01/02/etc. corresponding to each Centre) and of the sequence number of the patient (e.g., .001, which means the 1st patient enrolled). If the patient is declared a screening failure (one or more eligibility criteria is not fulfilled and the patient cannot participate in the study), the identification code will not be reassigned to another patient.

3.3.4. Patient Enrolment and allocation

Once the eligibility is established according to inclusion/exclusion criteria, ICF signed, patients will be enrolled

3.3.5. Number of patients

Fifty fully evaluable patients will be included in the study.

3.3.6. Withdrawal or discontinuation criteria and procedures; patient lost to follow up

Patients may withdraw at any time at their own request. The centre must inform the CRO personnel when a patient withdraws from the study.

The Investigator will complete and sign the appropriate CRF when a patient is lost to follow-up. The date and type of attempted communication with the patient will also be documented.

3.4. MEDICAL DEVICE DESCRIPTION

PROCTOeze® PLUS is a soft and light hydrophilic emulsion that provides protection to irritated areas. It is a specific adjuvant for the symptomatic relief of internal and external haemorrhoids and anal irritation. The product creates a physical barrier that protects the peri-anal tissue, minimizing the possibility of bacterial colonization and contact with local and environmental agents, which may exacerbate haemorrhoid conditions. Due to its formulation, it contributes to the physiological restoration of the anal and perianal tissues. PROCTOeze® PLUS has a protective, lubricating and refreshing action. PROCTOeze® PLUS has emollient properties, which help to prevent irritation and discomfort of the perianal area, providing relief from pain, burning, itching and other related complaints. Its application leaves the treated area soft and moisturised, avoiding the onset of irritation and cracking of the skin. The lubricating action helps to facilitate bowel movement, thus minimising the trauma and pain sensation associated with defecation. It also supports the physiological repairing process.

Key ingredients of IMD paraffinum liquidum, petrolatum, dimethicone and hydroxyethylcellulose (Annex 1 “Product composition”), appropriately provided with study-specific labels.

The MD will be supplied in the same package available on the market, and with the same leaflet / IFU – Instructions for Use.

3.4.1. Patient compliance monitoring

The investigator will assess patients’ compliance (adherence to the treatment) at the end of the study; the compliance will be assessed by means of the information about administration contained in the diary, completed by the patients for the whole study.

A patient will be declared as compliant with the treatment if he /she has used at least 75 % of the MD, according to Instruction for Use and to standard clinical practice.

3.4.2. Concomitant care and interventions that are permitted or prohibited during the study

Any drug or treatment mentioned in the eligibility criteria as not allowed will be forbidden during the study and its use will have to be avoided by patients, otherwise they are excluded from the participation: use of laser treatment, steroidal or non-steroidal anti-inflammatory drugs, analgesics, any anti-hemorrhoidal treatment (both drugs and dietary supplements), anticoagulants, and antiplatelet agents will be not allowed during the whole study.

No restriction on treatments taken previously by patients for medical conditions not related to this study protocol will be envisaged.

Patients will be advised to note any concomitant treatment or medications or any major modification to their diet and / or lifestyle in the diary.

3.5. STUDY PROCEDURES AND COLLECTED VARIABLES

3.5.1. Outcomes

The following outcomes will be evaluated:

Primary outcome

- The Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) (Annex 3 "Collected variables") (5,16,17) will be used to evaluate the QoL. The questionnaire will be administered by the Investigator to each patient during the study visit, at baseline and on day 30, in PAPI mode (Paper and Pen Interview) (15).

The Short Health Scale (SHS) is a patient-reported measurement instrument of subjective health originally developed for patients with inflammatory bowel disease (IBD) (16–18). SHS was proposed as a simplified HRQoL (Health-Related Quality of life) instrument with just 1 question in each of its 4 dimensions, including symptom burden, functional status, disease-specific worries, and general well-being. SHS was adapted for HD (Short Health Scale for Haemorrhoidal Disease - SHS_{HD}) in accordance with the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) guidelines; SHS_{HD} has shown to be a reliable and responsive measure for HRQoL. Patients are asked to report overall symptom load, interference with daily activities, and worries caused by HD. The fourth question regarded general well-being. A 7-point Likert scale, giving a total score ranging from 4 to 28 is used.

Secondary outcomes

- The Haemorrhoid Severity Score (HSS) (Annex 3 "Collected variables") (6), a physician-reported outcome, will be completed by Investigator at baseline and day 30, at the end of the treatment with the MD.

safety outcome

- Evaluation of AE, SAE, ADE, SADE, ASADE, USADE incidence assessed by Investigator and reported according to the current legislation for the whole study period. Device Deficiencies (DD) will be also evaluated.

The HS is a physician-reported measurement instrument based on PNR-Bleed classification, that classifies and describes the haemorrhoids based on the four main characteristics of the hemorrhoidal disease i.e., the degree of hemorrhoidal Prolapse (P), Number (N) of the primary hemorrhoidal columns involved, Relation (R) of the haemorrhoidal tissue to the dentate line and the amount of Bleeding (B) from it. All four components in this classification system are graded into five grades ranging from 1 to 5. Grade 1 is the normal anal cushions and Grade 5 is the worst grade in a specific characteristic. HSS is the total score obtained by the sum of the numerical grades of all four characteristics of haemorrhoids in the PNR-Bleed classification. The minimum HSS score is 4 and the maximum score can be 20. The HSS score of a normal person without any signs and symptoms of haemorrhoids is 4. Calculation of the HSS help in the quantification of the haemorrhoidal disease for further reference and is helpful in post-treatment patient follow-up to grade the response to treatment and to assess the effectiveness or failure of any particular treatment regimen for haemorrhoids. It may also be used in predicting and diagnosing the recurrence after any form of treatment for the haemorrhoids.

- The Haemorrhoidal Disease Symptom Score (HDSS) (Annex 3 "Collected variables") (5,19) is a patient-reported outcome. The questionnaire will be administered by Investigator to each patient at baseline and on day 30, at the end of the treatment with the MD.

The HDSS is a patient-reported measurement instrument. It comprises five items. Symptoms are assessed using the patient-reported frequency of the 5 symptoms, including pain, itching, bleeding, soiling, and prolapse. Patients are instructed to answer based on their experience during the previous period. Each symptom is graded on a 5-point scale (0 = never, 1 = less than once a month, 2 = less than once a week, 3 = 1–6 days per week, 4 = every day or always), giving a total score ranging from 0 to 20.

3.6. DEFINITIONS AND PROCEDURE FOR REPORTING OF ADVERSE EVENTS

3.6.1. DEFINITIONS

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the Investigational Medical Device (IMD).

a. This definition includes events that are anticipated as well as unanticipated events.

b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved (for the purpose of safety reporting all activities related to the use of a medical device may be considered procedures).

Serious Adverse Event (SAE)

Any adverse event that led to any of the following:

a) death,

b) serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury,

ii. permanent impairment of a body structure or a body function,

iii. hospitalization or prolongation of patient hospitalization,

iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

v. chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Device Deficiency (DD)

Device deficiency is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in the information supplied by the manufacturer.

Incident

Incident means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

Serious Incident

Serious Incident means any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat.

Serious Public Health Threat

Serious Public Health Threat means an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

Corrective Action

Corrective Action means action taken to eliminate the cause of a potential or actual non-conformity or other undesirable situation.

Field Safety Corrective Action

Field Safety Corrective Action means corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market.

Field Safety Notice

Field Safety Notice means a communication sent by a manufacturer to users or customers in relation to a field safety corrective action.

User

User means any healthcare professional or layperson who uses a device.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

This includes also any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristics of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated Serious Adverse Device Effect (ASADE)

Anticipated SADE is an effect that by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

3.6.2. CLASSIFICATION OF AN ADVERSE EVENT

The Investigator is responsible for the AE classification, following Annex F of ISO 14155 (reported in Annex 4).

The Investigator is responsible for the following assessment.

1. SEVERITY OF ADVERSE EVENT (AE) ASSESSMENT
   The severity (Intensity) of each AE will be evaluated according to the following 3/point scale: Grade 1, Mild (Events require minimal or no treatment and do not interfere with the participant's daily activities); Grade 2, Moderate (Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning); Grade 3, Severe (Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating).

2. CAUSALITY ASSESSMENT

   The Investigator will be responsible for assessing the causal relationship of the AE.

   The relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

   The investigators (and the Sponsor) will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

   Each SAE will be classified according to four different levels of causality:

   1. Not related

   2. Possible

   3. Probable

   4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure:

1. Not related: Relationship to the device, comparator or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to the application of the investigational device;

- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;

- the event involves a body-site or an organ that cannot be affected by the device or procedure;

- the serious adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

2. Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;

- the event involves a body-site or organ that

  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;

- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);

- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

- harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Only causality level 1 (i.e., “not related”) is excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event should be reported.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator’s Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illnesses or risk factors shall also be considered.

The above considerations apply also to the serious adverse events occurring in the comparison group.

3. TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care. At each visit/assessment, the participant should be assessed for the possible occurrence of an AE/SAE. Care will be taken not to introduce bias when detecting adverse events and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

Any medical condition that is present at the time that the participant is screened will be considered a baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of the onset and duration of each episode.

AE/SAE can occur during any period of the study. The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Each patient will receive a phone call from the investigator 30 days after the end of the study to check if there have been AEs. Events will be followed for outcome information until resolution or stabilization.

AE/SAE, as all medical occurrences, should be recorded by the Investigator in the subject’s medical records as source data.

Each identified AE is assessed by the Investigator for Seriousness and Causality relationships to the Investigational Medical device or procedure.

All AE/SAE will be recorded on the appropriate case report form (CRF) by the Investigator.

4. SAE REPORTING

The Investigator has the responsibility of reporting SAE/SADE to the Sponsor/CRO immediately and in any case no later than 24 hours of becoming aware by using the **SAE/SADE Reporting Form**, accompanied by the **SAE/SADE Reporting Form Instructions**.

The sponsor shall implement and maintain a system to ensure that the reporting of the reportable events, as above defined, is provided by the investigator to the sponsor immediately, but not later than 3 calendar days after the investigation site study personnel's awareness of the event.

The Sponsor must perform the evaluation of each SAE in order to assess of Seriousness, Expectedness and causality relationship to the Investigational Medical device (IMD) and/or the procedure.
The Sponsor must report to all NCAs where the clinical investigation is authorized to start:

a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where a such causal relationship is reasonably possible;

b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

c) any new findings in relation to any event referred to in points a) and b).

For all reportable events as described above which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **Immediately, but not later than 2 calendar days** after awareness by the sponsor of a new reportable event or new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals. These concerns may be identified by either the NCA or the manufacturer.

Any other reportable events or a new finding/update to it: **Immediately, but not later than 7 calendar days** following the date of awareness by the Sponsor of the new reportable event or new information in relation to the already reported event.

According to article 80 of Regulation 745/2017/EU, the sponsor shall fully record all of the following:

(a) any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of that clinical investigation;

(b) any serious adverse event;

(c) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

(d) any new findings in relation to any event referred to in points (a) to (c) furthermore.

<u>Reporting form</u>

The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan. The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported.

The sponsor shall report, without delay to all Member States in which the clinical investigation is being conducted, all of the following by means of the electronic system, if any:

(a)any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where a such causal relationship is reasonably possible;

(b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

(c) any new findings in relation to any event referred to in points (a) and (b).

Copies of any reports to regulatory bodies regarding serious and unexpected AEs will be provided to the investigators for review and submission to the EC. The communication of any SAEs to the EC and Competent Authority, will be done according to national requirements in Romania by the Investigator). Copies of SAEs correspondence with the investigators, regulatory bodies, and Sponsor must be retained with study records.

3.7. DATA COLLECTION

3.7.1. Collected variables

The details and template of the questionnaires are reported in Annex 3 with the corresponding references. Moreover, the questionnaires are contained in the CRF section of the ISF/TMF, as a separate document. The data collected will be saved on databases corresponding to the sites. Each database will be uniquely identified with the name of the location; each investigator will input data only in the database allocated to his location.

3.7.2. Schedule of assessments by visit

SCHEDULE OF ASSESSMENTS

Procedures	***Visit 1***	***Visit 2***	***Follow up call***
	Screening Baseline		Follow up ***visit***
	Day 0	***Day 14 (± 2)***	***Day 30 (± 1)***
Informed consent	X		
Inclusion Criteria	X		
Exclusion Criteria	X		
Demographics and Medical History	X		
Physical examination and Vital signs[1]	X	X	
Concomitant treatments and medications assessment	X	X	X
Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) (by patient)	X	X	
Haemorrhoid Severity Score (HSS) (by Investigator)	X	X	
Haemorrhoidal Disease Symptom Score (HDSS) (by patient)	X	X	
Compliance		X	X

Patient Diary supply	X		
Patient Diary collection		X	
MD supply	X		
MD collection		X	
AE / ADE / DD assessment	X	X	X

[1]Patients diagnosed with Grade I – II symptomatic haemorrhoids (according to Goligher classification) confirmed by clinical and anoscopic or proctoscopic examination performed within 3 months before baseline will be enrolled. Haemorrhoids evaluation, pulse, blood pressure (diastolic and systolic), weight / height and BMI (kg/m^2) will be collected.

3.7.2.1. Study visits

Visit 1 Screening / Baseline Visit (day 0)

At each Centre, patients will be enrolled consecutively. During this visit, patients who will meet the eligibility criteria (inclusion and exclusion criteria) will be enrolled after the signature of the informed consent form and will be informed verbally and in writing about the nature and requirements of the trial. Patients agreeing with the participation in the study will have to date and sign the informed consent form prior to any study-related procedure. All the screening procedures must be completed during this visit.

During this visit, the Investigator will collect information regarding medical history, demography, concomitant treatments and medications, AE/SAE if applicable. The Investigator will report data on the appropriate eCRF pages.

A physical examination will be performed, including evaluations of vital signs; pulse, blood pressure (diastolic and systolic), weight / height and BMI (kg/m^2) data will be collected. An evaluation of the haemorrhoidal disease will be performed, and a confirmation of the diagnosis and of the stage of haemorrhoids will take place, according to inclusion criteria (patients diagnosed with Grade I – II symptomatic haemorrhoids (according to Goligher classification, confirmed by clinical and anoscopic or proctoscopic examination performed within 3 months before baseline)

During this visit the following questionnaires will have to be completed:

- **HR-QoL questionnaire: SHS$_{HD}$ (by patient)**
- **HSS (by Investigator)**
- **HDSS (by patient)**

During this visit, the MD will be provided to each patient. The used, partially used and unused containers of the MD will have to be brought back to the centre on the last study visit. The MD will be supplied in the same package available on the market, and with the same leaflet / IFU – Instructions for Use.
A patient diary will be supplied; it will have to be completed at home by patients for the whole duration of the study. A series of information will have to be collected related to the health status of the patient (not an exhaustive list): use of any treatment or OTC or prescribed medications (concomitant treatments and medications), start and stop dates and name/dosage of the product will be collected; AE/ADE/DD occurrence; self-administration of the MD (according to IFU and standard clinical practice).
The importance of duly completing the diary will be stressed by the Investigator. The completed diary will be collected at the end of the study (at V2). Patients will be advised to note any major modification to their diet

and / or lifestyle in the diary. Moreover, patients will be informed (it will be written in the diary) that they will receive a phone call from the investigator 30 days after the end of the study to check if there have been AEs. The following visit (V2) will be scheduled 14 (± 2) days after V1; a phone call will be scheduled 30(± 1) days after V1.

Visit 2 (day 14 ± 2 days)

During this visit, the Investigator will perform the following examinations and the e-CRF will be completed accordingly:

- Physical examination (according to what was already performed at visit 1: pulse, blood pressure, weight / height and BMI will be evaluated), including haemorrhoidal disease evaluation.
- Concomitant treatments and medications assessment.
- Evaluation of compliance (MD administration assessment by means of the patient's diary carried out by Investigator).
- Diary and MD (used, partially used, or unused containers) collection.
- Safety assessment by AE/ADE/DD collection.

During this visit the following questionnaires will have to be completed:

- HR-QoL questionnaire: SHS_{HD} (by patient)
- HSS (by Investigator)
- HDSS (by patient)

Patients who discontinued the protocol, will be visited reporting on the last visit page all the safety assessments and (if possible) the examinations and questionnaires requested for the last visit.

Patients who discontinued the protocol, will be visited reporting on the last visit page all the safety assessments and (if possible) the questionnaires requested for the last visit.

Phone call (day 30 ± 1 day)

During this phone call the following evaluations will take place:

- **Safety assessment by AE / ADE / DD collection**

3.7.3 Case Report Form

The Case Report Form (CRF) of the study will be filled by investigator. The CRO will insert the data in the EDC

All data collected through CRO's EDC system will be checked for completeness and extreme values (outliers) presence. Any anomaly will be forwarded by the statistician/data manager to the Investigator and/or Clinical Research Associates. Such data queries will be solved with priority, in no more than 3 days from the query's opening. The statistician decides to use/accept the revised data for the subsequent statistical analyses.

Because of legal considerations (GDPR directive effective from 21.05.2018 in all European Union countries), patients or their legal surrogates may have an absolute right to request that their data are removed from the study database. As a result, there are potentially two datasets: the full list of enrolled patients, and the list containing the patients who have kept their data available. The latter is obtained after deleting the data for patients who withheld or withdrew their consent and did not allow their data to be submitted or maintained in the database. Only the latter dataset can be used in the analysis.

It is the CROs responsibility to keep all the above-mentioned software tools to their latest and most secure versions.

Data is stored according to existing legislation and current regulation (Directive 2001/20/EC and EU Regulation 1924/2006), and with the rules of Good Clinical Practice ICH E6 (R2). Succinctly, the Investigator Study File contains, among other study documents, the eCRFs printouts. The Sponsor will archive all the electronically collected data on DVDs. A copy of the eCRF printouts will be provided to the participating centres.

The collected data will be subjected to multiple checks for correctness (entry errors). Every information will be verified by an SDV (Source Data Verification) process, performed by the study monitors. Data Clarification Forms will be implemented to obtain clean data.

4. DATA MANAGEMENT AND ANALYSIS

4.1. Record keeping and archiving

At the end of the trial, all copies of all essential documentation will be archived securely by the Investigator for a minimum of 10 years starting when the last device has been put on the market. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements. Included in the records to be maintained are the signed protocol Trial, signed consent forms, ethics committee approval letters, correspondence with Sponsor/CRO and any other documents to identify the patients.

The CRO will notify the sites when the trial documentation can be archived. All archived documents must continue to be available for inspection by competent authorities or Sponsor audit upon request. In addition, if the Investigator moves/retires, etc., he/she should provide the Sponsor with the name and address of the person who will look after and be responsible for the trial-related records.

4.2. DATA MANAGEMENT

4.2.1. Data review, DB cleaning, issuing, and resolving queries

The Data Management process includes all activities related to data handling regarding:

- Set-up of study-specific DB for data processing and analysis.
- Supporting the Data entry / Data editing.
- Export of data to R statistical software.
- Creation of post-entry checks and listings.
- Clean-file process.

CRO will be responsible for all these activities. The confidentiality of records that could identify patients will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

4.2.2. Procedures for data retention and retention period definition

Electronic/physical data (study documents) will be retained by the Sponsor or other contracted third party for a minimum of 10 years starting when the last device has been put on the market, as required by clinical trial legislation.

4.3. STATISTICAL ANALYSIS

4.3.1. Sample size calculation

The Short Health Scale for Haemorrhoidal Disease (SHS_{HD}), the primary outcome of this clinical investigation, was used as the basis for the calculation of the required sample size. In a study published by Renato Pietroletti et al. (2022) (7), the researchers assessed the performance of a rectal ointment based on Zn-L-carnosine in the

treatment of haemorrhoidal disease by using the SHS_{HD} following 4 weeks of treatment with the medical device.

Their results showed an SHS_{HD} mean ± SD score of 7.90 ± 4.17 before treatment and 4.05 ± 0.22 after 4 weeks of treatment with Proctilor® rectal ointment.

Lacking the results of a similar emulsion (PROCTOeze® PLUS) we assumed a mean ± SD SHS_{HD} score of 6.20 ± 0.25 after 4 weeks of treatment for the haemorrhoidal disease, resulting in a moderate effect size of around 0.42.

By employing a one-tailed Wilcoxon signed-rank test for matched pairs at a significant level of 2.5 % and a power of 80 % we derived a sample size of 50 evaluable patients to prove PROCTOeze® PLUS performance.

Considering a possible screen failure rate of 10% we require 55 enrollable patients.

In addition, 5 patients should account for a possible 10% moderate drop-out rate, so 60 patients should be screened for enrolment in the clinical investigation.

The software used in the calculation was G*Power v3.1.9.7 (8).

4.3.2. Statistical design, method, and analytical procedures

Design: Open, non-comparative, multicentre, prospective, interventional trial.

The principle of intention-to-treat (ITT), as far as practically possible, will be the main strategy of the analysis adopted for the primary endpoint and all the secondary endpoints. These analyses will be conducted on all participants.

No imputations will be made on missing data.

The statistical plan details the following 3 analysis sets which will be evaluated in this study:

- The ITT population, which includes each patient enrolled in the study that used at least one dose of the investigational product and had at least one efficacy assessment.
- The Per-Protocol population, which excludes patients with major protocol deviations or violations (e.g., did not use the investigational product, did not attend all the visits, or had missing data regarding the primary endpoint) and includes those with valid observations on the primary endpoint.
- Safety population, which includes each patient enrolled in the study that used at least one dose of the investigational product.

The protocol outlines that a two-sided p-value of 0.05 or less will be used to declare statistical significance for all analyses. Similarly, all confidence intervals will be calculated at the 95% level.

No adjustment for multiplicity will be made to adjust the type 1 error rate for secondary endpoints. If necessary, relevant results from other studies already reported in the literature will be considered in the interpretation of results.

If a patient is missing information for one or more variables, the missing data will not be replaced.

All statistical analyses will be performed using the R statistical software v 4.2.2 (9), or the latest stable version at the time of statistical analysis.

The final analysis will be completed after all patients have been exited from the study, all queries have been resolved, and the database has been locked.

The overall type I error rate will be preserved at 5%. All tests will be two-sided. Data from unscheduled visits will not be included in the analysis.

Statistical analyses will be conducted on all patients who have successfully completed the study without a protocol deviation that is regarded as impacting the assessment of the key variables (as per protocol). The quality and completeness of the collected data will be evaluated preliminarily compared to data analysis. If a patient is missing information for one or more variables, even after the resolution of its query, the missing data will not be replaced. If a patient has been involved in violation of inclusion/exclusion criteria, the respective data will be excluded from the analysis. Quantitative variables (i.e., demographic) if normally distributed will be described through media, and standard deviation (SD); non-normally distributed variables will be described using median and range of interquartile. The Student's t-test and the Mann-Whitney U will be employed to perform comparative analysis in accordance with the distribution of these variables. Factorial variance analysis can also be used to evaluate any interactions between quantitative variables and linear progression models to relate possible confounding bias with independent variables.

Categorical variables will be finally described using frequencies and percentages and comparative analysis will use the $\chi 2$ test.

The safety analysis will be done on the safety population.

Minor deviations from the original statistical plan (SAP) will be considered acceptable (e.g., due to the non-parametrical form of the data, statistical tests will be adjusted accordingly). Major deviations from the SAP will be reported by the statistician to the Clinical Project Manager and will result in clinical trial protocol amendments.

Tables will include baseline characteristics of the participants, medical history and concomitant medications, and safety outcomes. A CONSORT diagram illustrating the flow of patients through the study is also planned.

Additional details about statistical analysis will be documented in the Statistical Analysis Plan (SAP), enclosed in the Trial Master File.

5. DEVIATIONS FROM THE PROTOCOL

The investigator is not allowed to deviate from the Protocol, except if the deviation affects the patient's rights, safety and well-being, or the scientific integrity of the trial.
Generally, any deviation from the protocol must be verified, reported and analysed by the Investigator and the Sponsor and, immediately after, communicated to the EC. The Investigator will not apply this statement under emergency circumstances (20,21).

All spontaneous protocol deviations shall be recorded and reported to the Sponsor. Deviations shall be also reported to the regulatory authorities if required by national regulations. All deviations will be included, as required, in the study report (SR).

6 TERMINATION OF THE STUDY

6.1. END OF THE TRIAL AND ITS DURATION

The end of trial will be estimated in 8 months from the site activation.

6.2. PREMATURE TERMINATION/SUSPENSION OF THE TRIAL

The Sponsor may stop this trial in a Centre for any of the following reasons:

- the Centre cannot include an adequate number of patients.
- Serious and/or persistent non-compliance with the protocol.
- Careless or premeditated false documentation in the trial documentation.
- Inadequate cooperation with the CRO and/or Centre.
- Non-compliance with GCP or Competent Authority (CA) or EC requirements.
- The Investigator asks to discontinue the trial.
- Lack of confidentiality.

If the trial is prematurely terminated or suspended for any reason:

- the patients will be informed promptly by the Investigator, and the EC and Regulatory Authorities will be notified.
- The Sponsor shall remain responsible for providing resources to fulfil the obligations from the protocol and existing agreements for following up with the patients enrolled in the clinical investigation.

7. COMPLIANCE TO ETHICS AND REGULATORY

7.1. GUIDELINE AND LEGISLATION

The protocol of the present trial is developed in accordance with ICH Harmonized Tripartite guidelines for GCP requirements and Local Romanian legislation.

7.2. ETHICS COMMITTEE APPROVAL

Prior to the initiation of the trial, the Investigator must submit all the documents requested by each centre EC for review and approval. The Investigator, and any other member of the team, if also a member of the EC, must not participate in the decision-making. A signed and dated letter identifying the members of the EC reviewing this protocol will be requested.

7.3. INFORMED CONSENT AND PATIENT INFORMATION

The Investigator is responsible for and will obtain the signed consent form from each patient in the trial. As this is not a clinical trial only data protection consent will be used as requested by GDPR legislation. All patients invited to participate in the trial are entitled to make their decision based on all currently available information provided to them by the Investigator/designee. In addition, they will be given the Data Privacy Sheet (DPS) a document in Romanian language, written in clear and concise lay language for review and consideration. These documents must have been previously approved by the relevant EC and may further be updated as new important information becomes available that may affect the patient's willingness to participate or continue in the trial.

The patients must be made aware that they can refuse to join the trial or can withdraw their consent at any time without prejudicing further medical care. The contact details of the Investigator (telephone no, etc.) will be provided. The patients must also know that their personal records may be reviewed in confidence by the

Sponsor's staff or representatives and by the authorities and that personal information will be collected and retained in a confidential database. Conditions for ensuring the anonymity of data and the security and confidentiality of the database will be explained.
Consent will always be given in writing after the patient had had adequate time to review the information and ask questions. The patient and the Investigator conducting the informed consent discussion will both personally write the name, sign and date these consent forms. Two copies of the data privacy consent form shall be signed. The Investigator shall provide one signed copy of the signed data privacy consent and one copy of the data privacy sheet to the patient and retain the second copies of the signed forms in the onsite study file. The forms will be reviewed by CRO personnel.

7.4. VULNERABLE POPULATION

No vulnerable population will be included in the present trial.

7.5. PATIENT'S DATA PROTECTION

The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society.
Study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective tasks.
This trial will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Systems with procedures will be implemented to assure the quality of every aspect of the trial.
The Sponsor, its delegates and regulatory authorities have direct access to patient records and for the protection of the enrolled patients, this study will be conducted respecting the current GDPR regulation.
According to local Legislation regarding the protection of personal data, the responsible for the data treatment/intervention of the patient in each clinical Centre is the medical doctor responsible for the Centre.

Electronic data capture forms are HIPAA, BAA and GDPR compliant. Data storing services are verified (SSAE 18 SOC 1 and 2 reports) with international and regional standards and terms.
Services are under contractual commitment to meet US and EU customer data residency requirements.
Privacy and security commitments:

- levels access structure.
- No mining of customer data for advertising.
- No voluntary disclosure of customer data to law enforcement agencies.

7.6. ETHICAL PRINCIPLES

This study will be conducted in accordance with the ethical principles originated in the Declaration of Helsinki (Seventh revision, 2013), the Convention of Oviedo, April 4th, 1997, and the additional Protocol January 12th, 1998, and will be consistent with GCP. In addition, the study will follow international laws and regulations and the national laws of Romania, the country in which the trial is performed, as well as any applicable guidelines. If there are conflicts between local laws and regulations, more stringent requirements will be adopted.

7.7. INSURANCE

The Sponsor needs to purchase additional insurance for the patients enrolled, specifically designed to cover the medical device trial. The insurance certificate will be attached to the TCF and the TMF. The payment of the insurance will be performed by the CRO (as the contracting party) and BIOKOSMES will be the insured.

7.8. DECLARATION OF INTERESTS

No competing interests or conflict of interest should exist between the involved Investigators and the Sponsor of the study.

8. QUALITY ASSURANCE

8.1. QUALITY CONTROL PROCEDURES

Quality control (QC) procedures will be implemented for the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Centres will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

8.2. AUDITS AND INSPECTIONS

Authorized representatives of the Sponsor or CA or EC may visit the investigation site to perform audits/inspections during the trial or after.

8.3. STAFF TRAINING

Before the site activation, CRO personnel will conduct a site initiation visit. The purpose of the visit is to provide training to the involved site personnel including, but not limited to the following items:

- protocol and execution thereof.
- Filling out the questionnaire.
- Maintenance of ISF.

The staff present at the site initiation visit will sign a confirmation document that they were trained. The original of this document will be included in the ISF and the TMF.

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10. ANNEX 1 Medical Device Composition

Quantitative composition and functions of the ingredients

INGREDIENTS			
RM NAME / INCI NAME	**QUANTITY %**	**Ingredient FUNCTION**	
ACQUA PURIFICATA Ph.Eur.	**60,60000**		Solvent
AQUA	60,600000	Solvent	
CREMEOL PS 17 / CEGESOFT PS 17	**6,00000**		Emollient
OLUS OIL	6,000000	Emollient	
CLAROWAX MS 4000 - ex SYNTEWAX MS4000 (ex GLYCMONOS A 4000)	**5,00000**		Emollient
GLYCERYL STEARATE	1,400000	Emulsifying	
PEG-75 STEARATE	1,400000	Emulsifying	
ISODECYL LAURATE	0,700000	Emollient	
PEG-8 STEARATE	0,700000	Emulsifying	
CETEARYL ALCOHOL	0,700000	Emulsifying / Emulsion Stabilising	
PARAFFIN	0,100000	Emollient	
ISOCET	**5,00000**		Emulsion stabilising
CETEARETH-20	3,125000	Emulsifying	
ISOSTEARYL ALCOHOL	1,875000	Emulsifying / Emulsion Stabilising	
OLIO VASELINA LEGGERA/OLIO DI VASELINA 102	**5,00000**		Useful for intended use
PARAFFINUM LIQUIDUM	5,000000	Film forming agent	
VASELINA FILANTE PH.142 G	**4,00000**		Useful for intended use
PETROLATUM	4,000000	Film forming agent	
SORBITOLO 70%/SORBITOL LGK	**3,00000**		Humectant
HYDROGENATED STARCH HYDROLYSATE	2,100000	Humectant	
AQUA	0,900000	Solvent	
E/GLICO CENTELLA ASIATICA / PENNYWORT GLYCOLIC EXTRACT 002880	**2,00000**		Skin conditioning
PROPYLENE GLYCOL	1,302000	Solvent - Humectant	
AQUA	0,349000	Solvent	
CENTELLA ASIATICA EXTRACT	0,349000	Skin conditioning	
OLIO MANDORLE DOLCI 001098	**2,00000**		Emollient
PRUNUS AMYGDALUS DULCIS OIL	2,000000	Emollient	
SABONAL C1618 30/70 (ex ecorol 68/30) / NAFOL 1618S	**2,00000**		Emulsion stabilising

CETEARYL ALCOHOL	2,000000	Emulsifying / Emulsion stabilising	
EUXYL K700	**1,50000**		Preservative
PHENOXYETHANOL	0,469500	Preservative	
BENZYL ALCOHOL	0,469500	Preservative	
POTASSIUM SORBATE	0,282000	Preservative	
AQUA	0,277500	Solvent	
TOCOPHEROL	0,001500	Antioxidant	
IPPOCASTANO 20% ESTRATTO SECCO IDROALCOLICO COD.3518320	**1,00000**		Skin conditioning
AESCULUS HIPPOCASTANUM SEED EXTRACT	0,650000	Skin conditioning	
AQUA	0,200000	Solvent	
MALTODEXTRIN	0,150000	Binding	
SOPSIL 350 G	**1,00000**		Useful for intended use
DIMETHICONE	1,000000	Film forming agent	
DIPOTASSIUM GLYCYRRHIZINATE	**0,50000**		Humectant
DIPOTASSIUM GLYCYRRHIZATE	0,500000	Humectant / Skin conditioning	
ZANTALENE (R)	**0,50000**		Skin conditioning
OLEYL ALCOHOL	0,400000	Solvent	
ZANTHOXYLUM BUNGEANUM FRUIT EXTRACT	0,100000	Skin conditioning	
LECINOL S 10	**0,30000**		Emulsifying
HYDROGENATED LECITHIN	0,300000	Emulsifying	
PANTROFINA Beta/STEARIL GLYCYRRHETINATE	**0,20000**		Skin conditioning
STEARYL GLYCYRRHETINATE	0,200000	Skin conditioning	
ACIDO LATTICO 80%	**0,10000**		pH regulator
LACTIC ACID	0,080000	Buffering – pH regulator	
AQUA	0,020000	Solvent	
CALMOSENSINE SP	**0,10000**		Useful for intended use
BUTYLENE GLYCOL	0,067200	Solvent	
AQUA	0,025000	Solvent	
LAURETH-3	0,004500	Emulsifying / Surfactant	
HYDROXYETHYLCELLULOSE	0,002000	Film forming agent	
ACETYL DIPEPTIDE-1 CETYL ESTER	0,001000	Skin conditioning	
POTASSIUM SORBATE	0,000300	Preservative	

DERMAFEEL ALLANTOIN (EX PHYLCARE ALLANTOINA)	**0,10000**		Skin conditioning
ALLANTOIN	0,100000	Skin conditioning	
EDTA SALE BISODICO NA2 / VERSENE Na2	**0,10000**		Chelating
DISODIUM EDTA	0,100000	Chelating	

11. ANNEX 2 Goligher Classification

The severity of hemorrhoids is classified into four stages, according to Goligher's classification (that refers to internal haemorrhoids) (Kestřánek, 2019).

Hemorrhoid degree	Features
Grade I	The anal cushions bleed but do not prolapse.
Grade II	The anal cushions prolapse through the anus on straining but reduce spontaneously.
Grade III	The anal cushions prolapse through the anus on straining or exertion and require manual replacement into the anal canal.
Grade IV	The prolapse stays out at all times and is irreducible. Acutely thrombosed, incarcerated internal hemorrhoids and incarcerated, thrombosed hemorrhoids involving circumferential rectal mucosal prolapse are also fourth-degree hemorrhoids.

Bibliographical references: (3,4)

12. ANNEX 3 Collected Variables

Short Health Scale for Haemorrhoidal Disease (SHS_{HD})

Short Health Scale$_{HD}$

The following questions deal with how your symptoms caused by hemorrhoids affect your daily life (one answer per question).

1. In your view, how severe are your symptoms caused by hemorrhoids? Please grade your symptoms on a 7-point scale, where 1 is "no symptoms" and 7 is "severe symptoms."

No symptoms						Severe symptoms
1 □	2 □	3 □	4 □	5 □	6 □	7 □

2. Do your symptoms interfere with your daily activities? Please grade your answer on a 7-point scale, where 1 is "not at all" and 7 is "interfere to a very high degree."

Not at all						Interfere to a very high degree
1 □	2 □	3 □	4 □	5 □	6 □	7 □

3. Do your symptoms cause much concern? Please grade your answer on a 7-point scale, where 1 is "no concerns" and 7 is "constant concerns.".

No concerns						Constant concerns
1 □	2 □	3 □	4 □	5 □	6 □	7 □

4. How is your general feeling of well-being? Please grade your answer on a 7-point scale, where 1 is "very good" and 7 is "very bad."

Very good						Very bad
1 □	2 □	3 □	4 □	5 □	6 □	7 □

Bibliographical references (5,16,17)

Haemorrhoidal Disease Symptom Score (HDSS)

1. How often do you feel pain from your hemorrhoids?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
2. How often do you feel itching or discomfort of the anus?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
3. How often do you bleed when passing stool?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
4. How often do you soil your underwear (soiling from the anus)?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)
5. How often do you feel a swelling or a prolapsing hemorrhoid?
   □ Never □ Less than once a month □ Less than once a week □ 1–6 days per week □ Every day (always)

Bibliographical references: (5,19)

Haemorrhoid Severity Score (HSS)

Table 1 – "PNR-Bleed" classification of hemorrhoids.

S. nº	Characteristic	Grade	Description
A	Degree of hemorrhoidal prolapse	1	No hemorrhoidal prolapse
		2	Prolapse upon straining that reduces spontaneously
		3	Prolapse upon straining that needs manual reduction
		4	Prolapsed and irreducible hemorrhoids but without ischemic changes.
		5	Prolapsed and irreducible hemorrhoids with ischemic (gangrenous) changes.
B	Number of hemorrhoidal columns involved	1	None
		2	One
		3	Two
		4	Three
		5	Circumferential (presence of secondary hemorrhoids along with the involvement of all primary hemorrhoids)
C	Relation to dentate line	1	Nil (normal anal cushions)
		2	External hemorrhoids
		3	Internal hemorrhoids
		4	Interno-external hemorrhoids
		5	Thrombosed external hemorrhoids
D	Bleeding	1	Nil
		2	Mild; occasional episodes (during defecation)
		3	Moderate; frequent episodes (during defecation)
		4	Severe; persistent bleeding even without defecation with fall in Hb level (<10 gm/dL); requiring hematinics.
		5	Very severe; bleeding in the form of jets and splashes with severe fall in Hb level (<7 gm/dL); requiring blood transfusion.

Bibliographical references: (6)

13. ANNEX 4 Adverse Event Classification

From ISO 14155:2020

Table 1: Categories of adverse events.

<table>
<tr><th>ADVERSE EVENTS</th><th>Non-device-related</th><th colspan="2">Device- or procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)[a]
(3.2)</td><td colspan="2">Adverse Device Effect
(ADE)
(3.1)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event
(SAE)[b]
(3.45)</td><td colspan="2">Serious Adverse Device Effect
(SADE)
(3.44)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect
(ASADE)[c]
(3.1, Note 1 to entry)</td><td>Unanticipated Serious Adverse Device Effect
(USADE)
(3.51)</td></tr>
<tr><td colspan="4">a Includes all categories.
b Includes all categories that are serious.
c Includes all categories that are related to the device or the investigational procedure</td></tr>
</table>

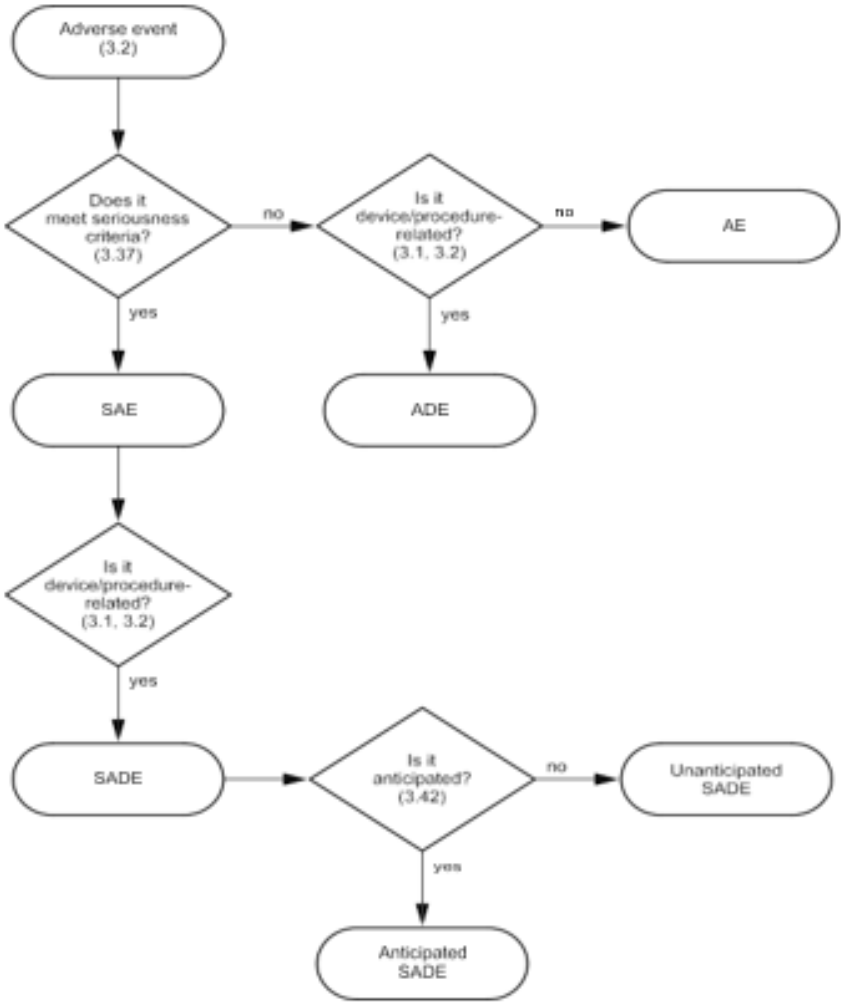

Figure 1: Adverse events categorization chart. This figure provides guidance on questions that can be asked to categorize adverse events and device deficiencies but is not intended to show the interrelationship of categories

14. ANNEX 5 Declaration of Helsinki

WMA Declaration of Helsinki

Ethical Principles for Medical Research involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

5. PATIENT DIARY

PATIENT CODE _ _. _ _ _ Visit data _ _. _ _. _ _ _ _

DATE	Application				Other drugs	Other diseses	Note

Compilation instruction

Please from tomorrow for 14 days each day fill this diary.

In the first column insert the data, in the column from two to six put a cross at any Proctinus cream application.

If you take any drug note in the other drug column the name of each drug taken

In the general health column insert information if you have any different disease than hemorroides.

In the column note insert any other relevant information.

For any doubt on the diary filling please contact the doctor of this study

Dr._____ contact number_____

6. CRF

Patient code ☐ ☐ ☐ ☐ ☐

CASE REPORT FORM

STUDY TITLE

Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief of haemorrhoidal disease and anal irritation symptoms

OpBio/0123/MD

1. INVESTIGATOR

2. CENTRE & PATIENT CODES

Site code	Patient code
☐ ☐	☐ ☐ ☐ ☐ ☐

3. INCLUSION EXCLUSION CRITERIA

3.1. INFORMED CONSENT

Has the subject freely signed the written informed consent?	Yes ☐ No ☐

Please note:
written informed consent must be given before any study specific procedures take place.

3.2. INCLUSION CRITERIA

1	Patients diagnosed with Grade I - II symptomatic haemorrhoids (according to Goligher classification) confirmed by clinical and anoscopic or proctoscopic examination performed within 3 months before baseline.	**Yes** ☐ **No** ☐
2	Patient ≥ 18 years old	**Yes** ☐ **No** ☐
3	Patients able to do self-administration at home of the MD to treat symptoms of haemorrhoids and anal irritation.	**Yes** ☐ **No** ☐
4	Patient free from the following treatments for haemorrhoids for at least 4 weeks: laser treatments for haemorrhoids, steroidal or non-steroidal anti-inflammatory drugs, analgesics, any anti-haemorrhoidal treatment, anticoagulants, and antiplatelet agents	**Yes** ☐ **No** ☐
5	Patients able to communicate adequately with the Investigator and understand the tral questionnaire.	
6	Patients able to understand and who can provide valid informed consent to the trial.	

3.3. EXCLUSION CRITERIA

1	Inflammatory and infectious disease of the digestive tract (e.g., IBD – Inflammatory Bowel Disease).	Yes ☐ No ☐
2	Frequent hemorraidal bleeding	Yes ☐ No ☐
3	Severe, uncontrolled hypertension, renal failure, cirrhosis, colorectal cancer, anal fissure or fistula.	Yes ☐ No ☐
4	Patients with any other medical condition that, in the opinion of the Investigator,would compromise participation or be likely to lead to hospitalisation during the study.	Yes ☐ No ☐
5	Vulnerable patient: a patient who is or may be for any reason unable to take care of him or herself, or unable to protect him or herself against significant harm or exploitation	Yes ☐ No ☐
6	Simultaneous involvement in any other research project	Yes ☐ No ☐

If any criteria are ticked yes the patient is not eligible for the study

3.4. PATIENT'S CONFIRMATION ADMISSION

Has the patient been included in the study ?	**Yes** ☐ **No** ☐

Note

4. VISIT 1 DATE

d	d	m	m	y	y	y	y

5. PATIENT'S CHARACTERISTICS AND PROCEDURE

AGE_____	**M** ☐ **F** ☐

Physical examination	☐ Yes ☐ No
Vital signs[1]	☐ Yes ☐ No
Medical History	☐ Yes ☐ No
Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) (by patient) filled	☐ Yes ☐ No
Haemorrhoid Severity Score (HSS) (by Investigator)	☐ Yes ☐ No
Haemorrhoidal Disease Symptom Score (HDSS) (by patient)	☐ Yes ☐ No
Patient Diary supply	☐ Yes ☐ No
MD supply	☐ Yes ☐ No
other	☐ Yes ☐ No ☐ N/A

Concomitant medication		
☐	No	
☐	yes	Please specify
☐	9=unknown	

6. VISIT 2 DATE

d	d	m	m	y	y	y	y

Physical examination	☐ Yes	☐ No
Vital signs[1]	☐ Yes	☐ No
Medical History	☐ Yes	☐ No
Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) (by patient) filled	☐ Yes	☐ No
Haemorrhoid Severity Score (HSS) (by Investigator)	☐ Yes	☐ No
Haemorrhoidal Disease Symptom Score (HDSS) (by patient)	☐ Yes	☐ No
Patient Diary collection	☐ Yes	☐ No
MD collection	☐ Yes	☐ No
other	☐ Yes ☐ N/A	☐ No

Concomitant medication		
☐	No	
☐	yes	Please specify
☐	9=unknown	

7. VISIT 3 DATE (CALL VISIT)

d	d	m	m	y	y	y	y

Physical examination	☐ Yes	☐ No
Vital signs[1]	☐ Yes	☐ No
Medical History	☐ Yes	☐ No
Short Health Scale for Haemorrhoidal Disease (SHS_{HD}) (by patient) filled	☐ Yes	☐ No
Haemorrhoid Severity Score (HSS) (by Investigator)	☐ Yes	☐ No
Haemorrhoidal Disease Symptom Score (HDSS) (by patient)	☐ Yes	☐ No
Patient Diary collection	☐ Yes	☐ No
MD collection	☐ Yes	☐ No
other	☐ Yes ☐ N/A	☐ No

Concomitant medication		
☐	No	
☐	yes	Please specify
☐	9=unknown	

8. END OF STUDY

Please mark **only the primary** reason. Reasons **other than Study Completed** require explanation

1 ☐ Study completed
2 ☐ AE/SAE (complete AE & SAE form, if applicable)
3 ☐ Non-compliant participant
4 ☐ Withdraw consent
5 ☐ Failure to meet inclusion/exclusion criteria
6 ☐ Other

Explanation

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature:

Date of signature: d d m m y y y y

Note

9. ADVERSE EVENTS

Has the patient experienced any Adverse Events since signing the Informed Consent? ☐ Yes, specify below ☐ No

AE no.	Adverse Event (diagnosis (if known) or signs/symptoms)	Start Date dd/mmm/yyyy and Time (24 hour clock)	Stop Date dd/mmm/yyyy and Time (24 hour clock)	Outcome 1=Recovered 2=Recovered with sequelae 3=Continuing 4=Patient Died 5=Change in AE 6=unknown	Severity 1=Mild 2=Moderate 3=Severe	Plausible relationship to the Study	Action taken with Study Drug 1=None 2=Dose Reduction Temporarily 3=Dose Reduced 4=Discontinued Temporarily 5=Discontinued	Withdrawn due to AE?	Serious AE (SAE)?	If SAE does it require immediate reporting?
1						☐ Yes ☐ No		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
2						☐ Yes ☐ No		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
3						☐ Yes ☐ No		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

In case complete the CIOMS form.

7. LABELLING AND INSTRUCTIONS FOR USE

LABELLING AND INSTRUCTION FOR USE *0VNL2FI00121_artwork Rev.01-2020* **ANNEX 9**	
Code and trade names	**Technical documentation ID**
0BIO4A004CPR	MDD:*TF_ENG_34*
Rev. N.	**Date**
20	17/05/2024

BIOkosmes
SKIN CARE CONTRACT MANUFACTURER

MASTER TEXT 0BIO4A004CPR

Tube

0BIO4A004CPR

Provides symptomatic relief from hemorrhoids and anal irritation

Helps to relieve pain, itching and burning

Emulsion with applicator

30mL e 1.06 fl.oz

0BIO4A004CPR provides symptomatic relief from hemorrhoids and anal irritation.
It has a protective, lubricating and refreshing action.
For directions on how to use, please read carefully instructions for use

Warnings
Intended for individual use only and not to be shared.
Keep out of reach of children.
Do not use after the expiry date.
Do not use if tube is damaged.

With a reusable applicator CE


Biokosmes s.r.l. – socio unico
Via dei Livelli 1, 23842 Bosisio Parini (LC) ITALY
Manufactured in Italy

DISTRIBUTOR: name and address

CE0477  LOT

BIOkosmes
SKIN CARE CONTRACT MANUFACTURER

Carton

0BIO4A004CPR

Provides symptomatic relief from hemorrhoids and anal irritation

Helps to relieve pain, itching and burning

Emulsion with applicator

30mL e 1.06 fl.oz

Biokosmes s.r.l. – socio unico
Via dei Livelli 1, 23842 Bosisio Parini (LC) ITALY

Manufactured in Italy

DISTRIBUTOR: name and address

CE 0477 5°C 30°C

With a reusable applicator CE

30mL e 1.06 fl.oz

0BIO4A004CPR is a protective emulsion.
It provides relief from hemorrhoids and anal irritation
It has a protective, lubricating and refreshing action.

For directions on how to use, please read carefully instructions for use

---

Composition:

AQUA, OLUS OIL, PARAFFINUM LIQUIDUM, PETROLATUM, CETEARETH-20, CETEARYL ALCOHOL, HYDROGENATED STARCH HYDROLYSATE, PRUNUS AMYGDALUS DULCIS OIL, ISOSTEARYL ALCOHOL, PEG-75 STEARATE, GLYCERYL STEARATE, PROPYLENE GLYCOL, DIMETHICONE, PEG-8 STEARATE, ISODECYL LAURATE, AESCULUS HIPPOCASTANUM SEED EXTRACT, DIPOTASSIUM GLYCYRRHIZATE, BENZYL ALCOHOL, PHENOXYETHANOL, OLEYL ALCOHOL, CENTELLA ASIATICA EXTRACT, HYDROGENATED LECITHIN, POTASSIUM SORBATE, STEARYL GLYCYRRHETINATE, MALTODEXTRIN, ALLANTOIN, PARAFFIN, DISODIUM EDTA, ZANTHOXYLUM BUNGEANUM FRUIT EXTRACT, LACTIC ACID, BUTYLENE GLYCOL, LAURETH-3, HYDROXYETHYLCELLULOSE, TOCOPHEROL, ACETYL DIPEPTIDE-1 CETYL ESTER

Warnings

Intended for individual use only and not to be shared.
Keep out of reach of children.
Do not use after the expiry date.

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Do not use if tube is damaged.
Store in a dry place and away from direct light

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Instructions for use

0BIO4A004CPR

Provides symptomatic relief of hemorrhoids and anal irritation

Helps to relieve pain, itching and burning

How it works

0BIO4A004CPR is a soft and light hydrophilic emulsion that offers protection to the irritated areas.

It is a specific adjuvant for the symptomatic relief of internal and external haemorrhoids and anal irritation. The product creates a physical barrier that protects the peri-anal tissue, minimizing the possibility of bacterial colonization and contact with environmental dirt, which may exacerbate haemorrhoid condition.

Due to its formulation, it contributes to physiological restoration of the anal and perianal 0BIO4A004CPR has a protective, lubricating and refreshing action.

0BIO4A004CPR has emollient properties, which help to prevent irritation and discomfort of the perianal area - this gives relief from pain, burning, itching and other related complaints.

Its application leaves the treated area soft and moisturised, avoiding the onset of irritation and cracking of the skin. The lubricating action helps to facilitate bowel movement, thus minimising the trauma and pain sensation associated with defecation.
It also supports the physiological repairing process.
The product is not evaluated during pregnancy and breastfeeding. In case of pregnancy or breast feeding, consult with your medical professional or pharmacist.

0BIO4A004CPR provides relief:

- ✓ when you are suffering from haemorrhoids both internal and external
- ✓ when you have discomfort of the anal and perianal areas, such as itching and burning
- ✓ when you are sensitive to anal irritations

How to use

0BIO4A004CPR is applied into the anal cavity and to the surrounding perianal area to relieve symptoms associated to haemorrhoids and anal irritation.

- EXTERNAL APPLICATION

In the case of discomfort on the outer anal area, you can apply 0BIO4A004CPR with your finger and gently massage in. The product can also be used before bowel movement to facilitate defecation (always take care to thoroughly wash the affected area and your hands before and after using the product).

- INTERNAL APPLICATION

0BIO4A004CPR has a special applicator and this can be screwed onto the tube. This special applicator will allow you to apply the product into the anal cavity.

Always take care to thoroughly wash the affected area and your hands before and after using the product.
1. Take the cap off the tube and use the backside of the cap to pierce the sealed tube, prior to initial use.

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2. Screw the applicator onto the opening of the tube and place gently inside the anal cavity (you can also apply a thin layer of the cream on the edge of the applicator to facilitate the insertion into the anal cavity).
3. Squeeze the tube to allow a sufficient quantity of emulsion to come out.
4. After use, carefully clean the applicator with a wet paper towel and leave to dry
5. When finished, cover the applicator with the cap.

Application

Apply the product as and when required, up to three/four times per day.
To prevent anal irritation and cracking of the skin, it is possible to apply 0BIO4A004CPR once a day.

Ingredients

AQUA, OLUS OIL, PARAFFINUM LIQUIDUM, PETROLATUM, CETEARETH-20, CETEARYL ALCOHOL, HYDROGENATED STARCH HYDROLYSATE, PRUNUS AMYGDALUS DULCIS OIL, ISOSTEARYL ALCOHOL, PEG-75 STEARATE, GLYCERYL STEARATE, PROPYLENE GLYCOL, DIMETHICONE, PEG-8 STEARATE, ISODECYL LAURATE, AESCULUS HIPPOCASTANUM SEED EXTRACT, DIPOTASSIUM GLYCYRRHIZATE, BENZYL ALCOHOL, PHENOXYETHANOL, OLEYL ALCOHOL, CENTELLA ASIATICA EXTRACT, HYDROGENATED LECITHIN, POTASSIUM SORBATE, STEARYL GLYCYRRHETINATE, MALTODEXTRIN, ALLANTOIN, PARAFFIN, DISODIUM EDTA, ZANTHOXYLUM BUNGEANUM FRUIT EXTRACT, LACTIC ACID, BUTYLENE GLYCOL, LAURETH-3, HYDROXYETHYLCELLULOSE, TOCOPHEROL, ACETYL DIPEPTIDE-1 CETYL ESTER.

Undesirable effects

There are no known undesirable effects deriving from the use of 0BIO4A004CPR, however:
* Do not use in the presence of hypersensitivity to any of the ingredients.
* If you have doubts, apply a small amount of the emulsion on the inside of the forearm. If irritable red spots appear, we advise you not to use the product.
* Inform your doctor or pharmacist of any undesirable effects or if symptoms persist.

Warnings

The product is intended for individual use only and not be shared.
Keep out of reach of children.
Store in a dry place, away from direct light at room temperature (between 5° and 30° C).
Do not use if the pack is damaged.
Do not use after the expiry date indicated on the packaging.
Do not ingest.
Avoid contact with eyes. In case of contact with eyes: flush thoroughly with water and eventually seek medical advice.
After use, carefully clean the applicator, leave to dry and cover the applicator with the cap.
If symptoms persist after initial 30 days, seek advice from a medical professional.
The product is not evaluated during pregnancy and breastfeeding. If you are pregnant/breastfeeding consult your doctor before use.

Please note

In case of persistent or recurrent complaints, you should always contact your physician.

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Also in the case of worsening or when symptoms of inflammation, allergic reaction or infection occur consult a doctor.

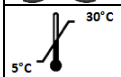
Possible interactions:
At present there are no known interactions between the product and drugs or other medical devices. However, in the case of concomitant, continuous and prolonged use of drugs, in particular anticoagulants, antiplatelets or sedative medications, it is advised to consult a physician before application of this product.

Size: 30ml tube with reusable applicator CE

CE 0477

Biokosmes s.r.l. – socio unico
Via dei Livelli 1, 23842 Bosisio Parini (LC) ITALY
Manufactured in Italy

DISTRIBUTOR: name and address
Revision 01-2020

SYMBOL	MEANING
CE 0477	CE mark issued by Notified Body 0477
	Manufacturer
	See instructions for use before using the product
	Store between 5°C and 30°C
	Expiry date
LOT	Batch number

8. INFORMED CONSENT FORM

Informed Consent form for adult patients invited to take part in
Post-Marketing Clinical Follow-Up trial to evaluate the performance and safety of the medical device PROCTOeze® PLUS in the relief of haemorrhoidal disease and anal irritation symptoms

Principal Investigator: Dr. Sisu Lucia - Cristina
Organization: C.M.I Dr. Sisu Lucia - Cristina
Sponsor: BIOKOSMES Srl
Protocol code: OpBio/0123/MD
Protocol version: 1.0/20231201

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**
- **You will be given a copy of the full Informed Consent Form**
-

PART I: Information Sheet

Introduction

The trial you are invited to join aims to conduct research on the haemorrhoidal disease and its impact on the patient's quality of life. Your study doctor is going to give you information about the trial and associated procedures and invite you to be part of this research. You do not have to decide today whether or not you will participate in the trial. Before you decide, you can talk to anyone you feel comfortable with about the trial.

There may be some words that you do not understand. If needed, please ask your study doctor to explain. Similarly, if you have any questions later, you can ask the study doctor or their staff.

Purpose of the research

The acute clinical manifestation of the haemorrhoidal disease is commonly known as haemorrhoidal crisis and it is characterized by rectal bleeding, itching, pain or swelling, all of which cause discomfort for the patient and have a negative effect on their quality of life.

The Sponsor has developed PROCTOeze® PLUS, a soft and light hydrophilic emulsion to help relieve the symptoms, which is largely used in the clinical practice of thousands of medical doctors in Italy, Romania, Iceland, Bulgaria, Taiwan, and Israel. PROCTOeze® PLUS is commercialized in Romania with the brand name PROCTINUM®

The reason the Sponsor is conducting this trial is to evaluate if the administration of PROCTOeze® PLUS will help improve the symptomatology in patients suffering from symptomatic haemorrhoids and anal irritation.

Type of Research Intervention

This trial involves 2 physical visits to the doctor's office, the administration of PROCTOeze® PLUS emulsion for 2 weeks and follow-up phone-call from the doctor.

Participant selection

You have been invited to participate in this trial by your doctor because you suffer from symptomatic haemorrhoids.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this trial, you will be recommended alternative standard of care treatment that is routinely recommended in this clinic for haemorrhoidal disease. You may change your mind later and stop participating even if you agreed earlier.

Information on the Trial Medical Device [PROCTOeze® PLUS]

The medical device we are testing in this research is called PROCTOeze® PLUS. It has been tested before with people who suffer from haemorrhoidal disease and anal irritation. Romanian National Authority (ANMDM) has already granted marketing authorisation for this medical device, as it has proven to be efficient, safe and well-tolerated by the patients. The present research is conducted to comply with the manufacturer's requirement to routinely present results of post-marketing clinical follow-up trials to the Authorities.

There are no known side-effects associated to the use of PROCTOeze® PLUS other than sensitivity to any of its components.

Procedures and Protocol

During the trial you make 2 visits to the clinic and will receive one follow-up phone-call.

- At the first visit, the study doctor will ask you a few questions about your general health and medical history, perform a general physical examination and record your vital signs, including haemorrhoids evaluation and confirmation of diagnosis. You will be asked to fill in 2 questionnaires to self-evaluate your quality of life in relation to the Haemorrhoidal Disease and you will receive the Patient Diary, the IMD for administration and instructions on how to use both of them during the next 2 weeks.
- At the next visit, which will take place 2 weeks later, you will again be asked some questions about your health, including haemorrhoids evaluation, your vital signs will be recorded and you will be asked to fill in again the 2 questionnaires to self-evaluate your quality of life in relation to the Haemorrhoidal Disease. At this visit, you will have to return the filled-in Patient Diary and IMD (unused IMD, empty tube/box) to the study doctor.
- After 2 weeks, you will receive a follow-up call from the study doctor to evaluate your general health and the effects of the treatment.

Duration

The trial takes place over 30 days. During that time, it will be necessary for you to come to the doctor's office on 2 days, for approximately 1 hour each day. We would like to call you 2 weeks after your last clinic visit for a final check-up.

In total, you will be asked to come 2 times to the doctor's office in 1 month. At the end that month, the trial will be finished.

Side Effects

As already mentioned, there are no known side-effects associated to the use of PROCTOeze® PLUS other than sensitivity to any of its components. However, your study doctor will follow you closely and keep track of any unwanted effects or any problems. You are also encouraged to inform your study doctor immediately if you experience any side-effects while under treatment in this trial.

Risks

By participating in this research, you will be not be at any knowed risk than you would otherwise be. There is, for example, a very low risk that your haemorrhoids symptoms will not get better. If this is the case, you can stop the administration of PROCTOeze® PLUS at any time and try other treatment option available on the market.

Benefits

If you participate in this research, you will benefit from a free-of-charge treatment for your Haemorrhoidal Disease and your participation will help us find the answer to the research question.

Reimbursements

You will not be given any money or gifts to take part in this research. The IMD under evaluation (PROCTOeze® PLUS) will be provided free of charge for the whole duration of the trial.

Confidentiality

Your study doctor will not be sharing the identity of those participating in the research and the information that is collected from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is. It will not be shared with or given to anyone.

Who will have access to your personal data collected during the trial?

Your data, in particular personal and health data, will be processed only to the extent that they are indispensable to the objective of the trial and for pharmacovigilance purposes, in compliance with EU Regulation 2016/679, known as GDPR (General Data Protection Regulation) and with Legislative Decree 10 August 2018, no. 101. In practical terms, the documents relating to the participant will be kept in a safe place and will not report his/her name in clear text, only known to the researchers, but an identification code.

The data, made anonymous, may be subject to control by regulatory bodies and used for scientific publications (journals, conferences).

Your clinical data collected for the purposes of the trial, as well as the results of the tests carried out, will be stored for the time required by the regulations and subsequently destroyed. They will not be destroyed only if a) it is no longer possible to trace them back to your identity, because they have been anonymized during the trial itself; b) in the presence of your specific informed consent.

If the personal data are transferred to a third country or to an international organization, all the guarantees will be adopted which are provided for by Article 46 of the GDPR 679/2016.

Further information is included in the attached data processing authorization form.

Sharing the Results

Once the trial is over and all the resulting data have been collected, they will be analyzed to draw conclusions. The investigators and the Sponsor undertake to make them available to the scientific community and Notified Body.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Early Termination

Your study doctor may decide to terminate your participation in the trial if:

- **Your health conditions were to change and participation in the trial proved potentially harmful;**
- **New information is available and the trial is no longer in your best interest;**
- **You do not follow the agreed rules for participation in the trial;**
- **For women: you get pregnant during the trial;**
- **The trial is stopped by the competent authorities.**

Alternatives to Participating

If you do not wish to take part in the research, your doctor will recommend alternative standard treatment available on the market for Haemorrhoidal Disease.

Who to Contact if you join the trial

For any doubt and unforeseeable or unscheduled event during the trial (doubts relating to the treatment in progress, side effects, decision to abandon the trial, etc.), you can contact:

Dr. Lucia Cristina Sisu

Phone: (+40) 0744960358

Email: dr.cristinasisu@gmail.com

Approvals

This trial and the present document have been reviewed and approved by the Bioethics Committee for Medicines and Medical Devices, which is a national Romanian committee whose task it is to make sure that research participants are protected from harm. Among other things, the Ethics Committee has verified the compliance of the trial with the standards of Good Clinical Practice and with the ethical principles expressed in the Declaration of Helsinki and that your safety, rights and well-being have been protected.

More details about the Ethics Committee are available at https://www.adsm.ro/comisia-de-bioetica-a-medicamentului-si-a-dispozitivelor-medicale/ .

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this trial.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose of the trial, the procedures, the possible risks and benefits and the possible alternatives.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____ Day/month/year

9. STATISTICAL ANALYSIS

Statistical Methods

Descriptive statistics (mean, standard deviation - SD- median, first and third quartile -Q1-Q3, min-max) have been calculated for quantitative variables.
Absolute and percent frequencies have been calculated for qualitative variables.
Comparison between gender on quantitative variables normally/symmetrically distributed have been carried out by means of the Student's t test.
The change of the total of the SHSDH (primary objective of the study), on the total of the HSS and HDSS (secondary objectives of the study) between baseline and the end of the study has been assessed, according to the protocol, by means of the Wilcoxon signed-rank test.
In addition, the change between Visit 1 and Visit 2 of SHSDH, HSS, and HDSS has been modeled between the two genders by means of the repeated measurement ANOVA with gender as a fixed factor between patients, time as a fixed factor within patients and their interaction.

Demographic Dataset

In this study have been enrolled 50 patients (34 - 68.0% - females and 16 - 32.0% males, Table 1).

Table 1

GENDER	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Females	34	68.00	34	68.00
Males	16	32.00	50	100.00

Their age was mean (±SD) equal to 49.9 years (13.9) (Table 2). Females had a mean age of 50.6 (±13.7) years; mean age of males was 48.6 (±14.7) years (Table 2.1).

Table 2

Analysis Variable : AGE								
Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
49.98	13.90	29.0	37.0	47.50	60.0	87.0	46.03	53.93

Table 2.1

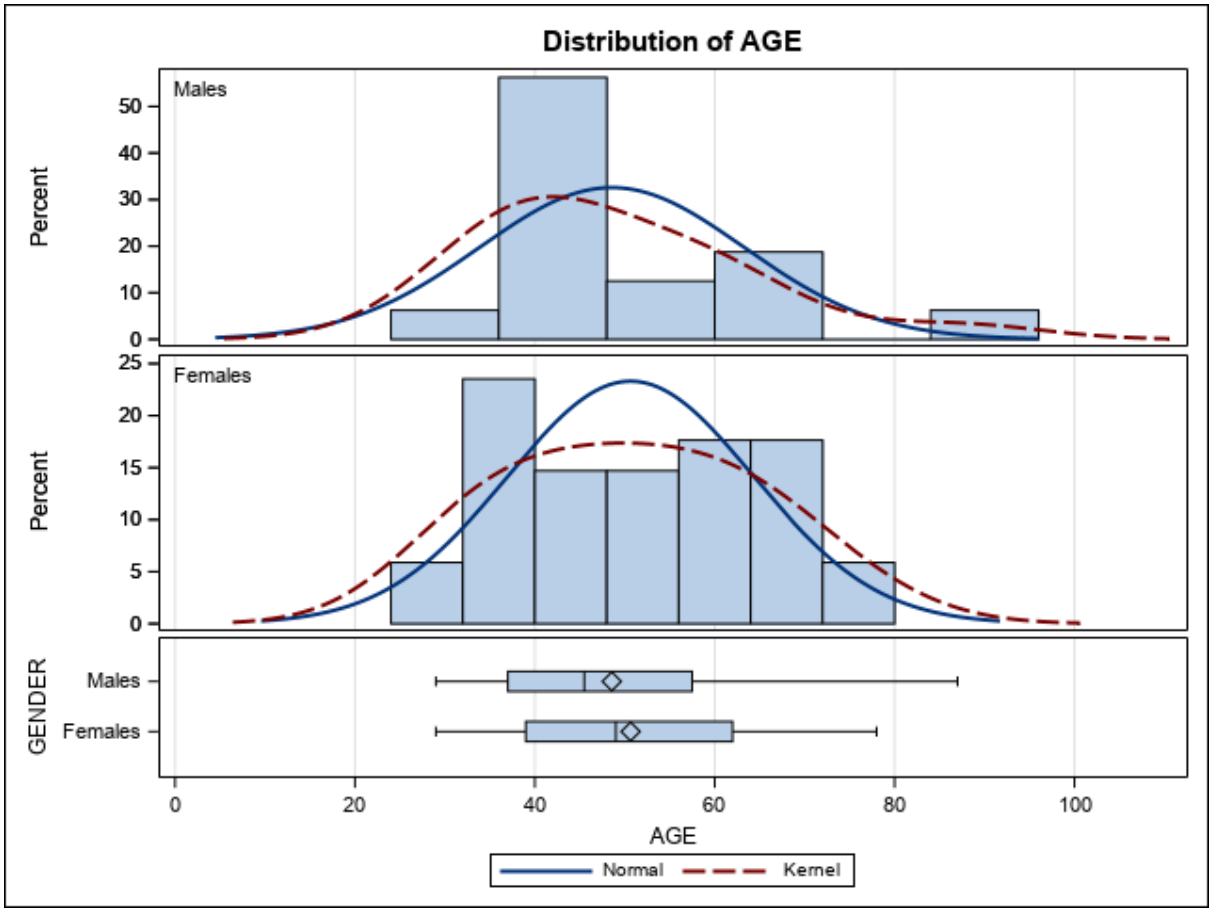
Analysis Variable : AGE										
GENDER	N Obs	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
Females	34	50.64	13.69	29.0	39.0	49.0	62.0	78.0	45.87	55.42
Males	16	48.56	14.69	29.0	37.0	45.5	57.5	87.0	40.73	56.39

The difference between the mean age of females and age was not statistically significant (Student's t test equal to -0.49, P = 0.6259; the test has been considered with the variances pooled owing to a statistically not significant difference between the variances of the age in the two groups) (Table 3).

Table 3

Variable	Method	Variances	T Value	DF	Prob t
AGE	Pooled	Equal	-0.49	48	0.6259

Figure 1



The above figure shows the distribution of the variable age in males (above) and females (under). Obviously, owing also the low number of samples in the two classes, practically no conclusions about the distribution of the variable age can be made. Superimposed there is the density function of a normal distribution and of a "kernel density function". The kernel density estimate (shown as a red *dashed line)* is a statistical method for smoothing the data distribution in comparison to the histogram

Diary dataset.

During the 14 days of the study, patients used a mean total of cream doses of 34.44 (6.23, median equal to 34, first and third quartile: 31-38, min-max: 14-56).

Table 4. shows the descriptive statistics (mean (±SD), median with first (Q1) and third (Q3) quartile, and the minimum and the maximum (min-max) of the total number of cream applications in the 14 days and at each day.

Table 4

Variable (N=50)	Mean Std Dev	Median (Q1- Q3)	Min - Max
Total n.	34.44 (6.23)	34.00 (31.00-38.00)	14.00 - 56.00
Day1	1.88 (0.87)	2.00 (1.00- 3.00)	1.00 - 4.00
Day2	2.52 (0.65)	3.00 (2.00- 3.00)	1.00 - 4.00
Day3	2.60 (0.76)	3.00 (2.00- 3.00)	0.00 - 4.00
Day4	2.60 (0.70)	3.00 (2.00- 3.00)	1.00 - 4.00
Day5	2.44 (0.79)	3.00 (2.00- 3.00)	0.00 - 4.00
Day6	2.58 (0.67)	3.00 (2.00- 3.00)	1.00 - 4.00
Day7	2.58 (0.64)	3.00 (2.00- 3.00)	1.00 - 4.00
Day8	2.60 (0.67)	3.00 (2.00- 3.00)	1.00 - 4.00
Day9	2.50 (0.61)	2.00 (2.00- 3.00)	1.00 - 4.00
Day10	2.52 (0.68)	3.00 (2.00- 3.00)	1.00 - 4.00
Day11	2.66 (0.69)	3.00 (2.00- 3.00)	1.00 - 4.00
Day12	2.42 (0.70)	2.00 (2.00- 3.00)	1.00 - 4.00
Day13	2.32 (0.65)	2.00 (2.00- 3.00)	1.00 - 4.00
Day14	2.22 (0.65)	2.00 (2.00- 3.00)	1.00 - 4.00

It is possible to see that, apart from the first day, the mean values are similar for all the days. In addition, only for two days (day 3 and day 5) have 0 cream application as the minimum value. However, it has to stress that it is better to describe a discrete variable with the absolute and percent frequencies as the following Table 4.1. shows the absolute frequency and percent of the number of cream applications for each day

Table 4.1

n.	Number	Frequency	Percent %
Day1	1	21	42.00
	2	15	30.00
	3	13	26.00
	4	1	2.00
Day2	1	2	4.00
	2	22	44.00
	3	24	48.00
	4	2	4.00
Day3	0	1	2.00
	1	1	2.00
	2	19	38.00
	3	25	50.00
	4	4	8.00
Day4	1	3	6.00
	2	17	34.00
	3	27	54.00
	4	3	6.00
Day5	0	1	2.00
	1	4	8.00
	2	19	38.00
	3	24	48.00
	4	2	4.00
Day6	1	1	2.00
	2	23	46.00
	3	22	44.00
	4	4	8.00
Day7	1	1	2.00
	2	22	44.00
	3	24	48.00
	4	3	6.00
Day8	1	3	6.00
	2	16	32.00
	3	29	58.00
	4	2	4.00
Day9	1	1	2.00
	2	25	50.00
	3	22	44.00
	4	2	4.00
Day10	1	3	6.00
	2	20	40.00
	3	25	50.00
	4	2	4.00

Day11	1	2	4.00
	2	17	34.00
	3	27	54.00
	4	4	8.00
Day12	1	3	6.00
	2	26	52.00
	3	18	36.00
	4	3	6.00
Day13	1	4	8.00
	2	27	54.00
	3	18	36.00
	4	1	2.00
Day14	1	5	10.00
	2	30	60.00
	3	14	28.00
	4	1	2.00

From this Table 4.1, it seems possible to see that in the last days of the clinical trial less that 4 cream application a day was done.

Scales

SHSHD

The total of the four items of the SHSHD scale was 14.04 (±7.79) Visit 1 and 7.80 (±3.69) Visit 2 giving a difference of 6.24 (±5.51) from Visit 1 minus Visit 2. Table 5 shows

The difference turned out to be statistically different ($P < 0.0001$) at the Wilcoxon signed-rank test. (Table 5.1, second row: Signed-Rank; then there is the value of the statistics equal to 540 and in the last column the p-value))

Furthermore, the mixed factorial ANOVA with gender as a fixed factor showed a statistically nonsignificant interaction "gender by visit" ($P = 0.2720$) leading to conclude that the decrease pattern was similar for females and males.

Indeed, the decrease is about of 43.7% for females and of 45.6 for males.

Table 5.2 shows the terms of the Table ANOVA for repeated measurements: The first two rows refer to the “Between subjects” part of the analysis represented by the two groups of the Gender. The last three rows refer to the “Within Subject” part of the analysis represented by the Visit (Visit 1 – Baseline - and Visit 2 – end of treatment) and by the interaction “Visit by Gender”. Finally, the last row of the “Between Subjects” and of the “Within Subject” refers to the error.

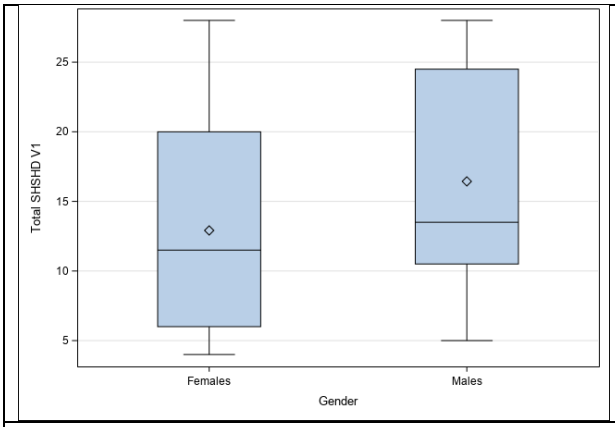
The table has to be read by starting from the interaction: if the interaction is not statistically significant it is possible to consider if the term “Visit” is statistically significant as the expression of a difference between the means value at Visit 1 and at visit 2, pooled on the two group of the fixed “Between Subjects” factor gender.

So, it is possible to see that the interaction is not statistically significant ($P=0.2720$) and that the difference between the two visits is statistically significant ($P<0.0001$) as a further confirmation of the result obtained on the difference by the Wilcoxon signed-rank test.

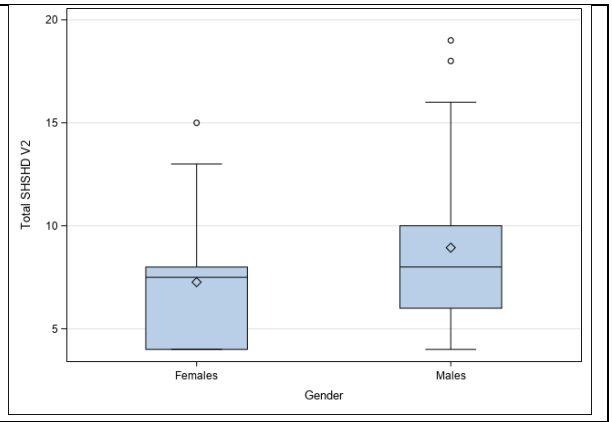
Finally, the gender term expresses the mean pattern of Females and Males on the two visits. A statistically significance means that there is a difference between the two genders starting from the baseline. In other terms Females (or Males) show a lower (greater) score of the total of the scale. A different behavior of the total score of the scale between the two genders under the treatment is given by the significance of the interaction term. The p-value of 0.1154 of the gender means that the means of the total score of the scale is similar both at baseline and at end of the trial-

Table 5.3 shows the mean (DS) of the total score of the scale at the two visits for females and males. Actually, males show a mean value greater than females particularly at baseline, but this conclusion is not supported by the evidence of a statistically significant result.

Figure 2



SHSHD: Panel A. Visit 1



Panel B. Visit 2

Figure 2 (panel A and Panel B) shows the box plot of the SHSHD total at baseline (visit 1) and at the end of the study (Visit 2). The upper and lower segment of the rectangle represent the third and first quartile, respectively. The line in the rectangle represents the median and the diamond in the rectangle represents the arithmetic mean. Finally, the two segments at the end of the two lines coming out the rectangle show the minimum and the maximum values. It is well known that if the arithmetic mean is too far the median, the data are skewed: positively if the median is greater then the median and negatively if the arithmetic mean if lower than the median. The asymmetry of the distribution is also demonstrated by the fact that the median is not at the middle of the rectangle fairly equidistant from the upper and lower sides of the rectangle.

HDSS

The total of the five items of the HDSS scale was 10.12 (±3.60) Visit 1 and 7.20 (±2.47) Visit 2 giving a difference of 2.92 (±2.51) from Visit 1 minus Visit 2. Table 6 shows in addition also the minimum-maximum values together with the median and the first and the third quartile.

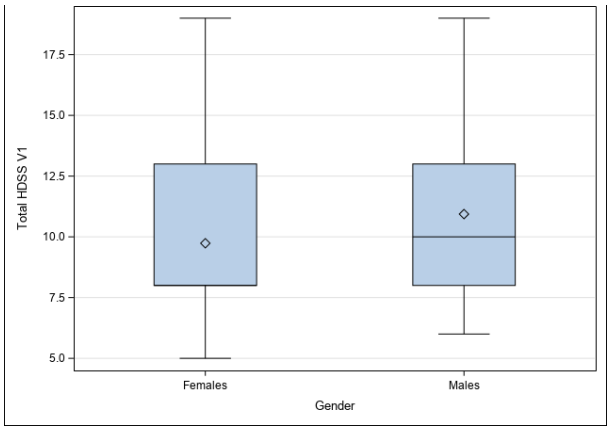
The difference turned out to be statistically different ($p < 0.0001$) at the Wilcoxon signed-rank test (Table 6.1).

Furthermore, the mixed factorial ANOVA with gender as a fixed factor showed a statistically nonsignificant interaction "gender by visit" ($P = 0.8792$) leading to conclude that the decrease pattern was similar for females and males. (Table 6.2)

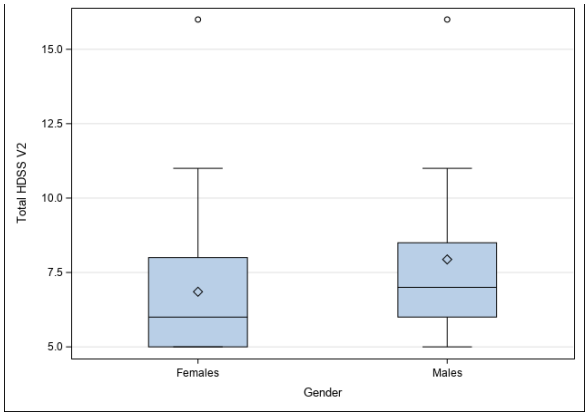
Indeed, the decrease is about of 29.6% for females and of 27.5 for males.

In addition. the difference between the two visits turned out to be statistically significant ($P<0.0001$). Finally. the two genders showed similar mean values of the total score of the scale both at baseline and at the end of the trial as Table 6.3 shows.

Figure 3



HDSS: Panel A. Visit 1



Panel B. Visit 2

HSS

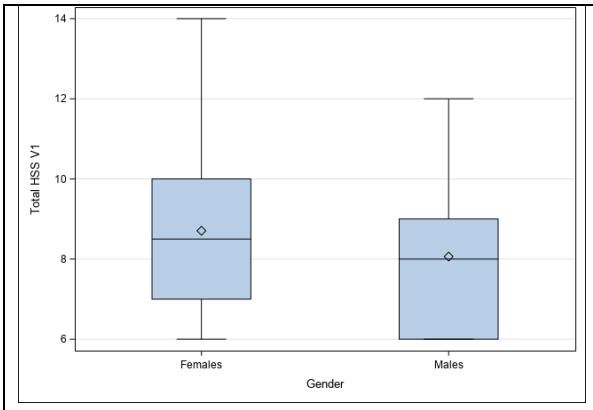
The total of the four items of the HSS scale was 8.50 (±2.11) Visit 1 and 6.48 (±2.17) Visit 2 giving a difference of 2.02 (±1.71) from Visit 1 minus Visit 2. (Table 7)

The difference turned out to be statistically different ($p < 0.0001$) at the Wilcoxon signed-rank test. (Table 7.1)

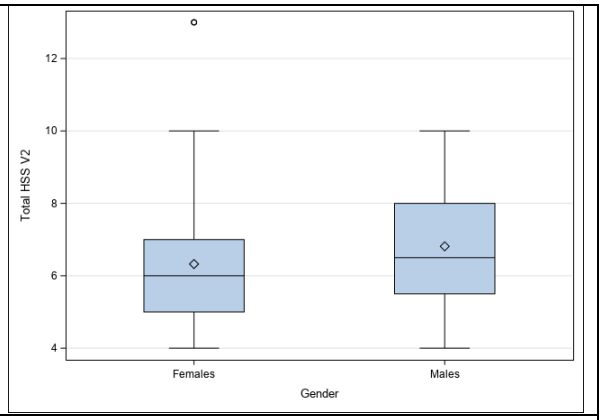
Furthermore, the mixed factorial ANOVA with gender as a fixed factor showed a statistically significant interaction gender by visit ($P = 0.0272$) leading to conclude that the decrease pattern was not similar for females and males. Table 7.2.

Indeed, the decrease is about of the 27.4% for females and of 15.5% for males (Table 7.3). In this case, the difference between the two visits has to be assessed separately within each gender by means of a multiple comparison procedure such as can be done by the Bonferroni's correction; the decrease is statistically significant for both genders.

Figure 4



HSS: Panel A. Visit 1



Panel B. Visit 2

Table 5

SHSHD
Means (SD) of total SHSHD at Visit1 Visit2 by Gender

Label	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
Total SHSHD V1	14.04	7.79	4.00	7.00	12.00	21.00	28.00	11.83	16.25
Total SHSHD V2	7.80	3.69	4.00	5.00	8.00	9.00	19.00	6.75	8.85
DIFF Total SHSHD V_1 - V_2	6.24	5.51	0.00	2.00	4.00	9.00	18.00	4.67	7.81

Table 5.1

SHSHD: Tests For Location
Wilcoxon signed-rank on the difference V1-V2

Test	Stat	pType	pValue
Student's t	8.003921	Pr > |t|	<.0001
Signed Rank	540.5	Pr >= |S|	<.0001

Table 5.2

SHSHD
Table of ANOVA for repeated measurements

Dependent	Source	DF	SS	MS	FValue	ProbF
Between Subjects	GENDER	1	147.01	147.01	2.57	0.1154
Between Subjects	Error	48	2744.35	57.17	_	_
Within Subject	VISIT	1	940.28	940.28	62.18	<.0001
Within Subject	VISIT*GENDER	1	18.68	18.68	1.24	0.2720
Within Subject	Error(VISIT)	48	725.88	15.12	_	_

Table 5.3

SHSHD
Means (SD) of total SHSHD at Visit1 Visit2 by Gender

GENDER	N	Mean Visit 1	SD Visit 1	Mean Visit 2	SD Visit 2
Females	34	12.91	7.67	7.26	2.99
Males	16	16.44	7.72	8.94	4.77

Table 6

HDSS: Table 6 - Descriptive statistics
Total of HDSS - V1, V2 and difference V1-V2

Label	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
Total HDSS V1	10.12	3.60	5.00	8.00	9.00	13.00	19.00	9.10	11.14
Total HDSS V2	7.20	2.47	5.00	5.00	7.00	8.00	16.00	6.50	7.90
DIFF Total HDSS V_1 - V_2	2.92	2.51	-2.00	1.00	2.00	5.00	9.00	2.21	3.63

Table 6.1

HDSS: Tests For Location
Wilcoxon signed-rank tests on the difference V1-V2

Test	Stat	pType	pValue
Student's t	8.213142	Pr > |t|	<.0001
Signed Rank	479	Pr >= |S|	<.0001

Table 6.2

HDSS
Table of ANOVA for repeated measurements

Dependent	Source	DF	SS	MS	FValue	ProbF
Between Subjects	GENDER	1	28.45	28.45	1.82	0.1836
Between Subjects	Error	48	749.99	15.62	_	_
Within Subject	VISIT	1	188.24	188.24	58.38	<.0001
Within Subject	VISIT*GENDER	1	0.08	0.08	0.02	0.8792
Within Subject	Error(VISIT)	48	154.76	3.22	_	_

Table 6.3

HDSS
Means (SD) of total HDSS at Visit1 Visit2 by Gender

GENDER	N	Mean Visit 1	SD Visit 1	Mean Visit 2	SD Visit 2
Females	34	9.74	3.48	6.85	2.27
Males	16	10.94	3.80	7.94	2.79

Table 7

HSS: Table 7 - Descriptive statistics
Total HSS - V1, V2 and difference V1-V2

Label	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Lower 95% CL for Mean	Upper 95% CL for Mean
Total HSS V1	8.50	2.11	6.00	7.00	8.00	10.00	14.00	7.90	9.10
Total HSS V2	6.48	2.17	4.00	5.00	6.00	7.00	13.00	5.86	7.10
DIFF TOT_HSS1 - TOT_HSS2	2.02	1.71	0.00	1.00	1.00	3.00	7.00	1.53	2.51

Table 7.1

Table 7.1 - HSS: Tests For Location
Wilcoxon signed-rank tests on the difference V1-V2

Test	Stat	pType	pValue
Student's t	8.361742	Pr > |t|	<.0001
Signed Rank	517.5	Pr >= |S|	<.0001

Table 7.2

Table 7.2 - HSS
Table of ANOVA for repeated measurements

Dependent	Source	DF	SS	MS	FValue	ProbF
Between Subjects	GENDER	1	0.13	0.13	0.02	0.8983
Between Subjects	Error	48	377.36	7.86	_	_
Within Subject	VISIT	1	71.78	71.78	53.40	<.0001
Within Subject	VISIT*GENDER	1	6.98	6.98	5.19	0.0272
Within Subject	Error(VISIT)	48	64.51	1.34	_	_

Table 7.3

Table 7.3 - HSS
Means (SD) of total HSS at Visit1 Visit2 by Gender

GENDER	N	Mean Visit 1	SD Visit 1	Mean Visit 2	SD Visit 2
Females	34	8.71	2.15	6.32	2.33
Males	16	8.06	2.02	6.81	1.80