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REPORT TITLE

A double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy and safety of Euphorbia prostrata Dry Extract tablets in patients of 1° and 2° internal haemorrhoids

Protocol No: Panbio/CR/0042006/CT
EudraCT No.: 2007-004526-24

Investigational product: Euphorbia prostrata dry extract, 100 mg tablet
Indication studied: 1° and 2° internal haemorrhoids
Development Phase: III

CLINICAL TRIAL REPORT

Panacea Biotec
Innovation in support of life
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Study Initiation Date:30 December 2008
Study Completion Date:15 March 2010
Date of Report Generation:16 July 2010

STATEMENT OF COMPLIANCE

This study was performed in accordance with 'Guidelines for clinical trials on pharmaceutical products in India – GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India.

REPORT APPROVAL SHEET

Study Title: A double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy and safety of Euphorbia prostrata Dry Extract tablets in patients of 1o and 2o internal haemorrhoids

Protocol No: Panbio/CR/0042006/CT
EudraCT No.: 2007-004526-24

Function	Name	Signature & Date
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Quality Assurance	Ms. Priyanka Chamoli Senior Executive - Quality and Compliance	21-09-10
Approved by	Dr. Arani Chatterjee Vice President – Clinical Research	Arani Chatterjee 21-09-10

SYNOPSIS

Name of Company: Panacea Biotec Ltd.	Name of Finished Product: Euphorbia prostrata dry extract tablets 100 mg	Name of Active Ingredients: E. prostrata dry extract ethanolic 80 % v/v [(35-70):1]

Title of Study:	A double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy and safety of Euphorbia prostrata Dry Extract tablets in patients of 1° and 2° internal haemorrhoids
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Study Period:	Study Initiation (First Patient, First Visit) Date: 30 December 2008 Study Completion (Last Patient, Last Visit) Date: 15 March 2010
Phase of Development:	III
Objectives:	**Primary** • To evaluate the efficacy of E. prostrata Dry Extract tablets compared to placebo in the treatment of 1° and 2° internal haemorrhoids, based on the proportion of subjects in each treatment group achieving cessation of per rectal bleeding as assessed by the subject (cessation of per rectal bleeding defined as the maintenance of bleeding cessation for at least 3 continuous days after initial "cessation of bleeding"). **Secondary** • To evaluate the efficacy of E. prostrata Dry Extract tablets compared to placebo in the

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	treatment of internal 1° and 2° haemorrhoids, based on the proportion of subjects in each treatment group without recurrence of bleeding (recurrence of bleeding defined as any episode of bleeding after maintenance of bleeding cessation and before the end of 14 days post-treatment). • To evaluate the efficacy of E. prostrata Dry Extract tablets compared to placebo, based on the change in following symptoms as assessed by subject, viz., pain, tenesmus, pruritus, anal discharge and following signs as assessed by the investigator, viz., congestion, oedema and exudation. • To evaluate the efficacy of E. prostrata Dry Extract tablets compared to placebo, based on the difference between the two treatment groups in overall assessment of disease condition as assessed by the subject. • To evaluate the safety of E. prostrata Dry Extract tablets compared to placebo, by comparing the incidences of clinical and laboratory adverse events (AEs) between the two treatment groups.	
Methodology:	**Description**: Double-blind, randomized, placebo-controlled, multicentre study **Duration of study**: 15 months **Duration of subject participation**: Approximately 34 days (duration of protocol specified therapy with IMP-14 days) At the baseline visit, after confirmation that the subject met the eligibility criteria for randomisation, the subject was assigned a randomisation number sequentially in the order in which the subject entered the study. A SAS program was used for generating the randomisation schedule, assigning subjects (identified by their randomisation numbers) at random to one of the two treatments (E. prostrata extract or placebo).. Supplies were pre-packed and assigned randomisation numbers according to the randomisation schedule and subjects and supplies were matched according to their randomisation numbers. Efficacy and safety evaluations were performed on Days 7, 14, and 28.	
Number of Patients:	495 subjects with a 2:1 study drug to placebo ratio (EU: 50%, INDIA: 50%)	
Diagnosis and Main Criteria for Inclusion:	• Adult subjects who are able to understand the nature, significance and scope of the clinical trial and express their will accordingly and agree to participate in the study by giving written informed consent. • Male or female subjects, at least 18 years of age with a diagnosis of 1° and 2° internal haemorrhoids confirmed by proctoscopic examination and suffering from an uncomplicated and untreated acute attack (defined as acute onset of per rectal bleeding within 3 days of inclusion into the study, with at least one of the symptoms, viz., pain, tenesmus, pruritus and anal discharge). • Except 1° and 2° internal haemorrhoids, the subjects are judged to be in general reasonable health, based on medical history, physical examination, and laboratory screening tests, enabling him or her to complete the trial without anticipated serious co-morbid event.	
Exclusion Criteria:	• Pregnant, lactating women. Women in post-partum period of up to 6 weeks were excluded. • Women of child bearing potential who do not agree to remain abstinent or use medically acceptable methods of contraception [which result in a low failure rate (i.e. < 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner] during the study therapy and for 4 weeks after the end of study therapy. • Subjects who have been previously enrolled in a study involving E. prostrata Dry Extract tablets. • History of permanent anal prolapse and/or anal fistula. • Previous history of surgery for anorectal disease (within 5 years) or any other procedures (including but not limited to injection sclerotherapy, rubber band ligation, photocoagulation, cryotherapy etc.) within 2 years. • Subjects who, in the opinion of the investigator, are mentally incapacitated such that informed consent cannot be obtained. • Clinically significant co-morbid condition that in the opinion of the investigator could affect the efficacy and safety outcome of the study. • Laboratory values falling outside the defined reference values for haemoglobin, total leucocyte count, differential count, bleeding time, clotting time, PT/INR, aPTT, platelet count, SGOT, SGPT, alkaline phosphatase, total bilirubin, random blood sugar, serum cholesterol, blood urea, serum creatinine and urine routine and microscopic examination. • Treatment with any of the following at inclusion or in the previous one month: venotropic, anticoagulant, and antiplatelet agent. Subjects on aspirin upto 160 mg for cardiovascular indication were not excluded from the trial. • Treatment with any of the following at inclusion or in the previous one week: anti-inflammatory and analgesic agent. • Other chronic medications not being used at a stable dosage for at least 2 weeks. • Current users (including "recreational use") of illicit drugs or history of drug abuse within the past 5 years.	

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	• Subjects who have donated a unit of blood or plasma or participated in another clinical study with an investigational agent within the last 4 weeks. • Associated anal fissures and/or infective anal pathology.	
Test Product, Dose and Mode of Administration:	Euphorbia prostrata Dry Extract tablets 100 mg, one tablet daily	
Duration of Treatment:	14 days	
Reference Product, Dose and Mode of Administration:	Placebo, 1 tablet daily	
Criteria for Evaluation:	**Efficacy Endpoints (Baseline vs. end of treatment)** ***Primary*** • Proportion of subjects in each treatment group achieving cessation of per rectal bleeding as assessed by the subject at day 14 (cessation of per rectal bleeding defined as the maintenance of bleeding cessation for at least 3 continuous days after initial "cessation of bleeding") ***Secondary*** Difference between treatment groups in: • Proportion of subjects in each treatment group without recurrence of bleeding (recurrence of bleeding defined as any episode of bleeding after maintenance of bleeding cessation and before the end of 14 days post-treatment). • Change in the following symptoms, viz., pain, tenesmus, pruritus and anal discharge as assessed by the subject at day 14 (categorized as none, mild, moderate and severe) • Change in the following objective signs, viz., congestion, oedema, and exudation as assessed by the investigator at day 14 (categorized as absent or present) • Change in overall assessment of disease condition as assessed by the subject on a 10 cm Visual Analogue Scale (VAS) at day 14, where 0 = Best Ever and 10 = Worst Ever **Safety Endpoints:** • Incidences of clinical and laboratory AEs between the treatment groups	
Statistical Methods:	Continuous variables such as vital signs were summarized using mean, standard deviation, median, and range (minimum and maximum), while categorical variables such as results of physical examinations were summarized using proportions (counts and percentages). The primary efficacy endpoint (cessation of bleeding defined as the maintenance of bleeding cessation for at least 3 continuous days after initial "cessation of bleeding") was evaluated using the 95% confidence interval (CI) for the difference between the two treatment groups in the proportion of subjects achieving cessation of per rectal bleeding as assessed by the subject at day 14 of treatment. Additionally, logistic regression analysis with response (cessation of bleeding per rectum at the end of the study) as the dependent variable and potentially relevant factors such as treatment, study region (EU/non-EU), age (patients aged 50 and older/others), and gender as independent variables was performed. To explore whether treatment effects are consistent across different subgroups, treatment-by-factor interactions were evaluated in the logistic regression model for the primary efficacy endpoint in the modified ITT population. The subject characteristics and baseline covariates of interest in the logistic regression analysis were: Study region (EU/non-EU) Gender (female/male) Age Category (patients aged 50 years or older/others) To assess the effects of the above factors, the logistic regression model included treatment, covariate, and treatment-by-covariate interaction. The secondary efficacy endpoint pertaining to recurrence of bleeding (recurrence of bleeding defined as any episode of bleeding after maintenance of bleeding cessation and before the end of 14 days post-treatment) was evaluated using the 95% CI for the difference between the two treatment groups in the proportion of subjects without recurrence of bleeding. The secondary efficacy endpoints pertaining to change in symptoms (pain, tenesmus, pruritus and anal discharge) as assessed by the subject (categorized as none, mild, moderate and severe) at day 14 and change in objective signs (congestion, oedema, and exudation) as assessed by the investigator at day 14 (categorized as absent or present) were analysed by comparing the proportions of subjects in the two groups with improvement, no change, or worsening from baseline in each of these symptoms/signs at day 14, using the stratified Cochran-Mantel-Haenszel test (with centre as the stratification variable) based on ordinal data. Change in overall assessment of disease condition as assessed on a 10 cm VAS scale at day 14 was analysed using 2-way analysis of covariance with change from baseline as the dependent variable and treatment, centre, and baseline as independent variables. For each treatment, the incidences of all treatment emergent AEs was tabulated by System Organ Class (SOC) and Preferred Term (PT) (to which each AE was mapped, using MedDRA (Medical Dictionary for Regulatory Activities). Other information regarding AEs, such as intensity, seriousness, causality, and discontinuation due to AEs, was also tabulated by treatment. AEs	

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	that were reported more than once by a subject were counted only once for that subject at the maximum intensity. Prior, concomitant, and rescue medications were summarized by treatment. Summary statistics (number of cases and incidence rates) were presented within relevant subgroups for the primary safety endpoints.	
Summary - Conclusions	The data from patients in Europe showed that Euphorbia was significantly superior to Placebo with 88% of patients in the Euphorbia group and 77% of patients in the Placebo group reporting cessation of bleeding within 14 days after start of treatment. However, the data from patients in India did not show a significant superiority of Euphorbia to Placebo, and had, in fact, a diluting effect on the overall results, which show a response rate of 79% of patients in the Euphorbia group and 74% in the Placebo group, with the difference being statistically not significant. The secondary efficacy results were consistent with the primary efficacy results. The primary efficacy results were supported by the secondary efficacy results for Europe, while the secondary efficacy results for India failed to demonstrate superiority of Euphorbia to Placebo. The data from patients in Europe showed that there was a substantially higher proportion of patients without recurrence of bleeding in the Euphorbia group, compared to the Placebo group, although the difference was not statistically significant. However, the data from patients in India and thereby the overall results showed similar proportions of patients without recurrence of bleeding in the two treatment groups. The data from Europe showed a consistently higher proportion of patients in the Euphorbia group with improvement of objective signs, compared to the Placebo group, with the difference between the two groups being statistically significant for congestion and oedema. The Indian data and the overall data did not show a statistically significant difference between the two groups for any of the objective sign assessments. For the overall assessment of efficacy, based on the combined data as well as data from India and data from Europe, the Euphorbia group showed better improvement, compared to Placebo, although the difference between the two groups was not statistically significant. In a regression analysis with cessation of bleeding as the dependent variable and region (Europe vs. India), gender, and age category as factors, the treatment by region interaction term was bordering on significance ($p = 0.0768$), indicating that the treatment effect in Europe was different from that seen in India. This confirmed the primary efficacy results, which showed that, in Europe, Euphorbia was significantly superior to Placebo, while in India, the proportions of patients achieving cessation of bleeding in the two treatment groups were similar. The incidence of AEs during the 14-day treatment period was comparable for the two treatment groups, with 24 (7.5%) patients in the Euphorbia group and 8 (4.9%) patients in the Placebo group reporting any AE. The difference in the incidence of AEs between the two groups was not statistically significant. There were two SAEs occurring in the Euphorbia group and no SAEs occurring in the Placebo group. Both SAEs were unlikely to be related to the study medication. One of the SAEs, Hb value 5.8 g/dl, led to withdrawal of the patient from the study. The other SAE, gastroenteritis, was resolved with no sequelae. There were 4 patients in the Euphorbia group (including the patient who experienced an SAE) and one patient in the Placebo group who dropped out of the study due to AEs. There were 2 (0.6%) patients in the Euphorbia group and 1 (0.6%) patient in the Placebo group with severe AEs. There were 8 (2.5%) patients in the Euphorbia group and 2 (1.2%) patients in the Placebo group with drug related (possibly and probably related) AEs. There was a statistically significant difference between the two groups with respect to change in platelet count from baseline to end of treatment. However, this was caused by a significant decrease in platelet count from baseline to end of treatment in the placebo group, and thus was not an AE attributable to Euphorbia. Also, there was a statistically significant difference between the two groups with respect to change in lymphocytes from baseline to end of treatment and to end of follow-up. However, change in lymphocytes from baseline to end of treatment or to end of follow-up was not significant within the Euphorbia group, and the difference between the two groups was caused by a significant increase from baseline in lymphocytes in the Placebo group, and thus was not an AE attributable to Euphorbia. For all other laboratory parameters, there was no statistically significant difference between the two groups. There was no significant difference between the two treatment groups with respect to change from baseline to end of treatment for pulse rate, respiratory rate, blood pressure or temperature. Although the high placebo effect (74%) in the Phase III clinical trial against the assumption of 59% reported efficacy of placebo in hemorrhoidal disease had a diluting effect on the overall results, the test product met the target efficacy of 79%. In summary, the results of this study show that Euphorbia is safe and effective in the treatment of 1° and 2° internal haemorrhoids.	

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
aPTT	Activated Partial Thromboplastin Time
BT	Bleeding Time
CDSCO	Central Drugs Standard Control Organization
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CI	Confidence Interval
CT	Clotting Time
DLC	Differential Leukocyte Count
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
Hb	Haemoglobin
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMR	Indian Council of Medical Research
IEC	Institutional Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SGOT	Serum Glutamate Oxalate Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase
SOC	System Organ Class
TLC	Total Leukocyte Count
WHO	World Health Organisation

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1. Ethics

1.1. Declaration of Helsinki

This study was conducted in full conformity with the current revision of the 1964 Declaration of Helsinki.

1.2. Good Clinical Practice

This study was conducted according to the protocol, the Indian Council of Medical Research (ICMR) guidelines, the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical trials and applicable local regulatory requirements.

1.3. Ethics Committee

The study protocol, amendments, the informed consent, and other information that required pre-approval were reviewed and approved by the investigational centers' Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

The written favourable opinion of the IEC/ IRB for the conduct of the study at the selected sites, the protocol, written patient information and Informed Consent Form, any other written information that was provided to the patients and any advertisements that were used was obtained prior to recruitment of patients into the study and shipment of investigational medicinal product (IMP) to the investigational sites.

Proposed amendments to the protocol and aforementioned documents were submitted to the sponsor for review and approval, and then to the IEC/IRB. Amendments were implemented only after a copy of the IEC's/IRB's letter of favourable opinion was transmitted to the sponsor.

The investigator reported serious or unexpected adverse events (AEs) that occurred during the study and those that were likely to affect the safety of the patients or the conduct of the trial to the IEC/IRB.

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Dr Katarzyna Łosak
Prof. Leszek Szczepański
Dr Piotr Malek

1.4. Regulatory Compliance

This study was conducted in compliance with regulatory requirements of the respective countries. In particular, the study was conducted in accordance with 'Guidelines for Clinical Trials on Pharmaceutical Products in India – GCP Guidelines', issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India.

1.5. Informed Consent

It was the investigator's responsibility to obtain written informed consent from each patient after an adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any study procedures are commenced. The patient was given a copy of the Patient Information Sheet and Informed Consent Form in their native language.

Written informed consent was obtained from each subject before the performance of any study-specific procedures. The original copy of the signed and dated Informed Consent Form was retained in the institution's records, and was subject to inspection by representatives of the sponsor, or representatives from competent authorities.

1.6. Contact with General Practitioner

It was the investigator's responsibility to inform the patient's General Practitioner (where applicable) by letter that the patient is taking part in the study, provided that the patient agreed to this contact. Information to this effect was included in the Patient information Sheet and Informed Consent Form.

1.7. Patient Confidentiality

The investigator ensured that the patient's privacy was maintained. Patients were identified anonymously (screening number, randomisation numbers, initials, date of birth) on the case report form (CRF) or other documents submitted to the sponsor. Documents that were not submitted to the sponsor e.g., signed and dated Informed Consent Forms were kept in a strictly confidential file by the investigator.

The investigator permitted authorised representatives of the sponsor, competent authorities and IECs/IRBs to review that portion of the patient's medical record that was directly related to the study. As part of the required content of informed consent, the patient was informed that his or her records would be reviewed in this manner.

1.8. Trial Documentation and Storage

The investigators maintained the trial documents in comprehensive and centralised filing systems that were suitable for inspection by representatives of the sponsor and regulatory authorities. The investigators have taken measures to prevent accidental or premature destruction of these documents.

Study documents, including CRFs, protocol, source data, patient identification code list, original Informed Consent Forms, study approvals, IMP logs and correspondence, were to be retained by the investigator for the maximum time permitted by local regulations. The patient identification code list and patients' original Informed Consent Forms were to be retained for at least 15 years. It would be the responsibility of the sponsor to inform the investigator as to when these documents no longer need to be retained.

2. Investigators and Administrative Structure

2.1. Investigators and Study Centers

Patients were enrolled at 30 study centers. The following table presents the names and addresses of the investigators:

List of Investigators in Poland		
S No	Name	Site Address
1	Dr. B. Grabowska	NZOZ Gabinet Lekarza Rodzinnego, Brzozówka 115, 32-088 Przybysławice
2	Dr. A. Burzej	Samodzielny Publiczny Zakład Opieki Zdrowotnej – Obwód Lecznictwa Kolejowego, ul. Batorego 77, 33-300 Nowy Sącz
3	Dr. J. Madej	Specjalistyczny Gabinet Chirurgiczny, oś. Złotej Jesieni 3, 31-826 Kraków
4	Dr. P. Walczak	Gabinet Endoskopii Przewodu Pokarmowego, ul. Szewska 4/5, 31-009 Kraków
5	Dr. K. Świerczek	NZOZ GALL-MED, ul.Galla 25, 30-053 Kraków
6	Dr. T. Łach	Niepubliczny Zakład Opieki Zdrowotnej PROMED, ul. Olszańska 5, 31-513 Kraków
7	Dr. J. Sułowska	Niepubliczny Zakład Opieki Zdrowotnej Praktyka Lekarzy Rodzinnych Zofia Kraj, Joanna Sułowska , oś. Oświecenia 45, 31-636 Kraków
8	Dr. M. Zawiślan	Praktyka Grupowa Lekarzy Rodzinnych Sp.J; NZOZ Ewa Drohomirecka-Zach& Malgorzata Zawiślan, oś. II Pułku Lotniczego 22, 31-869 Kraków
9	Dr Mirosław Szura	Specjalistyczne Centrum Diagnostyczno-Zabiegowe MEDICINA Sp. Z o. o. Bartka 12, Kraków 30-307
10	Dr Katarzyna Łosak	NZOZ GASTRO-ENDOMED lek.Katarzyna Łosak, ul. Kochanowskiego 2, 33-300 Nowy Sącz
11	Prof. Leszek Szczepański	Ośrodek Badań Klinicznych Prof. dr Leszek Szczepański Prywatna Praktyka Lekarska, ul. Krucza 5, 20-022 Lublin
12	Dr Piotr Małek	Prywatny Specjalistyczny Gabinet Chirurgiczny Dr n. med. Piotr Małek Specjalista Chirurgii Ogólnej, ul. Św. Faustyny 84, 35-330 Rzeszów

List of Investigators in Germany		
1	Dr. Doumit	Flach-Fengler-Strasse 114, 50389 Wesseling
2	Dr. Jongen	Proktologische Praxis Kiel, Beselerallee 67, 24105 Kiel
3	Dr. Liebich	Hackenstr 2, 80331 Munich
4	Dr. Kolbert	End-und Dickdarmzentrum Hannover, Hildesheimer Straße 6, 30169 Hannover
5	Dr. Hoesl	Weiltinger Straße 11, 90449 Nürnberg
6	Dr. Meier	Paradeplatz 8, 92224 Amberg
List of Investigators in India		
1	Dr. Vinod Kumar Malik	Vice-Chairman and Senior Consultant, Dept of General surgery, Sir Ganga Ram Hospital, , New Delhi -110060
2	Dr. K Sridhar Rao	Professor of General Surgery, Osmania General Hospital, Department of Surgery, Afzalgunj, Hyderabad, Andhra Pradesh - 500012
3	Dr. P.S. Sarangi	Department of Surgery, Deen Dayal Upadhyay Hospital, Hari Nagar, Near Ghanta Ghar, New Delhi110064
4	Dr. V. Mathai	Senior Consultant, Colorectal Surgeon, Global Hospital, 6-3-345/1, NIMS lane, Opp Vengul Rao Park, Road no. 1 Banjara Hils, Hyderabad-500034
5	Dr. Durganna	Professor of General Surgery, Room. No 95, Dept of Surgery, Victoria Hospital, Bangalore 560002
6	Dr. P.N Agarwal	Prof. Dept of Surgery, Maulana Azad Medical College, New Delhi - 110002
7	Dr. H. Ramesh	Director of Surgical Gastroenterology, Dept of GI Surgery, Lakeshore Hospital and research Centre, Cochin
8	Dr. Sivaraman Prem Kumar	Professor and HOD of GI and General Surgery, PSG Hospital, Peelameedu, Avanashi Road, Coimbatore-04
9	Dr. Siddarth P. Dubhashi	Associate Professor, Department of Surgery, DY Patil Medical College, Sant Tukaram Nagar Pimpri,Pune - 411018
10	Dr.Priyesh Naik	Prakruti Hospital,Sidheshwar Arcade, Opp to Manisha Nagar, Gate no 01,Kalwa (W), Thane.
11	Dr. Vaibhav J Lokhande	Nulife Hospital, 1st floor, Aniraj towers, LBS road, Opposite Metro Mall, Bhandup West, Mumbai-400078
12	Dr Sriram Bhatt	Athena Hospital, Falnir Road, Mangalore – 575 001, Karnataka

2.2. Study Administrative Structure

Panacea Biotec Ltd. was the sponsor of this study. The conduct of the study was outsourced to Clintec, a contract research organization (CRO) with offices in Bangalore, India and Munich, Germany. Data management, statistical analysis, and report writing were outsourced to Clinstitute, a CRO in Bangalore, India.

CRO: Clintec (India) International Pvt. Ltd.	**STATISTICIAN and DATA ANALYST**
ClinTec (India) International Pvt. Ltd #27, 2nd Floor, S.V.Towers, 6th Block, 80 Ft Road Koramangala, Bangalore- 560 097 Tel: +91 804150 1444 Fax: +91 8041745566	Dr. Lilly Sanathanan Clinstitute 600 AECS Layout, BrookFields Bangalore 560037 +91-80-28476567

3. Introduction

3.1 Background

Hemorrhoidal disease is a common condition of the anal canal characterized by recurrent, self-resolving acute episodes. Haemorrhoids are a common entity in the general population and in clinical practice. A common cause of hematochezia in adults, it remains high in the differential diagnosis of almost any anorectal complaint. Haemorrhoids are enlarged, bulging blood vessels in and around the anus and lower rectum which may be external or internal. External haemorrhoids develop near the anus

and are covered by sensitive skin while the internal haemorrhoid lies beneath the anal mucous membrane.

The basic pathological factor in haemorrhoids is the dilation of the anorectal venous plexuses. In the acute bleeding of internal haemorrhoids, one of the pathogenic processes implicated is the stagnation and stasis of blood in the vascular plexuses of the prolapsed anal cushions. It has also been demonstrated that stasis activates white blood cells to release inflammatory mediators and cause an inflammatory response leading to increased permeability, fragility and necrosis of the vessel wall. The anal cushions are therefore easily injured by the passage of stool and bleed.[1] Other contributory factors are the oedema and subsequent hyperplasia of underlying structures. Prominent among the symptoms complex of haemorrhoids are bleeding, prolapse during defecation, occasional pain, excessive mucus discharge and pruritus around the anus.[2] Subjects with acute internal haemorrhoids are frequently treated with outpatient procedures. However, in spite of careful techniques, many subjects experience pain and discomfort. Therefore, any pharmacological agent leading to effective and rapid noninvasive control of signs and symptoms is of immense clinical value.

Euphorbia prostrata Dry Extract tablets contain E. prostrata Dry Extract ethanolic 80% v/v [(35-70):1]. The E. prostrata Dry Extract ethanolic 80% v/v [(35-70):1] is obtained from the aerial parts (dried leaves, stems, flowers and fruits of *E. prostrata* Ait. (Euphorbiaceae). The active principles in E. prostrata Dry Extract tablets are chiefly flavonoids, phenolic acid and tannins. Flavonoids and phenolic acid have been reported to have anti-inflammatory,[3] analgesic,[3] antioxidant,[4,5] haemostatic,[6] antithrombotic and vasoprotective actions. Tannins are also known to possess astringent and haemostatic properties.[7] Various preclinical studies carried out on the extract have confirmed its wound healing and antihemorrhoidal activity. Also, preclinical studies on safety using standardized extract of E. prostrata Dry Extract tablets have demonstrated that it has no effect on cardiovascular, respiratory, central nervous or gastrointestinal systems.[8,9,10,11]

3.2. Rationale

Pharmacodynamic properties of flavonoids and tannins indicate that E. prostrata is useful in the management of haemorrhoids. Clinical studies with oral formulation of E. prostrata Dry Extract have revealed that 100 mg E. prostrata Dry Extract tablets once daily are useful in the treatment of haemorrhoids leading to substantial relief from bleeding per rectum, pain, anal discomfort and inflammation in haemorrhoids (especially 1° and 2° haemorrhoids). Also, it was seen to be well tolerated with minimal side effects.[12]

Keeping in view the properties of the E. prostrata Dry Extract tablets and also the results of previous non-clinical and clinical studies, it is intended to relieve bleeding, anal discomfort, pain and inflammation in subjects of haemorrhoids (especially 1° and 2° haemorrhoids). Though the tolerability of the product is good, the common adverse effects include nausea, dyspepsia, abdominal pain, diarrhoea, headache and dry mouth as reported in a previous clinical trial.[12]

The present trial was designed to assess the efficacy and safety of E. prostrata Dry Extract tablets in comparison with placebo in a double-blind, randomized, placebo-controlled, multicentre study.

4. Study Objectives

4.1. Primary Objective

- To evaluate the efficacy of E. prostrata Dry Extract tablets as compared to placebo in the treatment of internal 1° and 2° haemorrhoids, based on the proportion of subjects in each treatment group achieving cessation of per rectal bleeding as assessed by the subject (cessation of per rectal bleeding defined as the maintenance of bleeding cessation for at least 3 continuous days after initial "cessation of bleeding").

4.2. Secondary Objectives

- To evaluate the efficacy of E. prostrata Dry Extract tablets compared to placebo in the treatment of internal 1° and 2° haemorrhoids, based on the proportion of subjects in each treatment group without recurrence of bleeding (recurrence of bleeding defined as any episode of bleeding after maintenance of bleeding cessation and before the end of 14 days post-treatment).
- To evaluate the efficacy of E. prostrata Dry Extract tablets as compared to placebo based on the change in following symptoms as assessed by subject, viz., pain, tenesmus, pruritus, anal discharge and following signs as assessed by the investigator, viz., congestion, oedema and exudation.
- To evaluate the efficacy of E. prostrata Dry Extract tablets as compared to placebo based on the difference between the two treatment groups in overall assessment of disease condition as assessed by the subject.
- To evaluate the safety of E. prostrata Dry Extract tablets as compared to placebo, by comparing the incidences of clinical and laboratory adverse events (AEs) between the two treatment groups.

5. Design and Conduct of Study

5.1. Overview of Study Design

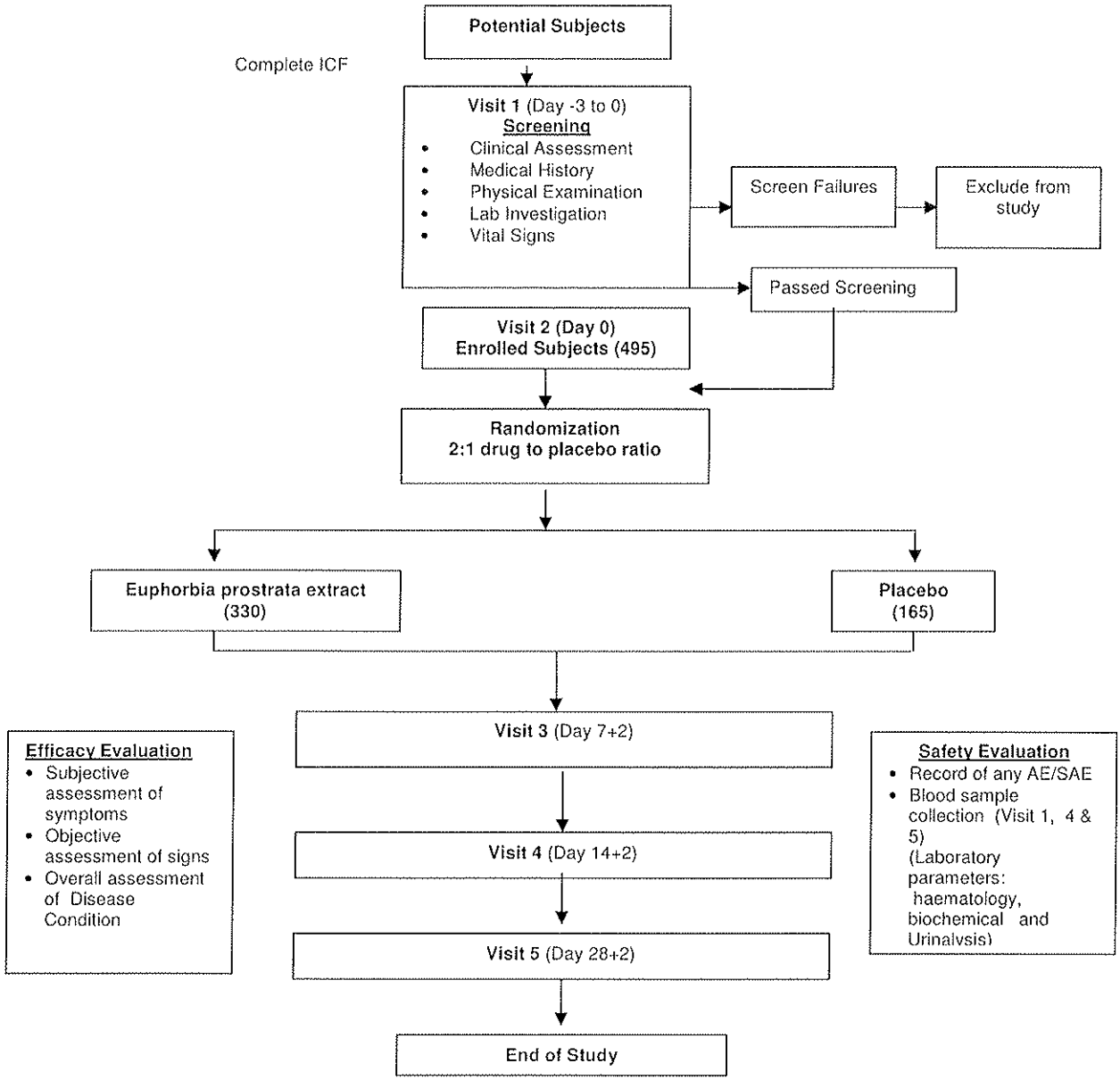
This was a double-blind, randomized, placebo-controlled, multicenter study to assess the efficacy and safety of E. prostrata tablets in haemorrhoidal disease. Subjects received treatment for 14 days. Duration of subject participation was approximately 34 days.

Randomization, Blinding and Unblinding Procedure

At the baseline visit, after confirmation that the subject met the eligibility criteria for randomisation, the subject was assigned a randomisation number sequentially in the order in which the subject enters the study. A statistician created a SAS program that generated the randomisation schedule, assigning subjects (identified by their randomisation numbers) at random to one of the two treatments. The final run of the randomisation program with a different seed number was performed by an independent person who was not involved in the study. This person ensured that the blind was maintained for all involved in the study conduct. Supplies were pre-packed and assigned

randomisation numbers according to the randomisation schedule and subjects and supplies were matched according to their randomisation numbers.

Each randomisation number with the allocated treatment information was sealed in a separate envelope (referred to as a code-break envelope) by the person who was responsible for the final creation of the randomisation schedule. This person supplied the code-break envelopes to the centre and to the sponsor. The randomisation code-break envelopes were to be opened only in the case of a medical emergency where knowledge of treatment allocation was essential for the management of the subject's condition. If any code-break envelope was opened, the person who opened it had to sign and date the envelope and give the reason for opening it.



5.2. Selection of Study Population

The sample size was calculated assuming 59%[14] efficacy of placebo in hemorrhoidal disease. The 20% superiority hypothesis was postulated for E. prostrata as compared to placebo. Under these assumptions, a sample size of 178 subjects in each arm yields 90% power to conclude that E. prostrata is 20% superior to placebo. To evaluate the safety adequately 300 subjects in the test arm subjects were considered. Thus the total number of subjects required for this comparative evaluation has been calculated to be 495 (Case: Control = 2:1).

5.2.1. Inclusion Criteria

To be eligible for the study, patients had to fulfill all of the following criteria:

- Adult subjects who are able to understand the nature, significance and scope of the clinical trial and express their will accordingly and agree to participate in the study by giving written informed consent.
- Male or female subjects, at least 18 years of age with a diagnosis of 1° and 2° internal haemorrhoids confirmed by proctoscopic examination* and suffering from an uncomplicated and untreated acute attack (defined as acute onset of per rectal bleeding within 3 days of inclusion into the study, with at least one of the symptoms, viz., pain, tenesmus, pruritus and anal discharge)
  * Proctoscopic Examination: Visibly distended or displaced anal cushions conforming to 1° and 2° haemorrhoids[13]
- Except 1° and 2° internal haemorrhoids, the subjects are judged to be in general reasonable health, based on medical history, physical examination, and laboratory screening tests, enabling him or her to complete the trial without anticipated serious co-morbid event.

5.2.2. Exclusion Criteria

Patients were excluded from the study if they fulfilled any of the following criteria:

- Women of child bearing potential who do not agree to remain abstinent or use medically acceptable methods of contraception [which result in a low failure rate (i.e. < 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner] during the study therapy and for 4 weeks after the end of study therapy.
- Subjects who have been previously enrolled in a study involving E. prostrata Dry Extract.
- Previous history of surgery for anorectal disease (including but not limited to haemorrhoidectomy) within 5 years or any other procedures (including but not limited to injection sclerotherapy, rubber band ligation, photo coagulation, cryotherapy etc.) within 2 years.
- History of permanent anal prolapse and/or anal fistula.
- Subjects who in the opinion of the investigator, are mentally incapacitated such that informed consent cannot be obtained.
- Clinically significant co-morbid condition that in the opinion of the investigator could affect the efficacy and safety outcome of the study.
- Laboratory values falling outside the defined reference values for haemoglobin (Hb), total leucocyte count (TLC), differential count (DLC), bleeding time (BT), clotting time (CT), PT/INR, aPTT, platelet count, SGOT, SGPT, alkaline phosphatase, total bilirubin, random blood sugar, serum cholesterol, blood urea, serum creatinine and urine routine and microscopic examination.
- Treatment with any of the following at inclusion or in the previous one month – venotropic, anticoagulant, and anti-platelet agent. Subjects on aspirin upto 160 mg for cardiovascular indication were excluded from the trial.
- Treatment with any of the following at inclusion or in the previous one week – anti-inflammatory and analgesic agent.
- Other chronic medications not being used at a stable dosage for at least 2 weeks.
- Current users (including "recreational use") of illicit drugs or history of drug abuse

within the past 5 years.
- Subjects who have donated a unit of blood or plasma or participated in another clinical study with an investigational agent within the last 4 weeks.
- Associated anal fissures, and/or infective anal pathology.

5.2.3 Withdrawal Criteria

- In accordance with the Declaration of Helsinki, subjects had the right to withdraw from the study at any time without providing a reason.
- The investigator also had the right to withdraw subjects from the study in case of occurrence of serious adverse events, protocol violations, non compliance to the IMP, failure to return for scheduled visit, pregnancy in case of female subjects, therapy during the study period that in the opinion of investigator is likely to interfere with results of study or other valid reason.
- The subjects could also be withdrawn if necessary to protect their health and the integrity of the study. In case of questionable situation the medical monitor had to be consulted.
- Subjects with inadequate laboratory parameters could be excluded from the study based on the discretion of the investigator.
- Subjects who were not evaluable due to protocol violations that were within the control of the investigator were considered as completed subjects. Subjects who withdrew due to AEs after the first dose were classified as "completed" and were not replaced. If a subject decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal was made with an explanation of why the subject was withdrawing from the study. Each case of subject's withdrawal had to be recorded in the CRF.
- In case the subject did not come for follow up, he/she was treated as a drop out from the study.

5.3. Composition and Administration of Study Medications

5.3.1. Study Medications

Investigational Medicinal Product (IMP)
E. prostrata Dry Extract 100 mg tablets presented as film- coated tablets.
Each film-coated tablet contains:
E. prostrata Dry Extract ethanolic 80 % v/v [(35-70):1]. .....100 mg

Placebo as comparator
Placebo was used as a comparator in the clinical trial. It is a dummy treatment which does not contain active ingredient and is designed to resemble the active product being studied with respect to physical characteristics and packaging.

5.3.2. Blinding, Packaging, and Labeling

The sponsor/CRO supplied controlled number of dosage units of E. prostrata Dry Extract 100 mg tablets and placebo in properly sealed labeled containers.

Sample Label

Individual Subject Pack Label

Protocol No.	:	Panbio/CR/0042006/CT		14 Tablets
EudraCT No.	:	2007-004526-24	**FOR CLINICAL TRIAL USE ONLY**	
Name of test product	:	Euphorbia Prostrata Dry Extract 100mg Tablet or Placebo		
Lot No.	:			
Dosage Form & route	:	Tablet, to be administered orally	Sponsor: Panacea Biotec Ltd. Baddi, (H.P.) 173 205 India Tel.: +91 1795 304000	
Use Before	:	Aug 2009		
Storage Conditions	:	Store at a temperature below 25°C, protect from light and moisture.	CRO: ClinTec (India) International Pvt. Ltd., 3rd Floor, 'A' Wing, Divyasree Chambers, Langford Road, Bangalore 560 025 India Tel: +91 80 4150 1444	
Directions for use	:	One tablet to be taken daily by mouth		
KEEP OUT OF REACH OF CHILDREN				

The IMP was labeled according to national regulatory requirements.

5.3.3. Storage, Disposition and Accountability of Supplies

The IMP was stored at a temperature below 25°C, and protected from light and moisture. The clinical study material for the study had to be used in accordance with the protocol. The principal investigator maintained complete and accurate records of IMP. Records showing the receipt and disposition of all materials included a drug accountability record, listing the date IMP shipment was received, the quantities received, and a dispensing record. These records included dates, quantities, batch/serial numbers, expiration dates (if applicable), unique code numbers assigned to the IMP and trial subjects, date of dispensing, return of unused IMP and the identification of the dispenser. All non-used IMP had to be returned to the Sponsor with proper records. Applicable SOPs as per sponsor norms had to be followed thereafter.

5.3.4. Administration of Treatment

After enrolment, subjects were randomised to receive either E. prostrata Dry Extract tablet or Placebo. The two treatments looked alike and the subjects as well as the investigator remained blinded to the nature of treatment the subject was receiving. All the subjects were given full course of therapy for 14 days, irrespective of whether they got relief in subsequent days or not. The IMP or placebo both was taken orally, once daily. Evaluation was done on day 7 and 14. The allowable window period for the scheduled visit was +2 days. Subjects were followed for another 14 days after the protocol therapy to assess the recurrence of per rectal bleeding. After the completion of the clinical trial, the subject was treated as per investigator's discretion/centre standard practice.

5.3.5. Treatment Compliance

Compliance was assessed by tablet counting method. Compliance cards were issued to subjects.

Compliant: ≥ 70% of test medication consumed over the duration of therapy.
Non-compliant: < 70% of test medication consumed over the duration of therapy.

5.3.6. Concomitant Medications

Subjects were allowed laxatives as concomitant medicines. The frequency of use, class and doses taken were recorded. Only water and no soap or other additives was allowed for sitz bath during the study. Use of any topical agent also was not allowed for the treatment of the haemorrhoids. Any other concomitant medication taken by subject was recorded in the CRF.

5.4. Study Measures and Procedures

5.4.1. Schedule of Events

The schedule of events is presented in detail as follows and is summarized in a table at the end of this section.

Assessment performed before start and during the therapy

Visit 1 [Day -3 to 0] SCREENING VISIT

- Written informed consent was taken.
- Demographic data, age, sex and weight were recorded.
- Medical history was taken including the intensity and frequency of haemorrhoidal attacks during the past one year, triggering factors, previous treatment and their results, and past illness was recorded.
- Confirmed diagnosis of either 1° or 2° hemorrhoids was recorded in CRF.
- Stool habits including consistency, frequency; constipation*, use of laxative (class, frequency, and dose) and use of sitz bath with or without additives was recorded.
  *Constipation defined as presence of < 3 stools per week
- General physical and vital examination was done.
- Concomitant medication was recorded in the CRF.
- Inclusion/exclusion criteria was checked.
- Blood sample 3-5 ml was taken for laboratory investigations (Hb, TLC, DLC, platelet count, BT, CT, PT/INR, aPTT, SGOT, SGPT, serum bilirubin, serum alkaline phosphatase, serum creatinine, blood urea, random blood sugar, serum cholesterol). Urinalysis (routine and microscopic examination) and urine pregnancy test (for female subjects only) was done before the start of the treatment.
- Subjects were evaluated by the investigator in order to assess the symptoms of bleeding (Yes/No; if Yes then whether spontaneous, on defecation or spotting), pain, tenesmus, pruritus and anal discharge (on a scale of 0-3 where; 0 = none, 1 = mild, 2 = moderate and 3 = severe).
- Objective signs of congestion, oedema and exudation were evaluated by the investigator as absent or present by proctoscopic examination. (Annexure III)
- Subjects were to be called after 0 to 3 days of screening.

- All subjects who were able to complete all the screening procedures in Visit 1 could enter Visit 2 of the study on the same day.

Visit 2 [Day 0] BASELINE VISIT or RANDOMISATION VISIT

- Medical history was taken including the intensity and frequency of haemorrhoidal attacks during the past one year, triggering factors, previous treatment and their results, and past illness was recorded.
- Confirmed diagnosis of either 1° or 2° hemorrhoids was recorded in CRF.
- Stool habits including consistency, frequency; constipation, use of laxative (class, frequency, and dose) and use of sitz bath with or without additives were recorded.
- General physical and vital examination was done.
- Concomitant medication was recorded in the CRF.
- Reports of the blood and urine investigation done at the screening visit was collected and reviewed.
- Those subjects meeting the inclusion/exclusion criteria were enrolled in the study and unique Subject ID was issued.
- Subjects were reassessed by the investigator for the symptoms of bleeding (Yes/No; if Yes then whether spontaneous, on defecation or spotting), pain, tenesmus, pruritus and anal discharge (on a scale of 0-3 where; 0 = none, 1 = mild, 2 = moderate and 3 = severe) (Annexure II).
- Objective signs of congestion, oedema, and exudation were re-assessed by the investigator as absent or present by proctoscopic examination. (Annexure III).
- Overall assessment of the disease condition was done by the subject on a 10 cm Visual Analogue Scale (VAS) and the same was entered in the CRF by the investigator.
- Baseline adverse events were recorded in the CRF.
- Randomization was done according to the randomization list.
- Study medication was issued for 14 days and subjects were instructed to take one tablet per day from the day of the baseline visit and continue taking the medication at the same time each day.
- Diary card and compliance card was given and instructions were given regarding, how to fill the cards. Daily records of symptoms and VAS score was maintained by the subjects.
- Urine pregnancy test (for female subjects only) was done at investigator's discretion.
- Subjects were instructed to return for follow up at day 7+2.

Visit 3 [Day 7+2 (Week 1)]

- Stool habits including consistency, frequency; constipation, use of laxative (class, frequency, and dose) and use of sitz bath were recorded.
- General physical and vital examination was done.
- Concomitant medication was recorded in the CRF.
- Subjects were assessed by the investigator for symptoms of bleeding (Yes/No; if Yes then whether spontaneous, on defecation or spotting), pain, tenesmus, pruritus and anal discharge (on a scale of 0-3 where; 0 = none, 1 = mild, 2 = moderate and 3 = severe). (Annexure II). Daily record of these subjective symptoms maintained by the subjects was evaluated.
- Objective signs of congestion, oedema and exudation were evaluated by the investigator as absent or present by proctoscopic examination. (Annexure III)

- Overall assessment of the disease condition was done by the subject on a 10 cm VAS and the same was entered in the CRF by the investigator.(Annexure IV).
- Urine pregnancy test (for female subjects only) was done at investigator's discretion.
- Record of AEs and follow up of the previous AE (if any) was made.
- Diary card and compliance cards were collected and reconciliation of Diary card data in the respective pages of CRF was done.
- Compliance and diary cards were reissued and instruction provided for completion.
- Subjects were instructed to return for follow up at day 14 +2 day from the baseline visit.

Visit 4 [Day 14+2 (Week 2)]

- Stool habits including consistency, frequency; constipation, use of laxative (class, frequency, and dose) and use of sitz bath were recorded.
- General physical and vital examination was done.
- Concomitant medication was recorded in the CRF.
- Subjects were assessed by the investigator for symptoms of bleeding (Yes/No; if Yes then whether spontaneous, on defecation or spotting), pain, tenesmus, pruritus and anal discharge (on a scale of 0-3 where; 0 = none, 1 = mild, 2 = moderate and 3 = severe). (Annexure II). Daily record of these subjective symptoms maintained by the subjects (in diary card) was evaluated.
- Objective signs of congestion, oedema and exudation were evaluated by the investigator as absent or present by proctoscopic examination. (Annexure III).
- Overall assessment of the disease condition was done by the subject on a 10 cm VAS and the same will be entered in the CRF by the investigator. (Annexure IV).
- Blood sample 3-5 ml was taken for laboratory investigations (Hb, TLC, DLC, platelet count, BT, CT, PT/INR, aPTT/control, SGOT, SGPT, serum bilirubin, serum alkaline phosphatase, serum creatinine, blood urea, random blood sugar, serum cholesterol). Urinalysis (routine and microscopic examination) was done.
- Urine pregnancy test (for female subjects only) was done at investigator's discretion.
- Record of AEs and follow up of the previous AE (if any) was made.
- Diary cards and the compliance cards were collected and reconciliation of Diary card data in the respective pages of CRF was done.
- Subjects were assessed for compliance to treatment.
- Diary cards were reissued.
- Unused study medication was collected.

Visit 5 [Day 28+2 days] FOLLOW UP VISIT

- Stool habits including consistency, frequency; constipation, use of laxative (class, frequency, and dose) and use of sitz bath were recorded.
- General physical and vital examination was done.
- Concomitant medication was recorded in the CRF.
- Blood sample 3-5 ml was taken for laboratory investigations (Hb, TLC, DLC, platelet count, BT, CT, PT/INR, PTT/control, SGOT, SGPT, serum bilirubin, serum alkaline phosphatase, serum creatinine, blood urea, random blood sugar, serum cholesterol). Urinalysis (routine and microscopic examination) was done.
- Subjects were assessed by the investigator for symptoms of bleeding (Yes/No; if Yes then whether spontaneous, on defecation or spotting).
- Urine pregnancy test (for female subjects only) was done at investigator's discretion.

- Diary cards were collected and reconciliation of Diary card data in the respective pages of CRF was done.
- Record of AEs and follow up of the previous AE (if any) was made.

Schedule of Study Measures and Procedures

Procedure/Assessment	Visit 1 Day-3 to 0 (Screening)	Visit 2 Day 0 (baseline)	Visit 3 Day 7+2 (Week 1)	Visit 4 Day14+2 (Week 2)	Visit 5 Day 28+2 (Week 4)
Informed consent (written)	✓				
Inclusion/Exclusion criteria	✓	✓ (Confirm)			
Demography	✓				
Medical history	✓	✓ (Confirm)			
Physical examination	✓	✓	✓	✓	✓
Study medication issue		✓			
Collection of unused study medication				✓	
Compliance card issue		✓			
Diary card issue		✓	✓	✓	
Compliance and diary card collection			✓	✓	✓
Concomitant medication	✓	✓ (Confirm)			
Hb, TLC, DLC, Platelet, Bilirubin, SGOT, SGPT, S. Cholesterol, Alkaline Phosphatase, Urea, Creatinine, RBS, BT, CT, PT/INR, aPTT/control, Urinalysis	✓			✓	✓
Urine pregnancy test	✓	✓ (optional)	✓ (optional)	✓ (optional)	✓
Investigator assessment including proctoscopic examination	✓	✓	✓	✓	
Assessment of bleeding by subject	✓	✓	✓	✓	✓
Assessment of symptoms by subject		✓	✓	✓	
Assessment of signs by physician		✓	✓	✓	✓
Overall assessment of the disease condition done by subject		✓	✓	✓	✓
Adverse events		✓ (Baseline)	✓	✓	✓
End of Study					✓

5.5. Efficacy and Safety Assessments

5.5.1. Efficacy Assessments

The efficacy assessment was based on the primary efficacy endpoint of "cessation of bleeding" at the end of day 14 (Visit 4). The secondary efficacy endpoints were change in signs (congestion, oedema, and exudation) and symptoms (pain, tenesmus, pruritus and anal discharge) at day14 (Visit 4), overall assessment of disease condition at day 14 (visit 4) and the proportion of patients without recurrence of bleeding at day 28 (visit 5).

5.5.2. Safety Assessments

Safety assessments included the occurrence of all AEs as assessed by history, clinical examination and derangement in laboratory parameters (which was done at screening, day 14 [Visit 4], and Day 28 [Visit 5]). All AEs were followed-up until the event had resolved or stabilized or the event was otherwise explained.

Adverse Event monitoring

Any AE occurring before the first IMP dose was regarded as a pre-IMP-administration event.

Adverse Event Documentation

Adverse Event (AE): An adverse event (AE) is defined as any untoward medical occurrence (including a symptom/disease or an abnormal laboratory finding) in a subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP. This definition includes inter-current illnesses or injuries and exacerbation of pre-existing conditions.

The AEs reported by the subjects and as observed by the investigator were filled in the CRF and maintained for the purpose of documentation.

All AEs observed or reported/volunteered by subjects were recorded in the CRFs with information about **severity** (i.e., whether mild, moderate or severe) and possible **relation** to the study medication.

Mild: usually transient in nature and generally not interfering with normal activities

Moderate**:** sufficiently discomforting to interfere with normal activities

Severe: prevents normal activities

The investigator had to report AEs, all abnormal findings from laboratory and other specific examinations, which were clinically apparent, or in the investigator's opinion clinically significant, in the part of the CRF concerning the recording of AEs.

Causality term Assessment criteria (WHO-UMC Causality Categories)

Certain	o Event or laboratory test abnormality, with plausible time relationship to drug intake o Cannot be explained by disease or other drugs o Response to withdrawal plausible (pharmacologically, pathologically) o Event definitive pharmacologically or phenomenologically (i.e. an o objective and specific medical disorder or a recognised pharmacological phenomenon) o Rechallenge satisfactory, if necessary
Probable/ Likely	o Event or laboratory test abnormality, with reasonable time relationship to drug intake o Unlikely to be attributed to disease or other drugs o Response to withdrawal clinically reasonable o Rechallenge not required
Possible	o Event or laboratory test abnormality, with reasonable time relationship to drug intake o Could also be explained by disease or other drugs o Information on drug withdrawal may be lacking or unclear
Unlikely	o Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) o Disease or other drugs provide plausible explanations
Conditional/ Unclassified	o Event or laboratory test abnormality o More data for proper assessment needed, or o Additional data under examination
Unassessable/ Unclassifiable	o Report suggesting an adverse reaction o Cannot be judged because information is insufficient or contradictory o Data cannot be supplemented or verified

This guidance was provided to help investigators making the medical decisions necessary to determine the IMP safety. It was the responsibility of the study physician to determine the relationship between the administration of an IMP and an AE, based on his/her best judgement, knowledge and experience. Cases, or study types, presenting unusual or complicating factors could make the above thought process unusable. In these cases, investigator was expected to use his/her best judgment as to the causal relationship (causality).

Factors that could assist in determining the ***Causality*** included:

- Timing of occurrence of the AE
- Absence of symptoms related to the event prior to exposure
- Consistency of the event with the established pharmacological/toxicological effects of the product
- Supporting evidence from other studies or absence of alternative explanations

Serious Adverse Event Reporting

For the purpose of this protocol, a **serious adverse event** (SAE) was defined as any unfavorable medical occurrence that results in any of the following outcomes:

- death
- a life-threatening event (see below)*
- hospitalization or prolongation of existing hospitalization
- persistent or significant disability/incapacity

- congenital anomaly/birth defect
- condition that required intervention to prevent permanent impairment or damage

*The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death from the reaction as it occurred; it does not refer to an event, which hypothetically might have caused death if it were more severe.

Study centres were instructed to report all SAEs to the Safety Officer immediately (within 24 hours) of becoming aware of the SAE.

Any SAE had to be reported to the Regulatory Agency and Ethics Committee according to the applicable regulatory guidelines of the region by the Sponsor/sponsor designee.

A summary of SAEs that were determined to be reportable by the sponsor was distributed within 15 working days to all investigators who had to immediately forward them to their IEC/IRB according to local regulations.

Appropriate measures were taken to safeguard the subjects.

SAEs were recorded in the part of the CRF concerning the recording of SAE.

Follow-up of Subjects with Adverse Events

All subjects who took at least one dose of study medication was followed up and included in the analysis.

Irrespective of the investigator's statutory obligations, the sponsor had to report all pharmacovigilance data to the competent authorities and to all investigators involved in accordance with requirements of the ICH Guidelines for GCP and as per the local regulatory requirements.

5.6. Study Monitoring and Documentation

5.6.1. Data Quality Assurance

All relevant study data was recorded in the CRF. Where relevant data already existed on other source documents such as laboratory reports, the information required was transcribed into the CRF. All other data was directly written into the CRF. The investigator permitted trial-related monitoring, audits, IEC/IRB review and competent authority inspection and provided direct access to source documents.

Regular monitoring visits were made by the monitor to check compliance with the protocol, the completeness, accuracy and consistency of the data, and adherence to good clinical practice guidelines.

Appropriately qualified and trained staff members were involved in this study. Staff members at investigational site were instructed in the conduct of the study according to the protocol.

Audits could be carried out by a quality assurance representative of the sponsor. The investigator provided access to authorised persons during competent authority inspections or sponsor audits.

A CRF was completed for each patient screened. The CRFs had to be completed legibly in English with a black ball-point pen. Errors had to be crossed through, but not obliterated, and the new value had to be written and the change initialed and dated by the investigator or designee. The use of correction fluid or tape was not allowed. The investigator signed and dated at the indicated places in the CRF. This signature indicated a thorough inspection of the data on the CRF had been made, and certified the contents of the form.

CRFs were completed promptly and were submitted to the monitor in person for checking and collection. When changes to CRF data were necessary following removal of the original CRF from the study site, these changes were documented on data clarification forms, which were signed by the investigator.

Data items from the CRF were entered centrally into the study database by Data Management using double data entry, with verification upon second entry. Concomitant medication entered onto the database was coded using the World Health Organisation (WHO) Drug Reference List. AEs were coded using MedDRA (Medical Dictionary for Regulatory Activities). Laboratory samples were processed and results sent electronically to Data Management.

5.6.2. Study Documentation

The investigators were required to maintain study documents which were reviewed by study monitors to ensure compliance with regulatory requirements. Study documentation included all workbooks/worksheets/CRFs/signature pages, data correction forms, source documents, monitoring logs and appointment schedules, Sponsor/CRO-investigator correspondence, and regulatory documents (e.g., signed protocol and amendments, IEC correspondence and approval, approved and signed subject consent forms, clinical supplies receipts, and distribution records).

5.7. Data Analysis and Statistical Methods

5.7.1. Sample Size

The sample size was calculated assuming 59%[14] efficacy of placebo in hemorrhoidal disease. The 20% superiority hypothesis was postulated for E. prostrata as compared to placebo. Under these assumptions, a sample size of 178 subjects in each arm yields 90% power to conclude that E. prostrata is 20% superior to placebo. To evaluate the safety adequately 300 subjects in the test arm subjects were considered. Thus the total number of subjects required for this comparative evaluation has been calculated to be 495 (Case: Control = 2:1).

Regional Distribution: EU = 249; India = 246

5.7.2. Analysis Populations

The primary approach for efficacy and safety endpoints is based on a modified intent-to-treat (mITT) population, where all subjects who take at least one dose of study medication are included. For the analysis of efficacy data, a subject had to have a baseline value and at least one on treatment value to be included in the analysis. Efficacy analyses and superiority conclusions are based primarily on the mITT population, following the conservative approach outlined in the ICH guidelines on

statistical issues. Toward this end, the Last Observation Carried Forward (LOCF) rule is used to fill in missing values. Since an effective medication would tend to improve symptom scores, with full rather than partial treatment, substituting an earlier observation in place of the missing observation at the end of treatment would tend to understate its efficacy. Therefore, the LOCF method provides a conservative way of filling in missing values and avoids the potential bias created by excluding from the efficacy analysis subjects who drop out due to safety reasons or lack of efficacy.

5.7.3. General Approach for Data Analysis

Statistical analyses were performed after all patients ended their participation in the study and the database was locked.

Continuous variables are summarized using descriptive statistics; (n, mean, standard deviation, median, minimum and maximum), while categorical variables are summarized as the number (and percentage) of patients in each category.

For continuous variables, values at baseline and at the end of treatment are analyzed using 2-way analysis of variance (ANOVA) with treatment group and center as factors, while change from baseline to end of treatment is analyzed using 2-way analysis of covariance (ANCOVA) with treatment group, center, and baseline as factors. Categorical variables are analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusted for center effect.

Statistical testing is two-sided and is based on the 5% significance level in accordance with standard practice.

5.7.4. Analysis of Demographic and Baseline Characteristics

Data on patient disposition (number of patients enrolled, number of withdrawals, and reasons for withdrawal) as well as the number of patients included in each population are appropriately summarized.

Demography (age, sex, ethnic origin, height, weight and smoking status), and baseline characteristics (medical history, physical examination, and vital signs (blood pressure, pulse and body temperature), laboratory assessments, and ECG assessments), are appropriately summarized.

5.7.5. Analysis of Efficacy

Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Proportion of subjects in each treatment group achieving cessation of per rectal bleeding as assessed by the subject at day 14 (cessation of per rectal bleeding defined as the maintenance of bleeding cessation for at least 3 continuous days after initial "cessation of bleeding")

Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Proportion of subjects in each treatment group without recurrence of bleeding (recurrence of bleeding defined as any episode of bleeding after maintenance of bleeding cessation and before the end of 14 days post-treatment).

- Change in the following symptoms, viz., pain, tenesmus, pruritus and anal discharge as assessed by the subject at day 14 (categorized as none, mild, moderate and severe)

- Change in the following objective signs, viz., congestion, oedema, and exudation as assessed by the investigator at day 14 (categorized as absent or present)

- Change in overall assessment of disease condition as assessed by the subject on a 10 cm VAS at day 14 of therapy, wher 0 = Best Ever and 10 = Worst Ever

The primary efficacy endpoint was evaluated using the 95% confidence interval (CI) for the difference between the two treatment groups in the proportion of subjects achieving cessation of per rectal bleeding as assessed by the subject at day 14 of treatment.

Additionally, logistic regression analysis with response (cessation of bleeding per rectum at the end of the study) as the dependent variable and potentially relevant factors such as treatment, region (EU/non-EU), age (patients aged 50 and older/ others), and gender as independent variables was performed. To explore whether treatment effects are consistent across different subgroups, treatment-by-factor interactions were evaluated in the logistic regression model for the primary efficacy endpoint in the modified ITT population. The subject characteristics and baseline covariates of interest in the logistic regression analysis were:

  - Study region (EU/non-EU)
  - Gender (female/male)
  - Age Category (patients aged 50 and older/others)

To assess the effects of the above factors, the logistic regression model included treatment, covariate, and treatment-by-covariate interaction.

The secondary efficacy endpoint pertaining to recurrence of bleeding was evaluated using the 95% CI for the difference between the two treatment groups in the proportion of subjects without recurrence of bleeding.

The secondary efficacy endpoints pertaining to change in symptoms (pain, tenesmus, pruritus and anal discharge) as assessed by the subject (categorized as none, mild, moderate and severe) at day 14 and change in objective signs (congestion, oedema, and exudation) as assessed by the investigator at day 14 (categorized as absent or present) were analysed by comparing the proportions of subjects in the two groups with improvement, no change, or worsening from baseline in each of these symptoms/signs at day 14, using the stratified CMH test (with centre as the stratification variable) based on ordinal data.

Change in overall assessment of disease condition as assessed on a 10 cm VAS at day 14 was analysed using 2-way ANCOVA with change from baseline as the dependent variable and treatment, centre, and baseline as independent variables.

5.7.6. Analysis of Safety

The safety endpoints are:

- Incidences of clinical and laboratory AEs in each treatment group

For each treatment, the incidences of all treatment emergent AEs was tabulated by System Organ Class (SOC) and Preferred Term (PT) (to which each AE was mapped, using MedDRA. Other information regarding AEs, such as intensity, seriousness, causality, and discontinuation due to AEs, were also tabulated by treatment. AEs that were reported more than once by a subject was counted only once for that subject at the maximum intensity. Prior, concomitant, and rescue medications were summarized by treatment. Summary statistics (number of cases and incidence rates) were presented within relevant subgroups for the primary safety endpoints. The proportions of subjects with clinical and laboratory AEs were compared using the Chi-square test or Fisher's exact test.

5.7.7. Multiplicity

Secondary analyses were used inferentially (i.e., their results contribute to the submitted evidence base) to support and help interpret the primary analyses. There is only one primary endpoint and thus there is no need for a p-value adjustment to maintain the same overall protection against false positive results.

6. Study Population Results

6.1. Patient Disposition

6.1.1. Patients Randomized at Each Center

550 patients were screened and 483 patients were randomized to one of two treatment groups in this study. Table 6.1 shows the distribution of patients across 26 centers, by treatment group.

Table 6.1: Patients Randomized at Each Center (ITT Population)

CENTRE	EUPHORBIA (N = 319)	PLACEBO (N = 164)	TOTAL (N = 483)
B13	1 (0.3%)	1 (0.6%)	2 (0.4%)
B14	0 (0.0%)	2 (1.2%)	2 (0.4%)
B15	26 (8.2%)	13 (7.9%)	39 (8.1%)
B16	21 (6.6%)	9 (5.5%)	30 (6.2%)
B17	1 (0.3%)	0 (0.0%)	1 (0.2%)
B18	40 (12.5%)	20 (12.2%)	60 (12.4%)
B19	46 (14.4%)	23 (14.0%)	69 (14.3%)
B20	2 (0.6%)	0 (0.0%)	2 (0.4%)
B21	6 (1.9%)	4 (2.4%)	10 (2.1%)
B22	14 (4.4%)	7 (4.3%)	21 (4.3%)
B23	32 (10.0%)	18 (11.0%)	50 (10.4%)
B24	9 (2.8%)	6 (3.7%)	15 (3.1%)
G10	15 (4.7%)	7 (4.3%)	22 (4.6%)
G11	1 (0.3%)	0 (0.0%)	1 (0.2%)

CENTRE	EUPHORBIA (N = 319)	PLACEBO (N = 164)	TOTAL (N = 483)
G13	6 (1.9%)	3 (1.8%)	9 (1.9%)
P14	12 (3.8%)	6 (3.7%)	18 (3.7%)
P15	18 (5.6%)	9 (5.5%)	27 (6.0%)
P16	12 (3.8%)	6 (3.7%)	18 (3.7%)
P17	18 (5.6%)	8 (4.9%)	26 (5.4%)
P18	19 (6.0%)	9 (5.5%)	28 (5.8%)
P19	5 (1.6%)	3 (1.8%)	8 (1.7%)
P20	2 (0.6%)	2 (1.2%)	4 (0.8%)
P21	12 (3.8%)	6 (3.7%)	18 (3.7%)
P23	1 (0.3%)	0 (0.0%)	1 (0.2%)
P27	0 (0.0%)	1 (0.6%)	1 (0.2%)
P28	0 (0.0%)	1 (0.6%)	1 (0.2%)

6.1.2. Study Completion and Drop-Out

Table 6.2 summarizes information on drop-outs (defined as subjects who did not come back for the final visit as foreseen in the protocol). Of the 319 patients enrolled in the Euphorbia group, there were 8 (2.5%) drop-outs, and of the 164 patients enrolled in the Placebo group, there were 6 (3.7%) drop-outs.

Table 6.2: Number of Subjects Enrolled, Completed, and Reasons for Drop-Out

	EUPHORBIA (N = 319)	PLACEBO (N = 164)	TOTAL (N = 483)
NO. OF SUBJECTS ENROLLED	319	164	483
NO. OF SUBJECTS DROPPED OUT	8 (2.5%)	6 (3.7%)	14 (2.9%)
NO. OF SUBJECTS COMPLETED	311 (97.5%)	158 (96.3%)	469 (97.1%)
REASONS FOR DROP-OUT			
ADVERSE EVENT	4 (1.3%)	1 (0.6%)	5 (1.0%)
FAILURE TO RETURN / LOST TO FOLLOW UP	2 (0.6%)	2 (1.2%)	4 (0.8%)
VIOLATION OF SELECTION CRITERIA	2 (0.6%)	2 (1.2%)	4 (0.8%)
WITHDREW CONSENT	0 (0.0%)	1 (0.6%)	1 (0.2%)

6.2. Protocol Violations

As shown in Table 6.2, 2 patients in the Euphorbia group and 2 patients in the Placebo group dropped out of the study, due to major protocol violations.

6.3. Analysis Data Sets

Analyses of demographics and other baseline characteristics as well as safety are performed for the total population. Table 6.3 presents the number patients in each analysis population, by treatment group. Efficacy analyses were performed for the mITT population, which is the same as the total population in this study.

Table 6.3: Populations Analyzed

	EUPHORBIA	PLACEBO	TOTAL
TOTAL POPULATION	319	164	483
SAFETY POPULATION	319	164	483
ITT POPULATION	319	164	483
mITT POPULATION	319	164	483
PER PROTOCOL POPULATION	311	156	467

7. Demographic and Other Baseline Characteristics

7.1 . Demographic Characteristics

Table 7.1 summarizes the demographic characteristics of the total population of patients enrolled in the study. The demographic profiles of the two treatment groups were similar, with no significant difference between them with respect to gender, age, or weight. There was a preponderance of males in both groups.

Table 7.1: Demographic Characteristics

		EUPHORBIA (N = 319)	PLACEBO (N = 164)	P-VALUE
GENDER	FEMALE	120 (37.6%)	51 (31.1%)	0.1563(a)
	MALE	199 (62.4%)	113 (68.9%)	0.1559 (b)
AGE (YEARS)	MEAN	40.3	40.9	0.6424 (c)
	SD	13.3	13.0	
	MEDIAN	39.0	39.5	
	RANGE	18 to 81	18 to 75	
WEIGHT (KG)	MEAN	66.4	67.8	0.1987 (c)
	SD	13.7	12.6	
	MEDIAN	65	65	
	RANGE	40 to 120	40 to 119	

(a) P-Value using Cochran-Mantel-Haenszel test (b) P-Value using Chisq test
(c) P-Values based on Two-Way Analysis of Variance (Regression model with treatment group and center as factors)

7.2. Medical History

Table 7.2 summarizes the number of subjects with significant and non-significant medical history for the total population. The two treatment groups were not significantly different with regard to medical history, with 20% and 23% of patients in these groups having had a significant medical history.

Table 7.2: Medical History

	EUPHORBIA (N = 319)	PLACEBO (N = 164)	P- Value
NO SIGNIFICANT MEDICAL HISTORY	256 (80.3%)	126 (76.8%)	0.3817
SIGNIFICANT MEDICAL HISTORY	63 (19.7%)	38 (23.2%)	
P-Values using Cochran-Mantel-Haenszel test			

8. Efficacy Analyses

8.1. Primary Efficacy Endpoint

Table 8.1 (a) summarizes for the mITT population, the proportion of subjects in each treatment group achieving cessation of per rectal bleeding as assessed by the subject at day 14 (cessation of per rectal bleeding defined as the maintenance of bleeding cessation for at least 3 continuous days after initial "cessation of bleeding"). Tables 8.1 (b) and 8.1 (c) summarize the same endpoint for patients in Europe and India, respectively.

The data from patients in Europe showed that Euphorbia was significantly superior to Placebo with 88% of patients in the Euphorbia group and 77% of patients in the Placebo group reporting cessation of bleeding within 14 days after start of treatment. However,

the data from patients in India did not show a significant superiority of Euphorbia to Placebo, and had, in fact, a diluting effect on the overall results, which show a response rate of 79% of patients in the Euphorbia group and 74% in the Placebo group, with the difference being statistically not significant.

Table 8.1 (a): Cessation of Bleeding

					DIFFERENCE IN RESPONSE RATE (EUPHORBIA - PLACEBO)			P-VALUE
	EUPHORBIA		PLACEBO			95 % CI		
	N	n (%)	N	n (%)	DIFFERENCE IN %	LL	UL	
SUBJECTS ACHIEVING CESSATION OF BLEEDING	319	251 (78.7%)	164	121 (73.8%)	4.9	-1.9	11.7	(a) 0.2252 (b) 0.2257
(a) P-Value using Chi-square test (b) P-Value using Cochran-Mantel-Haenszel test								

Table 8.1(b): Cessation of Bleeding (Europe)

					DIFFERENCE IN RESPONSE RATE (EUPHORBIA - PLACEBO)			P-VALUE
	EUPHORBIA		PLACEBO			95 % CI		
	N	n (%)	N	n (%)	DIFFERENCE IN %	LL	UL	
SUBJECTS ACHIEVING CESSATION OF BLEEDING	121	107 (88.4%)	61	47 (77.0%)	11.4	1.3	21.4	(a) 0.0446 (b) 0.0452
(a) P-Value using Chi-square test (b) P-Values using Cochran-Mantel-Haenszel test								

Table 8.1(c): Cessation of Bleeding (India)

					DIFFERENCE IN RESPONSE RATE (EUPHORBIA - PLACEBO)			P-VALUE
	EUPHORBIA		PLACEBO			95 % CI		
	N	n (%)	N	n (%)	DIFFERENCE IN %	LL	UL	
SUBJECTS ACHIEVING CESSATION OF BLEEDING	198	144 (72.7%)	103	74 (71.8%)	0.9	-8	9.8	(a) 0.8709 (b) 0.8711
(a) P-Value using Chi-square test (b) P-Values using Cochran-Mantel-Haenszel test								

8.2. Secondary Efficacy Analyses

8.2.1. Recurrence of Bleeding

Table 8.2 (a) summarizes for the mITT population, the proportion of subjects in each treatment group without recurrence of bleeding. Tables 8.2 (b) and 8.2 (c) summarize the same endpoint for patients in Europe and India, respectively.

The data from patients in Europe showed that there was a substantially higher proportion of patients without recurrence of bleeding in the Euphorbia group, compared to the Placebo group, although the difference was not statistically significant. However, the data from patients in India and thereby the overall results showed similar proportions of patients without recurrence of bleeding in the two treatment groups.

Table 8.2 (a): Proportion of Patients without Recurrence of Bleeding

					DIFFERENCE IN RESPONSE RATE (EUPHORBIA - PLACEBO)			P-VALUE
	EUPHORBIA		PLACEBO			95 % CI		
	N	n (%)	N	n (%)	DIFFERENCE IN %	LL	UL	
SUBJECTS ACHIEVING CESSATION OF BLEEDING	251	218 (86.9%)	121	104 (86.0%)	0.9	-5.4	7.2	(a) 0.8111 (b) 0.8114
(a) P-Value using Chi-square test (b) P-Value using Cochran-Mantel-Haenszel test								

Table 8.2 (b): Proportion of Patients without Recurrence of Bleeding (Europe)

					DIFFERENCE IN RESPONSE RATE (EUPHORBIA - PLACEBO)			P-VALUE
	EUPHORBIA		PLACEBO			95 % CI		
	N	n (%)	N	n (%)	DIFFERENCE IN %	LL	UL	
SUBJECTS ACHIEVING CESSATION OF BLEEDING	107	89 (83.2%)	47	37 (78.7%)	4.5	-7.0	15.9	(a) 0.5093 (b) 0.5107
(a) P-Value using Chi-square test (b) P-Value using Cochran-Mantel-Haenszel test								

Table 8.2 (c): Proportion of Patients without Recurrence of Bleeding (India)

					DIFFERENCE IN RESPONSE RATE (EUPHORBIA - PLACEBO)			P-VALUE
	EUPHORBIA		PLACEBO			95 % CI		
	N	n (%)	N	n (%)	DIFFERENCE IN %	LL	UL	
SUBJECTS ACHIEVING CESSATION OF BLEEDING	144	129 (89.6%)	74	67 (90.5%)	-1	-7.9	6.0	(a) 0.8242 (b) 0.8246
(a) P-Value using Chi-square test (b) P-Value using Cochran-Mantel-Haenszel test								

8.2.2. Change in Symptoms

Table 8.3 (a) summarizes for the mITT population, the proportion of subjects in each treatment group experiencing improvement, no change, or worsening of symptoms. Tables 8.3 (b) and 8.3 (c) summarize the same endpoint for patients in Europe and India, respectively. There was no statistically significant difference between the two groups with regard to these proportions.

Table 8.3 (a): Change from Baseline in Individual Symptom Assessments

		EUPHORBIA (N = 319)		PLACEBO (N = 164)		P-VALUE
SYPTOM	TYPE*	n	%	n	%	
PAIN	IMPROVEMENT	224	70.2	113	68.9	
	NO CHANGE	93	29.2	50	30.5	0.6405
	WORSENING	2	0.6	1	0.6	
PRURITUS	IMPROVEMENT	121	37.9	63	38.4	
	NO CHANGE	193	60.5	96	58.5	0.8189
	WORSENING	5	1.6	5	3.0	
DISCHRG	IMPROVEMENT	68	21.3	28	17.1	
	NO CHANGE	246	77.1	133	81.1	0.1758
	WORSENING	5	1.6	3	1.8	
TENESMUS	IMPROVEMENT	91	28.5	51	31.1	
	NO CHANGE	221	69.3	109	66.5	0.4123
	WORSENING	7	2.2	4	2.4	

		EUPHORBIA (N = 319)		PLACEBO (N = 164)		P-VALUE
SYPTOM	TYPE*	n	%	n	%	
P-Values using Cochran-Mantel-Haenszel test based on ordinal data *Type defined as: Improvement-change from the baseline higher severity to lower severity No Change- same as baseline value; Worsening-change from baseline lower severity to higher severity						

Table 8.3 (b): Change from Baseline in Individual Symptom Assessments (Europe)

		EUPHORBIA (N = 121)		PLACEBO (N = 61)		P-VALUE
SYPTOM	TYPE*	n	%	n	%	
PAIN	IMPROVEMENT	71	58.7	35	57.4	0.6842
	NO CHANGE	49	40.5	25	41.0	
	WORSENING	1	0.8	1	1.6	
PRURITUS	IMPROVEMENT	82	67.8	40	65.6	0.6140
	NO CHANGE	36	29.8	18	29.5	
	WORSENING	3	2.5	3	4.9	
DISCHRG	IMPROVEMENT	24	19.8	7	11.5	0.1679
	NO CHANGE	93	76.9	51	83.6	
	WORSENING	4	3.3	3	4.9	
TENESMUS	IMPROVEMENT	46	38.0	23	37.7	0.9045
	NO CHANGE	70	57.9	35	57.4	
	WORSENING	5	4.1	3	4.9	
P-Values using Cochran-Mantel-Haenszel test based on ordinal data *Type defined as: Improvement-change from the baseline higher severity to lower severity No Change- same as baseline value; Worsening-change from baseline lower severity to higher severity						

Table 8.3 (c): Change from Baseline in Individual Symptom Assessments (India)

		EUPHORBIA (N = 198)		PLACEBO (N = 103)		P-VALUE
SYPTOM	TYPE*	n	%	n	%	
PAIN	IMPROVEMENT	153	77.3	78	75.7	0.7930
	NO CHANGE	44	22.2	25	24.3	
	WORSENING	1	0.5	0	0.0	
PRURITUS	IMPROVEMENT	39	19.7	23	22.3	0.8851
	NO CHANGE	157	79.3	78	75.7	
	WORSENING	2	1.0	2	1.9	
DISCHRG	IMPROVEMENT	44	22.2	21	20.4	0.5677
	NO CHANGE	153	77.3	82	79.6	
	WORSENING	1	0.5	0	0.0	
TENESMUS	IMPROVEMENT	45	22.7	28	27.2	0.1674
	NO CHANGE	151	76.3	74	71.8	
	WORSENING	2	1.0	1	1.0	
P-Values using Cochran-Mantel-Haenszel test based on ordinal data *Type defined as: Improvement-change from the baseline higher severity to lower severity No Change- same as baseline value; Worsening-change from baseline lower severity to higher severity						

8.2.3. Change in Objective Sign Assessments

Table 8.4 (a) summarizes for the mITT population, the proportion of subjects in each treatment group experiencing improvement, no change, or worsening of objective signs.

Tables 8.4 (b) and 8.4 (c) summarize the same endpoint for patients in Europe and India, respectively. The data from Europe showed a consistently higher proportion of patients in the Euphorbia group with improvement of objective signs, compared to the Placebo group, with the difference between the two groups being statistically significant for congestion and oedema. The Indian data and the overall data did not show a statistically significant difference between the two groups for any of the objective sign assessments.

Table 8.4 (a): Change from Baseline in Objective Sign Assessments

		EUPHORBIA (N = 319)		PLACEBO (N = 164)		P-VALUE
SYPTOM	TYPE*	n	%	n	%	
CONGESTION	IMPROVEMENT	121	37.9	57	34.8	
	NO CHANGE	191	59.9	105	64.0	0.3777
	WORSENING	7	2.2	2	1.2	
OEDEMA	IMPROVEMENT	110	34.5	52	31.7	
	NO CHANGE	207	64.9	110	67.1	0.3328
	WORSENING	2	0.6	2	1.2	
EXUDATION	IMPROVEMENT	54	16.9	25	15.2	
	NO CHANGE	264	82.8	138	84.1	0.4433
	WORSENING	1	0.3	1	0.6	

P-Values using Cochran-Mantel-Haenszel test based on ordinal data
*Type defined as: Improvement-change from the baseline higher severity to lower severity
No Change- same as baseline value; Worsening-change from baseline lower severity to higher severity

Table 8.4 (b): Change from Baseline in Objective Sign Assessments (Europe)

		EUPHORBIA (N = 121)		PLACEBO (N = 61)		P-VALUE
SYPTOM	TYPE*	n	%	n	%	
CONGESTION	IMPROVEMENT	64	52.9	23	37.7	0.0219
	NO CHANGE	57	47.1	38	62.3	
OEDEMA	IMPROVEMENT	71	58.7	28	45.9	
	NO CHANGE	49	40.5	32	52.5	0.0294
	WORSENING	1	0.8	1	1.6	
EXUDATION	IMPROVEMENT	33	27.3	12	19.7	
	NO CHANGE	88	72.7	48	78.7	0.1012
	WORSENING	0	0.0	1	1.6	

P-Values using Cochran-Mantel-Haenszel test based on ordinal data
*Type defined as: Improvement-change from the baseline higher severity to lower severity
No Change- same as baseline value; Worsening-change from baseline lower severity to higher severity

Table 8.4 (b): Change from Baseline in Objective Sign Assessments (India)

		EUPHORBIA (N = 198)		PLACEBO (N = 103)		P-VALUE
SYPTOM	TYPE*	n	%	n	%	
CONGESTION	IMPROVEMENT	57	28.8	34	33.0	
	NO CHANGE	134	67.7	67	65.0	0.3953
	WORSENING	7	3.5	2	1.9	
OEDEMA	IMPROVEMENT	39	19.7	24	23.3	
	NO CHANGE	158	79.8	78	75.7	0.5117
	WORSENING	1	0.5	1	1.0	
EXUDATION	IMPROVEMENT	21	10.6	13	12.6	
	NO CHANGE	176	88.9	90	87.4	0.5642
	WORSENING	1	0.5	0	0.0	

P-Values using Cochran-Mantel-Haenszel test based on ordinal data
*Type defined as: Improvement-change from the baseline higher severity to lower severity
No Change- same as baseline value; Worsening-change from baseline lower severity to higher severity

8.2.4. Change in Overall Assessment of Efficacy

Table 8.5 (a) summarizes change in overall assessment of efficacy, as assessed by the subject on a 10 cm VAS where 0 = Best Ever and 10 = Worst Ever. A negative change from baseline implies improvement in disease condition. Tables 8.5 (b) and 8.5 (c) summarize the same endpoint for patients in Europe and India, respectively. Based on the overall data as well data from India and Europe, the Euphorbia group showed better improvement, compared to Placebo, although the difference between the two groups was not statistically significant.

Table 8.5 (a): Change in Overall Assessment of Efficacy on VAS Scale

	ESTIMATED EFFECT	P-VALUE
EUPHORBIA - PLACEBO	-0.1899	0.2647

Table 8.5 (b): Change in Overall Assessment of Efficacy on VAS Scale (Europe)

	ESTIMATED EFFECT	P-VALUE
EUPHORBIA - PLACEBO	-0.1997	0.5109

Table 8.5 (b): Change in Overall Assessment of Efficacy on VAS Scale (India)

	ESTIMATED EFFECT	P-VALUE
EUPHORBIA - PLACEBO	-0.1853	0.3645

8.2.5. Factors Affecting Cessation of Bleeding

Table 8.6 summarizes the results of the logistic regression analysis with cessation of bleeding as the dependent variable. The treatment by region interaction term was bordering on significance (p = 0.0768), indicating that the treatment effect in Europe was different from that that seen in India. This was explicitly demonstrated by Tables 8.1 (b) and 8.1 (c), which showed that, in Europe, Euphorbia was significantly superior to Placebo with 88% of patients in the Euphorbia group and 77% of patients in the Placebo group reporting cessation of bleeding, while in India, the proportions of patients achieving cessation of bleeding in the two treatment groups were similar.

The other factors, viz., gender and age category did not produce differential treatment effects.

Table 8.6: Logistic Regression Analysis of the Primary Efficacy Endpoint

	P-VALUE
TREATMENT	0.6076
REGION (Europe vs. India)	0.6930
GENDER	0.4758
AGE CATEGORY (50 years or older vs. others)	0.3982
TREATMENT BY REGION	0.0768
TREATMENT BY GENDER	0.3643

9. Safety Analyses

9.1. Extent of Exposure

Table 9.1 summarizes the extent of exposure (number of subjects at each of the visits) for the total population. 99% of patients enrolled in the Euphorbia group and 96% of patients enrolled in the Placebo group completed the 14-day treatment period, as shown in Table 9.1 and also in Table 6.2.

Table 9.1: Extent of Exposure

Number of Days Completed	EUPHORBIA (N = 319)	PLACEBO (N = 164)	TOTAL (N = 483)
0 Day s: n (%)	319 (100.0%)	164 (100.0%)	483 (100.0%)
7 Days: n (%)	313 (98.1%)	158 (96.3%)	471 (97.5%)
14 Days: n (%)	311 (97.5%)	158 (96.3%)	469 (97.1%)

9.2. Treatment Compliance

Treatment compliance is summarized in Table 9.2 for total population. The two treatment groups were similar with regard to compliance, with at least 98% of patients in the Euphorbia group and 96% of patients in the Placebo group showing treatment compliance.

Table 9.2: Study Medication Compliance

	EUPHORBIA	PLACEBO	TOTAL
VISIT 2: N	319	164	483
Compliant, n (%)	319 (100.0%)	164 (100.0%)	483 (100.0%)
VISIT 3: N	313	158	471
Compliant, n (%)	313 (98.1%)	158 (96.3%)	471 (97.5%)
VISIT 4: N	311	158	469
Compliant, n (%)	311 (97.5%)	158 (96.3%)	469 (97.1%)

9.3. Safety Endpoints

9.3.1. Adverse Events

Table 9.3 summarizes treatment emergent AEs for each treatment group, by SOC and PT based on MedDRA 9.0. Table 9.4 provides an overall summary of seriousness, causality, and severity, while Tables 9.5 and 9.6 provide more specific summaries of drug related (definitely, probably, or possibly related) AEs and severe AEs, respectively. Serious AEs and withdrawals due to AEs are listed.

As shown in Table 9.3, the incidence of AEs during the 14-day treatment period was fairly similar for the two treatment groups, with 24 (7.5%) patients in the Euphorbia group and 8 (4.9%) patients in the Placebo group reporting any AE. The difference in the incidence of AEs between the two groups was not statistically significant. There were two SAEs occurring in the Euphorbia group and no SAEs occurring in the Placebo group. Both SAEs were unlikely to be related to the study medication. One of the SAEs,

Hb value 5.8 g/dl, led to withdrawal of the patient from the study. The other SAE, gastroenteritis, was resolved with no sequelae. There were 4 patients in the Euphorbia group (including the patient who experienced an SAE) and one patient in the Placebo group who dropped out of the study due to AEs.

There were 2 (0.6%) patients in the Euphorbia group and 1 (0.6%) patient in the Placebo group with severe AEs. There were 8 (2.5%) patients in the Euphorbia group and 2 (1.2%) patients in the Placebo group with drug related (possibly and probably related) AEs.

Table 9.3: Treatment Emergent Adverse Events

SYSTEM ORGAN CLASS (SOC)	PREFERRED TERM	EUPHORBIA (N = 319)	PLACEBO (N = 164)
ALL SYSTEMS	ANY ADVERSE EVENT	24 (7.5%)	8 (4.9%)
GASTROINTESTINAL DISORDERS	ANY ADVERSE EVENT	9 (2.8%)	3 (1.8%)
	ABDOMINAL PAIN	1 (0.3%)	0 (0.0%)
	ABDOMINAL PAIN UPPER	0 (0.0%)	1 (0.6%)
	CONSTIPATION	2 (0.6%)	1 (0.6%)
	DIARRHOEA	1 (0.3%)	1 (0.6%)
	DYSPEPSIA	2 (0.6%)	1 (0.6%)
	FLATULENCE	1 (0.3%)	0 (0.0%)
	GASTROENTERITIS	1 (0.3%)	0 (0.0%)
	NAUSEA	1 (0.3%)	0 (0.0%)
	NAUSEA AND VOMITING SYMPTOMS	1 (0.3%)	0 (0.0%)
	STOMACH ACHE	1 (0.3%)	0 (0.0%)
	VOMITING	0 (0.0%)	1 (0.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ANY ADVERSE EVENT	1 (0.3%)	0 (0.0%)
	FEELING COLD	1 (0.3%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	ANY ADVERSE EVENT	4 (1.3%)	1 (0.6%)
	FEVER	1 (0.3%)	1 (0.6%)
	PHARYNGITIS	1 (0.3%)	0 (0.0%)
	RHINITIS	1 (0.3%)	1 (0.6%)
	UPPER RESPIRATORY TRACT INFECTION	1 (0.3%)	0 (0.0%)
	URINARY TRACT INFECTION	1 (0.3%)	0 (0.0%)
INVESTIGATIONS	ANY ADVERSE EVENT	3 (0.9%)	1 (0.6%)
	BLOOD CHOLESTEROL INCREASED	1 (0.3%)	0 (0.0%)
	BLOOD GLUCOSE INCREASED	2 (0.6%)	0 (0.0%)
	HAEMOGLOBIN DECREASED	1 (0.3%)	0 (0.0%)
	SGOT INCREASED	0 (0.0%)	1 (0.6%)
METABOLISM AND NUTRITION DISORDERS	ANY ADVERSE EVENT	1 (0.3%)	0 (0.0%)
	DIABETES	1 (0.3%)	0 (0.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ANY ADVERSE EVENT	1 (0.3%)	0 (0.0%)
	INJECTION SITE JOINT PAIN	1 (0.3%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	ANY ADVERSE EVENT	4 (1.3%)	4 (2.4%)
	BURNING SENSATION	0 (0.0%)	1 (0.6%)
	HEADACHE	4 (1.3%)	3 (1.8%)
RENAL AND URINARY DISORDERS	ANY ADVERSE EVENT	0 (0.0%)	1 (0.6%)
	DYSURIA	0 (0.0%)	1 (0.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANY ADVERSE EVENT	5 (1.6%)	1 (0.6%)
	HYPERHIDROSIS	0 (0.0%)	1 (0.6%)
	DENGUE FEVER	1 (0.3%)	0 (0.0%)
	ITCHING SCAR	1 (0.3%)	0 (0.0%)
	PRURITUS	1 (0.3%)	0 (0.0%)
	PRURITUS GENERALISED	1 (0.3%)	0 (0.0%)
	SKIN IRRITATION	1 (0.3%)	0 (0.0%)
P- Value using Cochran-Mantel-Haenszel test: 0.3223 P- Value using Chi-sq test: 0.2683			

Table 9.4: Adverse Events: Seriousness, Intensity, and Causality

		EUPHORBIA (N=319)	PLACEBO (N=164)
SERIOUSNESS	SERIOUS	2 (0.6%)	0 (0.0%)
	NOT SERIOUS	22 (6.9%)	8 (4.9%)
INTENSITY	SEVERE	2 (0.6%)	1 (0.6%)
	MODERATE	9 (2.9%)	4 (2.4%)
	MILD	13 (4.1%)	3 (1.8%)
RELATIONSHIP	POSSIBLE	6 (1.9%)	1 (0.6%)
	PROBABLE/LIKELY	2 (0.6%)	1 (0.6%)
	UNLIKELY	14 (4.4%)	5 (3.0%)
	UNASSESABLE/ UNCLASSIFIABLE	2 (0.6%)	1 (0.6%)

Table 9.5: Drug Related Adverse Events

SYSTEM ORGAN CLASS (SOC)	PREFERRED TERM	EUPHORBIA (N=319)	PLACEBO (N=164)
ALL SYSTEMS	ANY ADVERSE EVENT	8 (2.5%)	2 (1.2%)
GASTROINTESTINAL DISORDERS	ANY ADVERSE EVENT	3 (0.9%)	2 (1.2%)
	ABDOMINAL PAIN UPPER	0 (0.0%)	1 (0.6%)
	DIARRHOEA	0 (0.0%)	1 (0.6%)
	DYSPEPSIA	0 (0.0%)	1 (0.6%)
	FLATULENCE	1 (0.3%)	0 (0.0%)
	NAUSEA	1 (0.3%)	0 (0.0%)
	STOMACH ACHE	1 (0.3%)	0 (0.0%)
	VOMITING	0 (0.0%)	1 (0.6%)
INFECTIONS AND INFESTATIONS	ANY ADVERSE EVENT	0 (0.0%)	1 (0.6%)
	FEVER	0 (0.0%)	1 (0.6%)
INVESTIGATIONS	ANY ADVERSE EVENT	1 (0.3%)	0 (0.0%)
	BLOOD GLUCOSE INCREASED	1 (0.3%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	ANY ADVERSE EVENT	1 (0.3%)	1 (0.6%)
	BURNING SENSATION	0 (0.0%)	1 (0.6%)
	HEADACHE	1 (0.3%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANY ADVERSE EVENT	4 (1.2%)	0 (0.0%)
	ITCHING SCAR	1 (0.3%)	0 (0.0%)
	PRURITUS	1 (0.3%)	0 (0.0%)
	PRURITUS GENERALISED	1 (0.3%)	0 (0.0%)
	SKIN IRRITATION	1 (0.3%)	0 (0.0%)

Table 9.6: Severe Adverse Events

SYSTEM ORGAN CLASS (SOC)	PREFERRED TERM	EUPHORBIA (N=319)	PLACEBO (N=164)
ALL SYSTEMS	ANY ADVERSE EVENT	2 (0.6%)	1 (0.6%)
GASTROINTESTINAL DISORDERS	ANY ADVERSE EVENT	1 (0.3%)	1 (0.6%)
	DYSPEPSIA	0 (0.0%)	1 (0.6%)
	GASTROENTERITIS	1 (0.3%)	0 (0.0%)
INVESTIGATIONS	ANY ADVERSE EVENT	1 (0.3%)	0 (0.0%)
	HAEMOGLOBIN DECREASED	1 (0.3%)	0 (0.0%)

Table 9.7: Listing of Serious Adverse Events

SCREENING ID	SITE NUMBER	TREATMENT GROUP	EVENT	START DATE	STOP DATE	INTENSITY	CAUSALITY	OUTCOME
001	G10	EUPHORBIA	GASTROENTERITIS PAT COLLAPSED	19/01/2009	UNKNOWN	SEVERE	UNLIKELY	RESOLVED WITH NO SEQUELAE
008	G13	EUPHORBIA	Hb VALUE 5.8 G/DL	UNKNOWN	UNKNOWN	UNKNOWN	UNLIKELY	UNKNOWN

Table 9.8: Listing of Adverse Events Leading to Withdrawal

SCREENING ID	SITE NO.	TREATMENT GROUP	EVENT	START DATE	STOP DATE	SERIOUSNESS	INTENSITY	CAUSALITY	OUTCOME
003	G10	EUPHORBIA	PRURITUS OF THE WHOLE BODY	29/01/2009	UNKNOWN	NO	MODERATE	POSSIBLE	FINAL CONTACT
008	G13	EUPHORBIA	Hb VALUE 5.8 G/DL	Unknown	UNKNOWN	YES	UNKNOWN	UNLIKELY	UNKNOWN
011	B18	EUPHORBIA	TRENK UPPER AND LOWER LIMBS	04/02/2009	UNKNOWN	NO	MODERATE	POSSIBLE	FINAL CONTACT
016	P21	EUPHORBIA	NO UREA SINCE 19.11.2009	19/11/2009	25/11/2009	NO	MODERATE	PROBABLE/LIKELY	RESOLVED WITH NO SEQUELAE
004	P19	PLACEBO	DIARRHOEA,NAUSEA	21/03/2009	24/03/2009	NO	MODERATE	PROBABLE/LIKELY	RESOLVED WITH NO SEQUELAE

9.3.2. Laboratory Assessments

Tables 9.9 and 9.10 summarize change in laboratory parameters from baseline to end of treatment and to end of follow-up, respectively. Laboratory assessments at baseline and at the end of treatment are summarized in supplementary tables.

There was a statistically significant difference between the two groups with respect to change in platelet count from baseline to end of treatment. However, this was caused by a significant decrease in platelet count from baseline to end of treatment in the placebo group, and thus was not an AE attributable to Euphorbia. Also, there was a statistically significant difference between the two groups with respect to change in lymphocytes from baseline to end of treatment and to end of follow-up. However, change in lymphocytes from baseline to end of treatment or to end of follow-up was not significant within the Euphorbia group, and the difference between the two groups was caused by a significant increase from baseline in lymphocytes in the Placebo group, and thus was not an AE attributable to Euphorbia. For all other laboratory parameters, there was no statistically significant difference between the two groups.

Tale 9.9: Laboratory Assessments: Change from Baseline to End of Treatment

		EUPHORBIA	PLACEBO	P-VALUE
HEMOGLOBIN (Hb) (MG/DL)	N	307	158	
	MEAN	-0.1	-0.0	0.5166
	95% CI	(-0.1, 0.0)	(-0.1, 0.1)	
	SD	0.77	0.71	
	MEDIAN	0.0	0.0	
	RANGE	-4.2 to 2.3	-2.8 to 2	
WHITE CELL COUNT (THOU/MM3)	N	307	158	
	MEAN	-0.1	-0.2	0.4607
	95% CI	(-0.2, 0.1)	(-0.4, 0.1)	
	SD	1.47	1.63	

		EUPHORBIA	PLACEBO	P-VALUE
	MEDIAN	0.0	0.0	
	RANGE	-5.6 to 4.8	-5.7 to 5.1	
NEUTROPHILS (%)	N	303	156	
	MEAN	-0.4	-1.0	0.2345
	95% CI	(-1.3, 0.5)	(-2.1, 0.1)	
	SD	7.84	6.86	
	MEDIAN	0.0	-0.3	
	RANGE	-41 to 33.6	-27 to 18	
PLATELET COUNT (THOU/MM3)	N	307	158	
	MEAN	3.5	-8.3	0.0056
	95% CI	(-1.9, 8.8)	(-16.0, -0.7)	
	SD	47.68	48.79	
	MEDIAN	0.0	0.0	
	RANGE	-185 to 199	-155 to 123	
LYMPHOCYTES (%)	N	305	156	
	MEAN	0.3	1.6	0.0366
	95% CI	(-0.5, 1.0)	(0.6, 2.6)	
	SD	6.88	6.49	
	MEDIAN	0.0	1.0	
	RANGE	-17 to 29	-24 to 28	
MONOCYTES (%)	N	305	155	
	MEAN	0.0	-0.0	0.2377
	95% CI	(-0.2, 0.3)	(-0.3, 0.3)	
	SD	2.21	2.07	
	MEDIAN	0.0	0.0	
	RANGE	-10 to 8	-9.0 to 9	
EOSINOPHILS (%)	N	302	153	
	MEAN	-0.1	-0.0	0.5931
	95% CI	(-0.3, 0.1)	(-0.3, 0.3)	
	SD	2.14	1.83	
	MEDIAN	0.0	0.0	
	RANGE	-14 to 7	-5.0 to 10	
BASOPHILS (%)	N	299	151	
	MEAN	0.1	0.0	0.6356
	95% CI	(0.0, 0.2)	(-0.1, 0.2)	
	SD	0.87	1.06	
	MEDIAN	0.0	0.0	
	RANGE	-1.0 to 11	-5.0 to 11	
TOTAL BILIRUBIN (MG/DL)	N	296	154	
	MEAN	-0.0	-0.0	0.8766
	95% CI	(-0.1, 0.0)	(-0.1, 0.0)	
	SD	0.25	0.23	
	MEDIAN	0.0	0.0	
	RANGE	-1.3 to 0.9	-0.8 to 0.74	
SGOT(AST) (U/L)	N	306	158	
	MEAN	0.2	-0.2	0.4891
	95% CI	(-0.7, 1.1)	(-1.5, 1.1)	
	SD	7.78	8.36	
	MEDIAN	0.0	0.0	
	RANGE	-38 to 27	-48 to 21	
SGPT(ALT) (U/L)	N	307	158	
	MEAN	0.4	-0.2	0.4063
	95% CI	(-0.8, 1.6)	(-1.4, 1.0)	
	SD	11.06	7.73	
	MEDIAN	0.0	0.0	
	RANGE	-55 to 61	-33 to 25	
ALKALINE PHOSPHATASE (U/L)	N	298	158	
	MEAN	-1.9	0.5	0.3370
	95% CI	(-4.6, 0.8)	(-3.1, 4.2)	
	SD	24.00	23.12	
	MEDIAN	-1.0	0.9	
	RANGE	-140 to 110	-119 to 99	
BLOOD UREA ((MG/DL)	N	303	155	
	MEAN	0.5	0.5	0.7463
	95% CI	(-0.1, 1.2)	(-0.3, 1.4)	
	SD	5.70	5.34	
	MEDIAN	0.4	0.0	
	RANGE	-23 to 19	-13 to 18	

		EUPHORBIA	PLACEBO	P-VALUE
SERUM CREATININE (MG/DL)	N	306	157	
	MEAN	0.0	0.0	0.1868
	95% CI	(0.0, 0.0)	(-0.1, 0.0)	
	SD	0.18	0.29	
	MEDIAN	0.0	0.0	
	RANGE	-1.0 to 0.42	-2.9 to 0.4	
RANDOM BLOOD SUGAR (MG/DL)	N	305	157	
	MEAN	2.0	-0.3	0.1748
	95% CI	(0.1, 3.9)	(-2.7, 2.1)	
	SD	16.97	15.33	
	MEDIAN	1.0	0.0	
	RANGE	-70 to 65	-48 to 44.3	
SERUM CHOLESTEROL (MG/DL)	N	301	156	
	MEAN	-1.9	-1.7	0.5967
	95% CI	(-5.0, 1.2)	(-5.2, 1.8)	
	SD	27.49	22.01	
	MEDIAN	0.0	0.0	
	RANGE	-139 to 92	-85 to 77.4	
CT (MIN)	N	303	155	
	MEAN	-0.1	-0.1	0.6982
	95% CI	(-0.2, 0.1)	(-0.2, 0.0)	
	SD	1.01	0.86	
	MEDIAN	0.0	0.0	
	RANGE	-3.2 to 4.55	-3.5 to 2	
BT (MIN)	N	287	150	
	MEAN	0.0	0.0	0.8132
	95% CI	(-0.1, 0.1)	(-0.1, 0.2)	
	SD	0.79	0.76	
	MEDIAN	0.0	0.0	
	RANGE	-3.0 to 3.5	-2.0 to 5	

P-values based on two-way ANCOVA

Table 9.10: Laboratory Assessments: Change from Baseline to End of Follow-up

		EUPHORBIA	PLACEBO	P-VALUE
HEMOGLOBIN (Hb) (MG/DL)	N	301	157	
	MEAN	-0.1	-0.0	0.7663
	95% CI	(-0.2, 0.1)	(-0.2, 0.1)	
	SD	0.94	0.80	
	MEDIAN	0.0	0.0	
	RANGE	-3.6 to 5	-2.6 to 3.6	
WHITE CELL COUNT (THOU/MM3)	N	301	157	
	MEAN	-0.0	-0.2	0.2707
	95% CI	(-0.2, 0.1)	(-0.5, 0.0)	
	SD	1.60	1.44	
	MEDIAN	0.0	-0.1	
	RANGE	-8.6 to 3.9	-5.9 to 3.2	
SERUM CHOLESTEROL (MG/DL)	N	299	155	
	MEAN	-3.7	-1.2	0.6754
	95% CI	(-6.9, -0.5)	(-4.6, 2.2)	
	SD	28.35	21.38	
	MEDIAN	-1.0	-1.0	
	RANGE	-114 to 93	-62 to 48	
PLATELET COUNT (THOU/MM3)	N	301	157	
	MEAN	4.7	-0.9	0.3024
	95% CI	(-1.3, 10.7)	(-9.5, 7.8)	
	SD	52.65	54.59	
	MEDIAN	6.0	0.0	
	RANGE	-173 to 382	-212 to 154	
TOTAL BILIRUBIN (MG/DL)	N	291	153	
	MEAN	-0.0	0.0	0.3048
	95% CI	(0.0, 0.0)	(0.0, 0.1)	
	SD	0.25	0.24	
	MEDIAN	0.0	0.0	
	RANGE	-1.2 to 1.87	-0.7 to 1.1	
EOSINOPHILS (%)	N	298	153	
	MEAN	-0.1	-0.2	0.7158

		EUPHORBIA	PLACEBO	P-VALUE
	95% CI	(-0.4, 0.1)	(-0.4, 0.1)	
	SD	2.15	1.65	
	MEDIAN	0.0	0.0	
	RANGE	-14 to 8	-5.0 to 4	
BASOPHILS (%)	N	293	152	
	MEAN	0.1	-0.0	0.0825
	95% CI	(0.0, 0.2)	(-0.1, 0.1)	
	SD	0.75	0.54	
	MEDIAN	0.0	0.0	
	RANGE	-1.0 to 11	-5.0 to 2	
MONOCYTES (%)	N	300	155	
	MEAN	0.3	0.3	0.1280
	95% CI	(0.0, 0.6)	(0.0, 0.5)	
	SD	2.42	1.77	
	MEDIAN	0.0	0.0	
	RANGE	-8.0 to 9	-6.0 to 9	
LYMPOCYTES (%)	N	300	155	
	MEAN	-0.2	1.2	0.0466
	95% CI	(-1.0, 0.6)	(0.1, 2.3)	
	SD	7.10	6.74	
	MEDIAN	0.0	1.0	
	RANGE	-20 to 25	-19 to 19	
SGOT(AST) (U/L)	N	300	157	
	MEAN	-0.6	0.6	0.0891
	95% CI	(-1.5, 0.3)	(-1.0, 2.3)	
	SD	7.95	10.51	
	MEDIAN	0.0	0.0	
	RANGE	-40 to 28	-49 to 57	
SGPT(ALT) (U/L)	N	302	157	
	MEAN	-0.6	1.3	0.0735
	95% CI	(-1.8, 0.6)	(-0.4, 3.1)	
	SD	10.25	11.26	
	MEDIAN	0.0	1.0	
	RANGE	-56 to 47	-26 to 70	
ALKALINE PHOSPHATASE (U/L)	N	294	157	
	MEAN	-3.8	-1.7	0.2914
	95% CI	(-6.8, -0.7)	(-5.4, 2.0)	
	SD	26.75	23.30	
	MEDIAN	-0.9	0.0	
	RANGE	-141 to 124	-137 to 96	
BLOOD UREA (MG/DL)	N	295	155	
	MEAN	0.4	0.7	0.5817
	95% CI	(-0.4, 1.2)	(-0.6, 2.0)	
	SD	6.85	8.11	
	MEDIAN	0.0	0.0	
	RANGE	-22 to 30.8	-29 to 62	
SERUM CREATININE (MG/DL)	N	299	157	
	MEAN	0.0	-0.0	0.5499
	95% CI	(0.0, 0.0)	(-0.1, 0.0)	
	SD	0.17	0.29	
	MEDIAN	0.0	0.0	
	RANGE	-0.6 to 0.78	-3.0 to 0.4	
RANDOM BLOOD SUGAR (MG/DL)	N	301	155	
	MEAN	1.4	0.1	0.5578
	95% CI	(-0.5, 3.4)	(-2.5, 2.7)	
	SD	17.03	16.43	
	MEDIAN	1.3	1.0	
	RANGE	-67 to 64.8	-57 to 54	
CT (MIN)	N	298	155	
	MEAN	-0.0	-0.0	0.2879
	95% CI	(-0.2, 0.1)	(-0.2, 0.1)	
	SD	1.11	0.86	
	MEDIAN	0.0	0.0	
	RANGE	-6.8 to 5.3	-3.0 to 4	
BT (MIN)	N	284	149	
	MEAN	0.1	0.1	0.4074
	95% CI	(0.0, 0.2)	(-0.1, 0.2)	
	SD	0.83	0.83	

		EUPHORBIA	PLACEBO	P-VALUE
	MEDIAN	0.0	0.0	
	RANGE	-2.8 to 3.1	-2.7 to 3	
P-values based on two-way ANCOVA				

9.4. Physical Examination Results

There were no patients in either of the two groups with abnormal findings.

9.5. Vital Signs

Tables 9.11 shows no significant difference between the two treatment groups with respect to change from baseline to end of treatment for pulse rate, respiratory rate, blood pressure or temperature. Vital signs at baseline and at the end of treatment are summarized in supplementary tables.

Table 9.11: Vital Signs: Change from Baseline to End of Treatment

		EUPHORBIA (N=310)	PLACEBO (N=158)	Total (N=468)	P-VALUE
PULSE RATE (beats/min)	MEAN	0.1	0.2	0.1	0.3249
	95% CI	(-0.6, 0.8)	(-0.9, 1.2)	(-0.5, 0.7)	
	SD	6.07	6.74	6.30	
	MEDIAN	0.0	0.0	0.0	
	RANGE	-19.0 to 16.0	-18.0 to 22.0	-19.0 to 22.0	
RESPIRATORY RATE (beats/min)	MEAN	-0.1	0.1	-0.0	0.7175
	95% CI	(-0.3, 0.1)	(-0.2, 0.4)	(-0.2, 0.1)	
	SD	1.98	1.85	1.94	
	MEDIAN	0.0	0.0	0.0	
	RANGE	-10.0 to 7.0	-8.0 to 6.0	-10.0 to 7.0	
SYSTOLIC BP (mmHg)	MEAN	-0.5	-0.5	-0.5	0.7266
	95% CI	(-1.4, 0.5)	(-1.5, 0.6)	(-1.2, 0.2)	
	SD	8.34	6.61	7.79	
	MEDIAN	0.0	0.0	0.0	
	RANGE	-50.0 to 45.0	-25.0 to 20.0	-50.0 to 45.0	
DIASTOLIC BP (mmHg)	MEAN	-0.8	-0.9	-0.8	0.5458
	95% CI	(-1.5, -0.1)	(-1.8, -0.0)	(-1.4, -0.3)	
	SD	6.31	5.76	6.12	
	MEDIAN	0.0	0.0	0.0	
	RANGE	-30.0 to 15.0	-16.0 to 12.0	-30.0 to 15.0	
TEMPERATURE (C)	MEAN	0.0	-0.0	0.0	0.9092
	95% CI	(-0.0, 0.0)	(-0.0, 0.0)	(-0.0, 0.0)	
	SD	0.24	0.18	0.22	
	MEDIAN	0.0	0.0	0.0	
	RANGE	-0.9 to 1.1	-0.7 to 0.6	-0.9 to 1.1	
P-Values based on One-Way Analysis of Variance, CI: Confidence Interval, SD: Standard Deviation					

9.6. Concomitant Medications

As shown in Table 9.13 summarizing intake of concomitant medications, the two treatment groups were similar with regard to intake of concomitant medications, with 63 (19.7%) patients in the Euphorbia group and 38 (23.2%) patients in the Placebo group taking concomitant medications. Most of these medications were being taken before the start of the study and were continued during the study. Magnesium hydroxide was the most common concomitant medication, with 23 (7.2%) patients in the Euphorbia group and 9 (5.5%) patients in the Placebo group taking this medication.

Table 9.12: Summary of Concomitant Medications

		EUPHORBIA (N = 319)	PLACEBO (N = 164)
SUBJECTS TAKING ANY CONCOMITANT MEDICATIONS	YES	63 (19.7%)	38 (23.2%)
	NO	256 (80.3%)	126 (76.8%)
ALLOPURINOL		1 (0.3%)	0
AMLODIPINE		1 (0.3%)	0
ASPIRIN		1 (0.3%)	0
ASPIRIN/DIPYRIDAMOLE		1 (0.3%)	0
ATENOLOL		1 (0.3%)	0
BISOPROLOL		3 (0.9%)	1 (0.6%)
BRAN		0	1 (0.6%)
CARBAMAZEPINE		1 (0.3%)	0
CILEST		0	2 (1.2%)
CYANOCOBALAMIN		0	1 (0.6%)
DICYCLOMINE		0	2 (1.2%)
DIENOGEST & ETHINYL ESTRA		0	1 (0.6%)
DROSPIRENONE		1 (0.3%)	0
ENALAPRIL		1 (0.3%)	1 (0.6%)
ESTRADIOL		0	1 (0.6%)
ETHINYL ESTRADIOL/DROSPIR		4 (1.3%)	1 (0.6%)
FOLIC ACID		1 (0.3%)	0
INDAPAMIDE		3 (0.9%)	1 (0.6%)
INSULIN		1 (0.3%)	0
INSULIN ISOPHANE		1 (0.3%)	0
ISPAGHULA HUSK		3 (0.9%)	2 (1.2%)
LACIDIPINE		0	1 (0.6%)
LACTULOSE		1 (0.3%)	1 (0.6%)
LAXATIVES		0	1 (0.6%)
LEVOTHYROXINE		3 (0.9%)	0
LIQUID PARAFFIN		8 (2.5%)	5 (3.0%)
LISINOPRIL		1 (0.3%)	0
LITHIUM		0	1 (0.6%)
LOSARTAN		0	1 (0.6%)
MAGNESIUM HYDROXIDE		23 (7.2%)	9 (5.5%)
MESALAZINE		0	1 (0.6%)
METFORMIN		2 (0.6%)	1 (0.6%)
METOPROLOL		4 (1.3%)	5 (3.0%)
NORETHISTERONE		1 (0.3%)	0
NOT YET CODED		4 (1.3%)	1 (0.6%)
NYSTATIN		1 (0.3%)	0
OMEPRAZOLE		2 (0.6%)	0
PANTOPRAZOLE		0	1 (0.6%)
PAROXETINE		1 (0.3%)	0
PERINDOPRIL		2 (0.6%)	1 (0.6%)
POTASSIUM		1 (0.3%)	1 (0.6%)
PROPRANOLOL		0	1 (0.6%)
RAMIPRIL		3 (0.9%)	1 (0.6%)
SIMVASTATIN		1 (0.3%)	0
TELMISARTAN		1 (0.3%)	0
THYROID		0	1 (0.6%)
TRIAMCINOLONE		0	1 (0.6%)

10. Discussion and Conclusions

The present trial was designed to assess the efficacy and safety of E. prostrata Dry Extract tablets for the treatment of haemorrhoids, in a double-blind, randomized, placebo-controlled, multicentre study.

The data from patients in Europe showed that Euphorbia was significantly superior to Placebo with 88% of patients in the Euphorbia group and 77% of patients in the Placebo group reporting cessation of bleeding within 14 days after start of treatment. However, the data from patients in India did not show a significant superiority of Euphorbia to Placebo, and had, in fact, a diluting effect on the overall results, which show a response

rate of 79% of patients in the Euphorbia group and 74% in the Placebo group, with the difference being statistically not significant.

The secondary efficacy results were consistent with the primary efficacy results. The primary efficacy results were supported by the secondary efficacy results for Europe, while the secondary efficacy results for India failed to demonstrate superiority of Euphorbia. The data from patients in Europe showed that there was a substantially higher proportion of patients without recurrence of bleeding in the Euphorbia group, compared to the Placebo group, although the difference was not statistically significant. However, the data from patients in India and thereby the overall results showed similar proportions of patients without recurrence of bleeding in the two treatment groups.

The data from Europe showed a consistently higher proportion of patients in the Euphorbia group with improvement of objective signs, compared to the Placebo group, with the difference between the two groups being statistically significant for congestion and oedema. The Indian data and the overall data did not show a statistically significant difference between the two groups for any of the objective sign assessments.

For the overall assessment of efficacy, based on the combined data as well as data from India and data from Europe, the Euphorbia group showed better improvement, compared to Placebo, although the difference between the two groups was not statistically significant.

In a regression analysis with cessation of bleeding as the dependent variable and region (Europe vs. India), gender, and age category as factors, the treatment by region interaction term was bordering on significance ($p = 0.0768$), indicating that the treatment effect in Europe was different from that seen in India. This confirmed the primary efficacy results, which showed that, in Europe, Euphorbia was significantly superior to Placebo, while in India, the proportions of patients achieving cessation of bleeding in the two treatment groups were similar.

The incidence of AEs during the 14-day treatment period was comparable for the two treatment groups, with 24 (7.5%) patients in the Euphorbia group and 8 (4.9%) patients in the Placebo group reporting any AE. The difference in the incidence of AEs between the two groups was not statistically significant. There were two SAEs occurring in the Euphorbia group and no SAEs occurring in the Placebo group. Both SAEs were unlikely to be related to the study medication. One of the SAEs, Hb value 5.8 g/dl, led to withdrawal of the patient from the study. The other SAE, gastroenteristis, was resolved with no sequelae. There were 4 patients in the Euphorbia group (including the patient who experienced an SAE) and one patient in the Placebo group who dropped out of the study due to AEs.

There were 2 (0.6%) patients in the Euphorbia group and 1 (0.6%) patient in the Placebo group with severe AEs. There were 8 (2.5%) patients in the Euphorbia group and 2 (1.2%) patients in the Placebo group with drug related (possibly and probably related) AEs.

There was a statistically significant difference between the two groups with respect to change in platelet count from baseline to end of treatment. However, this was caused by a significant decrease in platelet count from baseline to end of treatment in the placebo group, and thus was not an adverse effect attributable to Euphorbia. Also, there was a statistically significant difference between the two groups with respect to change in

lymphocytes from baseline to end of treatment and to end of follow-up. However, change in lymphocytes from baseline to end of treatment or to end of follow-up was not significant within the Euphorbia group, and the difference between the two groups was caused by a significant increase from baseline in lymphocytes in the Placebo group, and thus was not an adverse effect attributable to Euphorbia. For all other laboratory parameters, there was no statistically significant difference between the two groups.

There was no significant difference between the two treatment groups with respect to change from baseline to end of treatment for pulse rate, respiratory rate, blood pressure or temperature.

The different efficacy results seen in the Phase III clinical trial are possibly attributable to regional/ethnic factors such as differences in lifestyle, eating habits and socio-cultural practices of Indian and European patients.

It is well known that vascular diseases such as haemorrhoids are most prevalent in economically developed countries while they are almost unknown in tribal communities, where the influence of Western culture is absent or limited. In geographies where Western dietary customs have been adopted, for example, in urban Africa, there is an increasing incidence of such diseases. In India, Pakistan, and the Middle East, the situation is midway between that of Africa and developed countries. It has been postulated that refining of carbohydrates, which is characteristic of Western civilization leads to fibre deficiency and the resulting constipation is believed to contribute to the pathogenesis of hemorrhoids. Haemorrhoids are also epidemiologically closely related to a number of diseases characteristic of economic development. These include such non-infective diseases of the bowel as appendicitis, cancer, polyps, and diverticular disease, and also apparently unrelated conditions like obesity, diabetes, atherosclerosis, cholecystitis, hiatus hernia, and femoral hernia. In less developed and developing societies such as India, where the adoption of Western dietary customs has not been widespread, low consumption of refined sugar and vegetarian diet with roughage cause less chance of developing hemorrhoids. The eating of large amounts of roughage leads to large, soft faeces, reducing constipation and requiring less straining for excretion.[16]

In addition to the dietary factors outlined above, another change brought about by Western industrialisation has been the posture for defaecation. The traditional posture of squatting remains the method used by most of the Indian population. In contrast, the use of the pedestal toilet is well and truly entrenched in Europe. It has been reported that partial straightening of the anorectal angle during squatting reduces the pressure required for defaecation and a hips-flexed position has been recommended for defaecation to help treat constipation and prevent haemorrhoids.[17] It is possible that the social custom of squatting during defecation, which is widely practiced by Indian population, may have a contributing role in the efficacy differences seen in Indian and European patients.

Although the high placebo effect (74%) in the Phase III clinical trial against the assumption of 59% reported efficacy of placebo in hemorrhoidal disease had a diluting effect on the overall results, the test product met the target efficacy of 79%.

In summary, the results of this study show that Euphorbia is safe and effective in the treatment of 1° and 2° internal haemorrhoids.

11. References

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SUPPLEMENTARY TABLES

Supplementary Table 1: Subjects Withdrawn from the Study

Screening ID	Treatment group	Reason	DSSPEC
B13_001	EUPHORBIA	Violation of selection criteria at entry-specify	Discontinued due to randomization on 3rd day of onset of bleeding
B13_004	PLACEBO	Violation of selection criteria at entry-specify	Discontinued due to randomization on 25th day of onset of bleeding
B15_001	EUPHORBIA	Failure to return/lost to follow up	
B16_016	EUPHORBIA	Other protocol violation or deviation-specify	Patient came late one week for fifth visit
B17_001	EUPHORBIA	Failure to return/lost to follow up	
B18_011	EUPHORBIA	Adverse event	
B18_055	PLACEBO	Violation of selection criteria at entry-specify	Pts SGOT screening value was found to be outside reference range so he was withdrew from study & asked to stop medication & return the same on v4. He was not issued diary card
B24_023	EUPHORBIA	Failure to return/lost to follow up	
B24_027	PLACEBO	Withdrew consent	
G10_003	EUPHORBIA	Adverse event	
G13_004	PLACEBO	Failure to return/lost to follow up	
G13_005	PLACEBO	Failure to return/lost to follow up	
G13_008	EUPHORBIA	Adverse event	
P17_002	EUPHORBIA	Violation of selection criteria at entry-specify	Inclusion criteria no 2
P19_004	PLACEBO	Adverse event	
P21_016	EUPHORBIA	Adverse event	

Supplementary Table 2: Protocol Deviations

SCREENING ID	TREATMENT GROUP	STUDY STATUS	REASON
B16_448	EUPHORBIA	NOT COMPLETED	PATIENT CAME LATE ONE WEEK FOR FIFTH VISIT

Supplementary Table 3: Physical Examination Results at Baseline (Summary of Abnormal Findings)

BODY SYSTEM	EUPHORBIA (N = 319)	PLACEBO (N = 164)
EAR,NOSE & THROAT	1(0.3%)	0
GENERAL APPEARANCE	1(0.3%)	1(0.6%)
HEAD,NECK & THYROID	1(0.3%)	0
RESPIRATORY SYSTEM	1(0.3%)	0

Supplementary Table 4: Summary of Medical History

TREATMENT	SCREENING ID	SITE	DIAGNOSIS	STAT DATE	STAT DATE	PAST ONGOING
EUPHORBIA |(N = 319)	B15_005	B15	RT HYDROCOCLE			ONGOING
	B15_007	B15	BLEEDING PER RECTUM			
	B15_012	B15	BLEEDING PER RECTUM	UK/01/2009	UK/01/2009	PREVIOUS
	B15_032	B15	KALA AZAR	UK/UK/2008	UK/UK/2008	PREVIOUS
	B15_041	B15	PULMONARY KOCHS	UK/UK/2002	UK/UK/2002	PREVIOUS
	B15_050	B15	JAUNDICE	UK/UK/2002	UK/UK/2002	PREVIOUS
	B20_002	B20	GASTRITIS	18/11/2008	18/11/2008	ONGOING
	B20_004	B20	VASCULAR HEAD ACHE	12/03/2009	12/03/2009	ONGOING
	B22_003	B22	GASTRITIS	28/01/2009	28/01/2009	PREVIOUS
	G10_001	G10	PSORIASIS	UK/UK/1974	UK/UK/1974	ONGOING
	G10_002	G10	HYPERTENSION	UK/UK/2005	UK/UK/2005	ONGOING
			GASTRITIS	UK/UK/2006	UK/UK/2006	ONGOING
	G10_003	G10	HYPERTENSION	12/10/1999	12/10/1999	ONGOING
			STRUMA	16/07/2002	16/07/2002	ONGOING

TREATMENT	SCREENING ID	SITE	DIAGNOSIS	STAT DATE	STAT DATE	PAST ONGOING
			HYPERLIPEMIA	17/07/2002	17/07/2002	ONGOING
			WS-OSTEOCHODROSE	02/08/2004	02/08/2004	ONGOING
			APOPLEX	10/10/2005	10/10/2005	PREVIOUS
			STENOSE ANTINTERMA	UK/10/2007	UK/10/2007	ONGOING
			COVONARY HEAT DESEASE	29/11/2007	29/11/2007	ONGOING
	G10_005	G10	SPLENOMEGALY	22/02/2008	22/02/2008	ONGOING
			UROLITHIASIS	18/12/2008	18/12/2008	ONGOING
			SLATE AFTER RENAL COLIC	18/12/2008	18/12/2008	PREVIOUS
			NYPERLIPEMIA	03/07/2008	03/07/2008	ONGOING
	G10_009	G10	HYPERTENSION	07/07/2004	07/07/2004	ONGOING
	G10_010	G10	POLLINOSIS	24/04/1995	24/04/1995	ONGOING
			HYPERLIPEMIA	18/04/2007	18/04/2007	ONGOING
	G10_012	G10	PHARYNGITIS	17/06/2009	17/06/2009	ONGOING
			PHARYNGITIS	16/06/2009	16/06/2009	
	G10_013	G10	HYPERTENSION			ONGOING
			BACK PAIN CHRON			ONGOING
			UTENUS POLYP	UK/06/2009	UK/06/2009	
	G10_017	G10	HWS-SYNDROME	04/03/1997	04/03/1997	ONGOING
			STRUMA	UK/UK/2004	UK/UK/2004	ONGOING
			SIGMADIVETITULOX	08/02/2008	08/02/2008	ONGOING
			HYPERTONIC	UK/UK/2004	UK/UK/2004	ONGOING
	G10_020	G10	SINUSITIS CHOON	01/09/2006	01/09/2006	ONGOING
	G10_023	G10	STRUMA	UK/UK/1997	UK/UK/1997	ONGOING
			HYPERLIPEMIA	UK/UK/2002	UK/UK/2002	ONGOING
			ABSIACUHYTHANE	UK/UK/2007	UK/UK/2007	PREVIOUS
	G11_001	G11	VAEMO(HROMHTOS)			ONGOING
			MIL ARTHRUSG			ONGOING
	P14_003	P14	MIGRENE	UK/UK/1979	UK/UK/1979	ONGOING
			YOUNTS PAIN	UK/UK/1979	UK/UK/1979	ONGOING
	P14_007	P14	THROMBOPHEBITIS	17/09/2007	17/09/2007	PREVIOUS
			ELEVATD CHOLESTEROL	UK/UK/2007	UK/UK/2007	ONGOING
			HEADACHES	UK/UK/1989	UK/UK/1989	ONGOING
	P14_010	P14	ARTERIAL HYPERTENSION	UK/UK/2005	UK/UK/2005	ONGOING
			HEMOROIDEL DISEASE	UK/UK/2004	UK/UK/2004	ONGOING
	P14_011	P14	HEMOROIDIAC DESEASE	UK/UK/2005	UK/UK/2005	ONGOING
	P14_013	P14	HEMORROID DISEASE	UK/UK/2003	UK/UK/2003	ONGOING
	P15_002	P15	MORBOS HEMORROIDALES	UK/UK/2006	UK/UK/2006	ONGOING
	P15_003	P15	HYPERTONIA ARTERIALIS	25/08/1999	25/08/1999	ONGOING
			NEUROSIS	16/03/2001	16/03/2001	ONGOING
			REFLUX	06/04/2005	06/04/2005	ONGOING
	P15_004	P15	NEUROSIS	UK/06/2003	UK/06/2003	ONGOING
	P15_006	P15	HEMOROIDS	UK/UK/1991	UK/UK/1991	ONGOING
	P15_007	P15	HYPERTONIA ARTERIALIS	UK/07/2004	UK/07/2004	ONGOING
	P15_011	P15	HYPERTENSION	UK/UK/2005	UK/UK/2005	ONGOING
			HYPERLIPDEMIA	UK/UK/2005	UK/UK/2005	ONGOING
			HEMORODS	UK/03/2009	UK/03/2009	ONGOING
	P15_012	P15	COMMOTIO CEREBRI	23/06/2005	23/06/2005	PREVIOUS
	P15_013	P15	HYPERTONIA ARTERIALIS	08/08/2006	08/08/2006	ONGOING
			NEURASTENIA	UK/UK/1995	UK/UK/1995	PREVIOUS
	P15_015	P15	HYPERTROPHY PROSTATAE	UK/09/2007	UK/09/2007	ONGOING
			SYNDR DEPRESSIUOM	UK/01/2006	UK/01/2006	ONGOING
			REFLUX OESOPHAGE	UK/UK/2003	UK/UK/2003	ONGOING
			MORB HEMOPROIDAL	UK/12/2003	UK/12/2003	ONGOING
			FRACT MALLEOLLAT	30/01/2008	30/01/2008	PREVIOUS
	P15_016	P15	HYPERTONIA ARTERIALIS	UK/10/2008	UK/10/2008	ONGOING
			HYPERURIKEMIA	UK/12/2007	UK/12/2007	ONGOING
	P15_018	P15	HYPOTHYREOSIS	UK/UK/2003	UK/UK/2003	ONGOING
			HEMOROIDS	UK/UK/2004	UK/UK/2004	ONGOING
	P15_019	P15	MORBUS HEMORROIDALES	18/04/2006	18/04/2006	ONGOING
			INSTABILITY OF CERAMICAL SPINE	16/07/2003	16/07/2003	ONGOING
	P15_022	P15	DISCOPATHY CERVICIAL	UK/08/2009	UK/08/2009	ONGOING
	P15_023	P15	COXARTHROSIS	UK/09/2009	UK/09/2009	ONGOING
			HYPOTHYREOSIS	UK/02/2009	UK/02/2009	ONGOING
			ARTHROPIATHY	UK/UK/1998	UK/UK/1998	ONGOING
			URTICIARIA CHRONICA	UK/06/2008	UK/06/2008	ONGOING
	P15_025	P15	HYPERTONIA ARTERIALIS	UK/UK/1997	UK/UK/1997	ONGOING
			HYPOTHYREOSIS	UK/UK/1999	UK/UK/1999	ONGOING

TREATMENT	SCREENING ID	SITE	DIAGNOSIS	STAT DATE	STAT DATE	PAST ONGOING
			REFLUX OESOPHAGE	UK/UK/2003	UK/UK/2003	ONGOING
			SYDPROM DEPRESSIVA	UK/UK/2004	UK/UK/2004	ONGOING
	P15_026	P15	HYPOTHYREOSIS	18/02/2005	18/02/2005	ONGOING
			MORBUS HEMOROIDIALES	UK/UK/2006	UK/UK/2006	ONGOING
	P15_027	P15	HYPERTONIA ARTERIALIS	UK/08/2006	UK/08/2006	ONGOING
	P15_029	P15	HYPERTROPHY PROSTATAE	08/02/10	08/02/10	ONGOING
	P16_002	P16	HAEMORRHOIDS	UK/UK/2001	UK/UK/2001	ONGOING
	P16_004	P16	HAEMORRHOIDS	UK/UK/2006	UK/UK/2006	ONGOING
	P16_005	P16	HAEMORRHOIDS	UK/UK/2000	UK/UK/2000	ONGOING
			TUMOR GUANDULAE THYROIDEAE	UK/UK/1995	UK/UK/1995	ONGOING
	P16_006	P16	HAEMORRHOIDS	UK/UK/2004	UK/UK/2004	ONGOING
			VARICES EXTR INF	UK/UK/2001	UK/UK/2001	ONGOING
			CHOLECYSTECTOMIA	UK/UK/2000	UK/UK/2000	PREVIOUS
	P16_008	P16	HAEMORRHOIDS	UK/UK/2006	UK/UK/2006	ONGOING
	P16_009	P16	HAEMORRHOIDS	UK/UK/1999	UK/UK/1999	ONGOING
	P16_010	P16	HAEMORRHOIDS	UK/UK/2002	UK/UK/2002	ONGOING
	P16_011	P16	HAEMORRHOIDS	UK/UK/2002	UK/UK/2002	ONGOING
	P16_013	P16	HAEMORRHOIDS	UK/UK/1999	UK/UK/1999	ONGOING
	P16_014	P16	MAEMORRHOIDS	UK/UK/2005	UK/UK/2005	ONGOING
			GERD	UU/UU/2001	UU/UU/2001	ONGOING
	P16_016	P16	HAEMORRHOIDS	UK/UK/2000	UK/UK/2000	ONGOING
			STERILITY PRIMARY			ONGOING
	P16_017	P16	HAEMORRHOIDS	UK/UK/2004	UK/UK/2004	ONGOING
			KIDNEY STONES	UK/UK/1979	UK/UK/1979	ONGOING
			CHOLESTROLTHIASIS	UK/UK/2003	UK/UK/2003	ONGOING
			HYPERTENSION	UK/UK/2004	UK/UK/2004	ONGOING
			HYPOTHYROIDOISM	UK/UK/2009	UK/UK/2009	ONGOING
	P17_006	P17	ARTERIAL HYPERTENTION	UK/UK/2003	UK/UK/2003	ONGOING
			(MIC) MORBUS ISCHAEMICUS CORDIS	UK/UK/2004	UK/UK/2004	ONGOING
	P17_010	P17	GERD	03/11/2004	03/11/2004	PREVIOUS
	P17_011	P17	HYPERTONIA ARTERIALIS	UK/UK/2000	UK/UK/2000	ONGOING
			HYPERTHYRETONIA	UK/UK/2002	UK/UK/2002	ONGOING
	P17_015	P17	1 BS	28/11/2007	28/11/2007	ONGOING
			GERD	30/10/2007	30/10/2007	ONGOING
			NADULI HAEMORHOIPALES	28/11/2007	28/11/2007	ONGOING
	P17_018	P17	HYPERTENSION	UK/UK/1995	UK/UK/1995	ONGOING
			MYOCARDIAL JSCHEMIC DISEASE	UK/UK/1995	UK/UK/1995	ONGOING
	P18_006	P18	DIABETES MCCLITES			ONGOING
			LGDRCEEMIC NECENT DIAERE			ONGOING
			ANTEINEL HYPERTENSION			ONGOING
	P18_007	P18	ONTERID HYPERTENSION	UK/12/2008	UK/12/2008	ONGOING
	P18_009	P18	ANTENICEL HYPERTENSION	UK/UK/1989	UK/UK/1989	ONGOING
	P18_020	P18	ANTENICEL HYPERTENSION	UK/UK/1995	UK/UK/1995	ONGOING
	P19_002	P19	HYPERTENSION	UK/UK/1995	UK/UK/1995	ONGOING
			MYOCARDIAL INFARCT	20/04/1995	20/04/1995	PREVIOUS
			DIABETES	UK/05/2005	UK/05/2005	ONGOING
			HEMORRHOIDES	UK/UK/2007	UK/UK/2007	ONGOING
			HYPERCHOLESTEROLTMIF	UK/UK/1995	UK/UK/1995	ONGOING
	P19_003	P19	HYPERTENSION	UK/UK/1989	UK/UK/1989	ONGOING
			HYPOTHYROIDISM	UK/UK/2004	UK/UK/2004	ONGOING
			HEART ISCITEMIC DISEASE			ONGOING
			HEMORRHIODS	UK/UK/2002	UK/UK/2002	ONGOING
	P19_005	P19	HEMORRHILDS	UK/UK/2007	UK/UK/2007	ONGOING
			STEATOSIS OF LIVER	UK/UK/2004	UK/UK/2004	ONGOING
	P19_006	P19	HEMORRHOIDS	UK/UK/2003	UK/UK/2003	ONGOING
	P19_008	P19	HYPERTENSION	UK/UK/2006	UK/UK/2006	ONGOING
			HYPERCHOLESTE ROLANIA	UK/UK/2008	UK/UK/2008	ONGOING
			HAEMORRHOIDES	UK/UK/2007	UK/UK/2007	ONGOING
	P20_001	P20	HAEMORROIDS	01/03/1989	01/03/1989	ONGOING
			ARRYTHMID	01/01/1995	01/01/1995	ONGOING
			AMPINE PECTORIS	01/04/2008	01/04/2008	ONGOING
			CHRONIC ULCER PERFIC	15/01/2004	15/01/2004	ONGOING
			HAEMORRHOIDS	01/03/1989	01/03/1989	ONGOING
			APRHYTMMIA	01/01/1995	01/01/1995	ONGOING
			ANGINA PECTORIS	01/04/2008	01/04/2008	ONGOING
			CHROCWC PEPTIC ULCER DISEASE	15/01/2004	15/01/2004	ONGOING
	P20_004	P20	DUODENAL ULCER	UK/10/2007	UK/10/2007	PREVIOUS

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	P21_001	P21	MUMPS	UK/UK/1983	UK/UK/1983	PREVIOUS
			HYPERTENSION	UK/UK/1997	UK/UK/1997	ONGOING
			HEMOROLDS	UK/UK/1989	UK/UK/1989	ONGOING
	P21_002	P21	RUBELA	UK/UK/1975	UK/UK/1975	PREVIOUS
			MUMPS	UK/UK/1976	UK/UK/1976	PREVIOUS
			PERTUSIS	UK/UK/1977	UK/UK/1977	PREVIOUS
			GERO	UK/UK/2008	UK/UK/2008	ONGOING
			HEMOROIDS	UK/UK/1999	UK/UK/1999	ONGOING
	P21_003	P21	MUMPS	UK/UK/1981	UK/UK/1981	PREVIOUS
			BENIGN POSITIONAL VERTI 60	UK/UK/2004	UK/UK/2004	ONGOING
			HEMOROIDS	UK/UK/1998	UK/UK/1998	ONGOING
	P21_004	P21	MUMPS	UK/UK/1981	UK/UK/1981	PREVIOUS
			VERICEUA ZOSTER	UK/UK/1984	UK/UK/1984	PREVIOUS
			RUBEOLLA	UK/UK/1980	UK/UK/1980	PREVIOUS
			HEMOHOIDES	UK/UK/2003	UK/UK/2003	ONGOING
			RHINALLERGY	UK/UK/1999	UK/UK/1999	ONGOING
	P21_007	P21	ECZENUNE	UK/UK/2003	UK/UK/2003	ONGOING
			DYSCOPETUIE	UK/UK/1994	UK/UK/1994	ONGOING
			HUUOSOIOLS	UK/UK/2001	UK/UK/2001	ONGOING
	P21_010	P21	HAEMORRHOIDS	UK/UK/1980	UK/UK/1980	ONGOING
			SPANDYLORTHOSIS	UK/UK/1980	UK/UK/1980	ONGOING
			DEMOTITIS ALLEGICE	UK/UK/2000	UK/UK/2000	ONGOING
			PHINALLERGY	UK/UK/2004	UK/UK/2004	ONGOING
	P21_012	P21	HEPATITIES B	UK/UK/1991	UK/UK/1991	PREVIOUS
			HYPERTONIA ARTERIALIS	UK/UK/1994	UK/UK/1994	ONGOING
			CARPAL TUNNEL SYNDROME	UK/03/2006	UK/03/2006	PREVIOUS
			OSTEOARTHROSIS	UK/UK/2002	UK/UK/2002	ONGOING
			CHROMIC LARYNGITIS	UK/UK/2008	UK/UK/2008	ONGOING
	P21_013	P21	PYELONEPUR TISACUJA	UK/UK/1965	UK/UK/1965	
			ANGINA PECTURIS	UK/UK/1984	UK/UK/1984	ONGOING
			SPONDNUSIS COLLUMNEB	UK/UK/1989	UK/UK/1989	ONGOING
			PHALONPHNITIS ACUTA	UK/UK/1965	UK/UK/1965	PREVIOUS
			ANGINA PECTORIS	UK/UK/1984	UK/UK/1984	ONGOING
			SPONDYSIS COLLUMNAEVENTE	UK/UK/1989	UK/UK/1989	ONGOING
	P21_015	P21	ARTHOSIS	UK/UK/1995	UK/UK/1995	ONGOING
			HYPERTENSION	22/11/2004	22/11/2004	ONGOING
			GERD	UK/UK/1994	UK/UK/1994	ONGOING
			HQEMORRHOIDS	UK/UK/2004	UK/UK/2004	ONGOING
	P21_016	P21	CA.MAMMEE(BREAST CANCER)	UK/03/2000	UK/03/2000	PREVIOUS
			HAEMMORHOIDS	UK/UK/2006	UK/UK/2006	ONGOING
	P21_017	P21	SPONDYLOARTHROSIS	UK/UK/2004	UK/UK/2004	ONGOING
			HYPERGLICAMIE	UK/UK/2008	UK/UK/2008	ONGOING
			HAEMORTHOIDS	UK/UK/1998	UK/UK/1998	ONGOING
	P21_018	P21	HAEMORRHOIDS	UK/10/2008	UK/10/2008	ONGOING
			CHRONIC VAGINITIS	UK/UK/2008	UK/UK/2008	ONGOING
	P23_001	P23	ANTENICEL HYPERTENSION	UK/UK/1990	UK/UK/1990	ONGOING
			DIABETES T-2	UK/UK/1990	UK/UK/1990	ONGOING
			CHRONIC RENAL FAILURE	UK/UK/2007	UK/UK/2007	ONGOING
			ISCHAEMIC HEART DIS	UK/UK/1990	UK/UK/1990	ONGOING
Placebo|(N = 164)	B14_001	B14	DRUG ALLRGY?			
			TINIA CRURIS	31/03/2003	31/03/2003	ONGOING
			OTITIS EHANA	12/10/2005	12/10/2005	PREVIOUS
	B14_002	B14	AMOEBIC CAECAL PERFORATION	05/08/2008	05/08/2008	PREVIOUS
	B15_002	B15	TAB CIPLA	UK/01/2009	UK/01/2009	PREVIOUS
			TAB METROGYL	UK/01/2009	UK/01/2009	PREVIOUS
			TAB VOREAN	UK/01/2009	UK/01/2009	PREVIOUS
			TAB RANTAC	UK/01/2009	UK/01/2009	PREVIOUS
			TAB CREMAFFIN	UK/01/2009	UK/01/2009	PREVIOUS
	B18_001	B18	SUBMUCUS FIBROIS	UK/UK/2008	UK/UK/2008	ONGOING
	B18_041	B18	HYPERTENSION	UK/UK/1994	UK/UK/1994	ONGOING
	B22_027	B22	HTN			ONGOING
	G10_004	G10	STRUMA(EVTHYREOT)	12/02/2001	12/02/2001	ONGOING
			HYPERTENSION	16/11/1998	16/11/1998	ONGOING
			OLIGOPHRENIC	08/02/1996	08/02/1996	ONGOING
			HYPERVVIKAMIE	05/09/1997	05/09/1997	ONGOING
			HYPERLIPEMIA	11/01/2001	11/01/2001	ONGOING
			BAD PAIN CHVON	22/09/1997	22/09/1997	ONGOING

TREATMENT	SCREENING ID	SITE	DIAGNOSIS	STAT DATE	STAT DATE	PAST ONGOING
			SHEATESIS HEPATIS	UK/UK/2005	UK/UK/2005	ONGOING
	G10_006	G10	LUMBAGO	05/07/1996	05/07/1996	ONGOING
			HORESEHOE KIDNEY	05/02/2009	05/02/2009	ONGOING
			HYPERLIPEMIA	13/07/2006	13/07/2006	ONGOING
	G10_008	G10	ARTHROSIS ANKLE JOINT RIGHT	09/10/1996	09/10/1996	ONGOING
			HEPATOSPLENOMEGNTIC	27/11/2006	27/11/2006	ONGOING
			STATE AFTER PERIMYOCANDITIS	27/11/2006	27/11/2006	ONGOING
	G10_016	G10	SUSPECTED HYPERTENSION	06/07/2009	06/07/2009	ONGOING
	G10_018	G10	GASTIHIS,CHVONIC	27/09/2006	27/09/2006	ONGOING
			STRUMA	02/11/2005	02/11/2005	ONGOING
			DISC PROLAPSC	07/04/2006	07/04/2006	ONGOING
	G10_019	G10	GASTIHIS,CHVONIC	14/02/1995	14/02/1995	ONGOING
			HEMORRHOIDS	11/02/1998	11/02/1998	ONGOING
			BACK PAIN CHVONIC	14/02/1995	14/02/1995	ONGOING
			COPD	07/10/1993	07/10/1993	ONGOING
			SPONDYLOS IS DEFORMANS	31/10/2007	31/10/2007	ONGOING
			CHONDVOPATHIC	09/06/2008	09/06/2008	ONGOING
	P14_004	P14	HYPERTENSION	UK/UK/2003	UK/UK/2003	ONGOING
			JOINTS ACHE	UK/UK/1994	UK/UK/1994	ONGOING
	P14_005	P14	HYPER TENSION	UK/UK/2003	UK/UK/2003	ONGOING
	P14_014	P14	OVARIAN CYST			PREVIOUS
			MYOMA			PREVIOUS
			MENINGIJOMA			PREVIOUS
			HYPERCLIDESTEROLENIA	UK/10/2008	UK/10/2008	ONGOING
			OESOPLUEGTIS	UK/09/2008	UK/09/2008	ONGOING
			HAEUOGRHORDAL DISEASE	UK/UK/2000	UK/UK/2000	ONGOING
	P15_005	P15	ARTHOROSIS COU VERTENALL	UK/09/2004	UK/09/2004	ONGOING
			DYSCOPATHY	UK/01/1993	UK/01/1993	ONGOING
			VARITES FXTR IMFRIORIS	25/03/2009	25/03/2009	ONGOING
			MEMROIDS	UK/UK/2007	UK/UK/2007	ONGOING
	P15_008	P15	STRUMA NODOSA	21/08/2002	21/08/2002	ONGOING
			LYMPHOPENIA	UK/UK/1980	UK/UK/1980	ONGOING
			DYSUOPATHY	UK/09/2007	UK/09/2007	ONGOING
	P15_009	P15	HB PHEOMIATHONDCOL	UK/03/2009	UK/03/2009	ONGOING
	P15_014	P15	HHYPERVIZUKEMID	02/01/2008	02/01/2008	PREVIOUS
			HIPERCHOLESTEROCEMIA	31/03/2009	31/03/2009	ONGOING
	P15_017	P15	HAEMORRHOIDS	UK/UK/1988	UK/UK/1988	ONGOING
			NEPHROLITHIASIS	UK/05/2004	UK/05/2004	ONGOING
	P15_020	P15	HEMOROIDIAC DESEASE	UK/11/2003	UK/11/2003	ONGOING
	P15_024	P15	HYPOTHYREOSIS	UK/UK/1970	UK/UK/1970	ONGOING
	P15_028	P15	HYPERTONIA ARTERIALIS	UK/01/2004	UK/01/2004	ONGOING
	P16_001	P16	HAEMORRHOIDS	UK/UK/2004	UK/UK/2004	ONGOING
	P16_003	P16	HAEMORRHOIDS	UK/UK/1999	UK/UK/1999	ONGOING
	P16_007	P16	HAEMORRHOIDS	UK/UK/2000	UK/UK/2000	ONGOING
	P16_012	P16	HEMORRHOIDS	UK/UK/2007	UK/UK/2007	ONGOING
			HYPOTHYREOSIS	UK/UK/2004	UK/UK/2004	ONGOING
			PRIMARY INFERTILITY	UK/UK/2008	UK/UK/2008	ONGOING
	P16_015	P16	HAEMORRHOIDS	UK/UK/2002	UK/UK/2002	ONGOING
	P16_018	P16	HAEMORRHOIDS	UK/UK/2007	UK/UK/2007	ONGOING
			KIDNEY STONES	UK/UK/2008	UK/UK/2008	ONGOING
			PROSTATE ENLARGEMENT	UK/UK/2008	UK/UK/2008	ONGOING
	P17_001	P17	IBS(IRRITABLE BOWEL SYNDROME)	05/02/2008	05/02/2008	ONGOING
	P17_007	P17	ARTERIAL HYPERTENTION	UK/06/2007	UK/06/2007	ONGOING
			GERD 1ST.L . A	05/03/2009	05/03/2009	ONGOING
	P17_013	P17	FISSURA ANI			PREVIOUS
			HAEMORRODIAL DISEASE	UK/UK/2008	UK/UK/2008	ONGOING
	P17_017	P17	GERD	27/08/2008	27/08/2008	PREVIOUS
			ULCUS DUODEN	UK/08/2006	UK/08/2006	PREVIOUS
	P17_019	P17	CHOLELITHIASIS	UK/UK/2007	UK/UK/2007	PREVIOUS
	P18_008	P18	ANTEIRD HYPER TENSION			ONGOING
			THE EMNOIDED DISEASE	UU/03/2009	UU/03/2009	ONGOING
			LBCHEMIC LEAST DISEASE			ONGOING
	P19_001	P19	HYPERTENSION	01/05/2008	01/05/2008	ONGOING
			HEMORRHOIDS	UK/UK/2004	UK/UK/2004	ONGOING
	P19_004	P19	HYPERTENSION	UK/UK/1994	UK/UK/1994	ONGOING
			MNOCARDIAL INFARCT	UK/UK/2001	UK/UK/2001	PREVIOUS
			HEART ISCHEMIC DISEASE	UK/UK/2001	UK/UK/2001	ONGOING

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			HEMDRAHOIDES	05/03/2009	05/03/2009	ONGOING
			DIABETES	UK/UK/2001	UK/UK/2001	ONGOING
	P19_007	P19	HEMORRHOIDES	UK/UK/2004	UK/UK/2004	ONGOING
	P20_002	P20	DUODENAL ULCER	UK/05/2003	UK/05/2003	PREVIOUS
			ARTERIAL HYPERTENSION	UK/04/2006	UK/04/2006	ONGOING
	P20_003	P20	ARTERIAL HYPERTENSION	UK/05/1992	UK/05/1992	ONGOING
	P21_005	P21	HYPERTENSION	UK/UK/2002	UK/UK/2002	ONGOING
			ADENOMA PROSTATE	UK/UK/2008	UK/UK/2008	ONGOING
			HEMOROLOGY	UK/UK/1993	UK/UK/1993	ONGOING
			HYPERTENSION	UK/UK/2002	UK/UK/2002	ONGOING
			A DENOMA PROSATAE	UK/UK/2008	UK/UK/2008	ONGOING
			HEMOROLD	UK/UK/1993	UK/UK/1993	ONGOING
	P21_008	P21	GERD	UK/UK/1993	UK/UK/1993	ONGOING
			HYPERCHOLESTROLEIM	UK/UK/2007	UK/UK/2007	ONGOING
	P21_009	P21	UTERUS MYOMOTOUS			PREVIOUS
			MORBUS DEGENARATIONS ARTICULORAM(ARTHROSIS)	UK/UK/2007	UK/UK/2007	ONGOING
			HAMEOROIDS	UK/UK/2001	UK/UK/2001	ONGOING
	P21_011	P21	VARIOLA	UK/UK/1988	UK/UK/1988	PREVIOUS
			MUMPS	UK/UK/1990	UK/UK/1990	PREVIOUS
			ROSACEA	UK/UK/2000	UK/UK/2000	PREVIOUS
	P21_014	P21	RHINALLERGY	UK/UK/1980	UK/UK/1980	ONGOING
			MIGRAINE	UK/UK/1999	UK/UK/1999	ONGOING
			HERNIA OF THE LINE ALBA	UK/04/2008	UK/04/2008	ONGOING
			HAEMORROIDS	UK/UK/2004	UK/UK/2004	ONGOING
	P21_019	P21	TONSILITIS CHRANICA			PREVIOUS
			HAEMMORHOIDS	UK/UK/2004	UK/UK/2004	ONGOING
			SPONDYLOARTHROSIS LUMBALIS	UK/04/2005	UK/04/2005	ONGOING
			HYPERTONIA ARTERIALIS	27/09/2006	27/09/2006	ONGOING
	P28_001	P28	HYPERTENSION	UK/UK/2000	UK/UK/2000	ONGOING
			SCICETICES	UK/UK/2000	UK/UK/2000	PREVIOUS

Supplementary Table 5: Vital Signs at Baseline

		EUPHORBIA (N = 319)	PLACEBO (N = 164)	P-VALUE
PULSE RATE (beats/min)	MEAN	76.0	76.7	0.3226
	95% CI	(75.3, 76.8)	(75.6, 77.7)	
	SD	6.68	6.70	
	MEDIAN	76.0	76.0	
	RANGE	58.0 to 96.0	58.0 to 96.0	
RESPIRATORY RATE(beats/min)	MEAN	15.9	15.8	0.6363
	95% CI	(15.6, 16.3)	(15.3, 16.2)	
	SD	3.19	2.94	
	MEDIAN	16.0	16.0	
	RANGE	9.0 to 26.0	10.0 to 24.0	
SYSTOLIC BP (mmHg)	MEAN	121.9	122.3	0.6309
	95% CI	(120.7, 123.0)	(121.0, 123.6)	
	SD	10.65	8.51	
	MEDIAN	120.0	120.0	
	RANGE	80.0 to 190.0	104.0 to 146.0	
DIASTOLIC BP (mmHg)	MEAN	77.7	77.2	0.4805
	95% CI	(76.9, 78.4)	(76.3, 78.2)	
	SD	6.77	6.28	
	MEDIAN	80.0	80.0	
	RANGE	50.0 to 100.0	60.0 to 95.0	
TEMPERATURE (C)	MEAN	36.7	36.7	0.8705
	95% CI	(36.6, 36.7)	(36.6, 36.7)	
	SD	0.32	0.29	
	MEDIAN	36.7	36.7	
	RANGE	35.2 to 37.6	35.9 to 37.4	

Supplementary Table 6 (a): Vital Signs at the End of Treatment

		EUPHORBIA (N = 310)	PLACEBO (N = 158)	P-VALUE
PULSE RATE (beats/min)	MEAN	76.2	76.9	0.2534
	95% CI	(75.5, 76.9)	(75.9, 77.9)	
	SD	6.52	6.49	
	MEDIAN	76.0	78.0	
	RANGE	58.0 to 96.0	60.0 to 92.0	
	MISSING	9	6	
RESPIRATORY RATE (beats/min)	MEAN	15.8	16.0	0.6672
	95% CI	(15.5, 16.2)	(15.5, 16.4)	
	SD	2.99	3.02	
	MEDIAN	16.0	16.0	
	RANGE	10.0 to 29.0	10.0 to 24.0	
	MISSING	9	6	
SYSTOLIC BP (mmHg)	MEAN	121.1	121.8	0.4184
	95% CI	(120.0, 122.1)	(120.4, 123.1)	
	SD	9.41	8.58	
	MEDIAN	120.0	120.0	
	RANGE	90.0 to 165.0	105.0 to 155.0	
	MISSING	9	6	
DIASTOLIC BP (mmHg)	MEAN	76.9	76.5	0.5283
	95% CI	(76.1, 77.6)	(75.5, 77.5)	
	SD	6.84	6.35	
	MEDIAN	80.0	80.0	
	RANGE	50.0 to 100.0	60.0 to 92.0	
	MISSING	9	6	
TEMPERATURE (C)	MEAN	36.7	36.7	0.8003
	95% CI	(36.6, 36.7)	(36.6, 36.7)	
	SD	0.29	0.30	
	MEDIAN	36.7	36.7	
	RANGE	35.8 to 37.6	35.8 to 37.6	
	MISSING	9	6	

Supplementary Table 6 (b): Vital Signs at the End of Follow-up

		EUPHORBIA	PLACEBO	P-VALUE
PULSE RATE (beats/min)	N	307	157	0.4450
	MEAN	76.1	76.6	
	95% CI	(75.4, 76.8)	(75.6, 77.7)	
	SD	6.24	6.74	
	MEDIAN	76.0	78.0	
	RANGE	60.0 to 92.0	60.0 to 92.0	
	MISSING	12	7	
RESPIRATORY RATE (beats/min)	N	307	156	0.7341
	MEAN	15.8	15.9	
	95% CI	(15.5, 16.2)	(15.4, 16.4)	
	SD	3.05	3.07	
	MEDIAN	16.0	16.0	
	RANGE	10.0 to 30.0	10.0 to 24.0	
	MISSING	12	8	
SYSTOLIC BP (mmHg)	N	307	157	0.1568
	MEAN	121.1	122.5	
	95% CI	(119.9, 122.3)	(121.2, 123.8)	
	SD	10.50	8.28	
	MEDIAN	120.0	120.0	
	RANGE	10.0 to 150.0	104.0 to 150.0	
	MISSING	12	7	
DIASTOLIC BP (mmHg)	N	307	157	0.6034
	MEAN	77.0	77.3	
	95% CI	(76.3, 77.7)	(76.3, 78.3)	
	SD	6.26	6.45	
	MEDIAN	80.0	80.0	
	RANGE	60.0 to 96.0	58.0 to 92.0	
	MISSING	12	7	

		EUPHORBIA	PLACEBO	P-VALUE
TEMPERATURE (C)	N	307	157	0.3572
	MEAN	36.6	36.7	
	95% CI	(36.5, 36.7)	(36.6, 36.7)	
	SD	0.73	0.28	
	MEDIAN	36.7	36.7	
	RANGE	24.8 to 37.4	36.0 to 37.6	
	MISSING	12	7	

Supplementary Table 7: Laboratory Assessments at Baseline

		EUPHORBIA	PLACEBO	P-VALUE
HEMOGLOBIN (Hb) (MG/DL)	N	319	164	0.9302
	MEAN	13.69182	13.70488	
	95% CI	(13.52, 13.87)	(13.48, 13.93)	
	SD	1.5908848	1.4693517	
	MEDIAN	13.8	13.8	
	RANGE	(8.6, 17.9)	(8.8, 17.2)	
WHITE CELL COUNT (THOU/MM3)	N	319	164	0.9188
	MEAN	7.240909	7.257317	
	95% CI	(7.059, 7.423)	(6.993, 7.521)	
	SD	1.655374	1.7125237	
	MEDIAN	7.2	7.2	
	RANGE	(3.4, 13.8)	(3.3, 12.9)	
BASOPHILS (%)	N	312	159	0.7137
	MEAN	0.168333	0.189371	
	95% CI	(0.107, 0.229)	(0.086, 0.293)	
	SD	0.5481026	0.659711	
	MEDIAN	0	0	
	RANGE	(0, 6)	(0, 7)	
	MISSING	7	5	
PLATELET COUNT (THOU/MM3)	N	319	164	0.7278
	MEAN	246.7367	244.7866	
	95% CI	(240.5, 253)	(235.4, 254.2)	
	SD	56.813218	61.010988	
	MEDIAN	240	238.5	
	RANGE	(108, 473)	(106, 435)	
SGOT(AST) (U/L)	N	318	164	0.6478
	MEAN	25.6983	25.32238	
	95% CI	(24.73, 26.66)	(24.06, 26.58)	
	SD	8.7506126	8.162569	
	MEDIAN	24.35	25.55	
	RANGE	(10, 81)	(10, 73)	
	MISSING	1	0	
SGPT(ALT) (U/L)	N	319	164	0.6351
	MEAN	27.06909	26.49268	
	95% CI	(25.61, 28.53)	(24.76, 28.23)	
	SD	13.280029	11.258338	
	MEDIAN	26	26	
	RANGE	(7.7, 115)	(8, 80)	
ALKALINE PHOSPHATASE (U/L)	N	312	164	0.4492
	MEAN	101.8572	98.41915	
	95% CI	(96.58, 107.1)	(91.25, 105.6)	
	SD	47.35421	46.494513	
	MEDIAN	97	97	
	RANGE	(20, 298)	(15, 302)	
	MISSING	7	0	
EOSINOPHILS (%)	N	314	159	0.7073
	MEAN	2.493599	2.420252	
	95% CI	(2.26, 2.727)	(2.14, 2.701)	

		EUPHORBIA	PLACEBO	P-VALUE
	SD	2.1051038	1.7922971	
	MEDIAN	2	2	
	RANGE	(0, 16)	(0, 9.1)	
	MISSING	5	5	
SERUM CREATININE (MG/DL)	N	318	164	0.2025
	MEAN	0.888679	0.915061	
	95% CI	(0.87, 0.908)	(0.872, 0.958)	
	SD	0.1736784	0.2783992	
	MEDIAN	0.9	0.9	
	RANGE	(0.37, 1.54)	(0.59, 3.8)	
	MISSING	1	0	
LYMPHOCYTES (%)	N	316	161	0.2369
	MEAN	32.4212	31.59317	
	95% CI	(31.6, 33.25)	(30.55, 32.64)	
	SD	7.4635427	6.720269	
	MEDIAN	31.85	30	
	RANGE	(9, 59)	(14.8, 49)	
	MISSING	3	3	
MONOCYTES (%)	N	316	161	0.6705
	MEAN	2.667278	2.551925	
	95% CI	(2.349, 2.985)	(2.14, 2.964)	
	SD	2.8719732	2.6460221	
	MEDIAN	2	2	
	RANGE	(0, 13)	(0, 9.7)	
	MISSING	3	3	
NEUTROPHILS (%)	N	314	161	0.8880
	MEAN	60.27611	60.41429	
	95% CI	(59.16, 61.39)	(58.82, 62.01)	
	SD	10.044952	10.25724	
	MEDIAN	61	62	
	RANGE	(19.4, 93.8)	(18, 78)	
	MISSING	5	3	
RANDOM BLOOD SUGAR (MG/DL)	N	318	164	0.6822
	MEAN	93.52186	94.22335	
	95% CI	(91.55, 95.49)	(91.49, 96.95)	
	SD	17.872415	17.695671	
	MEDIAN	92.395	92.395	
	RANGE	(17, 157.8)	(15, 149)	
	MISSING	1	0	
SERUM CHOLESTEROL (MG/DL)	N	315	162	0.2859
	MEAN	188.501	184.5636	
	95% CI	(184.1, 192.9)	(179.1, 190.1)	
	SD	39.393922	35.508156	
	MEDIAN	186.49	181	
	RANGE	(106, 326)	(63.32, 300)	
	MISSING	4	2	
TOTAL BILIRUBIN (MG/DL)	N	312	161	0.4881
	MEAN	0.73375	0.71441	
	95% CI	(0.698, 0.77)	(0.683, 0.746)	
	SD	0.321951	0.2034541	
	MEDIAN	0.7	0.7	
	RANGE	(0, 3.4)	(0.01, 1.51)	
	MISSING	7	3	
BT (MIN)	N	296	153	0.5538
	MEAN	3.10902	3.021111	
	95% CI	(2.934, 3.284)	(2.796, 3.247)	
	SD	1.5287915	1.4116273	
	MEDIAN	3	3	
	RANGE	(1, 8.8)	(1, 7)	
	MISSING	23	11	
CT (MIN)	N	312	161	0.6607

		EUPHORBIA	PLACEBO	P-VALUE
	MEAN	5.799712	5.888634	
	95% CI	(5.569, 6.031)	(5.56, 6.217)	
	SD	2.0737268	2.1110973	
	MEDIAN	6	6	
	RANGE	(0.14, 11.2)	(0.14, 11.2)	
	MISSING	7	3	
URINE MICROSCOPY	ABNORMAL	8 (2.5%)	2 (1.2%)	0.4922
	NORMAL	309 (96.9%)	162 (98.8%)	
	NOT DONE	1 (0.3%)	0	
URINE PREGNANCY TEST (FEMALE)	DONE	98 (30.7%)	39 (23.8%)	0.1000
	NOT DONE	217 (68.0%)	124 (75.6%)	
URINE PREGNANCY RESULT	NEGATIVE	90 (28.2%)	37 (22.6%)	0.5392
	MISSING	8 (2.5%)	2 (1.2%)	

Supplementary Table 8 (a): Laboratory Assessments at the End of Treatment

		EUPHORBIA	PLACEBO	P-VALUE
HEMOGLOBIN(Hb) (MG/DL)	N	307	158	0.8414
	MEAN	13.63515	13.6638	
	95% CI	(13.47, 13.8)	(13.44, 13.89)	
	SD	1.4836945	1.416696	
	MEDIAN	13.8	13.8	
	RANGE	(8, 17.3)	(10, 18)	
	MISSING	12	6	
WHITE CELL COUNT (THOU/MM3)	N	307	158	0.6670
	MEAN	7.183909	7.11962	
	95% CI	(7.017, 7.351)	(6.868, 7.371)	
	SD	1.485723	1.5985546	
	MEDIAN	7.1	7.4	
	RANGE	(3.4, 11.5)	(1, 12.2)	
	MISSING	12	6	
BASOPHILS (%)	N	302	154	0.6335
	MEAN	0.270894	0.224221	
	95% CI	(0.157, 0.385)	(0.072, 0.376)	
	SD	1.0045052	0.9545507	
	MEDIAN	0	0	
	RANGE	(0, 11)	(0, 11)	
	MISSING	17	10	
PLATELET COUNT (THOU/MM3)	N	307	158	0.0224
	MEAN	250.3941	237.6835	
	95% CI	(243.9, 256.9)	(229.1, 246.2)	
	SD	57.775012	54.356465	
	MEDIAN	240	227	
	RANGE	(137, 450)	(110, 390)	
	MISSING	12	6	
SGOT(AST) (U/L)	N	307	158	0.2542
	MEAN	25.87593	24.97892	
	95% CI	(24.93, 26.82)	(23.85, 26.11)	
	SD	8.42749	7.1769659	
	MEDIAN	25.8	24	
	RANGE	(10, 78)	(10, 43)	
	MISSING	12	6	
SGPT(ALT) (U/L)	N	307	158	0.2678
	MEAN	27.50241	26.12013	
	95% CI	(25.99, 29.02)	(24.37, 27.87)	
	SD	13.474678	11.120529	
	MEDIAN	26	24.5	
	RANGE	(8, 120)	(10, 105)	
	MISSING	12	6	
ALKALINE PHOSPHATASE (U/L)	N	303	158	0.9863
	MEAN	99.82112	99.74203	

		EUPHORBIA	PLACEBO	P-VALUE
	95% CI	(94.67, 105)	(91.96, 107.5)	
	SD	45.552143	49.504298	
	MEDIAN	94	91.5	
	RANGE	(21.5, 340)	(33.11, 333)	
	MISSING	16	6	
EOSINOPHILS (%)	N	305	155	0.9981
	MEAN	2.32623	2.325806	
	95% CI	(2.124, 2.529)	(2.033, 2.619)	
	SD	1.7988393	1.8467887	
	MEDIAN	2	2	
	RANGE	(0, 11)	(0, 11)	
	MISSING	14	9	
SERUM CREATININE (MG/DL)	N	307	157	0.5570
	MEAN	0.879055	0.868025	
	95% CI	(0.857, 0.901)	(0.839, 0.897)	
	SD	0.1939681	0.1857985	
	MEDIAN	0.9	0.9	
	RANGE	(0.1, 1.5)	(0.08, 1.36)	
	MISSING	12	7	
LYMPHOCYTES (%)	N	307	158	0.3082
	MEAN	32.79218	33.49051	
	95% CI	(32.06, 33.52)	(32.25, 34.73)	
	SD	6.4772758	7.898059	
	MEDIAN	32	32.65	
	RANGE	(12.4, 53)	(12.3, 55)	
	MISSING	12	6	
MONOCYTES (%)	N	307	157	0.4423
	MEAN	2.713681	2.512739	
	95% CI	(2.414, 3.014)	(2.095, 2.93)	
	SD	2.6716146	2.6467136	
	MEDIAN	2	2	
	RANGE	(0, 11)	(0, 11)	
	MISSING	12	7	
NEUTROPHILS (%)	N	306	158	0.8173
	MEAN	59.55425	59.32342	
	95% CI	(58.41, 60.7)	(57.72, 60.93)	
	SD	10.177255	10.22787	
	MEDIAN	61	61.5	
	RANGE	(0, 75)	(23.8, 78)	
	MISSING	13	6	
RANDOM BLOOD SUGAR (MG/DL)	N	305	157	0.4242
	MEAN	95.86938	94.62904	
	95% CI	(94.07, 97.67)	(92.2, 97.05)	
	SD	15.990703	15.38209	
	MEDIAN	94	92.16	
	RANGE	(39, 160.2)	(38, 152.46)	
	MISSING	14	7	
SERUM CHOLESTEROL (MG/DL)	N	304	157	0.3250
	MEAN	186.1393	182.6045	
	95% CI	(181.9, 190.4)	(177.3, 187.9)	
	SD	37.833478	33.781472	
	MEDIAN	180	179	
	RANGE	(114, 347)	(110, 308.88)	
	MISSING	15	7	
TOTAL BILIRUBIN (MG/DL)	N	300	155	0.8485
	MEAN	0.6952	0.690387	
	95% CI	(0.664, 0.726)	(0.656, 0.725)	
	SD	0.2722069	0.2164018	
	MEDIAN	0.7	0.7	
	RANGE	(0.06, 2.57)	(0.02, 1.63)	

		EUPHORBIA	PLACEBO	P-VALUE
	MISSING	19	9	
BT (MIN)	N	288	150	0.8397
	MEAN	3.072222	3.041267	
	95% CI	(2.897, 3.247)	(2.793, 3.289)	
	SD	1.5082539	1.538498	
	MEDIAN	2.48	2.47	
	RANGE	(1, 8)	(1, 10)	
	MISSING	31	14	
CT (MIN)	N	306	157	0.9311
	MEAN	5.668333	5.686561	
	95% CI	(5.424, 5.912)	(5.356, 6.017)	
	SD	2.1695604	2.0986365	
	MEDIAN	6	6	
	RANGE	(0.15, 11.2)	(0.15, 10.4)	
URINE MICROSCOPY	MISSING	13	7	
	ABNORMAL	9 (2.8%)	2 (1.2%)	0.2661
	NORMAL	297 (93.1%)	153 (93.3%)	
	NOT DONE	1 (0.3%)	2 (1.2%)	
URINE PREGNANCY TEST (FEMALE)	DONE	73 (22.9%)	33 (20.1%)	0.5149
	NOT DONE	235 (73.7%)	124 (75.6%)	
URINE PREGNANCY RESULT	NEGATIVE	64 (20.1%)	32 (19.5%)	0.1007
	MISSING	10 (3.1%)	1 (0.6%)	

Supplementary Table 8 (b): Laboratory Assessments at the End of Follow-up

		EUPHORBIA	PLACEBO	P-VALUE
HEMOGLOBIN(HB) (MG/DL)	N	301	157	0.7821
	MEAN	13.63289	13.6707	
	95% CI	(13.48, 13.79)	(13.45, 13.89)	
	SD	1.3838646	1.3949663	
	MEDIAN	13.8	13.9	
	RANGE	(8.5, 17.2)	(8.5, 16.9)	
	MISSING	18	7	
WHITE CELL COUNT (THOU/MM3)	N	301	157	0.2966
	MEAN	7.22289	7.063885	
	95% CI	(7.051, 7.395)	(6.812, 7.315)	
	SD	1.5190931	1.5951347	
	MEDIAN	7.35	7	
	RANGE	(1.68, 13)	(2.6, 12.7)	
	MISSING	18	7	
BASOPHILS (%)	N	295	153	0.2471
	MEAN	0.250169	0.161699	
	95% CI	(0.147, 0.353)	(0.097, 0.227)	
	SD	0.8970046	0.4079083	
	MEDIAN	0	0	
	RANGE	(0, 11)	(0, 2)	
	MISSING	24	11	
PLATELET COUNT (THOU/MM3)	N	301	157	0.2420
	MEAN	251.2226	244.6433	
	95% CI	(244.6, 257.8)	(236, 253.2)	
	SD	58.311579	54.531221	
	MEDIAN	240	239	
	RANGE	(104, 550)	(140, 392)	
	MISSING	18	7	
SGOT(AST) (U/L)	N	301	157	0.3029
	MEAN	25.04864	25.85987	
	95% CI	(24.22, 25.88)	(24.41, 27.31)	
	SD	7.2890207	9.1856067	
	MEDIAN	25	25	
	RANGE	(9, 50)	(10, 77)	

		EUPHORBIA	PLACEBO	P-VALUE
	MISSING	18	7	
SGPT(ALT) (U/L)	N	302	157	0.2394
	MEAN	26.42871	27.66809	
	95% CI	(25.3, 27.56)	(25.78, 29.56)	
	SD	9.9614989	11.977596	
	MEDIAN	26	27	
	RANGE	(8, 66)	(9, 98)	
	MISSING	17	7	
ALKALINE PHOSPHATASE (U/L)	N	299	157	0.8556
	MEAN	98.67789	97.88713	
	95% CI	(93.72, 103.6)	(90.77, 105)	
	SD	43.519469	45.126989	
	MEDIAN	91	94	
	RANGE	(17.84, 307)	(29.84, 320)	
	MISSING	20	7	
EOSINOPHILS (%)	N	301	156	0.5643
	MEAN	2.284718	2.196154	
	95% CI	(2.102, 2.467)	(1.966, 2.426)	
	SD	1.6068081	1.4528674	
	MEDIAN	2	2	
	RANGE	(0, 11)	(0, 9)	
	MISSING	18	8	
SERUM CREATININE (MG/DL)	N	300	157	0.6355
	MEAN	0.9019	0.909554	
	95% CI	(0.884, 0.92)	(0.883, 0.936)	
	SD	0.1605656	0.1699523	
	MEDIAN	0.9	0.9	
	RANGE	(0.57, 1.5)	(0.6, 1.5)	
	MISSING	19	7	
LYMPHOCYTES (%)	N	302	157	0.1836
	MEAN	32.24834	33.15185	
	95% CI	(31.5, 33)	(31.99, 34.32)	
	SD	6.6211165	7.3937038	
	MEDIAN	31	33	
	RANGE	(8.7, 64)	(2.64, 58)	
	MISSING	17	7	
MONOCYTES (%)	N	302	157	0.4254
	MEAN	2.932119	2.711911	
	95% CI	(2.609, 3.255)	(2.284, 3.14)	
	SD	2.8504814	2.7166304	
	MEDIAN	2	2	
	RANGE	(0, 13)	(0, 10)	
	MISSING	17	7	
NEUTROPHILS (%)	N	302	157	0.2817
	MEAN	83.29603	58.99809	
	95% CI	(51.33, 115.3)	(57.27, 60.72)	
	SD	282.24745	10.950714	
	MEDIAN	62	61	
	RANGE	(20.6, 3750)	(14.4, 80.1)	
	MISSING	17	7	
RANDOM BLOOD SUGAR (MG/DL)	N	301	155	0.7701
	MEAN	95.52445	95.09755	
	95% CI	(93.85, 97.2)	(92.75, 97.45)	
	SD	14.748776	14.802291	
	MEDIAN	94	94	
	RANGE	(56, 140)	(57.66, 140)	
	MISSING	18	9	
SERUM CHOLESTEROL (MG/DL)	N	302	156	0.6889
	MEAN	184.7232	183.3753	
	95% CI	(180.7, 188.7)	(178.3, 188.4)	
	SD	35.199943	31.935511	
	MEDIAN	180	181	

		EUPHORBIA	PLACEBO	P-VALUE
	RANGE	(98, 322)	(60.69, 274.13)	
	MISSING	17	8	
TOTAL BILIRUBIN (MG/DL)	N	294	153	0.9855
	MEAN	0.74085	0.741373	
	95% CI	(0.707, 0.775)	(0.697, 0.786)	
	SD	0.2943952	0.2764056	
	MEDIAN	0.715	0.71	
	RANGE	(0.22, 2.7)	(0.02, 2.47)	
	MISSING	25	11	
BT (MIN)	N	284	149	0.5706
	MEAN	3.129437	3.041765	
	95% CI	(2.946, 3.313)	(2.81, 3.274)	
	SD	1.5741708	1.4327402	
	MEDIAN	2.49	2.5	
	RANGE	(1, 8)	(1, 7)	
	MISSING	35	15	
CT (MIN)	N	301	157	0.9315
	MEAN	5.690166	5.707834	
	95% CI	(5.458, 5.923)	(5.368, 6.048)	
	SD	2.0492014	2.155772	
	MEDIAN	6	6	
	RANGE	(0.14, 10.5)	(0.15, 10.5)	
	MISSING	18	7	
URINE MICROSCOPY	ABNORMAL	5 (1.6%)	1 (0.6%)	0.3953
	NORMAL	298 (93.4%)	156 (95.1%)	
	NOT DONE	2 (0.6%)	0	
URINE PREGNANCY TEST (FEMALE)	DONE	67 (21.0%)	28 (17.1%)	0.2958
	NOT DONE	232 (72.7%)	126 (76.8%)	
URINE PREGNANCY RESULT	NEGATIVE	62 (19.4%)	28 (17.1%)	0.1396
	MISSING	5	0	