Title of the clinical study: An open label, double arm study to determine efficacy of LeFiber™ mixed with water, with food in regularizing bowel movements, reducing constipation and enriching gut flora as compared to Psyllium husk as soluble fiber.

Protocol number: PhytoQuest-CPN01

Protocol version number: 1.0

Date: 20th February 2017

Name of the Investigational Product: LeFiber™

Comparator: IGOL from Raptakos, Brett & Co (Psyllium husk as Soluble Fiber)

Form:

IP: Semi solid mass to be administered orally with liquid.

Comparator: Psyllium Husk

Sponsor: Phytabolites Neutraceuticals Pvt. Ltd., 4, Tapasvi Apartment, Prasanna colony, Indiranagar, Nashik - 422 009, India.

Contract research organization: Quest Clinical Services, 14, Samata, Ganesh Nagar, Chinchwad, 411044

Principle Investigator: Dr. Ragini Patil

Co-Investigator: Dr. Medha Joshi

Site: Ayurved Hospital and Sterling multispecialty Hospital, Nigdi, Pune 411044

Clinical laboratory: Associated with Sterling Hospital

## Contents

**Background and Introduction**

The functional gastrointestinal disorders or FGIDs include 6 major domains for adults: esophageal (category A), gastroduodenal (category B), bowel (category C), functional abdominal pain syndrome (category D), biliary (category E), and anorectal (category F). (http://www.jgld.ro/2006/3/5.pdf)

There is no single, generally accepted definition of constipation. The term "constipation" can refer to infrequent evacuation (bowel movement), difficult evacuation, incomplete evacuation, or evacuation of small or hard stools. Among these symptoms, only stool frequency is easily quantifiable and is usually defined as fewer than three bowel movements per week. Physicians often associate constipation with reduced stool frequency. Constipation refers to bowel movements that are infrequent or hard to pass[i].

Patients, however, typically define constipation as the occurrence of one of more symptoms of infrequent stools or difficult stool passage including hard or lumpy stools, straining, a feeling of incomplete evacuation, excessive time spent on the toilet, or the need to manually facilitate stool passage.

Researchers frequently use the Rome III criteria to define constipation.

Constipation is a common symptom. It affects virtually everyone at some point in their life. Occasional constipation may result from changes in diet or from inactivity and will generally respond to simple lifestyle measures. However, constipation that is chronic (constant or long-lasting) or recurrent may indicate the need to see a doctor for evaluation and treatment.

The magnitude of patients with functional gastrointestinal disorders visiting outpatient clinics is high and accounts for up to one third of outpatient consultations.

It is known that deficiency of dietary intake of dietary fiber is one of the major causes of constipation; and the solution lies in bridging up the gap between the current intake on an average of 12 to15 gram dietary fiber per day in adults to about 25-30 gram per day which is recommended intake.

Dark Green Leafy Vegetables are one of the sources of dietary fiber. However, these are available only seasonally and they also have almost 80% water in them, so that effective intake of fiber form Green Leafy vegetables is negligible.

However, it was shown by Savangikar and Savangikar (WO 2008/081472) that powder of fiber can be obtained from the fibrous fraction of Dark Green Leafy Vegetables opening up a

potential for use of fiber of Green Leafy vegetables as source of year-round supply of dietary fiber; and Savangikar and Savangikar (WO 2012/029075) showed that this powder of fiber, which by itself is low in palatability, can be converted into a palatable fiber rich food product – LeFiber™, which is very low in calories and free from fats so that it can be used for human consumption for making up deficiency of dietary fiber in food – which is the Investigational Product of this clinical trial. WHO recommends at least 6 grams per day supplementation for the same to be eligible to be termed as dietary fiber supplementation. This clinical trial proposes to make supplementation of around 10 grams per day through LeFIber™.

### (a) Preclinical experience

The rat studies conducted at FDA approved clinical trial laboratory, Bombay Veterinary College, Mumbai, for studies on rats concluded that the fiber extracted free from leaf matrix of from Green Leafy Vegetable was found to be safe for consumption.

(b) Clinical experience

Being Generally Regarded As Safe (GRAS), the product LeFiber™ made from this dietary fiber ingredient as one of the ingredients, the product LeFiber™ was prescribed by dieticians to more than 300 patients needing them, and results showed positive effects on normalizing bowel movements. Hence, it is proposed to take clinical trial to compare its effect on constipation in comparison with the most widely used medicine for overcoming constipation, Psyllium husk.

**Study Rationale**

Constipation is a problem for a significant number of people in the world which substantially affects the quality of life and may lead to secondary gastrointestinal complications such as hernia, piles, fissures etc. if it becomes chronic. In most of the cases, the cause is low daily intake of dietary fiber. However, instead of going to the root of the problem, i.e. making up deficiency of dietary fiber, conventional way is to resort to laxatives. The main reason is it is not easy to manage enough intake of dietary fiber because of shift in food pattern to inevitability of using processed food ingredients or prepared packaged processed food, from which dietary fiber has been removed to a great extent by processing. Most of the laxatives do give relief from constipation; however, use of laxatives for relief of constipation amounts to use of medicines everyday throughout the life, and using the laxatives as a matter of habit is advised to be avoided by refraining from their use [1].

In general, modern diets have about 12-15 gram of dietary fiber in them; and most of the countries recommend need of 25-30 gram dietary fiber in daily diet. On one hand fast life makes it imperative to use the low-fiber processed ingredients or prepared packaged foods in everyday life rather than use of whole grains and green leafy vegetables every day. Thereare too few dietary fiber from food sources available that are adaptable in a fast life. This makes it imperative to resort to chemical laxatives or non-food sources of dietary fiber such as Psyllium husk to overcome problem of constipation. However, like all medicines, Psyllium husk is also associated with history of serious side effects for persons who get sensitized with Psyllium husk. Hence, there is a need of a balanced food that is palatable also and also which has food sources of dietary fiber in high proportion good enough to make up the average deficiency of about 10 gram dietary fiber per day in food.

The Investigational Product, LeFiber™, used in his clinical trial has a nature of a high fiber supplement in the sense that it has very high proportion of dietary fiber in it; but it is actually a high fiber food because its dietary fibers are derived from food sources and are formulated such that divided between three meals and consumed with each meal, totally they supply about 10 grams of dietary fiber; thus taking the diet close to the recommended intake of food sources of dietary fiber.

What is more, the fiber component of the also has dietary fiber that is derived from dark Green Leafy Vegetables (DGLV) and made free from leaf matrix and powdered so that its enzymatic action retardant surface area is vastly increased to retard release of glucose from starches and about 10% lignin contained in it is available for sequestrating cholesterol rendering it unavailable for re-absorption in cholesterol re-absorption zone of small intestine. The leaf matrix is substantially indigestible by enzymes in upper digestive tract and when that is not made free, the fiber contained in it remains largely ineffective in providing above benefits. This component makes it possible to comply with recommendation that DGLV should be part of daily diet; which recommendation is very rarely complied by any person so far. There are practically no saturated fats and no non-fiber carbohydrates nor any digestible proteins in this formulation; yet the level of palatability is such that it invites for eating the powder as such, as much as desired by a person. This feature is totally absent in any of the currently available high fiber dietary formulations. Hence, LeFiber™ is a balanced composition of dietary fiber. The nitrogen bound in the fiber of Green Leafy Vegetables, which by-passes digestion in upper digestive tract, becomes available in colon to Bifido-bacteria to support their luxuriant growth resulting in substantial increase in bulk of stools by massive growth of bacteria, leading an optimum performance for preventing constipation and stimulating normal bowel movements in a natural

way. It needs to be realized here that the mechanism for constipation preventing effect in LeFiber™ is most natural. Luxuriant bacterial population provides benefits additional to normal bowel movements which are not available from non-food sources to overcome constipation: improvement in immunity, generation of small chain fatty acids for down-regulation of cholesterol metabolism and there is a good probability that the bacterial mass also supplies most essential Vitamin B12 to vegetarian population in sufficient quantity, whose normal diets are highly deficient in Vitamin B12.

The dietary fiber sources in LeFiber™ are a well balanced mix of insoluble and soluble dietary fiber; which is another feature that is totally absent in high fiber formulations currently available in the market.

Although Psyllium husk, a non-food source, actually a medicine, is erroneously considered by many as safe source of dietary fiber, it is known to trigger anaphylactic reaction upon oral consumption in people sensitized to the same. However, it is used very widely by people who need to overcome constipation. Hence, there is a need to evaluate whether the LeFiber™, a high fiber food having dietary fiber from food sources, which has features of what are commonly recognized as dietary supplement and is not a laxative, is equally dependable and effective to Psyllium husk in the context of constipation.

**Research in Context**

Although Psyllium husk is considered to be a safe laxative, if a person gets sensitized to it, upon ingestion, it does lead to anaphylactic reactions that are life threatening and it is advised that laxatives, even if regarded as safe, should be used judiciously and intermittantly[2-9]. The indications in anaphylactic reaction or adverse incidences are listed as Psyllium aspiration causing bronchiolitis, immediate allergic reaction after ingestion of a dietary bar containing Psyllium, asthma, and life threatening rhinitis, a pruritic macular, papular, and urticarial rash involving the entire body including the palms, soles, and oropharynx sparing only the face, sensation of chest and throat tightness and lip swelling.

Dietary fiber are credited with several benefits that cannot be provided by laxatives. Cummings and Stephen[10] pointed out that rather than water holding capacity of the structural components of dietary fiber, about 75% of the fecal mass is contributed by bacteria that grow in colon by breaking down fiber in colon. They point out that if dietary fibre is degraded in the gut by the colonic microflora, the products of this breakdown provide energy for the growth of bacteria, provided there is an adequate supply of nitrogen and other nutrients. Hence, by stimulating

bacterial growth a dietary fibre that is capable of supporting luxuriant growth of bacteria brings about an increase in fecal weight. Cummings and Stephen conclude that "the identification of the microbial contribution to human fecal mass adds a new dimension to theories as to how fibre exerts its effects on the colon. Many types of dietary fibre are substantially digested in the large bowel and thus provide a substrate for microbial growth. The increase in fecal mass seen with degradable fibres such as cabbage, apple and pectin is due to an increase in the number of bacteria excreted. Less digestible materials, such as bran, remain in the colon and hold water by virtue of their cellular structure. The effect a particular fibre has on colonic function therefore depends on its digestibility and, thus, its physical and chemical composition. How these factors control digestion by the microflora has yet to be established in humans. The differing response of individuals to the same fibre source may relate to the characteristics of their colonic bacteria." It becomes clear from the above view of Cummings and Stephen (1980) that a dietary fiber source which can be digested substantially by colonic bacteria and at the same time shall release significant quantity of nitrogen to support luxuriant growth of bacteria shall have special relevance in a high fiber supplement from the point of view of the efficacy of the same. Dietary fiber from DGLV is of this type. It is not indigestible as wheat bran and has nitrogen available from 12-15% proteins that are a part of structure of fiber that gets released upon bacterial digestion for consumption by the actively multiplying bacteria for supporting prolific growth in mass.

Baird[11] showed that Baird I.M. (1977) showed effect of dietary supplements of sugar-cane fiber (bagasse), on stool weight, solids, and water content were studied in normal ambulant volunteers over a 9-mo period; a second inpatient study was done with bran supplements. The addition on 10.5 g of bagasse containing 5.1 g of crude fiber to a normal diet containing 3.7 g of crude dietary fiber daily raised the mean fecal weight from 88.3 +/- 6.4 g to 139.7 +/- 10.2 g/day (p less than 0.005). There was also a significant rise in fecal solids and fecal water, although the percentage of water in the stools remained unchanged. Bagasse supplements accelerated gastrointestinal transit when measured by the carmine marker technique. Radiopaque "shapes" showed a trend toward more rapid transit with bagasse supplements. Daily supplements of 39 g of wheat bran or 10.5 g of bagasse increased the total daily excretion of fecal bacteria, but there were no changes in bacteria excreted per gram of feces. The composition of the bacterial flora showed no change. There was increased excretion of fecal acid sterols on the bagasse supplement, but this failed to occur with bran. No changes attributable to fiber supplements occurred in the plasma triglycerides or cholesterol.

However, daily supplement of 39 gram of bran is an impractical quantity in daily routine and bagasse is not a “food source” dietary fiber and is extremely unpalatable.

In vitro trials conducted on bifido-bacteria strains isolated from treated women failed to confirm the prebiotic potential of undigested Psyllium seed husk[12]. It was concluded that Psyllium seed husk can be metabolized by bifidobacteria only after partial hydrolysis.

During pregnancy in the context of constipation, not the laxatives but, fiber and fluid are acknowledged as keys to self-management[13].

Dietary fiber is more than a matter of dietetics. Its preventative and therapeutic uses were stated to have a preventive effect against constipation, colon diverticulosis, carcinoma of the large bowel and stomach, type 2-diabetes, metabolic syndrome and cardiovascular disease. Therapy with dietary fibre is indicated for constipation, colon diverticulosis, diarrhea, diabetes, and hypercholesterinemia. The individual dietary fibres differ substance-specifically[14].

Fibre supplement was seen to be a safe and convenient alternative to laxatives and decreased the cost of medical care[15].

The evidence surrounding the use of fiber for functional bowel disease is limited. Even when used judiciously, fiber can exacerbate abdominal distension, flatulence, constipation, and diarrhea[16]. There are also reports that reported that, high amounts of insoluble vegetable fiber such as those normally contained in fruits and vegetables, can lead to a further worsening of the digestive symptoms typical of chronic constipation, such as bloating and distension and pain. Better results can be obtained with soluble fibers, such as Psyllium[17]. These two reports make it necessary to ascertain that a food source high fiber concentrate of dietary fiber supplement can be relied for overcoming chronic constipation.

A 5g of a plum-derived mixed fiber supplement and Psyllium were reported to be equally efficacious in improving constipation and QoL. Mixed fibre was more effective in relieving flatulence, bloating and dissolved better. Mixed fibre is effective and well tolerated. Plum-derived mixed fiber was more effective in relieving bloating and flatulence and dissolved better in a solution, and therefore is better tolerated than Psyllium in the treatment of constipation[18].

High prevalence of constipation in long-term care (LTC) residents has been a long-standing issue for caregivers, attending health professionals, and the residents themselves. The traditional medical response has been to utilize pharmaceutical laxatives, enemas, and

suppositories for treatment. In a review to determine if fibre supplementation (including fibre added to foods) is effective in increasing stool frequency, improving stool consistency, and decreasing laxative use in LTC residents, it was confirmed that current evidence suggests that added fibre may be effective in increasing stool frequency and/or decreasing laxative use in LTC residents and, thus, may lessen the burden of constipation. However, it was concluded that randomized controlled trials are needed to clearly demonstrate the effects of adding fibre to foods, particularly insoluble and less fermentable sources, on constipation in LTC residents[19].

LeFiber™ is a high fiber concentrate that is a mix of soluble as well as insoluble dietary fiber of food sources, in which one of the components is also derived from DGLV, a feature absent in high fiber products so far, and the currently reported clinical trial fulfills above need of randomized clinical trial and also has a group on Psyllium husk as control.

Further, the challenges faced in using non-food laxatives like Psyllium husk, Lactulose, Maltitol, Ayurvedic medicines etc. are unpalatability, nausea and risk of choking when Psyllium husk is swallowed and water is drunk on it.

Hence, LeFiber™ is made from dietary fibers most of which are food sources.

The product is a semi solid, has 18·5 Kcal (0 KCal for dietary fiber) per 100g., Fat 0%, Protein 3·62%, Carbohydrate 24% contributing to Dietary fiber content of 23% and water. Thus, on dry matter basis, dietary fiber is 85%, which is one of the highest content of dietary fiber for currently available high fiber food supplements and is contributed 50:50 by insoluble and soluble dietary fibers. In view of preponderance of insoluble fiber in the average diets, after supplementation with LeFiber™, it is considered that probability of the final proportion of daily consumption of insoluble and soluble may come very close 75:25 proportion; which is considered as ideal. Usually high fiber food supplements do not become palatable unless substantial quantity of fats or digestible and non-fiber digestible carbohydrates are associated with the same. However, LeFiber™ has good palatability. One of the insoluble fiber component is sourced from Dark Green Leafy Vegetable, other sources are grain fiber and edible gum.

For providing about 3·3 gram dietary fiber with each meal, about 15 gram of the semi-solid LeFiber™ will have to be consumed. Spoon will be provided such that heaped spoonful gave average of 15 gram of the semisolid LeFiber™ composition containing an average of 3·3g of dietary fiber.

Ingredient composition is: Fiber of Green leafy vegetable, wheat fiber, oat fiber, fructo-oilgo saccharide, gum arabic, cellulose gum, xanthan gum, Garcinia indica syrup, citric acid, salt, beet root and sucralose.

Although semi-solid form was used for clinical trials, in actual practice it can also be prepared as a dry preparation by removal of the water since drying does not change dietary characteristics of a dietary fiber.

Chronic constipation is considered as cause for increase in the risk of several diseases that include diverticulitis, irritable bowel syndrome, hiatus hernia, hernia, piles, fissure, fistula, varicose veins etc. For people who are susceptible to piles, fissure and fistula, even a single or a couple of incidences of constipation are also enough to trigger these highly painful disorders that are difficult to manage. Flatulence caused along with constipation leads to heartburn, gastric discomfort and mimics the symptoms of heart attack. One of the reasons for Colon cancer is also chronic constipation.

It also hampers quality of life, decreases self-confidence and affects performance in otherwise normal individuals.

LeFiber™ the IP of this study contains soluble as well as insoluble fiber in equal proportion. Both the types of fibers are very essential in normal defecation. The IP contains 22.4% of fiber (soluble as well as insoluble) per 100g. Daily consumption of 30g of IP provides 6.72g of dietary fiber.

Study Objective(s)

**(a) Primary Objective**: To study the efficacy of LeFiber™ in reducing constipation as compared to Psyllium husk as soluble fiber

**(b) Secondary Objectives**:

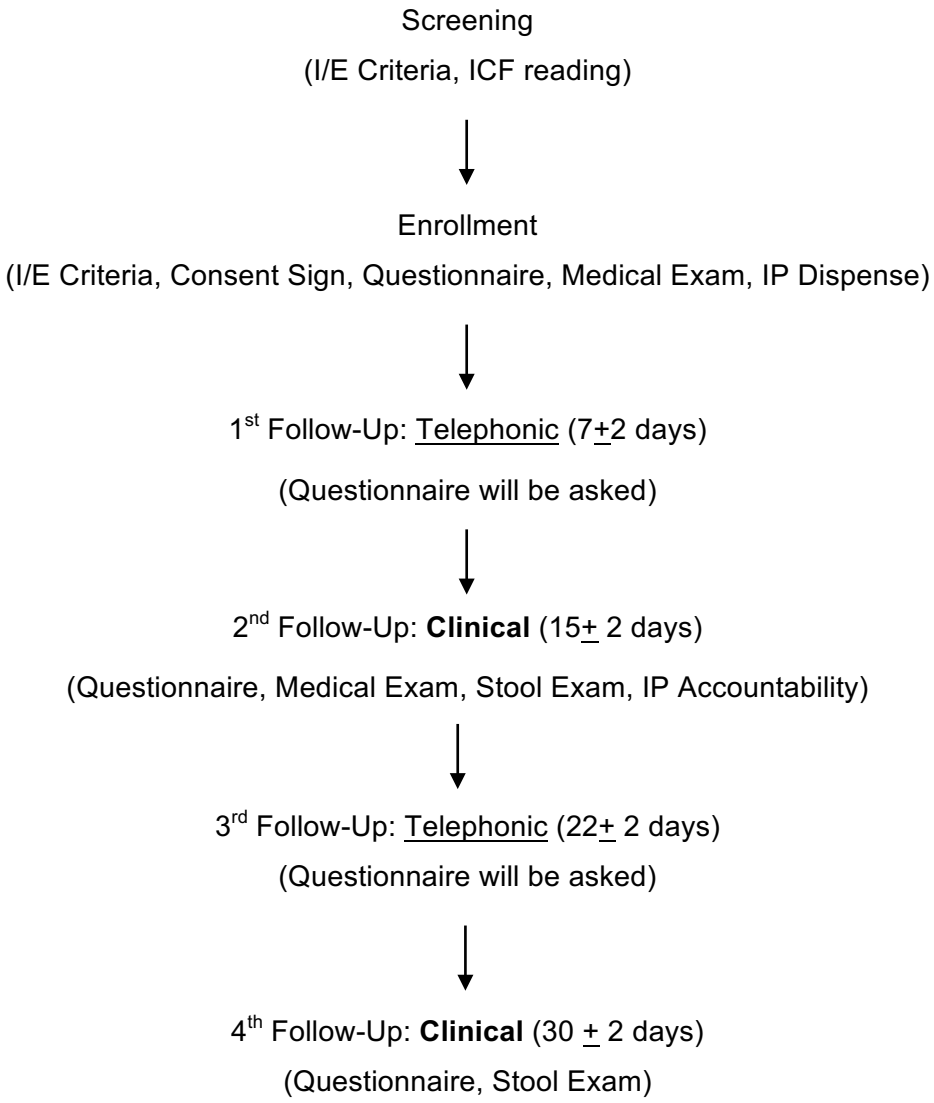
1. To see efficacy of LeFiber™ in regularizing bowel movements as compared to Psyllium husk
2. To see efficacy of LeFiber™ in enhancing gut flora as compared to Psyllium husk
3. Reduction in hyperacidity
4. Increase in quality of life.

## Study Design

### Overview of the Study Design:

This is a double arm study. A total of 72 patients suffering from constipation will be enrolled in the study. Patients will be enrolled in Ayurved Rugnalaya and Sterling hospital, Sector 27, Nigdi, Pune, 411044 after screening for eligibility criteria. Those fulfilling eligibility criteria and consenting in writing will be enrolled in the study. Each enrolled patient will be randomly allocated to either of the arms. Hence, enrolled patients will either get Psyllium husk to be taken per the prescribed method, dose and timing or will get LeFiber™ to be taken 15g twice a day. No medicine which his/her physician is giving/intends to give for any ailment other than constipation the subject is suffering from will be discontinued. Thus, patients enrolled in the study will get the IP/ comparator in addition to the standard of care for other ailments if any, with the patient would have received in absence of treatment for constipation. To expressly clarify, no medicine for constipation will be given to the enrolled subjects other than Lefiber™ or Psyllium husk and it will be ensured that the patients are not consuming already any remedy for constipation in addition to the IP/comparator during the tenure of the investigation: the subject will be receiving only IP/comparator for constipation. Though study period for enrolled patients is a month, IP/ comparator will be given for 15 days only. Thus patients will be off the IP/ comparator for last 15 days. Other regular medicines will be continued throughout.

**Flow chart**:


Screening
(I/E Criteria, ICF reading)
Enrollment
(I/E Criteria, Consent Sign, Questionnaire, Medical Exam, IP Dispense)
1st Follow-Up: Telephonic (7+2 days)
(Questionnaire will be asked)
2nd Follow-Up: Clinical (15+ 2 days)
(Questionnaire, Medical Exam, Stool Exam, IP Accountability)
3rd Follow-Up: Telephonic (22+ 2 days)
(Questionnaire will be asked)
4th Follow-Up: Clinical (30 + 2 days)
(Questionnaire, Stool Exam)

| Study Procedure | Screening | Enrollment | Treatment (IP/Comparator) Period | | | |
|---|---|---|---|---|---|---|
| | | Day 0 | Day 7 (±2) (Tele-Follow-Up) | Day 15 (±2) (Clinical Follow-Up) | Day 22 (±2) (Tele-Follow - Up) | Day 30 (±2) (Clinical Follow-Up) |
| ICF | Reading | X | | | | |
| I/E Criteria | X | X | | | | |
| Randomization | | X | | | | |
| Demographics | | X | | | | |
| Medical History | | X | | | | |
| Physical Exam | | X | | X | | |
| Stool Exam | | X | | X | | X |
| Drug Dispensing | | X | | | | |
| Questionnaire | | X | X | X | X | X |
| Drug Accountability | | | | X | | |
| AE | | | X | X | | |

**Methods and Procedures**:

Patients attending clinics of the physicians in Ayurved Rugnalaya and Sterling hospital, Nigdi, Pune will be screened for their participation in the study. Patients should be complaining of constipation within last 15 days of enrollment. Rome III (C-3) criteria for will be made use of for screening. No discretion for enrollment will be made based on gender, color, religion and caste. Information about the study will be shared with the patients and their eligibility will be checked during screening. There should be 'yes' for every inclusion criterion and 'no' for every exclusion criterion. Those fulfilling this requirement and who are willing to participate will be given informed consent document and patient information sheet for reading. Adequate time will be given for reading the same and the same will be explained verbally. All questions will be answered to the patients' satisfaction. For routine stool examination and for bacterial flora a sterilized plastic bottle will be given to patient. Patient will be asked to bring first stool sample the next day/next possible day. Only when patient brings the stool sample, he will be requested to sign the consent. Patient will be considered as enrolled only after consenting procedure is done. Randomization will be done after that.

Patients will be counseled about administration of IP (dose, timing, method etc.). Comparator or IP, to which patient is assigned, will be dispensed. 2 sterilized plastic bottles will be given for bringing stool sample for next two follow-ups.

Follow-Up:

After enrollment (Day 0), there will be two visits to the site: first follow-up visit at day 15 (±2 days), second follow-up visit at day 30 (±2 days). There will be telephonic follow-ups at day 7 (± 2 days) and 22 (± 2 days).

A person from site will call the patients for knowing health status and to remind them of taking the medicine and the standard of care at day 7 (± 2 days). Telephonic follow-up at day 22 (± 2 days) will comprise of knowing health status (questionnaire).

IP will be given for duration of 15 days during baseline visit. Patient needs to bring the empty bottles and the remaining medicine if any during their follow-up visit at day 15 (± 2 days).

Clinical examination will be done, questionnaire will be filled-in and stool examination will be done at baseline and during both the clinical follow-ups, that is at day 15 (± 2 days) and day 30 (± 2 days).

Patients can call the study coordinator anytime for the queries if any.

Unscheduled Visits:

Patients will continue to visit his/her physician at the site for medical care with prior appointments for routine and regular check-ups. Study coordinator will try and combine their study follow-up visit with their regular visit at the site. Patients should, as far as possible, visit the site in case of medical emergencies.

**Study Design**:

This is a double arm study to determine efficacy of LeFiber™ in regularizing bowel movements, reducing constipation and enriching gut flora as compared to Psyllium husk, the soluble fiber.

Patients having constipation will be enrolled. They will get the IP/comparator in addition to their regular treatment, if any, they might be receiving for other ailments.

Though study period for enrolled patients is 30 days, IP/comparator will be given for 15 days only. Thus, patients will be off the IP/comparator for last 15 days, though the standard of care or regular medicines for other ailments if any, will be continued throughout. Clinical assessment and stool examination will be done at baseline and at clinical follow-ups. Bacterial flora will be

assessed in addition to routine stool examination. Assessment of the patients at day 15 will provide us an overview of efficacy of IP/comparator. However, assessments at day 22 (± 2 days) and day 30 (± 2 days) will provide us the comparative information on which of the two viz. IP and comparator is providing sustained efficacy.

**Study Population**:

We intend to enroll 60 patients. Considering 20% of drop-outs, we will enroll 72 patients in the study.

**Subject Eligibility:**

**(a) Inclusion Criteria:**

1. Patients fulfilling the Rome III Diagnostic Criteria for Functional Gastrointestinal Disorder- C3 (section for functional constipation) and/or taking frequent laxatives
2. Age between 18 years to 65 years of either gender
3. Consenting

**(b) Exclusion Criteria:**

1. Constipation of drug induced or secondary to endocrine, metabolic or neurological disorders, surgery, known or suspected organic disorders of large intestine or colon cancer
2. Known Pregnant or breast-feeding woman
3. Patient with acute conditions like Appendicitis
4. Uncontrolled cardiovascular, kidney, liver or lung diseases; Epilepsy
5. H/o any significant weight loss, H/o blood mixed in stools
6. Patients having incontinence
7. Participant of other clinical trial

**Study Assessments**:

Participants will have two follow-ups as site-visits. Clinical assessment will be done; vitals will be noted, questionnaire will be filled-in and stool examination will be done during these follow-ups.

Assessment of fasting and PP blood sugar in diabetic patients and other parameters reports from their existing reports.

A person from site will call the patients on days 7 (± 2 days) and 22 (± 2 days) and will get the questionnaire filled.

**Study Conduct**:

Patients screened, eligible and willing will be enrolled in the study and will be randomized to either of the 2 groups. During screening, inclusion-exclusion criteria will be applied. Those fulfilling the criteria will be given detailed information about the study. Of those who are willing to participate will be given a container for stool sample collection. After patient gives this sample the same/next day, he will be asked to sign the informed consent form. Study coordinator with the principal or co-principal investigator will participate in the consent process.

Day of consenting will be called as Enrollment day or day zero. After signing the consent form, physical examinations will be done; case record form will be filled, randomization will be done and IP/comparator will be dispensed.

Adequate quantity will be given so that the drug will last for at least 15 days. A copy of duly signed informed consent form will be given to them.

Patients will be told that they will be contacted telephonically after 7 and 22 days.

Patients will be asked to visit for the first clinical follow-up at the 15 day ($\pm$ 2) of the day of enrollment and will be asked to bring the empty bottles and the remaining medicine during their follow-up visits.

Follow-up Visit 1 [$15^{th}$ day ($\pm$ 2) of the day of enrollment]: All the bottles, empty, part-filled etc. will be collected and noted by the study coordinator. Questions will be asked about adherence, missed doses if any and adverse events if any. Vital parameters will be noted and stool sample will be collected for routine and bacterial flora examination. Case record form (questionnaire) will be filled in.

Follow-up Visit 2 [$30^{th}$ day ($\pm$ 2) of the day of enrollment]: All the procedures for this visit will be the same as that of Visit 1, except drug accountability.

Discontinued Patients:

Patients will be withdrawn / dropped from the study if they violate the protocol e.g. by participating in other study, by not taking the IP/comparator, not coming to the hospital for follow-up etc. Patients developing any serious disease, patients wanting to withdraw will also be withdrawn from the study.

Patients who have not turned for clinical follow-up will be called telephonically up to three times after the window period is over. During consenting they will be asked if it is alright with them. Only those agreeing will be called.

However, as it is a 'intent-to-treat' (ITT) study design, data collected of such patients, till they are dropped out/withdrawn from the study will be included in the analysis.

Patients will be insisted to visit during the window-period. Those who miss this will still be continued into the study. On case-to-case basis, protocol waivers will be granted by the co-PI and/or the PI.

Protocol violations will be notified to the EC and to the concerned person responsible for such violations. Appropriate training will be given by the sponsor or by Quest clinical services. Quest clinical services have rights to change the person and notify the EC accordingly.

In case of continuous or repetitive violations hampering the study design in total or jeopardizing the safety of patients, study will be terminated after informing the EC.

**Study Treatment**:

(a) Dosing schedule (dose, frequency, and duration):

Participants will either get IP, which is LeFiber$^{TM}$ or the comparator, Psyllium husk.

Dose of the IP is 15 gms twice a day. It is to be mixed with a little water to form a paste. Then it is to be mixed with a glassful of water and to be taken with food during or at the end of lunch and dinner.

Comparator Psyllium husk's dose is 4.7gm twice a day. IP/comparator needs to be taken for a period of 15 days, from the day of enrollment. 15 days after the 1$^{st}$ clinical follow-up visit (15-day visit) will be devoid of IP/comparator.

Concomitant drug(s): Standard of care for any accompanying illness(es) will be allowed during the total study duration. Only, it will be noted in the case record form.

IP/comparator will be given from the study site by the study coordinator, free of cost. All other concomitant medicines prescribed by the treating physician/doctor willhave to be purchased by the patient.

(b) Study drug supplies and administration: Study medication and comparator will be provided by Phytabolites Nutraceuticals Pvt. Ltd, which is the sponsor of the trial. Quest clinical services will distribute the same to the enrolled patients in the manner mentioned in this protocol. Investigational drug formulation has been manufactured following all the regulations.

All the bottles of the IP and comparator will be securely stored in cupboards; at room temperature. Expiry date will be verified before giving the IP to the patients.

(c) Dose modification for study drug: For those patients who report an adverse reaction and they think it is due to the IP/comparator, it will be discontinued.

(d) Possible drug interactions: The other drugs, if any are to be taken at least 30 min before (preferably) or after consumption of the LeFiber$^{TM}$ / comparator.

(e) Concomitant therapy: As a part of the study design, all the medicines that the patient is supposed to take for his/her other condition(s), patient, will be allowed. There is no drug that is not allowed, provided, it is prescribed by the treating physician. However, no drug for constipation will be allowed, other than IP/comparator. If the PI or co-PI decides that by remaining in the study could be harmful for his/her health, patient will be discontinued from the study.

(f) Blinding procedures: Not applicable as it is an open label study.

**Adverse Events**:

Both, IP and comparator must be taken with at least a full glass of water so that it will not swell in the throat, causing choking. Patient needs to seek immediate medical attention if after taking IP/comparator patient has symptoms of choking such as: chest pain, vomiting, difficulty swallowing/breathing.
Very serious allergic reaction to this supplement is rare. However, patient will be asked to seek immediate medical attention if he/she notices any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

Of particular interest, these supplements are generally regarded as safe.

Reporting of the adverse events will be done in following format:

1. Patient Details:
   Initials and other relevant identifier (PID)*
   Gender:

Age:

Weight:

Height:

2. Suspected Drug(s)

   Generic name of the drug(s)*

   Indication(s) for which suspect drug was prescribed or tested

   Dosage form and strength

   Daily Dose and Regimen

   Route of administration

   Starting date and time of day

   Stopping date and time of day or duration of treatment

3. Other Treatment(s)

   The same information for concomitant drugs (including non-prescription/OTC drugs) and non-drug therapies, as for the suspected drug(s) will be provided.

4. Details of Suspected Adverse Drug Reaction(s)

   Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious will be provided. In addition to a description of the reported signs and symptoms, whenever possible, a specific diagnosis for the reaction will be described.*

   Start date (and time) of onset of reaction

   Stop date (and time) or duration of reaction

   De-challenge and re-challenge information

   Setting (e.g., hospital, out-patient clinic, home, nursing home)

5. Outcome

   Information on recovery and any sequelae; results of specific tests and/or treatment that may have been conducted will be provided. For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; any post-mortem findings will be included. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc. will also be included.

6. Details about the Investigator*

   Name

   Address

   Telephone number

Profession (specialty)

Date of reporting the event to Ethics Committee:

Signature of the Investigator

Information marked '*' must be provided.

**Ethical Considerations**:

(a) Risk/benefit assessment:

From the data available of the product, there are no major health risks to the participants. However, if investigators find any information that might be associated with the IP, it will be conveyed to all the participants.

(b) Ethics Committee review and communications:

Essential documents will be submitted to the Institutional Ethics Committee (IEC) for its review. No patient will be enrolled in the study unless the IEC approves it.

Every three monthly updates will be given to the IEC. Serious adverse events will be reported within 24 hours of their knowledge.

All the communication with the IEC will be filed separately. Quest clinical services will communicate with the IEC on behalf of the sponsor.

(c) Informed consent process:

Information about the IP, comparator and about the trial, procedures of the trial and risks-benefits will be conveyed to the patient so that s/he can take an informed decision. EC approved Patient Information Sheet (PIS) and Informed Consent Form (CRF) will be given to patients for reading. Illiterate patients will be read out in presence of an Impartial Witness. All questions and doubts of the patients will be resolved. Only eligible patients, fulfilling inclusion-exclusion criteria and willing to participate will be enrolled only through informed consent process. Each enrolled patient will get a unique identification number.

Study coordination in presence of PI and/or co-PI will conduct this process.

(d) Subject confidentiality; Ownership of data and Coding procedures: Name of the patient will not be mentioned in the case record form or in the reports. There will be a mention of Patient Identification Number (PID) and initials of the patient instead. Sheet linking this PID and name of the patient will be safely secured with the study coordinator. Only members of IEC, monitors,

auditors, regulatory persons will have access to the data of the enrolled patients. In all such cases, confidentiality about the participant's identity will be maintained.

In case such as managing adverse event, identity will be revealed only to the concerned.

All the data emerging out of this trial will be the sole property of the sponsor, Phytabolites Neutraceuticals Pvt. Ltd.

Coding will be done by the study coordinator. As this is an open-label double arm trial, there is no blinding involved. However, participants' identity will be concealed by a number. Study coordinator will keep the file linking these numbers to names in a safe and secured place.

**Data, Study Monitoring and Supervision**:

Data of the participants will be filled in by the study coordinator. Co-PI and PI will have rights to correct the data whenever needed. All the procedures will be carried out by adhering to the Good Clinical Practices (GCP). Monitor will have access to the study documents. Sponsor of the study can make audit of the study with prior appointment with the PI and the study coordinator.

**Investigational Product and Comparator Management**:

(a) Investigational product and comparator description and packaging:

LeFiber™ drink contains water, Garcinia extract, fiber from green leafy vegetable, wheat fiber, oat fiber, gum acacia, fructo-oligosaccharides, cellulose gum, black salt, beet root powder, acidity regulators (E330), sucralose, class II preservatives (E202, 211). A doser will be given to help the participant consume exact dose. Each bottle will have a paper carton.

A marketed brand of Psyllium husk will be given to those patients randomized to this arm.

(b) Dosing required during the study:

15 gms, twice a day for 15 days is the full dose of the IP. Bottles of IP will be given at enrollment only. Comparator Psyllium husk's dose is 4.7gm twice a day. Adequate quantity in bottles will be given at enrollment such that it lasts for 15 days.

(c) Method of packaging, labeling, and blinding of study substances:

Sealed bottles of IP/comparator will be given to the enrolled patients. Labeling of the bottles will have all the essentials required. As this is an open label double arm study, blinding of the IP and comparator is not required.

(d) Method of assigning treatments to Subjects and the Subject identification code numbering system:

Alfa-numeric identification numbers will be assigned to the participants. Either IP or comparator will be given to all enrolled participants as per randomization. Random number list will be generated from a source on the internet and it will be used.

(e) Storage conditions for study substances:

IP and comparator will be securely stored in cupboards; at room temperature. Expiry date will be verified before giving the IP to the patients.

(f) Investigational product accountability:

Sponsor will send the bottles of IP and of the comparator required for 35 participants each, for a period of 15 days. Receipt and dispensing book will be maintained for the IP.

Each time before dispensing expiry date will be checked and it will be made sure that enough of time is there before the patient consumes the IP / comparator.

Participants will be asked to return all the bottles, empty, partially empty and unopened. Proper recording will be maintained for dispensing and retrieval of these bottles. The recovered bottles will be handed over to the representatives of the sponsor.

(g)Policy and procedure for handling unused investigational products:

All the unused IP and comparator bottles will be sent to the sponsor.

**Data Analysis**:

Appropriate parametric and non-parametric tests will be applied for analysis. For primary end-point, which is change scores of constipation assessment scale, values at baseline, after 15 days (IP/comparator) and after 30 days (sustained effect) will be made use of. These values between the two groups will be compared. Stool exam and gut flora examination on day 0, 15 and 30 will be done and comparison between the IP and comparator group will be made.

As this is intent-to-treat design, all the data, even the dropped-out patients' and lost to follow-up patients' collected data will be analyzed.

**Undertaking by the Investigator**

1. Principal Investigator:

2. Name and address of the medical hospital where the clinical trial will be conducted: Sterling hospital, Sector 27, Nigdi, Pune 411044

3. Name and address of clinical laboratory facilities to be used in the study, especially for stool examination: Associated with Sterling Hospital

4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study: Institutional Ethics Committee, Pune -411044

5. Names of the other members of the research team (Co- or sub-Investigators) who will be assisting the Investigator in the conduct of the investigation (s):

6. Protocol Title: An open label, double arm study to determine efficacy of LeFiber$^{TM}$ mixed with water, with food in regularizing bowel movements, reducing constipation and enriching gut flora as compared to Psyllium husk as soluble fiber.

Protocol number: PhytoQuest-CPN01

7. Commitments:

(i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary Ethics Committee and regulatory approvals have been obtained.

(ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval / favorable opinion from the Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to the trial Subjects or when the change(s) involved are only logistical or administrative in nature.

(iii) I agree to personally conduct and/or supervise the clinical trial at my site.

(iv) I agree to inform all Subjects that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the GCP guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory and GCP guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit / inspection by the Sponsor, Ethics Committee, Licensing Authority or their authorized representatives, in accordance with regulatory and GCP provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized representatives of the Sponsor.

(ix) I agree to promptly report to the Ethics Committee all changes in the clinical trial activities and all unanticipated problems involving risks to human Subjects or others.

(x) I agree to inform all unexpected serious adverse events to the Sponsor as well as the Ethics Committee within seven days of their occurrence.

(xi) I will maintain confidentiality of the identification of all participating study patients and assure security and confidentiality of study data.

(xii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials

**Signature of Investigator with Date**

**Protocol Signing Page**

Title of the clinical study: An open label, double arm study to determine efficacy of LeFiber mixed with water, with food in regularizing bowel movements, reducing constipation and enriching gut flora as compared to Psyllium husk as soluble fiber.

Protocol number: PhytoQuest-CPN01

Protocol version number: 1.0

Date: 20th February 2017

Name of the Investigational Product: LeFiber™

Comparator: IGOL from Raptakos, Brett & Co (Psyllium husk as Soluble Fiber)

Form: Semi solid mass to be administered orally with liquid.

Sponsor: Phytabolites Neutraceuticals Pvt. Ltd., 4, Tapasvi Apartment, Prasanna colony, Indiranagar, Nashik - 422 009, India.

Contract research organization: Quest Clinical Services, 14, Samata, Ganesh Nagar, Chinchwad, 411044

Principal Investigator: TBD

Site: Sterling Hospital, Nigdi, Pune 411044

Clinical laboratory: Associated with Sterling Hospital

Dr.

Principal Investigator

References: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i