International Journal of Pharma and Bio Sciences V1 (2) 2010

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

Jogender K. Lalla*, Meena U.Shah* and Edward III Group**

***Corresponding Author* j.k.lalla@gmail.com**

Data Requirement: Rome Criteria for constipation,

Guidelines Followed:

(i) Good Clinical Practice described under ICH E6 document

(ii) World Medical Association's Bioethics Declaration of Helsinki (as adopted by the WMA General Assembly, Tokyo, October 18, 2004) on ethical principles for Medical Research involving human subjects.

(iii) Schedule Y in Drugs and Cosmetic Act (2nd Amendment) Rules, 2005, Ministry of Health and Family Welfare, Government of India ,

Project Sponsor in USA:

Dr. Edward F. Group III, CEO, GLOBAL HEALING CENTER INC. (GHC),

2040 North Loop West, Suite 108 Houston, Texas 77018, (USA)

Tel- (713) 476–001, Fax-(713) 476–0017,

e-mail: drgroup@ghchealth.com

Project Coordinators in India:

Prof.Jogender K. Lalla, PhD*, Dr.Deven V.Parmar M.D*, Dr.Meena U.Shah, M.D.*

Mayfair Clinical Education and Research Centre (MCERC),

Sanskruti.20/701, 90 Feet Road, Thakur Complex, Kandivli (E),

Mumbai- 400 101 (INDIA)

Phone: 91- 22- 28701161, Fax: 91- 22- 28543643

email: j.k.lalla@gmail.com

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

Investigators and Trial centers

1) Dr. Sharad C.Shah – Gastroenterologist and Clinical Investigator – Jaslok Hospital, Mumbai

2) Dr. Chetan B.Bhatt – Gastroenterologist and Clinical Investigator – Bhatia Hospital, Mumbai

KEYWORDS

GHC's Oxy Powder®, Dietary supplement vs. Dulcolax– Constipation – Multicentric Clinical Trial – Rome II Criteria – ICH E6 GCP Guidelines– WMA Declaration of Helsinki – Drug Rules Schedule Y (Amendment 2005)

ABSTRACT

To conduct a clinical trial for evaluating safety, tolerability and effectiveness of Oxy Powder® (OP) in patients of chronic constipation and Constipation – Predominant IBS. Constipation is the slow movement of feces through the large intestine resulting in the passage of dry, hard stools. Fecal impaction is a collection of dry, hard stool in the colon or rectum.

Study Design: 6 weeks open, comparative, randomized study enrolling 40 patients of constipation and 20 of IBS.

Trial Formulations:

(A) Oxy powder ® (Marketed by Global Healing Center, Inc., USA) - Test Product A.

(B) Dulcolax Tablets (DX), [manufactured by Zydus Cadila Ltd, (India)] - Reference Product B.

Guidelines followed:

(a) Rome criteria (b) GCP described under ICH E6 document (c) World Medical Association's (WMA) Bioethics Declaration of Helsinki. (d) Schedule Y in Drugs and Cosmetic Act and (2nd Amendment) Rules, 2005, Ministry of Health and Family Welfare, Government of India,

End Point(s):

1) Recording change in weight 2) The effectiveness of the product for Oxygen delivery in patients

3) Finding of (i) stool examination (ii) Barium Meal X-ray and (iii) Colonoscopy

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

4) Relief of constipation and IBS.

Results and Discussion: There were insignificant changes in **weight** and **blood oxygen levels** during treatment in both the Groups. Stool examination did not show abnormality in any patient. Patients in both Groups showed significant reduction in various symptoms including a) straining, (b) passing of lumpy stools(c) sensation of incomplete evacuation & Anorectal Blockage and (e) manual maneuvers to facilitate Bowel movements.

Overall Efficacy: In Group A, (out of 26), 11 (42.3%) had complete cure, 15 (57.7%) showed Improvement, In Group B, (out of13), 1 (7.7%) had complete cure,10 (76.9%) showed Improvement with 2 (15.9%) failures.

Conclusion:

Safety, Efficacy and tolerability of OP in treating constipation was significantly (P<.05) higher than DX

INTRODUCTION

Constipation is the slow movement of feces through the large intestine resulting in infrequent urge to void and is often associated with the passage of dry, hard stools, abdominal pain or bloating [1]. Constipation is a common problem in children [2] but it is temporary. When a child does not eat enough fiber, drink enough liquids, or get enough exercise, constipation is more likely to occur. It also happens when children ignore the urge to have a bowel movement, which they often do out of embarrassment to use a public bathroom. Sometimes, constipation is caused by medicines or a disease. Although constipation is annoying and uncomfortable; the **fecal impaction** which is a collection of dry, hard stool in the colon or rectum can be life-threatening. Patients with a fecal impaction may not have gastrointestinal symptoms. Instead, they may have circulation, heart, or breathing problems.

Despite constipation being a common condition, many sufferers do not visit a healthcare provider for treatment due to the availability of OTC medications. Many individuals with chronic constipation resist undergoing a flexible sigmoidoscopy or a colonoscopy for diagnosis.

LITERATURE

The estimates of the prevalence of constipation in North America ranged from 1.9% to 27.2%, with most estimates from 12% to 19%. Prevalence estimates by gender support a female-to-male ratio of 2.2:1. Constipation appears to increase with increasing age, particularly after age 65. Approximately 63 million people in North America meet the

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

Rome II criteria. [3a]. Chronic constipation is one of the most frequent gastrointestinal symptoms even in the Unites States [3b]. It accounts for nearly 2.5–2.7 million physicians' visits and 39000-90000 hospitalizations per year. Diagnosis of Functional Gastrointestinal Disorders (FGID) always presumes the absence of a structural or biochemical explanation for the symptoms. While these modalities may be employed to rule out other causes of abdominal symptoms, they are not necessary to make a diagnosis of Irritable bowel syndrome (IBS) [4]

IBS or spastic colon is a functional bowel disorder characterized by abdominal pain and changes in bowel habits which are not associated with any abnormalities seen on routine clinical testing. Rome II diagnostic criteria [5] for IBS have defined it in terms of frequency of multiple symptoms including straining, hard stools and/or a bowel movement frequency of less than three times per week. Some symptoms (Red flag symptoms) can be mistaken for IBS. Red flag symptoms which are not typical of IBS include (a) Pain that awakens or interferes with sleep (b) Diarrhea that awakens or interferes with sleep (c) Blood in the stool (visible or occult) (d) Weight loss (e) Abnormal physical examination [6].

The therapy in the treatment of constipation includes administration of enema, suppositories, oral laxatives and fibers [7]. Colon cleansing achieved by 'Medical Ozone Oxygen Therapy [8] through rectal insufflations is a natural alternative. Test Product, Oxy Powder® "OP" (Marketed by Global Healing Center, Inc., USA) is an oral Dietary Supplement offering convenient alternative to otherwise painful 'Ozone Oxygen Therapy' Each OP capsule contains Ozonated Magnesium Oxides (OMO), organic Germanium (Ge–132) and Natural Citric acid. OMO is presumed to release nascent oxygen in presence of Citric acid to give pH 4 [9] in the gi tract, the magnesium assisted by Ge-132 acts as a vehicle to transport oxygen throughout the body. Biochemical role of Ge-132 is reported by Sandra Goodman, [10] and others [11(a, b), 12, 13]. Organic Germanium has no known toxicities[14, 15].

4 capsules of Test Product, Oxy Powder® "OP", with average weight of 715mg.are administered with water in the evening

The Reference Product, Dulcolax (Bisacodyl) "DX" is a stimulant laxative. DX works by stimulating colon movement (peristalsis) [16] DX is administered orally with water at night as a 5mg tablet.

List of contributors to the Study (Table 1).

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

Table 1.

Contributors to the study

1	2	3	4	5	6	7
Prof.J. K. Lalla,PhD.	Dr.M.U Shah.MD	i)Dr.Parmar ii) Dr.Aditi	i) Ms Neeta M ii) Mr.Kamlesh	Dr.Sharad .Shah	Dr.Chetan Bhat	Mr. Vinayak Deshpande
Study Dir.	Study Monitor.	Study Coordinator	CRAs	Investigator1	Investigator 2	Statistician
MCERC+	i) MCERC ii) Bhatia Hospital	MCERC	MCERC	Dr.Shah's Clinic	Bhatia Hospital	Consultant

+ Mayfair Clinical, Education and Research Center

Investigators and Trial Centers (Table 2).

Table 2

Investigators and Study Centers:

Investigator	Name	Center	No. of patients Enrolled
1	Dr. Sharad C. Shah	Dr. Sharad C. Shah's Clinic	20

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

2	Dr. Chetan B. Bhatt	Bhatia Hospital	20*
	TOTAL NO.OF PATIENTS ENROLLED		40 *

*One patient withdrew two days after commencement of study

1) Dr. Sharad C.Shah – Gastroenterologist and Clinical Investigator – Jaslok Hospital, Mumbai

2) Dr. Chetan B.Bhatt – Gastroenterologist and Clinical Investigator – Bhatia Hospital, Mumbai

PATIENT SELECTION AND TREATMENT

(a) Selection Procedure for Participants:

(i) Before selection, **subjects** were counseled on Day1 prior to the enrolment and performance of any study–specific procedures. Written informed consent was obtained from each subject for his / her voluntary participation in the study and permitting performance of any study–specific procedures (determining body mass index, oxygen content of blood, stool examination, barium meal X-ray and colonoscopy).

(ii) Patients Inclusion and Exclusion criteria: Subjects enrolled included both vegetarians and non-vegetarians of either sex in the age group of 18 – 65 years with Height & Weight ratio conforming to (a) Height / Weight chart of Life Insurance Corporation of India (b) other eligibility criteria described in Oxy Powder Protocol Version – 02 and (c) satisfying Rome II criteria were followed by the investigators for inclusion.

Subjects excluded were (a) pregnant women, (b) breast feeding mothers, (c) those patients who had a previous history of hypersensitivity to either the Test or the Reference formulation (d) those not conforming to Rome II criteria (e) those with evidence of malignancy on colonoscopy / having diagnosed organic GI disorder (f) Those with history of cardiac arrhythmias, heart disease, glaucoma, urine retention, schizophrenia, addiction to substances of abuse/dependency, and intellectually unable or unwilling to complete daily gastrointestinal ratings.

(iii) Pre–inclusion Evaluation and Documentation: Before inclusion in the trial, each subject's height, body weight (for calculating BMI), sublingual temperature, eating habits (veg/non-veg), history of smoking, consumption of alcoholic beverages and medical history including (i) gi motility (duration of constipation symptoms, number of

bowels in a week, severity of constipation, earlier treatment taken and its effect) and (ii) previous history of other illnesses and drugs taken for the same were carefully recorded.

(iv) Pre–study evaluation: For every subject, his / her body mass index and oxygen content of Blood (determined using pulse oximeter) were recorded followed by stool examination, barium meal X-ray (to rule out any bowel organic lesion leading to constipation), and colonoscopy (to rule out any colonic organic lesion and any fecal impaction) evaluation.

After ruling out the presence of any organic lesion, the patients were included in the trial.

(b) Description of Participants Selected and Statistics:

(i) Randomization (Randomization Schedule in Table 3).

Table 3

Randomization Schedule

No. of Patients : 40 A = Oxy Powder (OP) B = Dulcolax (DX)

Sr. No.	Drug	Sr. No.	Drug
1	A	21	B
2	B	22	A
3	A	23	B
4	B	24	A
5	B	25	A
6	A	26	B
7	A	27	A
8	B	28	A
9	A	29	A
10	B	30	A
11	A	31	A
12	A	32	B
13	B	33	B
14	A	34	A
15	A	35	A
16	A	36	A

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

17	A	37	A
18	B	38	B
19	A	39	A
20	A	40	A

The randomization of the patients was done as 2:1 i.e. 2 patients were given OP & 1 patient was given DX. Out of 40 patients, 27 patients received OP (A) & 13 patients received DX (B).

(ii) Demography: Patients of both the sexes were included in the trial. In OP group (Group. A), out of 27 patients, 19 (70.4%) were males and remaining 8 (29.6%) were females while in DX group (Group. B), out of 13 patients, 8 (61.5%) were males and remaining 5 (38.5%) were females. The baseline demographic characteristics of patients were similar in two treatment groups of the study (P> 05).

Mean 'Minimum' and 'Maximum' age in years of 27 patients in Group A was 20.58 and 37.77 (± Mean SD 11.251) as compared to 22.61 and 40.62 (± Mean SD 11.666) in 13 patients in. Group B.

Mean 'Minimum' and 'Maximum' weight in kg of 27 patients in Group A was 42.96 and 64.26 (Mean ±SD 12.841) as compared to 30.89 and 62.31 (Mean ±SD 14.419) in 13 patients in. Group B

(iii) Living Habits– (a) Vegetarians / Non vegetarians (b) Smokers / Non smokers:

13 (48.1%) in Group A and 7 (53.8%) in Group B were Non vegetarians while 14 (51.9%) in Group A and 6 (46.2%) in Group B were vegetarians. 4 patients (14.8%) in Group A and 2 (15.4%) in Group B were smokers while 23 (85.2%) in Group A and 11 (84.6%) in Group B were Non smokers.

(iv) Categorization of Patients based on Duration of constipation in months, number of bowels passed in a week and severity of constipation:

Treatment Assignment in each group was done by categorization of patients on the basis of duration of constipation in months (3–12, 12–24 and >24) (category1). They were further grouped according to number of bowels passed in a week (1–4, 5–7 and 8–14) (category 2) and severity of constipation (Mild, Moderate and Severe) (category 3).

(c) Technical information:

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

(i) Regulatory Approvals: Before commencing the studies, approval for the protocol was obtained from Independent Ethics Committee (IEC) of MCERC and of Bhatia Hospital, Mumbai.

(ii) Regulatory Guidelines followed: (a) Rome II criteria [5] (b) GCP guidelines described under ICH E6 document [17] (c) WMA's Bioethics Declaration of Helsinki [18] (d) Schedule Y in Drugs and Cosmetic Act and (2nd Amendment) Rules, 2005, Ministry of Health and Family Welfare, Government of India [19].

(iii) Trial Centers, No. of Patients and Trial Duration:

The trial was **completed** in 2 centers with 39 patients (26 on OP and 13 on DX) during 6 weeks treatment from the date of administration of study products. Contributors to the study are described in **Table 1** while investigators, selected subjects and study centers are Included in **Table 2.** The Randomization Schedule is depicted in **Table 3**.

MATERIALS AND METHODS

(i) Investigational Products:

(A) Oxy powder ® (Marketed by Global Healing Center, Inc., USA) **Test Product A**

Each capsule contains 685 mg Ozonated Magnesium Oxides, 5.5 mg Ge–132 and 25 mg Natural Citric acid encapsulated in Kosher certified "00" vegetarian capsules .

(B) Dulcolax Tablets, [manufactured by Zydus Cadila Ltd., (India)]– **Reference Product B.**

Each tablet contained Bisacodyl 5 mg (One tablet was encapsulated in '00' size opaque, white, empty hard gelatin capsule to match the size and color of OP capsule for administration to patients in DX group).

(ii) Handling and Storage of Investigational Products:

All Investigational products were stored in a secured area with access limited to the investigator and authorized site staff and under prescribed physical conditions. They were dispensed by authorized site staff.

Methods:

(i) Dosage & Administration: Selected patients were divided in two Groups; Patients in Group1(OP) (assigned 27 patients) were administered Product A while Patients in Group 2 (DX) (assigned 13 patients) were administered Product B. Out of the 27 patients in Group 1, one patient (from Dr.Chetan Bhatt's group) dropped out on 3rd day. Remaining 26 patients continued with the study till end of the trial.

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

Test Product OP (A)

(a) Cleansing Procedure:

27 Patients were directed by the investigators to take four (4) capsules in the evening on an empty stomach with 240 mL water. If 3-5 bowel movements were not achieved the following day, the dosage was increased to 6 capsules every night until 3–5 bowel movements were achieved the following day. This was considered as "Day one" of cleansing cycle. This dosage was continued for seven consecutive days after which the maintenance dose was started.

(b) OP Maintenance Dose:

Patients were supplied 28 capsules for first week with instructions to take four capsules per day with plenty of water. For subsequent 5 weeks, the same dose was repeated by the patients on alternate days. They were assured that the capsules were not habit forming or harmful to the body and could be taken indefinitely.

Comparative Product DX (B):

13 patients assigned to DX Group were directed by the investigators to take two capsules, each containing one 5 mg tablet of DX with water every day for first 7 days in the evening on empty stomach as a cleansing procedure. Thereafter, the subjects were instructed to take the same dose of DX capsules on alternate days on empty stomach in the evening for 6 weeks.

Administration on Day '0', '3 weeks' and '6 weeks' was done on empty stomach (to enable measuring Oxygen levels) in the morning. Subjects were asked to report to the hospital on empty stomach in the morning for administration of Investigational products and their oxygen level in the blood was measured 15 minutes and 30 minutes after administration of capsules.

On the remaining days, the subjects were asked to take same dose of the DX capsules at their residence in the evening on empty stomach followed by dinner two hours post–administration of the dose.

Drug Accountability and Patient monitoring:

Each patient was provided with a formatted diary to record date and time of intake of dose at home. At the end of every week, every patient handed over the filled diary. Fresh supply of the capsules and the diary pages formatted

for the next 7 days were given to the patient till the end of trial. The recorded missed doses data has been carefully correlated with efficacy and safety.

Study Evaluation and Monitoring end points:

Efficacy Criteria: a) Findings of (i) Stool examination (ii) Barium meal X-Ray and (iii) Colonoscopy

b) Relief of Constipation

The evaluated parameters for OP – administered patients were compared with those obtained with DX – administered patients

Safety: During conduct of study, patients were continuously monitored for any ADRs and SAE

Grading of Response for Efficacy and Safety

Efficacy:

(a) Overall therapeutic response was graded individually by the investigator with each patient as 'Excellent', 'Good', 'Fair' & 'Poor'. It was also simultaneously graded independently by Patients using same scale.

(b) Therapeutic efficacy was correlated and graded as 'Complete Cure', 'Improvement' and 'Failure'.

Safety: Severity of each Adverse Event was rated as 'Mild' (no limitation of usual activity), 'Moderate' (some limitation of usual activity), and 'Severe' (inability to carry out usual activities).

Tolerability: Tolerability was judged from (i) the comfort response of patients administered Study formulations and (ii) side effects experienced by them.

Withdrawal from Study:

One male patient in OP group out of 27 had severe diarrhea on the 2nd day of treatment. He could not carry out his usual activities and felt dehydrated. He voluntarily withdrew from the study on 3rd day. Remaining 26 patients continued with the study.

RESULTS AND DISCUSIONS

Study Medication and Efficacy evaluation.

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

(a) Weight Variation: All the patients were checked daily for their weight for 7 days (0 to 6 days) & then on day 21 & day 42. Mean weight during this period ranged from maximum 65.19 (± Mean SD 12.670) (day 0) to minimum 64.96 (± Mean SD 12.820) kg for patients in Group A and 64.00 (± Mean SD 11.255) (day 0) to minimum 63.19 (± Mean SD 11.640) kg for patients in Group B thus indicating minor weight loss from day 2 onwards in case of both treatments.

(b) No. of bowels in a Week (Category 2) by number of patients:

These are depicted in Table 4.

Table 4

No. of bowels in a Week (category 2) by number of patients

Category □□	No. of Patients In treatment Gr.A and Gr.B					
	Day 0		*Day 21*		*Day 42*	
Treatment Group □ □	A (OP)	B (DX)	A (OP)	B (DX)	A (OP)	B (DX)
1 – 4	11 (40.7%)	8 (61.5%)	1 (3.8%)	1 (7.7%)	- (0%)	1 (7.7%)
5 – 7	12 (44.4%)	4 (30.8%)	10 (30.5%)	7 (53.8%)	6 (23.1%)	2 (15.4%)
8–14	4 (14.8%)	1 (7.7%)	12 (46.2%)	5 (38.5%)	19 (73.1%)	8) 61.5%)
> 14	NIL	NIL	3 (11.5%)	- (0%)	1 (3.8%)	2 (15.4%)
Total No.of Patients □	27	13	26	13	26	13

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

(c) Straining During >25% of Bowel Movement–Response of Patients in Treatment Groups A and B on Days 0, 21 and 42:

Group A treatment: No. of patients reduced from 25 (92.6%) on day 0 through 13 ((50%) on day 21 to 2 (7.7%) on day 42.

Group B treatment: No. of patients reduced from 12 (92.3%) on day 0 through 8 (61.5%) on day 21 to 4 (30.8%) on day 42.

(d) Passing of Lumpy Stools–Response of Patients in Treatment Groups A and B on Days 0, 21 and 42

Group A treatment: No. of patients reduced from 26 (96.3%) on day 0 through 5 (19.2%) on day 21 to 2 (7.7%) on day 42.

Group B treatment, No. of patients reduced from 11 (84.6%) on day 0 through 5 (38.5%) on day 21 to 2 (15.4%) on day 42.

(e) Sensation of incomplete evacuation for >25% of Bowel movement – Response of Patients in Treatment Groups A and B on Days 0, 21 and 42.

Group A treatment: No. of patients reduced from 25 (92.6%) on day 0 through 17(65.4%) on day 21 to 5 (19.2%) on day 42.

Group B treatment: No. of patients changed from 9 (69.2%) on day 0 through 10 (76.9%) on day 21 to 7 (53.8%) on day 42.

(f) Sensation of Anorectal Blockage for >25% of Bowel Movement – Response of Patients in Treatment Groups A and B on Days 0, 21 and 42.

Group A treatment: No. of patients reduced from 15 (55.6%) on day 0 through 1 (3.8%) on day 21 and remained at 1 (3.8%) on day 42...

Group B treatment: No. of patients reduced from 7 (53.8%) on day 0 through 2 (15.4%) on day 21 and remained at 2 (15.4%) on day 42.

(g) Manual Maneuvers to facilitate >25% of Bowel Movements – Response of Patients in Treatment Groups A and B on Days 0, 21 and 42

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

Group A treatment: No. of patients who resorted to manual maneuvers reduced from 11 (40.7%) on day 0 through 0 (0.0%) on days 21 and 42.

Group B treatment: None of the patients resorted to manual maneuvers on days 0, 21and 42.

OVERALL EFFICACY.

Efficacy was independently judged by the Investigators & the patients. It was graded as Excellent, Good, Fair and Poor. The results were statistically analyzed using Fisher's Exact Test.

Investigators' Assessment [IA*****] and Patient's Assessment [PA******]

Group A, (out of 26) **IA* –** Excellent for 13 (50.0%), Good for 12 (46.2%) and Fair for 1 (3.8%)
PA –** 12 (46.2%) 13 (50.0%) and Poor for 1

Group B, (out of 13) **IA* –** Excellent for 1(7.7%), Good for 6 (46.2%), Fair for 4 (30.8%), Poor for 2 (15.4%)
PA –** 1(7.7%), 5 (38.5%) 5 (38.5%) 2 (15.4%)

Overall efficacy was also judged as complete cure, Improvement and Failure.

Group A, (out of 26) **IA–** Complete cure, 11 (42.3%), Improvement,15 (57.7%), failure, 0 (0.0%)

Group B, (out of13), **IA–** 1 (7.7%), 10 (76.9%), 2 (15.9%)

Note: [IA***** = Investigators' Assessment and PA****** = Patient's Assessment (P< 0, 05),

SAFETY

Side effects, Adverse Events (ADRs) and Serious Adverse Events (SAEs)

2 patients had abdominal fullness after taking OP for 2-3 days and then they were symptom – free.

Remaining 24 patients did not experience any side effects.

In DX group, 1 patient had mild abdominal pain which disappeared without medication; remaining 12 patients did not experience any side effects**.** No ADRs and SAEs were reported by the investigators.

TOLERABILITY

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

As per the reports of both the Investigators, none of the patients on Oxy Powder experienced any discomfort. They showed excellent tolerability towards the product and wanted to continue using the product.

DISCUSSION

According to Rome II criteria for constipation, all the patients included were suffering from constipation for 12 weeks or more. They were suitably assigned to groups for meaningful conduct of the trial. The baseline demographic characteristics of patients were similar in the two treatment groups of the study (P>.05).

- Changes in weight during 42 days treatment in both the Groups were insignificant.
- All 39 patients had normal Barium meal X-ray and colonoscopy before starting with the treatment.
- During the course of study, 5 patients among those having multiple spasmodic contractions in sigmoid and descending colon with impacted fecal matter and randomly selected from both groups showed no differences in colonoscopy and Barium meal X-ray conducted on days 0, 21 and 42

(no organic lesions). Since no significant differences were observed, it was decided to drop conduct of both these tests on day 42. However, the patients continued with these two tests on day 0.

- Routine stool examination done on days 0 and 42 did not show any abnormality in all 39 patients included in this study.
- Analysis of oxygen content on days 0, 21and 42 showed marginal changes as compared to the baseline values
- During the course of study, patients in both Groups showed significant reduction in various symptoms including (a) straining during >25% of bowel movement (b) passing of lumpy stools(c) sensation of incomplete evacuation for >25% of bowel movement (d) sensation of Anorectal Blockage for >25% of bowel movement and (e) manual maneuvers to facilitate >25% of bowel movements.

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

CONCLUSIONS

Efficacy, Safety and Tolerability assessment done independently by (a) two investigators and (b) the patients demonstrated that

(i) **Efficacy of OP** in treating constipation was significantly (P<.05) higher than DX indicating that OP was more efficacious in treating constipation than DX.

(ii)As regards **Safety,** there were no side effects, ADRs or SAEs associated with administration of OP proving that the product was **"Safe".**

(iii) As regards **Tolerability**, Patients on OP showed Excellent Tolerability towards the product and wanted to continue using the product after completion of the course.

Although, in this study, the side effects of DX did not precipitate, literature report [16] have several of them recorded. In comparison, Oxy–Powder has a better safety profile as there are no ADRs reported so far. OP is well tolerated by the patients.

ACKNOWLEDGEMENT

The Authors express their gratitude to ACG group, Mumbai for generous donation of gift sample of '00' size opaque, white, empty hard gelatin capsules

CONFLICTS OF INTEREST NOTIFICATION PAGE

POTENTIAL CONFLICTS OF INTEREST RELATED TO

(A) Individual Authors' Commitments

(B) Project Support (Financial Disclosure – DISCLAIMER) for

Publication Paper 1: Evaluation of Safety, Tolerability and Efficacy of Oxy-Powder in Treating Chronic Constipation and

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

Publication Paper 2: Safety, Tolerability and Efficacy of Oxy powder in treating IBS-associated with or without Constipation in Phase II Clinical trial (Published Separate) authored by

1) Prof. Jogender K. Lalla, the Main author, 2) Dr.Meena U. Shah, MBBS, MD, Co–author, 3) Dr.Deven Parmar, MBBS, MD, Co–author, 4) Dr.Edward F. Group III, DC, ND, DACBN, Co–author, hereby state as follows:

- Author at Sr.No. 1, Prof.Jogender K. Lalla, B.Pharm, PhD, Study Director of the Contract Clinical Trial Project and Executive Director + President of Mayfair Clinical, Education & Research Center (MCERC) (INDIA), a contract CRO,
- Author at Sr.No.2, Dr.Meena U. Shah, MBBS, MD., Study Monitor, QA Director and Clinical Pharmacologist of the Contract Clinical Trial project
- Author at Sr.No. 3, Dr.Deven Parmar, MBBS, MD, Study Coordinator of the Contract Clinical Trial project represent MCERC in the capacity enunciated above and are not connected to Global Healing Centre, USA in any manner financially except for the payment received from GHC towards conduct of Clinical Trial by MCERC and the payments made there from to investigators and other parties associated with conduct of this trial.
- Author at Sr.No. 4, Dr. Edward F. Group III, DC, ND, DACBN, CEO of GLOBAL HEALING CENTER INC. (GHC), USA, Project Sponsor, Study Advisor and Monitor of GHC, does not have any financial stake or interest in MCERC except and only for the business deal in terms of the above clinical trial
- MCERC does not have any financial stake or interest in GHC except for the only business deal in terms of the completed clinical trial

(C) None of the authors are in any way known or related to Editors, Journal Staff or Reviewers.

(Dr.J.K.Lalla on behalf of all authors)

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

REFERENCES

1) Thompson W., Longstreth G., Drossman D., Heaton K., Irvine E., and Muller-Lissner S., "Functional Bowel disorders and functional abdominal pain", Gut. 1999 September; 45(Suppl 2): II43–II47.

2) 'Constipation in Children", NIDDK Health Information, NIH publication No.04–4633 March 2004

3a) Peter D.R., Higgins, M.D., and Johanson J.F.," Epidemiology of Constipation in North America: A Systematic Review "The American Journal of Gastroenterology, 2004, 99, 750-759.

3b) Lembo, A and Camilleri, M., "Chronic Constipation", THE NEW ENGLAND JOURNAL of MEDICINE, 2003, Volume 349 (No.14), 1360-1368.

4) **"**Irritable bowel syndrome - Symptoms, Diagnosis, Pathophysiology, Treatment, Epidemiology, Prognosis", Cambridge Encyclopedia Vol. 36 (http://encyclopedia.stateuniversity.com/pages/10747)

5) Drossman, D.A., The functional gastrointestinal disorders and the Rome II process *Gut* online, 1999; 45 (Suppl 2): II, 1-II

6) IBS Self Help and Support Group at http://www.ibsgroup.org Last updated November 11, 2008

7) Satoskar, R.S., Bhandarkar, S, D., and Ainapure, S.S.; Pharmacology and Pharmacotherapeutics, 1999, 16th ed., Popular Prakashan Private Ltd., pp 574-581

8) "Ozone Oxygen Therapy– dreddyclinic_com –Medical ozone therapy oxygen therapies, natural alternative, detoxify kill infectious disease bacteria, mycoplasma, virus organism" [Available at http://www.dreddyclinic.com/integrated_med/ozone_oxygen.htm] (Last modified 05/26/06)

9). "Independent Laboratory Tests on Oxygen Based Colon Cleansers; Scientific Analysis of Commercial Products for Oxidative Ability" quoted In 'Oxy powder TESTED AGAINST COMPETITION COMES OUT #1 IN LAB TESTS' at http://www.greenwillowtree.com/Page.bok

10) Sandra Goodman, PhD, "Germanium-The Health and the Life Enhancer " Chapter 4 ,'Organic Germanium enriches Oxygen supply', Sections 5 and 6

Evaluation of Safety, Tolerability and Efficacy in Treating Chronic Constipation

GLOBAL HEALING CENTER'S OXY POWDER® IN TREATING CONSTIPATION AND IBS

CLINICAL TRIAL PHASE III

11). Aso H, Suzuki F, Yamaguchi T, Hayashi Y, Ebina T, Ishida N. Induction of interferon and activation of NK cells and Macrophages in mice by oral administration of Ge-132, an organic germanium compound, 1985, Microbiol. Immunol. 29, 65-74.

12) (a) Asai K., "Miracle Cure: Organic Germanium". Japan Publications Inc. 1980,
(b) Mizushima M, Satoh H, and Miyao K. Some pharmacological and clinical aspects of a novel organic germanium compound Ge–132. In: 1st Int. Conf. on Germanium. Hanover, Oct. 1984. (Through Lekim & Samochowiec, eds. Semmelweis-Verlag. 1985. GE132; PHAR. NER)

13) Dr.Edward F.Group III; The Health Benefits of Oxygen based colon cleansers with Germanium, an article. (Available at http:// www.shanti .com.au/oxy benefits_ oxygen .htm.)

14) Tao S.H., Bolger, P. Hazard assessment of germanium supplements. Regulat Toxicol Pharmacol. 1997, 25, 211–219

15) Miyao K, Onishi T, Asai K. Tomizawa S & Suzuki F. Toxicology and Phase I Studies on a Novel Organo-germanium Compound, Ge–132. Current Chemotherapy & Inf. Dis. Proc. 11th ICC & 19th ICAAC Amer. Soc. Micro., 80-82. 1980.

16). Drug Information: "Bisacodyl", Medline Plus at http://www.nlm.nih.gov/medlineplus/ drug Information / med master /a 601027.html] (Last Reviewed 08/01/07).

17) ICH E6 (R 1): Good Clinical Practice issued as (i) CPMP/ICH/135/95/Step5 July 1996
(ii) Federal Register, Vol. 62, No.90, May 9, 1997, pages 25691–25709E7

18) De Roy PG. Helsinki and the Declaration of Helsinki. *World Med J* 2004; 50/1: 9-11

19) Schedule Y in Drugs and Cosmetics Act (II Amendment) Rules, 2005, Ministry of Health and Family Welfare, Government of India.