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CLINICAL EVALUATION OF FENFURO (FENUGREEK SEED EXTRACT) IN TYPE-2 DIABETIC SUBJECTS: AN ADD-ON STUDY

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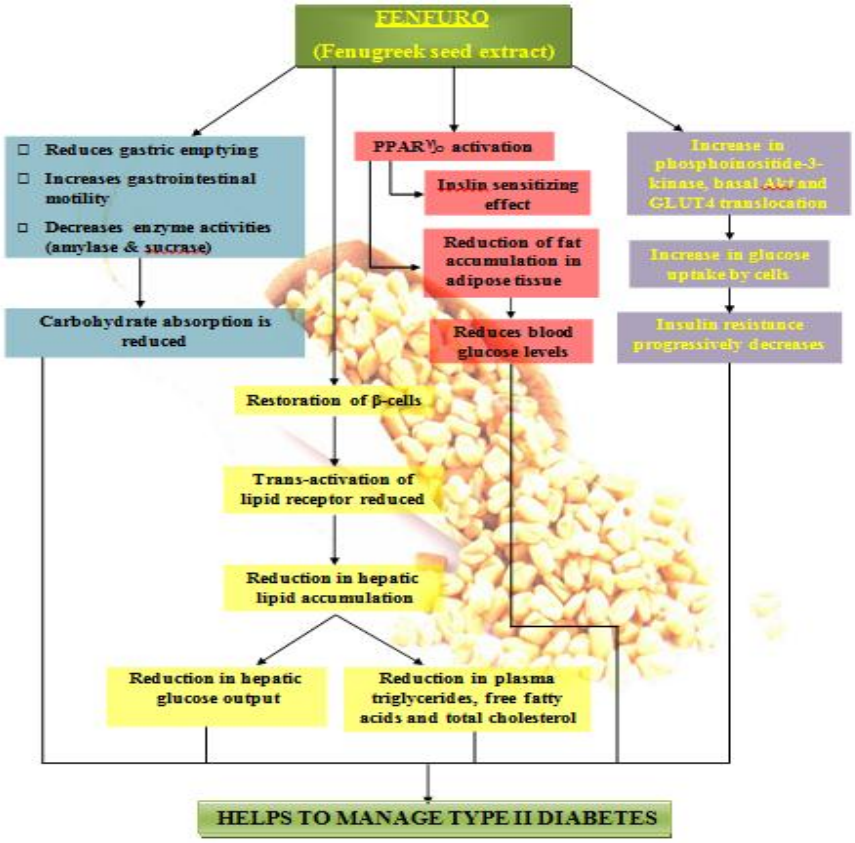
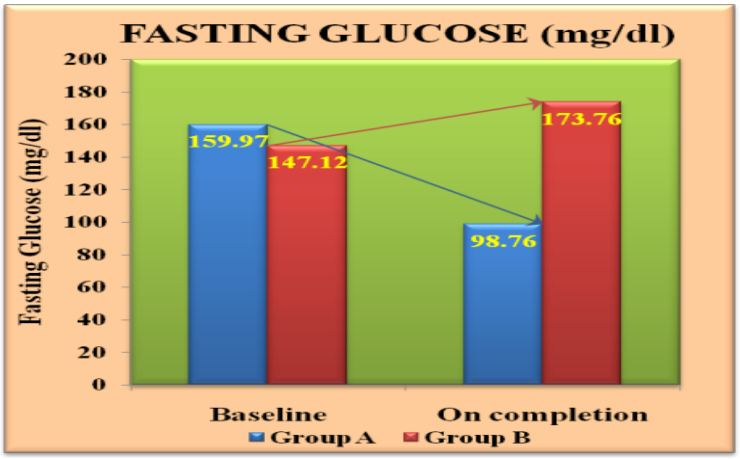


Efficacy conclusions

On completion of the study, following efficacy conclusions were made:

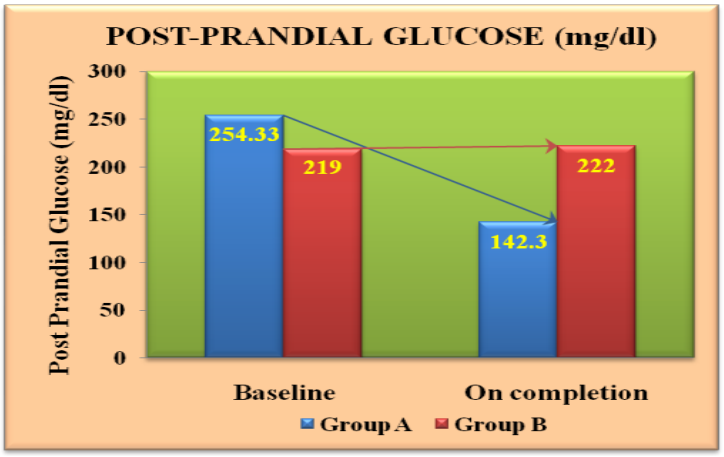
- **Fasting glucose:** The mean fasting glucose levels were significantly decreased in FENFURO-treated patients, whereas these levels increased in on-going anti-diabetic therapy-treated patients.

FENFURO caused 38.26% decrease in fasting glucose levels on completion of the treatment. Such decrease in fasting glucose levels was observed in 95.2% of the study population on completion of the treatment with FENFURO.



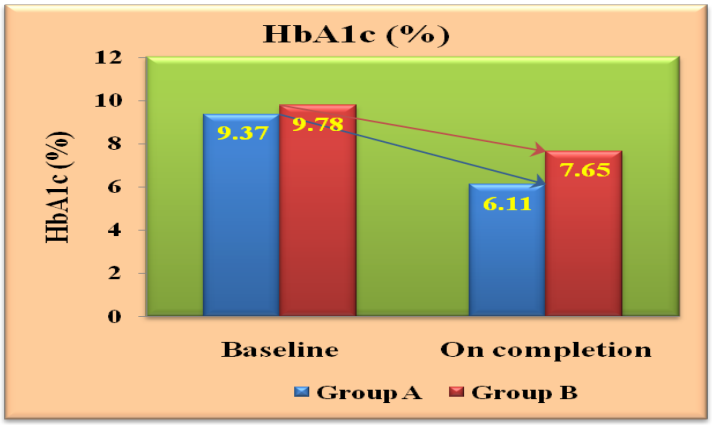
- **Post-prandial (PP) glucose:** FENFURO caused significant decrease in PP glucose levels on completion of the treatment as compared to the on- going anti-diabetic therapy-treated population. The decrease in mean PP glucose levels were up to 44.04% in the FENFURO-treated study population on completion of the treatment.

As observed on completion of the treatment with FENFURO, 88.10% of study population shown to have decrease in PP glucose levels.



- **Glycated hemoglobin (HbA1c):** FENFURO treatment resulted in normalizing the mean HbA1c levels of the study population. The HbA1c levels decreased significantly in the study population of both groups on completion of the treatment. Mean HbA1c levels decreased up to 34.70% in FENFURO-treated group whereas on-going anti- diabetic therapy caused 21.51% decrease in HbA1c levels.

These HbA1c levels came to normal range (Good control range - 4.5-6.3%) in FENFURO-treated study population whereas they were still abnormal (Poor control levels – 7.6%) in on-going anti-diabetic therapy treated population till 12 weeks of treatment.



SAFETY CONCLUSIONS

On completion of the study, following safety conclusions were made:

- No significant change in the liver function tests (serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphates activities and serum bilirubin levels) was observed on completion of the treatment.
- No significant change in the serum urea levels and creatinine levels was observed on completion of the treatment.
- No significant change in the hematological parameters was observed on completion of the treatment.

1. INSTITUTIONAL ETHICS COMMITTEE (IEC) APPROVAL

The present study was duly approved by ethics committee named as Institution Ethics Committee situated at Gian Sagar Medical College, Village Ram Nagar, Rajpura, Patiala.

No. PHMA/GSMCH-15/IEC-35 Dated 23rd November, 2015

Institution Ethics Committee,
Gian Sagar Medical College,
Village Ram Nagar, Rajpura, Patiala (Punjab)

23rd November, 2015

Dr. R S Gupta
Professor and Head,
Department of Medicine
Gian Sagar Medical College and Hospital,
Ram Nagar, Rajpura, Patiala,
Punjab.

Ref: Protocol CR-FEN/PREDIA/02/15 "Clinical Evalauation of Fenfuro (Fenugreek Seed Extract) in Type-2 Diabetic Subjects – An Add-on Study"

Subject: Ethics Committee Approval for the above referenced study

Dear Dr. Gupta,

The following documents were reviewed by the **Institutional Ethics Committee** in its meeting dated 23rd November, 2015 at (11:00) hours

[illegible] conducted a scientific and ethical review of the study and hereby grants you permission to conduct the clinical study. This approval is valid for a period of one year as per the IEC norms.

Sr.No.	Documents
1	Clinical Study Protocol
2	Case Record Form
3	Patient Information Sheet and Informed Consent Form in English
4	Patient Information Sheet and Informed Consent Form in Punjabi
5	Patient Information Sheet and Informed Consent Form in Hindi
6	Investigator Brochure
7	FSSAI Approval
8	Insurance Statement
9	Certificate of Analysis
10	Sponsor Declaration and Approval
11	Toxicity Report

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Institution Ethics Committee,
Gian Sagar Medical College,
Village Ram Nagar, Rajpura, Patiala (Punjab)

The following members attended the ethics committee meeting for the review of this clinical study. This satisfies the quorum necessary for such meetings of this ethics committee.

Sr. No.	Name and Gender	Affiliation/Designation within EC
1	Dr. Balbir Kaur (F)	Chairperson
2	Dr. Vinod Kapoor (M)	Member
3	Dr. A S Grover (M)	Member
4	Dr. Harbir K Rao (F)	Member
5	Prof. Pritam Kaur (F)	Member
6	Dr. Amandeep Singh (M)	Member
7	Ms. Kamaljit Kaur (F)	Member, Social Worker
8	Ms. Natasha Chopra (F)	Member, Lay Person
9	Mr. B S Sodhi (M)	Member, Legal Representative
10	Dr. Prithpal S Matreja (M)	Member Secretary, Basic Medical Scientist

The study was approved with 8 votes in favour of the study. We confirm that you did not participate in the deliberations of the ethics committee for this study and did not vote on the proposal for this study.

Please note that you are required to follow the requirements given below for this study:

- Do not implement any deviation from, or change to, the protocol approved by this ethics committee without the prior written approval of this ethics committee. Deviations/ changes to the approved protocol may be implemented without prior approval of this ethics committee only when necessary to eliminate immediate hazards to subjects or when changes involve only logistical or administrative aspects of the trial [e.g. change of study monitor(s), telephone numbers(s)].
- You are to submit a 6-monthly report to IEC on the progress of the Study

Promptly report to this ethics committee:

- Any changes to or deviations to the protocol approved by this ethics committee that you may implement to eliminate hazards to the trial subjects.
- All serious adverse events.
- New information that may affect adversely the safety of the subjects or the conduct of the trial.

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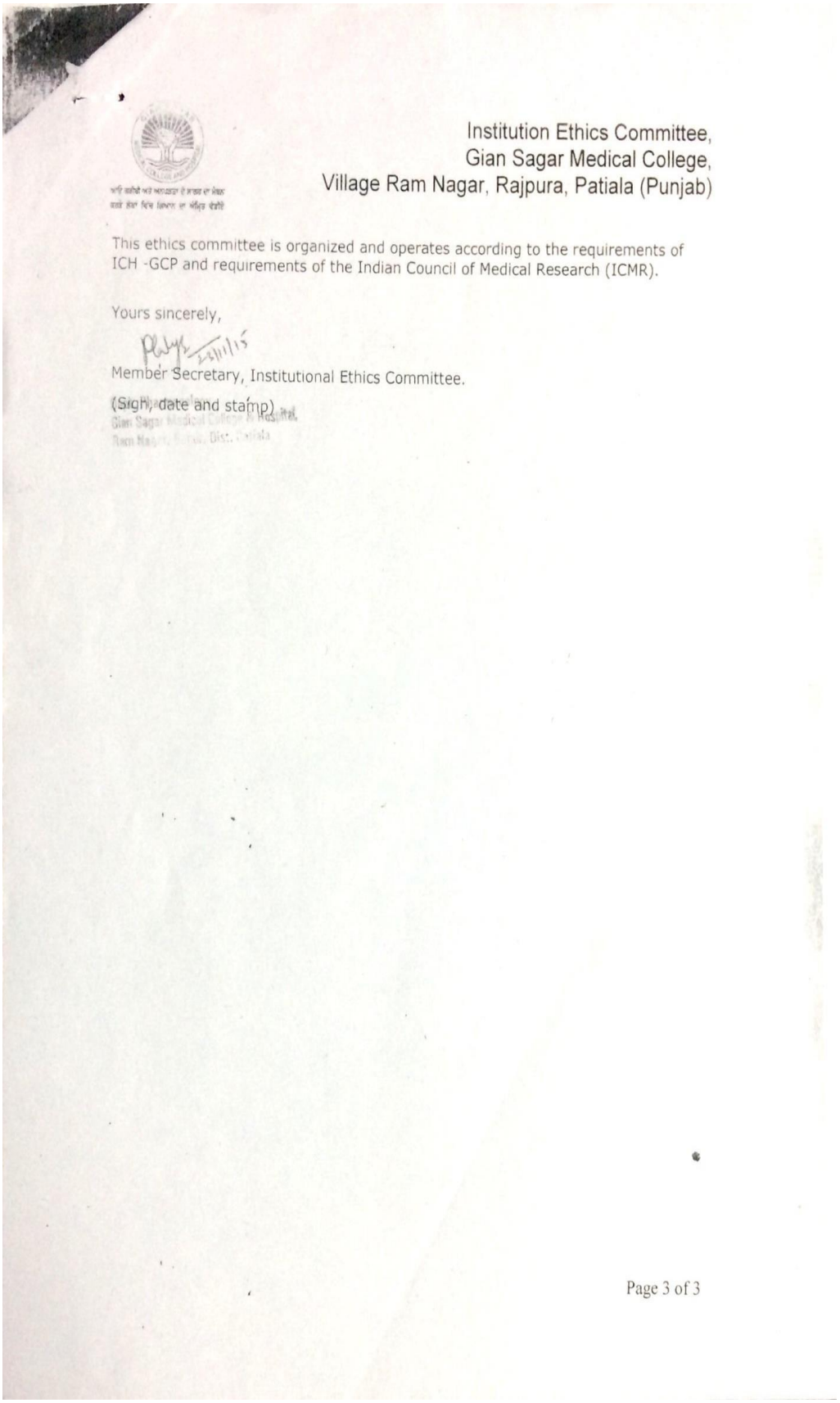

Institution Ethics Committee,
Gian Sagar Medical College,
Village Ram Nagar, Rajpura, Patiala (Punjab)

This ethics committee is organized and operates according to the requirements of ICH -GCP and requirements of the Indian Council of Medical Research (ICMR).

Yours sincerely,

23/11/15

Member Secretary, Institutional Ethics Committee.

(Sign, date and stamp)

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DCGI approval of Ethics Committee

File No. ECR/856/Gian/Inst/PB/2013

From:

Office of Drugs Controller General (India)
Directorate General of Health Services

FDA Bhawan, Kotla Road,
New Delhi – 110 002, India
Dated: 09/05/2014

To,

The Chairman,
Ethics Committee,
Gian Sagar Medical College & Hospital,
Department of Pharmacology, Village Ram Nagar,
Tehsil Rajpura, Patiala 140601, Punjab, India.

SUB: - Ethics Committee Registration No.ECR/572/Inst/PB/2014 issued under Rule 122DD of the Drugs & Cosmetics Rules1945.

Sir/Madam,

Please refer to your application no. Nil dated Nil submitted to this office for the Registration of Ethics Committee.

Based on the documents submitted by you, this office hereby Registers the **ETHICS COMMITTEE, GIAN SAGAR MEDICAL COLLEGE & HOSPITAL** situated at **DEPARTMENT OF PHARMACOLOGY, VILLAGE RAM NAGAR, TEHSIL RAJPURA, PATIALA 140601, PUNJAB, INDIA** with Registration number **ECR/572/Inst/PB/2014** as per the provisions of Rule 122DD of the Drugs and Cosmetics Rules, 1945 subject to the following conditions:

1. This Registration is subject to the conditions specified under Rule 122DD and Appendix VIII of Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945.
2. The Ethics Committee shall review and accord its approval to a clinical trial at appropriate intervals as specified in Schedule Y and the Good Clinical Practice Guidelines for Clinical Trials in India and other applicable regulatory requirements for safeguarding the rights, safety and well-being of the trial subjects.
3. In the case of any serious adverse event occurring to the clinical trial subjects during the clinical trial, the Ethics Committee shall analyze and forward its opinion as per procedures specified under APPENDIX XII of Schedule Y.
4. The Ethics Committee shall allow inspectors or officials authorized by the Central Drugs Standard Control Organization to enter its premises to inspect any record, data or any document related to clinical trial and provide adequate replies to any query raised by such inspectors or officials, as the case may be, in relation to the conduct of clinical trial.
5. The licensing authority shall be informed in writing in case of any change in the membership or the constitution of the ethics committee takes place.
6. All the records of the ethics committee shall be safely maintained after the completion or termination of the study for not less than five years from the date of completion or termination of the trial (Both in hard and soft copies).

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File No. ECR/856/Gian/Inst/PB/2013

7. If the Ethics Committee fails to comply with any of the conditions of registration, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, suspend or cancel the registration of the Ethics Committee for such period as considered necessary.

8. This registration shall be in force for a period of three years from the date of issue, unless it is sooner suspended or cancelled.

9. Ethics Committee shall consist of not less than seven members and is subject to a maximum of 15. One among its members, who is from outside the institute, shall be appointed as chairman, one member as a Member Secretary and rest of the members shall be from Medical, Scientific, Non-Medical and Non-scientific fields including lay public.

10. The committee shall include at least one member whose primary area of interest or specialization is Non-scientific and at least one member who is independent of the institution besides; there should be appropriate gender representation on the Ethics Committee.

11. The Ethics committee can have as its members, individuals from other Institutions or Communities, if required.

12. Members should be conversant with the provisions of clinical trials under this Schedule, Good Clinical Practice Guidelines for clinical trials in India and other regulatory requirements to safeguard the rights, safety and well-being of the trial subjects.

13. For review of each protocol the quorum of Ethics Committee shall be at least five members with the following representations:

    I. Basic medical scientist (preferably one pharmacologist)
    II. Clinician
    III. Legal expert
    IV. Social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person.
    V. Lay person from community

14. The members representing medical scientist and clinicians should have Post graduate qualification and adequate experience in their respective fields and aware of their role and responsibilities as committee members.
15. As far as possible, based on the requirement of research area such as HIV, Genetic disorder, etc., specific patient group may also be represented in the Ethics Committee.
16. There should be no conflict of interest. The members shall voluntarily withdraw from the Ethics Committee meeting while making a decision on an application which evokes a conflict of interest which may be indicated in writing to the Chairman prior to the review and be recorded so in the minutes. All members shall sign a declaration on conflict of interest.
17. Subject experts or other experts may be invited to the meetings for their advice. But no such expert shall have voting rights.
18. This certificate is issued to you on the basis of declaration/submission by you that yours is an Institution and registration is sought for Institutional Ethics Committee.

9/5/2014

(A. Visala)
Deputy Drugs Controller (I) & Licensing Authority

A. Visala
Deputy Drugs Controller (I)
Dte. General of Health Services
Central Drugs Standard Control Organisation
FDA Bhawan, Kotla Road, New Delhi-110002

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- **Ethical conduct of the study**

The study was performed in compliance and accordance with ICH guidelines for Good Clinical Practices (GCP), including the archiving of essential documents as per International Ethical Standards guaranteed by the Declaration of Helsinki and its subsequent amendments. Patient confidentiality was maintained throughout the study.

- **Patient information and consent**

All subjects for the study were provided a consent form and provided sufficient information for subjects to make an informed decision about their participation in this study. This consent form was submitted with the protocol for review and approval by IEC for the study. The formal consent of the subjects was obtained before the subject is submitted to any study procedure using the IEC-approved consent form. Consent form was signed by the subject or legally accepted representative and the investigator- designated research professional obtained the consent.

2. INTRODUCTION

Type II diabetes is a fast spreading metabolic disease worldwide. It has been known to affect 415 million people from which 193 million people are known to have undiagnosed diabetes. From all the patients diagnosed with diabetes, 90% are those affected specifically with type 2 diabetes. Thus, type I diabetes is found to affect only 10% patients.[1]

Diabetes is the outcome of unbalanced sugar levels in the blood. The blood sugar is unbalanced only under two situations *i.e.* either the insulin production is limited by the β-cells of pancreas or the cells of the body become unable to detect insulin to use it to convert blood sugar into energy. In both cases, sugar present in blood becomes unable to enter the cells resulting in raised blood sugar levels. Type II diabetes originates in those cases, when cells become unable to respond to insulin properly, which is known as ‘insulin resistance’. This happens because the insulin binds to its receptor normally, but the signal is not sent into the cell and the cells do not take up glucose. This causes rise in blood sugar levels. There are many risk factors for causing insulin resistance inside body which contributes in development as well as progression of type II diabetes such as[2][3],

- Obesity.
- Dyslipidemia.
- Oxidative stress.
- Non-alcoholic fatty liver disease.

- Stress.
- Genetical and lifestyle factors.
- Sleep apnea.
- Smoking.
- Overweight and many more.

Insulin resistance is responsible for developing type II diabetes which further gives rise to many complications, ranging from microvascular to macrovascular complications. It has been observed that type I diabetes is associated with much lesser complications than type II diabetes. The microvascular complications associated with type II diabetes include nephropathy, retinopathy, neuropathy, etc and macrovascular complications include renal diseases, cardiac diseases, cerebrovascular diseases, peripheral vascular diseases, etc.[4]

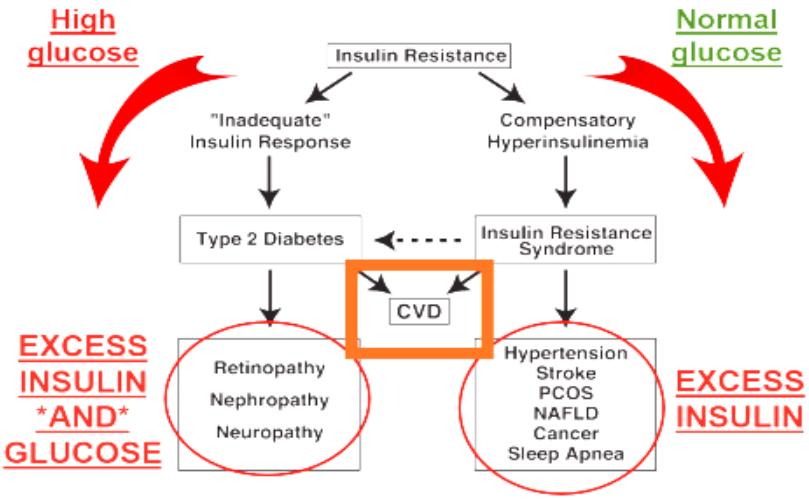


Fig 1: Effect of insulin resistance during diabetes.

Development of these complications with diabetes weakens the body to much higher extent. These complications also interfere with the treatment of diabetes. The number of people with diabetic complications is increasing day-by-day. According to the year 2013 data, 381.8 million adults from 219 countries were suffering from type II diabetes and there are estimates that this number will raise to 591.9 million adults till 2035. The lifestyle choices of diabetic patients and complications interfering in the treatment of diabetes are major reasons behind this prevalence. It has been observed that countries with large number of adult population are associated with high number of people with diabetes. Among this list, India is on 2nd number with 65.1 million people with diabetes (among top 10 countries most prevalent with diabetes).[5]

Table 1: Top 10 countries with prevalence of diabetes (20-79 years), Year 2013 and 2035[5]

2013		2035	
Country	**Prevalence (Millions)**	**Country**	**Prevalence (Millions)**
China	98.4	China	142.7
India	65.1	India	109
USA	24.4	USA	29.7
Brazil	11.9	Brazil	19.2
Russian Federation	10.9	Mexico	15.7
Mexico	8.7	Indonesia	14.1
Indonesia	8.5	Egypt	13.1
Germany	7.6	Pakistan	12.8
Egypt	7.5	Turkey	11.8
Japan	7.2	Russian Federation	11.1

This evidence shows that diabetes continues to be a large and increasing global health burden and is likely to continually grow substantially in the next decades. Thus, effective treatments are required which could solely trigger type II diabetes. As it has been told that lifestyle factors play a major role in developing type II diabetes, thus, well-planned and effective lifestyle choices are recommended by doctors to prevent the development and minimise the progression of diabetes. It has been suggested that diets rich in whole grains, fruits, vegetables, legumes, nuts, and lower in refined grains, red/processed meats and sugar-sweetened beverages have demonstrated to reduce diabetes risk and improve glycemic control and blood lipid levels in patients with diabetes.[6]

Beside lifestyle changes, medications are prescribed by doctor to slow down or treat the progression of type II diabetes. There are a large number of medications available for managing type II diabetes but the disease still develops in the population of every age group and every region of the world. It has been observed that these medications never cure diabetes but may slow down its development. The reason behind this might be the incomplete effectiveness of the medications. Recent clinical trials have provided important information regarding approaches to prevent and treat type II diabetes as well as some of the adverse effects of these interventions. A number of new treatment approaches have been developed, but more effective therapies that target insulin resistance are needed.[2]

Investigational product - FENFURO

Numerous herbs are reported to possess anti-diabetic activity but a significant amount of research and traditional usage suggest that Fenugreek seeds are among the best in terms of safety and efficacy. The anti-diabetic action of Fenugreek is known to be mediated by improving insulin sensitivity and decreasing insulin resistance along with reduced glucose absorption.[7]

FENFURO™ is a natural product developed innovatively from Fenugreek seed extract. It contains many bioactive components from Fenugreek which help to lower the blood glucose levels. FENFURO contains furostanolic saponins from the seeds of fenugreek which exerts hypoglycaemic effect in type II diabetic patients. It has been suggested that saponins and fiber component (32% insoluble & 13% soluble) present in fenugreek seeds help to lower blood sugar levels. These bioactive components of fenugreek seeds delay the gastric emptying and cause the inhibition of glucose transport (by inhibiting lipid and carbohydrate-hydrolyzing enzymes).

Fenugreek seeds are reported to affect insulin resistance. It has been observed in animal studies that bioactive components of fenugreek seeds increase the sensitivity of tissues to available insulin by increasing insulin receptor sites. Increase in insulin receptor sites helps to send the signals from insulin to the tissues more effectively making the tissues sensitive to the insulin levels. Thereby, more glucose starts to enter the tissues from blood to be converted to energy, decreasing the blood glucose levels.[8]

All these mechanisms might be responsible for the anti-diabetic action of FENFURO. Such anti-diabetic action has also been observed in the previous clinical as well as preclinical studies on FENFURO™.

Table 2: Preclinical & Clinical study on FENFURO™.

Preclinical studies - FENFURO™			
Study title	**Authors**	**Study design**	**Result**
Safety, efficacy and toxicological evaluation of a novel, patented anti-diabetic extract of *Trigonella Foenum-Graecum* seed extract (FENFURO)[9]	Swaroop A, Bagchi M, Kumar P, Preuss HG, Tiwari K, Marone PA and Bagchi D	Acute oral toxicity, 28- day sub-chronic toxicity and Ames' bacterial reverse mutation assay in male Sprague-Dawley rats	*In vitro* and *in vivo* safety and efficacy studies concluded that FENFURO is safe and effective in treating type 2 diabetes.

Furostanolic saponins from *Trigonella-foenum graecum* alleviate diet-induced glucose intolerance and hepatic fat accumulation[10]	Hua Y, Ren SY, Guo R, Rogers O, Nair RP, Bagchi D, Swaroop A and Nair S	Male C57BL/6J mice subjected to a normal or high-fat diet (HFD), randomly assigned to receive FENFURO™ for 24 weeks	FENFURO™ had potential effect in treating insulin resistance and related conditions.
Clinical studies - FENFURO™			
Study title	Authors	Study design	Result
A multicenter clinical study to determine the efficacy of a novel fenugreek seed (*Trigonella foenumgraecum*) extract (FENFURO™) in patients with type 2 diabetes[11]	Verma N, Usman K, Patel N, Jain A, Dhakre S, Swaroop A, Bagchi M, Kumar P, Preuss HG and Bagchi D	Multicentric, randomized, placebo-controlled, double-blind and add-on study evaluated over a period of 90 consecutive days for the efficacy of FENFURO (500 mg BD) in 154 subjects	FENFURO proved safe and efficacious in ameliorating the symptoms of type 2 diabetes in humans.

As we look at the prevalence of type II diabetes and its complications, natural treatments are opted and required by the suffering individuals. The above given preclinical and clinical studies evaluated the safety and efficacy of FENFURO in animals and humans as well.

On the basis of these studies, present clinical study has been planned to evaluate the efficacy and safety of FENFURO in human population suffering from type II diabetes.

3. AIMS AND OBJECTIVES

The aim of the study was to evaluate the effect of FENFURO in patients suffering from type 2 diabetes. This effect was evaluated by considering following given objectives:

Objectives

Primary objective

- To determine decrease in plasma glucose levels due to FENFURO in type 2 diabetic patients

Secondary objective

- To determine safety of FENFURO in type 2 diabetic patients

End Points

Primary End Points

- Change in fasting plasma sugar levels
- Change in PP sugar levels
- Change in HbA1c levels

Secondary End Points

- Change in biochemical parameters including:
- Liver function tests (SGOT, SGPT, ALP, serum bilirubin)
- Renal function tests (Urea, creatinine)
- Blood parameters (Hb, TLC, DLC)

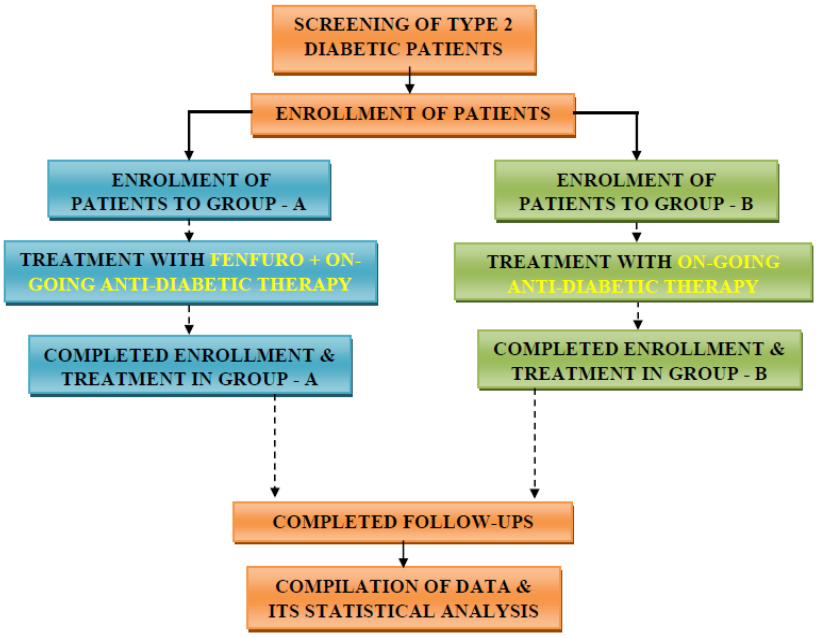
4. INVESTIGATIONAL PLAN

Overall study design

This was an open labeled and two armed study which was carried out on Indian population suffering from type 2 diabetes. The study was carried out at Gian Sagar Medical College & Hospital situated at Village Ram Nagar, Near Banur, Rajpura, Patiala - 140601.

Description

There were two groups, *i.e.* Group - A & Group - B, in this study in which 50 patients each were planned to be enrolled. Group - A with type 2 diabetes patients were planned to consume investigational product (FENFURO) along with their on-going anti-diabetic therapy. Group - B with type 2 diabetes patients were planned to be on their on-going anti-diabetic therapy only.



5. SELECTION OF STUDY POPULATION

1. Eligible age for the study participation: Between 18 to 65 years.
2. Gender eligible for study participation: Male & Female.

Inclusion Criteria

1. Agrees to written informed consent.
2. Fasting plasma glucose level <180 mg/dL.
3. HbA1c level more than 7.5%.
4. Not receiving any steroids.
5. Patient on anti-diabetic therapy.

Exclusion Criteria

1. Uncooperative Subjects
2. Diabetes other than type-2 diabetes mellitus.
3. Evidence of renal & liver disease.
4. History of any hemoglobinopathy that may affect determination of HbA1c.
5. Lactating and Pregnant or planning to conceive females.
6. Physically/ mentally unwell as certified by physician-in-charge.
7. Participation in any other clinical trial within the last 30 days.
8. Subjects with allergy to investigational product.

Stopping Rules

The criteria for the "stopping" of trial or "discontinuation criteria" was only in the case of serious adverse event (as defined in safety assessments clause).

6. TREATMENTS

Screening and treatment of the subjects

The subjects were screened for the clinical study on the basis of given inclusion and exclusion criteria. The investigational product along with on-going anti-diabetic medication was allotted to Group - A after screening & enrolment of the study subjects, where as for subjects of Group - B only on-going anti-diabetic medication was continued. The subjects were followed up after 4 weeks, 8 weeks and 12 weeks. Safety was assessed at each follow-up visit. Subjects complaining of significant symptoms following administration of investigational product were planned to be evaluated for objective parameters of adverse drug reactions. Investigational product was considered to be discontinued in case of any serious adverse drug reaction.

Investigational Product

- **Product name**

FENFURO (Fenugreek seed extract)

- **Batch no.**

FEN0615 and FEN0715.

- **Formulation**

Each capsule contained 500mg of investigational product and this investigational product was to be taken orally as BD dosage.

- **Packaging**

Each pack contained 60 capsules.

- **Storage**

The investigational product was stored at room temperature in a cool and dark place and protected from direct sunlight, as instructed.

- **Accountability procedure**

Allocation of the investigational product was done by the site staff only. Distribution of the product was maintained in the IP accountability log provided by the sponsor to the site staff. Each entry was maintained separately with the date/signature of the principal investigator & study coordinator. The person responsible for the distribution of the product was instructed to sign on the IP accountability log.

- **Concomitant medication**

All concomitant prescription medications taken during the study by the participants were recorded on the case report forms (CRFs). Reported medications included concomitant prescription medications, over-the-counter medications (OTC) and non-prescription medications taken at the time of adverse events (all grades) too.

- **Selection of dose in the study**

500 mg of investigational product capsules were decided to be given to the subjects of Group A in the form of BD dosage. This dose was chosen on the basis of toxicity study in animals as well as previous clinical studies on humans. Those studies proved the safety of this dose (500 mg, BD) in animals and humans. Investigational product was proved to be effective too.

Certificate of Analysis

Product Name: (Fenfuro) Fenugreek Seed Extract	**Batch No.:** FEN0615
Manufacturing Date: JUN.2015	**Quantity:** 100 packs x 60 capsules
Best before: MAY.2018	**Country of Origin:** India

TEST	SPECIFICATION	RESULT	METHOD
Physical Parameters			
Appearance	Transparent cellulose capsule body containing yellowish brown powder	Complies	Visual
Average weight	600 ± 7.5%	617.27 mg	USP 37
Uniformity of weight	500 ± 7.5%	520.19 mg	USP 37
Disintegration test	All capsules should disintegrate within 30 minutes	All capsules disintegrate in 6.5 min.	USP 37
Loss on drying (LOD)	NMT 5.0 %	3.9 %	USP 37
Impurities			
Heavy Metals (By AAS):	NMT 20 ppm		USP 37
a) Lead (as Pb)		0.456 ppm	
b) Cadmium (as Cd)		0.07 ppm	
c) Arsenic (as As)		Not detected	
d) Mercury (as Hg)		Not detected	
Microbiological Test:			USP 37
a) Total bacterial count	NMT 1000 cfu/g	200 cfu/g	
b) Total fungal count	NMT 100 cfu/g	Absent	
c) E.coli	Absent/g	Absent	
d) Salmonella sp.	Absent/g	Absent	
e) S. aureus	Absent/g	Absent	
f) Coliform	Absent/g	Absent	

Remarks: The above analysis results comply with the specification.

Analyzed By Satish Kumar (Sr. Exe. QC)

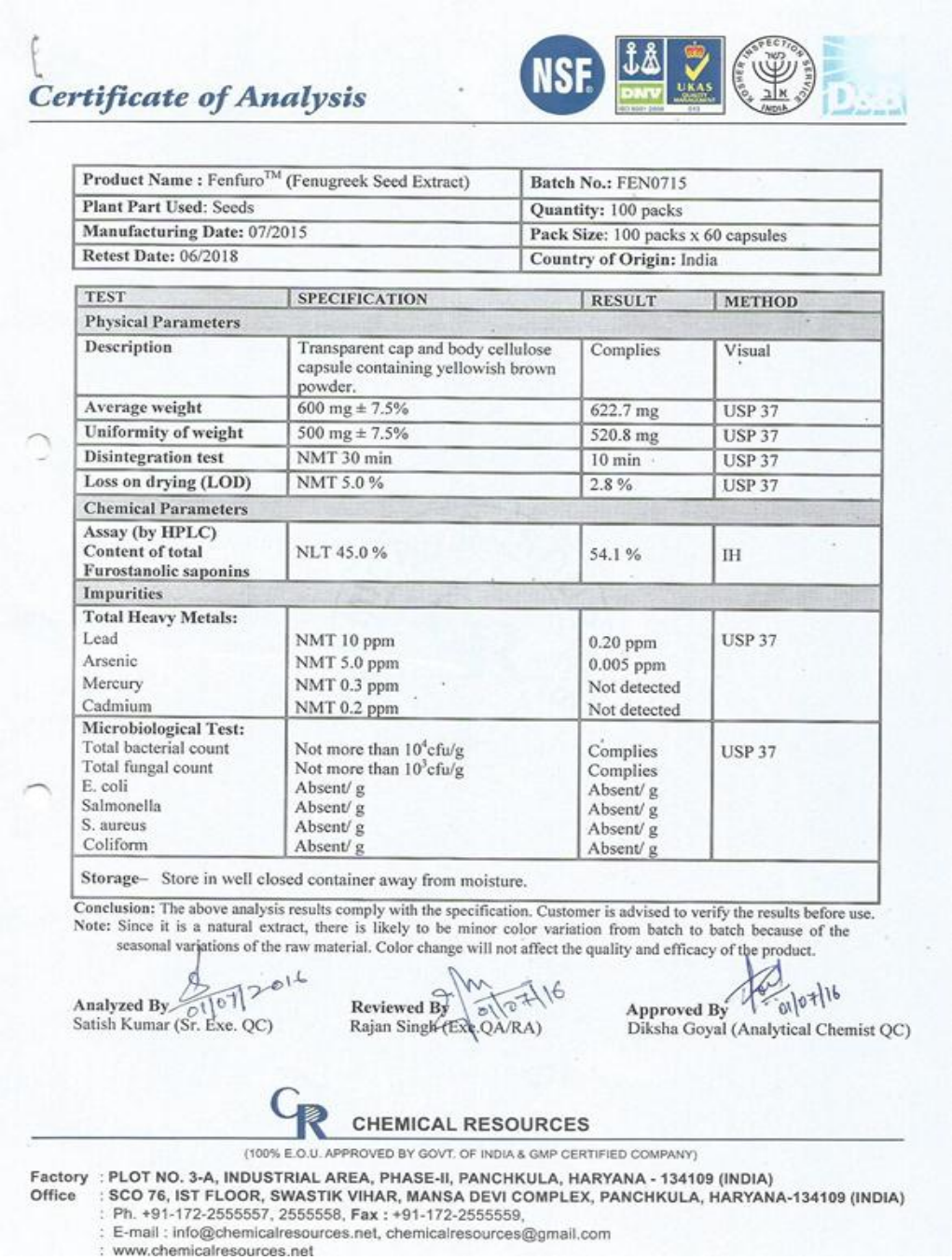
Reviewed By Rajan Singh (Asst. Exe.QA/RA)

Approved By Kiran Tiwari (Head R & D)

CHEMICAL RESOURCES

(100% E.O.U. APPROVED BY GOVT. OF INDIA & GMP CERTIFIED COMPANY)

Factory : PLOT NO. 3-A, INDUSTRIAL AREA, PHASE-II, PANCHKULA, HARYANA - 134109 (INDIA)
Office : SCO 76, IST FLOOR, SWASTIK VIHAR, MANSA DEVI COMPLEX, PANCHKULA, HARYANA-134109 (INDIA)
: Ph. +91-172-2555557, 2555558, Fax : +91-172-2555559,
: E-mail : info@chemicalresources.net, chemicalresources@gmail.com
: www.chemicalresources.net



Certificate of Analysis

Product Name : Fenfuro™ (Fenugreek Seed Extract)	**Batch No.:** FEN0715
Plant Part Used: Seeds	**Quantity:** 100 packs
Manufacturing Date: 07/2015	**Pack Size:** 100 packs x 60 capsules
Retest Date: 06/2018	**Country of Origin:** India

TEST	SPECIFICATION	RESULT	METHOD
Physical Parameters			
Description	Transparent cap and body cellulose capsule containing yellowish brown powder.	Complies	Visual
Average weight	600 mg ± 7.5%	622.7 mg	USP 37
Uniformity of weight	500 mg ± 7.5%	520.8 mg	USP 37
Disintegration test	NMT 30 min	10 min	USP 37
Loss on drying (LOD)	NMT 5.0 %	2.8 %	USP 37
Chemical Parameters			
Assay (by HPLC) Content of total Furostanolic saponins	NLT 45.0 %	54.1 %	IH
Impurities			
Total Heavy Metals: Lead Arsenic Mercury Cadmium	 NMT 10 ppm NMT 5.0 ppm NMT 0.3 ppm NMT 0.2 ppm	 0.20 ppm 0.005 ppm Not detected Not detected	USP 37
Microbiological Test: Total bacterial count Total fungal count E. coli Salmonella S. aureus Coliform	 Not more than 10^4cfu/g Not more than 10^3cfu/g Absent/ g Absent/ g Absent/ g Absent/ g	 Complies Complies Absent/ g Absent/ g Absent/ g Absent/ g	USP 37
Storage– Store in well closed container away from moisture.			

Conclusion: The above analysis results comply with the specification. Customer is advised to verify the results before use.
Note: Since it is a natural extract, there is likely to be minor color variation from batch to batch because of the seasonal variations of the raw material. Color change will not affect the quality and efficacy of the product.

Analyzed By 01/07/2016
Satish Kumar (Sr. Exe. QC)

Reviewed By 01/07/16
Rajan Singh (Exe.QA/RA)

Approved By 01/07/16
Diksha Goyal (Analytical Chemist QC)

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7. Statistical Method Planned in The Protocol And Determination of Sample Size

- **Sample size**

Total number of planned patients for the study was 100 (50 patients in each arm).

- **Statistical methods**

Data was decided to be described as mean ± standard deviation. Appropriate statistical tests such as t-test and chi-square test were to be done to evaluate efficacy and safety of FENFURO in type 2 diabetic patients.

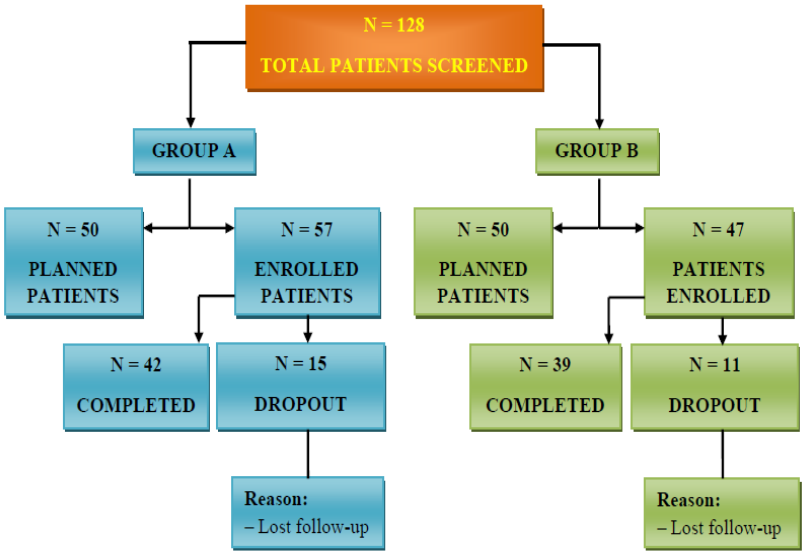
- **Subject population(s) for analysis**

All population was used for whole study-related analyses. For the purposes of this study, all population is defined as subjects who participate in the study.

8. Study Patients

Disposition of patients

The complete account of the number of patients entered in the study in each arm and their participation as well as withdrawal has been provided in the below given flow chart:



9. Efficacy Evaluation

The efficacy of investigational product (FENFURO) in type 2 diabetes patients was evaluated by the laboratory investigations. The following investigations were done at baseline and at the end of the study (12 weeks):

- Blood pressure
- Body weight
- BMI
- Waist circumference
- Fasting glucose
- Post-prandial (PP) glucose
- HbA1c
- C-peptide levels
- TSH

10. Safety Evaluation

Safety of the investigational product of the enrolled subjects was evaluated by following laboratory investigations during baseline and final follow-up (12 weeks):

- Urea
- Creatinine
- Serum bilirubin
- Haemoglobin (Hb)
- Total Leukocyte count (TLC)
- Differential Leukocyte Count (DLC)
- Serum Glutamic Oxaloacetic Transaminase (SGOT)
- Serum Glutamic-Pyruvic Transaminase (SGPT)
- Serum Alkaline Phosphatase (ALP)

Assessment of Safety

Safety of patients consuming investigational product was assessed whenever the patient visited the clinical study site. At each follow-up visit, the safety was assessed by checking physical signs of any adverse drug reaction. At baseline and last follow-up visit, the safety was assessed by laboratory investigations also as described above. Investigational product was planned to be discontinued in case of any serious adverse reaction followed by management of patient according to the clinical condition.

Definitions

Adverse Reaction

According to WHO technical report no 498 (1972) "a response to a drug which is noxious and unintended, and which occurs at normal doses normally used in man for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function"

According to ICH Guideline E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), "All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions"

Adverse Events / Adverse Experience

Any untoward medical occurrence that may present during the clinical study with the product at the same time does not necessarily have a causal relationship with this treatment.

According to ICH Guideline E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment"

Serious Adverse Event or Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is life-threatening
- Congenital anomaly/birth defect.

Reporting of Adverse Events

At the time of screening of subjects any clinical abnormality should be noted as All Ready Exist (ARE) condition in the CRF's. The adverse event will be considered only if it matches the above defined criteria or any new clinical finding in the subjects or abnormal laboratory values, not to ARE conditions.

All the adverse events should be reported as mentioned in the schedule Y of the drug and cosmetics act and rules 1940.

Reporting to the Sponsor

All the serious adverse events will be reported by the principal investigator to the sponsor via phone call within 24 hours and details of clinical findings at the time of SAE's will be sent to the sponsor via fax or email within 24 hours.

Reporting to the Ethics Committee (EC)

All the serious adverse events will be reported by the principal investigator to the EC within 7 working Days.

Ethical Justification

There was no additional financial burden on the study participants as the cost of the study and procedures will be borne by the sponsor. In case of development of untoward medical

incident related to the investigational product, the investigators and the sponsor will take responsibility for the management.

11. Results

Demographic parameters

There were two groups in the study population *i.e.* Group A & Group B. Group A contained those patients with type II diabetes who were treated with investigational product-FENFURO along with their on-going anti-diabetic therapy and Group B contained those patients of type II diabetes who were treated only with their on-going anti-diabetic therapy. Both the groups contained both male and female patients of type II diabetes.

Age-wise distribution

In FENFURO-treated group, average age of the study population was 52.45 years, with minimum age of 28 years and maximum age of 64 years. In on-going anti-diabetic therapy-treated group, average age of the study population was 50.69 years with minimum age of 28 years and maximum age of 65 years.

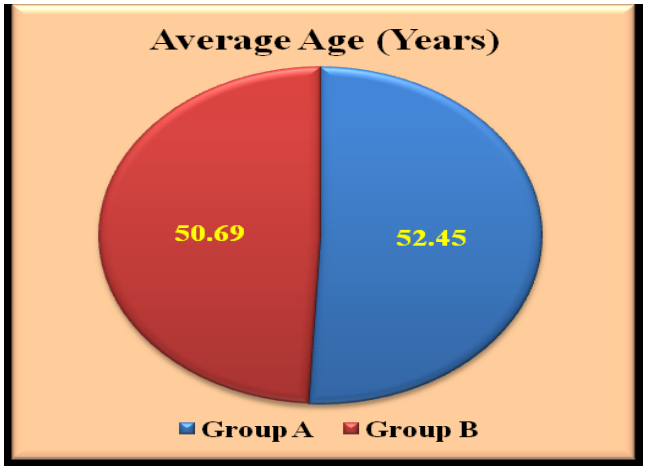


Fig 2: Age-wise distribution of study population.

Gender-wise distribution

In FENFURO-treated group, 50% patients were male and 50% patients were females whereas in on-going anti-diabetic therapy-treated group, 43.6% patients were male and 56.4% patients were females. From the complete study population, there were 46.9% male and 53.1% patients were females.

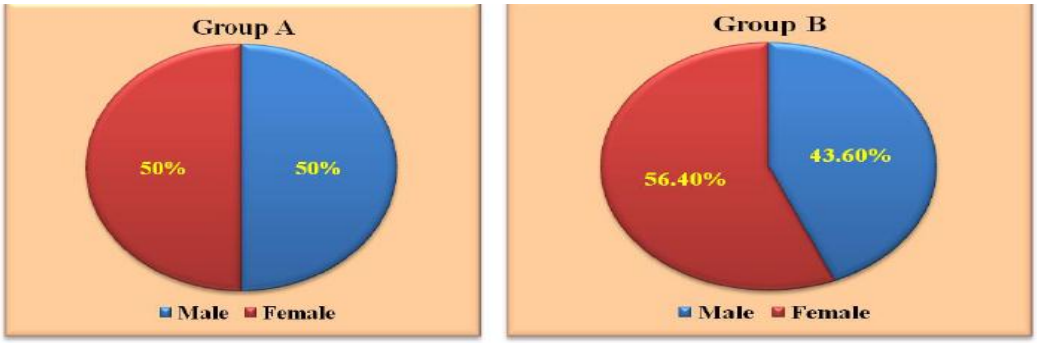


Fig 3: Gender-wise distribution of study population.

Height

In FENFURO-treated group, average height of the study population was 161.86cm, with minimum height of 146cm and maximum height of 187cm. In on-going anti-diabetic therapy-treated group, average height of the study population was 163.74cm with minimum height of 151cm and maximum height of 178cm.

Pulse

In FENFURO-treated group, average pulse rate of the study population was 81.71 per minute with minimum pulse rate of 74 per minute and maximum pulse rate of 90 per minute. In on-going anti-diabetic therapy-treated group, average pulse rate of the study population was 73.16 per minute with minimum pulse rate of 53 per minute and maximum pulse rate of 118 per minute.

Table 3: Demographic data of study population.

Parameter		Group A	Group B	Total
Age (years)	Mean	52.45	50.69	51.60
	Minimum	28	28	28
	Maximum	64	65	65
Height (cm)	Mean	161.86	163.74	162.77
	Minimum	146.00	151.00	146.00
	Maximum	187.00	178.00	187.00
Pulse (per minute)	Mean	81.71	73.16	77.60
	Minimum	74.00	53.00	53.00
	Maximum	90.00	118.00	118.00
Gender	Male	21	17	38
		50%	43.6%	46.9%
	Female	21	22	43
		50%	56.4%	53.1%

Blood pressure

Mean systolic blood pressure of study population of Group A was 129.04 mmHg and Group B was 125.64 mmHg. Mean diastolic blood pressure of study population of Group A was 84.9 mmHg and Group B was 77.43 mmHg.

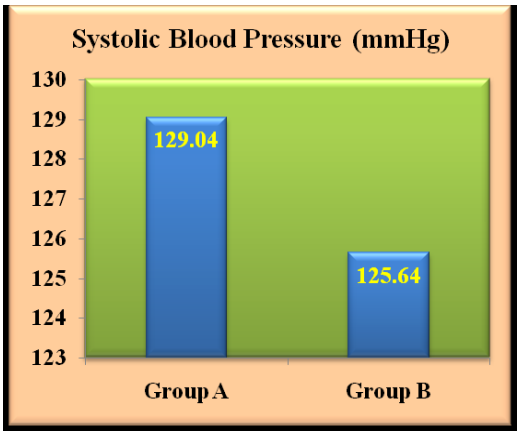


Fig 5: Mean diastolic blood pressure of study population of Group A & Group B

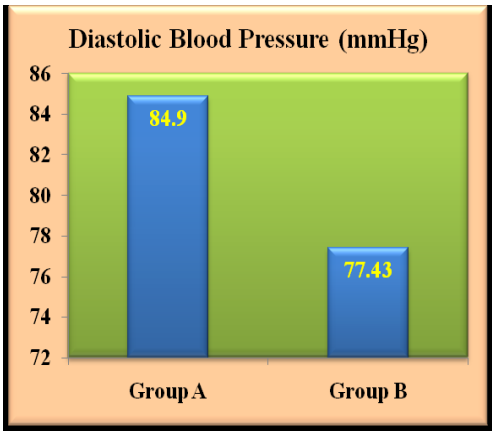


Fig 4: Mean systolic blood pressure of study population of Group A & Group B

Body weight (Kg)

No significant change was observed in the mean body weight of the study population in Group A and Group B.

Table 4: Statistical data of mean body weight of study population in Group A & B.

Body Weight (Kg)		**Mean ± Standard Deviation**	**t-value**	**p-value**
Baseline	Group A (FENFURO)	74.47 ± 12.178	0.541	0.590
	Group B (On-going anti-diabetic therapy)	73.00 ± 12.239		
Completion of treatment (12 weeks)	Group A (FENFURO)	74.18 ± 12.013	0.680	0.499
	Group B (On-going anti-diabetic therapy)	72.34 ± 12.259		

BMI (Kg/m2)

No significant change was observed in the mean body mass index (BMI) of the study population in Group A and Group B.

Table 5: Statistical data of mean BMI of study population in Group A & B.

BODY MASS INDEX (BMI) (Kg/m2)		Mean ± Standard Deviation	t-value	p-value
Baseline	Group A (FENFURO)	28.36 ± 3.796	1.583	0.117
	Group B (On-going anti-diabetic therapy)	27.08 ± 3.434		
Completion of treatment (12 weeks)	Group A (FENFURO)	28.20 ± 3.665	1.833	0.071
	Group B (On-going anti-diabetic therapy)	26.74 ± 3.435		

Waist circumference (inches)

No significant change was observed in the mean waist circumference of study population in Group A and Group B on completion of the treatment.

Table 6: Statistical data of mean waist circumference of study population in Group A & Group B.

WAIST CIRCUMFERENCE (Inches)		Mean ± Standard Deviation	t- value	p-value
Baseline	**Group A (FENFURO)**	**38.76 ± 3.656**	**3.725**	0.0001**
	Group B (On-going anti-diabetic therapy)	**46.74 ± 13.364**		
Completion of treatment (12 weeks)	**Group A (FENFURO)**	**38.09 ± 3.413**	**1.424**	0.158
	Group B (On-going anti-diabetic therapy)	40.07 ± 8.286		

A. Efficacy evaluation

- **Fasting glucose (mg/dl)**

Mean fasting glucose levels were significantly decreased (p = 0.0001*) in FENFURO-treated study population on completion of the treatment as compared to on-going anti-diabetic therapy-treated study population on completion of the treatment.

In FENFURO treated group, the mean fasting glucose levels significantly (p = 0.0001**) decreased from baseline value of 159.97 mg/dl to 98.76 mg/dl on completion of the treatment whereas in on-going anti-diabetic therapy-treated group, these levels were significantly (p = 0.023*) increased from baseline levels of 147.12 mg/dl to 173.76 g/dl on completion of the treatment.

Table 7: Statistical data of mean fasting glucose levels of study population in Group A & Group B.

FASTING GLUCOSE (mg/dl)		Mean ± Standard Deviation	t-value	p-value	
				Between Groups	Within Group
Baseline	Group A (FENFURO)	159.97 ± 21.311	2.401	0.019*	0.0001**
	Group B (On-going anti-diabetic therapy)	147.12 ± 26.719			0.023*
Completion of treatment (12 weeks)	Group A (FENFURO)	98.76 ± 23.464	6.194	0.0001*	
	Group B (On-going anti-diabetic therapy)	173.76 ± 74.534			

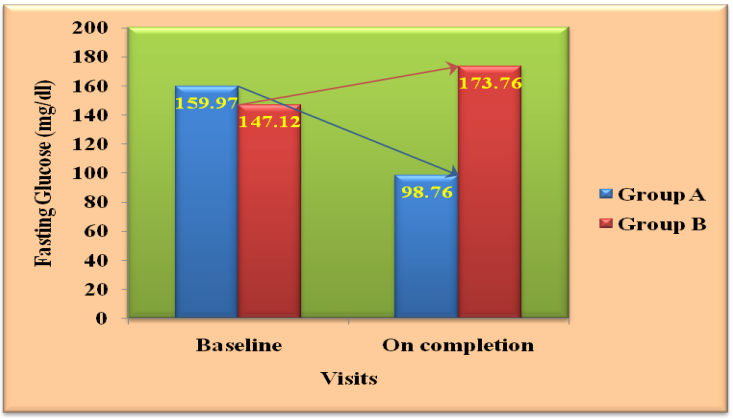


Fig 6: Mean fasting glucose levels of study population of Group A & Group B.

Percent population with change in fasting glucose levels

In FENFURO-treated group, 95.20% study population showed decrease in fasting blood glucose levels on completion of the treatment. In on-going anti-diabetic therapy-treated group, 60.50% study population showed increase in fasting blood sugar levels on completion of the treatment.

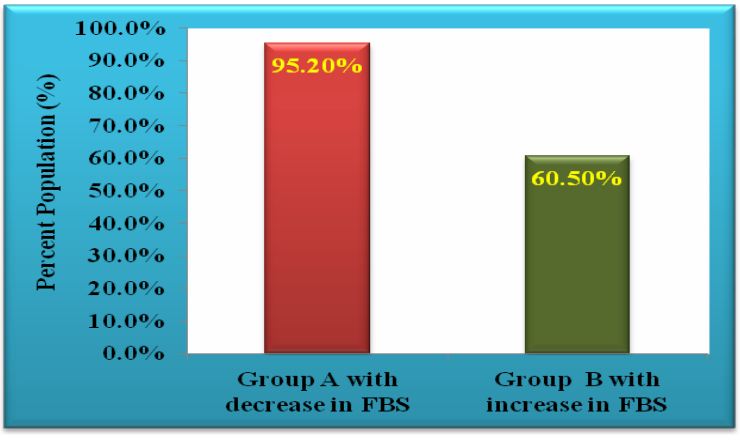


Fig 7: Percent population with change in fasting glucose levels.

In FENFURO-treated group, 38.26% decrease in fasting glucose levels was observed in study population on completion of the treatment. In the on-going anti-diabetic therapy- treated group, there was 18.6% increase in fasting glucose levels of study population on completion of the treatment.

- **Post-prandial (PP) glucose (mg/dl)**

Mean post prandial glucose levels were significantly decreased (p = 0.0001**) in FENFURO-treated group on completion of the treatment as compared to on-going anti-diabetic therapy-treated group on completion of the treatment.

In FENFURO-treated study population, the mean PP glucose levels decreased significantly (p = 0.0001**) from baseline levels of 254.33 mg/dl to 142.30 mg/dl on completion of the treatment whereas in on-going anti-diabetic therapy-treated study population, they were non-significantly (p = 0.839) increased from baseline levels of 219 mg/dl to 222 mg/dl on completion of the treatment.

Table 8: Statistical data of mean PP glucose levels of study population in Group A & Group B.

Post-Prandial Glucose (mg/dl)		Mean ± Standard Deviation	t-value	p-value	
				Between Groups	Within Group
Baseline	Group A (FENFURO)	254.33 ± 86.689	1.949	0.055	0.0001**
	Group B (On-going anti-diabetic therapy)	219 ± 75.548			0.839
Completion of treatment (12 weeks)	Group A (FENFURO)	142.30 ± 48.090	4.458	0.0001**	
	Group B (On-going anti-diabetic therapy)	222 ± 103.65			

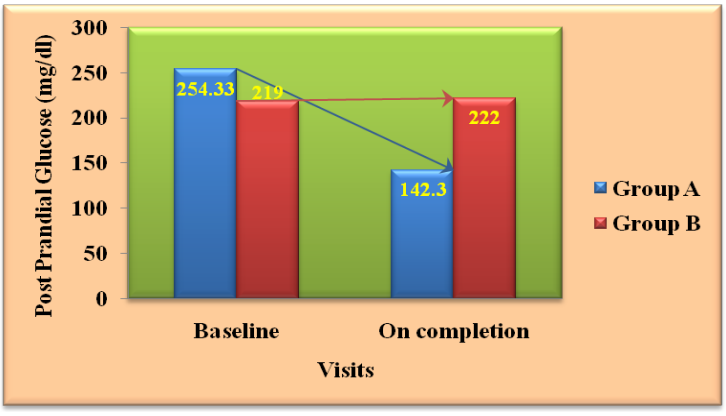


Fig 8: Mean PP glucose levels of study population of Group A & Group B

In FENFURO-treated group, 44.04% decrease in the PP glucose levels was observed in the study population on completion of the treatment whereas in on-going anti-diabetic therapy-treated group, 1.71% decrease in PP glucose levels was observed on completion of the treatment.

Percent population with change in PP glucose levels

In FENFURO-treated group, 88.10% study population showed decrease in PP glucose levels on completion of the treatment. In on-going anti-diabetic therapy-treated group, 47.40% study population showed increase in PP sugar levels on completion of the treatment.

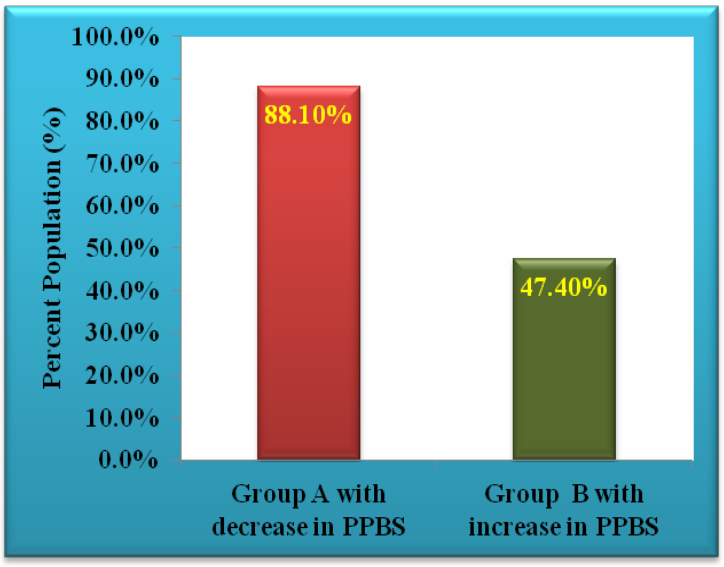


Fig 9: Percent population with change in PP glucose levels.

- **Glycated hemoglobin (HbA1c) (%)**

Mean Glycated hemoglobin levels were significantly decreased (p = 0.0001**) in FENFURO-treated group on completion of the treatment as compared to on-going anti-diabetic therapy-treated group.

The mean HbA1c levels decreased significantly (p = 0.0001**) in FENFURO-treated group from baseline levels of 9.37% to 6.11% on completion of the treatment and these levels also decreased significantly (p = 0.0001**) in on-going anti-diabetic therapy- treated group from baseline levels of 9.78% to 7.65% on completion of the treatment.

Table 9: Statistical data of mean HbA1c levels of study population in Group A and Group B.

HbA1c (%)		Mean ± Standard Deviation	t- value	p-value	
				Between Groups	Within Group
Baseline	Group A (FENFURO)	9.37 ± 1.454	1.199	0.234	0.0001**
	Group B (On-going anti-diabetic therapy)	9.78 ± 1.645			0.0001**
Completion of treatment (12 weeks)	Group A (FENFURO)	6.11 ± 1.303	3.963	0.0001**	
	Group B (On-going anti-diabetic therapy)	7.65 ± 2.096			

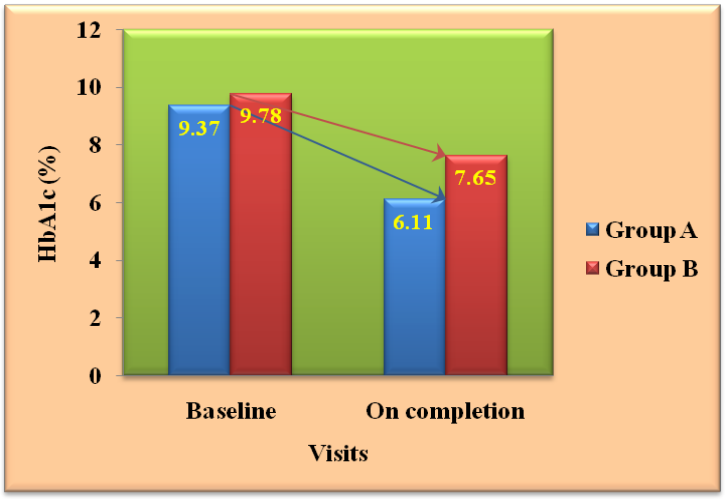


Fig 10: Mean HbA1c levels of study population of Group A & Group B Percent population with change in HbA1c levels.

Mean HbA1c levels of the FENFURO-treated group decreased in the whole study population (100%) of the group whereas they were decreased in 86.8% of the study population of on-going anti-diabetic therapy-treated group on completion of the treatment.

Mean HbA1c levels decreased up to 34.7% in FENFURO-treated group and up to 21.51% in on-going anti-diabetic therapy-treated group.

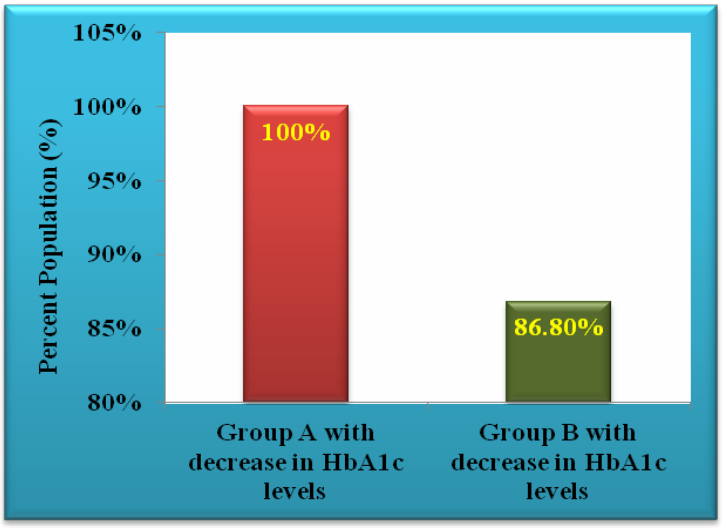


Fig 11: Percent population with change in HbA1c levels.

- **C-peptide levels (ng/ml)**

There was non-significant change in C-peptide levels of the study population of Group A & Group B on completion of the treatment.

Table 10: Statistical data of mean C-peptide levels of study population in Group A & Group B.

C-PEPTIDE (ng/ml)		Mean ± Standard Deviation	t-value	p-value
Baseline	Group A (FENFURO)	1.91 ± 2.131	4.806	0.0001**
	Group B (On-going anti-diabetic therapy)	3.89 ± 1.491		
Completion of treatment (12 weeks)	Group A (FENFURO)	1.8 ± 1.554	1.467	0.146
	Group B (On-going anti-diabetic therapy)	2.34 ± 1.766		

- **Thyroid stimulating hormone (TSH) levels (□IU/ml)**

There was non-significant change observed in the mean TSH levels of the study population of both Group A & Group B on completion of treatment.

Table 11: Statistical data of mean TSH levels of study population in Group A and Group B.

THYROID STIMULATING HORMONE (TSH) (□IU/ml)		Mean ± Standard Deviation	t-value	p-value
Baseline	Group A (FENFURO)	2.70 ± 1.872	1.328	0.188
	Group B (On-going anti-diabetic therapy)	9.17 ± 31.509		
Completion of treatment (12 weeks)	Group A (FENFURO)	4.23 ± 5.298	0.402	0.688
	Group B (On-going anti-diabetic therapy)	5.02 ± 11.373		

Efficacy conclusions

On completion of the study, following efficacy conclusions were made:

- **Fasting glucose:** The mean fasting glucose levels were significantly decreased in FENFURO-treated patients whereas these levels increased in on-going anti-diabetic therapy-treated patients.

FENFURO caused 38.26% decrease in fasting glucose levels on completion of the treatment. Such decrease in fasting glucose levels was observed in 95.2% of the study population on completion of the treatment with FENFURO.

- **Post-prandial (PP) glucose:** FENFURO caused significant decrease in PP glucose levels on completion of the treatment as compared to the on-going anti-diabetic therapy-treated population. The decrease in mean PP glucose levels were up to 44.04% in the FENFURO-treated study population on completion of the treatment.

As observed on completion of the treatment with FENFURO, 88.10% of study population shown to have decrease in PP glucose levels.

- **Glycated hemoglobin (HbA1c):** FENFURO treatment resulted in normalizing the mean HbA1c levels of the study population. The HbA1c levels decreased significantly in the study population of both groups on completion of the treatment. Mean HbA1c levels decreased up to 34.70% in FENFURO-treated group whereas on-going anti- diabetic therapy caused 21.51% decrease in HbA1c levels.

These HbA1c levels came to normal range (Good control range - 4.5-6.3%) in FENFURO-

treated study population whereas they were still abnormal (Poor control levels – 7.6%) in on-going anti-diabetic therapy treated population till 12 weeks of treatment.

B. Safety Evaluation

Liver Function Tests

- **Serum glutamic oxaloacetic transaminase (SGOT) activity (U/L)**

There was non-significant change in the mean SGOT/AST activity of the study population in both the groups on completion of the treatment.

Table 12: Statistical data of mean SGOT / AST activity of the study population in Group A & Group B.

SGOT / AST ACTIVITY (U/L)		Mean ± Standard Deviation	t- value	p-value
Baseline	Group A (FENFURO)	23.11 ± 8.696	0.314	0.754
	Group B (On-going anti-diabetic therapy)	23.79 ± 10.362		
Completion of treatment (12 weeks)	Group A (FENFURO)	24.95 ± 7.679	0.420	0.675
	Group B (On-going anti-diabetic therapy)	25.78 ± 10.075		

- **Serum glutamic pyruvic transaminase (SGPT) activity (U/L)**

There was non-significant change in the mean SGPT/ALT activity of the study population in both the groups on completion of the treatment.

Table 13: Statistical data of mean SGPT / ALT activity of the study population in Group A & Group B.

SGPT / ALT ACTIVITY (U/L)		Mean ± Standard Deviation	t- value	p-value
Baseline	Group A (FENFURO)	23.83 ± 9.815	1.443	0.153
	Group B (On-going anti-diabetic therapy)	32.20 ± 36.216		
Completion of treatment (12 weeks)	Group A (FENFURO)	30.64 ± 16.990	1.684	0.096
	Group B (On-going anti-diabetic therapy)	38.02 ± 22.110		

- **Serum alkaline phosphatase (ALP) activity (U/L)**

There was decrease in the mean ALP activity of the study population in both the groups on completion of the treatment.

Table 14: Statistical data of mean ALP activity of the study population in Group A & Group B.

ALP ACTIVITY (U/L)		Mean ± Standard Deviation	t-value	p-value
Baseline	Group A (FENFURO)	106.54 ± 29.280	1.069	0.288
	Group B (On-going anti-diabetic therapy)	114.61 ± 38.325		
Completion of treatment (12 weeks)	Group A (FENFURO)	88.90 ± 29.441	3.619	0.001**
	Group B (On-going anti-diabetic therapy)	111.55 ± 26.204		

- **Serum Bilirubin (mg/dl)**

There was non-significant change in serum bilirubin levels of the study population of both the groups on completion of the treatment.

Table 15: Statistical data of mean serum bilirubin levels of the study population in Group A & Group B.

Serum Bilirubin Levels (mg/dl)		Mean ± Standard Deviation	t- value	p-value
Baseline	Group A (FENFURO)	0.54 ± 0.188	1.324	0.189
	Group B (On-going anti-diabetic therapy)	0.48 ± 0.207		
Completion of treatment (12 weeks)	Group A (FENFURO)	0.50 ± 0.253	0.015	0.988
	Group B (On-going anti-diabetic therapy)	0.50 ± 0.169		

Renal Function Tests

- **Urea levels (mg/dl)**

There was non-significant change in urea levels of the study population of both the groups on completion of the treatment.

Table 16: Statistical data of mean urea levels of the study population in Group A & Group B.

UREA LEVELS (mg/dl)		Mean ± Standard Deviation	t-value	p-value
Baseline	Group A (FENFURO)	30.30 ± 12.642	0.307	0.759
	Group B (On-going anti-diabetic therapy)	31.07 ± 9.476		
Completion of treatment (12 weeks)	Group A (FENFURO)	26.23 ± 7.524	0.197	0.845
	Group B (On-going anti-diabetic therapy)	25.60 ± 19.489		

- **Creatinine levels (mg/dl)**

There was non-significant change in creatinine levels of the study population of both the groups on completion of the treatment.

Table 17: Statistical data of mean creatinine levels of the study population in Group A & Group B.

CREATININE LEVELS (mg/dl)		Mean ± Standard Deviation	t-value	p-value
Baseline	Group A (FENFURO)	0.93 ± 0.380	1.614	0.110
	Group B (On-going anti-diabetic therapy)	0.81 ± 0.223		
Completion of treatment (12 weeks)	Group A (FENFURO)	0.87 ± 0.215	0.967	0.336
	Group B (On-going anti-diabetic therapy)	0.93 ± 0.294		

Effect on hemogram

- **Hemoglobin (Hb) levels (gm/dl)**

There was non-significant change in hemoglobin levels of the study population of both the groups on completion of the treatment.

Table 18: Statistical data of mean hemoglobin levels of the study population in Group A & Group B.

HEMOGLOBIN LEVELS (gm/dl)		Mean ± Standard Deviation	t- value	p-value
Baseline	**Group A (FENFURO)**	**13.19 ± 1.610**	**0.163**	0.871
	Group B (On-going anti-diabetic therapy)	**13.24 ± 1.598**		
Completion of treatment (12 weeks)	**Group A (FENFURO)**	**12.29 ± 1.795**	**0.948**	0.346
	Group B (On-going anti-diabetic therapy)	12.69 ± 1.951		

- **Total leukocyte count (TLC) (cells/cumm)**

There was significant decrease in total leukocyte count in the study population of both FENFURO-treated group and on-going anti-diabetic therapy treated group. But the TLC levels remained in the normal range (4000 – 11000 cell/cumm).

Table 19: Statistical data of mean TLC of the study population in Group A & Group B.

Total Leukocyte Count (Cells/cumm)		Mean ± Standard Deviation	t-value	p-value
Baseline	**Group A (FENFURO)**	**7542.85 ± 1903.929**	**1.728**	**0.088**
	Group B (On-going anti-diabetic therapy)	**8520.51 ± 3088.704**		
Completion of treatment (12 weeks)	**Group A (FENFURO)**	**6438.09 ± 1722.441**	**2.199**	**0.031***
	Group B (On-going anti-diabetic therapy)	**7331.57 ± 1911.855**		

- **Differential leukocyte count (%)**

Neutrophil count: The mean neutrophils count was not changed significantly in the study population of both groups (Group A & Group B) on the completion of the treatment.

Lymphocyte count: The mean lymphocytes count was significantly changed very slightly in the study population of both groups (Group A & Group B) on the completion of the treatment. But the count remained in the normal range (20 – 40 %).

Monocyte count: The mean monocytes count was significantly changed very slightly in the study population of both groups (Group A & Group B) on the completion of the treatment. But the count remained in the normal range (2 - 20 %).

Basophil count: There was non-significant change in mean basophils count of the study population of both groups (Group A & Group B) on completion of the treatment.

Eosinophil count: There was non-significant change in mean eosinophils count of the study population of both groups (Group A & Group B) on completion of the treatment.

Table 20: Statistical data of mean DLC of the study population in Group A & Group B.

PARAMETER		Mean ± Standard Deviation	t- value	p-value
Neutrophil count (Baseline)	Group A (FENFURO)	60.11 ± 7.856	2.412	0.018*
	Group B (On-going anti-diabetic therapy)	64.53 ± 8.632		
Neutrophil count (Completion of treatment)	Group A (FENFURO)	60.02 ± 7.376	1.783	0.079
	Group B (On-going anti-diabetic therapy)	63.31 ± 9.118		
Lymphocyte count (Baseline)	Group A (FENFURO)	31.83 ± 7.913	1.695	0.094
	Group B (On-going anti-diabetic therapy)	28.61 ± 9.161		
Lymphocyte count (Completion of treatment)	Group A (FENFURO)	32.85 ± 6.553	2.374	0.020*
	Group B (On-going anti-diabetic therapy)	29 ± 7.962		
Monocyte count (Baseline)	Group A (FENFURO)	4.11 ± 1.684	2.534	0.013*
	Group B (On-going anti-diabetic therapy)	3.28 ± 1.234		
Monocyte count (Completion of treatment)	Group A (FENFURO)	3.90 ± 1.664	0.505	0.615
	Group B (On-going anti-diabetic therapy)	4.10 ± 1.885		
Basophil count (Baseline)	Group A (FENFURO)	0.00 ± 0.000[a]		
	Group B (On-going anti-diabetic therapy)	0.00 ± 0.000[a]		
Basophil count (Completion of treatment)	Group A (FENFURO)	0.00 ± 0.000	2.332	0.022*
	Group B (On-going anti-diabetic therapy)	0.184 ± 0.512		
Eosinophil count (Baseline)	Group A (FENFURO)	4.47 ± 5.037	0.854	0.396
	Group B (On-going anti-diabetic therapy)	3.56 ± 4.535		
Eosinophil count (Completion of treatment)	Group A (FENFURO)	3.21 ± 2.236	0.250	0.803
	Group B (On-going anti-diabetic therapy)	3.36 ± 3.233		

Safety conclusions

On completion of the study, following safety conclusions were made:

- No significant change in the liver function tests (serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, alkaline phosphates activities and serum bilirubin levels) was observed on completion of the treatment.
- No significant change in the serum urea levels and creatinine levels was observed on completion of the treatment.
- No significant change in the hematological parameters was observed on completion of the treatment.

12. DISCUSSION

Type II diabetes is a disease involving increase in blood sugar (glucose) levels due to the inability of cells to respond properly to insulin. Response towards insulin is a very critical step in balancing blood sugar levels as this response will transfer the sugar dissolved in blood towards tissues to convert it to energy.

The risk for diabetes is mostly at the age after 35 years but diabetes is not limited to this age-group as diabetes cases have been observed in childhood population also. Diabetes has been observed to be mostly prevalent in urban population as compared to rural population due to the unhealthy lifestyle. Doctors have also reported the contribution of unhealthy eating pattern and limited physical activity in the development of diabetes. Beside this, genetical factors also contribute in developing diabetes.

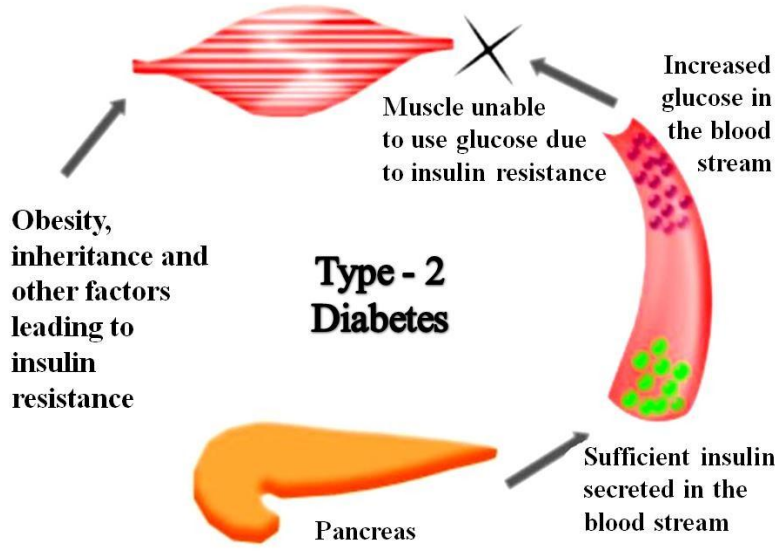


Fig 12: Cycle of development of type II diabetes.

Diabetes is generally diagnosed by the symptoms generated and confirmed by the blood glucose test. Each individual is suggested to remain careful for the development of symptoms of diabetes which include:

- Continuous hunger
- Unexplained weight loss
- Numb or tingling hands / feet
- Frequent urination
- Extreme fatigue
- Always thirsty

Whenever these symptoms arise in any individual, whether male or female, these are recommended to be immediately discussed with doctors. Most of the time, doctors suggest lifestyle changes and exercise as first remedy for diabetes. Then, medications are prescribed, if diabetes is not reverted to normal.

People are turning towards nutraceuticals for treating any kind of disease as they are effective to treat disease and they are devoid of any adverse effects. One such natural product is FENFURO which was evaluated in the present study for its efficacy and safety in type II diabetic patients.

In the present study, two groups were made from which Group A included type II diabetic patients to be administered with FENFURO along with their on-going anti- diabetic therapy. The effect of FENFURO alone was evaluated by comparing Group A with Group B which included those patients who were administered only with on-going anti-diabetic therapy. Thus, the anti-diabetic effect of FENFURO was evaluated by comparing results of both the groups.

Fasting glucose levels

Fasting glucose level is the most affected parameter under diabetic condition which is raised above 110 mg/dl during diabetes. It is the primary test to be recommended to ensure the presence of diabetes. Fasting blood glucose is suggested because during fasting condition, no food is eaten and the body required energy which is supplied through glucagon hormone. During fasting condition, glucagon is secreted by the pancreatic cells and stimulates the conversion of glycogen to glucose which results in the increase in blood sugar (glucose) levels. Thus, during diabetic condition, increase in fasting sugar levels contributes in

worsening diabetes.

In the present study, FENFURO caused the decrease in fasting glucose levels up to 38.26% on completion of the treatment. This means that FENFURO has a role in inhibiting the production of glucose by glucagon or inhibit the production of glucagon itself which resulted in decrease in fasting glucose levels.

Post-Prandial (PP) glucose levels

PP glucose is another laboratory test recommended during diabetes. It confirms the presence of diabetes along with fasting glucose levels. It is recommended because as the food contains carbohydrates, thus, the blood glucose levels always raise after having meal. PP glucose levels measure the amount of blood glucose levels raised after eating food. As the blood glucose levels rise after eating, doctors always restrict the carbohydrate intake during diabetes.

In the present study, FENFURO was successfully able to decrease the PP glucose levels in blood. They were decreased up to 44.04% in the FENFURO-treated study population. But PP glucose levels significantly increased in on-going anti-diabetic therapy-treated study population.

HbA1c levels

HbA1c or Glycated hemoglobin is originated when hemoglobin (protein within RBCs carrying oxygen in whole body) attaches itself to blood glucose. Thus, more is the available glucose; more will be the chances of attaching hemoglobin to it raising HbA1c levels. In other words, the amount of glucose that combines with hemoglobin is directly proportional to the total amount of sugar in the human body at that time. Thus, under diabetic condition, HbA1c levels will also become high. It has been suggested that if HbA1c is improved by even 1% in people with type II diabetes, it cuts the risk of microvascular complications of type II diabetes by 25%.

In the present study, FENFURO was able to lower the HbA1c levels up to 34.70% in the type II diabetic study population on completion of the treatment meaning it is able to lower the glucose levels in blood resulting in reduction in HbA1c levels. This indicates that FENFURO is able to lower the risk of development of microvascular complications of type II diabetes.

As the safety parameters of the study are considered, FENFURO did not alter the liver profile

or renal profile or haematological parameters of the study population proving the safety of FENFURO in human-beings.

CONCLUSION

Efficacy and safety data of the present clinical study in type II diabetic patients clearly indicates that the addition of FENFURO to on-going anti-diabetic therapy is more effective than the anti-diabetic therapy alone in the patients.

FENFURO is able to safely lower the fasting glucose levels, PP glucose levels and HbA1c levels of type II diabetic patients.

FENFURO is also proved to be completely safe in the type II diabetic patients.

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