Efficacy and Safety of Voglibose v/s Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(PHARMACOLOGY)

Dr SUMAN S V

JULY, 2020

AIIMS, JODHPUR

All India Institute of Medical Sciences, Jodhpur

DECLARATION

I hereby declare that thesis entitled "**Efficacy and Safety of Voglibose v/s Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial**" embodies the original work carried out by me.

Dr Suman S V
Department of Pharmacology
AIIMS, Jodhpur

All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

This is to certify that the thesis entitled "**Efficacy and Safety of Voglibose v/s Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial**" is an original work of **Dr Suman S V** carried out under our guidance and supervision, at All India Institute of Medical Sciences, Jodhpur.

Guide:

Dr. Jaykaran Charan
Additional Professor,
Department of Pharmacology,
AIIMS, Jodhpur.

Co-Guides:

Dr. Surjit Singh
Additional Professor,
Department of Pharmacology,
AIIMS, Jodhpur.

Dr. Dharmveer Yadav
Additional Professor,
Department of Biochemistry,
AIIMS, Jodhpur.

Dr. Ravindra Shukla
Additional Professor,
Department of Endocrinology,
AIIMS, Jodhpur.

Dr. Shoban Babu Varthya
Associate Professor,
Department of Pharmacology,
AIIMS, Jodhpur.

All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

This is to certify that the thesis entitled "**Efficacy and Safety of Voglibose v/s Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial**" is the bona fide work of **Dr Suman S V** carried out under my supervision, in the Department of Pharmacology, AIIMS, Jodhpur.

The work done by Dr Suman S V is satisfactory for its submission in partial fulfillment of the requirement for the Degree of Doctor of Medicine (Pharmacology) by the institute.

Dr. Sneha Ambwani
Professor and Head,
Department of Pharmacology,
AIIMS, Jodhpur.

ACKNOWLEDGEMENT

First and foremost, I thank God Almighty for giving me the knowledge and strength to complete this study successfully.

I am profoundly grateful, and it is a proud privilege to express my gratitude and sincere thanks to my guide **Dr Jaykaran Charan**, Additional Professor, Department of Pharmacology, AIIMS, Jodhpur, who provided me with an opportunity to work under his guidance. His guidance was paramount in providing a well-rounded experience and knowledge. He has always been a source of encouragement and inspiration. I am indebted to him for devoting valuable time out of his busy schedule and being concerned with completing this project. I shall remain grateful to him forever.

Special gratitude is owed to my co-guide, great adviser, and a wonderful person **Dr Ravindra Shukla**, Associate Professor, Department of Endocrinology, AIIMS, Jodhpur, for providing me with an opportunity to carry out the study at their department. He has been generous in sharing his knowledge on various aspects related to my thesis. His invaluable guidance, understanding and insight into the subject helped me complete the work successfully.

I express my sincere gratitude to my co-guides, **Dr Surjit Singh**, Additional Professor, Department of Pharmacology; **Dr Dharmveer Yadav,** Additional Professor, Department of Biochemistry; **Dr Shoban Babu Varthya,** Associate Professor, Department of Pharmacology, for their constant support, encouragement, guidance and help throughout the work.

I extend my sincere thanks and gratitude to **Dr Sneha Ambwani**, Professor and Head; **Dr Pradeep Dwivedi**, Additional Professor; **Dr Rimple Jeet Kaur**, Assistant Professor; **Dr Tarun Kumar**, Assistant Professor, Department of Pharmacology, AIIMS, Jodhpur for enlightening me on the critical points of the research topic, guiding me, paving the way to create a path and making me what I am today.

A special thanks to **Dr Siddhartha Dutta**, **Dr Kishna Ram Chaudhary**, **Dr Hina Lal, and Dr Arun S,** Senior Residents, Department of Pharmacology.

I pay my gratitude and special thanks to my dear seniors **Dr Govind Mishra, Dr Sameer Khasbage, Dr Ravi Prakash Sharma, Dr Jyoti Sharma**, **Dr Jha Pallavi Abhayanand**, **Dr Sakshi Sharma, Dr Shanmugapriya Seshatri, Dr Sanchi Sukhija, Dr Abisha T, Dr Anindita Pradhan** for their co-operation and encouragement during this research.

I am also highly thankful to my friends **Dr Sachin J**, Junior Resident, Department of Pharmacology, and **Dr Bindiya C Gowda**, Junior Resident**,** Department of Community Medicine and Family Medicine, for giving me the most straightforward solutions to all my problems with ease.

A special thanks to my outstanding juniors, **Dr Sravanth Chowdary**, **Dr Abhishek Kondapalli**, **Dr Abhishek Anil**, **Dr Aswini Saravanan, Dr Pravesh Aggarwal, Dr Muhammad Aaqib Shamim, Dr Simi Bridjit Gomez** for the fun and their selfless help during my day-to-day work.

I am thankful to the Director of AIIMS, Jodhpur, for permitting me to avail all the facilities available in the institute for conducting this study. Most importantly, I thank my parents, **Mr Venkatesh S K** and **Mrs Leelavathi,** for always being my guiding light through all the ups and downs in my life. I would also like to thank my caring sister, **Mrs Kavya**, brother-in-law **Mr Narendra** and my little nephew **Vruthvik** for their support, encouragement and unconditional love that was undeniably the bedrock upon which my life has been built.

SPECIAL ACKNOWLEDGEMENTS

My special acknowledgements go to those who made the difficult task of completing my MD thesis possible. My warm appreciation to all the Pharmacology and Biochemistry staff who cooperated in my long working hours and supported me constantly during my work at their department. At last, words are short of expressing my sincere thanks to all the participants who willingly and selflessly participated in my research endeavour.

Dr Suman S V

DEDICATED TO

MY PARENTS,

MY GUIDE

AND

DEPARTMENT OF PHARMACOLOGY,

AIIMS, JODHPUR.

LIST OF ABBREVIATIONS

Sr. No.	Abbreviation	Full Form
1.	DM	Diabetes Mellitus
2.	QoL	Quality of Life
3.	HbA1c	Glycated Hemoglobin
4.	FPG	Fasting Plasma Glucose
5.	PPG	Postprandial Plasma Glucose
6.	BMI	Body Mass Index
7.	LDL-C	Low-Density Lipoprotein Cholesterol
8.	HDL-C	High-Density Lipoprotein Cholesterol
9.	TC	Total Cholesterol
10.	TG	Triglyceride
11.	VLDL-C	Very Low-Density Lipoprotein Cholesterol
12.	CAD	Coronary Artery Disease
13.	CVA	Cerebrovascular Accidents
14.	CKD	Chronic Kidney Disease
15.	NAFLD	Non-Alcoholic Fatty Liver Disease
16.	IDF	International Diabetes Federation
17.	GDM	Gestational Diabetes Mellitus
18.	HTN	Hypertension
19.	ADA	American Diabetic Association
20.	GLP-1	Glucagon-Like Peptide

21.	iSGLT-2	Sodium-Glucose Co-transporter-2 inhibitor
22.	α-GI	Alpha-Glucosidase Inhibitor
23.	MOA	Mechanism Of Action
24.	OHA	Oral Hypoglycaemic Agent
25.	TZD	Thiazolidinediones
26.	PPAR-γ	Peroxisome Proliferator-Activated Receptor- γ
27.	iDPP-4	Dipeptidyl Peptidase - 4 inhibitor
28.	GIP	Gastric Inhibitory Polypeptide
29.	GI	Gastro-Intestinal
30.	HOMA–IR	Homeostatic Model Assessment of Insulin Resistance
31.	HOMA–B%	Homeostatic Model Assessment of Beta Cell Function
32.	HOMA-S%	Homeostatic Model Assessment of Insulin Sensitivity
33.	IGT	Impaired Glucose Tolerance
34.	CRP	C-Reactive Protein
35.	sICAM	soluble Intracellular Adhesion Molecule
36.	PGF2α	Prostaglandin F2α
37.	PPH	Postprandial Hypotension
38.	sd-LDL	small density - LDL
39.	SAT	Subcutaneous Adipose Tissue
40.	VAT	Visceral Adipose Tissue
41.	HMW adiponectin	High Molecular Weight Adiponectin
42.	IMT	Intima - Media Thickness

43.	RLP-C	Remnant Like Particle-Cholesterol
44.	FDC	Fixed-Dose Combination
45.	AUC	Area Under Curve
46.	CD	Cluster Of Differentiation
47.	1,5-AG	1,5-Anhydroglucitol
48.	SMBG	Self-Monitoring of Blood Glucose
49.	IRI	Immunoreactive Insulin
50.	MCP-1	Monocyte Chemoattractant Protein-1
51.	ICH-GCP	International Conference on Harmonization-Good Clinical Practice
52.	ICMR	Indian Council of Medical Research
53.	RBS	Random Blood Sugar
54.	NYHA	New York Heart Association
55.	COPD	Chronic Obstructive Pulmonary Disease
56.	HPLC	High-Performance Liquid Chromatography
57.	CLIA	Chemiluminescence Immunoassay
58.	DCCT	Diabetes Control and Complications Trial
59.	IHD	Ischemic Heart Disease
60.	EC	Enterochromaffin
61.	GLUT-4	Glucose Transporter Type 4

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SUMMARY

Diabetes mellitus (DM) is a metabolic disease with high mortality and morbidity. Type-2 DM is common after around 30 years of age. Long-term uncontrolled DM will lead to micro and macrovascular complications that affect patients' quality of life (QoL). Hence, early and effective management will help reduce complications and improve QoL.

Diet management, exercise, and a healthy lifestyle remain the primary and most crucial modalities for managing and preventing type-2 DM. Metformin is the preferred first-line treatment option for type-2 DM patients. After considering the patient's comorbidities and side effects, tailored add-on combination therapy is advised. Despite the availability of many options, it is a topic of debate to know which drug to prefer as the second line of the drug because most patients have a multifactorial origin of type-2 DM, and the presence of comorbidities restricts the use of certain drugs in certain patients. Voglibose is an α-glucosidase inhibitor which can also be used as an add-on to metformin. Glimepiride is also used with metformin to treat type -2 DM. There was only one study on voglibose efficacy as an add-on treatment to metformin. There was no direct comparison available between the metformin + voglibose v/s metformin + glimepiride combination in databases. There is uncertainty about the superiority of the metformin + glimepiride combination v/s metformin + voglibose combination. Hence, assessing the effectiveness and safety of these combinations was worthwhile.

This was a 12-week study; 73 patients aged 18 to 60 were enrolled and randomized in a 1:1 ratio into voglibose and glimepiride groups. The voglibose group was given Metformin + Voglibose, and the glimepiride group was given metformin + glimepiride. The patient's follow-up was done for three months. Patients were assessed for changes in glycated haemoglobin (HbA1c), Postprandial plasma glucose (PPG), lipid profile, fasting plasma glucose (FPG), insulin resistance (IR), beta cell function, body mass index (BMI), body weight and QoL.

There was a significant improvement in HbA1c, FPG, and PPG within both groups, but there was no statistically significant difference between the groups. The Voglibose group had a significant reduction in body weight and BMI but not the glimepiride group. The Voglibose group had a significant reduction of low-density lipoprotein cholesterol (LDL-C) and an increase in high-density lipoprotein cholesterol (HDL-C), but other lipid parameters showed no significant changes; meanwhile, there were a significant reduction in total cholesterol (TC),

triglycerides (TG), and LDL-C but not HDL-C and very low-density lipoprotein cholesterol (VLDL-C) in the glimepiride group. The Voglibose group showed significant improvement in beta cell function, whereas the glimepiride combination significantly reduced fasting insulin and improved beta cell function and insulin resistance. Voglibose and glimepiride groups had significant improvement in QoL total score, satisfaction and Impact domain scores but not worry domain scores in both the groups but the comparison of QoL between the two groups was nonsignificant. Both the combinations were well tolerated; GI side effects were seen with voglibose, whereas hypoglycemia was a concern with glimepiride.

Metformin + Voglibose is an effective treatment option for type-2 DM. The added benefits of weight loss, BMI reduction, HDL-C increase and less risk of hypoglycemia make it a good option for type-2 DM management. Further studies with large sample sizes might provide more concise information.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of high blood sugar levels (1,2). There are two types of DM, type-1 DM, which is due to insulin deficiency seen at a young age and type-2 DM, which is multifactorial, like age-related reduction of insulin production, insulin resistance, overweight, obesity, metabolic factors and genetic factors (3,4). Type-2 DM is common after around 30 years of age. Like hypertension, diabetes is considered a silent killer, as it is diagnosed very late, and patients often consult clinicians in the late stages of the disease after developing micro or macrovascular complications (5). Micro and macrovascular complications result in vascular obliteration and tissue death leading to diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, peripheral vascular disease and end-organ damage (6). These complications are seen with both type-1 & type-2 DM because of ignorance of the disease by patients and improper disease management. Type-2 DM is associated with obesity and IR, which can lead to dyslipidemia and atherosclerosis. Atherosclerosis of cardiac and cranial vessels can have a life-threatening impact on patients in the form of cardiac morbidity and mortality. Diabetes is like an initiating factor which can lead to a cascade of events like dyslipidemia, atherosclerosis, hypertension, coronary artery disease (CAD), cerebrovascular accidents (CVA), chronic kidney disease (CKD), retinopathy, and nephropathy which all together can lead to decrease in quality of life and drastically increase mortality (7,8). Diabetes mellitus with increased adiposity can cause non-alcoholic fatty liver disease (NAFLD) and cardiac dysfunction, i.e., heart failure or coronary artery disease (9). Half of diabetes-related deaths are due to cardiovascular complications (6,8,10). The complications of type-2 DM are slowly progressing but are highly morbid. Since the disease is common in adulthood, the working population is affected, impacting dependent families, work output and the economy. The number of people suffering from type-2 DM worldwide has made it a topic of interest to discuss, develop, and dedicate time and resources to prevent, control and treat the disease.

India has the second-highest number of type-2 DM cases worldwide (11). Type-2 DM comprises about 90% of all cases of diabetes. According to the International Diabetes Federation (IDF) diabetes atlas 10th edition, the global diabetes prevalence increased from 4.7% (1980) to 9.8% in adults (2021) (10,12,13). The prevalence is around 6% in men and 5% in women (2019), which was around 3.9% in men and 3.5% in women in 1990 (14). About 537 million people (20-79 years) are suffering from DM worldwide, and the numbers might increase to 783 million by

2045, and 542 million adults have impaired glucose tolerance (IGT), putting them at increased risk for developing diabetes mellitus (13). Most of the disease burden (79% & 3 out of 4 cases) is seen in low and middle-income countries (15,16). Almost 44.7% of people with type-2 DM are undiagnosed (13). About 7 million people died from diabetes in 2021 (1 death every 5 seconds); high blood glucose led to additional 2.2 million deaths (13,17). Around 3% of global blindness is caused by diabetic retinopathy (17). Diabetes in pregnancy with poor control increases the risk of maternal and fetal complications, including fetal death (12). Worldwide 1 in 6 live births are affected by diabetes during pregnancy, with a gestational diabetes mellitus (GDM) prevalence of 16.7% (13,15). In India, 37 million livebirths are affected by diabetes during pregnancy, with a GDM prevalence of 29.3% (18). These events affect an individual's health and lifespan and put an economic burden on the individual, family and nation, contributed by treatment costs for the disease and its complications, loss of work and reduced quality of life (QOL) (12,16). Diabetes alone consumed health expenditure of at least 966 billion USD globally in 2021, and the expenditure in India was around 8.5 billion USD (13,18). Seventy-four million people (20-79 years) are affected by diabetes in India, with a prevalence of 9.6%, and among them, more than 39 million are undiagnosed (18). Around 40 million are prediabetic in India. DM contributes to around 6.5 lakh deaths in India. Around 2.3 lakh individuals are affected by type-1 DM (0-19years), with around 24 thousand new cases diagnosed yearly. Diabetes also accounts for 2.5% of CAD, 5.9% of nephropathy, 10.6% of neuropathy, 0.8% of retinopathy and 0.3% of cerebrovascular disease in India (18). Keeping the disease itself aside, its complications like dyslipidemia, HTN, cardiovascular and cerebrovascular, and renal complications mandate separate and enormous resources from the treasury. It is seen that DM is associated with less seroconversion in covid-19 patients and a high risk of severe respiratory disease, intensive care unit admissions and mortality (19,20). Diagnosis of diabetes mellitus can lead to depression and diabetes distress in patients, especially the elderly with type-2 DM (21). This will affect the QoL of the patient. Hence, it is necessary to treat the disease as early as possible and as effectively as possible. If possible, prevent the disease itself so that consequences can be avoided and a person can lead a normal and healthy lifestyle.

The main objective of diabetes treatment is to reduce blood glucose levels (2,10). Diet management, exercise, and a healthy lifestyle remain the primary and most crucial modalities for

treating and preventing type-2 DM (22). In most patients, type-2 DM is either due to obesity or insulin resistance rather than low insulin levels, seen in the disease's later stages or in old age. Technological advances, a sedentary lifestyle, stress, and high-calorie fast foods are major contributing factors to obesity, increasing type-2 DM risk. Obesity can be managed by diet and regular exercise, improving IR and reducing the risk of type-2 DM development (8,23,24). Most diabetic people cannot follow proper diet and precautions either because of unawareness about the disease, ignorance, unavailability of resources, or poor socio-economic status (25–28). All these factors, which are preventing the population at risk from maintaining a healthy lifestyle, led to more type-2 DM cases.

When a disease cannot be prevented, it should be adequately treated before it can cause any harm to the person/population/nation. Hence, over a century, many treatment modalities have been developed to treat the disease, among which insulin therapy remains the gold standard. It works by directly acting like indigenous insulin. It is the drug of choice in type-1 DM. In type-2 DM, its use is limited to later stages of the disease or in uncontrolled type-2 DM due to its common side effects like hypoglycemia and the necessity of regular dose adjustments, add-ons, cost-effectiveness and it is an injectable drug, which might lead to improper drug administration and treatment failure (5,22). Metformin, a simpler, cheaper and effective oral drug, is the only preferred 1st line of treatment for type-2 DM (10,29). American diabetic association (ADA) 2022 guidelines suggest Metformin as the 1st line drug in type-2 DM patients, along with lifestyle modifications. After consideration of the patient's comorbidities and side effects, the use of different combination therapy tailored for the patient is advised. In patients with cardiovascular disease, glucagon-like peptide (GLP-1) analogues or Sodium-glucose co-transporter-2 inhibitors (iSGLT-2) are recommended. iSGLT-2 with Metformin is recommended in heart failure patients. Metformin has a limited role in severe CKD patients; in such cases, iSGLT-2 or GLP-1 analogues are recommended depending on the glomerular filtration rate and albuminuria. When cost and drug accessibility are issues, sulfonylureas or insulin biosimilars can be considered at risk of hypoglycemia. GLP-1 analogues are preferred over insulin in type-2 DM patients when possible (30). Insulin secretagogues such as sulfonylureas and meglitinides/glinides stimulate beta cells of the pancreas and increase insulin secretion (31). Sulfonylureas can be used as part of 2nd line therapy in type-2 DM. Current ADA guidelines recommend sulfonylureas only when the

cost (GLP-1 RA, SGLT-2i are costlier) and availability of other drugs is an issue and in cases where other add-on drugs are contraindicated (30,32). Alpha-glucosidase inhibitors (α-GIs) are another treatment option for DM. They show a unique mechanism of action (MOA) compared to other oral hypoglycaemic agents (OHAs). They inhibit the intestinal enzyme alpha-glucosidase, which breaks down polysaccharides into simpler sugars, thus delaying glucose absorption (33). They effectively reduce post-prandial glucose (PPG) and triglyceride levels, and unlike insulin secretagogues, they rarely cause hypoglycaemia. Alpha-glucose inhibitors moderately reduce HbA1c levels and stand next to Metformin and sulfonylureas in their efficacy (34). Thiazolidinediones (TZD) are nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists used to treat type-2 DM. They stimulate PPARs and increase the insulin sensitivity of cells (35). TZDs are as effective as metformin but are not used routinely because of their adverse effects and cost. Dipeptidyl peptidase-4 inhibitors (iDPP-4) act by inhibiting DPP-4 and thus increase the incretin agents (GLP-1 and gastric inhibitory polypeptide (GIP)), which leads to improvement in insulin secretion and decreases glucagon. iSGLT-2 inhibit renal glucose reabsorption and thus reduce hyperglycaemia. This new treatment modality can lower plasma glucose levels and reduce body weight and blood pressure by inducing diuresis. They also reduce all-cause mortality in DM patients (36). Glucagon-like peptide-1 receptor agonists (GLP-1 RA) mimic GLP-1 action and are used in type-2 DM. This drug class has effectively decreased HbA1c, body weight, fasting plasma glucose (FPG), and systolic BP with less chance of hypoglycaemia.

Despite the availability of the above options, it is still a topic of debate to know which drug to prefer as the second line of the drug because most of the patients have a multifactorial origin of type-2 DM, and the presence of comorbidities restrict the use of certain drugs in certain patients (30). Ideally, treatment of type-2 DM starts with Metformin, but many times based on clinical situations and previous drug history, other drugs are added to Metformin. Every add-on second-line drug has its limitations, as SGLT-2 inhibitors and GLP-1 analogues are recommended drugs as add-on therapy. However, they are costly, so it is challenging to prescribe them to poor patients and patients without comorbidities. GLP-1 analogues carry the risk of thyroid C-cell tumours, pancreatitis and gastrointestinal (GI) side effects. SGLT-2 inhibitors increase the risk of diabetes keto acidosis, bone fractures (canagliflozin), genitourinary infections and gangrene.

TZDs cause fluid retention and increase the risk of heart failure, weight gain, bladder cancer (pioglitazone), and bone fractures. iDPP-4 side effects include pancreatitis and joint pain and are costly (30). Glimepiride, a sulfonylurea, is frequently used with Metformin in type-2 DM. As per the studies, when glimepiride is used in patients on metformin as background treatment, it decreases HbA1c by around 0.7% to 1% (37–40). However, metformin+glimepiride can cause hypoglycaemia, weight gain, headache and weakness (37,39–41). Voglibose is an α-glucosidase inhibitor which can also be used as an add-on to metformin. When used as monotherapy, voglibose can cause an HbA1c reduction of 0.7% to 1.2% in type-2 DM patients (42–44). As per a study, metformin + voglibose combination can reduce HbA1c by 1.6% and produce self-limiting gastrointestinal side effects without a propensity for weight gain or hypoglycaemia (45). There were no studies on voglibose efficacy in patients already on metformin treatment, and no direct comparison was available between the metformin + voglibose v/s metformin + glimepiride combination in databases, as per our knowledge. There is uncertainty about the superiority of the metformin + glimepiride combination v/s metformin + voglibose combination. It is worthwhile to evaluate the safety and effectiveness of voglibose and glimepiride with metformin as basal therapy so that clinicians can better judge the preferred add-on drug to Metformin. Hence this study was planned to compare the efficacy and safety of Metformin + glimepiride v/s metformin + voglibose in type-2 DM patients.

AIMS AND OBJECTIVES

AIM:

To compare the efficacy and safety of voglibose and glimepiride in combination with Metformin in type-2 diabetes.

Objectives:

• Primary objectives

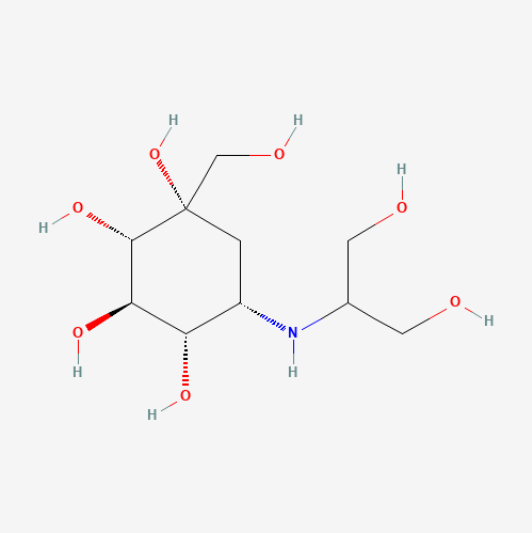
1. Difference of HbA1c reduction in between voglibose and glimepiride group after three months.
2. Difference in decrease in FBG & PPG between voglibose and glimepiride group after three months.

• Secondary objectives

1. Adverse events in both the groups.
2. Difference in lipid parameters (Triglycerides, Total Cholesterol, LDL, VLDL, and HDL) in both the groups after three months.
3. Difference in quality-of-life indicators between voglibose and glimepiride group after three months.
4. Difference in HOMA–IR, HOMA–B% and HOMA-S% of voglibose and glimepiride group after three months.
5. Difference in need and use of rescue medicines in both the groups during three-month study period.

REVIEW OF LITERATURE

Voglibose is a valiolamine derivative with alpha-glucosidase inhibitory activity. It was discovered in 1981 in Japan. Commercial use of voglibose to treat type-2 DM started in 1994 (46). Voglibose delays intestinal glucose absorption by preventing the breakdown of complex carbohydrates by inhibiting the digestive enzyme alpha-glucosidases.



Structure of voglibose ($C_{10}H_{21}NO_7$)

Since 1994 voglibose has been used for the management of DM along with metformin, sulfonylureas and other drugs, and its use is increasing with time. Many studies have evaluated the pharmacodynamics and pharmacokinetics of voglibose alone and in combination with other drugs. The literature is summarized as follows,

1. Voglibose v/s Placebo

A study by Goto *et al.* (1994) demonstrated the effect of the alpha-glucosidase inhibitor on carbohydrate absorption in rats and humans. The study used different doses of voglibose (0.2/0.4/0.5/1 mg), and the results showed that 0.2 and 0.4 mg showed promising inhibition of glucose absorption with a better safety profile than higher doses. The study also established the side effects of the drug, which are GI-related (Soft faeces, diarrhoea and abdominal distention, pain abdomen and borborygmus). These adverse events are due to unabsorbed carbohydrates in

the gut rather than the drug itself (47). Voglibose reduced PPG, C-peptide, and serum insulin dose-dependently and increased plasma GLP-1 levels (48). Kawamori *et al.,* Studied the type-2 DM prevention ability of voglibose in patients with impaired glucose tolerance (IGT). The study concluded that long-term prophylaxis with voglibose in high-risk patients with IGT could provide pharmacological options, along with lifestyle modification, to reduce the incidence of type-2 DM in Japan (49).

Studies to see the voglibose effect on vascular endothelial function and cardiovascular events in type-2 DM patients did not yield any positive results (50,51). However, as per the study by Satoh N *et al.,* on the effect of voglibose on oxidative stress markers and intracellular adhesion molecules, it was seen that voglibose reduced plasma triglycerides, free fatty acids, with reasonable glycemic control and improvement in oxidative stress markers (CRP, sICAM-1, and urinary excretion of 8-iso-PGF2α and 8-OHDG). The study concluded that voglibose reduces oxidative stress generation and sICAM-1 by improving post-prandial hyperglycemia and hyperlipidemia in obese type-2 DM patients, thereby potentially reducing the development of atherosclerosis and CVD (52). Long-term therapy with voglibose as an add-on to insulin or sulfonylurea reduced the progression of average carotid intima-media thickness in type-2 DM patients with reduction in plasma TG, TC levels and increasing HDL-C as per the study by Yamasaki *et al*., And the authors concluded that voglibose might be a potential anti-atherogenic drug in Japanese type-2 DM patients (53). Maruta *et al.* studied voglibose's effectiveness in inhibiting post-prandial hypotension and has shown efficacy in controlling postprandial hypotension (PPH) in neurologic disorders and the elderly population (54).

2. Metformin and Voglibose

Voglibose can be safely used with Metformin as a fixed dose combination or co-administration without altering the bioequivalence of Metformin, as concluded by Choi *et al.* in a two-way crossover trial. The combination was well tolerated, and apart from loose stools and abdominal discomfort, which resolved without any intervention or consequences, no serious side effects were observed (55). Metformin and voglibose combination (Vogmet 0.2/500 mg t.i.d.) is proven significantly more effective than Metformin (500mg t.i.d.) alone in improving glycemic parameters of type-2 DM patients. The combination also showed a significant reduction in body

weight with a good safety profile. Common side effects were gastrointestinal system (GI) related. This study by Oh *et al.* concluded that vogmet could be given safely as initial therapy to patients with type-2 DM (45). A recent study (2020) by Bhansali *et al.* comparing the efficacy of Metformin 2g/day v/s voglibose 0.3mg t.i.d. showed that both metformin and voglibose have an equal glucose-lowering effect as both the groups showed a similar, significant reduction in FPG, 2-h PPG, and HbA1c levels. The study concluded that Metformin and voglibose reduced glucotoxicity and mitochondrial oxidative stress indices (44).

3. Voglibose and Sulfonylureas

In 1997, Kleist *et al.,* Studied the drug interaction between voglibose and sulfonylurea glibenclamide. Concomitant administration of voglibose with glibenclamide did not affect absorption, peak plasma concentration, elimination, or bioavailability of glibenclamide, unlike the other alpha-glucosidase inhibitor miglitol. The study concluded that the combination was safe and effective. Voglibose increased the glibenclamide-induced fall of plasma glucose (56). Voglibose can be safely used in combination with sulfonylureas in naïve type-2 DM patients and patients who are already on sulfonylurea therapy; as per the results of a study by Saito *et al.*, the combination is effective in reducing plasma glucose levels. The efficacy of the combination was better in patients with HbA1c < 8.5% and BMI < 25. The combination did not affect body weight (57). When used as an adjunct to sulfonylurea in type-2 DM patients, voglibose showed a significant reduction in HbA1c without much change in FPG and fasting insulin, HOMA-B, HOMA-IS as per the study by Hirose *et al.* (58). When given with sulfonylureas or insulin, voglibose reduces the dose requirement of co-administered drugs. It also reduces the hypoglycemic episodes due to sulfonylureas and Insulin with improvement in c-peptide levels as per the study by Okada *et al.* (59). Study by Matsumoto *et al.* to see whether sulfonylurea and alpha-GI combination therapy can prolong the duration of good glycemic control in type-2 DM patients showed that, the combination was significantly better than sulfonylurea alone in prolonging the period of reasonable glycemic control (60). Voglibose and glibenclamide have no effect on urinary endothelin-1 and albumin excretion in diabetes patients with microalbuminuria, unlike pioglitazone (61). As per the study by Fujimoto K *et al.*, the voglibose/mitiglinide combination provides better glycemic control than glimepiride when used as an add-on therapy

to vildagliptin. The combination significantly reduced glucose excursions and hypoglycemic episodes compared to glimepiride (62).

Mitiglinide + voglibose combination was compared with glimepiride to see the effect on blood glucose, LDL-C, small density (sd)-LDL, and sd-LDL proportion. The study was done by Tani *et al.*, and the results were that FPG control was better in the glimepiride group, but the mitiglinide/voglibose group had better HbA1c reduction. Mitiglinide/voglibose group showed a significant reduction in sd-LDL and sd-LDL proportion, but LDL-C levels were unchanged. There was a significant reduction in LDL-C and sd-LDL levels in the glimepiride group, but the sd-LDL proportion remained unchanged. There was a significant increase in the LDL-C/apo-B ratio in the Mitiglinide + voglibose group but not in the glimepiride group. However, the study failed to conclude the anti-atherosclerotic effect of these drugs(63). In a clinical trial, Takami et al. studied the effects of diet management, voglibose and glyburide on metabolic profile and abdominal adipose tissue in newly diagnosed type-2 DM patients. Diet alone compared with diet + voglibose (0.9mg/day) or diet + glyburide (1.25mg/day) for three months. Blood glucose control was seen in all three groups with similar weight loss. The Voglibose and glyburide groups showed significant improvement in insulin sensitivity and acute insulin response but not in the diet-alone group. Female patients treated with voglibose had a significantly lower subcutaneous adipose tissue area (SAT) to visceral adipose tissue area (VAT) ratio but not the other patients (64).

4. Voglibose and Insulin

Voglibose, when given with insulin or sulfonylureas, reduces the dose requirement of co-administered drugs and reduces the hypoglycemic episodes due to insulin or sulfonylureas with improvement in C-peptide levels as per the study by Okada *et al.* (59). In a study conducted by Taira *et al.*, an evening dose of voglibose given to patients on intensive insulin therapy reduced the plasma glucose changes overnight, and significantly reduced hypoglycemic episodes. The study concluded that voglibose significantly improved nocturnal hypoglycemic episodes in type-1 DM patients (65). To switch from insulin, Voglibose can be used as an effective oral replacement therapy In combination with pioglitazone and glimepiride. The combination had no episodes of severe hypoglycemia, as per Okamoto *et al.* (66).

5. Voglibose and Pioglitazone

Studies comparing the efficacy of voglibose and pioglitazone as an add-on to OHA or insulin showed that voglibose was as effective as pioglitazone in HbA1c reduction, but FPG control was better with pioglitazone. The Pioglitazone group showed an increase in BMI but not voglibose. Pioglitazone significantly reduced serum triglyceride levels and increased plasma HDL cholesterol levels but not voglibose. Voglibose had no effect on plasma HMW adiponectin which was increased by pioglitazone (67,68). When used as monotherapy, both voglibose and pioglitazone showed significant HbA1c reduction, but pioglitazone had significantly better FPG control than voglibose. Voglibose showed a significant reduction in BMI compared to pioglitazone. Insulin resistance, HDL-C, LDL-C, and adiponectin were improved by pioglitazone but not voglibose. The study concluded that voglibose is better at improving obesity, and pioglitazone is better at improving insulin sensitivity in newly diagnosed type-2 DM patients with metabolic syndrome (69). Pioglitazone-induced weight gain can be effectively prevented by using voglibose as an add-on therapy to pioglitazone (70). Voglibose does not affect carotid intima-media thickness (IMT), urinary endothelin-1 and albumin excretion in diabetes patients; meanwhile, pioglitazone improves these parameters implying pioglitazone improves endothelial dysfunction, prevents atherosclerosis and is helpful in diabetic nephropathy but not voglibose as per the studies by Nakamura *et al.,* (61,71,72).

6. Voglibose and DPP-4 inhibitors

Voglibose monotherapy compared to linagliptin on postprandial glycemic control and lipid profile. Voglibose delayed plasma glucose peak from 1 hour to 2 hours, which was not seen with linagliptin. Linagliptin reduced plasma glucagon levels but not voglibose. Linagliptin was superior to voglibose in reducing 4-hour PPG, FPG and HbA1c levels, lipid metabolism parameters such as apoB-48, TG, LDL-C and remnant-like particle-cholesterol (RLP-C) with weight neutrality (73–75). Monotherapy with linagliptin was compared against monotherapy with voglibose by Araki *et al.* for their effectiveness and safety in type-2 DM. The study showed that both drugs cause significant reduction in FPG and HbA1c, but linagliptin had superior HbA1c reduction compared to voglibose. Both drugs improved beta cell function. Voglibose and linagliptin had similar safety profiles and were well tolerated. The common side effects in both

groups were gastrointestinal-related (76). Voglibose was more effective in PPG control, reducing glucose excursions and weight reduction compared to linagliptin, as per H Satoh *et al.* (77). Parthan *et al.* compared the efficacy of voglibose and linagliptin on metabolic profile in type-2 DM patients uncontrolled on metformin. When used with metformin, both drugs reduced FPG and HbA1c significantly. HOMA-IR, HOMA-B, insulin sensitivity, glucose disposal rate, and area under the curve (AUC) of C-peptide levels after 24 weeks of treatment in either group were unchanged (43). Ihana-Sugiyama *et al.* compared the postprandial glycemic control by the fixed-dose combination (FDC) of mitiglinide + voglibose against linagliptin in type-2 DM patients taking basal insulin. Both the groups had a significant, similar reduction of HbA1c, but the 0 to 120 min AUC of PPG was significantly reduced by the mitiglinide + voglibose compared to linagliptin. Mitiglinide + voglibose with basal insulin therapy improved PPG more efficiently than linagliptin in type-2 DM patients(78). Goto *et al.,* Compared the changes in glycemic parameters and treatment-related QoL in patients with type-2 DM, where linagliptin showed better glycemic control with more remarkable improvement in treatment-related QoL than voglibose (79).

When type-2 DM patients were treated with sitagliptin and voglibose monotherapies, sitagliptin showed better glycemic control than voglibose. Beta cell function improved by both the drugs, and sitagliptin was significantly better than voglibose. Insulin resistance and lipid profile were unaffected by the drugs. Voglibose was superior to sitagliptin in weight reduction (80). Similar results were observed when sitagliptin and voglibose were added to sulfonylureas (81). A study by Nakamura *et al.* comparing voglibose and sitagliptin implied that the drugs equally reduced HbA1c and improved vascular endothelial function without much effect on lipid profile. Sitagliptin increased circulating cluster of differentiation (CD)-34 levels but not voglibose, favouring the cardiovascular benefits in type-2 DM patients (82). A study by Oe *et al.* contradicted these results, saying neither voglibose nor sitagliptin improved/affected cardiac function parameters and inflammatory markers in type-2 DM patients despite HbA1c reduction (83,84). Shi *et al.* studied voglibose versus sitagliptin in type-2 DM patients on metformin and insulin, and the results showed sitagliptin treatment was superior to the voglibose treatment in HbA1c and FPG reduction after 12 weeks of therapy with significant improvement in HOMA-B levels. Both groups showed similar and significant PPG reduction. Weight loss in the sitagliptin combination was more than voglibose combination group (85). Mitiglinide+voglibose

combination showed better PPG glycemic control than sitagliptin and improved PPG excursions. Both the groups had little effect on FPG, HbA1c, AUC-Insulin, HOMA-B and HOMA-IR (86,87).

A 52-week study by Seino *et al.,* comparing the safety and effectiveness of alogliptin and voglibose in patients with type-2 DM poorly controlled by diet and exercise, imparted that alogliptin is better than voglibose in improving plasma glucose and HbA1c levels. Other study parameters such as AUC 0-2h, glycoalbumin and 1,5-AG levels were significantly improved by alogliptin compared to voglibose. Both drugs were safe without any drug-related serious adverse events (88). Voglibose used in combination with alogliptin led to significantly better glycemic control. The combination produced a significant reduction in HbA1c, glycoalbumin, FPG, total and LDL-cholesterol, fasting proinsulin/insulin ratio and an increase in HOMA-B and 1,5-AG levels compared to voglibose therapy alone. The Voglibose alogliptin combination is safe to use with very few adverse events, low chances of hypoglycemia, and minimum body weight change (89). Takahara *et al.* investigated the efficacy of once-daily (O.D.) and thrice-daily (t.i.d.) voglibose in patients of type-2 DM on alogliptin treatment. Results concluded that o.d. and t.i.d. voglibose, when used with alogliptin, substantially improved HbA1c levels. 1,5-AG change was more in the t.i.d. voglibose than in the o.d. voglibose (90). Iwamoto *et al.* compared voglibose and vildagliptin in patients with type-2 DM; vildagliptin showed significantly better FPG reduction and similar PPG reduction compared to voglibose at 12 weeks. Voglibose has better weight reduction compared to vildagliptin. Vildagliptin showed a beta cell preservation effect but not voglibose (91).

7. Voglibose and Meglitinides

Voglibose is effective as nateglinide in glycemic control. Nateglinide caused weight gain but not voglibose, and the difference was nonsignificant. Voglibose was associated with GI side effects, while the primary concern with nateglinide was hypoglycemia. The patients preferred nateglinide over voglibose, as per the study by Kurebayashi *et al*., comparing nateglinide and voglibose (92). Kataoka *et al.* studied the effects of voglibose and nateglinide on glucose levels and coronary atherosclerosis in early-stage type-2 DM patients. The study showed that voglibose led to higher rates of normal glucose tolerance achievement than nateglinide after one year of treatment.

Voglibose had superior glycemic control than nateglinide, which might have attenuated atheroma progression (93).

The effect of mitiglinide and voglibose as add-on drugs to long-acting insulin in patients with type-2 DM was studied by Son *et al.;* both groups showed a significant reduction in HbA1c, FPG and self-monitoring of blood glucose (SMBG) levels and mitiglinide combination was slightly superior to voglibose group. There was no effect on inflammatory markers by both combinations. Mitiglinide led to weight gain but not voglibose. Both drugs were safe to use as add-on therapy. This study concluded that concurrent use of mitiglinide with insulin glargine would be more effective in obese individuals with type-2 DM with relatively normal pancreatic islet function (94). Inoue et *al.* studied the efficacy of mitiglinide/voglibose FDC for effective control of post-prandial hyperglycemia in type-2 DM patients. Voglibose and mitiglinide monotherapies were compared with mitiglinide + voglibose FDC. The combination therapy had the best PPG control, followed by mitiglinide alone and voglibose alone. Voglibose caused a significant reduction in serum insulin levels, and mitiglinide showed increased serum insulin, but the combination therapy showed a neutral effect on serum insulin. Voglibose alone and the combination group improved serum triglycerides and RLP-C; meanwhile, the free fatty acid reduction was seen with combination therapy and mitiglinide therapy (95). Mitiglinide+voglibose combination provides significantly better PPG control with improvement in PPG excursions compared to mitiglinide monotherapy, as per Ono *et al.* (96). voglibose used in combination with mitiglinide provided superior glycemic control than voglibose alone in type-2 DM patients on haemodialysis, along with the reduction in glycated albumin, HOMA-IR and triglycerides (97). Mitiglinide+voglibose FDC thrice a day is significantly better than twice daily dosing reducing PPG and serum insulin. Twice daily dosing had significantly lesser GLP-1 and free fatty acid levels than t.i.d. dosing (98).

8. Voglibose v/s other Alpha-glucosidase inhibitors

In healthy individuals, the effects of acarbose and voglibose on glycemic parameters were studied by Kageyama *et al.,* both acarbose and voglibose reduced postprandial plasma glucose, and insulin levels and these changes were more significant at dinner than at breakfast; this might have been because of more intake of carbohydrates at dinner. This study concludes that acarbose more potently reduced plasma immunoreactive insulin (IRI) and urinary CRP levels than

voglibose in healthy individuals (99). Vichayanrat et *al.* evaluated the efficacy and safety of voglibose compared to acarbose in type-2 DM patients. The study concluded that voglibose and acarbose significantly improved postprandial glycemic parameters and HbA1c levels without any effect on fasting IRI and FPG in patients with type-2 DM, uncontrolled with diet and exercise. Voglibose resulted in fewer side effects and fewer chances of postprandial hypoglycemia (100). A study by Lee *et al.* compared the efficacy and safety of acarbose and voglibose in type-2 DM patients who were inadequately controlled with basal insulin therapy alone or in combination with Metformin. The results showed that acarbose and voglibose could effectively reduce blood glucose and HbA1c levels as an add-on therapy to insulin and insulin + metformin. There were no significant changes in total cholesterol, HDL-C, non-HDL-C, and LDL-C, but both drugs caused a significant rise in Apo-B levels. Gastrointestinal adverse effects like flatulence and diarrhoea were the most common in this study. Hypoglycemia was not a concern, as per the study (101).

Narita *et al.* compared the effect of miglitol and voglibose on plasma incretin levels after a mixed meal in Japanese patients with type-2 DM. The study concluded that long-term usage of miglitol and voglibose reduces GIP response and significantly increases active GLP-1 levels after a meal in type-2 DM patients (102). A study by Hariya *et al.* on switching from voglibose to miglitol on glucose fluctuations and circulating cardiovascular risk factors in Japanese patients with type-2 DM. The study concluded that changing from acarbose or voglibose to miglitol improved glucose fluctuations and serum protein concentrations of chemokine monocyte chemoattractant protein-1 (MCP-1) and soluble E-selectin more effectively than the prior alpha-GI (103). Miglitol has lesser PPG AUC 0-120min than voglibose and better TG reduction post-meal. miglitol has superior GLP-1 rise and GIP reduction than voglibose. The study demonstrated that a single dose of miglitol type-2 DM with CAD has beneficial effects on their post-prandial state of hyperglycemia, insulinemia, hyper-lipidaemia, vascular endothelial dysfunction, and incretin secretion. A single dose of miglitol, but not voglibose, improved PPG shortly after a meal (50). Tomoko Kimura *et al.* studied the additive effects of alpha-glucosidase inhibitors on PPG and lipid profile in type-2 DM patients controlled with insulin lispro mix 50/50. The results were that miglitol significantly reduced PPG and C-peptide levels but not voglibose compared to mix50 alone. Miglitol significantly reduced postprandial TG, 1-hour RLP-C, and VLDL levels, whereas voglibose increased RLP-C and VLDL levels and showed no

effect on TG levels. 1-hour postprandial plasma HDL-C and apo A-1 concentrations were increased by miglitol but reduced by voglibose and mix-50 alone groups (104).

9. Studies on voglibose and glimepiride and the rationale of the study

A study by Muller-Wieland *et al.* comparing the safety and efficacy of dapagliflozin against glimepiride with basal metformin therapy in type-2 DM patients was a 52-week duration, active-controlled, double-blind, randomized study. Patients of 18-75 years with type-2 DM not controlled on metformin ≥1500mg/day and BMI ≤ 45kg/m2 and HbA1c of 7.5% - 10.5% were included in the study. 939 patients were allocated in 3 groups and were given either dapagliflozin + saxagliptin (10mg/5 mg), dapagliflozin 10 mg, or glimepiride 1 to 6 mg, an add-on treatment. The baseline mean HbA1c was 8.3%. By the end of 52 weeks, mean HbA1c reduction was 1.2% in the dapagliflozin + saxagliptin group, 0.99% with glimepiride, and 0.82% in the dapagliflozin group. Dapagliflozin groups showed reduction in body weight, whereas the glimepiride group had a weight gain of 1.8kg. Dapagliflozin + saxagliptin had significantly better FPG reduction than glimepiride. Chances of hypoglycemia were more in glimepiride-treated patients. The study concluded that dapagliflozin addon showed good glycemic control, reduced body weight and less chances of hypoglycemia compared to glimepiride (37).

A study by Kim HJ *et al.* to compare the efficiency of alogliptin, glimepiride, and alogliptin + pioglitazone as addon to metformin, the study included 99 patients of 19 to 80 years with HbA1c between 7.5% to 10% who either uncontrolled on metformin 1000mg or newly diagnosed type-2 DM. Patients were randomized into 3 groups in this study. Patients were given either alogliptin 25 mg, glimepiride 1-2mg/day, or alogliptin + pioglitazone 25mg/15 mg for 24 weeks. Endpoints evaluated were HbA1c, FPG, fasting insulin, C-peptide, and HOMA. At 24 weeks mean HbA1c reduction was 0.96 % in the alogliptin+pioglitazone group and 0.75% in the glimepiride group. HbA1c reduction was significant from baseline but not between these two groups. There was a substantial decrease in FPG in all the groups. Alogliptin + pioglitazone showed a reduction in HDL-C but not glimepiride. The side effects across the groups were similar, and the study concluded alogliptin+pioglitazone combination has better glycemic control than glimepiride therapy as an add-on to metformin (38).

Derosa *et al.* compared the effect of glimepiride and rosiglitazone with metformin as basal therapy in metabolic syndrome patients. It was a randomized, double-blind study. Type-2 DM patients diagnosed with metabolic syndrome on metformin treatment with high plasma glucose were included. They were randomized into two groups and were given 1500mg/day metformin as basal therapy; one group was given glimepiride 2mg/day and the other group rosiglitazone 4mg/day for 1 year. Changes in HbA1c, FPG, PPG, fasting insulin, BMI, and HOMA were assessed. 99 patients were enrolled into the study, and there was a significant decrease in HbA1c, FPG, and PPG in both groups by the end of 12 months. Mean HbA1c reduction was from 7.7% to 7% in the glimepiride group and 7.4% to 7.8% in the rosiglitazone group. There was no change in fasting insulin and HOMA index in the glimepiride group, but in the rosiglitazone group significantly decreased. The study concluded that in patients of type-2 DM with metabolic syndrome, treatment with the rosiglitazone combination improved long-term glycemic control with improvement in insulin resistance-related parameters (40).

Voglibose as an addon to metformin was compared with metformin alone for its safety and effectiveness in patients of type-2 DM by Oh TJ *et al.* It was a 24-week randomized controlled trial. Patients between 20 to 70 years of age with HbA1c of 7% to 11% who were drug naïve were enrolled. 187 patients were randomized into 2 groups in a 1:1 ratio. One group was given metformin + voglibose 250mg/0.2 mg thrice a day, and the other group was given metformin 500mg thrice a day. Dose escalation was done if blood glucose was uncontrolled. Patients were evaluated for HbA1c, FPG, PPG, and safety. 95 patients were enrolled in the voglibose/metformin group and 92 patients in the metformin group. The results showed that the voglibose/metformin group had an HbA1c reduction of 1.62%, and metformin showed a 1.31% reduction. The change was significant across the groups. There was a substantial reduction in FPG and PPG in both groups, metformin/voglibose being significantly better than metformin alone. There was a substantial decrease in body weight by metformin/voglibose (1.63kg) but not metformin alone. GI side effects were lower in the metformin/voglibose group compared to metformin alone. The study concluded that metformin/voglibose treatment is superior to metformin alone in type-2 DM patients (45).

As seen with the above studies, there is inconsistency in the glycemic control provided by the metformin and glimepiride combination, where HbA1c reduction is around 0.6% to 1%;

meanwhile, metformin + voglibose provided an HbA1c reduction of 1.6%. The drawbacks of these studies are that only one study on the plane metformin + voglibose combination was available in the databases; hence more studies for concrete evidence are necessary to establish the results. No direct comparison studies are available between glimepiride and voglibose. Hence, this study provides the data necessary to fill these lacunae. With these things in mind, this study was planned.

MATERIALS AND METHODS

Study Setting

The study took place in the Department of Pharmacology in collaboration with the Department of Endocrinology at All India institute of medical sciences (AIIMS), Jodhpur. Patient recruitment was done in the outpatient division of the department of endocrinology, AIIMS, which is a tertiary health care centre located in Jodhpur city, Rajasthan state of India. Patient enrolment was done from February 2021 to July 2022.

Study Design

It was a prospective, single-centre, randomized, active-controlled, parallel-group, open-label clinical trial. The Institutional ethics committee (AIIMS, Jodhpur) approved the study (**AIIMS/IEC/2021/3462**) dated 12th March 2021 (**ANNEXURE I**). The study was registered with the Clinical Trial Registry of India (CTRI) with registration number - **CTRI/2021/04/033005** (**ANNEXURE XI**).

The study was conducted as per the International Conference on Harmonization-Good clinical practice (ICH-GCP) and ICMR (National Ethical Guidelines for Biomedical and Health Research involving Human Participants 2017) guidelines. Patients who satisfied inclusion/exclusion criteria were randomized into two groups, allocated in a 1:1 ratio and given either test drug Metformin + voglibose or active control Metformin + glimepiride. We made no changes to the protocol after the commencement of the study, and no interim analysis was planned.

Patient Selection Criteria

Type-2 DM patients were screened in the outpatient department for the eligibility criteria.

The **inclusion criteria** were,

1. Patients of either gender with age 18-60 yrs.
2. Newly diagnosed Type 2 Diabetes mellitus patients with HbA1c between 7% to 11%

   (or)
3. Patients who were uncontrolled on Tab. Metformin 500mg BD (RBS > 200mg at least on 3 occasions or HbA1C between 7% -11%).

Newly diagnosed Type-2 Diabetes was defined as patients with HbA1c from 7% to 11% and who were not on any type-2 DM medications. Patients were labelled as uncontrolled on Metformin when random blood sugar (RBS) was >200mg/dl on at least three occasions or HbA1c was from 7% to 11%.

The **exclusion criteria** were,

1. Type-1 DM patients.
2. Pregnant and Lactating women.
3. Patients with history of Heart failure (NYHA class 2-4).
4. Patients with history of chronic kidney disease (serum creatinine > 1.5mg/dl).
5. Patients with history of liver failure.
6. Patients with history of autoimmune disorders.
7. Patients with history of COPD.

Randomization, Concealment, and Blinding

Block Randomization sequence (1:1) was generated using online random sequence generating software ‘Research randomizer’ by the principal investigator. Forty blocks were generated with a block size of 2 with unique numbers in each block. Each block had one voglibose group and one glimepiride group patient.

Allocation concealment

The principal investigator did the allocation sequence generation and concealment. After confirming with the principal investigator, the junior resident revealed the sequence to the treating physician during patient enrolment. The eligible patients enrolled on either of the two groups

Group 1 – It was an intervention group that received Metformin + voglibose.

Group 2 – An active control group that received Metformin + glimepiride.

Blinding

It was an open-labelled study. Participants and investigators were aware of the treatment given. All the assessments were done by investigators who were not blinded.

Study Flow

Patients were allocated into two groups (1:1), Metformin + Voglibose (Voglibose group) and Metformin + Glimepiride group (Glimepiride group). Patients in the voglibose group were given a fixed drug combination (FDC) tablet of Metformin 500mg + voglibose 0.2mg twice a day (morning and night) orally with a meal. The Glimepiride group received Tablet Metformin 500 mg twice a day (morning and night) + Glimepiride 1mg once a day in the morning before breakfast. Patients were advised to have a healthy lifestyle and dietary modification, which included foods with a low glycemic index, a high-fibre diet, and daily exercise. Metformin + Voglibose was given twice daily, and if the blood glucose was uncontrolled, then 0.2mg of voglibose at noon with meals was added to the therapy; meanwhile, no dose upgradation was done in the glimepiride group. If blood glucose was uncontrolled despite the allocated therapy, rescue medicines were started based on clinicians' judgement.

It was a 3-month study, and patient follow-up was done monthly. At baseline and three months, the efficacy of the treatment was assessed. Safety was assessed at each visit and telephonically every fortnight.

Study Endpoints

The **Primary endpoints**,

1. Difference of HbA1c reduction in between voglibose and glimepiride group after three months.
2. The difference in decrease in FBG & PPG between the voglibose and glimepiride group after three months.

The **Secondary endpoints**,

1. Adverse events in both the groups.
2. The difference in lipid parameters (Triglycerides, Total Cholesterol, LDL, VLDL, and HDL) in both the groups after three months.
3. The difference in quality-of-life indicators between the voglibose and glimepiride group after three months.
4. The difference in HOMA – IR, HOMA - β% and HOMA - S% of voglibose and glimepiride group after three months.
5. The difference in need and use of rescue medicines in both the groups during 3-month study period.

No changes were made to trial endpoints during the study period.

Endpoints Assessment

Parameters such as FPG, and PPG, during every visit (1^{st}, 2^{nd}, 3^{rd} month). HbA1c, fasting insulin, lipid profile (TG, TC, LDL, VLDL, and HDL), Homeostatic model assessment 2 (HOMA2), and QoL were assessed at baseline and 12 weeks. Safety and side effects were recorded telephonically every two weeks and during the follow-up visit. The patients were informed to contact us in case of an emergency. Patients were told to fast overnight before the day of their visit, and venous blood samples were collected for FPG, HbA1c, fasting insulin, and lipid profile in the morning, and they were told to have breakfast. PPG samples were collected 2hours after breakfast. All the samples were collected in the outpatient block sample collection unit and processed in the Central Biochemistry laboratory of the hospital.

- **HbA1c assessment**

  Venous blood samples were collected and processed on the same day using high-performance liquid chromatography (HPLC), VARIANT II Bio-Rad.

- **FPG and PPG assessment**

  Venous blood samples were taken after overnight fasting for FPG and 2 hours after food for PPG analysis, and the samples were analysed on the same day. The parameters were evaluated by Hexokinase method spectrophotometry using a Beckman Coulter AU680 analyser.

- **Lipid Profile assessment**

  Fasting lipid parameters were assessed on the same day of sample collection. Total cholesterol was analysed by enzymatic (CHOD-POD) method, and triglyceride levels were analysed by a spectrometric method based on enzymatic reaction (Lipase, Glycerol Kinase, Glycerol Phosphate Oxidase, Ascorbate Oxidase and Peroxidase) using Beckman Coulter AU680 analyser. The machine computed HDL-C and LDL-C automatically, and VLDL-C calculation was done using the Friedewald equation.

- **Fasting Insulin assessment**

  Fasting blood samples were taken during the patient's follow-up visit. The sample was collected in a yellow tube. The samples were centrifuged at 4000 rpm for 8 minutes. The serum samples were stored away at -80 degree Celsius. After completion of the study, *en masse* analysis of the samples was done after thawing. Fasting insulin (Immunoreactive insulin) was analysed by chemiluminescence immunoassay (CLIA) using the ADVIA Centaur®XP machine.

- **Homeostatic model assessment** (**HOMA**)

  Homeostatic model assessment 2 was used as it is more sensitive than HOMA. HOMA2-IR (insulin resistance), HOMA2-S% (insulin sensitivity), and HOMA2-B% (beta cell function) were calculated at baseline and the third month based on FPG and fasting insulin levels using the HOMA2 calculator v2.2.3 (Diabetes Trial Unit, University of Oxford) (105–107). FPG in

mg/dl and fasting insulin in µU/ml were used to calculate HOMA2-IR, HOMA2-B% and HOMA2-S%.

- **Quality of life assessment**

  A revised version of the Diabetes quality of life (DQoL) instrument issued by the Diabetes Control and Complications Trial (DCCT) Research Group was used to assess the QoL in these patients. The questionnaire consists of 13 questions, subdivided into three domains, impact, satisfaction and worry domains consisting of 6, 4 and 3 questions, respectively. Each question scored 1 to 5 in the satisfaction and impact domain and 0 to 5 in the worry domain. Reduction in score was considered an improvement in domains and QoL. The questionnaire was used at baseline and three months. The scores were recorded, and changes in scores were analysed at the end (**ANNEXURE V**).

Sample Size

No similar study was available. G-power software was used to calculate the sample size based on Cohen's predefined effect size for the unpaired t-test. With 5% type 1 error, 80% power and an effect size of 0.8. The sample size was 26 patients per group. Considering dropouts, 35 subjects were randomized in each group. No interim analysis was done.

Study instrument

Appropriate recording format in paper form (Case record form) was used to record patients' demography, complaints, symptoms, comorbidities, concomitant treatment, clinical and lab evaluation results, and adverse events (**ANNEXURE VI**).

STATISTICAL ANALYSIS

Descriptive statistics were reported as frequency, percentage, mean and Standard Deviation. Paired t-test was used to compare before and after values of HbA1c, FBG, PPG, Triglycerides, Total Cholesterol, LDL, VLDL, HDL, Quality of life Indicators, HOMA2-IR, HOMA2-B% and HOMA2-S% within the groups. Unpaired t-test was used for the intergroup comparison of parameters. Fisher's exact test compared differences in adverse events between groups. A p-value of <0.05 was considered significant. Both intention to treat and per-protocol analysis were done. Analysis of data was done with the help of SPSS Statistics for windows, version 23.0., SPSS Inc, Chicago, IL, USA.

RESULTS

A total of 128 type-2 DM patients were screened for eligibility in the Department of Endocrinology, AIIMS, Jodhpur, from February 2021 to June 2023. 73 patients were enrolled, and the patients who were not satisfying inclusion/exclusion criteria or refused to give consent were excluded. 73 type-2 DM patients were randomized into voglibose and glimepiride groups in a 1:1 ratio. Thirty-seven patients with type-2 DM were allocated to the voglibose treatment and 36 to the glimepiride treatment. Patient follow-up was done every month for safety and at the end of 3 months to assess efficacy parameters. By the end of the study, three patients were lost to follow-up in the Voglibose group, whereas one patient was lost to follow-up in the glimepiride group (**Figure 1**).

Comparison Baseline parameters between the groups
Demographic data

All the parameters were equally distributed across the voglibose and glimepiride group at baseline except for HDL-Cholesterol. The mean age was 48.05 (10.12) and 48.58 (8.59) years in the voglibose and glimepiride groups (p=0.811), respectively. Gender distribution was 19/18 (Male/Female) and 18/18 (M/F) in the voglibose and glimepiride groups (p=1.000), respectively. Newly diagnosed type-2 DM patients were 29 (78.38%) in the voglibose-treated group and 27 (75.00%) in the glimepiride group (p=0.787), and the rest were uncontrolled type-2 DM on Metformin 500 mg BD., (p=0.787) (**Table 1**).

Clinical symptoms and comorbidities

In the voglibose group, common clinical presentations were polyuria (56.75%), polydipsia (51.35%), polyphagia (40.54%), visual symptoms (13.51%), paraesthesia (48.64%), easy fatiguability (51.35%) and weight loss (16.21%). Meanwhile, in the glimepiride group, common clinical presentations were polyurea (55.55%), polydipsia (38.88%), polyphagia (33.33%), visual symptoms (11.11%), paraesthesia (47.22%), diabetic ulcer (5.55%), gangrene (2.77%), easy fatiguability (27.77%), and weight loss (8.33%). Presenting symptoms were equally distributed across the groups (**Table 1**).

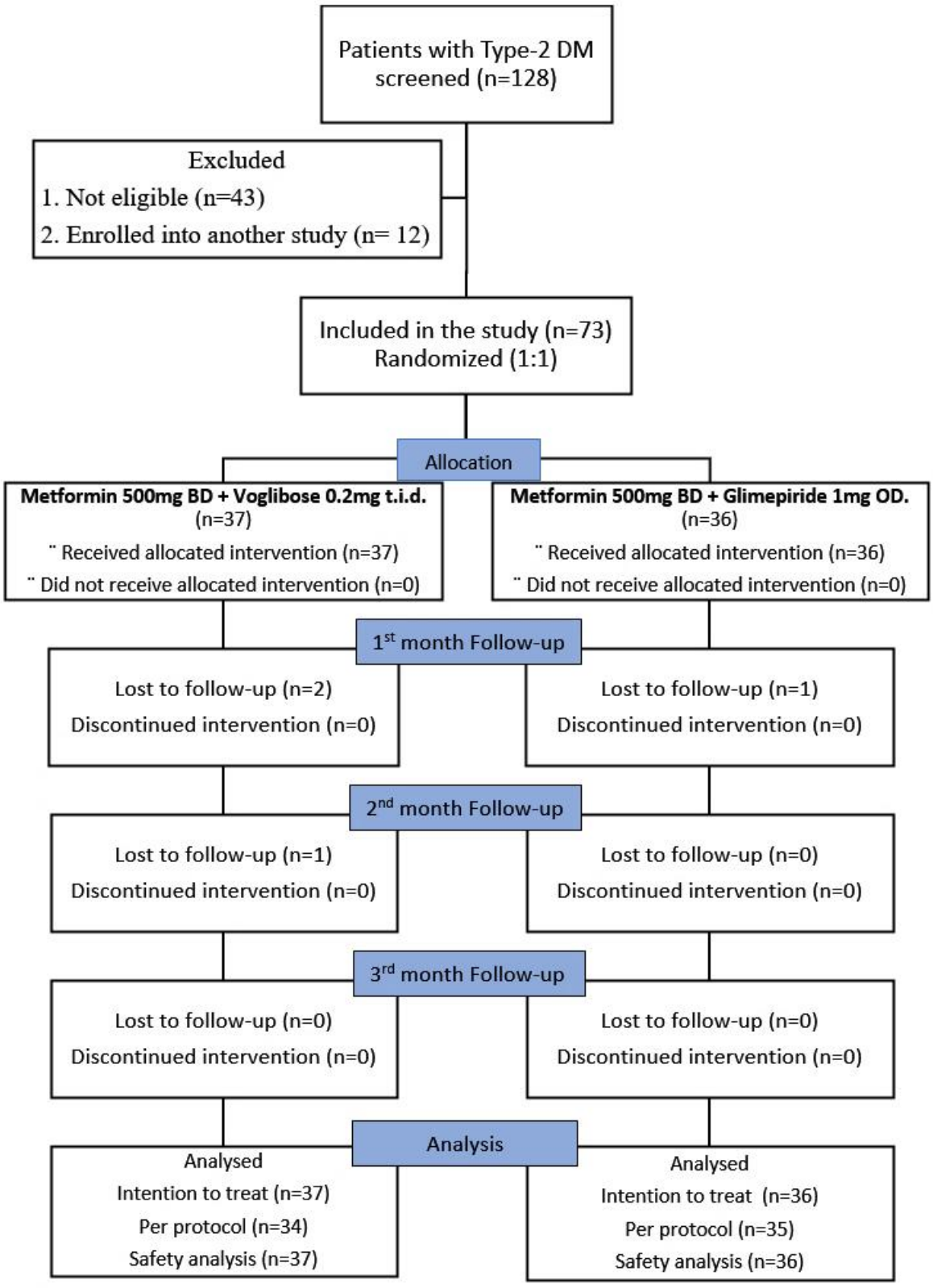


Figure 1. CONSORT diagram

In the voglibose group, comorbidities seen were hypertension (16.21%), IHD (5.40%), skin infections (10.81%), and hypothyroidism (8.10%), whereas, in the glimepiride group, hypertension (16.66%), IHD (5.55%), skin infections (8.33%), CVA (2.77%), and hypothyroidism (13.88%) were the associated comorbidities. The groups had no statistically significant difference in comorbidities (**Table 1**).

Weight and BMI

Mean (SD) weight in kg was 71.25 (12.86) in the voglibose group and 71.46 (15.25) in the glimepiride group (p=0.948). Mean BMI (Kg/m^2) was 27.04 (4.31) in the voglibose treated & 27.11 (5.97) in the glimepiride-treated group (p=0.931) (**Table 1**).

HbA1c, Fasting and Postprandial blood glucose

At baseline, mean (SD) HbA1c (%) was 8.80 (1.46) & 8.82 (1.51) in the voglibose and glimepiride groups, respectively (p=0.961). Mean FPG (mg/dl) was 189.08 (67.33) in the voglibose group & 179.83 (47.90) in the glimepiride group (p=0.502). Voglibose group had mean post-prandial plasma glucose (mg/dl) of 297.56 (76.37) & glimepiride group 280.33 (80.38) (p=0.351) (**Table 1**).

Lipid profile

Total cholesterol (mg/dl) was 187.29 (47.28) in the voglibose group and 190.69 (51.92) in the glimepiride group (p=0.771). Triglycerides (mg/dl) were 159.67 (83.35) in the voglibose group and 156.41 (64.84) in the glimepiride-treated group (p=0.853). LDL-C (mg/dl) was 125.97 (35.39) in the voglibose group and 127.78 (38.16) in the glimepiride-treated group (p=0.835). VLDL-C (mg/dl) was 31.78 (16.73) in the voglibose-treated group and 31.11 (13.02) in the glimepiride-treatment group (p=0.849). These parameters were similar between the groups at baseline except HDL-C; in the voglibose group HDL-C was 40.46 (8.22), and in the glimepiride group 45.67 (10.71) with significant difference (p=0.022) (**Table 1**).

Fasting serum Insulin and HOMA2

The mean (SD) of Fasting serum insulin (μU/ml) at baseline was 14.72 (11.84) in the voglibose-treated group and 16.92 (14.51) in the glimepiride group (p=0.479). HOMA2-IR was 2.67 (2.59) and 3.22 (5.41) in the voglibose and glimepiride groups, respectively (p=0.576). HOMA2-B% was 45.88 (32.57) in the voglibose group and 53.69 (44.01) in the glimepiride-treated group (p=0.391). HOMA2-S% was 71.46 (61.36) in the voglibose group and 63.45 (48.90) in the glimepiride-treated group (p=0.539). These p-values were statistically nonsignificant between the groups at baseline (**Table 1**).

Table 1. Patients' Demographic Data and Baseline Characteristics

Characteristics	Voglibose treated group (n=37)	Glimepiride-treated group (n=36)	*p-value*
Age in years [#]	48.05 (10.12)	48.58 (8.59)	0.811
Gender (M/F) [§]	19/18	18/18	1.000
Weight in Kg [#]	71.25 (12.86)	71.46 (15.25)	0.948
BMI [#]	27.04 (4.31)	27.11 (5.97)	0.931
New type-2 DM (%) [¶]	29 (78.38)	27 (75.00)	0.787
Type-2 DM Uncontrolled on Metformin (%) [¶]	8 (21.62)	9 (25.00)	0.787
HbA1c (%) [#]	8.80 (1.46)	8.82(1.51)	0.961
FPG (mg/dl) [#]	189.08 (67.33)	179.83 (47.90)	0.502
PPG (mg/dl) [#]	297.56 (76.37)	280.33 (80.38)	0.351
Fasting Insulin (µU/ml) [#]	14.72 (11.84)	16.92 (14.51)	0.479
Total Cholesterol (mg/dl) [#]	187.29 (47.28)	190.69 (51.92)	0.771
Triglycerides (mg/dl) [#]	159.67 (83.35)	156.41 (64.84)	0.853
HDL-C (mg/dl) [#]	40.46 (8.22)	45.67 (10.71)	0.022
LDL-C (mg/dl) [#]	125.97 (35.39)	127.78 (38.16)	0.835
VLDL-C (mg/dl) [#]	31.78 (16.73)	31.11 (13.02)	0.849
HOMA2-IR [#]	2.67 (2.59)	3.22 (5.41)	0.576
HOMA2-B% [#]	45.88 (32.57)	53.69 (44.01)	0.391
HOMA2-S% [#]	71.46 (61.36)	63.45 (48.9)	0.539
Hypertension (%) [¶]	6 (16.21)	6 (16.66)	1.000
IHD (%) [¶]	2 (5.40)	2 (5.55)	1.000
Skin infections (%) [¶]	4 (10.81)	3 (8.33)	1.000
CVA (%) [¶]	0 (0.00)	1 (2.77)	0.493
Hypothyroidism (%) [¶]	3 (8.10)	5 (13.88)	0.479
Polyurea (%) [¶]	21 (56.75)	20 (55.55)	1.000
Polydipsia (%) [¶]	19 (51.35)	14 (38.88)	0.350

Characteristics	Voglibose treated group (n=37)	Glimepiride-treated group (n=36)	*p-value*
Polyphagia (%) ¶	15 (40.54)	12 (33.33)	0.630
Visual symptoms (%) ¶	5 (13.51)	4 (11.11)	1.000
Paraesthesia (%) ¶	18 (48.64)	17 (47.22)	1.000
Ulcer (%) ¶	0 (0.00)	2 (5.55)	0.240
Gangrene (%) ¶	0 (0.00)	1 (2.77)	0.493
Easy fatiguability (%) ¶	19 (51.35)	10 (27.77)	0.056
Weight loss (%) ¶	6 (16.21)	3 (8.33)	0.479
§ data presented as numerical, **#** Data presented as Mean (SD), **¶** data presented as n (percentage) FPG – Fasting plasma glucose, BMI – Body mass index, PPG – Postprandial plasma glucose, IHD – Ischemic heart disease, CVA – Cerebrovascular accident			

Change in Efficacy parameters in the voglibose and glimepiride group at week 12

Change in primary endpoints

The difference in change in HbA1c

The Voglibose group had HbA1c reduction from 8.80 (1.46) baseline to 7.46 (1.25) at 12 weeks with a mean difference of HbA1c reduction 1.34 (95% CI = 0.99 to 1.68; p-value < 0.001), which was statistically significant. The change in the glimepiride group was from 8.82 (1.51) to 7.07 (0.96) with a mean difference of HbA1c reduction of 1.75 (95% CI = 1.38 to 2.13; p < 0.001), which was significant.

The difference in change in HbA1c from the baseline was statistically nonsignificant across the groups (Mean difference = - 0.41 (95% CI = -0.92 to 0.09) p = 0.104)). Similar findings were seen in the per-protocol analysis (**Table 2 - 4, Figure 2, ANNEXURE II-IV**).

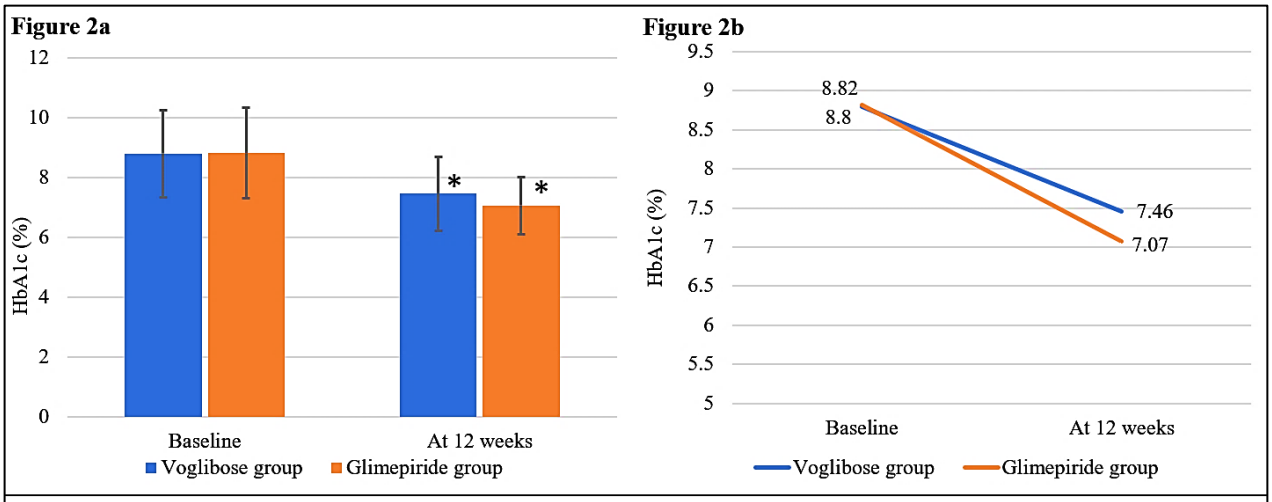


Figure 2. Change in HbA1c from baseline to 12 weeks in Voglibose group v/s Glimepiride group
2a. Shows a clustered column plot representing HbA1c at baseline and at 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
2b. Shows line plot depicting change in HbA1c from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in HbA1c within the group after 12 weeks of treatment.

Figure 2. Change in HbA1c

The difference in change in Fasting plasma glucose (FPG)

The Voglibose group showed an FPG reduction from 189.08 (67.34) to 129.78 (33.04) with a mean difference of FPG reduction of 59.29 (95%CI = 39.7-78.89; $p < 0.001$), which was significant. The Glimepiride group showed an FPG reduction from 179.83 (47.91) to 118.5 (27.28) with a mean difference of FPG reduction of 61.33 (95%CI = 44.01 to 78.65; $p < 0.001$), which was significant.

The difference in change in FPG from the baseline was statistically nonsignificant between the groups (Mean difference = -2.04 (95%CI = -27.78 to 23.71; p=0.448)). The per-protocol analysis showed equivalent results (**Table 2 - 4, Figure 3, ANNEXURE II-IV**).

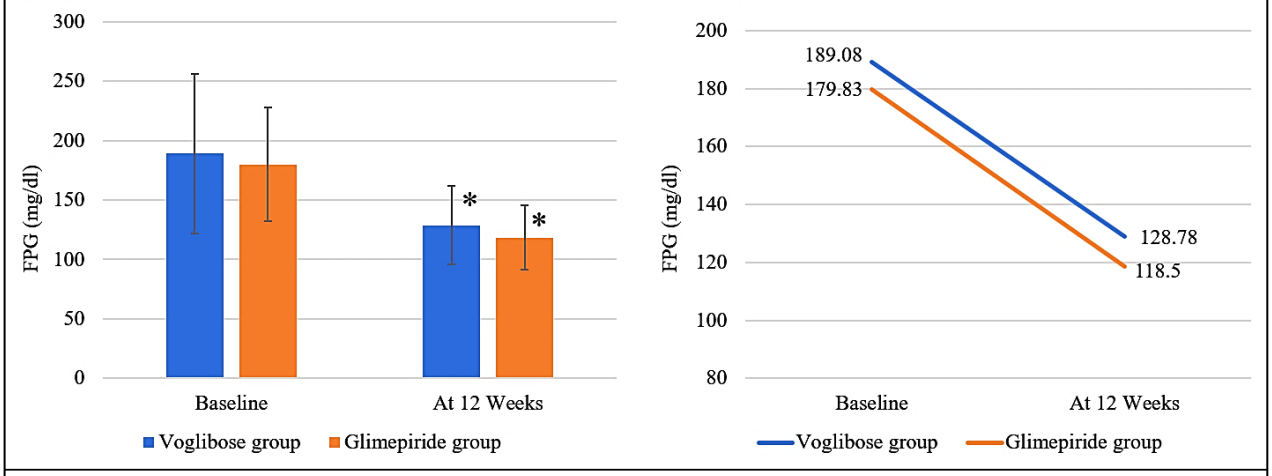


Figure 3. Change in Fasting plasma glucose (FPG) from baseline to 12 weeks in Voglibose group v/s Glimepiride group.
3a. Shows a clustered column plot representing FPG at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
3b. Shows line plot depicting change in FPG from baseline to 12 weeks in voglibose and glimepiride group.
***** represents statistically significant change in HbA1c within the group after 12 weeks of treatment.

Figure 3. Change in Fasting Plasma Glucose

The difference in change in postprandial plasma glucose (PPG)

The mean PPG in the voglibose group changed from 297.56 (76.38) to 176.75 (52.29) with a mean difference of PPG reduction of 120.81 (95%CI = 97.26 to 114.35; $p < 0.001$), which was significant. The Glimepiride group showed a change from 280.33 (80.38) to 146.08 (52.44) with a mean difference of PPG reduction of 134.25 (95%CI = 107.31 to 161.19; $p < 0.001$), which was also significant.

The difference in change in PPG from the baseline was statistically nonsignificant between the groups (Mean difference = -13.44 (95%CI = -48.54 to 21.66; p=0.448)). The per-protocol analysis showed equivalent results (**Table 2 - 4, Figure 4, ANNEXURE II-IV**).

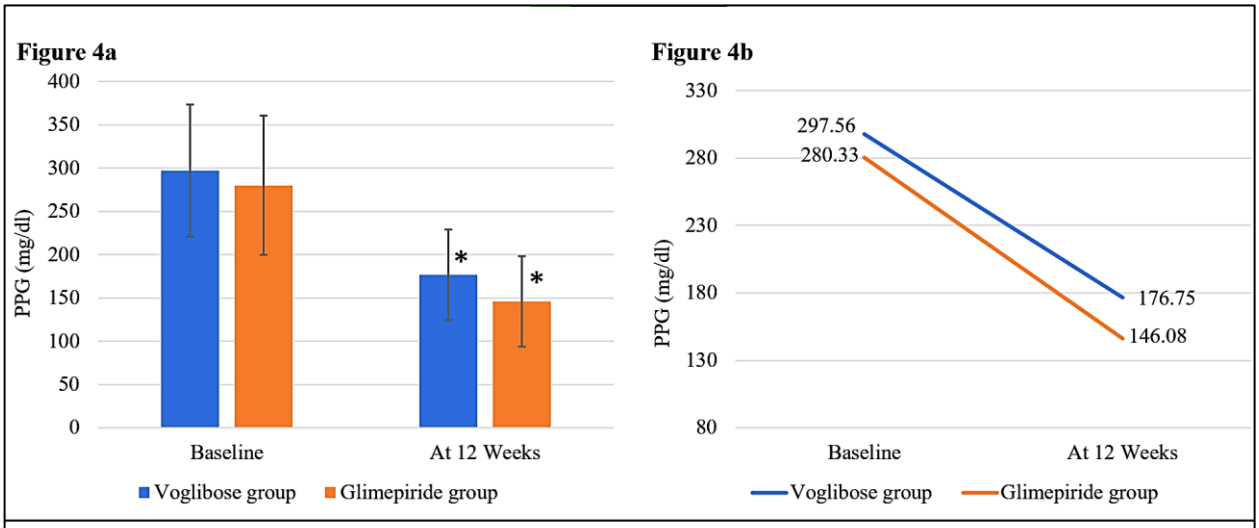


Figure 4. Change in Post prandial glucose (PPG) from baseline to 12 weeks in Voglibose group v/s Glimepiride group.
4a. Shows a clustered column plot representing PPG at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
4b. Shows line plot depicting change in PPG from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in HbA1c within the group after 12 weeks of treatment.

Figure 4. Change in Postprandial glucose

Change in secondary endpoints

The difference in change in Body weight and BMI

The difference in change in Body weight

Body weight reduced from 71.25 (12.86) to 68.78 (12.38), with a mean difference of body weight reduction of 2.54 (95%CI=1.86 to 3.22; p < 0.001) with voglibose treatment. It changed from 71.47 (15.25) to 71.38 (14.75) with a mean difference of body weight reduction of 0.08 (95%CI = -0.90 to 1.07; p=0.865) with glimepiride treatment. The weight reduction was significant in the voglibose group but not in the glimepiride group.

At 12 weeks, the Voglibose group had a significant decrease in body weight compared to the glimepiride group (Mean difference = 2.46 (95%CI = 1.28 to 3.63; p<0.001)). Similar results were seen with per-protocol analysis (**Table 2 - 4, Figure 5, ANNEXURE II-IV**).

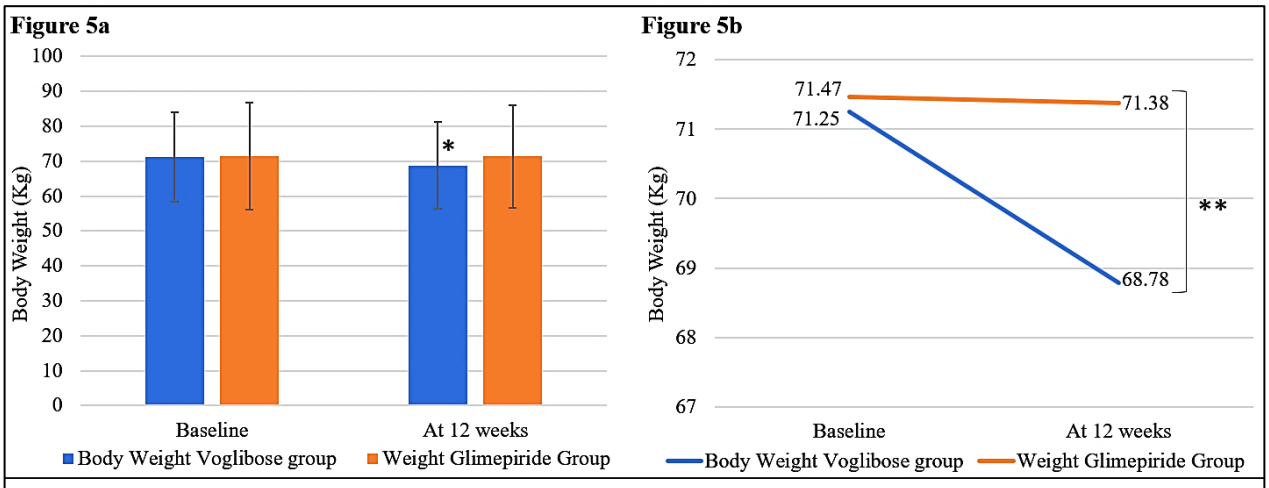


Figure 5. Change in Body Weight from baseline to 12 weeks in Voglibose group v/s Glimepiride group
5a. Shows a clustered column plot representing Body weight at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
5b. Shows line plot depicting change in Body weight from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in HbA1c within the group after 12 weeks of treatment with *p-value* <0.05.
** represents statistically significant difference in change in body weight between voglibose group and glimepiride group *p-value* <0.05.

Figure 5. Change in Body weight

The difference in change in BMI

The Voglibose group showed a mean BMI (kg/m^2) reduction from 27.05 (4.31) to 25.99 (3.90) with a mean difference of BMI reduction of 1.05 (95%CI = 0.75 to 1.36; P<0.001) which was significant; meanwhile in glimepiride group BMI change was from 27.15 (5.97) to 27.10 (5.75) with a mean difference of BMI reduction of 0.05 (95%CI = -0.31 to 0.42; p=0.777) which was statistically nonsignificant.

At 12 weeks, the Voglibose group had a significant decrease in BMI compared to the glimepiride group (Mean difference = 1.00 (95%CI = 0.53 to 1.48; p<0.001)). Similar changes were seen with per-protocol analysis (**Table 2 - 4, Figure 6, ANNEXURE II-IV**).

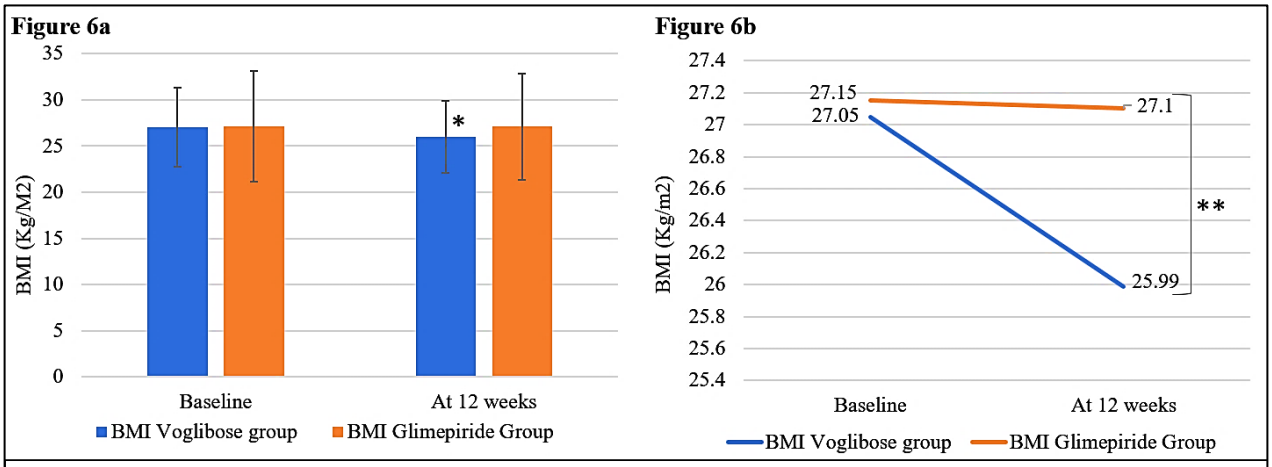


Figure 6. Change in BMI from baseline to 12 weeks in Voglibose group v/s Glimepiride group
6a. Shows a clustered column plot representing BMI at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
6b. Shows line plot depicting change in BMI from baseline to 12 weeks in voglibose and glimepiride group.
***** represents statistically significant change in BMI within the group after 12 weeks of treatment with *p-value* <0.05.
****** represents statistically significant difference in BMI between voglibose group and glimepiride group *p-value* <0.05.

Figure 6. Change in BMI

The difference in change in Lipid profile

The difference in change in Total Cholesterol (TC)

The Voglibose group had a Mean TC reduction from 187.30 (47.29) to 181.05 (41.59). The mean difference of TC reduction was 6.24 (95%CI = -1.44 to 13.92; p=0.108) without significance. In the glimepiride group, the change was from 190.69 (51.92) to 178.89 (48.82) with a mean difference of TC reduction of 11.8 (95%CI = 2.83 to 20.78; p=0.011), and the change was significant.

The difference in change in TC from the baseline was statistically nonsignificant between the groups (Mean difference = -5.56 (95%CI = -17.14 to 6.02; p=0.342)). The per-protocol analysis showed similar results (**Table 2 - 4, Figure 7, ANNEXURE II-IV**).

The difference in change in Triglycerides (TG)

The Voglibose group had a TG reduction from 159.67 (83.35) to 149.89 (83.18) with a mean difference of TG reduction of 9.78 (95%CI = -3.82 to 23.38; p=0.153), which statistically nonsignificant. The Glimepiride group had a TG reduction from 156.42 (64.84) to 143.17 (52.89) with a mean difference of TG reduction of 13.25 (95%CI = 0.28 to 26.22; p=0.045) with significance.

The difference in change in triglycerides from the baseline was statistically nonsignificant across the groups (Mean difference = -3.47 (95%CI = -21.95 to 15.02; p=0.710)). Similar results were seen with per-protocol analysis (**Table 2 - 4, Figure 7, ANNEXURE II-IV**).

The difference in change in LDL-Cholesterol (LDL-C)

LDL-C in the voglibose group changed from 125.97 (35.39) to 119.35 (32.49) with a mean difference of LDL-C reduction of 6.62 (95%CI = 1.12 to 12.11; p=0.020) and which was significant. The change in the glimepiride group was from 127.78 (38.17) to 119.36 (39.15) with a mean difference of LDL-C reduction 8.42 (95%CI = 1.93 to 14.90; p=0.012) with significance.

The difference in change in LDL-C from the baseline was statistically nonsignificant between the groups (Mean difference = -1.79 (95%CI = -10.13 to 6.54; p=0.669)). Similar results were seen with per-protocol analysis (**Table 2 - 4, Figure 7, ANNEXURE II-IV**).

The difference in change in HDL-Cholesterol (HDL-C)

The Voglibose group had HDL-C change from 40.46 (8.22) to 42.89 (8.39) with a mean difference of HDL-C increase of -2.43 (95%CI = -4.85 to -0.02; p=0.048), which was statistically significant. In the glimepiride group, HDL-C change was from 45.67 (10.88) to 44.50 (9.79) with a mean difference of HDL-C reduction of 1.17 without significance (95%CI = -0.76 to 3.10; p=0.228).

At 12 weeks, the voglibose group had a significant increase in HDL-C compared to the glimepiride group (Mean difference = -3.60 (95%CI = -6.64 to -0.55; p=0.021)). Per-protocol analysis results were similar (**Table 2 - 4, Figure 7, ANNEXURE II-IV**).

The difference in change in VLDL-Cholesterol (VLDL-C)

The VLDL-C change in the voglibose group was from 31.78 (16.73) to 30.78 (16.33) with a mean difference of VLDL-C reduction 1.40 (95%CI = -1.44 to 4.25; p=0.324) which was statistically nonsignificant. The change in the glimepiride group was from 31.11 (13.02) to 28.56 (10.60) with a mean difference of VLDL-C reduction 2.55 (95%CI = -0.12 to 5.13; p=0.052) without significance.

There was no significant difference observed with the change in VLDL-C from the baseline between the groups (Mean difference = -1.12 (95%CI = -4.91 to 2.65; p=0.556)). Similar results were seen with per-protocol analysis (**Table 2 - 4, Figure 7, ANNEXURE II-IV**).

Figure 7a

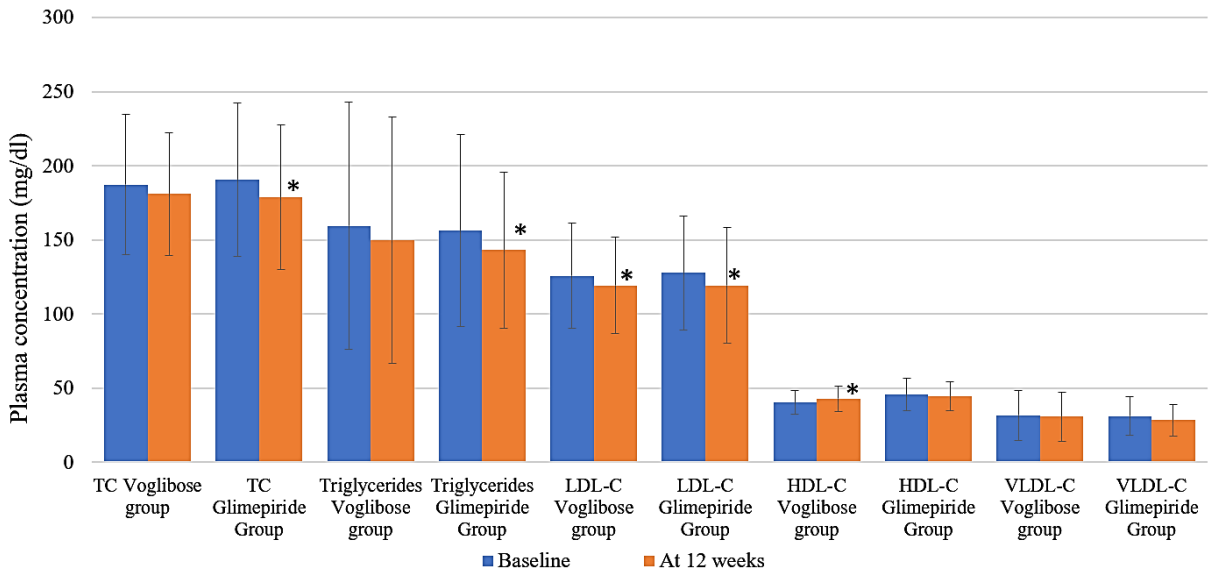


Figure 7. Change in Lipid profile from baseline to 12 weeks in Voglibose group v/s Glimepiride group
7a. Figure Shows a clustered column plot representing Lipid profile at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
TC = Total cholesterol, LDL-C = Low-Density Lipoprotein Cholesterol, HDL-C = High-Density Lipoprotein Cholesterol, VLDL-C = Very Low-Density Lipoprotein Cholesterol
***** represents statistically significant change in designated parameter within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 7. Change in Lipid profile

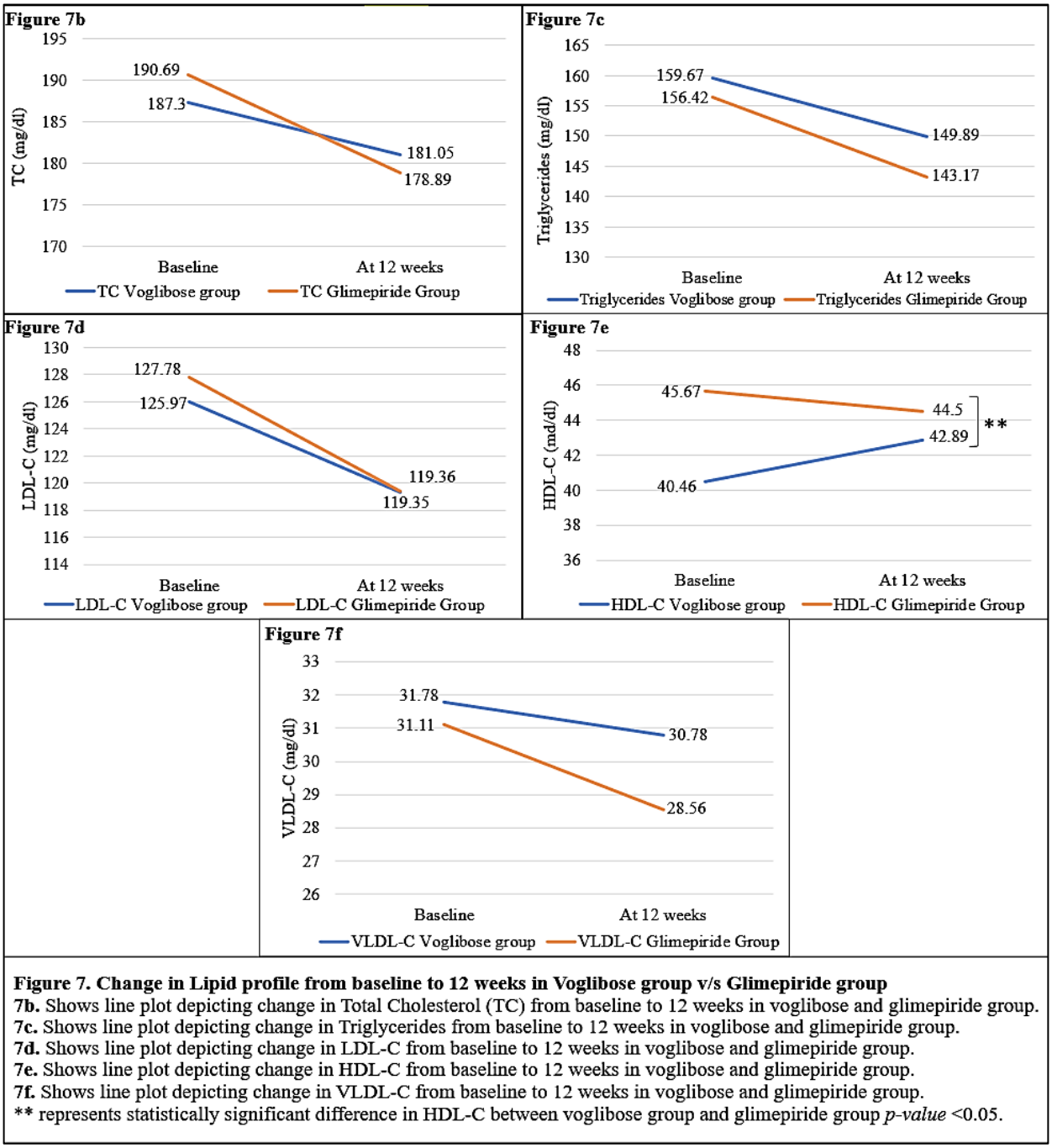


Figure 7. Change in Lipid profile from baseline to 12 weeks in Voglibose group v/s Glimepiride group
7b. Shows line plot depicting change in Total Cholesterol (TC) from baseline to 12 weeks in voglibose and glimepiride group.
7c. Shows line plot depicting change in Triglycerides from baseline to 12 weeks in voglibose and glimepiride group.
7d. Shows line plot depicting change in LDL-C from baseline to 12 weeks in voglibose and glimepiride group.
7e. Shows line plot depicting change in HDL-C from baseline to 12 weeks in voglibose and glimepiride group.
7f. Shows line plot depicting change in VLDL-C from baseline to 12 weeks in voglibose and glimepiride group.
** represents statistically significant difference in HDL-C between voglibose group and glimepiride group *p-value* <0.05.

Figure 7. Change in Lipid profile

The difference in change in Fasting Insulin and Homeostatic model

The difference in change in fasting serum insulin

In the voglibose group fasting insulin change was from 14.71 (11.84) to 13.77 (10.50) with a mean difference of insulin reduction 0.94 (95%CI = -2.07 to 3.95; p=0.529) without significance. The glimepiride group had a change from 16.92 (14.52) to 13.29 (14.18) with a mean difference of insulin reduction of 3.63 (95% CI = 1.48 to 5.78; p=0.002), which was statistically significant.

The difference in change in fasting insulin from the baseline was not significant across the groups (Mean difference = -2.69 (95%CI = -6.34 to 0.96; p=0.146)). The per-protocol analysis showed similar results (**Table 2 - 4, Figure 8, ANNEXURE II-IV**).

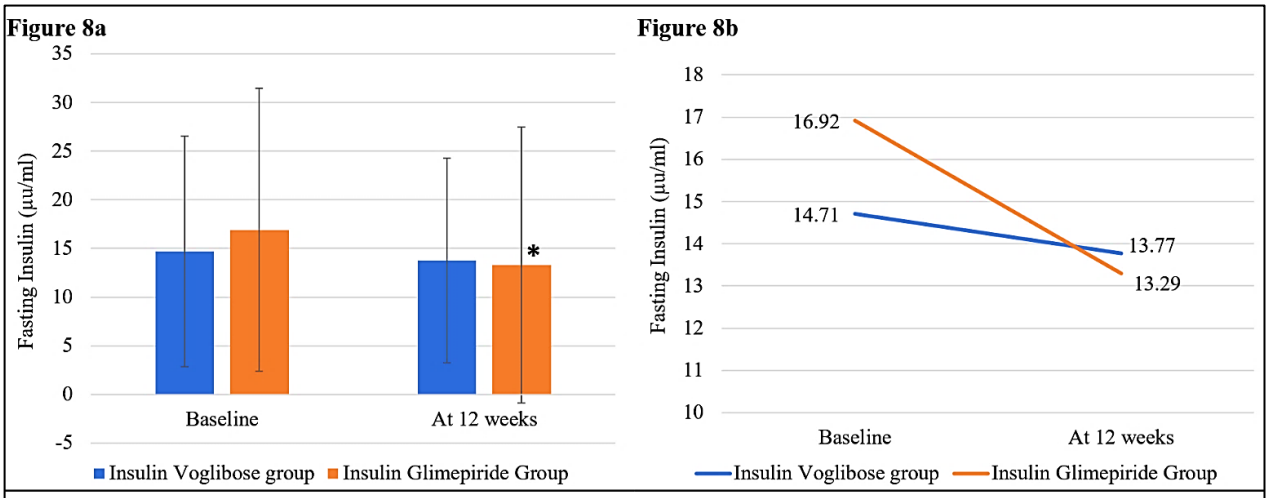


Figure 8. Change in Fasting Insulin from baseline to 12 weeks in Voglibose group v/s Glimepiride group
8a. Shows a clustered column plot representing Fasting Insulin at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
8b. Shows line plot depicting change in Fasting Insulin from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in Fasting Insulin within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 8. Change in Fasting Insulin

The difference in change in HOMA2-IR

The Voglibose group had HOMA2-IR change from 2.67 (2.59) to 1.88 (1.35) with a mean difference of HOMA2-IR reduction 0.78 (95%CI = -0.07 to 1.63; p=0.072) which nonsignificant. The change in the glimepiride group was from 3.23 (5.42) to 2.05 (3.18) with a mean difference of HOMA2-IR reduction 1.18 (95%CI = 0.35 to 2.00; p=0.006) which was statistically significant.

The difference in change in HOMA2-IR from the baseline was statistically nonsignificant across the groups (Mean difference = -0.39 (95%CI = -1.56 to 0.77; p=0.501)). Per-protocol analysis showed similar results (**Table 2 - 4, Figure 9, ANNEXURE II-IV**).

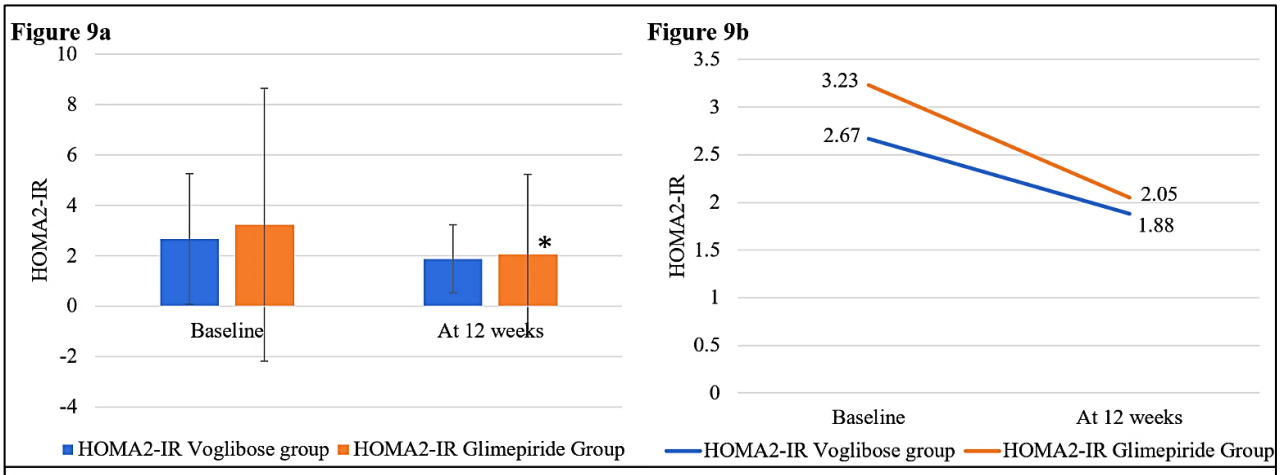


Table 9. Change in HOMA2-IR from baseline to 12 weeks in Voglibose group v/s Glimepiride group
9a. Shows a clustered column plot representing HOMA2-IR at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
9b. Shows line plot depicting change in HOMA2-IR from baseline to 12 weeks in voglibose and glimepiride group.
***** represents statistically significant change in HOMA2-IR within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 9. Change in HOMA2-IR

The difference in change in HOMA2-B%

HOMA2-B% change in the voglibose group was from 45.88 (32.57) to 79.25 (63.80) with a mean difference of HOMA2-B% increase of -33.36 (95%CI = -49.14 to -17.18; p<0.001) which was statistically significant. In the glimepiride group, the change was from 53.69 (44.02) to 93.72 (116.82), which was statistically significant with a mean difference of HOMA2-B% increase of -40.03 (95%CI = -69.52 to -10.54 p=0.009).

The difference in change in HOMA2-B% from the baseline was statistically nonsignificant across the groups (Mean difference = 6.66 (95%CI = -25.94 to 39.27; p=0.685)). Per-protocol analysis showed similar results (**Table 2 - 4, Figure 10, ANNEXURE II-IV**).

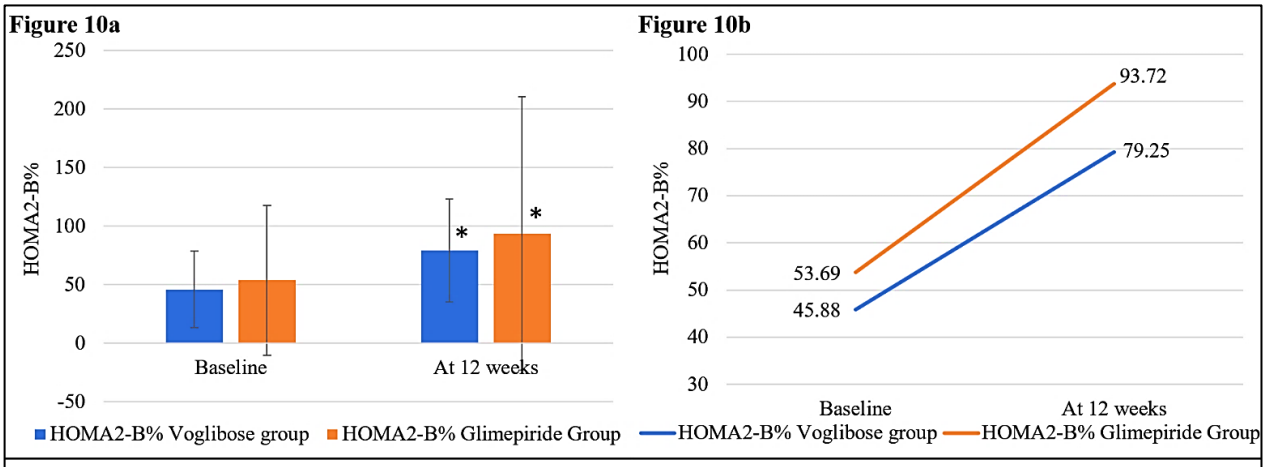


Figure 10. Change in HOMA2-B% from baseline to 12 weeks in Voglibose group v/s Glimepiride group.
10a. Shows a clustered column plot representing HOMA2-B% at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
10b. Shows line plot depicting change in HOMA2-B% from baseline to 12 weeks in voglibose and glimepiride group.
***** represents statistically significant change in HOMA2-B% within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 10. Change in HOMA2-B%

The difference in change in HOMA2-S%

The Voglibose group had HOMA2-S% change from 71.46 (61.36) to 82.96 (65.46) with a mean difference of HOMA2-S% increase -11.5 (95%CI = -24.35-1.34; p=0.078) which was not significant. The glimepiride group had a statistically significant increase in HOMA2-S% from 63.42 (48.9) to 93.76 (63.05) with a mean difference of HOMA2-S% increase -30.34 (95%CI = -42.67 to -18.00; p<0.001.

The glimepiride group had a statistically significant increase of HOMA2-S% compared to the voglibose group (Mean difference = 18.83 (95%CI = 1.32 to 36.35; p=0.035)). Similar results were seen with per-protocol analysis (**Table 2 - 4, Figure 11, ANNEXURE II-IV**).

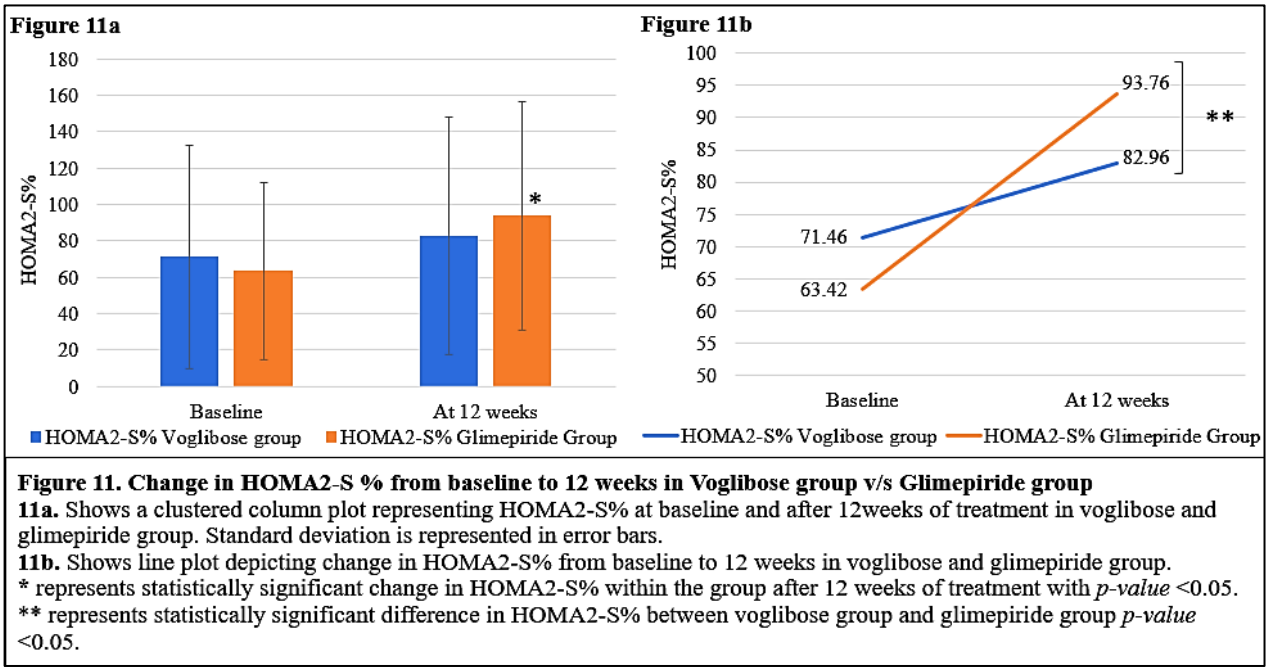


Figure 11. Change in HOMA2-S % from baseline to 12 weeks in Voglibose group v/s Glimepiride group
11a. Shows a clustered column plot representing HOMA2-S% at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
11b. Shows line plot depicting change in HOMA2-S% from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in HOMA2-S% within the group after 12 weeks of treatment with *p-value* <0.05.
** represents statistically significant difference in HOMA2-S% between voglibose group and glimepiride group *p-value* <0.05.

Figure 11. Change in HOMA2-S%

The difference in change in Quality of life

The difference in change in QoL Total score

In the voglibose group, QoL total score changed from 30.43 (8.56) to 25.92 (6.90), which was significant, with a mean difference of total score reduction of 4.51 (95%CI = 3.1 to 5.92; p<0.001). The Glimepiride group had a change from 31.44 (9.57) to 26.89 (6.70), which was significant, with a mean difference of total score reduction of 4.55 (95%CI = 3.03 to 6.08; p<0.001).

The difference in change in total QoL score from baseline was statistically nonsignificant between the groups (Mean difference = -0.04(95%CI = -2.08 to 1.99; p=0.967)). Similar results were seen with per-protocol analysis (**Table 2 - 4, Figure 12, ANNEXURE II-IV**).

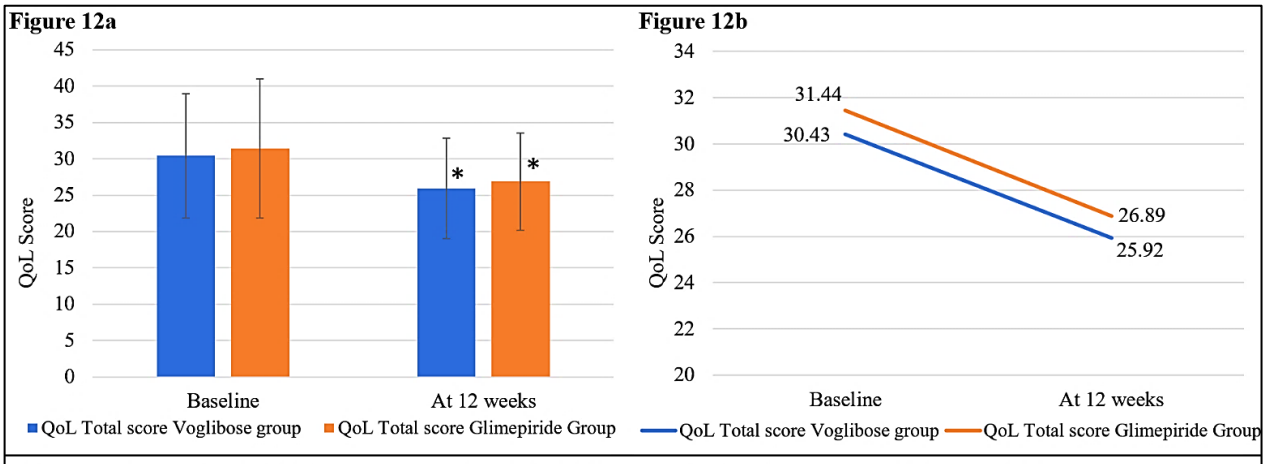


Figure 12. Change in QoL Total score from baseline to 12 weeks in Voglibose group v/s Glimepiride group
12a. Shows a clustered column plot representing QoL Total score at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
12b. Shows line plot depicting change in QoL Total score from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in QoL Total score within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 12. Change in QoL Total Score

The difference in change in the QoL Satisfaction domain score

The Voglibose group's total satisfaction domain score change was from 13.81 (4.60) to 10.45 (3.52) with a mean difference of score reduction of 3.35 (95%CI = 2.41 to 4.29; p<0.001), which was significant. Meanwhile, glimepiride group scores reduced from 14.36 (4.84) to 10.53 (2.66), with a mean difference of score reduction of 3.83 (95%CI = 2.68 to 4.99; p<0.001), which was significant.

The difference in change in satisfaction domain score from the baseline was statistically nonsignificant between the groups (Mean difference = -0.48 (95%CI = -1.94 to 0.98; p=0.512)). Per-protocol results were similar (**Table 2 - 4, Figure 13, ANNEXURE II-IV**).

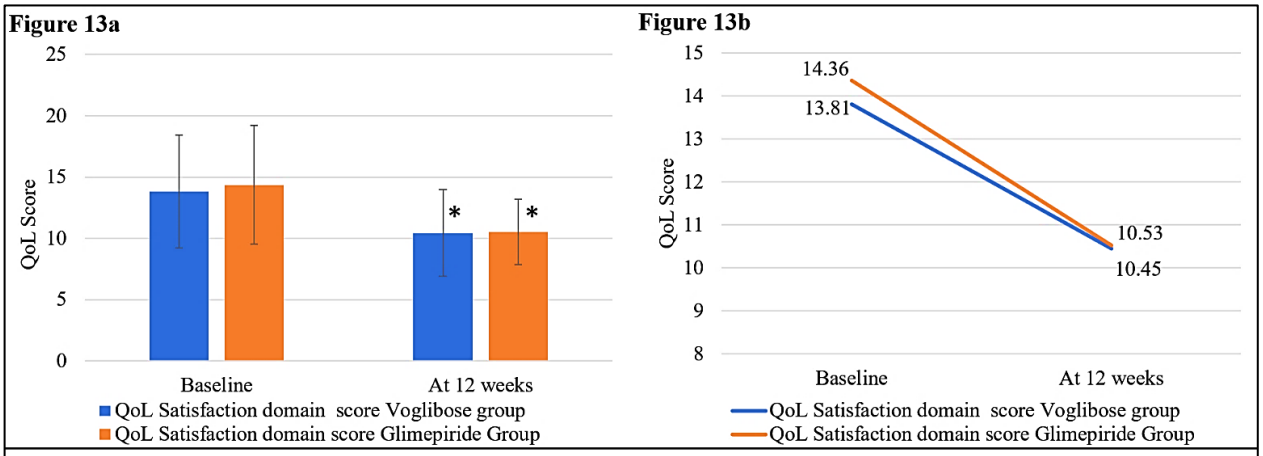


Figure 13. Change in QoL Satisfaction domain score from baseline to 12 weeks in Voglibose group v/s Glimepiride group
13a. Shows a clustered column plot representing QoL Satisfaction domain score at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
13b. Shows line plot depicting change in QoL Satisfaction domain score from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in QoL Satisfaction domain score within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 13. Change in QoL Satisfaction domain score

The difference in change in the QoL Impact domain score

The impact domain score in the voglibose group reduced from 10.00 (3.02) to 9.16 (2.58) with a mean difference of score reduction of 0.84 (95%CI = 0.39 to 1.28; p=0.001) with a significant difference. The glimepiride group's change was from 10.36 (3.83) to 9.78 (3.20), which was significant, with a mean difference of score reduction of 0.58 (95%CI = 0.14 to 1.03; p=0.012).

The difference in change in impact domain score from the baseline was statistically nonsignificant between the groups (Mean difference = 0.25 (95%CI = -0.37 to 0.87; p=0.417)). Similar results were seen with per-protocol analysis (**Table 2 - 4, Figure 14, ANNEXURE II-IV**).

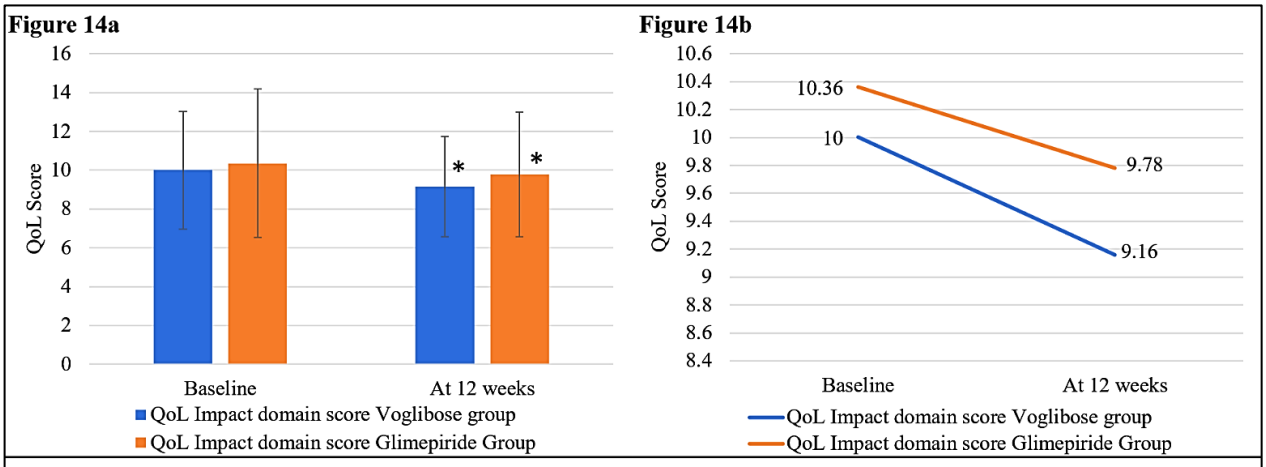


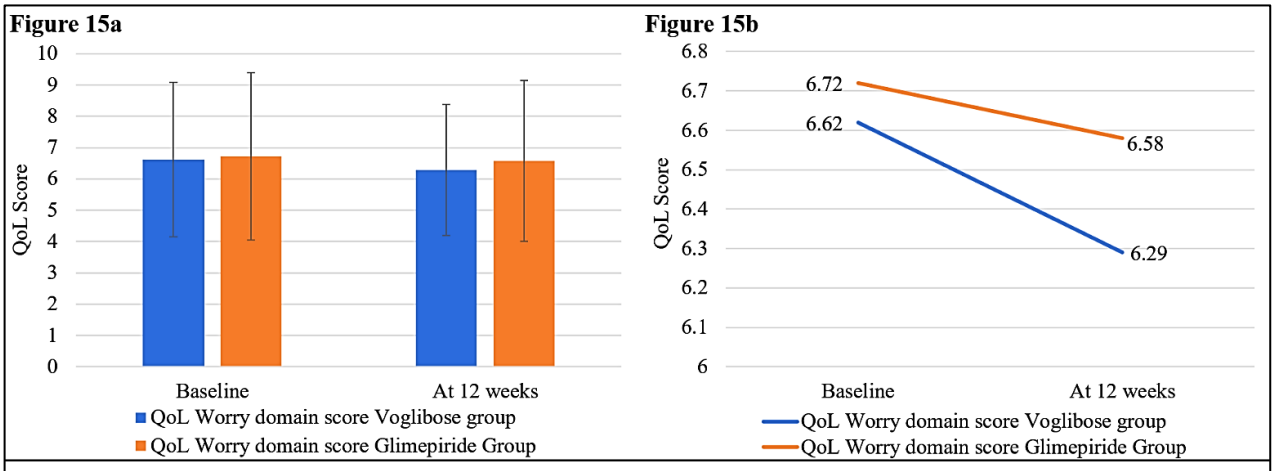
Figure 14. Change in QoL Impact domain score from baseline to 12 weeks in Voglibose group v/s Glimepiride group.
14a. Shows a clustered column plot representing QoL Impact domain score at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
14b. Shows line plot depicting change in QoL Impact domain score from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in QoL Impact domain score within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 14. Change in QoL Impact domain score

The difference in change in the QoL Worry domain score

The Voglibose group showed a change in worry domain score from 6.62 (2.47) to 6.29 (2.09), which was not significant, with a mean difference of score reduction of 0.32 (95%CI = -0.01 to 0.66; p=0.057). The change in the glimepiride group was from 6.72 (2.67) to 6.58 (2.57), which was nonsignificant, with a mean difference of score reduction of 0.14 (95%CI = -0.15 to 0.43; p=0.343).

The difference in change in worry domain score from the baseline was statistically nonsignificant between the groups (Mean difference = 0.18 (95%CI = -0.25 to 0.62; p=0.401)). Per-protocol analysis showed similar results (**Table 2 - 4, Figure 15, ANNEXURE II-IV**).



Change in QoL Worry domain score from baseline to 12 weeks in Voglibose group v/s Glimepiride group
15a. Shows a clustered column plot representing QoL Worry domain score at baseline and after 12weeks of treatment in voglibose and glimepiride group. Standard deviation is represented in error bars.
15b. Shows line plot depicting change in QoL Worry domain score from baseline to 12 weeks in voglibose and glimepiride group.
* represents statistically significant change in QoL Worry domain score within the group after 12 weeks of treatment with *p-value* <0.05.

Figure 15. Change in QoL Worry domain score

Change in individual QoL scores

QoL was assessed for individual questions and in domains (satisfaction (S), impact (I) and worry (W) domain and total score). Voglibose group had significant difference ($p<0.05$) in scores of S1, S2, S3, S4, S5, I2, I4, W1, W2, but not in S6, I1, I3 and W3. Glimepiride group scores significantly changed ($p<0.05$) in questions S1, S2, S3, S4, S5, I2 and the change was not significant in S6, I1, I3, I4, W1, W2, W3.

Intergroup comparison of scores of individual questions was not significant for all of them. Similar results were observed in the per-protocol analysis (**ANNEXURE II-IV**).

Table 2. Clinical parameters in the Metformin + Voglibose group at baseline and after 12 weeks of treatment

Parameters	Baseline (n=37) [Mean (SD)]	At 12 weeks (n=37) [Mean (SD)]	Mean difference (95%CI)	*p-value*
Primary endpoints				
HbA1c (%)	8.80 (1.46)	7.46 (1.25)	1.34 (0.99 to 1.68)	<0.001
Fasting plasma glucose (mg/dl)	189.08 (67.34)	129.78 (33.04)	59.29 (39.7 to 78.89)	<0.001
Post-prandial plasma glucose (mg/dl)	297.56 (76.38)	176.75 (52.29)	120.81 (97.26 to 114.35)	<0.001
Secondary endpoints				
Body weight (kg)	71.25 (12.86)	68.78 (12.38)	2.54 (1.86 to 3.22)	<0.001
BMI (kg/m^2)	27.05 (4.31)	25.99 (3.90)	1.05 (0.75 to 1.36)	<0.001
Total cholesterol (mg/dl)	187.30 (47.29)	181.05 (41.59)	6.24 (-1.44 to 13.92)	0.108
Triglycerides (mg/dl)	159.67 (83.35)	149.89 (83.18)	9.78 (-3.82 to 23.38)	0.153
LDL-C (mg/dl)	125.97 (35.39)	119.35 (32.49)	6.62 (1.12 to 12.11)	0.020
HDL-C (mg/dl)	40.46 (8.22)	42.89 (8.39)	-2.43 (-4.85 to -0.02)	0.048
VLDL-C (mg/dl)	31.78 (16.73)	30.78 (16.33)	1.40 (-1.44 to 4.25)	0.324
Fasting Insulin (µU/ml)	14.71 (11.84)	13.77 (10.50)	0.94 (-2.07 to 3.95)	0.529
HOMA2-IR	2.67 (2.59)	1.88 (1.35)	0.78 (-0.07 to 1.63)	0.072
HOMA2-B%	45.88 (32.57)	79.25 (63.80)	-33.36(-49.14 to -17.18)	<0.001
HOMA2-S%	71.46 (61.36)	82.96 (65.46)	-11.5 (-24.35 to 1.34)	0.078
S1	2.05 (1.15)	1.59 (0.64)	0.45 (0.18 to 0.73)	0.002

Parameters	Baseline (n=37) [Mean (SD)]	At 12 weeks (n=37) [Mean (SD)]	Mean difference (95%CI)	*p-value*
S2	2.32 (1.24)	1.89 (1.04)	0.43 (0.16 to 0.70)	0.002
S3	1.97 (1.16)	1.32 (0.62)	0.64 (0.33 to 0.96)	<0.001
S4	3.02 (0.89)	1.78 (1.03)	1.24 (0.89 to 1.60)	<0.001
S5	2.24 (0.72)	1.83 (0.50)	0.40 (0.20 to 0.60)	<0.001
S6	2.18 (1.07)	2.02 (1.01)	0.16 (-0.09 to 0.42)	0.205
I1	2.27 (1.17)	2.27 (1.17)	<0.01 (-0.13 to 0.13)	1.000
I2	3.21 (1.06)	2.62 (0.89)	0.59 (0.34 to 0.85)	<0.001
I3	2.24 (0.92)	2.13 (0.85)	0.11 (-0.02 to 0.23)	0.103
I4	2.27 (1.07)	2.13 (1.00)	0.13 (0.01 to 0.25)	0.023
W1	1.54 (0.90)	1.32 (0.58)	0.21 (0.02 to 0.41)	0.030
W2	2.35 (1.27)	2.18 (1.15)	0.16 (0.01 to 0.31)	0.032
W3	2.73 (1.07)	2.78 (0.95)	-0.05 (-0.19 to 0.08)	0.422
QoL Total score	30.43 (8.56)	25.92 (6.90)	4.51 (3.1 to 5.92)	<0.001
QoL Satisfaction domain score	13.81(4.60)	10.45 (3.52)	3.35 (2.41 to 4.29)	<0.001
QoL Impact domain score	10.00 (3.02)	9.16 (2.58)	0.84 (0.39 to 1.28)	0.001
QoL Worry domain score	6.62 (2.47)	6.29 (2.09)	0.32 (-0.01 to 0.66)	0.057

All the data is presented as Mean (SD).

Data shown are analysed as per intention to treat analysis.

S- Satisfaction, I-Impact, W-Worry are individual question scores of QoL questionnaire (Refer **ANNEXURE V**)

Table 3. Clinical parameters in the Metformin + Glimepiride group at baseline and after 12 weeks of treatment

Parameters	Baseline (n=36) [Mean (SD)]	At 12 Weeks (n=36) [Mean (SD)]	Mean difference (95% CI)	*p-value*
Primary endpoints				
HbA1c (%)	8.82 (1.51)	7.07 (0.96)	1.75 (1.38 to 2.13)	<0.001
Fasting plasma glucose (mg/dl)	179.83 (47.91)	118.5 (27.28)	61.33 (44.01 to 78.65)	<0.001
Post-prandial plasma glucose (mg/dl)	280.33 (80.38)	146.08 (52.44)	134.25 (107.31 to 161.19)	<0.001
Secondary endpoints				
Body weight (kg)	71.47 (15.25)	71.38 (14.75)	0.08 (-0.90 to 1.07)	0.865
BMI (kg/m^2)	27.15 (5.97)	27.10 (5.75)	0.05 (-0.31 to 0.42)	0.777
Total cholesterol (mg/dl)	190.69 (51.92)	178.89 (48.82)	11.8 (2.83 to 20.78)	0.011
Triglycerides (mg/dl)	156.42 (64.84)	143.17 (52.89)	13.25 (0.28 to 26.22)	0.045
LDL-C (mg/dl)	127.78 (38.17)	119.36 (39.15)	8.42 (1.93 to 14.90)	0.012
HDL-C (mg/dl)	45.67 (10.88)	44.50 (9.79)	1.17 (-0.76 to 3.10)	0.228
VLDL-C (mg/dl)	31.11 (13.02)	28.56 (10.60)	2.55 (-0.12 to 5.13)	0.052
Fasting Insulin (µU/ml)	16.92 (14.52)	13.29 (14.18)	3.63 (1.48 to 5.78)	0.002
HOMA2-IR	3.23 (5.42)	2.05 (3.18)	1.18 (0.35 to 2.00)	0.006
HOMA2-B%	53.69 (44.02)	93.72 (116.82)	-40.03 (-69.52 to -10.54)	0.009
HOMA2-S%	63.42 (48.9)	93.76 (63.05)	-30.34 (-42.67 to -18.00)	<0.001

Parameters	Baseline (n=36) [Mean (SD)]	At 12 Weeks (n=36) [Mean (SD)]	Mean difference (95% CI)	*p-value*
S1	2.28 (1.21)	1.75 (0.65)	0.53 (0.24 to 0.81)	0.001
S2	2.67 (1.35)	2.11 (1.01)	0.55 (0.24 to 0.87)	0.001
S3	1.81 (1.04)	1.39 (0.64)	0.42 (0.13 to 0.70)	0.005
S4	2.94 (0.67)	1.44 (0.77)	1.50 (1.15 to 1.85)	<0.001
S5	2.31 (0.95)	1.61 (0.49)	0.69 (0.42 to 0.96)	<0.001
S6	2.36 (1.20)	2.22 (1.04)	0.14 (-0.004 to 0.28)	0.058
I1	2.28 (1.18)	2.28 (1.18)	-	-
I2	3.31 (1.17)	2.86 (0.96)	0.44 (0.24 to 0.65)	<0.001
I3	2.33 (0.96)	2.28 (0.88)	0.05 (-0.06 to 0.17)	0.324
I4	2.44 (1.34)	2.36 (1.12)	0.08 (-0.12 to 0.28)	0.413
W1	1.56 (0.99)	1.56 (0.91)	<0.01 (-0.25 to 0.25)	1.000
W2	2.25 (1.29)	2.17 (1.23)	0.08 (-0.01 to 0.18)	0.083
W3	2.92 (1.10)	2.86 (1.12)	0.05 (-0.02 to 0.13)	0.160
QoL Total score	31.44 (9.57)	26.89 (6.70)	4.55 (3.03 to 6.08)	<0.001
QoL Satisfaction domain score	14.36 (4.84)	10.53 (2.66)	3.83 (2.68 to 4.99)	<0.001
QoL Impact domain score	10.36 (3.83)	9.78 (3.20)	0.58 (0.14 to 1.03)	0.012
QoL Worry domain score	6.72 (2.67)	6.58 (2.57)	0.14 (-0.15 to 0.43)	0.343

All the data is presented as Mean (SD).

Data shown are analysed as per intention to treat analysis.

S- Satisfaction, I-Impact, W-Worry are individual question scores of QoL questionnaire (Refer **ANNEXURE V**)

Table 4. The difference in change in parameters in the Voglibose group v/s Glimepiride group at 12 weeks

Parameters	Voglibose (n=37) [Mean (SD)]	Glimepiride (n=36) [Mean (SD)]	Mean difference (95% CI)	*p*-value
Primary endpoints				
HbA1c (%)	1.34 (1.04)	1.75 (1.11)	-0.41(-0.92 to 0.09)	0.104
Fasting plasma glucose (mg/dl)	59.30 (58.77)	61.33 (51.19)	-2.04 (-27.78 to 23.71)	0.875
Post-prandial plasma glucose (mg/dl)	120.81 (70.61)	134.25 (79.62)	-13.44 (-48.54 to 21.66)	0.448
Secondary endpoints				
Body weight (kg)	2.54 (2.03)	0.08 (2.92)	2.46 (1.28 to 3.63)	<0.001
BMI (kg/m^2)	1.06 (0.93)	0.05 (1.08)	1.00 (0.53 to 1.48)	<0.001
Total cholesterol (mg/dl)	6.24 (23.04)	11.8 (26.52)	-5.56 (-17.14 to 6.02)	0.342
Triglycerides (mg/dl)	9.78 (40.80)	13.25 (38.32)	-3.47 (-21.95 to 15.02)	0.710
LDL-C (mg/dl)	6.62 (16.48)	8.41 (19.16)	-1.79 (-10.13 to 6.54)	0.669
HDL-C (mg/dl)	-2.43 (7.24)	1.17 (5.70)	-3.60 (-6.64 to -0.55)	0.021
VLDL-C (mg/dl)	1.40 (8.55)	2.53 (7.63)	-1.12 (-4.91 to 2.65)	0.556
Fasting Insulin (µU/ml)	0.94 (9.02)	3.63 (6.36)	-2.69 (-6.34 to 0.96)	0.146
HOMA2-IR	0.78 (2.56)	1.18 (2.44)	-0.39 (-1.56 to 0.77)	0.501
HOMA2-B%	-33.36 (47.33)	-40.03 (87.15)	6.66 (-25.94 to 39.27)	0.685

Parameters	Voglibose (n=37) [Mean (SD)]	Glimepiride (n=36) [Mean (SD)]	Mean difference (95% CI)	*p*-value
HOMA2-S%	-11.50 (38.54)	-30.34 (36.45)	18.83 (1.32 to 36.35)	0.035
S1	0.46 (0.84)	0.53 (0.84)	-0.07 (-0.46 to 0.32)	0.729
S2	0.43 (0.80)	0.55 (0.94)	-0.12 (-0.53 to 0.28)	0.548
S3	1.24 (1.06)	1.50 (1.03)	-0.26 (-0.74 to 0.23)	0.298
S4	1.24 (1.06)	1.50 (1.03)	-0.26 (-0.74 to 0.23)	0.298
S5	0.40 (0.6)	0.69 (0.78)	-0.29 (-0.61 to 0.04)	0.081
S6	0.16 (0.76)	0.14 (0.42)	0.02 (-0.27 to 0.31)	0.873
I1	<0.01 (0.41)	<0.01 (<0.01)	<0.01 (-0.13 to 0.13)	1.000
I2	0.59 (0.76)	0.44 (0.61)	0.15 (-0.17 to 0.47)	0.356
I3	0.11 (0.39)	0.05 (0.33)	0.05 (-0.12 to 0.22)	0.540
I4	0.13 (0.35)	0.08 (0.6)	0.05 (-0.18 to 0.28)	0.653
W1	0.22 (0.58)	<0.01 (0.75)	0.22 (-0.10 to 0.53)	0.175
W2	0.16 (0.44)	0.08 (0.28)	0.08 (-0.09 to 0.25)	0.367
W3	-0.05 (0.40)	0.05 (0.23)	-0.11 (-0.26 to 0.04)	0.162
QoL Total score	4.51 (4.22)	4.55 (4.5)	-0.04 (-2.08 to 1.99)	0.967
QoL Satisfaction domain score	3.35 (2.82)	3.83 (3.41)	-0.48 (-1.94 to 0.98)	0.512
QoL Impact domain score	0.83 (1.34)	0.58 (1.32)	0.25 (-0.37 to 0.87)	0.417
QoL Worry domain score	0.32 (1)	0.14 (0.87)	0.18 (-0.25 to 0.62)	0.401

All the voglibose and glimepiride column data are presented as Mean (SD).

Data shown are analysed as per intention to treat analysis.

S- Satisfaction, I-Impact, W-Worry are individual question scores of QoL questionnaire (Refer **ANNEXURE V**)

Use of Rescue medicines

One patient in the voglibose was given rescue medicine, and two patients in the glimepiride group required rescue medicines. Rescue medicines used were, one patient was given pioglitazone, another patient was given metformin + vildagliptin, and the glimepiride dose was escalated in another patient.

Adverse events in the voglibose group and glimepiride group

In the voglibose group, there were 4 (10.81%) events of abdominal distension, 5 (13.51%) events of diarrhoea, 2 (5.40%) events of vomiting, 5 (13.51%) events of generalized weakness and 1 (2.70%) event of dizziness recorded.

In the glimepiride group, 2 (5.55%) events of hypoglycemia, 4 (11.11%) events of generalized weakness and 1 (2.77%) event of dizziness were recorded.

Intergroup comparison of these events was nonsignificant ($p>0.05$).

Table 5. Adverse events

Adverse event	Voglibose group (n=37) (%)	Glimepiride group (n=36) (%)	*p-value*
Abdominal distension	4 (10.81)	0 (0.00)	0.115
Diarrhoea	5 (13.51)	0 (0.00)	0.054
Vomiting	2 (5.40)	0 (0.00)	0.493
Hypoglycemia	0 (0.00)	2 (5.55)	0.240
Weakness	5 (13.51)	4 (11.11)	1.000
Dizziness	1 (2.70)	1 (2.77)	1.000

DISCUSSION

This study evaluated the effectiveness and safety of voglibose and glimepiride in patients with type-2 DM. The study evaluated efficacy using changes in HbA1c, PPG, FPG, lipid profile and homeostatic models of insulin resistance, beta cell function and insulin sensitivity (HOMA2). Safety assessment was done by recording adverse events in the study groups and changes in QoL outcomes.

The Voglibose and glimepiride groups showed significant glycemic parameters improvement from the baseline. There was a significant decrease in HbA1c, PPG, and FPG in both groups. HbA1c change was from 8.80% (1.46) to 7.46% (1.25) and 8.82% (1.51) to 7.07% (0.96) in the voglibose and glimepiride groups, respectively. FPG reduced from 189.08 mg/dl (67.34) to 129.78mg/dl (33.04) and from 179.83 mg/dl (47.91) to 118.5 mg/dl (27.28) in the voglibose group and glimepiride group respectively. PPG change in the voglibose group was from 297.56 mg/dl (76.38) to 176.75 mg/dl (52.29) and 279.51 mg/dl (81.41) to 141.43 mg/dl (45.03) in glimepiride group by the end of 12 weeks of treatment. Voglibose is an α-GI that competitively inhibits the enzyme α-Glucosidase on the brush border of intestinal epithelial cells, which is responsible for degrading complex sugars into simple sugars. α-GI inhibition results in the inhibition of digestion and absorption of maltose and sucrose (46,48). Long-term treatment with voglibose increases plasma incretin GLP-1 but not GIP. This effect is because GIP-producing enterochromaffin (EC) cells are more in proximal parts of the intestine, and GLP-1-secreting EC cells are present in the distal intestine and colon. As voglibose reduces carbohydrate absorption in the proximal intestine, more nutrients reach the distal intestine triggering GLP-1 secretion. Chronic voglibose administration also reduces plasma DPP-4 levels, but the exact mechanism is unknown. Voglibose increases plasma GLP-1 levels, which is insulinotropic, and beta-cell protective, thus contributing to glycemic control (108,109). A meta-analysis by P. Nowrouzi-Sohrabi, *et al.* said that voglibose significantly reduced HbA1c and PPG, but the effect on FPG was insignificant. However, voglibose FPG reduction effects are pronounced in patients less than 55 years of age (109). Fujitani *et al.* demonstrated similar changes in HbA1c in their study comparing voglibose and linagliptin (74). As per Dabhi *et al.*, FPG-reducing properties of voglibose are explained by its effect on endogenous incretins, GLP-1, which has the insulinotropic effect; it increases insulin levels and reduces glucagon levels and hepatic glucose output, thus contributing to the reduction in FPG and also PPG reduction which reduces the

overall glucose toxicity and thus FPG levels (45,46,48,110). Voglibose, along with metformin, led to a significant reduction in FPG. These results were consistent with a study by Oh TJ *et al.*, where a similar HbA1c reduction was seen (45). Metformin glimepiride combination also showed a significant reduction in glycemic parameters.

The insulin secretagogue effect of glimepiride is well established, and glimepiride works in synergy with metformin in blood glucose control. Glimepiride has pleiotropic effects which contribute to glycemic control, such as increasing insulin secretion from islet cells by stimulating ATP-sensitive potassium channels on beta cells of the pancreas, enhancing peripheral tissue insulin sensitivity, GLUT-4 upregulation in peripheral tissues, activity on adipocytes and increasing non-oxidative glucose metabolism and stimulate glycogen synthesis which reduces blood glucose levels and improves glycemic control and reduces HbA1c (111–113). Glimepiride FPG reduction properties are attributed to its long duration of action, maintaining the insulin secretory activity throughout, upregulating GLUT-4 transporters in peripheral tissues increasing glucose utilization. Glimepiride directly increases insulin secretion after meal contributing to significant PPG reduction and act synergistically with metformin in peripheral tissues increasing peripheral glucose uptake (111–114). The results are consistent with most of the studies. As per the studies by Charpentier *et al.* and Gonzalez-Ortiz *et al.*, the metformin + glimepiride combination provided significant glycemic control (115,116). Adding glimepiride to metformin improves the glycemic profile significantly, as per a study by G Kim *et al.* (117,118). As per a meta-analysis, alpha-GIs are inferior to sulfonylureas in glycemic control. In this analysis, glycemic control provided by metformin + glimepiride was more than that of metformin + voglibose. However, the difference was statistically nonsignificant (34).

Body weight and BMI decreased significantly in the voglibose group but not in the glimepiride group. The voglibose group had a mean body weight change from 71.25kg (12.86) to 68.78kg (12.38). Body weight change in the glimepiride group was from 71.47kg (15.25) to 71.38kg (14.75). Metformin is associated with weight loss of up to 0.9kg when used at a dose of more than 1000mg/day (119). The weight reduction properties of voglibose are due to its ability to delay and reduce carbohydrate absorption. Other mechanisms include the voglibose effect on GLP-1, providing satiety and decreasing food intake. Voglibose is proven to improve the leptin sensitivity in the hypothalamus, upregulate leptin receptors, and appetite-related genes in the

hypothalamus and thus reduce appetite and food intake (45,74,120). These findings are consistent with earlier research where voglibose reduced body fat, mainly visceral fat, as seen by Fujitaka *et al.* (69). Meta-analysis by Gao *et al.* concluded that alpha-GIs have superior weight reduction than placebo (121). A recent study concluded that the voglibose metformin combination has better body weight reduction than metformin alone, and the weight reduction might contribute to improvement in insulin resistance (45). Most of the patients on glimepiride exhibited a trend towards gain in weight, and two patients had significant weight loss in the glimepiride group, which might have neutralized the weight gain. A meta-analysis by Domecq *et al.* said that glimepiride is associated with weight gain of around 2.1kg (122). In another 16-week study by yang *et al.*, patients had a weight gain of 1kg with glimepiride (118,123). The Voglibose group significantly reduced body weight more than the glimepiride group after 12 weeks of treatment.

The Voglibose group had a statistically significant decrease in LDL-C and an increase in HDL-C, and the rest of the lipid parameters did not change much. The glimepiride group had a significant decrease in TC, TG, and LDL-C and no changes in other lipid parameters. Mean total cholesterol changed from 187.30mg/dl (47.29) to 181.05 (41.59) and 190.69 (51.92) to 178.89 (48.82) in the voglibose and glimepiride group, respectively. Mean triglycerides change was from 159.67 (83.35) to 149.89 (83.18) and 156.42 (64.84) to 143.17 (52.89) in the voglibose and glimepiride group, respectively. The Voglibose group had a mean LDL-C change from 125.97 (35.39) to 119.35 (32.49); meanwhile, in the glimepiride group change was from 127.78 (38.17) to 119.36 (39.15). At baseline, there was a significant variation in HDL-C across the groups, 40.46 (8.22) and 45.67 (10.71) in the voglibose and glimepiride groups, respectively, with p-value = 0.022. The exact reason for this is not known. The mean HDL-C change was from 40.46 (8.22) to 42.89 (8.39) and from 45.67 (10.88) to 44.50 (9.79) in the voglibose group and glimepiride group, respectively. Both the groups showed a slight reduction in VLDL-C, and glimepiride was better than voglibose, but statistically, a significant change was not attained by either group. Mechanisms affecting the lipid profile in the voglibose group are insulin sensitivity and insulin levels directly affecting triglyceride and LDL-C. The adipose tissue lipoprotein lipase (LPL) activity is increased by insulin, and thus utilization of small dense LDL and triglycerides, thus reducing their plasma levels (52,110,124,125). Total cholesterol change was consistent with

the results seen by Shinozaki *et al.* (124). Few studies showed a significant reduction in triglycerides which was not significant in our study. This might be because the study duration was short; the TG values at baseline in our study were low compared to other studies, where it was around 200mg/dl and finally attained the values of around 145mg/dl by 12 weeks of treatment with voglibose. So, the TG reduction might depend on the baseline values (69,124). In contrast, the results of research work by Fujitaka *et al.* showed a reduction in HDL-C and LDL-C without significance, unlike significant changes in our study. Using metformin as basal therapy, weight loss seen with voglibose might have led to significant changes in these parameters (69). A meta-analysis by P. Nowrouzi-Sohrabi *et al.* said that voglibose reduced triglycerides and increased LDL-C, with no effect on HDL-C and TC. However, the study implied controversial outcomes on lipid profiles and the need for further studies, and the meta-analysis included only a small number of studies (109). The effects of metformin+glimepiride on TC, Triglycerides, and LDL-C are consistent with the other studies (126–128). As per a meta-analysis by Zhang *et al.*, metformin improves HDL-C levels, but metformin + glimepiride combination slightly reduces HDL-C levels. Similarly, our study also had a slight reduction in HDL-C in the glimepiride group (129). Research work by G. Charpentier *et al.* showed an improvement in TC, triglycerides, and HDL-C, but only TC achieved significance by the combination but not the other parameters (115). Hypolipidemic effects of metformin and glimepiride were in line with a study by G Derosa *et al.*, where there was reduction in Total cholesterol, LDL-C but inconsistent variation in HDL-C was seen (130). A study by Werida *et al.*, reported improvement in lipid profile with exception of triglycerides and HDL - C (131).

The Voglibose group had a slight reduction in Fasting insulin which was not significant. The Glimepiride group had a significant decrease in fasting insulin levels. The change in fasting insulin was from 14.71 (11.84) to 13.77 (10.50) in the voglibose group and 16.92 (14.52) to 13.29 (14.18) in the glimepiride group. There was an improvement in insulin resistance and sensitivity in the voglibose group but neither attained statistical significance. HOMA2-IR, HOMA2-B% and HOMA2-S% were significantly improved in the glimepiride group. Beta cell function improvement effects of voglibose might be because of synergism between the incretin effect of voglibose and the pleiotropic effects of metformin. Voglibose reduces post-prandial insulin AUC by reducing the postprandial glucose load, thus reducing glucose toxicity on beta

cells; incretins inhibit the pancreatic beta cell apoptosis and promote their proliferation which might contribute to improvement in beta cell function (85). According to a meta-analysis by Van de Laar et al., alpha-GIs lower post-prandial and fasting Insulin levels (34). Alpha-GIs show incremental postprandial insulin reduction of ~20–75% (132). Voglibose alone did not produce significant changes in HOMA-IR despite weight loss, but a study by Shi *et al.*, where voglibose was used in addition to metformin and insulin, improved insulin resistance and beta cell function, showed these values are more significant than the ones seen with our study, which might be because of lesser dose of metformin used in our study and no insulin was used in our study, as early insulin in newly diagnosed type-2 DM alleviates glucotoxicity and lipotoxicity and insulin resistance (69,80,85). Glimepiride is an insulin secretagogue which also acts as an insulin sensitizer in peripheral tissues; when used in low doses, its insulin-sensitizing activity predominates secretagogue activity. This causes improvement in insulin resistance when used with insulin sensitizer like metformin; additionally, it stops the downregulation of insulin receptors in peripheral organs, unlike moderate to high doses of glimepiride which produces hyperinsulinemia, worsens insulin resistance, and causes beta cell fatigue and failure. Our study results were consistent with this theory, and identical outcomes were seen in research by Bermúdez-Pirela *et al.* (133). The findings of a study by Derosa et al. were in opposition to our study's changes in fasting plasma insulin, where there was a rise in insulin levels (118). According to a meta-analysis by Van de Laar et al., alpha-GIs reduce fasting insulin more effectively than sulfonylureas. Which was opposite to our study, which might be because the meta-analysis included only one study with voglibose, and glimepiride effect on insulin slightly differs when compared to other sulfonylureas, and in the trials that were part of the meta-analysis, metformin was not consistently used. (34). Compared to the voglibose group, glimepiride significantly improved HOMA2-S% but not HOMA2-IR or HOMA2-B%, which might be because of less sample size. This study may not be powered to produce meaningful changes in HOMA2-IR & HOMA2-B%. Short study duration might also be the contributing factor. More study time may be required to see a noticeable improvement in insulin resistance and beta cell activity.

The overall QOL score in the voglibose group significantly improved. The change was significant in the satisfaction and impact domain but not the worry domain. A similar change was

seen in the glimepiride group. As per individual question scores, the voglibose group had a more significant decrease in all the domains compared to glimepiride which had a decrease in satisfaction scores but little change in impact and worry domain question scores. Clinically, patients on voglibose therapy were more satisfied with the therapy than glimepiride therapy. Four patients in the voglibose group were pleased with the treatment. They said to have improved daily life activities, overall health, clinical symptoms, appetite, and mental health, which was seen with one patient with glimepiride treatment. Improvement in glycemic control and reduction of glucose excursions positively impact treatment satisfaction and adherence (134). Goto *et al.* showed improvement in satisfaction and hypoglycemia-related scores with voglibose in their work, and similar results were observed in this study (79). The glimepiride group had significant improvement in satisfaction and impact domain. However, the worry of hypoglycemia did not change much as the risk of hypoglycemia with glimepiride is higher than that of voglibose (135). There was an improvement in QoL outcomes despite the adverse events seen with the drugs.

Both medications were well-tolerated and safe. The most frequent side effects in the voglibose group were GI-related side effects like pain abdomen, diarrhoea, flatulence, and vomiting, as seen in the other studies (45,47). These GI symptoms were usually seen in the first week of starting the therapy, and the symptoms were self-limiting and subsided within a few days. These symptoms seen with voglibose treatment are because the drug increases the amount of unabsorbed carbohydrates in the intestine, which is metabolized by gut flora and produces undesired effects (80). Two patients complained of hypoglycemia in the glimepiride group, but no hypoglycemia was seen with voglibose. Hypoglycemia is because of consistent beta cell stimulation of glimepiride to release insulin even at low plasma glucose. Studies have shown that the combination of metformin and glimepiride can result in hypoglycemia (115,135). Compared to other sulfonylureas, glimepiride has the second-lowest risk of hypoglycemia and mortality after gliclazide (136).

In the voglibose group, one patient was given rescue medicine, whereas two patients in the glimepiride group were given rescue medicine. One patient in the glimepiride group was scheduled for surgery due to diabetic gangrene; hence rescue medications were started.

Statistical comparison between the groups was not made as only a small number of patients required rescue medicines which were not comparable.

Strengths and limitations

The study's strengths were; it was conducted on the Indian population, making the data more relevant for use in Indian patients. It will help the clinician decide on better treatment options for patients with different comorbidities. It was a randomized controlled study removing most of the biases and providing data with a similar distribution of confounders. It was the first head-on study comparing metformin + voglibose v/s metformin + glimepiride combination in western Rajasthan as per our knowledge, so the data is more relevant to the local population and gives an idea about the outcomes associated with these combinations when used clinically.

Study limitations include; a small sample size, few patients with significant data variation can alter the overall results, and the study might not have been powered enough to produce a significant difference in secondary endpoints. The study was not blinded, which might add to bias and data variation, but most of the outcomes were objective except QoL minimizing the bias. The full effects of drugs might not have been seen, as usually, it will take 6 to 9 months to see so the full effects of the antidiabetic drugs on homeostatic models, lipid profile, and BMI.

Future Perspectives

Even though the study provided necessary data, it might have been underpowered to produce significant changes in secondary endpoints. Further studies with large samples size, and long study duration involving other parameters like glucose excursions, inflammatory markers, endothelial function markers, cardiovascular benefits, kidney function, etc., will provide additional data. Studies with blinding will provide more concise data, and studies with long study duration will give the full extent of the drug’s efficacy and long-term safety.

CONCLUSION

When combined with metformin, voglibose and glimepiride offered effective glycemic management. FPG, PPG, and HbA1c significantly improved in both groups. Body weight and BMI were significantly decreased in the voglibose group but not in the glimepiride group. The voglibose group had a significant reduction of LDL-C and an increase in HDL-C, but other lipid parameters had no significant changes; meanwhile, the glimepiride group significantly reduced TC, TG, and LDL-C but not HDL-C and VLDL-C. Voglibose treatment had a significant increase in HDL-C compared to the glimepiride treatment. Voglibose treatment significantly enhanced beta cell function, whereas the glimepiride treatment significantly decreased fasting insulin, improved beta cell function and lowered insulin resistance. The glimepiride combination significantly enhanced insulin sensitivity compared to the voglibose combination by the end of 12 weeks. Voglibose and glimepiride groups significantly improved QoL total score, satisfaction and Impact domain scores but not worry domain scores. However, there was no significant difference in the comparison of the groups. Both the combinations were well tolerated; GI side effects were seen with voglibose, whereas hypoglycemia was a concern with glimepiride. In conclusion, the voglibose and glimepiride groups did not significantly differ in their ability to improve glycemic parameters. Further studies with large sample sizes and long study duration might provide more concise information.

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ANNEXURES

Annexure I - Ethical Clearance Certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3462 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3297**

Project title: **"Efficacy and Safety of Voglibose v/s Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Suman S V**
Guide:	**Dr. Jayakaran Charan**
Co-Guide:	**Dr. Surjit Singh, Dr. Ravindra Shukla, Dr. Dharmveer Yadav & Dr. Shoban Babu Varthya**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.
- In case of any issue related to compensation, the responsibility lies with the Investigator and Co-Investigators.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation. If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

Annexure II - Voglibose group Per protocol results

Characteristics of patients before and after 12 weeks of Metformin+voglibose treatment				
Parameters	**Baseline (n=34) [Mean (SD)]**	**After 3months (n=34) [Mean (SD)]**	**Mean difference (95%CI)**	***p*-value**
Primary endpoints				
HbA1c (%)	8.80 (1.47)	7.37 (1.15)	1.43 (1.07 to 1.79)	<0.001
Fasting plasma glucose (mg/dl)	193.76 (67.99)	129.14 (33.86)	64.62 (44.24 to 84.98)	<0.001
Post-prandial plasma glucose (mg/dl)	304.56 (74.99)	174.97 (51.13)	129.59 (106.50 to 152.67)	<0.001
Secondary endpoints				
Body weight (kg)	71.82 (12.86)	69.06 (12.44)	2.77 (2.08 to 3.45)	<0.001
BMI (kg/m^2)	27.36 (4.22)	26.21 (3.86)	1.15 (0.16 to 1.47)	<0.001
Total cholesterol (mg/dl)	186.11 (47.88)	179.32 (41.47)	6.79 (-1.57 to 15.16)	0.108
Triglycerides (mg/dl)	163.50 (84.77)	152.85 (85.03)	10.65 (-4.18 to 25.48)	0.154
LDL-C (mg/dl)	124.47 (35.68)	117.26 (32.12)	7.20 (1.24 to 13.17)	0.019
HDL-C (mg/dl)	40.09 (8.19)	42.73 (8.46)	-2.65 (-5.27 to -0.02)	0.048
VLDL-C (mg/dl)	32.56 (17.02)	31.03 (16.66)	1.53 (-1.58 to 4.64)	0.325
Fasting Insulin (µU/ml)	15.15 (12.16)	14.12 (10.77)	1.03 (-2.26 to 4.31)	0.530
HOMA2-IR	2.78 (2.67)	1.93 (1.38)	0.85 (-0.08 to 1.78)	0.072
HOMA2-B%	45.46 (33.57)	81.78 (65.82)	-36.31 (-53.16 to -19.45)	<0.001
HOMA2-S%	69.38 (62.38)	81.9 (67.08)	-12.52 (-26.51 to 1.47)	0.078
S1	2.12 (1.17)	1.62 (0.65)	0.50 (0.20 to 0.80)	0.002

Parameters	Baseline (n=34) [Mean (SD)]	After 3months (n=34) [Mean (SD)]	Mean difference (95%CI)	*p*-value
S2	2.41 (1.25)	1.94 (1.07)	0.47 (0.18 to 0.76)	<0.001
S3	2.03 (1.19)	1.32 (0.64)	0.70 (0.37 to 1.04)	<0.001
S4	3.15 (0.78)	1.79 (1.04)	1.35 (0.99 to 1.72)	<0.001
S5	2.23 (0.74)	1.79 (0.48)	0.44 (0.23 to 0.65)	<0.001
S6	2.26 (1.08)	2.09 (1.02)	0.18 (-0.10 to 0.45)	0.205
I1	2.35 (1.18)	2.35 (1.12)	<0.01 (-0.15 to 0.15)	1.000
I2	3.26 (1.08)	2.61 (0.92)	0.65 (0.38 to 0.92)	<0.001
I3	2.32 (0.91)	2.21 (0.84)	0.12 (-0.02 to 0.26)	0.103
I4	2.38 (1.04)	2.23 (0.99)	0.15 (0.02 to 0.27)	0.023
W1	1.59 (0.92)	1.35 (0.6)	0.23 (0.02 to 0.45)	0.030
W2	2.38 (1.33)	2.21 (1.2)	0.18 (0.02 to 0.34)	0.032
W3	2.73 (1.11)	2.79 (0.98)	-0.06 (-0.21 to 0.09)	0.422
QoL Total score	31.23 (8.42)	26.32 (6.99)	4.91 (3.45 to 6.37)	<0.001
QoL Satisfaction domain score	14.20 (4.48)	10.56 (3.53)	3.65 (2.69 to 4.61)	<0.001
QoL Impact domain score	10.32 (2.93)	9.41 (2.55)	0.91 (0.43 to 1.39)	0.001
QoL Worry domain score	6.70 (2.56)	6.35 (2.17)	0.35 (0.01 to 0.72)	0.056

Annexure III - Glimepiride group Per protocol results

Characteristics of patients before and after 12 weeks of Metformin+glimepiride treatment				
Parameters	**Baseline (n=35) [Mean (SD)]**	**After 3months (n=35) [Mean (SD)]**	**Mean difference (95% CI)**	***p*-value**
Primary endpoints				
HbA1c (%)	8.84 (1.53)	7.03 (0.96)	1.80 (1.43 to 2.18)	<0.001
Fasting plasma glucose (mg/dl)	181.25 (47.83)	118.17 (27.61)	63.08 (45.62 to 80.55)	<0.001
Post-prandial plasma glucose (mg/dl)	279.51 (81.41)	141.43 (45.03)	138.08 (111.52 to 164.65)	<0.001
Secondary endpoints				
Body weight (kg)	71.42 (15.47)	71.34 (14.96)	0.08 (-0.93 to 1.10)	0.865
BMI (kg/m^2)	27.04 (6.02)	26.99 (5.79)	0.05 (-0.32 to 0.43)	0.778
Total cholesterol (mg/dl)	189.74 (52.36)	177.60 (48.91)	12.14 (2.93 to 21.36)	0.011
Triglycerides (mg/dl)	157.74 (65.29)	144.11 (53.39)	13.63 (0.29 to 26.96)	0.045
LDL-C (mg/dl)	126.42 (37.84)	117.77 (38.53)	8.66 (2.00 to 15.32)	0.012
HDL-C (mg/dl)	44.74 (9.30)	43.54 (8.05)	1.20 (-0.79 to 3.19)	0.228
VLDL-C (mg/dl)	31.37 (13.11)	28.73 (10.70)	2.63 (-0.02 to 5.28)	0.052
Fasting Insulin (µU/ml)	16.43 (14.41)	12.69 (13.91)	3.74 (1.53 to 5.94)	0.002
HOMA2-IR	3.18 (5.49)	1.97 (3.20)	1.21 (0.36 to 2.06)	0.006
HOMA2-B%	51.39 (44.40)	92.57 (118.32)	-41.17 (-71.45 to -10.89)	0.009
HOMA2-S%	64.62 (49.08)	95.82 (62.73)	-31.20 (-43.78 to -18.63)	0.001

Parameters	Baseline (n=35) [Mean (SD)]	After 3months (n=35) [Mean (SD)]	Mean difference (95% CI)	*p*-value
S1	2.31 (1.21)	1.77 (0.64)	0.54 (0.25 to 0.83)	0.001
S2	2.66 (1.37)	2.09 (1.01)	0.57 (0.24 to 0.90)	0.001
S3	1.83 (1.04)	1.40 (0.65)	0.43 (0.14 to 0.72)	0.005
S4	3.00 (0.59)	1.46 (0.78)	1.54 (1.19 to 1.89)	<0.001
S5	2.31 (0.96)	1.6 (0.50)	0.71 (0.44 to 0.98)	<0.001
S6	2.37 (1.21)	2.23 (1.06)	0.14 (-0.005 to 0.29)	0.058
I1	2.31 (1.18)	2.31 (1.18)	-	-
I2	3.31 (1.18)	2.86 (0.97)	0.46 (0.25 to 0.67)	<0.001
I3	2.29 (0.92)	2.23 (0.84)	0.06 (-0.06 to 0.17)	0.324
I4	2.37 (1.28)	2.29 (1.04)	0.08 (-0.12 to 0.30)	0.413
W1	1.49 (0.92)	1.49 (0.82)	<0.01 (-0.26 to 0.26)	1.000
W2	2.20 (1.28)	2.11 (1.21)	0.08 (-0.01 to 0.18)	0.083
W3	2.89 (1.10)	2.83 (1.12)	0.06 (-0.02 to 0.14)	0.160
QoL Total score	31.34 (9.69)	26.66 (6.65)	4.68 (3.14 to 6.23)	<0.001
QoL Satisfaction domain score	14.48 (4.85)	10.54 (2.69)	3.94 (2.78 to 5.11)	<0.001
QoL Impact domain score	10.28 (3.86)	9.68 (3.20)	0.60 (0.14 to 1.06)	0.012
QoL Worry domain score	6.57 (2.55)	6.42 (2.43)	0.14 (-0.16 to 0.44)	0.343

Annexure IV - Intergroup analysis (Per protocol)

Difference in change in parameters in Voglibose group v/s Glimepiride group at 12 weeks				
Parameters	**Voglibose (n=34) [Mean (SD)]**	**Glimepiride(n=35) [Mean (SD)]**	**Mean difference (95% CI)**	***p*-value**
Primary endpoints				
HbA1c (%)	1.43 (1.03)	1.80 (1.08)	-0.37 (-0.88 to 0.13)	0.147
Fasting plasma glucose (mg/dl)	64.62 (58.37)	63.08 (50.83)	1.53 (-24.75 to 27.81)	0.908
Post-prandial plasma glucose (mg/dl)	129.59 (66.16)	138.08 (77.34)	-8.50 (-43.13 to 26.13)	0.626
Secondary endpoints				
Body weight (kg)	2.77 (1.97)	0.08 (2.96)	2.68 (1.47 to 3.89)	<0.001
BMI (kg/m^2)	1.15 (0.92)	0.05 (1.10)	1.10 (0.61 to 1.58)	<0.001
Total cholesterol (mg/dl)	6.79 (23.99)	12.14 (26.83)	-5.35 (-17.59 to 6.89)	0.386
Triglycerides (mg/dl)	10.64 (42.51)	13.63 (38.81)	-2.98 (-22.53 to 16.57)	0.762
LDL-C (mg/dl)	7.20 (17.08)	8.66 (19.39)	-1.45 (-10.24 to 7.34)	0.743
HDL-C (mg/dl)	-2.65 (7.52)	1.20 (5.78)	-3.85 (-7.06 to -0.63)	0.020
VLDL-C (mg/dl)	1.53 (8.92)	2.60 (7.73)	-1.07 (-5.08 to 2.94)	0.596
Fasting Insulin	1.03 (9.42)	3.74 (6.42)	-2.71 (-6.57 to 1.15)	0.166
HOMA2-IR (µU/ml)	0.85 (2.66)	1.21 (2.47)	-0.36 (-1.59 to 0.87)	0.561
HOMA2-B%	-36.31 (48.31)	-41.17 (88.15)	4.87 (-29.43 to 39.16)	0.778
HOMA2-S%	-12.52 (40.09)	-31.20 (36.60)	18.68 (0.25 to 37.12)	0.047
S1	0.50 (0.86)	0.54 (0.85)	-0.04 (-0.45 to 0.37)	0.836
S2	0.47 (0.82)	0.57 (0.95)	-0.10 (-0.53 to 0.33)	0.639
S3	1.35 (1.04)	1.54 (1.01)	-0.19 (-0.68 to 0.30)	0.445
S4	1.35 (1.04)	1.54 (1.01)	-0.19 (-0.68 to 0.30)	0.445
S5	0.44 (0.61)	0.71 (0.79)	-0.27 (-0.61 to 0.07)	0.114
S6	0.18 (0.80)	0.14 (0.43)	0.03 (-0.27 to 0.34)	0.827

Parameters	Voglibose (n=34) [Mean (SD)]	Glimepiride(n=35) [Mean (SD)]	Mean difference (95% CI)	*p*-value
I1	<0.01 (0.43)	<0.01 (<0.01)	<0.01 (-0.14 to 0.14)	1.000
I2	0.65 (0.77)	0.46 (0.61)	0.19 (-0.14 to 0.52)	0.261
I3	0.12 (0.41)	0.06 (0.34)	0.06 (-0.12 to 0.24)	0.505
I4	0.15 (0.36)	0.08 (0.61)	0.06 (-0.18 to 0.30)	0.615
W1	0.23 (0.60)	<0.01 (0.77)	0.23 (-0.10 to 0.57)	0.163
W2	0.18 (0.46)	0.08 (0.28)	0.09 (-0.09 to 0.27)	0.325
W3	-0.06 (0.42)	0.06 (0.23)	-0.11 (-0.28 to 0.05)	0.162
QoL Total score	4.91 (4.17)	4.68 (4.50)	0.23 (-1.86 to 2.31)	0.829
QoL Satisfaction domain score	3.65 (2.75)	3.94 (3.39)	-0.29 (-1.78 to 1.19)	0.693
QoL Impact domain score	0.9 (1.38)	0.60 (1.33)	0.31 (-0.34 to 0.96)	0.343
QoL Worry domain score	0.35 (1.04)	0.14 (0.88)	0.21 (-0.25 to 0.67)	0.368

Annexure V - Revised DQoL Questionnaire

	Questions	1	2	3	4	5
S1	How satisfied are you with the amount of time it takes to manage your diabetes?					
S2	How satisfied are you with the amount of time you spend getting check-ups?					
S3	How satisfied are you with the time it takes to determine your sugar level?					
S4	How satisfied are you with your current treatment?					
S5	How satisfied are you with your knowledge about your diabetes?					
S6	How satisfied are you with life in general?					
I1	How often do you feel pain associated with the treatment for your diabetes?					
I2	How often do you feel physically ill?					
I3	How often does your diabetes interfere with your family life?					
I4	How often do you find your diabetes limiting your social relationships and friendships?					
W1	How often do you worry about whether you will pass out?					
W2	How often do you worry that your body looks different because you have diabetes?					
W3	How often do your worry that you will get complications from your diabetes?					

Domain: Satisfaction
(1 = very satisfied; 2 = moderately satisfied; 3 = neither; 4 = moderately dissatisfied; 5 = very dissatisfied)
Domain: Impact
(1 =never; 2 = very seldom; 3 = sometimes; 4 = often; 5 = all the time)
Domain: Worry
(0 = does not apply; 1 = never; 2 = very seldom; 3 = sometimes; 4 = often; 5 = all the time)

Annexure VI - Case record form

Case Record Form

Sr. No.

Name: CR No.

Address: Age/Sex:

contact number: Date:

Occupation:

Randomization Code:

Inclusion criteria

1. Patients of either sex with type 2 DM, aged 18 -60 years. Y/N
2. Newly diagnosed type-2 DM patients with HbA1c > 7%. Y/N
   (2 or 3)
3. Patients with type-2 DM uncontrolled on metformin 500mg BD
   (RBS > 200mg at least on 3 occasions or HbA1c > 7%). Y/N

Exclusion criteria

1. Type 1 DM patients. Y/N
2. Pregnancy and Lactating women. Y/N
3. Patients with history of Heart failure (NYHA class 2-4). Y/N
4. Patients with history of chronic kidney disease (serum creatinine > 1.5mg/dl).
   Y/N
5. Patients with history liver failure. Y/N
6. Patients with history of autoimmune disorders. Y/N
7. Patients with history of COPD. Y/N

Patient – **Included / Excluded**

Chief complaints

1.
2.

Total duration Age of onset:

EVALUATION

Symptoms	**Yes**	**No**
Polyurea		
Polydipsia		
Polyphagia		
Visual symptoms		
Paraesthesia and hyperesthesia		
Wound/ ulcers		
Gangrene		

PAST HISTORY: HTN / CAD / Any H/o of any chronic drug intake /Any past surgeries etc.

FAMILY HISTORY:

PERSONAL HISTORY: Smoker/Alcoholic/Veg/non-veg

Drug	Dose	Duration	Response

TREATMENT HISTORY:

GENERAL PHYSICAL EXAMINATION

Pallor: Cyanosis: Icterus: Clubbing:

Oedema: Lymphadenopathy:

Baseline characteristics:

Weight- Pulse- B.P.- BMI-

Waist circumference - Hip Cir. - Height-

SYSTEMIC EXAMINATION

RS -

CVS -

P/A -

CNS -

Investigation	**Baseline**	**1st visit**	**2nd visit**	**3rd visit**
HbA1c				
FPG				
PPG				
HOMA-IR				
HOMA-β%				
HOMA-S%				
Triglyceride				
Total cholesterol				
HDL				
LDL				
VLDL				

Quality of life assessment (Revised version of DQoL)

	Questions	1	2	3	4	5
S1	How satisfied are you with the amount of time it takes to manage your diabetes?					
S2	How satisfied are you with the amount of time you spend getting check-ups?					
S3	How satisfied are you with the time it takes to determine your sugar level?					
S4	How satisfied are you with your current treatment?					
S5	How satisfied are you with your knowledge about your diabetes?					
S6	How satisfied are you with life in general?					
I1	How often do you feel pain associated with the treatment for your diabetes?					
I2	How often do you feel physically ill?					
I3	How often does your diabetes interfere with your family life?					
I4	How often do you find your diabetes limiting your social relationships and friendships?					
W1	How often do you worry about whether you will pass out?					
W2	How often do you worry that your body looks different because you have diabetes?					
W3	How often do your worry that you will get complications from your diabetes?					

Domain: **Satisfaction (S)**

(1 = very satisfied; 2 = moderately satisfied; 3 = neither; 4 = moderately dissatisfied; 5 = very dissatisfied)

Domain: **Impact (I)**
(1 =never; 2 = very seldom; 3 = sometimes; 4 = often; 5 = all the time)
Domain: **Worry (W)**
(0 = does not apply; 1 = never; 2 = very seldom; 3 = sometimes; 4 = often; 5 = all the time)

ADVERSE EVENTS	1st visit	2nd visit	3rd visit
Abdominal distension & flatulence			
Allergic reactions			
Diarrhoea and abdominal pain			
Dysgeusia			
Flu like symptoms			
Haemolytic anaemia			
Headache			
Hypoglycemia			
Impairment of LFT			
Lactic acidosis			
Nausea & vomiting			
Pancytopenia & agranulocytosis			
Porphyria cutanea tarda			
Vit-B12 deficiency			
Weakness			
Weight gain			

Grading of hypoglycaemia

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ADA grading					
Clinical grading				-	-

Grading of vomiting

CTC	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Vomiting					

Grading of diarrhoea

Grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea				

Annexure VII - Informed Consent form (English)

Informed Consent Form

Title of the project: "**Efficacy and Safety of Voglibose Vs Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial"**

Name of the Principal Investigator: Dr. Jaykaran Charan

Tel. No. (Mobile): 9825219196

Patient OPD No: _____

I, _____S/o or D/o_____

R/o _____give my full, free, voluntary consent to be a part of the study "Efficacy and Safety of Voglibose Vs Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary, and I am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____ _____

Place: _____ Patient Caregiver

Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ Signature of Principal Investigator

1. Witness 1

Signature

Name: _____

Address: _____

2. Witness 2

Signature

Name: _____

Address: _____

Annexure VIII - Informed Consent form (Hindi)

सूचित सहमति प्रपत्र

परियोजना का शीर्षक:- ‘‘टाइप 2 मधुमेह में मेटफॉर्मिन के संयोजन में वोगिबोस बनाम ग्लीमपीराइड की प्रभावकारिता और सुरक्षा: एक यादृच्छिक नियंत्रित परीक्षण’’

प्रधान अन्वेषक: डॉ जयकरन चरन

टेलीफोन नंबर: 9825219196

रोगी / स्वयंसेवी पहचान संख्या: _____

मैं,_____पुत्र/पुत्री_____

निवासी_____स्वयं को अध्ययन का हिस्सा होने के लिए अपनी पूर्ण स्वैच्छिक सहमति देता हूँ। इस अध्ययन का शीर्षक है टाइप 2 मधुमेह में मेटफॉर्मिन के संयोजन में वोगिबोस बनाम ग्लीमपीराइड की प्रभावकारिता और सुरक्षा: एक यादृच्छिक नियंत्रित परीक्षण मेरी पूर्ण संतुष्टि के लिए मेरी खुद की भाषा में मुझे समझाया गया है। मैं इस बात की पुष्टि करता हूं कि मुझे सवाल पूछने का पूर्ण अवसर मिला है।

मैं यह समझता हूँ कि मेरी भागीदारी स्वैच्छिक है और बिना कोई कारण बताए किसी भी समय इस अध्ययन से स्वयं को वापस लेने के लिए मेरे अधिकार के बारे में मुझे पता है।

मैं यह समझता हूँ कि मेरे मेडिकल रिकॉर्ड की एकत्रित की गई जानकारी "अखिल भारतीय आयुर्विज्ञान संस्थान जोधपुर" या नियामक अधिकारियों द्वारा देखी जा सकती है। मैं इन व्यक्तियों को मेरे रिकॉर्ड के उपयोग के लिए अनुमति देता हूँ।

दिनांक:

स्थान: **हस्ताक्षर / वाम अंगूठे का निशान**

यह प्रमाणित किया जाता कि इस संस्करण की सहमति मेरी उपस्थिति में प्राप्त की गयी है:

दिनांक: **प्रमुख अन्वेषक के हस्ताक्षरस्थान**

1. साक्षी 1	2. साक्षी 2
हस्ताक्षर: _____	**हस्ताक्षर:_____**
नाम: _____	**नाम: _____**
पता: _____	**पता:_____**

Annexure IX - Patient information leaflet (English)

Patient information leaflet

You are being invited to willing fully participate in the study entitled **"Efficacy and Safety of Voglibose Vs Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial".**

Purpose of research

Diabetes mellitus is characterized by abnormally high levels of sugar (glucose) in the blood. Diabetes is fast gaining the status of a potential epidemic in India with more than 77 million diabetic individuals currently diagnosed with the disease. The most common forms of diabetes are type 1 diabetes (5%), which is an autoimmune disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes is a form of diabetes that occurs in pregnancy, and other forms of diabetes are very rare and are caused by a single gene mutation. Increased blood glucose levels do not only alter the metabolic profile but also cause end organ damage leading to diabetic retinopathy, nephropathy, neuropathy, cardiovascular and cerebrovascular adverse events including premature death.so, it is necessary to control blood glucose level to avoid its complications. In this study we are comparing two drugs i.e., voglibose and glimepiride given with metformin for their Efficacy, and Safety in treating type-2 DM.

Study Design

This study involves two groups comprising of about 50% patients in voglibose group and 50% patients in glimepiride group. If you are eligible for systemic drug administration, you will be given either metformin 500mg BD plus voglibose 0.2mg t.i.d. just before food (Voglibose group) or metformin 500mg BD plus glimepiride 1 mg OD before food (Glimepiride group). You as well as your physician will be aware of the group you belong to.

Voglibose

- Voglibose is a valiolamine derivative and alpha-glucosidase inhibitor, which reduces post-prandial blood glucose levels in DM.
- Voglibose is given in 0.2 mg t.i.d. per day if you enrol in voglibose group.
- Side effects: voglibose has been safely used in large number of patients. If side effects do occur, they may be flatulence, diarrhoea, and abdominal pain

Metformin

- Metformin is a Biguanide used in the treatment of type-2 DM.
- Metformin is given in 500 mg B.D per day if you are enrolled in any of the groups.

- Side effects: Metformin has been safely used in large number of patients. If side effects do occur, they may be diarrhoea, bloating, pain abdomen, metallic taste, myalgia, rash, headache, lactic acidosis, vit-B12 deficiency.

Glimepiride

- Glimepiride is a sulfonylurea used in the treatment of type-2 DM
- Glimepiride is given in 1mg per day if you are enrolled in glimepiride group.
- Side effects: glimepiride has been safely used in large number of patients. If side effects do occur, they may be hypoglycemia, Allergic reactions, Dysgeusia, Flu like symptoms, Haemolytic anaemia, Impairment of LFT, Nausea & vomiting, Pancytopenia & agranulocytosis, Porphyria cutanea tarda, Weight gain, weakness, disulfiram like reactions.

Precautions you should take:

- Women: to use reliable contraception while on treatment.
- Avoid alcohol while on treatment.

If patients,

a) Take an overdose of medication (whether by accident or by design),
b) Have severe fever, diarrhoea, vomiting, pain abdomen, jaundice, rashes, symptoms of hypoglycemia.

see your doctor immediately.

General instructions:

- **If side effects occur**, you are advised to contact anyone of the investigators whose contact number is given below.
- **In case of serious side effect,** we will treat you as per the standard treatment practices and you need not have to bear the cost of treatment.
- **Be sure to keep all your appointments** so that your progress can be checked. Some blood, liver function and other tests may have to be done from time to time to check on your progress and detect any unwanted side effects.
- **After taking the medicines:**
  - ✓ Ensure that you take them as instructed.
  - ✓ Bring the container with the medicines back at your next visit. You should bring all the medicines which are left in the container.
  - ✓ In case you need to take any additional medicine on account of fever, sore throat or any minor illness, please feel free to contact the study doctor.

Confidentiality

Your medical records and identity will be treated as confidential documents. They will only be revealed to other doctors/scientists/monitors/auditors of the study if required. The results of the study may be published in a scientific journal, but you will not be identified by name.

Ethics committee approval has been obtained for the study.

Your participation and rights

Your participation in the study is fully voluntary and you may withdraw from the study anytime without having to give reasons for the same. In any case, you will receive the appropriate treatment for your condition. You will not be paid any amount for the participation in the study. You will have to pay for the routine investigations that will be done.

For further queries/questions or help in emergency please contact.

1. **Dr. Suman S V - 9845196021**
2. **Dr. Jaykaran Charan - 9825219196**

Annexure X - Patient information leaflet (Hindi)

रोगी की जानकारी

आपको अध्ययन के अधिकार में पूरी तरह से भाग लेने के लिए आमंत्रित किया जा रहा है **"टाइप 2 मधुमेह में मेटफॉर्मिन के साथ संयोजन में वोगलिबोज बनाम ग्लिम्पिराइड की प्रभावकारिता और सुरक्षा: एक यादृच्छिक नियंत्रित परीक्षण"**

अनुसंधान का उद्देश्य-

मधुमेह को रक्त में शर्करा के उच्च स्तर (ग्लूकोज) की विशेषता होती है। मधुमेह तेजी से भारत में एक संभावित महामारी की स्थिति प्राप्त कर रहा है जिसमें 77 मिलियन से अधिक मधुमेह के व्यक्ति वर्तमान में इस बीमारी का निदान कर रहे हैं। मधुमेह के सबसे आम प्रकार टाइप 1 मधुमेह (5%) हैं, जो एक स्व-प्रतिरक्षित विकार है, और टाइप 2 मधुमेह (95%), जो मोटापे से जुड़ा हुआ है। गर्भकालीन मधुमेह मधुमेह का एक रूप है जो गर्भावस्था में होता है, और मधुमेह के अन्य रूप बहुत कम होते हैं और यह एकल जीन उत्परिवर्तन के कारण होते हैं। रक्त शर्करा के स्तर में वृद्धि से न केवल चयापचय प्रोफाइल में परिवर्तन होता है, बल्कि इससे डायबिटिक रेटिनोपैथी, नेफ्रोपैथी, न्यूरोपैथी, कार्डियोवस्कुलर और सेरेब्रोवास्कुलर प्रतिकूल घटनाओं के कारण होने वाली अंतिम क्षति भी होती है, जिसमें समय से पहले मृत्यु हो जाती है। इसलिए, इसकी जटिलताओं से बचने के लिए रक्त शर्करा के स्तर को नियंत्रित करना आवश्यक है। इस अध्ययन में हम दो दवाओं की तुलना करते हैं, अर्थात टाइप 2 मधुमेह के इलाज में उनकी प्रभावकारिता और सुरक्षा के लिए मेटफॉर्मिन के साथ दिए गए वोग्लिबोस और ग्लिम्पिराइड।

अध्ययन योजना-

इस अध्ययन में वोग्लिबोस समूह में लगभग 50% रोगियों और ग्लिम्पीराइड समूह में 50% रोगियों के दो समूह शामिल हैं। यदि आप प्रणालीगत दवा प्रशासन के लिए पात्र हैं, तो आपको मेटफॉर्मिन 500mg BD प्लस वोग्लिबोस 0.2mg t.i.d दिया जाएगा। भोजन से ठीक पहले (Voglibose group) या मेटफोर्मिन 500mg BD प्लस ग्लिम्पिराइड 1mg OD भोजन से पहले (Glimepiride group)। आप और साथ ही साथ आपके चिकित्सक उस समूह से अवगत होंगे जो आप के हैं।

वोग्लिबोस-

- वोगलिबोज एक वैलिओमाइन व्युत्पन्न और अल्फा-ग्लूकोसिडेस अवरोधक है, जो मधुमेह में भोजन के बाद रक्त के स्तर को कम करता है।
- वोगलिबोज को 0.2mg दिन में तीन बार दिया जाता है, अगर आप वोगलिबोज समूह में दाखिला लेते हैं।
- प्रतिकूल प्रभाव: वोगलिबोज को बड़ी संख्या में रोगियों में सुरक्षित रूप से उपयोग किया गया है। यदि प्रतिकूल प्रभाव पड़ता है, तो वे हो सकते हैं: पेट फूलना, दस्त और पेट दर्द।

मेटफोर्मिन-

- मेटफॉर्मिन एक बिगुआनइड है जिसका उपयोग टाइप 2 मधुमेह के उपचार में किया जाता है।
- यदि आप किसी भी समूह में नामांकित हैं, तो मेटफॉर्मिन 500 मिलीग्राम प्रति दिन दो बार दिया जाता है।
- प्रतिकूल प्रभाव: मेटफोर्मिन का उपयोग बड़ी संख्या में रोगियों में सुरक्षित रूप से किया गया है। यदि प्रतिकूल प्रभाव होते हैं, तो वे हो सकते हैं: दस्त, सूजन, पेट में दर्द, धातु स्वाद, शरीर में दर्द, दाने, सिरदर्द, लैक्टिक एसिडोसिस, विटामिन-बी12 की कमी।

ग्लिम्पिराइड-

- ग्लिम्पिराइड एक सल्फोनील्यूरिया है जिसका उपयोग टाइप 2 मधुमेह के उपचार में किया जाता है।
- यदि आप ग्लिमेप्राइड समूह में नामांकित हैं, तो इसे प्रति दिन 1mg में दिया जाता है।

- प्रतिकूल प्रभाव: ग्लिम्पीराइड को बड़ी संख्या में रोगियों में सुरक्षित रूप से उपयोग किया गया है। यदि प्रतिकूल प्रभाव होता है, तो वे हो सकते हैं: हाइपोग्लाइसीमिया, एलर्जी प्रतिक्रियाएं, डिस्पेसिया, फ्लू जैसे लक्षण, रक्तलायी अरक्तता, यकृत की दुर्बलता, मतली और उल्टी, अग्नाशयशोथ और एग्रानुलोसाइटोसिस, पोर्फिरीया कटानिया टार्डा, वजन बढ़ना, कमजोरी, अरुचि।

आपको जो सावधानियां बरतनी चाहिए-

- महिला: उपचार के दौरान विश्वसनीय गर्भनिरोधक का उपयोग करना।
- उपचार के दौरान शराब से बचें।

यदि रोगियों,

a) दवा का ओवरडोज लें (चाहे दुर्घटना से या डिजाइन से),
b) तेज बुखार, दस्त, उल्टी, पेट में दर्द, पीलिया, चकत्ते, हाइपोग्लाइसीमिया के लक्षण हैं।

तुरंत अपने डॉक्टर से मिलें।

सामान्य निर्देश-

- यदि प्रतिकूल प्रभाव होता है, तो आप किसी भी जांचकर्ता से संपर्क कर सकते हैं जिसका संपर्क नंबर नीचे दिया गया है।
- यदि कोई गंभीर प्रतिकूल प्रभाव पड़ता है, तो हम आपको मानक उपचार प्रथाओं के अनुसार इलाज करेंगे और आपको उपचार की लागत वहन करने की आवश्यकता नहीं है।
- अपनी सभी नियुक्तियों को सुनिश्चित रखें ताकि आपकी प्रगति की जाँच की जा सके। आपकी प्रगति की जांच करने और किसी भी अवांछित दुष्प्रभाव का पता लगाने के लिए कुछ रक्त, यकृत परीक्षण और अन्य परीक्षण समय-समय पर किए जा सकते हैं।
- दवाएं लेने के बाद:
    - ✓ सुनिश्चित करें कि आप उन्हें निर्देशानुसार ले जाएं।
    - ✓ अपने अगले दौरे में दवाओं के साथ कंटेनर वापस लाएँ। आपको सभी दवाइयां लानी चाहिए जो बची हैं।
    - ✓ यदि आपको बुखार, गले में खराश या किसी छोटी बीमारी के कारण कोई अतिरिक्त दवा लेने की जरूरत है, तो कृपया अध्ययन चिकित्सक से संपर्क करें।

गोपनीयता-

आपके मेडिकल रिकॉर्ड और पहचान को गोपनीय दस्तावेजों के रूप में माना जाएगा। यदि आवश्यक हो तो वे केवल अध्ययन के अन्य डॉक्टरों / वैज्ञानिकों / मॉनिटर / ऑडिटर्स के सामने आएंगे। अध्ययन के परिणाम एक वैज्ञानिक पत्रिका में प्रकाशित हो सकते हैं लेकिन आपको नाम से नहीं पहचाना जाएगा। अध्ययन के लिए आचार समिति की मंजूरी मिल गई है।

आपकी भागीदारी और अधिकार -

अध्ययन में आपकी भागीदारी पूरी तरह से स्वैच्छिक है और आप बिना कारण बताए कभी भी अध्ययन से हट सकते हैं। किसी भी मामले में, आप अपनी स्थिति के लिए उपयुक्त उपचार प्राप्त करेंगे। अध्ययन में भाग लेने के लिए आपको कोई पैसा नहीं दिया जाएगा। आपको नियमित जांच के लिए भुगतान करना होगा।

किसी भी प्रश्न या आपात स्थिति में मदद के लिए संपर्क करें।

1. **डॉ सुमन एस वी - 9845196021**
2. **डॉ जयकरन चरन – 9825219196**

Annexure XI - CTRI Registration

CTRI Number	CTRI/2021/04/033005 [Registered on: 22/04/2021] - **Trial Registered Prospectively**
Last Modified On	30/11/2022
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Drug
Study Design	Randomized, Parallel Group, Active Controlled Trial
Public Title of Study	Voglibose v/s Glimepiride Efficacy and Safety in Combination with Metformin in Type-2 Diabetes Mellitus patients
Scientific Title of Study	Efficacy and Safety of Voglibose v/s Glimepiride in Combination with Metformin in Type-2 Diabetes: A Randomized Controlled Trial

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	SUMAN S V
Designation	Junior Resident
Affiliation	AIIMS JODHPUR
Address	Department of Pharmacology, AIIMS College building, AIIMS, MIA-2, BASNI, JODHPUR Jodhpur RAJASTHAN 342005 India
Phone	9845196021
Fax	
Email	Sumanmra@gmail.com

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	JAYKARAN CHARAN
Designation	ASSOCIATE PROFESSOR
Affiliation	AIIMS JODHPUR
Address	Department of Pharmacology, AIIMS College building, AIIMS, MIA-2, BASNI, JODHPUR Jodhpur RAJASTHAN 342005 India
Phone	9825219196
Fax	
Email	dr.jaykaran78@gmail.com

Annexure XII - Plagiarism Certificate

iThenticate

Thesis draft 31.12.22.docx

2646 words • 307 matches • 127 sources

14%

Match Overview

All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

This is to certify that the thesis entitled "**Efficacy and Safety of Voglibose v/s Glimepiride in Combination with Metformin in Type 2 Diabetes: A Randomized Controlled Trial**" is an original work of **Dr Suman S V** carried out under our guidance and supervision at All India Institute of Medical Sciences, Jodhpur.

Guide:

Dr Jaykaran Charan

Additional Professor,

Department of Pharmacology,

AIIMS, Jodhpur.