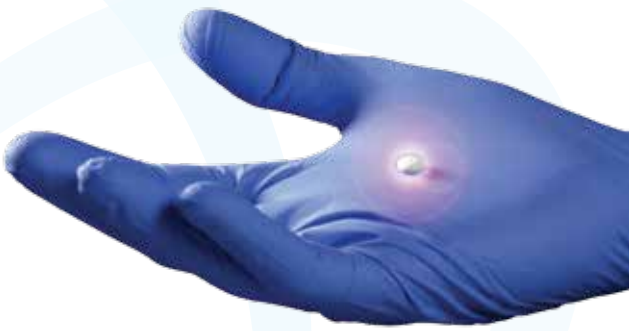
Product Monograph

Lipaglyn™

Saroglitazar

Novel. Superior. Dual acting.



Zydus dedicated to life | Zydus Discovery

Lipaglyn™
Saroglitazar

Message from the Chairman's Desk

Dear Doctor,

Greetings at a historic moment!

We are indeed very pleased to announce the launch of our Novel, Superior, Dual Acting patented molecule **Lipaglyn™** ***(Saroglitazar)***. This is the first drug ever to receive an approval for diabetic dyslipidemia - An Unmet Healthcare need. This is a landmark achievement not only for us, but for the entire healthcare fraternity in India.

Discovered and developed by Zydus, Saroglitazar is a first-in-class molecule to be approved by the Drug Controller General of India to treat diabetic dyslipidemia or hypertriglyceridemia in type-2 diabetes not controlled by statins alone.

Researched & developed over a span of 12 years, **Lipaglyn™** is the first New Chemical Entity (NCE) from India to successfully complete the journey from the lab to the market. A team of over 400 dedicated research scientists at the Zydus Research Centre, Ahmedabad, guided the molecule through every stage, from the lab to the market.

For patients with diabetic dyslipidemia, **Lipaglyn™** is unique –

- Superior safety profile - with a lower incidence of side events vs. current standard of care
- Greater efficacy on lipid regulation (especially when taken in combination with statins)
- Additionally, the drug also offers excellent glycemic control

We are also embarking on a long term drug development program to globalize the molecule – in other emerging markets and in developed markets like Europe & USA.

To familiarize you with our Novel, Superior & Dual Acting **Lipaglyn™**, our medical team has compiled a product monograph specially for physicians like you. For further details you may visit www.lipaglyn.com

Looking forward for your feedback on the therapeutic use of **Lipaglyn™**.

Warm Regards,

Pankaj R. Patel
Chairman and Managing Director

Lipaglyn™
Saroglitazar

Message from the Sr. VP's Desk

Dear Doctor,

Greetings from Zydus Discovery!!!

It is indeed a great pleasure to share this breakthrough of Zydus - **Lipaglyn™** (Saroglitazar), India's 1st NCE. This novel drug, discovered and developed through indigenous efforts, is approved for treating Diabetic Dyslipidemia – a global unmet healthcare need.

This is a step forward in our commitment to serve the nation by strengthening the medical fraternity. The success of **Lipaglyn™** can be a source of pride, not just for Zydus, but also for the Indian pharmaceutical industry and for the nation; encouraging more focus and investment on indigenous research.

As you would know that today India is inching towards having the largest pool of diabetic patients globally. Moreover, nearly 80% of diabetic population have concomitant dyslipidemia and need a drug intervention for treatment.

Our medical & R&D teams have compiled this product monograph with comprehensive information on Diabetic Dyslipidemia, current therapies and role of **Lipaglyn™** in treatment of this condition.

This monograph is comprised of three major sections–

- Diabetic Dyslipidemia therapy area
- **Lipaglyn™** preclinical studies
- **Lipaglyn™** clinical studies

Looking forward for your co-operation and guidance to enable **Lipaglyn™** help every Diabetic Dyslipidemia patient in India lead a healthier life.

Regards,

M S Nath
Sr. Vice President & Head SBU 2 (CVD)

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Preface

Every fourth diabetic in the world is an Indian. As per an Indian Council of Medical Research (ICMR) study in 2011, the prevalence of diabetes has increased to 12-18% in urban India, 3-6% in rural India and another 14% having pre-diabetes. Translated into numbers, there were already 62.4 million diabetics and 77.2 million pre-diabetics in 2011 in India. The numbers are increasing exponentially. The reason is that the genetic susceptibility to develop diabetes is high in Indians. Indians have a low threshold for the risk factors like obesity, sedentary life habits and stress. These risk factors are applicable to all Indians irrespective of the place they live. Indians living in other countries too have a higher prevalence of diabetes compared to the natives and the Caucasian population.

Diabetics have an increased cardiovascular risk. This risk gets exaggerated by lipid abnormalities additionally. Diabetics have an increased propensity to develop dyslipidemia (also known as 'Atherogenic Diabetic Dyslipidemia'-ADD) characterized by high TG and/or low HDL-C and/or small dense LDL-C. Indian type 2 diabetics are highly prone to be dyslipidemic, as a study found that 85.5% male, and, as high as 97.2% female Indian diabetics have dyslipidemia.

Traditionally, diabetes and its accompanying dyslipidemia are managed by a variety of permutations and combinations of anti-diabetic and lipid-lowering drugs. The glycemic and lipid goals are not being met in the majority of patients because meeting these goals are a challenge. In the management of diabetes, insulin or the secretagogues cause hypoglycaemia, and the secretagogues can lead to exhaustion of the pancreatic beta cells. Metformin alone is not always sufficient, and the other insulin sensitizers like pioglitazone, acting by stimulating the nuclear peroxisome proliferator-activated receptors-γ (PPAR-γ) receptors, are under a cloud for their side effect profile. As far as lipids are concerned, statins at best are able to benefit 20-30% patients only. Fibrates, by stimulating the PPAR-α receptors, either alone or in combination with the statins, pose hazards of muscle toxicity. Niacin and fish-oils also do not meet the expectations. In such a scenario research got directed at developing dual PPAR-α/γ agonists which could address both the abnormalities of lipids and hyperglycemia in diabetic dyslipidemia.

The potential of PPAR agonists to positively influence the cardiovascular disease risk in type 2 diabetics has remained an area of continuous medical interest. PPAR-α agonists (fenofibrate) and PPAR-γ agonist (pioglitazone) are approved respectively for lipid control and glycemic control in type 2 diabetes. However, increasing safety concerns with thiazolidinediones with regard to fluid retention, weight gain and congestive cardiac failure have resulted in new label warning for these agents. Hence, there was a strong need for a dual PPAR-α/γ agonist with beneficial effects in controlling both lipids and glycemic levels with all the necessary safety parameters.

We bring to you the world's first approved dual PPAR-α/γ agonist, Lipaglyn™ (saroglitazar), for your patients suffering from diabetic dyslipidemia, which has shown efficacy in improving both, the lipid as well as the glycemic parameters, with an excellent safety profile. Read the entire story of Lipaglyn™ in this monograph. Happy reading!

Dr Anil J. Jaiswal
VP – Medical Services

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1. Introduction: Burden of cardiovascular disease in India and its risk factors

India accounts for 21% of the world's global burden of disease. Non-communicable diseases (NCDs) are responsible for two-thirds of the total morbidity burden and about 53% of total deaths in India. This figure is expected to rise from 40.4% in 1990 to 59% by 2015. And, most importantly, two out of four leading NCDs in India are:

- Cardiovascular diseases (CVDs)
- Diabetes Mellitus (DM)[1]

India experienced the highest loss in potentially productive years of life worldwide. The leading cause of death was CVD; mostly affecting people aged 35-64 years. It has been calculated that, in 2000, 9.2 million years of productive life were lost in India.[2]

There are six leading risk factors associated with NCDs. They are:

- High blood glucose levels
- Altered lipid levels
- Physical inactivity
- Overweight/Obesity
- High blood pressure
- Tobacco use

The prevalence of coronary heart disease (CHD) during 2003 in India was estimated to be 3-4% in rural areas (two-fold higher compared to 40 years ago), and 8-10% in urban areas (six-fold higher compared to 40 years ago), with a total affected population of 29.8 million (14.1 million in urban areas, and 15.7 million in rural areas).

This estimate is comparable to the figure of 31.8 million affected, derived from extrapolations of the "Global Burden of Diseases Study". These numbers likely underestimate the affected population as they do not account for those with silent myocardial infarction (MI) or otherwise asymptomatic CHD. In 1990, there were an estimated 1.17 million deaths from CHD in India, and the number was expected to almost double to 2.03 million by 2010. Also, CHD manifests almost 10 years earlier on an average in this region compared with the rest of the world, resulting in a substantial number of CHD deaths occurring in the working age group.[3]

In Western countries where CVD is considered a disease of the aged, 23 per cent of CVD deaths occur below the age of 70; whereas in Indians, 52 per cent of CVD deaths occur among people under 70 years of age. As a result, the Indian subcontinent suffers from a tremendous loss of productive working years due to CVD deaths: an estimated 9.2 million productive years of life were lost in India in 2000, with an expected increase to 17.9 million years in 2030 which is almost ten times the projected loss of productive life in the United States.[4]

2. Global and Indian diabetes prevalence

A report by International Diabetes Federation (IDF) on the Global Burden of Diabetes highlighted the following important facts[5]:

(i) 366 million people had diabetes in 2011; by 2030 this will have risen to 552 million.

(ii) The number of people with type 2 diabetes (T2DM) is increasing in every country.

(iii) 80% of people with diabetes live in low- and middle-income countries.

(iv) The greatest number of people with diabetes are between 40 to 59 years of age.

(v) 183 million people (50%) with diabetes are undiagnosed.

(vi) Diabetes caused 4.6 million deaths in 2011.

IDF Diabetes Atlas Update 2012[6]

(i) More than 371 million people have diabetes.

(ii) The number of people with diabetes is increasing in every country.

(iii) Half of the people with diabetes are undiagnosed.

(iv) 4.8 million people died due to diabetes.

ICMR- INDIAB study[7]

In 2011, there were already 62.4 million diabetics and 77.2 million pre-diabetics in India.

(i) India is facing an epidemic of diabetes, with high prevalence in urban areas. Over the past 30 years, the prevalence of diabetes has increased to 12-18% in urban India and 3-6% in rural India with significant regional variations.

(ii) Another 14% having prediabetes - a harbinger of future diabetes.

(iii) More than 90% of all Indian diabetics suffer from T2DM.

This study overshadows all the previous estimates of diabetes prevalence in India. Diabetic population in India has grown more than that predicted by the earlier studies.

Table 2.1 : Prevalence of diabetes & prediabetes in Indian population (Number in Millions. Prevalence in % adult >20 years)

Tamil Nadu		Maharashtra		Jharkhand		Chandigarh	
Diabetes	Pre-diabetes	Diabetes	Pre-diabetes	Diabetes	Pre-diabetes	Diabetes	Pre-diabetes
4.8 (10.4%)	3.9 (8.3%)	6 (8.4%)	9.2 (12.8%)	0.96 (5.3%)	1.5 (8.1%)	0.12 (13.6%)	0.13 (14.6%)

*Adapted from - Anjana RM *et al.* Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian council of medical research-INdiaDIABetes (ICMR-INDIAB) study. Diabetologia. 2011 Dec;54(12):3022-7.

3. Diabetic dyslipidemia and its prevalence in India

Dyslipidemia is an abnormal amount of lipids (e.g. cholesterol and/or triglycerides) in the blood and dyslipidemia is one of the major risk factors for CVDs in DM.

Diabetic Dyslipidemia (DD) consists of specifically mild to marked elevation of triglyceride-rich lipoproteins- very low density lipoprotein-cholesterol (VLDL-C) and VLDL-C remnants, and low levels of high density lipoprotein-cholesterol (HDL-C). **Raised serum triglycerides (TG) and low HDL-C often precede the onset of T2DM**. In addition, low density lipoprotein-cholesterol (LDL-C) particles are converted to smaller, perhaps more atherogenic, lipoproteins termed 'small dense LDL-C' (sd-LDL-C).[8]

This combination of hypertriglyceridemia, low HDL-C and high levels of sd-LDL-C, termed as 'Atherogenic Dyslipidemia' – better addressed as Atherogenic Diabetic Dyslipidemia (ADD), is particularly seen in Asian Indians. Although precise reason for such dyslipidemia is unknown, genetic predisposition and characteristic body composition (excess intra-abdominal fat) may be important contributors. A common outcome of such a body composition and dyslipidemia in Asian Indians is the tendency to develop insulin resistance.[9]

A study by Parikh R M *et al* found that the majority of Indian type 2 diabetics are dyslipidemic at baseline. The most common pattern of dyslipidemia is high LDL-C and low HDL-C. The most prevalent problem among males is high LDL-C while among females it was low HDL-C. **Majority of these diabetic patients failed to achieve all standard goals of dyslipidemia management.** In a substantial number of patients this was attributable to the fact that the HDL-C target was not met.[10]

The risk for coronary artery disease (CAD) is 2-4 times higher in diabetic subjects, and in Indians, CAD occurs prematurely, i.e. one to two decades earlier than in the West.

The 'Chennai Urban Population Study' showed 11% prevalence of CAD, which is 10 times more than what it was in 1970. Clustering of risk factors for CAD such as **hyperglycemia**, central obesity, **dyslipidemia**, and hypertension (HTN) tend to occur, and, interplay of these risk factors could explain the enhanced CAD risk in Indians. Additionally, low-grade inflammation and a possible inherent genetic susceptibility are other contributing factors.[11]

4. Prevalence of hypertriglyceridemia in Indian diabetics

A study published in 2010 shows, 37% males and 40% females in India have hypertriglyceridemia.[10]

Table 4.1 : Prevalence and pattern of dyslipidemia in type 2 diabetic males and females at baseline (not on any lipid lowering agent)

	Males (422)	Females (366)
Mixed dyslipidemia		
High TG, high LDL-C and low HDL-C	51 (12.1%)	88 (24.0%)
Combined dyslipidemia		
High TG and low HDL-C	37 (8.8%)	34 (9.3%)
High TG and high LDL-C	43 (10.2%)	19 (5.2%)
High LDL-C and low HDL-C	82 (19.4%)	118 (32.2%)
Isolated single parameter dyslipidemia		
High TG	27 (6.4%)	5 (1.4%)
High LDL-C	77 (18.2%)	46 (12.6%)
Low HDL-C	44 (10.4%)	48 (13.1%)
Total	361 (85.5%)	358 (97.8)

TG-triglyceride; HDL-C-high-density lipoprotein cholesterol; LDL-C-low-density lipoprotein cholesterol.

In an article, Sawant AM *et al*, pointed out a high prevalence of hypercholesterolemia, **hypertriglyceridemia** and low HDL-C, especially in the 31-40 years age group. It has been observed that in comparison to the western population, a relatively lower level of cholesterol appears to predispose Indians to CAD.[12]

Sawant AM *et al* also quote that in a Chennai based hospital study, it was shown that around 75% of patients with MI had total cholesterol (TC) levels <200mg/dL, indicating that the threshold for the TC levels above which it poses a risk for CAD, is low in Indians.[12]

The crude prevalence of hypertriglyceridemia differs between the age groups and it was higher in men than in women. The contributing factor for hypertriglyceridemia in the Indian population could be diet rich in carbohydrates. High TG levels have been associated with increased levels of sd-LDL-C which are considered to be highly atherogenic.[12]

Hypertriglyceridemia could lead to endothelial dysfunction, atherosclerosis, HTN, and ischemic heart disease (IHD). In addition, studies have demonstrated the myocardial susceptibility to ischemia-reperfusion injury in the hypertriglyceridemic condition. Importantly, hypertriglyceridemia alone may cause cardiovascular (CV) abnormalities like atherosclerosis even in the absence of hypercholesterolemia.[13]

5. Classification of lipid parameters

The National Cholesterol Education Program - Adult Treatment Panel III (NCEP ATP III) classification of lipid parameters is as follows:

Table 5.1 : NCEP ATP III classification of lipid parameters

Lipoprotein	Concentration (mg/dL)	Interpretation
TC	< 200	Desirable
	200-239	Borderline high
	≥240	High
LDL-C	<100	Optimal
	100-129	Near/above optimal
	130-159	Borderline high
	160-189	High
	≥190	Very high
HDL-C	<40	Low
	≥60	High
TG	<150	Normal
	150-199	Borderline high
	200-499	High
	≥500	Very high

The primary focus in treatment targets is to reduce CV risk and thereby reduce CHD events. LDL-C is the primary target for initiating and titrating therapy (if TG<200 mg/dL). As the primary target of therapy in the management of dyslipidemia, LDL-C has been a central focus.

NCEP guidelines advocate lowering LDL-C levels to outlined therapeutic targets and statins are the primary agents widely used for this purpose. A substantial body of evidence has also been generated in this regard.

Non-high-density lipoprotein-cholesterol (Non-HDL-C) is identified as a secondary target in patients with fasting TG >200 mg/dL. But, when fasting TG is > 500 mg/dL, **then TG is the primary target** because of the risk of pancreatitis.[14]

In recent times the focus is shifting on reducing the non-HDL–C (all the atherogenic lipoproteins) as many trials have demonstrated non-HDL-C levels are a better predictor of CVD risk than is LDL-C. LDL-C may actually be underestimating the burden of atherogenic, cholesterol-carrying lipoproteins .[15]

6. Role of statins and fibrates in Atherogenic Diabetic Dyslipidemia (ADD)

Lifestyle changes are suggested to all patients of ADD. Still, most patients with T2DM would require medications to lower their lipid levels. The most potent medications to reduce LDL-C levels are statins. They are considered a first-line treatment for lowering LDL-C in patients with ADD.

6.1 Statins

Statins are capable of decreasing the LDL-C levels by as much as 50%. They may have additional benefit on HDL-C and TG levels. These medications may be used in monotherapy, or they may need to be used in combination for the patient with multiple lipid abnormalities in addition to high LDL-C, like high TG and low HDL-C.

Statins are also used for treatment of diabetics who do not have dyslipidemia, aged > 40 years with ≥1 risk factor, because of their pleotropic benefits, including anti-inflammatory properties and potential to increase nitric oxide and enhance vasodilation. These medications have years of patient evaluations that have shown a decrease in CV mortality as well as in total mortality. Data from both primary and secondary prevention trials strongly support starting lipid-lowering therapy with a statin in most patients with diabetes and that the benefit of statins increases in patients with low levels of HDL-C.[16, 17, 18]

Among the statins, the four most commonly prescribed statins for managing dyslipidemia among diabetic patients are simvastatin, atorvastatin, rosuvastatin, and pravastatin.[19]

The Heart Protection Study (HPS) in patients with diabetes (n = 5963) showed simvastatin therapy reduced CVD risk by 22%.[20]

In the Collaborative Atorvastatin Diabetes Study (CARDS) of 2838 patients with diabetes, atorvastatin therapy reduced CVD risk by 32%. This shows that significant residual CV risk remains in diabetic patients treated with statins as evidenced in HPS and CARDS (78% and 68%, respectively).[21]

The most common issue related to statin use is the effect of statins on muscle function. Muscle symptoms range from myalgia, which includes muscle pain without creatine kinase (CK) elevations, to myositis which is muscle symptoms with CK elevations. Hepatic function is also known to be affected by statin use.[22]

Recent data also suggests that statin therapy for long term, especially in high dose can worsen the glycemic control and can lead to new onset of T2DM. On the basis of these findings, the United States Food and Drug Administration (US FDA) has recently added information to statin labels regarding the impact of these agents on T2DM. This finding is more important for T2DM where insulin resistance is already established.[23]

6.2 Fibric acid derivatives

The peroxisome proliferator-activated receptor-α (PPAR-α) agonists are beneficial in the treatment of ADD, lowering TG, and raising HDL-C levels, though with minimal impact on

LDL-C. Outcome studies have shown that fibric acid derivatives are especially effective drugs in decreasing CV events in patients with diabetes given the lipid derangements are in TG and HDL-C levels.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study assessed the effect of fenofibrate (200 mg/day) compared with placebo on CV events in patients with T2DM. Although fenofibrate did not significantly reduce the risk of primary outcome, it did reduce total CV events, mainly because of fewer nonfatal MIs. However in the sub-analysis of those patients who had high TG or high TG + low HDL-C, significant reduction in CV events was observed.[24]

Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: There is no evidence from this trial to indicate that fenofibrate should be routinely added to a statin for the treatment of lipids in patients with T2DM. It suggested that routine addition of fenofibrate might even be harmful for women with T2DM. However, the ACCORD data, together with post hoc analyses of three other fibrate trials, suggests that, when TG is >200 mg/dL and HDL-C is <35 mg/dL after statin therapy has significantly reduced LDL-C levels, fibrate treatment can be considered, at least in men.[25]

But, the fibrate users also encounter adverse effects (AEs). The most common AEs are gastrointestinal (GI) complaints (e.g., nausea, abdominal pain), which affect approximately 5% of patients. Fibrates can also cause myopathy, occurring at a rate similar to that of statin therapy. The risk for myopathy appears to be elevated in patients with renal dysfunction, and fibrates generally should be avoided in populations with severe renal impairment. This may be especially true with fenofibrate, as this agent has been reported to increase serum creatinine concentrations to a greater extent than does gemfibrozil.

In one of the studies, an increase in the range of mean serum creatinine level (8-18%) with fenofibrate was reported among patients with normal or impaired renal function. It is suggested that this AE is caused due to inhibition of vasodilatory prostaglandins by fibrate. Other notable AEs include cholelithiasis secondary to an increase in biliary cholesterol concentration, elevated transaminase concentrations, and an increase in the need for gallbladder surgery and/or appendectomy. Fibrate users have also reported rash, nausea and/or vomiting, eczema, headache, fatigue, vertigo, taste perversion, and hair loss.[26]

7. Beyond LDL-C: The non-HDL-C guidelines

In the study conducted by *Alagona P. Jr.*, titled "Beyond LDL cholesterol: the role of elevated triglycerides and low HDL cholesterol in residual CVD risk remaining after statin therapy", the author cites –

"Managed care initiatives to reduce CVD risk have, to date, focused almost exclusively on statins, which are primarily LDL-C lowering agents and have limited effects on TGs and HDL-C at commonly used doses. Significant residual CVD risk (i.e. risk of recurrent CVD events) remains after treatment with statins and may stem, at least partially, from low HDL-C and/or elevated TG. Treatment guidelines suggest that therapy may be necessary to address multiple lipid targets".[27]

Another study echoes similar sentiments, "Most clinicians recognize the importance of reducing LDL-C and, therefore, address this therapeutic need to decrease CVD risk. In addition to the critical role that LDL-C plays, recent studies have shown the contribution of other lipid fractions, such as HDL-C and TG, to overall CV health".

Several large trials and meta-analyses have investigated the effects of lipid-lowering statin therapy and have consistently demonstrated that statin therapy significantly reduces LDL-C levels and incidence of CV events. In spite of the efficacy of statin therapy in these studies, statins did not eliminate CV risk. Rather, significant residual CV risk remains after treatment with statins, especially in high-risk patients such as those with diabetes. Residual CV risk stems, at least partially, from low HDL-C and elevated TG. With elevated TG levels, a combination of LDL-C with VLDL-C in the measure of non-HDL-C may be a better predictor of CV risk than LDL-C alone." Here also it has been said, 'treatment guidelines suggest that therapy may be necessary to address multiple lipid targets i.e., LDL-C, non-HDL-C, HDL-C, and TG'.[28]

In an interesting article in Circulation published in 2008, the authors' question - Is lowering low-density lipoprotein an effective strategy to reduce cardiac risk? And suggest that in lipid management to reduce CV risk, a new strategy is required; LDL-C reduction alone is not adequate to control the epidemic of CHD events when LDL-C values are below "hypercholesterolemic" levels.

The results of 5 large statin trials show that it is a dangerous misconception and that it leaves large numbers of patients still at risk for CV events. The article concludes that although a focus on LDL-C reduction has benefited some patients by reducing CHD risk, large numbers of patients remain at elevated risk despite substantial reductions in LDL-C. The well-intentioned focus on LDL-C reduction alone ignores the other multiple lipoprotein disorders contributing to CHD risk.[29]

Level of risks and desired goals:

Table 7.1 : ADA/ACC treatment goals in patients with lipoprotein abnormalities and cardiometabolic risk			
	LDL-C (mg/dL)	**Non-HDL-C (mg/dL)**	**ApoB (mg/dL)**
Very High Risk Established CVD DM and ≥ 1 major CVD risk factors*	<70	<100	<80
High Risk No CVD and ≥ 2 major CVD risk factors* DM and no major CVD risk factors*	<100	<130	<90

**Risk factors: Dyslipidemia, Smoking, HTN, Family history of premature CAD*

**ADA - American Diabetes Association; ACC - American College of Cardiology*

ApoB- Apolipoprotein B

8. Triglycerides and CVD risk: Pathophysiology

Nearly 35% of T2DM adults have fasting TG levels ≥200 mg/dL associated with decreased HDL-C and increased sd-LDL-C particles.

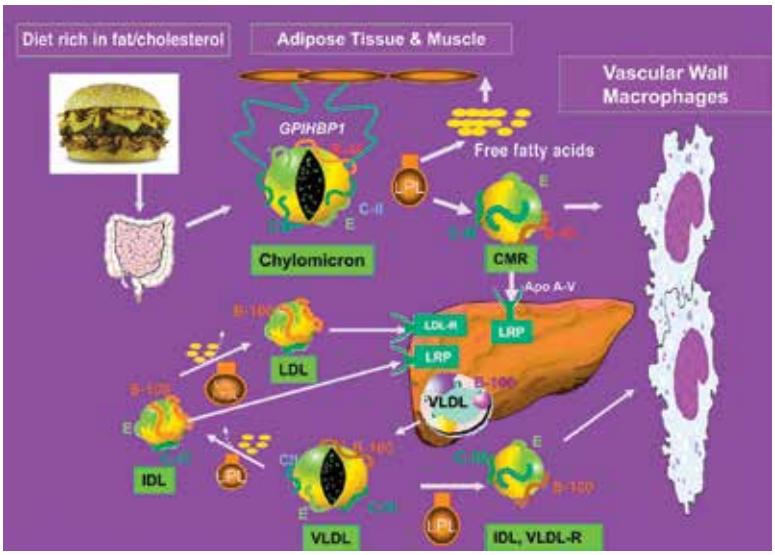
Association between elevated TG levels and CVD has been cited since long.[30]

Serum TGs have been shown to be an important and independent predictor of CHD and stroke risk in the Asia-Pacific region. The Asia Pacific Cohort Studies Collaboration (APCSC) is a meta-analysis of prospective cohort studies conducted in a number of Asian countries, Australia and New Zealand. This is one of the largest prospective analyses, which associates TG with CV events. The results show that serum TG level is an independent determinant of CV risk in Asians. The evidence is particularly strong for CHD. The analysis provides strong evidence that increased serum TG levels are associated with the risk of developing CVD independently of other major risk factors, including low HDL-C.[31]

It is justified to target TG as a vascular risk factor because of the role of TG-rich lipoproteins in atherogenesis. Evidence supports a potential role for TG as vascular risk factors, owing in part to the accompanying burden of atherogenic remnant particles, sd-LDL-C, reduced HDL-C and a high frequency of accompanying insulin resistance. TG-associated CVD risk occurs even in subjects with low LDL-C, and lowering both lipids provides greater benefit than reducing LDL-C alone.[32]

Causes of hypertriglyceridemia in diabetes include increased hepatic VLDL-C production and defective removal of chylomicrons (CM) and chylomicron remnants (CMRs), which often reflects poor glycemic control.[30]

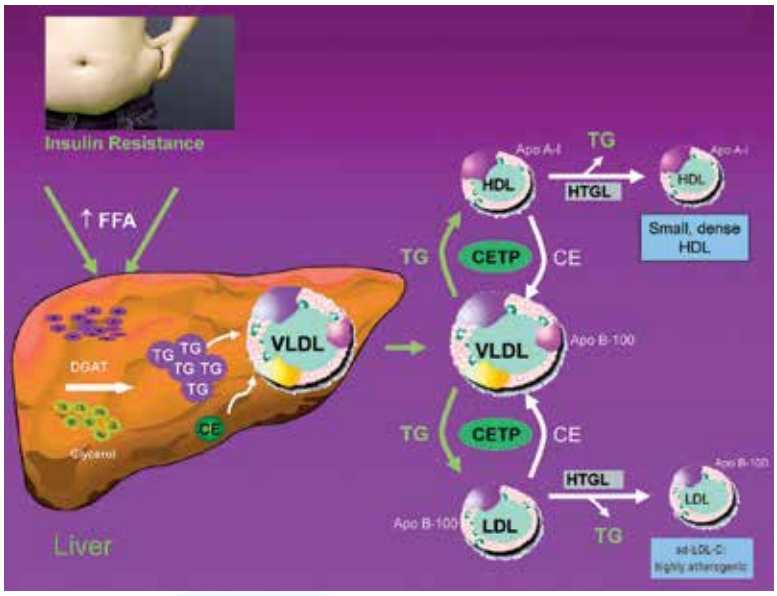
Figure 8.1 - Overview of triglyceride metabolism



ApoA-V - Apolipoprotein A-V; CMR - Chylomicron Remnant; FFAs - Free Fatty Acids; HTGL - Hepatic Triglyceride Lipase; IDL - Intermediate-Density Lipoprotein; LDL - Low-Density Lipoprotein; LDL-R - Low-Density Lipoprotein Receptor; LPL - Lipoprotein Lipase; LRP - LDL Receptor–Related Protein; VLDL - Very Low-Density Lipoprotein; VLDL-R - Very Low-Density Lipoprotein Receptor; GPIHBP1 - Glycosylphosphatidylinositol-Anchored HDL Binding Protein 1

**Adapted from Miller M et al. Triglyerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation, 2011. May 24:123(20):2292-333*

Figure 8.2 - Metabolic Consequences Of Hypertriglyceridemia



ApoA-I - Apolipoprotein A-I; ApoB-100 - Apolipoprotein B-100; CE - Cholesteryl Ester; CETP - Cholesteryl Ester Transfer Protein; DGAT - Diacylglycerolacyltransferase; FFA - Free Fatty Acid; HDL - High-Density Lipoprotein; HTGL - Hepatic Triglyceride Lipase; LDL - Low-Density Lipoprotein; TG - Triglyceride; VLDL - Very Low-Density Lipoprotein.

**Adapted from Miller M et al. Triglyerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation, 2011. May 24:123(20):2292-333*

Basis of Diabetic dyslipidemia: Diabetics often have increased VLDL-C concentration. Diminished insulin action influences Apolipoprotein B (ApoB) synthesis, while increased activity of hormone-sensitive lipase (HSL) leads to enhanced influx of free fatty acids (FFAs) through the portal vein system.

In diabetes, greater amounts of FFAs returning to the liver are reassembled into TG and secreted in VLDL-C. Another mechanism implicated in increased VLDL-C production in T2DM is increased liver production of ApoB, the major protein component of VLDL-C and LDL-C. The results of different studies suggest that fatty acids (FAs) modulate liver ApoB secretion. Thus, lipid concentration in the liver regulates ApoB production. Decreased insulin secretion in diabetes characterized by increased lipolysis in adipocytes, increased FA release from fat cells and increased return to the liver lend credence to this mechanism.[8]

9. Diabetic Dyslipidemia, unmet needs and emerging role for dual PPAR-α/γ agonists

9.1 NCEP ATP III Guidelines

The Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in ATP III, suggests the lipid-modifying therapies as shown below:

Lipid-Modifying Therapies

- Lifestyle Changes
  - Exercise
    - Increased physical activity (150 min of moderate exercise / week)
  - Diet
    - Reduced consumption of refined sugar
    - Saturated fats to account for less than 7% of calories
    - Cholesterol intake to be less than 200 mg/day
- Statins
- Fibrates
- Niacin
- Omega-3 Polyunsturated Fatty Acids
- Cholesterol Absorption Inhibitor - Ezetimibe
- Bile Acid Sequestrants

But there are gaps in the treatment with each of the agents mentioned above except, of course, the life-style changes. We analyse the gaps one by one.

(A) If TG<200 mg/dL, then LDL Goal is the primary goal, to be achieved by:

Lifestyle therapy, statins, bile acid sequestrants (BAS), ezetimibe.

Lifestyle modifications consist of a low-fat/cholesterol diet and physical activity. Statins are considered the first line treatment of dyslipidemia in diabetic patients. Lowering of LDL-C levels is the main benefit of statin therapy; although, effects on HDL-C and other lipoproteins also play a role. But statins, like all other pharmacological treatments, have AEs. The skeletal muscles, liver function, and kidney function have all been documented to be affected by statins.[33]

In a recent article, "Statins Linked With Risk of Musculoskeletal Injury", the authors mention that treatment with a statin was associated with a 19% increased risk of any type of musculoskeletal injury (p<0.001), a 13% increased risk of dislocations, strains, and sprains (p=0.001), and a 9% increased risk of musculoskeletal pain (p=0.02). There was a trend toward a 7% higher risk of osteoarthritis/arthropathies.[34]

Recent data also suggests that statin therapy for long term, especially at high dose can worsen the glycemic control and can lead to new onset T2DM. On the basis of these

findings, the US FDA has recently added information to statin labels regarding the impact of these agents on T2DM. This finding is more important for T2DM where insulin resistance is already established.[23]

Since long, BAS have been used in the treatment of hypercholesterolemia. Bile acids are emerging as integrated regulators of metabolism via induction of various signal transduction pathways. Consequently, BAS treatment may exert unexpected AEs too.[35]

In ezetimibe, we have a potent inhibitor of intestinal cholesterol absorption, which has been shown to be safe, tolerable and effective in lowering LDL-C, non-HDL-C and ApoB, each of which has been correlated with improved clinical outcomes, alone or in combination with a statin. However, because of randomized trials that have demonstrated mixed results about atherosclerotic plaque regression via carotid intima-media thickness and a concern about cancer risk, ezetimibe's role in lipid therapy has become questionable.[36]

(B) If TG≥200 - after LDL-C goal, non-HDL-C goal is a secondary goal: Non-HDL-C has recently been shown to be considered more important as a CV risk factor than LDL-C as conceptually they contain all the pro-atherogenic lipoproteins.

Statins alone will be sufficient to attain the non-HDL-C goal in some persons, but not in the majority. A combination of statins and nicotinic acid (or fibrates) can be helpful in others. Niacin too has been used to treat dyslipidemia in patients with T2DM for over 50 years. Although niacin is the most effective agent for raising HDL-C levels, high doses can worsen diabetes control. Additional AEs associated with niacin include flushing, itching, nausea, GI upset, hypotension, and tachycardia. It has been suggested that combination lipid-lowering therapy (e.g., a statin with a fibrate or niacin) may be necessary for patients with DD to achieve optimal lipid levels; however, to date, such strategies have not been adequately evaluated for their long-term effect on CVD risk reduction or safety compared with lipid-lowering monotherapy. Moreover, the risk of myopathy is thought to be greater when niacin is used with a statin.

Fibrates, which are PPAR-α agonists, are useful for lowering TG and non-HDL-C levels and increasing HDL-C, yet results from trials in patients with T2DM have been controversial. In the FIELD study in 9795 patients with T2DM, fenofibrate did not significantly affect the primary endpoint, coronary event rate, relative to placebo (11% reduction). Common AEs associated with fibrates include GI disturbance, rash, headache, pancreatitis, myalgia, and myotoxicity (in rare instances - and possibly more likely with gemfibrozil than with fenofibrate). Adjuvant fibrate therapy is not recommended in patients with severe renal dysfunction, severe hepatic dysfunction, and pre-existing gall bladder disease. Secondary analysis, however, showed better risk reduction in patients having high TG with or without low HDL-C. Similarly, even in the ACCORD study, fenofibrate showed better outcomes in patients with high TG and low HDL-C.[37]

(C) If TG≥500 – then TG lowering is the primary goal: to prevent acute pancreatitis (first priority) and to prevent CVD (second priority).

Statins are not the first-line agents for very high TG as statins are not powerful TG-lowering drugs. BAS are contraindicated as they tend to raise TG.

Omega-3 fatty acids have to be taken in large quantities & its fishy odour is repulsive for some. They reduce serum TG, increase HDL-C and LDL-C.

Therefore, **conceptually, combined PPAR-α/γ action can target simultaneously insulin resistance and atherogenic dyslipidemia.**[38] The PPAR-α/γ agonists are therapeutic targets for hypertriglyceridemia and insulin resistance, respectively, and seem ideal for ADD.

9.2 Emerging Therapy Approaches

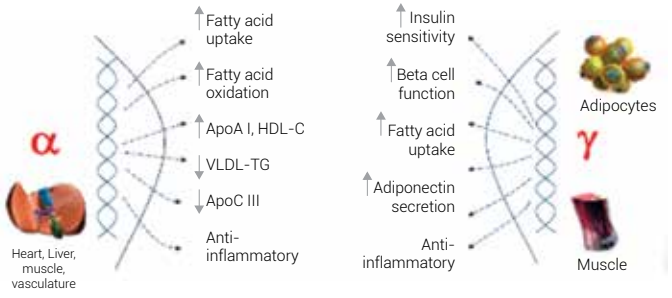
PPAR-α activated by polyunsaturated fatty acids and fibrates, is implicated in the regulation of lipid metabolism, lipoprotein synthesis and metabolism, as well as inflammatory response in liver and other tissues. PPAR-α plays a crucial role in regulating the β-oxidation of FAs, a major source of cellular energy. Consistent with this, PPAR-α is highly expressed in tissues with high FA oxidation (like liver, kidney, heart and skeletal muscle), in which it controls a comprehensive set of genes that regulate most aspects of lipid catabolism. PPAR-α activation increases HDL-C synthesis, stimulates "reverse" cholesterol transport and reduces TG.

Peroxisome proliferator-activated receptor-γ (PPAR-γ) regulates adipogenesis, lipid metabolism, glucose control, and inflammation/vascular pathways. Clinically, selective PPAR-γ agonists like thiazolidinediones (TZDs; glitazones) are used to treat T2DM. They improve insulin sensitivity by up-regulating adipogenesis, decreasing FFA levels, and reversing insulin resistance. However, selective PPAR-γ agonists also cause water retention, weight gain, peripheral edema, and congestive heart failure. Such AEs may contribute to controversial CV outcomes despite apparent improvements in other risk factors.

The concept of dual agonists, which can activate both PPAR-α and PPAR-γ simultaneously emerged as a fascinating target by a logical hypothesis that these dual agonists may not only control both glucose and lipid levels but also mitigate the weight gain induced by PPAR-γ activation based on the observation that fibrates in addition to their hypolipidemic effects, reduce body weight gain without affecting food intake. Several PPAR-α/γ dual agonists, commonly termed as glitazars were developed by many pharmaceutical companies. But none of the dual agonists had been marketed till now because of failures.

The PPAR-α and PPAR-γ are nuclear receptors that function as transcription factors:

Figure 9.1 : Effects of PPAR-α/γ activation
Nuclear receptors that function as transcription factors



Though the withdrawals appeared to be discouraging to the scientists engaged in the development of PPAR-α/γ agonists, the fact that the reasons for the failure of all these

compounds were quite different from each other, left a ray of hope of developing new agents with modifications in these compounds, in order to develop efficacious and relatively safer PPAR agonists as the medical need for metabolic disorders is still largely unmet.[39]

Zydus Cadila has been successful in developing its new chemical entity (NCE) Lipaglyn™ (Saroglitazar), a dual PPAR-α/γ agonist, for treating ADD. It may fill the gaps in the current treatment modalities.

Lipaglyn™ is the first glitazar to be approved in the world and the first NCE discovered and developed indigenously by an Indian pharmaceutical company. Lipaglyn™ is the world's first drug for treating ADD and combines lipid- and glucose-lowering effects in one single molecule ensuring a comprehensive management of ADD. Saroglitazar is predominantly a PPAR-α agonist with moderate PPAR-γ agonism which is just optimal.

The details of all the studies of Lipaglyn™ appear in the following sections.

10. Development of Glitazars

10.1 What are PPARs?

Peroxisome Proliferator-Activated Receptors - PPARs are nuclear lipid-activated transcription factors that regulate the expression of genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes. Their wide range of potential therapeutic actions make them attractive targets for the development of oral agents targeting risk factors associated with the metabolic syndrome, T2DM and CVDs.[40] These receptors were identified in the 1990s in rodents and named after their property of peroxisome proliferation. Three distinct receptor subtypes, PPAR-α, PPAR-γ and PPAR-β/δ have been identified and cloned in most of the rodent and mammalian species. These three subtypes share a high level of sequence and structural homology and yet have distinct physiological functions and each PPAR subtype exhibits unique tissue expression pattern and physiological functions. PPAR-α is found in the liver, kidney, heart, and muscle and is implicated in the uptake and oxidation of FAs and lipoprotein metabolism. PPAR-β/δ is expressed in most cell types and plays an important role in lipid metabolism and cell differentiation and growth. PPAR-γ is mainly expressed in adipose tissue with lower expression detected in a wide range of differing tissues like spleen, intestine, pancreas, colon, kidney, skeletal muscle and macrophages.[41] PPAR-γ agonists have beneficial effects on glucose homeostasis by increasing insulin sensitivity and glucose disposal and prevent the loss of beta cell mass in the pancreas.[40] Fibrates are PPAR-α agonists used for TG lowering in clinics and PPAR-γ agonists, rosiglitazone and pioglitazone are proven to be efficacious as insulin sensitizing agents for the treatment of T2DM.

10.2 Mechanism of action of PPAR agonists

When activated by the ligand, PPARs form heterodimers with another nuclear receptor named retinoid X-receptor - RXR. Subsequent conformational changes in the receptor lead to dissociation of co-repressors and recruitment of co-activators. This process ultimately results in up- or down-regulation of various genes involved in metabolic pathways. PPAR-α activation causes up-regulation of genes involved in lipid metabolism including fatty acid transporter protein (FATP), AcylCoA synthase, carnitine palmitoyl transferase- CPT I and II, lipoprotein lipase (LPL) and down-regulation of ApoC III.[42] On the other hand, PPAR-γ activation leads to up-regulation of numerous genes involved in glucose & lipid metabolism including, aP2, PEPCK, acyl-CoA synthase, LPL, FATP-1 and CD36, adiponectin etc.[43, 44]

Each PPAR agonist activates or represses an unique set of co-activators and co-repressors in a tissue specific manner.[45] This property of differential regulation of genes by different PPAR agonists is responsible for unique pharmacodynamics & safety profile of each PPAR agonist. It also explains why some PPAR agonists are unsafe whereas others are efficacious & safe.

10.3 Rationale for developing Dual PPAR-α/γ agonist

Since PPAR-α agonists are effective in managing lipids and PPAR-γ agonists are insulin sensitizers that control hyperglycemia in T2DM[40], by using dual PPAR-α/γ agonists one

can control both the lipid and glucose levels simultaneously. Moreover, a recent study has demonstrated that combination therapy with PPAR-α and PPAR-γ agonists, rosiglitazone and fenofibrate, results in normalization of TG and TC levels without increasing body mass index and improves the atherogenic dyslipidemic profile in T2DM patients.[46] The importance of controlling both glucose and lipid levels in metabolic syndrome gave rise to the concept of identifying dual agonists, which can activate both PPAR-α and PPAR-γ receptors. The hypothesis that PPAR-α/γ dual agonism would provide synergistic pharmacological effects has encouraged many research groups to develop these agents.

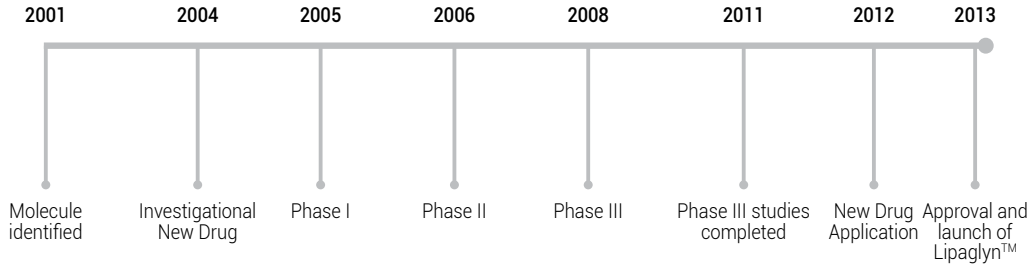
10.4 History of development of Dual PPAR-α/γ agonists

To date, a large number of structurally diverse PPAR-α/γ dual agonists have been disclosed in the literature and in patent applications. Many of these compounds have been evaluated in clinical trials and some of them have progressed into late-stage development. The first PPAR-α/γ dual agonist to be reported was KRP-297 (MK-0767).[47] However, further development was discontinued due to toxicity. Muraglitazar (BMS-298585) was the first PPAR-α/γ dual agonist reviewed by the US FDA advisory committee. This non-thiazolidinedione (non-TZD) oxybenzylglycine analogue was reported to exhibit potent *in vitro* activities against both PPAR-α and PPAR-γ subtypes and exert excellent glucose- and lipid-lowering effects in rodent models but its development was discontinued due to increased CV risk.[48] In between many structurally diversified compounds were discovered as PPAR-α/γ dual agonists. They were effective in animal models, however, further development was discontinued due to various toxicological reasons or a risk benefit assessment. These included farglitazar, MK-0676, tesaglitazar (AZ-242) ragaglitazar (DRF-2725) and imiglitazar (TAK-559)-each compound had shown different kinds of side effect profile. Thus the reason for discontinuation of their development could have been compound specific. An important observation is that most of these failed compounds had higher selectivity towards PPAR-γ receptor.[40]

11. Introduction to Lipaglyn™ (Saroglitazar)

Lipaglyn™ (Saroglitazar) is the first glitazar class compound that has been approved as a therapeutic agent. Structurally, saroglitazar is a non-TZD and non-fibrate molecule and belongs to aryl alkoxy propionic acid class. Saroglitazar was designed as a dual PPAR-α/γ agonist having strong PPAR-α effect with moderate PPAR-γ effect.

Figure 11.1 : Development of Lipaglyn™ (Saroglitazar)



11.1 Lipaglyn™ – Physical and chemical properties

Lipaglyn™ contains saroglitazar, a dual regulator that corrects both, the lipid profile and the glycemic parameters by its predominant PPAR-α and moderate PPAR-γ agonist activity. It is available as an oral tablet containing 4 mg of saroglitazar.

Zydus Cadila Compound Code : ZYH1

INN name : Saroglitazar

Chemical name (IUPAC) : (S)-a-ethoxy-4-[2-[2-methyl-5-[4-(methylthio) phenyl]-1H-pyrrol-1-yl]ethoxy] benzenepropanoic acid magnesium salt (2:1)

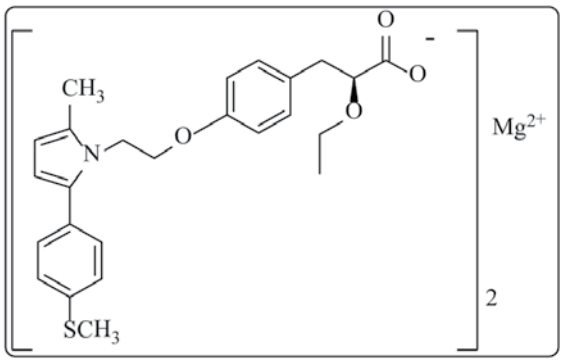
Molecular formula : $[C_{25}H_{28}NO_4S]_2Mg$

Molecular weight : 900 atomic mass unit (amu)

Physical form : Off-white, amorphous powder

Structural formula:

Figure 11.2 Structural formula of saroglitazar



11.2 Lipaglyn™ - Formulation

Each uncoated tablet contains:

Saroglitazar .....4 mg

Excipients ..... q.s.

Inactive ingredients in the tablet are microcrystalline cellulose, lactose, magnesium oxide, povidone, talc, magnesium stearate, croscarmellose sodium and colloidal silicon dioxide.

Storage and handling instructions: Lipaglyn™ tablets should be stored below 25°C and in dry place. Protect from light. Keep out of reach of children.

In an *in vitro* transactivation assay, saroglitazar showed significant activation of both PPAR-α and PPAR-γ. Saroglitazar shows much higher potency for PPAR-α (EC_{50} in picomole range) as compared to fenofibrate (EC_{50} in micromole range). Saroglitazar also showed PPAR-γ activation but at relatively higher concentrations (EC_{50} in nanomole range) as compared to PPAR-α. The PPAR-γ activation by saroglitazar was similar to those seen with TZDs. These studies showed that saroglitazar is a predominantly PPAR-α agonist that has moderate PPAR-γ activity.

Figure 11.3 : Spectrum of PPAR activity of various agents : Each PPAR agonist is unique

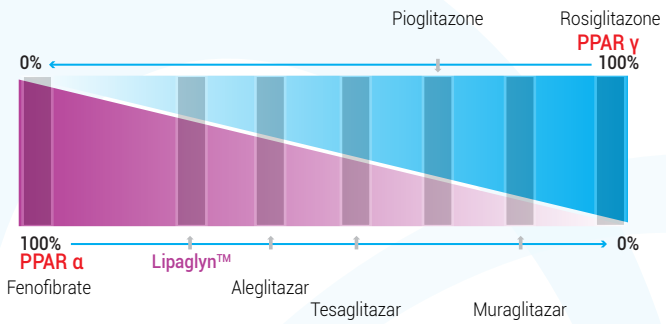


Table 11.1 : *In vitro* PPAR-α Agonistic activity in HepG2 Cells	
Test compound	PPAR activation EC_{50}
	hPPAR-α
Fenofibrate	10800 nM
Lipaglyn™	**0.00065 nM**

Table 11.2 : *In vitro* PPAR-α Agonistic activity in HepG2 Cells		
Test Compound	PPAR activation EC_{50}	
	hPPAR-α	hPPAR-γ
Lipaglyn™	**0.00065 nM**	3 nM

12. Lipaglyn™ – Pre-clinical studies

The pharmacodynamic activity of saroglitazar was extensively evaluated in various preclinical models of dyslipidemia & T2DM. The pre-clinical data confirmed that saroglitazar has dual lipid lowering and anti-hyperglycemic effects. The lipid lowering effects were evaluated in diabetic db/db mice, obese & insulin resistant Zucker fa/fa rats and ob/ob mice; Swiss albino mice, high-fat-high cholesterol fed Golden Syrian hamsters, Sprague Dawley rats fed on high cholesterol (HC) diet and non-human primates (Marmosets).

Table 12.1 : Percentage reduction in Serum Triglycerides

Animal Species	1 mg/kg	3 mg/kg	10 mg/kg
Zucker fa/fa Rats	45	42	86
Swiss albino Mice	60	67	76
Hamster (HF-HC diet)	40	80	90
SD Rats (HC diet)	35	40	53
db/db Mice	38	55	n.d.

n.d. - not determined

Saroglitazar showed up to 90% serum TG reduction in preclinical models. It also improved lipid clearance by up to 68%. It reduced total serum cholesterol in cholesterol-fed rats by up to 77% and LDL-C by 67%. In diabetic models saroglitazar was found to reduce serum glucose by up to 65% and improve oral glucose tolerance by 59%. It also reduced fasting insulin and FFA levels in db/db mice and Zucker fa/fa rats. Furthermore, in hyperinsulinemic-euglycemic clamp study saroglitazar showed significant improvement in glucose infusion rate indicating insulin sensitizing effect.

Figure 12.1 : Effect on triglycerides after 12 days of repeated dose treatment in db/db mice (n=6)

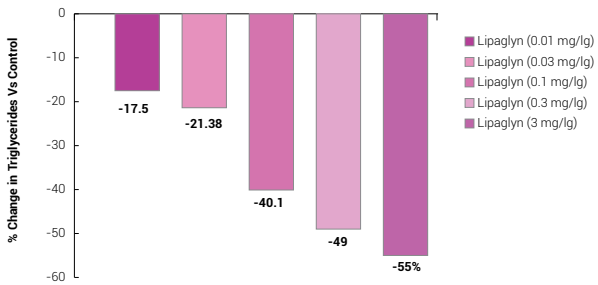


Figure 12.2 : Effect on triglycerides after 14 days of repeated dose treatment in Zucker fa/fa rats (n=8)

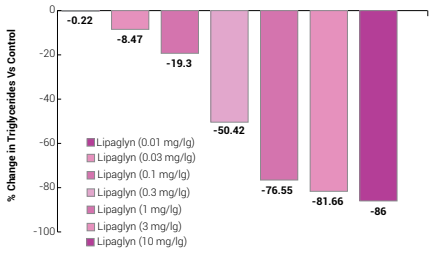


Figure 12.3 : Effect on triglycerides after 6 days of repeated dose treatment in Swiss albino mice (n=6)

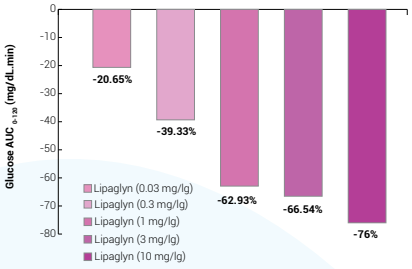


Figure 12.4 : Effect on lipolytic activity (Reduction in triglycerides $AUC_{0\text{-}60\ min}$) in intravenous lipid tolerance test after 6 days of repeated treatment with Lipaglyn in Swiss albino mice

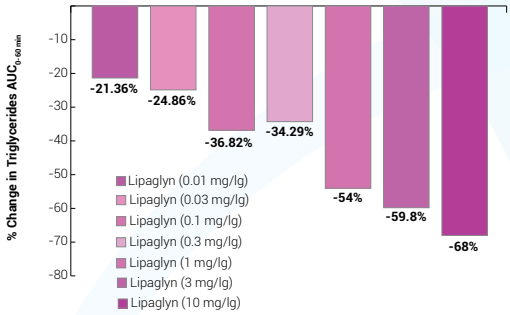


Figure 12.5 : Effect on triglycerides after 14 days of repeated treatment in high fat, high cholesterol (HF-HC) diet-fed Hamsters

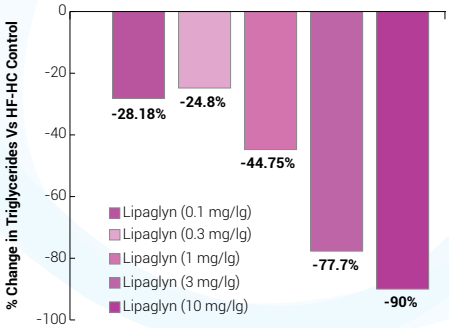


Figure 12.6 : Effect of Lipaglyn (1.5 mg/kg) on serum triglycerides after 90 days of repeated dose treatment in Female Non-Human Primates (Marmosets)

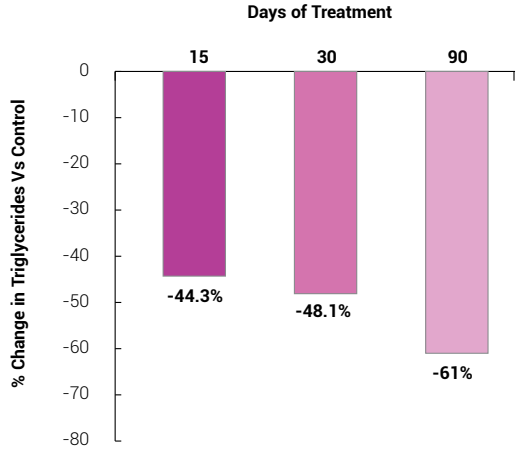
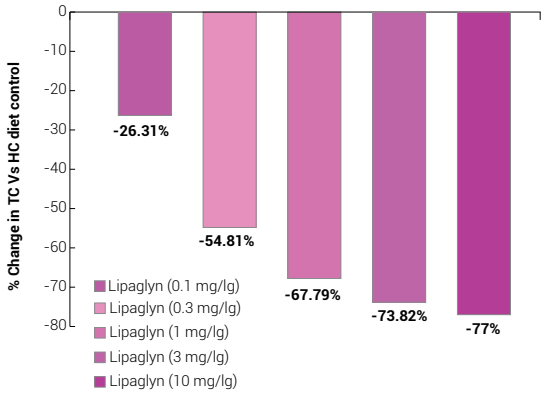


Figure 12.7 : Effect on total cholesterol after 4 days of repeated treatment in high cholesterol diet-fed Sprague-Dawley rats



12.1 Preclinical safety and toxicity evaluation

Extensive safety pharmacology studies were conducted, which demonstrated that saroglitazar does not affect central nervous system (CNS), cardiovascular system (CVS), respiratory system (RS) and gastrointestinal (GI) functions at doses several fold higher than therapeutic doses.

Additionally, comparative mechanistic studies in rats and non-human primates employing molecular biomarkers indicated no carcinogenic risk to humans.

12.2 Safety pharmacology

Essential safety pharmacology studies were conducted to investigate the potential undesirable effects of saroglitazar on physiological functions at doses including and exceeding the primary pharmacodynamic or therapeutic range. These studies were designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety. Safety pharmacology studies were carried out to study the effects of saroglitazar on vital organ systems such as CVS, RS and CNS.

Dose selection in safety pharmacology studies was based on pharmacodynamic efficacy study in Swiss albino mice. A dose of 0.14 mg/kg, per oral (PO) was found to be effective in reducing the serum TG levels in Swiss albino mice by about 50% as compared to control animals (ID_{50} = 0.14 mg/kg). Hence, the doses selected for safety studies were within therapeutic range or higher.

12.3 Effects on the Cardiovascular system

Effects of saroglitazar on blood pressure (BP), heart rate (HR) and electrocardiogram (ECG) were studied in conscious, freely moving beagle dogs at 0.1, 1 and 10 mg/kg, PO. Treatment with saroglitazar in telemetered beagle dogs revealed no effect on systolic, diastolic and mean BP and HR. P-wave amplitude, P-wave duration, PQ interval, QRS interval, QTcV and QT interval of the ECG were also unaffected in the same study.

In an *in vitro* system using HEK293 cells expressing HERG-1 type K^+ channels, the ability of saroglitazar to affect the delayed rectifier current was investigated using whole cell clamp technique. Saroglitazar caused a dose-dependent decrease in tail current amplitude and acceleration of tail current decay constant which both reached statistical significance only at 100 mM concentration. The concentration of 1 mM had no effect on these parameters. The 100 mM concentration may be too high to be achieved during therapeutic use of saroglitazar.

12.4 Effects on the respiratory system

Effects on the RS were studied in telemetered Beagle dogs. No changes were observed in respiratory rate, tidal volume and minute volume at 0.1, 1, and 10 mg/kg, PO dose of saroglitazar.

12.5 Supplemental and follow-up safety pharmacology studies

In addition to the essential pharmacology studies few additional studies were conducted.

Cardiovascular system

Effect of saroglitazar on bleeding time was investigated in Swiss albino mice. No significant effect was seen on bleeding time after treatment with saroglitazar (14 mg/kg, PO). Saroglitazar had no significant effect on *in vitro* adenosine diphosphate-ADP induced platelet aggregation up to 1000 µM concentration in platelet rich plasma derived from Sprague Dawley rat.

Central nervous system

Saroglitazar (14, 42 and 140 mg/kg, p o) did not show antidepressant effect in tail suspension test in Swiss albino mice. Saroglitazar showed no antinociceptive effect in hot plate method at all the doses (14, 42 and 140 mg/kg, PO) when administered once daily for 14 days in Swiss albino mice. In the same study no dependence liability was observed.

Gastrointestinal system

Treatment with saroglitazar (14 mg/kg, PO) was not found to cause a significant change in the GI transit as evaluated by charcoal meal test or gastric mucosal integrity in Swiss albino mice.

Non-clinical toxicology

Acute and chronic toxicity studies

Various acute and chronic toxicity studies were performed in mice, rats and dogs up to a duration of 12 months. In acute dose studies, the maximum tolerated dose (MTD) in Swiss albino mice was 500 mg/kg, and in Wistar rat it was 1200 mg/kg. Safety pharmacology studies did not reveal any adverse changes in CNS, CVS, respiratory and GI parameters. In repeat dose toxicity studies, saroglitazar was shown to have an acceptable safety profile at doses several-fold higher than the approved human doses. At high doses, the toxic effects observed were mainly the exaggerated pharmacological effects mediated by PPAR mechanisms.

Impairment of fertility

Saroglitazar did not show any AEs on mating or fertility in male rats up to 125 mg/kg (more than 250 times the approved human dose on body surface area basis). In female rats no AEs on fertility were observed up to 3 mg/kg (7 times the approved human dose on body surface area basis). Saroglitazar altered the estrus cyclicity and litter indices at 15 mg/kg which is 35 times the human recommended dose.

During pre- and post-natal developmental study in rats, saroglitazar did not show any AEs on reproductive performance and lactating indices up to 1 mg/kg which is more than the human therapeutic dose.

Carcinogenicity

Two-year carcinogenicity study of saroglitazar was conducted in Wistar rats. No potential carcinogenic concern for humans was identified, which was further confirmed by a mechanistic study in non-human primates employing molecular biomarkers.

Mutagenicity

Saroglitazar was found to be non-mutagenic and non-genotoxic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity test, chromosomal aberration assay using the peripheral human blood lymphocytes and the mouse micronucleus assay.

13. Clinical evidences of lipaglyn™ (Saroglitazar)

13.1 Phase I Studies

This was a prospective, randomized, double blind, placebo controlled, single-center study to evaluate the pharmacokinetics (PK), safety and tolerability of saroglitazar in 136 healthy volunteers. This study had 4 parts:

1. Single ascending dose of saroglitazar from 0.125 mg to 128 mg in healthy fasting male volunteers
2. Single dose of saroglitazar 1 mg in healthy male volunteers before and after food administration
3. Single dose of saroglitazar 1 mg in female healthy volunteers before and after food administration
4. Multiple ascending dose of saroglitazar, either once (1, 4, and 8 mg) or twice a day (8 mg and 16 mg), upto 10 days in fasting healthy male volunteers

Saroglitazar was rapidly and well absorbed across all doses in single dose pharmacokinetic study with a median T_{max} of less than 1 hour (range: 0.63 to 1 h) under fasting conditions across the doses studied. The maximum plasma concentration ranged from 3.98 to 7461 ng/mL across the dose range. The area under the plasma concentration-time curve increased in a dose-related manner. The average terminal half-life of saroglitazar was 5.6 h. Saroglitazar was not eliminated by the renal route. There was no effect of sex difference on PK of saroglitazar except for the terminal half-life which was significantly shorter in females.

Single and multiple doses PK of saroglitazar have demonstrated dose dependent linearity. Single dose and multiple dose PK of saroglitazar at 4 mg and 8 mg doses are given in table 13.2. Saroglitazar has not resulted in dose accumulation at any of the doses.

Saroglitazar was safe and well tolerated upto 128 mg single dose and upto 8 mg once a day upto 10 days. Adverse events were generally mild and moderate in nature. Saroglitazar did not show any clinically relevant finding in clinical laboratory investigations, physical examination, vital signs and electrocardiogram (ECG). No serious adverse events (SAEs) were reported.

Multiple dose escalation was discontinued at 16 mg BID dose due to frequent, but not SAEs.

Table 13.1 : Single dose pharmacokinetics of Saroglitazar 4 mg (N = 6)

Parameter	Lipaglyn™ 4 mg
C_{max} (ng/mL)	337.07 ± 90.99
T_{max} (hr)	0.71 ± 0.25
AUC_{last} (hr*ng/mL)	806.40 ± 160.43
AUC_{inf} (hr*ng/mL)	855.96 ± 172.53
$t_{1/2}$ (hr)	2.93 ± 0.87

Table 13.2 : Pharmacokinetics of 4 mg & 8 mg Saroglitazar in Healthy Volunteers in multiple dose study					
Pharmacokinetic parameters	**Saroglitazar 4 mg OD for 10 days (N = 6)**		**Saroglitazar 8mg OD for 10 days (N = 6)**		**Saroglitazar 8 mg BID for 10 days (N = 6)**
	After 1st dose	After 10th Dose	After 1st Dose	After 10th dose	After 20th dose
C_{max} (ng/ml)	332.23±87.21	335.68±147.31	807.11±121.62	589.93±130.63	711.78±338.45
$t_{1/2}$ (Hours)	3.75±1.50	3.76±1.98	3.78±2.98	7.70±8.29	7.24±3.89
$AUC_{0-\infty}$	955.54±250.08	965.37±266.52	1881.56±710.44	2758.51±512.07	3753.36±1820.23

13.2 Phase II Studies

Prospective Randomized Efficacy and Safety study of Saroglitazar (PRESS) was conducted during four phase II programs for proof of concept and dose finding. Saroglitazar doses studied were 0.5, 1, 2, and 4 mg once daily for 12 weeks. In these studies, 222 subjects participated. Summary of the studies are given in table 13.3.

Table 13.3 : Phase II Studies of Saroglitazar				
Study Design	A 12 week randomized, double blind, parallel group, prospective dose ranging study with open comparator arm			
Protocol	2001 Ver.01	2002 Ver.01	2003 Ver.02	2004* Ver.02
Study identity	**PRESS-I**	**PRESS II**	**PRESS-III**	**PRESS IV**
Subjects	Dyslipidemic and non-diabetics	Dyslipidemic and diabetics	Dyslipidemic and diabetics	Dyslipidemic with impaired glucose tolerance
Comparator	Fenofibrate 160 mg	Rosiglitazone 8/16 mg	Pioglitazone 45 mg	Pioglitazone 45 mg
Number of subjects	63	66	66	27
Primary Objectives	Reduction in following parameters: • Triglyceride			
Secondary Objectives	Reduction in following parameters: • Glycosylated hemoglobin • Insulin • Fasting glucose • Low density lipoproteins • Total cholesterol • C - reactive protein Increase in: • High density lipoproteins			
Duration	12 weeks			
*Trial was not completed due to insufficient patient recruitment.				

Summary of efficacy of saroglitazar during Phase II studies

Being first-in-patient study, sample size was not determined as previously available results were not available.

The efficacy results obtained from pooled analysis for saroglitazar against fenofibrate, rosiglitazone and pioglitazone are as follows:

TG level: TG reduction in the saroglitazar arms were dose related and were numerically comparable to fenofibrate and statistically significant compared to rosiglitazone and pioglitazone.

Fasting plasma glucose (FPG) level: Saroglitazar 4 mg has shown decrease in FPG upto 8.15% during studies. There was no statistical difference among saroglitazar 4 mg and rosiglitazone and pioglitazone.

Glycosylated hemoglobin (HbA1c): The percent reduction in HbA1c with saroglitazar seemed to be dose related in 2002 and 2003 studies.

HDL-C level: Saroglitazar showed dose related increase in HDL-C levels and comparable to fenofibrate and better than rosiglitazone and pioglitazone.

LDL-C level: Reduction in LDL-C with saroglitazar 4 mg was better than rosiglitazone and pioglitazone. Saroglitazar was comparable to fenofibrate.

TC level: There was statistically non-significant difference in TC level between saroglitazar (2 mg & 4 mg) and fenofibrate 160 mg. Overall effect on TC was poor in rosiglitazone and pioglitazone arms. These groups did not exhibit TC reducing action.

Summary of safety of saroglitazar during Phase II studies

Overall saroglitazar was well tolerated and safe upto 4 mg in phase II studies. There were no SAEs and/or deaths reported during these studies.

From the laboratory analysis, the following could be concluded for saroglitazar -

- Liver function test (LFT) studies have shown no potential for drug induced liver injury (DILI).
- Renal function test (RFT) has not shown any potential for renal toxicity.
- No report of musculoskeletal abnormalities (myositis or rhabdomyolysis) reported during the study. There was no incidence of creatine phosphokinase (CPK) more than 10X of upper normal limit.

Taking into account inherent subject and experimental variability resulting from small sample sizes per arm, these results together indicated that the effect of saroglitazar was better with 2 mg & 4 mg.

13.3 Phase III Studies

Prospective Randomized Efficacy and Safety study of Saroglitazar (PRESS) was conducted during two phase III programs. In these pivotal studies, saroglitazar 2 mg & 4 mg, once daily for 12 and 24 weeks were evaluated. Total of 424 subjects participated in these studies. Summary of the studies is given in table 13.4.

Table 13.4 : Phase III Studies of Saroglitazar		
Protocol	ZYH1.08.001.01.1.PROT	ZYH1.09.002.01.1.PROT
Study identifier	**PRESS V**	**PRESS VI**
Study design	A multicentric, randomized double blind study to evaluate safety and efficacy of saroglitazar 2 mg and 4mg compared to pioglitazone 45 mg in diabetic dyslipidemia	A multicentric, prospective randomized, double blind study to evaluate safety and efficacy of saroglitazar,2 and 4mg compared to placebo in hypertriglyceridemia with type 2 diabetes mellitus not controlled with atorvastatin therapy
Indication	Diabetic Dyslipidemia	Hypertriglyceridemia with type 2 diabetes mellitus not controlled with atorvastatin therapy
Comparator	Pioglitazone 45 mg	Placebo
Numbers of subject	122	302
Primary Objectives	Reduction in Triglyceride	Reduction in Triglyceride
Secondary Objectives	Lipid Parameters: ApoA, ApoB, HDL-C, LDL-C, non-HDL-C, TC, VLDL-C Glycemic Indices: FPG, HbA1c Safety criteria: 2-D ECHO and cardiac events Clinical, ECG, laboratory	Lipid Parameters: ApoA, ApoB, HDL-C, LDL-C, non-HDL-C, TC, VLDL-C Glycemic Indices: FPG, HbA1c Safety criteria: 2-D ECHO and cardiac events Clinical, ECG, laboratory
Duration	24 weeks	12 weeks

Sample size for these trials was determined for primary efficacy criteria based on phase II results and published reports on pioglitazone and placebo.

PRESS V : Saroglitazar vs. Pioglitazone in Diabetic Dyslipidemia

Of the 353 patients screened and participated in the 2 week lifestyle and dietary modification program, 122 patients were enrolled and randomly assigned to one of the treatment groups. The demographic characteristics and other baseline characteristics were well balanced between all the treatment groups.

The primary end point of the study was to assess the percent change in triglyceride levels after a 24 week treatment as compared to baseline. There was 45% decrease in serum TG levels with saroglitazar 4 mg, which was statistically significant compared to

baseline and also compared to pioglitazone 45 mg (15·5%) (Table 13.5). The maximum effect of saroglitazar on TG was achieved by week 12 and it was sustained at week 24. Saroglitazar reduced VLDL-C, LDL-C and TC significantly compared to pioglitazone and/or baseline (Table 13.5). ApoB, the marker of atherogenic dyslipidemia, was significantly reduced compared to baseline in the saroglitazar 4 mg arm, but not with pioglitazone 45 mg. The increase in HDL-C levels was observed in all treatment groups. Apolipoprotein A1 concentrations were numerically increased after treatment with saroglitazar as compared to pioglitazone.

Both the glycemic parameters, FPG and glycosylated hemoglobin (HbA1c), were significantly reduced at week 24 as compared to baseline in the saroglitazar and pioglitazone arms. An antiglycemic effect of saroglitazar was comparable to pioglitazone and there was no significant difference between saroglitazar 4 mg and pioglitazone 45 mg arm at the end of the study period.

The inflammatory biomarker, high sensitivity C-reactive protein (hs-CRP) and CPK have not increased significantly in the saroglitazar and pioglitazone arms. There was no significant change in any other safety parameter in any of the treatment arms, except body weight, which was increased in the pioglitazone arm. (Table 13.6)

Saroglitazar 2 mg & 4 mg dose were well tolerated throughout the study. Less number of patients reported adverse events in the saroglitazar 2 mg & 4 mg arms as compared to the pioglitazone 45 mg arm. The most frequently reported adverse events were asthenia, gastritis, chest discomfort, peripheral edema, dizziness and tremors (Table 13.7). Most of the adverse events were considered unrelated to treatment and were of mild intensity.

No SAEs were reported in the saroglitazar treatment arm. Three patients had three SAEs in the pioglitazone treatment arm (acute myocardial infarction, hematemesis and renal impairment), of which one was fatal and was due to acute myocardial infarction. However, none of the SAEs was considered treatment emergent.

There were no significant changes from baseline in any laboratory parameter (Table 13.6). Most AE were mild in nature and were considered as not clinically significant.

No clinically significant changes in 2-D ECHO or electrocardiography parameters were seen after treatment with saroglitazar. There was no significant decrease from baseline in bodyweight over time with saroglitazar treatment, while there was a numerical increase from baseline in bodyweight over time with pioglitazone.

Table 13.5 PRESS V : Change From Baseline in Efficacy Variable at Week 24 (mITT Population-LOCF Method)

Efficacy Parameter	Saroglitazar 2 mg (N=37)	Saroglitazar 4 mg (N=39)	Pioglitazone 45 mg (N=33)
Triglyceride (mg/dL)			
Baseline Mean ±SE	253.9 ± 11.25	257.0 ± 8.39	265.0 ± 10.73
Absolute change LSM ±SE	-78.2±17.60[#]	-115.4±17.13[*#]	-33.3±18.65
Percentage change LSM ±SE	-26.4±6.29[#]	-45.0±6.12[*#]	-15.5±6.67

LDL-Cholesterol-Direct (mg/dL)			
Baseline Mean ±SE	134.8 ± 7.00	130.8 ± 6.22	116.6 ± 5.09
Absolute change LSM ±SE	3.6±4.96	-12.0±4.81*#	3.5±5.30
Percentage change LSM ±SE	12.2±5.50	-5.0±5.33	4.8±5.87
VLDL Cholesterol (mg/dL)			
Baseline Mean ±SE	50.3 ± 2.33	52.4 ± 1.98	55.1 ± 3.27
Absolute change LSM ±SE	-15.2±3.13#	-23.9±3.04*#	-8.8±3.32#
Percentage change LSM ±SE	-25.1±5.50	-45.5±5.33*	-20.0±5.83
Total Cholesterol (mg/dL)			
Baseline Mean ±SE	202.4 ± 7.83	197.3 ± 6.56	185.8 ± 5.21
Absolute change LSM ±SE	2.5±5.61	-18.5±5.44*#	9.1±5.97#
Percentage change LSM ±SE	5.0±3.42	-7.7±3.31*	5.5±3.63
Apo-lipoproteins B (mg/dL)			
Baseline Mean ±SE	101.3 ± 4.40	98.3 ± 4.00	89.3 ± 3.14
Absolute change LSM ±SE	-5.4±3.42	-13.4±3.31#	-6.4±3.65
Percentage change LSM ±SE	2.9±4.80	-10.9±4.65	-4.8±5.12
HDL-Cholesterol (mg/dL)			
Baseline Mean ±SE	36.8 ± 1.99	35.3 ± 1.54	38.3 ± 1.89
Absolute change LSM ±SE	2.8±1.16	0.2±1.14	2.0±1.24
Percentage change LSM ±SE	12.7±3.54	3.8±3.46	7.1±3.76
Fasting Plasma Glucose (mg/dL)			
Baseline Mean ±SE	143.9 ± 6.96	152.7 ± 10.57	138.2 ± 5.56
Absolute change LSM ±SE	-11.3±6.51	-22.6±6.37#	-21.8±6.92
Percentage change LSM ±SE	-1.5±4.98	-8.3±4.87	-12.8±5.29
HbA1c (%)			
Baseline Mean ±SE	8.1±0.14	7.9±0.09	8.2±0.13
Absolute change LSM ±SE	-0.3±0.11#	-0.3±0.11#	-0.4±0.12#

Abbreviations: LSM=least square mean; SE= standard error; SD= standard deviation; mg=milligram; dL=deciliter; LOCF = last observation carried forward; Note: * indicates significant as compared to Pioglitazone; # significant compare to base line

Table 13.6 PRESS V: Assessment of safety laboratory parameter at Week 24 (mITT Population)			
Safety Parameter	**Saroglitazar 2mg (N=37)**	**Saroglitazar 4mg (N=39)**	**Pioglitazone 45 mg (N=33)**
Hemoglobin (gm/dL)			
Baseline Mean ± SD (SE)	13.6 ± 1.95 (0.32)	13.7 ± 1.71 (0.27)	13.5 ± 1.52 (0.26)
Absolute change Mean ± SD (SE)	-0.0 ± 0.06 (0.01)	-0.0 ± 0.08 (0.01)	-0.0 ± 0.11 (0.02)
M.C.H. (pg)			
Baseline Mean ± SD (SE)	27.1 ± 2.99 (0.49)	27.8 ± 2.15 (0.34)	27.3 ± 3.70 (0.64)
Absolute change Mean ± SD (SE)	0.0 ± 0.05 (0.01)	0.0 ± 0.06 (0.01)	0.1 ± 0.42 (0.07)
M.C.H.C.(g/dL)			
Baseline Mean ± SD (SE)	29.5 ± 2.43 (0.40)	29.8 ± 2.39 (0.38)	29.6 ± 2.21 (0.38)
Absolute change Mean ± SD (SE)	0.0 ± 0.09 (0.01)	-0.0 ± 0.08 (0.01)	0.0 ± 0.17 (0.03)
M.C.V. (fL)			
Baseline Mean ± SD (SE)	91.8 ± 9.21 (1.51)	93.8 ± 8.54 (1.37)	92.2 ± 11.24 (1.96)
Absolute change Mean ± SD (SE)	0.0 ± 0.08 (0.01)	0.0 ± 0.08 (0.01)	0.1 ± 0.17 (0.03)
P.C.V. (%)			
Baseline Mean ± SD (SE)	46.1 ± 6.09 (1.00)	45.9 ± 5.69 (0.91)	45.8 ± 5.84 (1.02)
Absolute change Mean ± SD (SE)	-0.0 ± 0.1 (0.02)	-0.0 ± 0.12 (0.02)	-0.0 ± 0.13 (0.02)
Total Leucocyte Count (10^3/uL)			
Baseline Mean ± SD (SE)	8.5 ± 2.48 (0.41)	7.8 ± 1.73 (0.28)	8.2 ± 2.33 (0.41)
Absolute change Mean ± SD (SE)	-0.1 ± 0.16 (0.03)	-0.0 ± 0.31 (0.05)	-0.1 ± 0.16 (0.03)
Total Platelet Count (10^3/uL)			
Baseline Mean ± SD (SE)	248.6 ± 74.76 (12.29)	255.9 ± 73.99 (11.85)	281.3 ± 99.73 (17.36)
Absolute change Mean ± SD (SE)	0.1 ± 0.21 (0.03)	0.0 ± 0.24 (0.04)	0.0 ± 0.25 (0.04)
Total R.B.C.(10^6/uL)			
Baseline Mean ± SD (SE)	5.0 ± 0.52 (0.09)	4.9 ± 0.53 (0.08)	5.0 ± 0.71 (0.12)
Absolute change Mean ± SD (SE)	-0.0 ± 0.08 (0.01)	-0.0 ± 0.12 (0.02)	-0.1 ± 0.19 (0.03)
ALP (U/L)			
Baseline Mean ± SD (SE)	81.9 ± 24.93 (4.10)	85.0 ± 31.78 (5.09)	84.1 ± 26.57 (4.63)
Absolute change Mean ± SD (SE)	-0.2 ± 0.28 (0.05)	-0.2 ± 0.56 (0.09)	-0.1 ± 0.24 (0.04)
ALT (U/L)			
Baseline Mean ± SD (SE)	31.5 ± 16.48 (2.71)	29.7 ± 15.91 (2.55)	26.3 ± 9.13 (1.59)
Absolute change Mean ± SD (SE)	-0.1 ± 0.36 (0.06)	-0.2 ± 0.30 (0.05)	-0.2 ± 0.25 (0.04)

AST (U/L)			
Baseline Mean ± SD (SE)	25.9 ± 15.75 (2.59)	23.6 ± 9.69 (1.55)	22.1 ± 5.81 (1.01)
Absolute change Mean ± SD (SE)	0.2 ± 0.63 (0.10)	0.1 ± 0.43 (0.07)	0.0 ± 0.42 (0.07)
G.G.T.P. (U/L)			
Baseline Mean ± SD (SE)	37.6 ± 22.85 (3.76)	35.3 ± 18.75 (3.00)	36.4 ± 22.86 (3.98)
Absolute change Mean ± SD (SE)	-0.2 ± 0.40 (0.07)	-0.3 ± 0.43 (0.07)	-0.3 ± 0.25 (0.04)
Bilirubin (mg/dL)			
Baseline Mean ± SD (SE)	0.5 ± 0.20 (0.03)	0.5 ± 0.34 (0.05)	0.5 ± 0.24 (0.04)
Absolute change Mean ± SD (SE)	-0.2 ± 0.32 (0.05)	-0.0 ± 0.54 (0.09)	0.1 ± 0.85 (0.15)
Creatinine (mg/dL)			
Baseline Mean ± SD (SE)	0.7 ± 0.21 (0.03)	0.7 ± 0.19 (0.03)	0.7 ± 0.2 (0.03)
Absolute change Mean ± SD (SE)	0.1 ± 0.26 (0.04)	0.2 ± 0.44 (0.07)	0.0 ± 0.2 (0.03)
BUN (mg/dL)			
Baseline Mean ± SD (SE)	10.8 ± 3.66 (0.60)	9.5 ± 2.75 (0.44)	11.1 ± 2.74 (0.48)
Absolute change Mean ± SD (SE)	0.1 ± 0.28 (0.05)	0.2 ± 0.47 (0.08)	0.2 ± 0.37 (0.06)
CPK (U/L)			
Baseline Mean ± SD (SE)	91.3 ± 62.48 (10.27)	96.3 ± 49.4 (7.91)	97.2 ± 47.82 (8.32)
Absolute change Mean ± SD (SE)	0.3 ± 0.94 (0.15)	0.3 ± 0.49 (0.08)	0.3 ± 0.46 (0.08)
Uric Acid (mg/dL)			
Baseline Mean ± SD (SE)	5.0 ± 1.32 (0.22)	5.0 ± 1.76 (0.28)	4.6 ± 1.22 (0.21)
Absolute change Mean ± SD (SE)	-0.1 ± 0.17 (0.03)	0.0 ± 0.11 (0.02)	-0.3 ± 0.56 (0.10)
hs-CRP (mg/L)			
Baseline Mean ± SD (SE)	3.1 ± 3.23 (0.53)	4.5 ± 5.31 (0.85)	3.3 ± 3.37 (0.59)
Absolute change Mean ± SD (SE)	0.6 ± 2.11 (0.35)	0.2 ± 1.61 (0.26)	0.1 ± 1.43 (0.25)
Body weight (kg)			
Baseline Mean ± SD (SE)	69.8 ± 12.72 (2.09)	73.0 ± 11.49 (1.84)	71.0 ± 12.94 (2.25)
Absolute change Mean ± SD (SE)	-0.8 ± 5.35 (0.88)	-0.1 ± 2.70 (0.43)	1.6 ± 3.44 (0.60)

Abbreviations: SD = standard deviation; mg = milligram; gm = gram; dL = deciliter; L = liter; kg = kilogram; U/L = unit per liter; % = percentage; pg = picograms.

Table 13.7 PRESS V: Summary of Adverse Events* by System Organ Class and Preferred Term Among Treatment Groups (Safety Population)				
System Organ Class term	**Preferred term**	**Saroglitazar 2 mg (N=41) n (%)**	**Saroglitazar 4 mg (N=41) n (%)**	**Pioglitazone 45 mg (N=40) n (%)**
Total number of subjects with at least one adverse event		7 (17.1)	7 (17.1)	11 (27.5)
Ear and labyrinth disorders	Tinnitus	0 (0.0)	0 (0.0)	1 (2.5)
Gastrointestinal disorders	Gastritis	0 (0.0)	2 (4.9)	2 (5.0)
	Nausea	0 (0.0)	0 (0.0)	1 (2.5)
	Oedema mouth	0 (0.0)	0 (0.0)	1 (2.5)
	Oral dysaesthesia	0 (0.0)	1 (2.4)	0 (0.0)
	Vomiting	0 (0.0)	0 (0.0)	1 (2.5)
General disorders and administration site conditions	Asthenia	1 (2.4)	3 (7.3)	1 (2.5)
	Chest discomfort	1 (2.4)	1 (2.4)	1 (2.5)
	Death	0 (0.0)	0 (0.0)	1 (2.5)
	Oedema peripheral	1 (2.4)	0 (0.0)	2 (5.0)
	Swelling	1 (2.4)	0 (0.0)	0 (0.0)
Infections and infestations	Mumps	1 (2.4)	0 (0.0)	0 (0.0)
	Sinusitis	1 (2.4)	0 (0.0)	0 (0.0)
	Tonsillitis	1 (2.4)	0 (0.0)	0 (0.0)
Laboratory Investigations	Blood creatinine phosphokinase increased (<2X UNL). Clinically insignificant	1 (2.4)	1 (2.4)	0 (0.0)
Weight increased		0 (0.0)	0 (0.0)	2 (5.0)
Musculoskeletal and connective tissue disorders	Arthralgia	1 (2.4)	0 (0.0)	0 (0.0)
	Muscular weakness	0 (0.0)	1 (2.4)	0 (0.0)
	Myalgia	0 (0.0)	0 (0.0)	1 (2.5)

Nervous system disorders	Dizziness	1 (2.4)	1 (2.4)	1 (2.5)
	Tremor	1 (2.4)	1 (2.4)	1 (2.5)
Renal and urinary disorders	Renal impairment	0 (0.0)	0 (0.0)	1 (2.5)
Respiratory, thoracic and mediastinal disorders	Cough	1 (2.4)	0 (0.0)	0 (0.0)
	Dyspnoea	0 (0.0)	0 (0.0)	1 (2.5)
	Pharyngitis	1 (2.4)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	Skin disorder	0 (0.0)	1 (2.4)	0 (0.0)
Vascular disorders	Hypertension	0 (0.0)	0 (0.0)	1 (2.5)
Note: Most of the above adverse events were classified as unrelated to treatment				

PRESS VI : Saroglitazar vs placebo in hypertriglyceridemia with T2DM not controlled with atorvastatin therapy

The study consisted of a 4 week run-in period involving discontinuation of any anti-dyslipidemic drugs other than atorvastatin 10 mg; also patients were put on dietary and lifestyle modification program at this time. Following the completion of the run-in period, a double-blind treatment period of 12 weeks was initiated, following which there was a voluntary follow-up visit for safety assessment at 24 weeks.

A total of 302 subjects across 29 centers in India were randomized to receive one of the treatment, saroglitazar 2 mg (n=101 subjects) or saroglitazar 4 mg (n=99 subjects) or matching placebo (n=102 subjects). Baseline demographic, clinical and laboratory characteristics of the study population after run-in period were comparable across the treatment groups

Saroglitazar 2 mg & 4 mg decreased TG levels by -45.5% ± 3.03% & -46.7% ± 3.02% respectively. Mean TG reduction from baseline to end of the treatment was 131.71 ± 8.30 mg/dL & 139.5 ± 8.29 mg/dL with saroglitazar 2 mg & 4 mg respectively. This decrease in TG level was statistically significant compared to baseline and placebo (Table 13.8). There was significant reduction in non–HDL-C, LDL-C, VLDL-C, TC and ApoB as compared to the placebo arm at week 12. Saroglitazar 2 mg & 4 mg showed significant increase in HDL-C as compared to placebo. There was also statistically significant decrease in FPG level after 12 weeks of treatment with saroglitazar 2 mg & 4 mg as compared to placebo arm.

Both the doses of saroglitazar were well tolerated. There were similar numbers of adverse events in the saroglitazar and placebo arms. Most of the adverse events were not related to treatment and were mild to moderate in intensity. The summary of adverse events reported by subjects in the study are presented in Table 13.10.

There were two hospitalizations reported during the study which were considered not related to the study drug. Both the subjects have recovered without any sequalae.

After 12 weeks treatment, there were no significant changes in hemoglobin, liver enzymes (ALP, ALT, AST, GTT), renal function (creatinine, eGFR, BUN), CPK, and hs-CRP in saroglitazar and placebo arms. There was no edema or weight gain reported in any of the study arms. (Table 13.9).

During this study, subjects were monitored for cardiac events. ECG abnormalities and cardiac function by 2-D ECHO were done at the start of the study, at the end of 12 weeks and after 24 weeks of last dose of the study. There was no adverse event reported as far as cardiac safety is concerned.

Table 13.8 PRESS VI: Change From Baseline in Efficacy Variable at Week 12 (mITT Population)

Efficacy Parameter	Saroglitazar 2mg (N=86)	Saroglitazar 4mg (N=86)	Placebo (N=94)
Triglyceride (mg/dL)			
Baseline Mean ±SE	273.3 ± 8.47	287.3 ± 9.27	286.6 ± 8.14
Absolute change LSM ±SE	-132.7±8.30*#	-139.5±8.29*#	-78.0±7.93#
Percentage change LSM ±SE	-45.5±3.03*	-46.7±3.02*	-24.9±2.89
LDL-Cholesterol-Direct (mg/dL)			
Baseline Mean ±SE	132.5 ± 3.28	140.2 ± 3.17	140.1 ± 3.46
Absolute change LSM ±SE	-40.1±3.01#	-45.5±3.00*#	-35.6±2.88#
Percentage change LSM ±SE	-27.5±2.31	-31.3±2.31*	-22.9±2.22
VLDL Cholesterol (mg/dL)			
Baseline Mean ±SE	52.6 ± 1.77	57.2 ± 1.88	57.1 ± 1.64
Absolute change LSM ±SE	-23.3±2.03*#	-27.2±2.02*#	-15.0±1.94#
Percentage change LSM ±SE	-39.6±3.71*	-46.0±3.70*	-24.5±3.54
Total Cholesterol (mg/dL)			
Baseline Mean ±SE	200.6 ± 4.11	210.4 ± 4.01	209.5 ± 4.05
Absolute change LSM ±SE	-48.7±3.54#	-56.4±3.53*#	-40.3±3.38#
Percentage change LSM ±SE	-22.6±1.75*	-26.1±1.74*	-17.7±1.66
Apo-lipoproteins B (mg/dL)			
Baseline Mean ±SE	98.2 ± 2.36	101.7 ± 2.30	104.1 ± 2.40
Absolute change LSM ±SE	-29.9±2.11#	-34.3±2.09*#	-25.6±2.00#
Percentage change LSM ±SE	-27.4±2.17	-32.0±2.15*	-22.9±2.06
HDL-Cholesterol (mg/dL)			
Baseline Mean ±SE	36.6 ± 0.91	39.1 ± 1.21	38.5 ± 1.24
Absolute change LSM ±SE	2.5±0.89*#	1.3±0.89*	-1.6±0.85
Percentage change LSM ±SE	9.5±2.36*	7.6±2.36*	-0.7±2.26

Non-HDL-Cholesterol (mg/dL)			
Baseline Mean ±SE	164.0 ± 3.98	171.3 ± 4.07	171.0 ± 4.22
Absolute change LSM ±SE	-51.4±3.59*#	-57.7±3.58*#	-38.6±3.43#
Percentage change LSM ±SE	-29.2±2.25*	-32.5±2.25*	-20.1±2.15
Fasting Plasma Glucose (mg/dL)			
Baseline Mean ±SD	179.6 ± 71.23	176.3 ± 71.58	184.1 ± 68.27
Absolute change Mean ±SD	-22.7 ± 76.76#	-27.2 ± 69.10#	0.5 ± 86.79
Percentage change Mean ±SD	-9.3 ± 36.26	-10.0 ± 34.47	6.2 ± 46.98
HbA1c(%)			
Baseline Mean ±SD	8.9±1.84	8.9±1.77	9.2±1.81
Absolute change Mean ±SE	-0.3±-0.08	-0.3±0.08	-0.2±0.07

Abbreviations: LSM=least square mean; SE= standard error; SD= standard deviation; mg=milligram; dL=deciliter; Note: * significant as compared to Placebo; # significant compare to base line

Table 13.9 PRESS VI: Change From Baseline in Safety Variable at Week 12 (ITT Population)

Safety Parameter	Saroglitazar 2mg (N=86)	Saroglitazar 4mg (N=86)	Placebo (N=94)
Hemoglobin (gm/dL)			
Baseline Mean ±SD	13.9 ± 1.85	13.7 ± 1.72	13.9 ± 1.92
Absolute change Mean ±SD	-0.4 ± 1.46	-0.7 ± 0.79	-0.2 ± 0.86
ALP (U/L)			
Baseline Mean ±SD	83.6 ± 26.51	87.7 ± 23.93	86.7 ± 22.55
Absolute change Mean ±SD	-16.3 ± 22.34	-29.0 ± 22.48	-2.5 ± 20.96
ALT (U/L)			
Baseline Mean ±SD	26.9 ± 14.46	26.6 ± 15.70	27.9 ± 14.00
Absolute change Mean ±SD	-4.0 ± 13.73	-3.9 ± 15.21	-0.7 ± 12.46
AST (U/L)			
Baseline Mean ±SD	23.8 ± 11.11	24.0 ± 12.61	24.4 ± 10.72
Absolute change Mean ±SD	1.1 ± 12.86	0.5 ± 13.09	0.7 ± 16.32
GGTP (U/L)			
Baseline Mean ±SD	38.6 ± 36.00	35.9 ± 26.87	36.8 ± 22.82
Absolute change Mean ±SD	-12.0 ± 25.49	-16.2 ± 22.83	-1.1 ± 14.63
Creatinine (mg/dL)			
Baseline Mean ±SD	0.8 ± 0.22	0.8 ± 0.22	0.8 ± 0.22
Absolute change Mean ±SD	0.0 ± 0.18	0.1 ± 0.20	0.0 ± 0.21

Creatinine Clearance (ml/min)			
Baseline Mean ±SD	117.9 ± 45.92	110.6 ± 42.18	115.6 ± 38.95
Absolute change Mean ±SD	-12.1 ± 35.27	-7.4 ± 26.34	-4.9 ± 32.12
BUN (mg/dL)			
Baseline Mean ±SD	11.1 ± 3.20	11.1 ± 3.90	11.4 ± 3.40
Absolute change Mean ±SD	0.4 ± 4.13	1.0 ± 3.66	-0.3 ± 4.29
CPK (U/L)			
Baseline Mean ±SD	93.3 ± 51.90	85.5 ± 43.67	96.1 ± 63.79
Absolute change Mean ±SD	8.4 ± 53.41	32.3 ± 61.27	5.7 ± 69.26
hs-CRP (mg/L)			
Baseline Mean ±SD	4.0 ± 4.47	3.6 ± 5.25	4.4 ± 6.91
Absolute change Mean ±SD	-0.9 ± 4.08	-1.0 ± 4.19	-0.0 ± 4.47
Body weight (kg)			
Baseline Mean ±SD	71.3 ± 13.56	69.1 ± 10.83	69.9 ± 11.53
Absolute change Mean ±SD	-0.6 ± 2.63	0.3 ± 2.83	-0.5 ± 2.40

Safety data used for Baseline Bodyweight; Intention-to- treat population used for all other parameters, Abbreviations: kg = kilograms; m2 = meter square; mg = milligram; gm = gram; dL = decilitre; N = number of subjects in the treatment group;

Table 13.10 PRESS VI: Summary of Adverse Events by System Organ Class and Preferred Term Among Treatment Groups (Safety Population)

System Organ Class term	Saroglitazar 2 mg (N=100) n (%)	Saroglitazar 4 mg (N=99) n (%)	Placebo (N=102) n (%)
Gastrointestinal Disorder	7 (7.0)	9 (9.0)	3 (3.0)
General Disorder and Administration Site Condition	3 (3.0)	4 (4.0)	4 (4.0)
Injury and procedural complications	0 (0.0)	1 (1.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.0)	1 (1.0)	2 (2.0)
Nervous system disorders	1 (1.0)	3 (3.0)	2 (2.0)
Renal and urinary disorders	1 (1.0)	1 (1.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (3.0)	2 (2.0)	0 (0.0)

Note: Most of the above adverse events were classified as unrelated to treatment

14. Lipaglyn™ (Saroglitazar) in the management of Atherogenic Diabetic Dyslipidemia

CVD is the leading cause of death in individuals with T2DM, accounting for 50% of all deaths.[49] Some clinical guidelines state that CV risk in patients with T2DM can be reduced by controlling dyslipidemia as well as hyperglycemia.[50, 51] but most patients still do not achieve recommended goals for these risk factors.[50, 52] Glycemic control alone may not be enough in Type 2 diabetics. Data from two intensive glycemic control strategies in the ACCORD[53] and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation – ADVANCE[54] clinical trials in patients with T2DM at high risk of CV events confirmed the improvement of microvascular parameters associated with intensive glycemic control. But, CV risk was not reduced in patients who received intensive therapy for glycemic control compared with those who received standard therapy. The Veterans Affairs Diabetes Trial- VADT also did not show any benefit over standard therapy for major CV events in patients with poorly controlled T2DM despite not achieving the same amount of glycemic control as in the ACCORD and ADVANCE trials.[55] All these observations suggest that a multifactorial intervention may be most appropriate for optimum reduction of CV risk.[56]

PPARs agonism may positively affect CV disease risk in patients with T2DM looking into the mechanism of actions of fibrates and TZD. The fibrates are agonists of PPAR-α, and their use in patients with T2DM leads to improvements in lipid profiles.[50] The PPAR-γ agonist pioglitazone is approved for glycaemic control in T2DM. Pioglitazone therapy has been associated with reduced risk of negative CV outcomes in T2DM[57] although the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) did not achieve the primary endpoint.[58] However, increasing safety concerns with the TZDs with regard to fluid retention, weight gain, and particularly congestive heart failure have resulted in the implementation of new label warnings for the use of these agents. Pioglitazone was recently in the news for its propensity to cause bladder cancer.

Many researchers felt that the answer may be locked in dual PPAR agonists. Since the 1990s many such agents were developed which were efficacious but issues related to safety (probably due to the ratios of PPAR-α/γ agonistic activity not being appropriate) forced them to be abandoned at various stages of development. Clearly, an optimum PPAR agent with the appropriate ratio of PPAR-α/γ agonistic activity which can improve the safety profile, and, that provides both effective glycaemic control and an improved lipid profile was the need of the hour. Such a dual PPAR-α/γ agonist might prove especially beneficial for patients with DD uncontrolled by agents or combination of agents currently available.

Lipaglyn™ is a new, dual PPAR-α/γ agonist designed to optimise glycaemic control and lipid benefits, and minimise PPAR-related adverse effects in the treatment of patients with T2DM. Preclinical and clinical studies have shown favourable effects of Lipaglyn™ on glycaemic control, insulin sensitivity, and dyslipidemia. The overall toxicity profile from non-clinical and clinical safety studies with saroglitazar was very much acceptable. Lipaglyn™ treatment produced significant, dose-dependent improvements in HbA1c concentrations and FPG and significant improvements in all lipid parameters, including LDL-C. The 4 mg dose has provided (as shown earlier in the Clinical Trials section) good

glycaemic control too. Effects on lipids were noted early during treatment and the 4 mg dose of Lipaglyn™ approaches an optimum treatment effect on TG and HDL-C. Also was recorded a reduction from baseline LDL-C with the 4 mg dose of Lipaglyn™. Importantly, Lipaglyn™ seems to be safe and well tolerated over the course of the study durations. The broad range of lipid improvements associated with Lipaglyn™ addresses the pattern of dyslipidemia often noted in patients with T2DM, which includes high concentrations of TGs, low concentrations of HDL-C, and moderate increase in LDL-C, with an increased concentration of small, dense, and potentially more atherogenic particles. Although raised LDL-C is the most recognised primary target of lipid-lowering therapy in diabetes, non-HDL-C goals are now considered to be more important. Correction of hypertriglyceridemia and low concentrations of HDL-C is recommended for patients with T2DM with or without significantly raised LDL-C.[50, 59] Significant changes in lipids and glycaemic endpoints, coupled with the favourable safety profile, which reflects in the promising data of Lipaglyn™ clinical trials, establishes the safety and efficacy of this promising new agent. It is an important agent now where statins, fibrates and the TZDs alone may not have shown the desired result in reaching the goals. Hence, it can be added to metformin plus statin in the management of DD and in hypertriglyceridemia in DD not controlled by statins alone.

The reason why Lipaglyn™ has been able to improve the lipid as well as glycemic parameters with a very acceptable adverse event profile seems to lie in its predominant PPAR-α agonism with moderate PPAR-γ activity.

- In different clinical trials, Lipaglyn™ has been used in patients who were concurrently on atorvastatin or metformin and / or sulfonylureas. No drug-drug interactions were reported.
- Although there is no report of hypoglycaemia following Lipaglyn™ treatment in healthy subjects or patients during the trials, it is advisable to monitor blood glucose levels in patients who are one or more anti-diabetic drugs specially on insulin.
- Concurrent administration of Lipaglyn™ with any other PPAR-α and/or PPAR-γ agonist is not recommended, as there is potential for drug-drug interactions mechanistically. Like other PPAR-α/γ agonists, Lipaglyn™ has not been studied for such drug-drug interactions.

*Proposed guideline for management of Diabetic Dyslipidemia

Algorithm/Treatment Protocol

Healthy eating, weight control, increased physical activity

Initial Drug Therapy: Metformin + Statin

	Metformin + Statin
Efficacy (ADD*)	Low
Efficacy (↓HbA1c)	High
Risk of Hypoglycemia	Low
Weight Gain/Edema	Neutral/Loss
Major side effect(s)	GI/Lactic acidosis/Myopathy
Costs	Intermediate

If needed to reach individualized HbA1c & lipid targets after ~3 months, proceed for first additional drug (Order not meant to denote any specific preferences)

1st Additional Drug

	Metformin + Statin + Lipaglyn	Metformin + Statin + Sulfonylurea	Metformin + Statin + Thiazolidinedione	Metformin + Statin + DPP-IV Inhibitor	Metformin + Statin + GLP-1 Agonist	Metformin + Statin + Insulin
Efficacy (ADD*)	High	Low	Low	Low	Low	Low
Efficacy (↓HbA1c)	Intermediate	High	High	Intermediate	High	High
Risk of Hypoglycemia	Low	Moderate	Low	Low	Low	High
Weight Gain/Edema	Neutral/Neutral	High/Neutral	High/High	Neutral/Neutral	Loss/Neutral	Gain/Intermediate
Major side effect(s)	GI	Hypoglycemia	Edema, HF	URTI	GI	Hypoglycemia
Costs	Intermediate	Low	Intermediate	High	High	Variable

If needed to reach individualized HbA1c & lipid targets after ~3 months, proceed for second additional drug (Order not meant to denote any specific preferences)

2nd Additional Drug

Metformin + Statin +	Metformin + Statin +	Metformin + Statin +	Metformin + Statin +	Metformin + Statin +	Metformin + Statin +
Lipaglyn + SU or DPP-IV Inhibitor or GLP-1 Agonist or Insulin or AGI	Sulfonylurea + Lipaglyn or TZD or DPP-IV Inhibitor or GLP-1 Agonist or Insulin	Thiazolidinedione + SU or DPP-IV Inhibitor or GLP-1 Agonist or Insulin	DPP-IV Inhibitor + Lipaglyn or SU or TZD or Insulin	GLP-1 Agonist + Lipaglyn or SU or TZD or Insulin	Insulin + Lipaglyn or TZD or DPP-IV Inhibitor or GLP-1 Agonist

Important ADRs: (Adverse Drug Reactions)

SU - Hypoglycemia
DPP-IV Inhibitors - URTI
Insulin - Hypoglycemia, Weight Gain
TZD - Weight Gain, Edeme
GLP-1 - Nausea, Vomiting, Pancreatitis
AGIs - Diarrhea, Flatulance
Lipaglyn™ - GI Intolerance

*ADD - Atherogenic Diabetic Dyslipidemia (Presents with High TG, Low HDL-C, sd-LDL-C)

SU-Sulfonylurea TZD-Thiazolidinedione AGI-Alpha Glucosidase Inhibitor URTI-Upper Respiratory Tract Infection HF-Heart failure GI-Gastrointestinal

*Proposed by Zydus Discovery

15. Prescribing information of Lipaglyn™

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Saroglitazar Tablets

Lipaglyn™

1. Composition

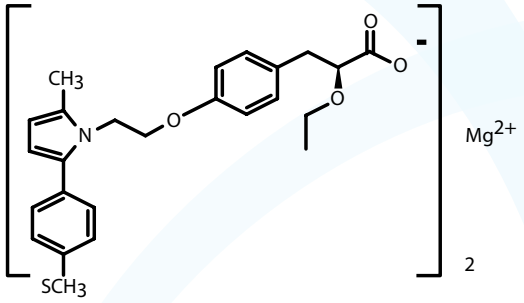
Each uncoated tablet contains:

Saroglitazar	4 mg
Excipients	q.s.

Inactive ingredients in the tablet are microcrystalline cellulose, lactose, magnesium oxide, povidone, talc, magnesium stearate, croscarmellose sodium and colloidal silicon dioxide.

2. Drug description

Lipaglyn™ (Saroglitazar) is a dual regulator that corrects both the lipid profile and the glycemic indices. It is available as an oral tablet containing 4 mg of saroglitazar. The chemical name for saroglitazar is Benzenepropanoic acid, α-ethoxy-4-[2-[2-methyl-5-[4-(methylthio)phenyl]-1H-pyrrol-1-yl]ethoxy]-, magnesium salt (2:1), (αS) - with the following structural formula:



The empirical formula of saroglitazar is $[C_{25}H_{28}NO_4S]_2Mg$ and the molecular mass is 900 g/mole.

3. Indications and usage

Lipaglyn™ is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy. In clinical studies, Lipaglyn™ has demonstrated reduction of triglycerides (TG), Low Density Lipoprotein (LDL) cholesterol, Very Low Density Lipoprotein (VLDL) cholesterol, non - High Density Lipoprotein (non- HDL) cholesterol and an increase in HDL cholesterol. It has also shown favorable glycemic indices by reducing the fasting plasma glucose and glycosylated hemoglobin in diabetic patients.

4. Dosage and administration

The recommended dose of Lipaglyn™ is one tablet of 4 mg once a day.

5. Dosage forms and strengths

Lipaglyn™ is available as uncoated tablets for oral administration.

Each uncoated tablet of Lipaglyn™ contains 4 mg of saroglitazar.

6. Contraindications

Hypersensitivity to saroglitazar or any of the excipients used in the formulation.

7. Warnings and precautions

Although clinical studies with Lipaglyn™ have not demonstrated any potential for myopathies or derangement of liver and/or renal function, Lipaglyn™ treatment should be initiated with caution in patients with abnormal liver or renal function, or history of myopathies.

Lipaglyn™ has not been studied in patients with established New York Heart Association (NYHA) Class III or IV heart failure. Lipaglyn™ should be initiated with caution in patients with type 2 diabetes having cardiac disease with episodic congestive heart failure and such patients should be monitored for signs and symptoms of congestive heart failure.

Although during the clinical studies, no significant weight gain and edema was reported with Lipaglyn™, patients who experience rapid increase in weight should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

8. Adverse events

In two controlled phase III clinical studies of 12 to 24 weeks treatment duration with Lipaglyn™, the most common adverse events (AEs ≥ 2%) reported were gastritis, asthenia and pyrexia. Most of the AEs were mild to moderate in nature and did not result in discontinuation of the study.

Because clinical studies are conducted under widely varying conditions, AE rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

9. Drug interactions

In vitro studies using recombinant human cytochrome P-450 (CYP) isozymes indicate that saroglitazar does not significantly inhibit CYP1A2, 2C9, 2C19, 2D6 and 3A4 at concentration of 10 µM. Similarly, saroglitazar did not show any potential for CYP3A4 enzyme induction when tested up to 100 µM concentration in luciferase based reporter assay in transiently transfected HepG2 cells. Although no clinical drug-drug interaction studies have been conducted with Lipaglyn™ so far, because the tested concentrations (10 µM and 100 µM) are several times higher than the mean C_{max} of saroglitazar, it can be inferred that Lipaglyn™ would not cause clinically significant drug-drug interactions related to the above evaluated CYPs.

10. Use in specific populations

10.1 Pregnancy

Pregnancy: Category C

The safety of Lipaglyn™ in pregnant women has not been established as there is no adequate and well controlled study carried out in pregnant women.

Women who become pregnant during Lipaglyn™ treatment should contact their physicians. Lipaglyn™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, effects of saroglitazar on the embryo-fetal development were assessed in pregnant rats given repeated oral doses of 5, 25 and 125mg/kg/day. No maternal or fetal toxicity was noticed at 5 mg/kg, which is about 12-fold higher on body surface area basis than the maximum recommended human dose (MRHD) of Lipaglyn™ 4 mg. Saroglitazar was found to be non-teratogenic up to the highest dose of 125 mg/kg day in rats.

In pregnant rabbits given repeated oral doses of 10, 50 and 200 mg/kg/day of saroglitazar, no maternal toxicity was noticed up to 10 mg/kg and no fetal toxicity up to 50 mg/kg. Saroglitazar was found to be non-teratogenic up to the highest dose of 200 mg/kg/day in rabbits.

10.2 Nursing mothers

Nursing mothers should not use Lipaglyn™ because it is not known whether saroglitazar is excreted into the breast milk.

10.3 Pediatric use

Safety and efficacy of Lipaglyn™ in pediatric patients have not been established.

10.4 Geriatric use

Considering the comorbidity and concomitant medications in elderly patients, Lipaglyn™ should be used with caution in geriatric patients.

11. Overdose

During clinical studies, no incidence of overdose with Lipaglyn™ has been reported. In case of overdose with Lipaglyn™, general supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status.

12. Clinical pharmacology

12.1 Mechanism of action

Saroglitazar is a potent and predominantly Peroxisome Proliferator Activated Receptor (PPAR)-alpha agonist with moderate PPAR-gamma agonistic activity. PPARs are nuclear lipid-activated transcription factors that regulate the expression of various genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes. The pharmacological effects of saroglitazar were extensively evaluated in various preclinical models. Saroglitazar showed both anti-dyslipidemic and anti-diabetic effects mainly mediated via activation of PPARα and PPARγ respectively.

PPARα activation by saroglitazar increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of TG. This in turn increases diversion of FA from peripheral tissues (e.g. skeletal muscle and fat tissue) to the liver, and thereby decreasing both FA synthesis and delivery of TG to peripheral tissues. Saroglitazar also causes increased lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase (LPL) and reducing production of apolipoprotein C-III (an inhibitor of LPL activity). Consistent with the above mechanism, saroglitazar was also found to reduce plasma LDL cholesterol. PPARα activation by saroglitazar also induces an increase in the synthesis of apolipoproteins A-I, A-II and HDL-cholesterol.

Although saroglitazar is predominantly a PPARα agonist, it also causes activation of PPARγ and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Saroglitazar increases the expression of numerous PPARγ-responsive genes involved in carbohydrate and lipid metabolism, including adiponectin, adipocyte fatty-acid-binding protein (aP2), LPL, fatty acid transport protein (FATP) and fatty acid translocase (CD36). By increasing the expression of these genes, saroglitazar decreases the post prandial rise of plasma free fatty acids, improves post-absorptive insulin-mediated suppression of hepatic glucose output, reduces the metabolic burden on liver & muscle and promotes glucose utilization. Robust anti-diabetic and insulin sensitizing effects of saroglitazar were observed in preclinical models, in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues.

12.2 Pharmacodynamics

12.2.1 Dyslipidemia with Type-II Diabetes Mellitus (T2DM):

The effects of Lipaglyn™ at a dose of 4 mg per day were assessed in two Phase-III randomized, double-blind, parallel-group studies including diabetic patients with Triglycerides >200 mg/dL. In one study, the patients were treated with Lipaglyn™ 4 mg or Pioglitazone (45 mg) for 24 weeks. The results are presented in Table 1 below:

Table 15.1: Percent change in lipid and glycemic parameters following Lipaglyn™ 4 mg treatment

Time point	Week 12	Week 24
TG	-46.1 ±5.6*#	-45.7 ±5.1*#
TC	-7.3 ±3.6*	-6.9 ±3.8*#
LDL-C	-0.4 ±6.5	-4.8 ±6.2*
VLDL-C	-46.1 ±5.6*#	-46.1 ±5.2*#
HDL-C	10.0 ±3.7*	4.6 ±3.9
Apo A1	0.7 ±4.8	2.2 ±8.2
Apo B	-11.9 ±5.4*	-9.8 ±5.4*
FPG^	-15.2 ±3.5*	-11.5 ±5.8*
HbA1c	-0.3 ±0.1*	-0.3 ±0.1*

All values are presented as Least Square Mean (LSM) ± Standard Error (SE) of Per Protocol (PP) population,
*Statistically significant change as compared to the baseline
#Statistically significant change as compared to Pioglitazone,
^ FPG values presented as Mean ± SE of PP population

When compared to Pioglitazone, Lipaglyn™ 4 mg achieved the ATP III goal in more subjects as depicted in Table 2.

Table 15.2: Percentage of patients achieving ATP III Goal following Lipaglyn™ 4 mg treatment as compared to Pioglitazone		
ATP Goal*	**Lipaglyn™ 4 mg (%)**	**Pioglitazone 45 mg (%)**
Not achieved even one criteria	29.4	50.0
Achieved one criteria	26.5	22.7
Achieved two criteria	35.3	27.3
Achieved all three criteria	8.8	0.0

* ATP – Adult Treatment Panel III of US National Cholesterol Educational Program, 2002-2003,
Male : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 40 mg/dl,
Female : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 50 mg/dl

In another study, the effect of Lipaglyn™ at 4 mg per day was assessed in diabetic patients with hypertriglyceridemia not controlled with Atorvastatin 10 mg therapy. The patients were treated with Lipaglyn™ 4 mg or placebo for 12 weeks along with Atorvastatin 10 mg. The results are presented in Table 3 below:

Table 15.3: Percent change in lipid and glycemic parameters following Lipaglyn™ 4 mg treatment		
Time point	**Week 6**	**Week 12**
TG	-46.4 ±3.1*#	-47.2 ±3.2*#
TC	-23.6 ±1.9*	-25.8 ±1.8*#
LDL-C	-28.1 ±2.5*	-30.7 ±2.4*#
VLDL-C	-45.1 ±3.3*#	-46.5 ±3.2*#
HDL-C	8.3 ±2.8	8.1 ±2.5#
ApoA 1	8.1 ±3.2	9.2 ±4.5
ApoB	-29.1 ±2.4*	-32.1 ±2.3*#
FPG	-14.9 ±3.7*#	-10.5 ±4.2*#

All values are presented as LSM ± SE of PP population,
*Statistically significant change as compared to the baseline,
#Statistically significant change as compared to the placebo

In combination with Atorvastatin, Lipaglyn™ achieved the ATP-III goal in more subjects than Atorvastatin alone; hence demonstrating better cardiovascular risk reduction. (Table 4)

Table 15.4: Percentage of patients achieving ATP Goal following Lipaglyn™ 4 mg treatment as compared to placebo in combination with atorvastatin		
ATP Goal*	**Lipaglyn™ 4 mg + Atorvastatin 10 mg (%)**	**Placebo + Atorvastatin 10 mg (%)**
Not achieved even one criteria	10.3#	30.1
Achieved one criteria	30.8	38.6
Achieved two criteria	43.6	24.1
Achieved all three criteria	15.4	6.0

* Male : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 40 mg/dl
Female : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 50 mg/dl
significantly different from placebo + Atorvastatin 10 mg

Lipaglyn™ has also shown a decrease in TG, LDL, VLDL, non-HDL cholesterol and TC with an increase in HDL in non-diabetic patients.

There was no incidence of hypoglycemia reported during Phase I-III trials in both diabetic and non-diabetic subjects.

12.3 Human Pharmacokinetics

The single dose pharmacokinetics of Lipaglyn™ was assessed across the dose range of 0.125 to 128 mg.

12.3.1 Absorption

Following oral administration in healthy volunteers, peak plasma levels of saroglitazar occurred at approximately 1 hour post-dosing in both the genders.

Maximum plasma concentration (C_{max}) and area under the curve ($AUC_{0-\infty}$) of saroglitazar increased proportionally with the administered single doses of 0.125 mg - 128 mg per day. After single oral dose of Lipaglyn™ 4 mg in healthy volunteers, Cmax of 337.1 ± 91.0 ng/ml (Mean ± SD, n=6) was observed.

Pooled analysis of male and female healthy volunteers showed no gender effect or food effect on pharmacokinetics of saroglitazar.

12.3.2 Distribution

The mean apparent oral volume of distribution (Vd/F) of saroglitazar following single-dose administration of Lipaglyn™ 4 mg was 20.14 ± 6.92 L. *In vitro* saroglitazar is extensively protein bound (~96%) in human plasma. The mean plasma half-life of saroglitazar following single dose administration of Lipaglyn™ 4 mg is 2.9 ± 0.9 hours. Multiple-dose studies in humans have shown that saroglitazar does not undergo accumulation on repeat dosing once daily for 10 days.

12.3.3 Metabolism

In healthy volunteers, Lipaglyn™ 4 mg has an apparent oral clearance, CL/F, calculated to be 4.8 ± 0.93 L/hr.

In vitro studies using pooled human liver microsomes showed that saroglitazar is metabolically stable.

Following Lipaglyn™ 4 mg administration, saroglitazar was found to be metabolized into three minor oxidative metabolites. The exposure of the most abundant oxidative metabolite was found to be less than 10% of the exposure of saroglitazar.

12.3.4 Excretion

In healthy volunteers, saroglitazar was not excreted in the urine indicating that it has non-renal route of elimination.

Preclinical studies have shown that saroglitazar is predominantly eliminated unchanged by the hepatobiliary route.

13. Non clinical toxicology

13.1 Acute and Chronic Toxicity Studies

Various acute and chronic toxicity studies were performed in mice, rats and dogs up to a duration of 12 months. In acute dose studies, the maximum tolerated dose (MTD) in Swiss albino mice was 500 mg/kg, and in Wistar rat it was 1200 mg/kg. Safety pharmacology studies did not reveal any adverse changes in CNS, CVS, respiratory and gastrointestinal parameters. In repeat dose toxicity studies, saroglitazar was shown to have an acceptable safety profile at doses several-fold higher than the approved human doses. At high doses, the toxic effects observed were mainly the exaggerated pharmacological effects mediated by PPAR mechanisms.

13.2 Impairment of Fertility

Saroglitazar did not show any adverse effects on mating or fertility in male rats up to 125 mg/kg (more than 250 times the approved human dose on body surface area basis). In female rats no adverse effects on fertility were observed up to 3 mg/kg (7 times the approved human dose on body surface area basis). Saroglitazar altered the estrus cyclicity and litter indices at 15 mg/kg which is 35 times the human recommended dose.

During pre- and post-natal developmental study in rats, saroglitazar did not show any adverse effects on reproductive performance and lactating indices up to 1 mg/kg which is more than the human therapeutic dose.

13.3 Carcinogenicity

Two-year carcinogenicity study of saroglitazar was conducted in Wistar rats. No potential carcinogenic concern for humans was identified, which was further confirmed by a mechanistic study in non-human primates employing molecular biomarkers.

13.4 Mutagenicity

Saroglitazar was found to be non-mutagenic and non-genotoxic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity test, chromosomal aberration assay using the peripheral human blood lymphocytes and the mouse micronucleus assay.

14. How supplied

Lipaglyn™ is supplied as uncoated round biconvex tablets with "4" written on one side and plain on the other side. Available as 4 mg strength.

Lipaglyn™ tablets are supplied as 10 tablets in an alu-alu blister. Each blister is packed in a mono-carton.

15. Storage and handling instructions

Store below 25°C and in dry place. Protect from light. Keep out of reach of children.

16. Manufactured by

CADILA HEALTHCARE LIMITED, Sarkhej-Bavla National Highway No. 8A, Moraiya, Tal.: Sanand, Dist.: Ahmedabad - 382 210, Gujarat.

17. Marketed by

Zydus Discovery

(A division of Cadila Healthcare Limited)

Lipaglyn™
Saroglitazar

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17. Abbreviations

NCD	Non Communicable Disease
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
CHD	Coronary Heart Disease
MI	Myocardial Infarction
IDF	International Diabetes Foundation
T2DM	Type 2 Diabetes Mellitus
DD	Diabetic Dyslipidemia
VLDL-C	Very Low Density Lipoprotein-Cholesterol
HDL-C	High Density Lipoprotein- Cholesterol
TG	Triglycerides
LDL-C	Low Density Lipoprotein-Cholesterol
sd-LDL-C	small-dense Low Density Lipoprotein-Cholesterol
ADD	Atherogenic Diabetic Dyslipidemia
CAD	Coronary Artery Disease
HTN	Hypertension
TC	Total Cholesterol
IHD	Ischemic Heart Disease
CV	Cardiovascular
NCEP ATP III	National Cholesterol Education Program - Adult Treatment Panel III
Non-HDL-C	Non-High Density Lipoprotein-Cholesterol
HPS	Heart Protection Study
CARDS	Collaborative Atorvastatin Diabetes Study
CK/CPK	Creatine Kinase/Creatine Phosphokinase
US FDA	United States Food and Drug Administration
PPAR-α	Peroxisome Proliferator-Activated Receptors - Alpha
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
ACCORD	Action to Control Cardiovascular Risk in Diabetes
AE	Adverse Effects
GI	Gastrointestinal
APCSC	The Asia Pacific Cohort Studies Collaboration
CM	Chylomicron
CMRs	Chylomicron Remnants
ApoB	Apoprotein B

HSL	Hormone-Sensitive Lipase
FFA	Free Fatty Acids
FA	Fatty Acid
BAS	Bile Acid Sequestrants
PPAR-γ	Peroxisome Proliferator-Activated Receptors – Gamma
TZD	Thiazolidinediones
NCE	New Chemical Entity
FATP	Fatty Acid Transporter Protein
LPL	Lipoprotein Lipase
ApoC III	Apoprotein C III
Non-TZD	Non-Thiazolidinediones
HC	High Cholesterol
CNS	Central Nervous System
RS	Respiratory System
CVS	Cardiovascular System
PO	Per Oral
BP	Blood Pressure
HR	Heart Rate
ECG	Electrocardiogram
MTD	Maximum Tolerated Dose
PK	Pharmacokinetics
C_{max}	Concentration Maximum
T_{max}	Time Maximum
$t_{1/2}$	Plasma half life
AUC	Area Under Curve
SAE	Serious Adverse Events
FPG	Fasting Plasma Glucose
HbA1c	Glycosylated Hemoglobin
CRP	C-Reactive Protein
LFT	Liver Function Test
DILI	Drug Induced Liver Injury
RFT	Renal Function Test
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation

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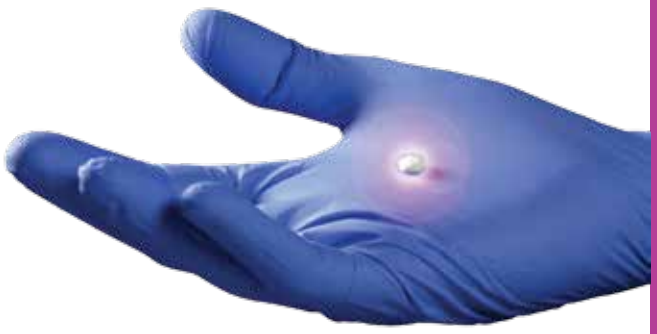

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