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Review

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Saroglitazar: A New Drug to Treat Diabetic Hypertriglyceridemia

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INTRODUCTION

Dyslipidemia alone has been considered as one of the major modifiable risk factor for cardiovascular diseases (CVD) accounting for 50% of the 1st myocardial infarction (MI) cases worldwide.[1] A recent epidemiological survey on prevalence of lipid abnormalities of the Indian population by Indian Council of Medical Research-India Diabetes Study (ICMR-INDIAB), has shown that 79% of Indian subjects above 20 years of age have abnormalities in at least one of the lipid parameters.[2] In this survey, the most commonly found lipid abnormality was low-high density lipoprotein cholesterol (low HDL-C) in 72% subjects followed by high triglycerides (TG) in 29.5% subjects and then high low-density lipoprotein cholesterol (LDL-C) in 11.8% subjects.[3] Prevalence of dyslipidemia is high in India, which calls for urgent lifestyle and pharmacological intervention strategies to prevent and manage this important cardiovascular risk factor.

Statins the 1st line therapy for dyslipidemia reduce not only LDL-C levels but also the risk of cardiovascular events in patients with or without cardiovascular disease.[4] Intensive statin therapy as compared with moderate-dose statin therapy incrementally lowers LDL cholesterol levels and rates of non-fatal cardiovascular events.[5] The magnitude of CVD risk reduction as a consequence of LDL-C lowering mostly ranges between 25% and 35%.[2] This statistically significant but clinically inadequate control of CVD risk is in part due to a lipid treatment focus on LDL-C alone with a resultant neglect of other important aspects of lipoprotein metabolism.[6] Statin therapy may not eliminate CVD Risk associated with low HDL and high triglycerides.[7,8] This review article focuses on elevated serum triglycerides (TG) and triglyceride rich lipoproteins as potential factors limiting further reduction in CVD events despite low on-treatment LDL-C.[9]

HYPERTRIGLYCERIDEMIA AS A CVD RISK FACTOR

Hypertriglyceridemia is a prevalent and independent risk factor for CVD and increasingly important in the setting of current coronary heart disease (CHD) and metabolic syndrome epidemics.[10] Increased CVD risk can be due to below mentioned consequences of hypertriglyceridemia (Table 1) .[11]

A recent 34-years follow-up study involving 75,725 participants from Copenhagen City Heart Study (CCHS) and Copenhagen General Population Study (CGPS), has shed light on the role of non-fasting TG levels as a risk factor for cardiovascular disease. Results of the study have shown that those with non-fasting TG levels ≤90 mg/dL (Hazard ratio 0.43, $p<0.001$) have approximately 60% reduction in the cardiovascular events as compared to those with non-fasting TG levels ≥350 mg/dL (Hazard ratio 1).[12]

Patients who have hypertriglyceridemia are at significant risk for CVD even if patients

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Triglyceride-rich lipoproteins carry cholesterol and promote atherosclerosis
Very low density lipoprotein (VLDL) is precursor to LDL-C
Hypertriglyceridemia drives Cholesterol esters enrichment of VLDL (more atherogenic) Decrease LDL-C size (small, dense LDL are more atherogenic) Decrease HDL-C size (small dense HDL are unstable)
Hypertriglyceridemia is linked to other pro-atherogenic states Insulin resistance Pro-oxidative state Pro-thrombotic state Endothelial dysfunction

Table 1: Consequences of high triglycerides causing increased CVD risk.[11]

are on statins and LDL-C levels are at goal.[11] PROVE IT-TIMI 22 trial, have shown reduced risk of CHD with low on-treatment TG (<150 mg/dL) and it was independent of the level of LDL-C. For each 10 mg/dL decline in on treatment TG, there was a 1.6% lower risk of the composite end point (p<0.001) after adjustment for LDL-C and other covariates. Moreover, the combination of low LDL-C (<70 mg/dL) and low TG (<150 mg/dL) was associated with the lowest event rates compared with higher LDL-C, higher TG, or both.[13]

In year 2015, a study analyzed the results of 2 trials, dal-OUTCOME and MIRACL, to predict effect of fasting TGs on recurrent ischemic events in acute coronary syndrome (ACS) patients on statins. Results showed that high TG (>175 mg/dL on long-term and >195 mg/dL on short-term) in spite of statin therapy in post-acute coronary syndrome (ACS) patients leads to 60% (Hazard ratio 1.6) and 50% (Hazard ratio 1.5) higher cardiovascular risk compared to those with lower TG (≤ 80 mg/dL on long-term and ≤135/dL on short-term) respectively.[14] This relationship of triglycerides to CVD risk was independent of LDL-C in both studies. This study suggests the association of triglycerides with both long-term and short-term risk after ACS despite optimal statin therapy.[14]

Statin therapy alone doesn't eliminate CVD risk (residual risk) associated with high triglycerides, therefore triglyceride-rich lipoproteins may be an important additional target for therapy. In a meta-analysis of 5 landmark studies (ACCORD, FIELD, BIP, VA-HIT and HHS) involving 4726 T2DM patients, PPAR-α agonists have been found to reduced cardiovascular events significantly by 35% in patients with high TG≥204 mg/dL and low HDL-C≤34 mg/dL.[15] The latest American Association of Clinical Endocrinology (AACE 2016) dyslipidemia guidelines in diabetes also recommends a non-HDLC calculation rather than LDL-C calculation alone when TG is above 200 mg/dL but less than 500 mg/dL for better risk assessment. The AACE diabetes guidelines suggest that non-HDL-C goal is to be achieved with TG lowering therapy after achievement of desirable LDL-C level.[16] Recent lipid guidelines by Lipid Association of India (LAI) have also recommended use of non-statin therapy when serum TG levels remain persistently elevated (>200 mg/dL) despite optimum dose of statins.[17] Very recently published European Society of Cardiology (ESC) guidelines on dyslipidemia suggest that non-fasting TGs may carry information regarding remnant lipoproteins associated with increased risk. Therefore for general screening and risk evaluation, non-fasting TGs should be used. Drug treatment should be considered in high-risk patients with TG >200 mg/dL with statins or triglyceride lowering therapies.[18]

NEWER CONCEPT- DUAL PPAR α/γ AGONIST

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. There are 3 PPARs subtypes which are commonly designated PPAR alpha, PPAR gamma and PPAR β/δ. PPAR α activation increases high density lipoprotein cholesterol synthesis, stimulates "reverse" cholesterol transport and reduces triglycerides. PPAR γ activation results in insulin sensitization and antidiabetic action. Combined treatments with PPAR γ and α agonists may potentially improve insulin resistance and alleviate atherogenic dyslipidemia, whereas PPAR δ properties may prevent the development of overweight which typically accompanies "pure" PPAR γ ligands. The new generation of dual-action PPARs offer a hope of a new approach to diabetes care addressing not just glycemia, but dyslipidemia and other components of the metabolic syndrome.[19]

Saroglitazar is a novel dual PPAR α/γ agonist, non-thiazolidinediones (TZD) and non-fibric acid derivative, with a predominant PPAR α agonistic activity. It is a glitazar approved by Drug Controller General of India (DCGI) and has been found to have an excellent pre-clinical and clinical safety profile together with a higher efficacy in optimizing lipid and glycemic targets.[20,21]

EFFICACY AND SAFETY STUDIES OF SAROGLITAZAR

Saroglitazar was designed in the year 2001 following which it was extensively evaluated in various preclinical and clinical trials for 12 years following which it was finally approved in 2013 for marketing in India in patients suffering from diabetic dyslipidemia and hypertriglyceridemia in type 2 diabetic patients not controlled by statins alone.

Preclinical Studies

Saroglitazar has been extensively profiled for efficacy and safety

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in various diabetic and non-diabetic animal models of dyslipidemia. It showed a dose dependent reduction in triglyceride (TG) levels of up to 90%, improved lipid clearance and reduced post meal serum cholesterol levels. In diabetic and insulin resistant animal models, saroglitazar showed a dose dependent reduction in serum glucose (upto 65%) and insulin levels upto 91% oral glucose tolerance test (OGTT). The euglycemic clamp study also showed that the glucose infusion rate required to maintain the blood glucose concentrations in steady state was significantly higher in the saroglitazar treated Zucker (fa/fa) rats than in the controls indicating saroglitazar led to increase in insulin sensitivity. Safety studies on non-human primates and rodents did not lead to any significant change in behavioral, clinical, laboratory parameters or body weight. At doses equivalent to 66 fold higher than the human exposure dose, PPAR γ mediated effects such as reduction in hematocrit and increase in body weight were noted. It is non-genotoxic and non-teratogenic and had passed the 2-year carcinogenicity study in rodents. Preclinical studies have shown that saroglitazar is mainly eliminated by the enterohepatic route.[22]

Clinical Evidences

The phase I (randomized, double-blind, placebo-controlled) clinical study done to establish the safety and pharmacokinetics of Saroglitazar revealed that it is a safe medicine with favorable pharmacokinetics. Highest dose of 128 mg saroglitazar, several times the estimated therapeutic doses (1-4 mg) was evaluated and was found to be safe and well tolerated. Pooled analysis of male and female volunteers showed no gender or food effect on pharmacokinetics of Saroglitazar. No serious adverse events, significant alterations in clinical or lab parameters or alterations in ECG findings were noted. Saroglitazar was well absorbed through oral route with alinear kinetics and median time to the peak plasma concentration (tmax) of less than 1 hr. Multiple-dose studies in humans have shown that it does not undergo accumulation on repeat dosing. The elimination and mean plasma half-lives are 5.6 hours and 2.9±0.9 hours respectively. It has non-renal route of elimination and is predominantly eliminated unchanged by the hepatobiliary route. Since kidney function is compromised in the advanced stage of T2DM, a non-renal route of elimination may be beneficial. Saroglitazar dose adjustment may not be required in such patients. The pharmacokinetics (refer Table 2) of saroglitazar is supportive of once daily dosing for this class.[23]

In a phase III randomized, multicenter, prospective double-blind clinical trial (PRESS V) prospective randomized efficacy and safety of saroglitazar V), saroglitazar 4 mg once daily reduced plasma triglyceride by 45% ($p<0.001$) compared to pioglitazone which reduced TGs by 15.5% at end of 24 weeks. It also demonstrated marked decrease in very-low-density lipoprotein (45.5%), total cholesterol (7.7%), low-density lipoprotein (5%) and apolipoprotein-B (10.9%). The study revealed there were statistically significant absolute reduction of 0.3% and 0.4% in HbA1c in saroglitazar 4 mg and pioglitazone arm respectively. The safety analysis revealed that there was a 0.1 kg decrease in weight in saroglitazar 4 mg arm compared to 1.6 kg increase in weight in pioglitazone arm. Saroglitazar 4 mg was better in reducing lipids and as efficacious as pioglitazone in reducing HbA1c without increase in bodyweight.[24]

Another study PRESS VI, a randomized prospective, multicenter, double-blind, placebo controlled, 3 arm study was carried out for 16 weeks in subjects with hypertriglyceridemia (>200 and <500 mg/dL) with T2DM not controlled with atorvastatin 10 mg. In short, the study consisted of a run in period of 4 weeks with lifestyle modification followed by 12 weeks of treatment with saroglitazar 2 mg or 4 mg *versus* placebo. At the end of 12 weeks, subjects treated with saroglitazar 2 mg and 4 mg tablets had shown significant reduction in mean plasma TG levels by around 46.7% compared to placebo. Moreover, saroglitazar 2 mg had shown a significant decrease in levels of non-HDL-C (32.5%), LDL-C (31.3%), Apo-B (32%), total cholesterol (26.1%). HDL-C levels improved significantly by 7.6%. Additionally, saroglitazar 4 mg also significantly reduced fasting plasma glucose levels by 25.4 mg/dL as compared to just 2 mg/dL fall in comparator group (Figure 1).[25]

CLINICAL SAFETY/ADVERSE EVENTS WITH SAROGLITAZAR

During the clinical trials (PRESS V and VI), all patients on saroglitazar were evaluated for renal, liver, muscle, cardiac functions at baseline, while on treatment and at end of study. Saroglitazar was well tolerated over the course of clinical trials and no significant changes were observed in these parameters. 2D echo and ECG findings before and after saroglitazar treatment and during the follow-up period did not reveal any alteration in cardiac function. Edema, weight gain, bone changes, and muscle pain were also not reported. The most common adverse events

- Good Oral Bioavailability
- $T_{1/2}$ of about 3-4 hrs
- Pharmacokinetics (C_{max}, AUC) are dose dependent and linear.
- No potential for CYP-mediated drug-drug interactions
- Eliminated by non-renal route
- Mainly eliminated by hepato-biliary route
- Lipaglyn up to 128 mg once orally was well tolerated

Table 2: Pharmacokinetics of saroglitazar.

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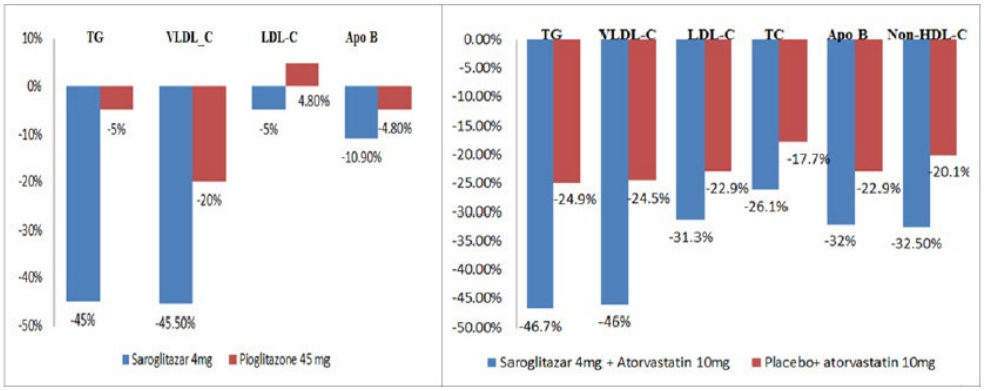

Figure 1: Graphical presentation of effect of saroglitazar on lipids in PRESS V and VI.

(AEs≥2%) reported were gastritis, asthenia and pyrexia which were mild to moderate in nature and did not result in discontinuation of the drug (Table 3).

Saroglitazar has completed almost 12 years of preclinical and clinical evaluation journey successfully without raising any alarm of toxicity and is approved since September 2013 for clinical use in diabetic dyslipidemia and hypertriglyceridemia not controlled by statins alone. The recommended dose of saroglitazar is 4 mg once daily orally.

POST-MARKETING SURVEILLANCE EVIDENCES OF EFFICACY AND SAFETY (PHASE IV STUDIES)

An observational, multicenter, post-marketing study (phase IV) involving 2804 subjects by Shetty R et al[26] revealed that saroglitazar in addition to oral antidiabetic medication (at outpatient clinics) showed significant improvement in all lipid and glycemic parameters at 3 month follow-up. The mean baseline TG was 312.3 mg/dL *vs.* 188.7 mg/dL at 3 month follow-up, a significant reduction of 35.8% (mean of % change from baseline). Non-HDLC levels also reported a significant 23.4% mean reduction at 3 month follow-up. A statistically significant improvement in all other lipid parameters was also noted (a mean reduction of 16.4% in LDL-C levels, 31.5% in VLDL-C levels, 19% in total cholesterol levels and mean increase of 7.3% in HDL-C levels). Analysis of glycemic parameters revealed a statistically significant 0.9% absolute reduction in glycated hemoglobin (HbA1c) from baseline value of 8.3% to 7.4% at 3 month follow-up. There were no serious adverse events or weight gain reported in study.

Saroglitazar has been presented at various International platforms, recently 2 years post-marketing surveillance data of saroglitazar was presented at American Diabetic Association (ADA) conference, 2016. According to the data presented in ADA 2016, 2 years use of saroglitazar in diabetic patients with high triglycerides showed a significant 41% reduction in TGs. Other lipid parameters like non-HDL-C and LDL-C also reduced significantly by 28% and 12% respectively. There was significant improvement in glycemic parameters as well (HbA1c reduced by 0.7%) and it was concluded that 2 years treatment with saroglitazar is effective, safe, well tolerated and is not associated with edema, weight gain or any other serious adverse event.[27]

CONCLUSION

Because of the different ethnicity of Indians, atherogenic dyslipidemia is highly prevalent in the Indian population which comprises of high concentrations of TGs, low concentrations of HDL-C, and moderate increase in LDL-C, with an increased

Phase 3 RCTs	Saroglitazar 2 mg (%)	Saroglitazar 2 mg +Atorvastatin 10 mg (%)	Saroglitazar 4 mg (%)	Saroglitazar 4 mg +Atorvastatin 10 mg (%)	Pioglitazone 45 mg (%)	Placebo +Atorvastatin 10 mg (%)
Peripheral edema	2.4	-	0	-	5	-
Asthema	2.4	-	7.3	-	2.5	-
Gastritis	0	1	4.9	4.0	5	1
Chest Discomfort	2.4	0	2.4	1.0	2.5	2.0
Dizziness	2.4	-	2.4	-	2.5	-
Tremors	2.4	-	2.4	-	2.5	-
Pain	0	0	-	2.0	-	1
Pyrexia	-	3	-	1.0	-	0.0
Dyspepsia	-	2	-	0.0	0.0	0.0

Table 3: The list of adverse events reported PRESS V and VI.[24,25]

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concentration of small, dense, and potentially more atherogenic particles. There is a growing support for unadjusted elevated triglyceride levels as an independent CVD risk factor and control of hypertriglyceridemia has now become equally vital in reducing the CVD events. The drugs available for the current management of hypertriglyceridemia in T2DM have their own specific limitations. Therefore, in the management of AD, many unmet needs still exist and a significant residual CVD risk prevails despite the current optimal therapy. A dual PPAR α/γ agonist, by reducing both the TG & insulin resistance with a favorable safety profile could provide an optimal lipid and glycemic targets. Saroglitazar (a dual PPAR α/γ agonist) is the first glitazar class compound that has been approved as a therapeutic agent for the comprehensive management of atherogenic diabetic dyslipidemia or hypertriglyceridemia in diabetes not controlled by statins alone. The broad range of lipid improvements associated with saroglitazar addresses the pattern of dyslipidemia commonly seen in Indians. Additionally, by improving the insulin sensitivity, saroglitazar provides an optimal glycemic control also. It is novel as it is the first in its class approved anywhere in the world, with superior efficacy in reducing TG and non-HDL-C and a dual action of controlling both dyslipidemia and hyperglycemia. However, In spite of proven therapeutic benefits, large outcome study of saroglitazar showing long-term therapeutic efficacy and safety is required.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study). *Lancet.* 2004; 364: 937-952. doi: 10.1016/S0140-6736(04)17018-9

2. La Rosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *JAMA*. 1999; 282: 2340-2346. Web site. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.596.2772&rep=rep1&type=pdf. Accessed October 4, 2016.

3. Joshi SR, Anjana RM, Deepa M, et al. Prevalence of dyslipidemia in urban and rural India: The ICMR–INDIAB Study. *PLOS ONE.* 2014; 9(5): e96808. doi: 10.1371/journal.pone.0096808

4. Baigent C, Keech A, Kearney PM, et al. Cholesterol treatment trialists (CTT) collaborators. Efficacy and safety of cholesterol lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet.* 2005; 366: 1267-1278. doi: 10.1016/S0140-6736(05)67394-1

5. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *Journal of the American College of Cardiology*. 2006; 483: 438-445.

6. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004; 350: 1495-1504. doi: 10.1056/NEJMoa040583

7. Adapted from HPS Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: A randomized placebo-controlled trial. *Lancet.* 2002; 360: 7-22.

8. Sacks FM, Tonkin AM, Shepherd J, et al. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors, the prospective pravastatin pooling project. *Circulation.* 2000; 102: 1893-900. doi: 10.1161/01.CIR.102.16.1893

9. Miller M. Current perspectives on the management of hypertriglyceridemia. *Am Heart J.* 2000; 140: 232-240. doi: 10.1067/mhj.2000.108001

10. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol.* 1998; 81: 7B-12B. doi: 10.1016/S0002-9149(98)00031-9

11. Miller M. Is hypertriglyceridaemia an independent risk factor for coronary heart disease? The epidemiological evidence. *Eur Heart J*. 1998; 19 (Suppl H): H18-H22. Web site. http://europepmc.org/abstract/med/9717060. Accessed October 4, 2016.

12. Jørgensen A, Frikke-Schmidt R, Nordestgaard B. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med*. 2014; 371: 32-41. doi: 10.1056/NEJMoa1308027

13. Miller M, Cannon CP, Murphy SA, et al. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol.* 2008; 724-730. doi: 10.1016/j.jacc.2007.10.038

14. Schwartz G, Abt M, Bao W, et al. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. *J Am Coll Cardiol.* 2015; 65(21): 2267-2275. doi: 10.1016/j.jacc.2015.03.544

15. Sacks FM, Carey VJ, Fruchart JC. Combination lipid therapy in type 2 diabetes. *N Engl J Med*. 2010; 363(7): 692-694. doi: 10.1056/NEJMc1006407

16. Garber A, Abrahamson M, Barzilay J, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm–2016 Executive Summary. *Endocr Pract*. 2016; 22: 84-113. doi: 10.4158/EP151126.CS

ISSN 2377-164X http://dx.doi.org/10.17140/HROJ-4-135

17. Iyengar S, Puri R, Narasingan SN. Lipid association of India expert consensus statement on management of dyslipidemia in Indians 2016, Part 1. *J Assoc Physicians India*. 2016; 7-52.

18. Reiner Ž, Catapano AL, de Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias. *European Heart Journal.* doi: 10.1093/eurheartj/ehr158

19. Fredenrich A, Grimaldi PA. PPAR delta. An uncompletely known nuclear receptor. *Diabetes Metab.* 2005; 31: 23-27. doi: 10.1016/S1262-3636(07)70162-3

20. Munigoti SP, Harinarayan CV. Role of glitazars in atherogenic dyslipidemia and diabetes: Two birds with one stone. *Indian J Endocrinol Metab*. 2014; 18(3): 283-287. doi: 10.4103/2230-8210.131134

21. Jani H, Kansagra K, Jain MR, Patel H. Pharmacokinetics, safety, and tolerability of saroglitazar (ZYH1), a predominantly PPARα agonist with moderate PPARγ agonist activity in healthy human subjects. *Clin Drug Investig.* 2013; 33(11): 809-816. doi: 10.1007/s40261-013-0128-3

22. Jain M, Giri S, Trivedi C, et al. Saroglitazar, a novel PPAR α/γ agonist with predominant PPAR α activity, shows lipid-lowering and insulin-sensitizing effects in preclinical models. *Pharmacol Res Perspect.* 2015; 3(3): e00136. doi: 10.1002/prp2.136

23. Jani RH, Kansagra K, Jain MR, Patel H. Pharmacokinetics, safety, and tolerability of saroglitazar (ZYH1), a predominantly PPARα agonist with moderate PPARγ agonist activity in healthy human subjects. *Clin Drug Investig*. 2013; 33(11): 809-816. doi: 10.1007/s40261-013-0128-3

24. Pai V, Paneerselvam A, Mukhopadhyay S, et al. A Multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of saroglitazar 2 and 4 mg compared to pioglitazone 45 mg in diabetic dyslipidemia (PRESS V). *J Diabetes Sci Technol*. 2014; 8(1):132-141. doi: 10.1177/1932296813518680

25. Jani R, Pai V, Jha P, et al. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of saroglitazar 2 and 4 mg compared with placebo in type 2 diabetes mellitus patients having hypertriglyceridemia not controlled with atorvastatin therapy (PRESS VI). *Diabetes Technology & Therapeutics.* 2014; 16(2): 63-71. doi: 10.1089/dia.2013.0253

26. Shetty S, Kumar S, Mathur R, Sharma K, Jaiswal A. Observational study to evaluate the safety and efficacy of saroglitazar in Indian diabetic dyslipidemia patients. *Indian Heart Journal*. 2015; 67(1): 23-26. doi: 10.1016/j.ihj.2015.02.007

27. Joshi S, Sound R, Saboo B. Efficacy and Safety of Saroglitazar in Indian Diabetics-two year data. Adapted from ADA 2016; Poster no: 40-LB: http://www.prnewswire.com/news-releases/new-scientific-data-of-investigational-lipaglyntm-saroglitazar-and-real-world-data-in-patients-will-be-featured-at-american-diabetes-association-ada-76th-scientific-sessions-582573961.html. Accessed October 4, 2016.