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# Effectiveness of the PPAR Agonist Saroglitazar in Nonalcoholic Steatohepatitis: Positive Data from Preclinical and Clinical Studies

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## Abstract

**Background:** Saroglitazar, a novel Peroxisome Proliferator-Activated Receptor (PPAR) α/γ agonist, was evaluated in preclinical and clinical studies to evaluate its effectiveness in NASH.

**Methods:** Preclinical studies included: (a) Choline Deficient L-amino Acid-defined High Fat Diet (CDAHFD) murine NASH model; (b) Long Evans and Wistar rats model for hepatotropic activity; (c) DIAMOND™ NASH mice model. Clinical studies included: Phase 2 and Phase 3 studies in patients with biopsy proven NASH in India.

**Results:** In CDAHFD murine NASH model, Saroglitazar improved aspartate aminotransferase (AST), Alanine Aminotransferase (ALT) and prevented hepatocellular steatosis, hepatocyte ballooning and lobular inflammation. In Long Evans and Wistarrats model, Saroglitazar was found to be hepatotropic. In the DIAMOND™ NASH mice model, Saroglitazar showed a systemic effect with resolution of steatohepatitis and improvement in all the key histological features of NASH, dyslipidemia and insulin sensitivity. In the phase 2 study, Saroglitazar 4 mg significantly reduced ALT levels (U/L) from baseline (95.86 ± 37.65) to week 12 (44.37 ± 35.43). In the phase 3 study, there was a significantly higher proportion of patients with decrease in NAS ≥ 2 spread across at least 2 of the NAS components without worsening of fibrosis at week 52 in Saroglitazar 4 mg group (52.3%) compared to placebo group (23.5%) (p value-0.0427), achieving the primary efficacy endpoint. In the phase 3 study, there were no concerns with the safety profile of Saroglitazar.

**Conclusion:** Positive results from the preclinical and clinical studies provide evidence for the effectiveness of Saroglitazar in the treatment of NASH.

**Keywords:** NASH• NAFLD• Saroglitazar• PPAR agonist

## Introduction

Nonalcoholic Steatohepatitis (NASH) is the most severe form of Nonalcoholic Fatty Liver Disease (NAFLD) and is associated with a high risk of progression to NASH related cirrhosis and NASH related hepatocellular carcinoma. NASH is considered as the hepatic component of the metabolic syndrome, which is a clinical syndrome characterized by obesity, dyslipidemia, Type 2 Diabetes Mellitus (T2DM), and hypertension. Patients with NASH are at risk not only for the liver-related morbidity and mortality but also at a higher risk of morbidity and mortality due to Cardiovascular Diseases (CVDs) [1-3].

Histologically, NASH is defined as steatosis and inflammation associated with the presence of one of the three additional features: mallory hyaline, ballooning of hepatocytes, and fibrosis.NASH mainly develops due to excess adiposity and systemic insulin resistance.The pathogenesis of NASH initiates with increased delivery of Free Fatty Acids (FFA), carbohydrates, inflammatory cytokines and gut-microbiome-derived products such as endotoxin to the liver [4]. This leads toan overloading of the hepatocellular metabolic machinery, which results in accumulation of lipids (mainly triglycerides) and induces cell stress that can trigger inflammatory and apoptotic signalling. Further, inflammation leads to fibrogenic remodelling, which progresses to cirrhosis.

Peroxisome Proliferator-Activated Receptors (PPARs) are ligand-activated transcription factors involved in the transcriptional regulation of glucose homeostasis, lipid metabolism, inflammation, atherosclerosis, and energy balance. PPAR agonists have the potential for treatment of NASH as they could act at various targets involved in the pathogenesis of NASH [5].

Saroglitazar is a dual PPAR alpha/gamma (PPAR α/γ) agonist (predominant PPAR-α and moderate PPAR-γ). Through its PPAR-α agonist action, Saroglitazar increases lipoprotein lipase activity and thereby reduces serum triglyceride levels and Very Low-Density Lipoprotein Cholesterol (VLDL-C) levels, and increases High-Density Lipoprotein Cholesterol (HDL-C) levels. Saroglitazar, through its PPAR-γ agonist action, improves insulin sensitivity in peripheral tissues, increases glucose uptake and reduces blood glucose levels [6-7]. Overall, Saroglitazar improves lipid and glycemic profiles without significant increase in body weight and edema/fluid retention (commonly seen in PPAR-γ agonists such as thiazolidinediones).

Saroglitazar has the potential to provide therapeutic benefit all along the pathologic spectrum of insulin resistance, diabetic dyslipidemia, T2DM, NAFLD and NASH.Clinical development has been completed in many of these indications and Saroglitazar has received marketing approval in a few countries [8].

Diabetic dyslipidemia was the first indication for which clinical development was completed and in clinical studies completed in India, Saroglitazar improved dyslipidemia by reducing triglyceride, total cholesterol, Low-Density Lipoprotein Cholesterol (LDL-C), VLDL-C, non HDL-C and increasing HDL-C and improved glycemic indices by reducing Fasting Plasma Glucose (FPG) and Glycosylated Hemoglobin (HbA1c). Subsequent to the completion of the randomized controlled studies and marketing approval, numerous investigator initiated studies were performed across India leading to a considerable data of real world evidence.[9] In an integrated analysis of real world clinical studies, which included 18 such studies, involving about 5,800 patients, effects of Saroglitazar on lipid and glycemic parameters in patients with diabetic dyslipidemia were analysed.

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Saroglitazar effectively improved lipid and glycemic parameters in patients with diabetic dyslipidemia from 12 weeks upto to 58 weeks of therapy in different IIT's. Across these studies it reduced mean triglyceride levels by 45%-62%, LDL-C levels by 11%-27%, total cholesterol levels by 17%-26%, non-HDL-C levels by 21%-36%, HbA1c levels by 0.7%-1.6%, and increased mean HDL-C levels (up to 9%) from baseline.It also reduced mean Alanine Aminotransferase(ALT) levels by 28%-67% in NAFLD patients with diabetic dyslipidemia. Saroglitazar use was not associated with significant change in body weight and significant Adverse Events (AEs)/cardiovascular AEs [10-11].

Saroglitazar is currently approved in India for treating "diabetic dyslipidemia and hypertriglyceridemia in T2DM not controlled by statin", "add-on therapy to metformin for treatment of T2DM", "non-cirrhotic NASH". In addition, Saroglitazar has been approved in Mexico, Burundi and Kenya for "diabetic dyslipidemia and hypertriglyceridemia with T2DM not controlled by statin" [12].

This article aims to discuss the efficacy of Saroglitazar in NASH in the pre-clinical animal models and the phase 2 and 3 clinical trials. We believe that such a comprehensive discussion of the pre-clinical efficacy and the clinical efficacy in the same article, in which the effect on the typical pathological features of NASH can be correlated and understood, will provide the scientific community a comprehensive and holistic understanding of the effect of Saroglitazar in NASH. All the data depicted and discussed in this article are 'data on file'. The pre-clinical DIAMOND mice model study results have been published in Scientific Reports (a nature research journal)/presented at the Liver Meeting, AASLD, and the USA (Abstract # 1297, 1768, and 1795). The data from the phase 2 clinical trial though not published anywhere as on original investigation, but was presented at the 5th Annual Meeting of EASLNAFLD Study Group 2017. The data from the phase 3 clinical trial has not been published anywhere as on original investigation, but wasaccepted as an oral presentation at the 29th Annual Conference of Asian Pacific Association for the Study of the Liver (APASL) at Bali, Indonesia [13-14].

## Materials and Methods

### Saroglitazar efficacy in NASH pre-clinical animal models

All the below mentioned pre-clinical animal model protocols were approved by Institutional Animal Ethics Committee of Zydus Research Centre, Cadila Healthcare Ltd.

### Choline deficient L-amino acid-defined high fat diet (CDAHFD) murine NASH model

In a murine NASH model, histological examination of liver tissue of mice fed with Choline Deficient L-amino Acid-defined High Fat Diet (CDAHFD) for 8 weeks revealed hepatocellular steatosis, hepatocyte ballooning, lobular inflammation and mild perisinusoidal or periportal fibrosis. Serum aspartate aminotransferase (AST) and ALT levels were also increased significantly along with increased serum levels of MCP-1, an inflammatory marker. Saroglitazar improved AST, ALT and other parameters (Table 1). Saroglitazar 3 mg/kg/ day completely prevented CDAHFD induced hepatocellular steatosis, hepatocyte ballooning and lobular inflammation.The mild hepatic fibrosis observed in CDAHFD-fed mice was reduced by Saroglitazar treatment, but the effect was not significant. Pioglitazone did not exhibit any improvement in hepatocellular steatosis, hepatocyte ballooning, lobular inflammation or fibrosis.

### Long evans and wistar rats model for assessing hepatotropic activity

In this animal model, Quantitative Whole Body Autoradiography (QWBA) was evaluated in male Long Evans (LE) and male Wistar Hanover (WH) rats. Following oral administration of C Saroglitazar at nominal dose of 4 mg/kg (approximately 200 µ Ci/kg radioactive dose) in the QWBA, the radioactivity persisted in the liver through the last sampling time of 168 hour post-dose in LE rats and 72 hour post-dose in WH rats, indicating that Saroglitazar is hepatotropic.

### Preclinical DIAMOND™ NASH mice model

In the preclinical DIAMOND™ NASH mice model, mice received chow diet and normal water (CDNW) or high fat western diet and ad lib sugar water (WDSW) and following 12 weeks, WDSW fed mice were randomized to receive: (a) WDSW alone; (b) WDSW+vehicle, (c) WDSW+Pioglitazone or (d) WDSW+Saroglitazar for 12 weeks duration.Laboratory indices, histology, metabolomics and molecular markers were studied.

### Fatty liver, steatohepatitis and fibrosis

Mice fed WDSW with vehicle control had developed grade 3 macro vesicular steatosis and somemicro vesicular steatosis. All WDSW mice had developed steatohepatitis. Pioglitazone reduced mean SAF activity to 2 (± 0.6) and mean NAS to 4.9 (± 0.7). Saroglitazar significantly reduced steatosis, lobular inflammation, and hepatocellular ballooning ($p<0.01$). In the Saroglitazar treated group, hepatocellular ballooning was absent in all mice, steatohepatitis was resolved in all the mice, 3 out of 12 mice had no histological evidence of NAFLD. Saroglitazar reduced mean NAS to 1.45 (± 0.9), which was significantly lower than that in the WDSW vehicle group. Saroglitazar reduced mean fibrosis stage to 0.54 and Pioglitazone reduced mean fibrosis stage to 0.6. Overall, the effects of Saroglitazar were superior to Pioglitazone histologically.

### Liver and lipid parameters

Saroglitazar had improved circulating cholesterol parameters and triglycerides compared to WDSW with or without vehicle control groups. WDSW controls had increased levels of serum ALT and AST, which were reduced significantly by Saroglitazar and Pioglitazone at comparable levels. Saroglitazar decreased TNF-$\alpha$ and increased circulating adiponectin compared to WDSW vehicle control.

### Diet-induced obesity and insulin resistance

DIAMOND mice fed with WDSW gained weight rapidly along with development of insulin resistance. Saroglitazar treatment for 12 weeks reduced the body weight, fasting insulin levels, and insulin resistance in DIAMOND mice. The degree of improvement with Saroglitazar was at par with Pioglitazone.

## Results

### Saroglitazar efficacy in clinical studies of NASH

Phase 2-NASH study of 12 weeks duration in India: In India, a phase 2 study of 12 weeks duration was conducted to evaluate the safety and efficacy of Saroglitazar 4 mg in 32 patients with biopsy proven NASH along with ALT>1.5 times the Upper Limit of Normal (ULN). This study was conducted from November 2010 to July 2012 at 10 centres in India. The study was conducted in compliance to Good Clinical Practice standards and was initiated after obtaining the approvals of the Drug Controller General of India (DCGI) and registering the study with Clinical Trial Registry of India (CTRI) (CTRI identifier: CTRI/2010/091/000108).

In this study Saroglitazar 4 mg significantly reduced ALT levels (U/L) from baseline (95.86 ± 37.65) to week 6 (52.79 ± 28.42) and week 12 (44.37 ± 35.43) (Table 2). In patients with baseline triglyceride ≥ 150 mg/dL, Saroglitazar 4 mg significantly reduced triglyceride (mg/dL) from baseline (247.15 ± 63.24) to week 12 (185.31 ± 72.01) (Table 2).

Safety: Overall, Saroglitazar 4 mg was safe and well tolerated. No deaths or Serious Adverse Events (SAEs) were reported during in the study. There were no persistent changes from baseline in any laboratory parameters and no statistically significant change observed in body weight following treatment with Saroglitazar 4 mg. Fiveevents of raised creatinine phosphokinase were reported during the study. These events were mild and none of these events were considered clinically significant by the investigator.

| Test (dose) | % Reduction in serum parameters versus CDAHFD vehicle control group | | | % Reduction in liver parameters versus CDAHFD vehicle control group | | |
|---|---|---|---|---|---|---|
| | ALT | AST | MCP-1 | TG | TC | Hydroxyproline |
| Saroglitazar Magnesium (0.3 mg/kg) | 57 | 46 | 53 | 39 | 70 | 15 |
| Saroglitazar Magnesium (1 mg/kg) | 46 | 40 | 43 | 74 | 88 | 49 |
| Saroglitazar Magnesium (3 mg/kg) | 63 | 57 | 54 | 62 | 83 | 48 |
| Pioglitazone (25 mg/kg) | 34 | 9 | 29 | 2 | -20 | -40 |

**Abbreviations:** CDAHFD: Choline Deficient L-Amino Acid-Defined High Fat Diet; NASH: Non-alcoholic Steatohepatitis; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; TG: Triglyceride; TC: Total Cholesterol.

**Table 1.** Effects of saroglitazar on Various Serum and Liver Biomarkers (VSLB) of NASH in preventive treatment protocol for 8 weeks in CDAHFD fed C57 mice.

| Variables | N | Baseline Mean± SD | Absolute change at week 6 from baseline LSM± SE | P- value | % change at week 6 from baseline LSM±SE | P- value | Absolute change at week 12 from baseline LSM± SE | P- value | % change At week 12 from baseline LSM± SE | P- value |
|---|---|---|---|---|---|---|---|---|---|---|
| Primary efficacy end point | | | | | | | | | | |
| ALT (U/L) | 30 | 94.64 ± 46.50 | -43.79 ± 3.84 | <.0001 | -40.56 ± 4.63 | <.0001 | -49.30 ± 5.04 | <.0001 | -49.36 ± 4.56 | <.0001 |
| Secondary efficacy end point | | | | | | | | | | |
| Triglyceride (mg/dL) <150 | 15 | 113.05 ± 25.81 | 28.25 ± 24.94 | 0.2794 | 35.36 ± 26.71 | 0.2102 | 13.79 ± 23.70 | 0.5706 | 11.44 ± 20.01 | 0.5774 |
| Triglyceride (mg/dL) ≥ 150 | 15 | 245.67 ± 61.35 | -50.03 ± 21.83 | 0.0392 | -17.41± 9.27 | 0.0831 | -75.88 ± 19.64 | 0.0026 | -28.46 ± 8.97 | 0.0089 |

**Abbreviations:** LSM:1east Square Mean; SD: Standard Deviation; SE:Standard Error; AT:Alanine Aminotransferase;
**Note:** N:Number of Subjects in the Treatment Group; P–Values <0.05 Indicates Significant and from ANCOVA Model; *= By applying dixon text, percent change of two patient were found to be an outlier and the percent change value were also>3 SD. So data were presented including and excluding these patients.

**Table 2.** Summary of efficacy endpoints in phase 2 study in India.

## Phase 3-NASH study of 52 weeks duration in India

In India, a phase 3, double-blind, randomized trial of 52 weeks was conducted to determine efficacy and safety of Saroglitazar 4 mg compared to placebo in 102 adult patients with biopsy proven NASH without cirrhosis (fibrosis stage 1, 2, or 3) with a NAFLD activity score (NAS) of ≥ 4 with a score of at least 1 in each component (steatosis, hepatocyte ballooning, lobular inflammation). This study was conducted from July 2016 to October 2019 at 10 centres in India. This study was initiated after obtaining the approvals of Institutional Ethics Committees (IECs), receiving the regulatory clearance from the Drugs Controller General of India (DCGI) and registering the study with Clinical Trial Registry of India (CTRI) (CTRI identifier: CTRI/2015/10/006236). The study was conducted in accordance with the ethical principles of Declaration of Helsinki, International Council for Harmonisation-Good Clinical Practice (ICH-GCP) guidelines, Indian Council of Medical Research's (ICMR) ethical guidelines for biomedical research on human participants, and other applicable regulatory agencies in India.

Primary efficacy endpoint: There was a significantly higher proportion of patients with decrease in NAS ≥ 2 spread across at least 2 of the NAS components without worsening of fibrosis at week 52 in Saroglitazar 4 mg group (52.3%) compared to placebo group (23.5%) (p-value-0.0427), achieving the study primary efficacy endpoint (Figure 1).

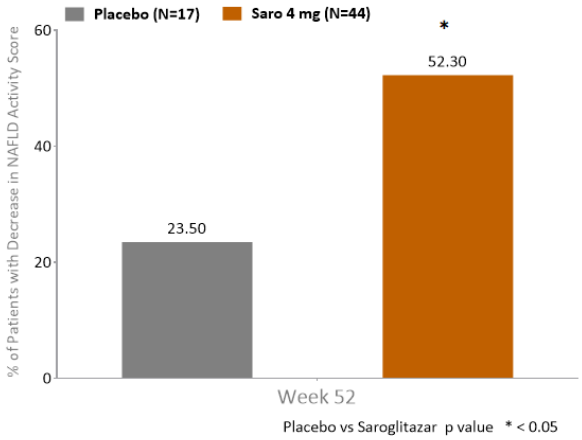



**Figure 1.** Primary efficacy endpoint in phase 3 clinical trial in India. Decrease in NAFLD activity score (NAS) ≥ 2 spread across at least 2 of the NAS components without worsening of fibrosis at week 52.

Secondary efficacy endpoints: Saroglitazar 4 mg significantly reduced mean score of NAS (%change from baseline:-34.66 ± 26.03; pvalue:<0.0001), mean score of steatosis (% change from baseline: -41.29 ± 52.02; pvalue:<0.0001), and mean score of hepatocyte ballooning (% change from baseline: -35.23 ± 42.56; pvalue:<0.0001) at week 52 (Table 3). Saroglitazar 4 mg reduced mean score of lobular inflammation (% change from baseline: 12.50 ± 47.16; pvalue:0.0526) at week 52 (Table 3). Saroglitazar 4 mg significantly reduced ALT (U/L) [% change from baseline: 27.79 ± 36.41; pvalue:<0.0001], AST (U/L) [% change from baseline: 18.10 ± 34.00; pvalue:<0.0001], ALP (U/L) [% change from baseline: 32.14 ± 19.22; pvalue:<0.0001], and GGT (U/L) [% change from baseline: 29.27 ± 37.13; pvalue:<0.0001] at week 52 (Table 3) (Figure 2). Saroglitazar 4 mg significantly reduced TG (mg/dL) [% change from baseline: 24.51 ± 31.93; pvalue:<0.0001], LDL-C (mg/dL) [% change from baseline: 8.68 ± 20.58; pvalue:<0.0001], sd LDL (mg/dL) [% change from baseline: 22.02 ± 40.19; pvalue:<0.0001], VLDL-C (mg/dL) [% change from baseline: 24.39 ± 32.01; pvalue:<0.0001], total cholesterol (mg/dL) [% change from baseline: 9.27 ± 15.77; pvalue:<0.0001], and non-HDL-C (mg/dL) [% change from baseline: 11.92 ± 20.88; pvalue:<0.0001] at week 52, and significantly increased HDL-C (mg/dL) [% change from baseline: 3.64v ± 27.74; pvalue:<0.0001] at week 52 (Table 3) (Figure 3).

Safety: Overall, Saroglitazar 4 mg was found to be safe and well tolerated. No death or major cardiovascular events were reported during the study. No fluid retention and no significant change in body weight were observed during the study. In the Saroglitazar 4 mg group, body weight (Kg) reduced from 75.57 ± 12.33 at baseline to 74.95 ± 11.79 at week-52 [Change from baseline: -0.83 ± 4.41]. In placebo group, body weight (Kg) reduced from 77.48 ± 11.79 at baseline to 75.08 ± 12.44 at week-52 [Change from baseline: -2.10 ± 4.45]. Three SAEs (severe abdominal pain, bladder outlet obstruction, pain at biopsy site) were reported in the Saroglitazar 4 mg group but none were related to Saroglitazar treatment. No subject discontinued the study due to SAEs.

Severity of AEs in Saroglitazar 4 mg group: mild (38.2%; events=57), moderate (14.7%; events=13), and severe (4.4%; events=3); and in placebo group: mild (32.4%; events=35), moderate (17.6%; events=8), and severe (0%; events=0). The most common reported treatment emergent AEs (in ≥ 5% of patients) in Saroglitazar 4 mg group were flatulence (7.4%; events=5), dyspepsia (8.8%; events=8), abdominal pain (7.4%; events=6), abdominal distension (5.9%; events=5), asthenia (5.9%; events=4) and in placebo group were flatulence (17.6%; events=8), abdominal pain (14.7%; events=6), constipation (5.9%; events=3), gastrointestinal motility disorder (5.9%; events=2), asthenia (5.9%; events=2), pyrexia (8.8%; events=3), cough (5.9%; events=2), pruritus (5.9%; events=3).

## Conclusion

Lifestyle modifications and weight loss are the only recommended modalities and no drug is yet approved for the treatment of patients with NASH by the USFDA or EMA.The ideal drugs/therapies for the treatment of NASH should improve liver parameters and liver histology along with reducing the risk of CVDs.

Peroxisome proliferator-activated receptors, ligand-activated transcription factors, are involved in the transcriptional regulation of glucose homeostasis, lipid metabolism, atherosclerosis, inflammation, and energy balance. Saroglitazar is a novel PPAR agonist with dual PPAR agonistic properties (predominant PPAR-$\alpha$ agonist with moderate PPAR-$\gamma$ agonistic activity). The PPAR agonistic properties of Saroglitazar signify its potential positive effects on liver histology, liver parameters, and lipid parameters in NASH.

In the preclinical DIAMOND™ NASH mice model, Saroglitazar exhibited a systemic effect with resolution of steatohepatitis and improvement in all of the key histological features of NASH, improving dyslipidemia (triglycerides and cholesterol) and insulin sensitivity, and reducing weight. Preclinical effects of Saroglitazar look promising to reduce the CV risk along with improving liver histology and liver parameters. These provide a strong rationale for clinical trials of Saroglitazar in NASH. In the phase 2 clinical trial in 32 patients with NASH in India, Saroglitazar 4 mg significantly reduced ALT (U/L) from baseline (95.86 ± 37.65) to week-12 (44.37 ± 35.43), which is a clinically accepted endpoint for the NASH trials. In the phase 3 clinical trial in 102 patients with NASH in India, the primary study endpoint was achieved by demonstrating a significantly higher proportion of patients with decrease in NAS ≥ 2 spread across at least 2 of the NAS components without worsening of fibrosis at week 52 in Saroglitazar 4 mg (52.3%) compared to placebo group (23.5%) (pvalue: 0.0427). Moreover, Saroglitazar 4 mg also significantly reduced the mean NAS score, steatosis, and hepatocyte ballooning at week 52.Saroglitazar 4 mg also showed benefit by demonstrating a significant decrease in the liver enzymes, namely, ALT, AST, ALP and GGT. Saroglitazar 4 mg significantly reduced lipid parameters such as triglyceride, LDL-C, sd-LDL, VLDL-C, total cholesterol, non-HDL-C and significantly increased HDL-C at week 52. The drug was found to be safe in patients with NASH as there were no major cardiovascular events or mortality reported during the study period and subsequent 12 week follow-up. In this study, Saroglitazar 4 mg, given for a period of 52 weeks, resulted in improvement in liver histology (Figure 4), liver biochemistry, and lipid parameters in adult patients with NASH.These beneficial effects are likely to result in a reduction in the risk of CVDs.

| Efficacy endpoints | Treatment | Baseline (M ± SD) | Week-52 (M ± SD) | % Change from baseline | |
|---|---|---|---|---|---|
| | | | | (M ± SD) | p value |
| **NAS and components** | | | | | |
| NAS | Saroglitazar 4 mg (n=44) | 5.30 ± 0.95 | 3.41 ± 1.32 | -34.66 ± 26.03 | <0.0001 |
| | Placebo (n=17) | 5.06 ± 0.90 | 4.18 ±1.70 | -17.55 ± 28.57 | 0.0049 |
| Steatosis | Saroglitazar 4 mg (n=44) | 1.93 ± 0.70 | 1.02 ± 0.70 | -41.29 ± 52.02 | <0.0001 |
| | Placebo (n=17) | 1.82 ± 0.73 | 1.35 ± 0.86 | -22.55 ± 46.75 | 0.0478 |
| Hepatocyte ballooning | Saroglitazar 4 mg (n=44) | 1.61± 0.49 | 0.98 ± 0.59 | -35.23 ± 42.56 | <0.0001 |
| | Placebo (n=17) | 1.53 ± 0.51 | 1.35 ± 0.61 | -2.94 ± 48.32 | 0.7095 |
| Lobular inflammation | Saroglitazar 4 mg (n=44) | 1.75 ± 0.44 | 1.41 ± 0.62 | -12.50 ± 47.16 | 0.0526 |
| | Placebo (n=17) | 1.71 ± 0.69 | 1.47 ± 0.62 | -5.88 ± 49.98 | 0.5425 |
| **Liver parameters** | | | | | |
| ALT (U/L) | Saroglitazar 4 mg (n=44) | 81.19 ± 68.80 | 46.86 ± 35.41 | -27.79 ± 36.41 | <0.0001 |
| | Placebo (n=17) | 74.06 ± 50.24 | 64.65 ± 53.59 | -12.32 ± 28.16 | <0.0001 |
| AST (U/L) | Saroglitazar 4 mg (n=44) | 47.37 ± 33.33 | 32.16 ± 16.16 | -18.10 ± 34.00 | <0.0001 |
| | Placebo (n=17) | 45.25 ± 26.55 | 38.00 ± 18.39 | -9.21 ± 28.56 | 0.0004 |
| GGT (U/L) | Saroglitazar 4 mg (n=44) | 73.05 ± 93.31 | 43.44 ± 33.53 | -29.27 ± 37.13 | <0.0001 |
| | Placebo (n=17) | 51.75 ± 40.66 | 44.18 ± 22.70 | -3.46 ± 26.75 | 0.0022 |
| ALP (U/L) | Saroglitazar 4 mg (n=44) | 100.37 ± 24.78 | 68.98 ± 29.28 | -32.14 ± 19.22 | <0.0001 |
| | Placebo (n=17) | 96.69 ± 28.25 | 100.59 ± 30.17 | 8.48 ± 33.12 | <0.0001 |

| | | | | | |
|---|---|---|---|---|---|
| **Lipid parameters** | | | | | |
| Triglyceride (mg/dL) | Saroglitazar 4 mg (n=44) | 158.60 ± 77.55 | 114.79 ± 63.50 | -24.51 ± 31.93 | <0.0001 |
| | Placebo (n=17) | 128.06 ± 52.82 | 133.24 ± 47.00 | 5.74 ± 28.98 | <0.0001 |
| LDL-C (mg/dL) | Saroglitazar 4 mg (n=44) | 120.63 ± 36.74 | 108.30 ± 36.92 | -8.68 ± 20.58 | <0.0001 |
| | Placebo (n=17) | 123.88 ± 25.60 | 140.06 ± 45.53 | 6.24 ± 10.35 | <0.0001 |
| Sd-LDL (mg/dL) | Saroglitazar 4 mg (n=44) | 32.99 ± 18.65 | 23.41 ± 14.89 | -22.02 ± 40.19 | <0.0001 |
| | Placebo (n=17) | 27.69 ± 10.52 | 30.12 ±15.06 | 19.16 ± 60.40 | 0.6021 |
| VLDL-C (mg/dL) | Saroglitazar 4 mg (n=44) | 30.55 ± 13.65 | 22.98 ± 12.64 | -24.39 ± 32.01 | <0.0001 |
| | Placebo (n=17) | 25.56 ± 10.51 | 26.53 ± 9.44 | 5.07 ± 28.69 | 0.0367 |
| Total cholesterol (mg/dL) | Saroglitazar 4 mg (n=44) | 185.53 ± 45.52 | 166.70 ± 45.61 | -9.27 ± 15.77 | <0.0001 |
| | Placebo (n=17) | 184.13 ± 30.19 | 199.06 ± 51.93 | 3.14 ± 10.34 | <0.0001 |
| HDL-C (mg/dL) | Saroglitazar 4 mg (n=44) | 41.60 ± 10.17 | 42.68 ± 15.10 | 3.64 ± 27.74 | <0.0001 |
| | Placebo (n=17) | 42.06 ± 8.27 | 41.35 ± 8.42 | -1.13 ± 8.42 | <0.0001 |
| Non-HDL-C (mg/dL) | Saroglitazar 4 mg (n=44) | 143.93 ± 43.41 | 124.81 ± 44.04 | -11.92 ± 20.88 | <0.0001 |
| | Placebo (n=17) | 142.50 ± 28.47 | 157.71 ± 51.59 | 4.30 ±13.21 | <0.0001 |

**Note:** P Value was Calculated for Percent (%) Changes from Baseline to Week-52 Using Paired T-Test
% Change=(Value at Week-52 - Baseline Value) X 100/Baseline Value.
**Abbreviations:** NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-alcoholic Steatohepatitis; NAS: Nafld Activity Score; M:Mean; SD: Standard Deviation; AST:Aspartate Aminotransferase; ALT:Alanine Aminotransferase; ALP:Alkaline Phosphatase; GGT:Gamma Glutamyl Transferase; LDL-C:Low-Density Lipoprotein Cholesterol; Hdl-C, High-Density Lipoprotein Cholesterol; SD-Ldl:Small Dense Ldl; VLDL-C:Very Low-Density Lipoprotein Cholesterol; MG:Milligram; DI:Decilitre; U/L:Unit/Litre

**Table 3.** Change in efficacy endpoints of NAS and components, liver parameters, and lipid parameters in phase 3 study in India.

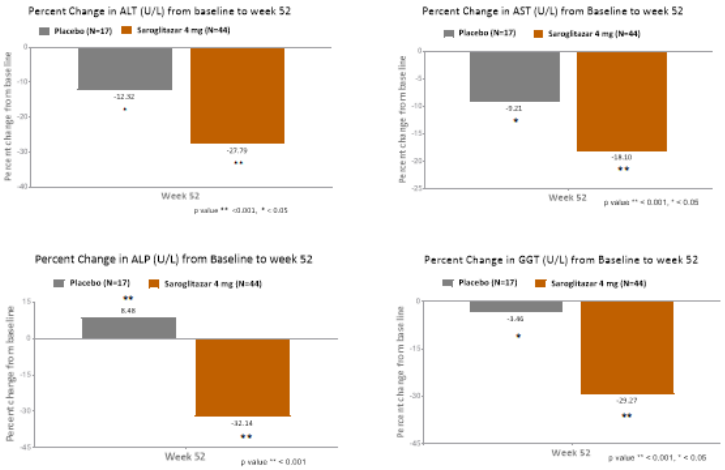



**Figure 2.** Percent change in liver parameters from baseline to week 52 in phase 3 clinical trial in India: Saroglitazar 4 mg versus placebo.

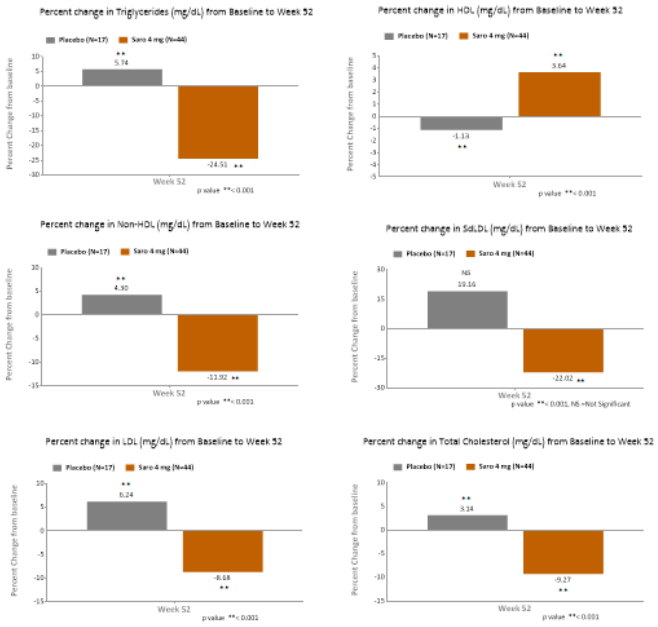
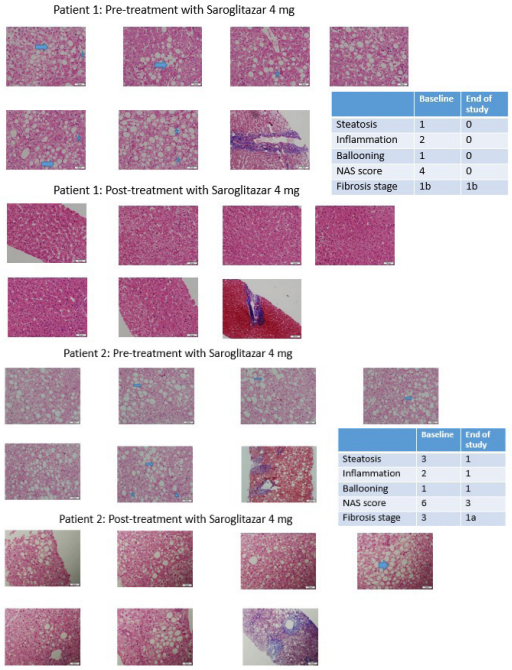



**Figure 3.** Percent change in lipid parameters from baseline to week 52 in phase 3 clinical trial in India: Saroglitazar 4 mg versus placebo.




| | Baseline | End of study |
|---|---|---|
| Steatosis | 1 | 0 |
| Inflammation | 2 | 0 |
| Ballooning | 1 | 0 |
| NAS score | 4 | 0 |
| Fibrosis stage | 1b | 1b |

| | Baseline | End of study |
|---|---|---|
| Steatosis | 3 | 1 |
| Inflammation | 2 | 1 |
| Ballooning | 1 | 1 |
| NAS score | 6 | 3 |
| Fibrosis stage | 3 | 1a |

**Figure 4.** Histological improvement with saroglitazar 4 mg in NASH patients in phase 3 clinical trial in India [patients identity-not revealed].

Saroglitazar has also been studied in patients with NAFLD/NASH in the US.12In the US, a phase 2 study of 16 weeks duration was conducted to determine the efficacy and safety of Saroglitazar 1 mg, 2 mg, and 4 mg compared to placebo in 106 adult patients with NAFLD/NASH along with ALT ≥ 50 U/L (ClinicalTrials.gov Identifier: NCT03061721). The change in mean ALT from baseline to week 16 (primary efficacy endpoint) was-26.2 ± 33.4% with Saroglitazar 1 mg, 27.0 ± 26.5% with Saroglitazar 2 mg, and -44.9 ± 26.2% with Saroglitazar 4 mg compared to 2.6 ± 32.1% with placebo (p<0.001 for all). Saroglitazar 4 mg, compared to placebo, significantly reduced mean liver fat content (LFC) [ 4.21 ± 6.23% versus -0.28 ± 5.41%, p=0.002] at week 16. Saroglitazar 4 mg was associated with improvements in enhanced liver fibrosis score, atherogenicdyslipidemia, and glycemic parameters at week 16.

Also, the effect of Saroglitazar 4 mg on various lipid parameters was studied in three individual clinical trials conducted in patients with NAFLD/NASH in the USA, Mexico, and India, respectively. Saroglitazar 4 mg improved triglycerides, total cholesterol, LDL-C, non-HDL-C, HDL-C from baseline in the USA, India and Mexico, respectively [abstract accepted at EAS 2020]. This signifies that Saroglitazar can potentially reduce the CVD risk in different populations with NAFLD/NASH across a global population.

Overall, preclinical studies indicate that Saroglitazar reduces ALT, AST, and improves steatohepatitis, hepatocellular ballooning, and fibrosis. Clinical studies showed similar effects of Saroglitazar on liver parameters and components of NAS and fibrosis. Moreover, preclinical and clinical studies showed that Saroglitazar improved lipid parameters, which could reduce the CVD risk. Thus, Saroglitazar could be an ideal drug to treat NASH in different populations globally.

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