Introduction.
Saroglitazar is a novel dual PPARα/γ agonist recently approved in India for the treatment of diabetes, hypertriglyceridemia. The mode of action of this drug is unclear and there is a need to understand its underlying molecular mechanism.

Hypothesis.
We hypothesized that Saroglitazar reduces the fatty acid absorption and consequently reduces circulating triglyceride.

Methods.
To understand the mechanisms of action of saroglitazar in vivo, we treated Zucker fa/fa (n=10-12 in each group) with vehicle, fenofibrate (F; 170 mg/kg) or saroglitazar (Saro) (0-4 mg/kg/day) for 14 days. On day 15, rats were gavaged with 5mC labeled or unlabeled (15-30µCi/ml) [13C]-palmitate and plasma was collected 14 days later.

Results.
In all animals, insertion and turnover of labeled fatty acid into plasma and tissue lipids (n=5 for tissue metabolomics studies). The major M+16 labeling of fatty acid was measured in visceral adipose tissue gastrocnemius muscles. Total lipids were extracted from tissues and analyzed by gas chromatography-mass spectrometry. Lipid extraction Lipids extraction LC-MS-TOF GC-MS Results.

Discussion.
NAFLD and NASH. To define the mechanism for modulation of fatty acid metabolism by saroglitazar, we measured the uptake of U-13C palmitate into plasma and tissue lipids (n=5 for tissue metabolomics studies). The major M+16 labeling of fatty acid was measured in visceral adipose tissue gastrocnemius muscles. Total lipids were extracted from tissues and analyzed by gas chromatography-mass spectrometry. Lipid extraction Lipids extraction LC-MS-TOF GC-MS Results.

Conclusions.
We observed the production of [13C]-palmitic (PC), which is contained primarily in HDL and LDL particles produced by resident and uptake of [13C]-palmitic acid (PC) at baseline with a lesser effect on PC(34:2) and A (B). The corresponding M+16 labeled PC species did not show significant difference between the groups (C). Consistent with the production in the liver, the levels of PC in rats increased starting at 2h post-Saro. The percent label of PC in chylomicrons and VLDL was similar in all groups with a peak at ~2 hours and another increase at 8 hours (F) suggesting the reduction of TG-LDL-GDL. Fenofibrate did not show the same significant decrease suggesting a reduction in VLDL production.

References.

Conclusion.
Saroglitazar demonstrates evidence of both PPARα and PPARγ effects in vivo. Low dose saroglitazar which achieves in vivo levels equivalent to that seen in humans has potent ability to lower post-prandial triglyceride levels without affecting body weight. The clinical effect of fenofibrate may be primarily due to enhanced clearance of chylomicron particles by increase uptake into adipose tissue.