PS-110

Ketohexokinase inhibitor PF-06835919 administered for 6 weeks reduces whole liver fat as measured by magnetic resonance imaging-proton density fat fraction in subjects with non-alcoholic fatty liver disease

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Background and aims: Preclinical studies show that fructose rapidly enriches glycolytic metabolite pools, leading to activation of the Carbohydrate Response Element Binding Protein (ChREBP), a highly lipogenic transcription factor, that can promote steatosis and insulin resistance. Excessive fructose consumption has been shown to cause features of metabolic syndrome and NAFLD. KHK catalyzes phosphorylation of fructose to mediate its entry into the glycolytic pool. PF is a potent, reversible inhibitor of human KHK, and is expected to decrease hepatic de novo lipogenesis and steatosis, thereby ameliorating the pathogenesis of NAFLD. This clinical study was designed to test the hypothesis that KHK inhibition would lead to reduction in WLF.
Method: 53 subjects with NAFLD (> 6% WLF by MRI-PDFF) were randomized and 48 subjects completed the trial. Subjects were stratified by presence or absence of diabetes and baseline WLF. Participants received placebo (17), PF 75 mg (17) or PF 300 mg (14) once daily for 6 weeks.
Results: Incidence of treatment emergent adverse events was low and similar across treatment groups. No SAEs were reported. Pharmacodynamic observations are summarized below.
Conclusion: PF administered for 6 weeks is well-tolerated with an acceptable safety profile in adults with NAFLD. PF 300 mg showed a statistically greater reduction from baseline compared to placebo in WLF. Dose-dependent percent changes from baseline were observed for hs-CRP (reductions), and adiponectin (increases) in PF treated groups. A trend for a dose-dependent decrease in insulin resistance (by HOMA-IR) was observed. Small numerical decreases in ALT, AST and GGT change from baseline were observed in the PF 300 mg group relative to placebo (not shown). No notable differences were found for changes from baseline in IL-6. These results suggest that additional studies are warranted to assess the potential of PF for the treatment of NAFLD/NASH.

Figure:

	Week 6 Percent Change from Baseline [LS Mean (90%CI)]		
	Placebo	75 mg/day	300 mg/day
WLF PDFF	-7.78 (-17.72, 2.17)	3.67 (-6.32, 13.66)	-26.50 (-38.15, -14.86)*
Hs-CRP	8.33 (-9.82, 30.12)	-16.42 (-30.39, 0.36)	-31.01 (-44.00, -15.01)
Uric Acid #	6.52 (1.01, 12.03)	4.44 (-4.15, 13.04)	-11.53 (-16.48, -6.57)
Adiponectin	-14.25 (-25.12, -1.79)	18.29 (3.10, 35.73)	38.59 (18.63, 61.92)
HOMA-IR	0.13 (-0.43, 0.69)	-0.61 (-1.34, 0.12)	-0.53 (-1.16, 0.10)
IL-6	8.48 (-11.51, 32.98)	-0.72 (-19.43, 22.32)	-7.14 (-26.51, 17.34)

*p < 0.0395; #median (90% CI)