their enzymes to alternative pathways for ammonia detoxification, disrupting normal energy metabolism.

Materials and Methods: Adult male Sprague Dawley rats were randomly assigned to a control group on a standard diet (2.93 kcal/g, n=10), an intervention group on a high-fat diet deficient in choline (MASLD, HDCF, 4.3 kcal/g, n=10), and two treatment groups, MASLD +NAC (n=12) and MASLD+LOLA (n=12), over a period of 16 weeks.

Results: In MASLD, there was an increase in the expression of D3, colocalized with M1 macrophages and TR beta protein levels, while MCT8 levels remained unchanged. Additionally, mitochondrial respiration decreased, and no effects were observed with treatments. Furthermore, Glutamate Dehydrogenase (GDH) activity diminished, whereas α-Ketoglutarate Dehydrogenase (α-KGDH) activity increased. It was also determined that Grp78 (decreased by 74%) and Grp75 (increased by 60%) are regulated by T3 and are endoplasmic reticulum (ER) chaperones meaning ER stress.

Conclusions: Our study corroborates the interaction between TH metabolism and compensatory mechanisms that counteract elevated ammonia levels, as well as the enzymes regulating this process in MASLD. Both NAC and LOLA demonstrated potential in correcting TH metabolism and enhancing ammonia detoxification in MASLD, which may help alleviate symptoms or slow the progression of the disease.

Conflict of interest: None

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EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS PREVIOUSLY TREATED WITH FIBRATES OR OBETICHOLIC ACID

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Introduction and Objectives: Seladelpar was evaluated as monotherapy or with ursodeoxycholic acid in RESPONSE (NCT04620733) among patients with primary biliary cholangitis. Patients completing RESPONSE could roll over into ASSURE (NCT03301506).

Here, we present 18-month (M) data (6M of ASSURE) in patients with or without prior use of fibrates or obeticholic acid (OCA) continuing into ASSURE from RESPONSE.

Patients and Methods: Patients received oral seladelpar 10 mg or placebo during RESPONSE, followed by open-label seladelpar in ASSURE. Fibrates/OCA were prohibited during RESPONSE. Analyses included patients with or without prior fibrates/OCA use, categorized by RESPONSE assignment: continuous seladelpar or crossover from placebo. Efficacy included the proportion of patients achieving a composite biochemical response (CBR; ALP $<1.67 \times$ ULN, ALP decrease $\geq$15%, and total bilirubin $\leq$ULN). Safety evaluations included adverse events (AEs).

Results: Among patients who continued into ASSURE from RESPONSE (n=158), 16 continuous seladelpar and 11 crossover patients reported prior use of fibrates/OCA (n=27; 17%); 88 continuous seladelpar and 43 crossover patients reported no prior use of fibrates/OCA (n=131; 83%). At 18M, 9/15 (60%) continuous seladelpar patients with prior fibrates/OCA use achieved a CBR vs 54/87 (62%) patients without prior fibrates/OCA use. Among crossover patients, 7/11 (64%) patients with prior fibrates/OCA use vs 32/41 (78%) patients without prior fibrates/OCA use achieved a CBR at 6M of ASSURE. From ASSURE initiation to 6M, AE incidence was similar across all patients, regardless of prior fibrates/OCA use; no treatment-related serious AEs were reported.

Conclusions: Interim results show seladelpar achieved comparable, sustained biochemical responses and favorable safety irrespective of prior fibrates/OCA use.

Conflict of interest: Yes, Gilead Sciences, Inc.

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EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND COMPENSATED CIRRHOSIS IN THE PHASE 3 PLACEBO-CONTROLLED RESPONSE TRIAL

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Introduction and Objectives: In the Phase 3 RESPONSE trial (NCT04620733), seladelpar, a first-in-class delpar (selective peroxisome proliferator–activated receptor delta agonist), significantly improved biomarkers of cholestasis in patients with primary biliary cholangitis (PBC) over 12 months vs placebo. More patients with cirrhosis met the primary endpoint in the seladelpar arm (39%) vs placebo (22%).

We now report data on additional biochemical results and safety in patients with or without cirrhosis in RESPONSE.

Patients and Methods: Eligible patients had an inadequate response or intolerance to ursodeoxycholic acid, alkaline