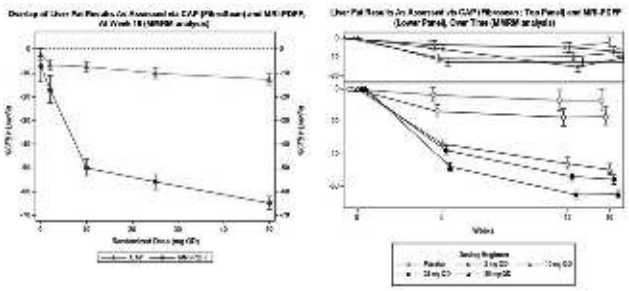

Disclosures:

Theresa Tuthill – Pfizer Inc: Employment

Santos Carvajal-Gonzalez – Pfizer: Employment

Neeta Amin: PF-05221304 is an investigational product; not approved for use in any country, globally

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OBESE PATIENTS CARRYING NAFLD-ASSOCIATED GENETIC VARIANTS PRESENT SPECIFIC SERUM AND LIVER LIPIDOMIC PROFILES: IDENTIFICATION OF A LIPIDOMIC SIGNATURE IN SERUM TO ESTIMATE THE LIVER FAT CONTENT

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Background: Novel serum-derived metabolomic tests were generated to diagnose NAFL and NASH in obese patients. Here, we investigated: 1) whether obese individuals harboring the *PNPLA3* p.I148M, *TM6SF2* p.E167K, and *MBOAT7* p.G17E variants, associated with increased risk of steatosis and fibrosis, present specific lipidomic profiles in both serum and liver, and 2) the potential of particular lipidomic signatures to estimate the liver fat content. **Methods:** Hepatic steatosis was determined by magnetic resonance imaging (MRI fat fraction), and by histopathology of liver tissue from obese individuals (n=114; BMI>35kg/m^2). Serum lipidomic profile was analyzed by UPLC-MS and a specific signature was correlated with the liver fat content. In parallel, 225 obese patients were genotyped the *PNPLA3* p.I148M, *TM6SF2* p.E167K, and *MBOAT7* p.G17E variants using allelic discrimination TaqMan assays. Serum (n=225) and liver (n=53) lipidomic profiles were measured. **Results:** The *PNPLA3* p.I148M, *TM6SF2* p.E167K, and *MBOAT7* p.G17E variants were found in 42%, 10% and 72% patients, respectively. Patients harboring the *PNPLA3* p.I148M variant (in hetero- or homozygosity) were characterized by reduced levels of certain triglycerides (p<0.05) in serum, while liver presented an accumulation of multiple di- and triglycerides (at least p<0.05). Patients with the *TM6SF2* p.E167K variant showed decreased levels of certain ceramides, di- and triglycerides in serum compared to WT patients (at least p<0.05). In addition, circulating glycerophospholipids, ceramides, and certain FA were decreased in patients with the *MBOAT7* p.G17E variant compared to WT patients (at least p<0.05). Patients harboring the 3 variants (in hetero- or homozygosis) presented a completely altered lipidomic profile in serum compared to obese controls, namely a decrease in di-, triglycerides and saturated, mono- and polyunsaturated FA (at least p<0.01). On the other hand, we identified 11 lipids in serum that, within a new algorithm, correlated with MRI fat fraction (r=0.815; r^2=0.664; p<0.001), the grade of steatosis and NAS score measured by histopathology. **Conclusion:** Obese patients harboring genetic risk variants for NAFLD/NASH are characterized by specific lipidomic profiles, which may participate in disease pathogenesis and represent new tools to estimate prognosis. We also describe a novel lipidomic signature in serum that allows to estimate fat content in the liver of obese patients, embodying an innovative tool to monitor fat accumulation.

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Cristina Alonso – OWL Metabolomics: Employment

Enara Arretxe – OWL metabolomics: Employment

Pablo Ortiz – OWL Metabolomics: Employment

Jesus Banales – OWL Metabolomics: Advisory Committee or Review Panel

The following people have nothing to disclose: Alvaro Santos-Laso, Leyre Velaz, Emma Eizaguirre, Ibon Martínez-Arranz, Maria Jesus Pareja, Ioana Riaño, Jesper Andersen, Itziar Mincholé, Maria Jesus Perugorria, Ana Landa, Marcin Krawczyk, Frank Lammert, Rui Eduardo Castro, Patricia Aspichueta, Manuel Romero-Gomez, Luis Bujanda, Pedro Miguel Rodrigues

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DISPARATE CIRCULATING LIPIDOMIC SIGNATURES IN OBESE AND NON-OBESE SUBJECTS WITH NONALCOHOLIC FATTY LIVER DISEASE

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Background: Nonalcoholic fatty liver disease (NAFLD) can affect both obese and non-obese individuals. The mechanism underlying non-obese nonalcoholic steatohepatitis (NASH), however, remains unclear. Moreover, the lack of relevant noninvasive biomarkers precludes early recognition of subjects at risk for development and progression of non-obese NAFLD. Therefore, we attempted to elucidate the metabolic perturbation associated with non-obese and obese NAFLD using a lipidomics approach. **Methods:** A cross-