Seladelpar, a PPAR-delta agonist, is currently in late-stage clinical development for liver disease including non-alcoholic steatohepatitis (NASH). The present study aimed to evaluate the metabolic, biochemical, histopathological and transcriptomic effects of seladelpar treatment in the Guba-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH.

**Study outline**

- **A**: NAFLD Activity Score
- **B**: Fibrosis stage
- **C**: Liver total cholesterol
- **D**: Body weight

**Improvement in NASH Activity Score**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pre</th>
<th>Post</th>
<th>Fold change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOW</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
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<td>0</td>
<td>1</td>
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</tr>
<tr>
<td>DIO-NASH</td>
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<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Seladelpar</td>
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<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**Improvement in quantitative histology of steatosis, inflammation and fibrosis**

- **A**: CHOW vs. DIO-NASH
- **B**: DIO-MASH Seladelpar

**Hepatic transcriptomic profile for fibrosis and inflammation**

- **A**: Differential expression analysis (DEA) of samples based on low FDR and selected gene expression levels
- **B**: volcano diagram showing shared and separate differentially expressed genes in treatment groups
- **C**: analysis of hepatic transcriptomics data (RNAseq) and inflammation candidate genes (high fold change compared to DIO-NASH vehicle), blue and red colors gradient indicate significantly (p-value) down-regulated and up-regulated gene expression, respectively. While baseline estimates genes not significantly regulated (p-value) compared to DIO-NASH vehicle

**CONCLUSION**

- Seladelpar reduces body weight, plasma ALT and liver total cholesterol levels.
- Seladelpar promotes 22-point significant improvement in NAFLD Activity Score.
- Fibrosis stage was unaffected by Seladelpar.
- Seladelpar reduces quantitative histological markers of steatosis, inflammation, fibrosis and stellate cell activation.
- Seladelpar demonstrated transcriptomic effects on fibrosis-associated gene expression.
- These findings agree with clinical findings, further highlighting the clinical translatability of the GAN DIO-NASH mouse model.