Comparative Efficacy of INT-767 vs. Liraglutide in Gubra AMLN Mice

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*Intercept Pharmaceuticals, Inc.*
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- Jonathan Roth and Mark Young are employed by and hold equity in Intercept Pharmaceuticals, Inc.
Based upon ALIOS high-trans fat diet (Tetri et al. 2008) with a few modifications:
- Fructose included in the diet vs. drinking water
- Diet in $Lep^{ob/ob}$ vs. C57 Bl6
- Mice are biopsied and those with a baseline NASH phenotype are “enrolled”

### Gubra AMLN NASH Model vs. FLINT

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>FLINT (Vehicle Group @ Baseline)</th>
<th>$Lep^{ob/ob}$ mice on AMLN diet (Vehicle Group @ Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis Score</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>NAS</td>
<td>5.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Steatosis Score</td>
<td>2.1</td>
<td>3</td>
</tr>
<tr>
<td>Inflammation Score</td>
<td>Lobular = 1.8</td>
<td>Portal = 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.3</td>
</tr>
<tr>
<td>Ballooning Score</td>
<td>1.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>
**Background and Rationale**

**INT-767**
- Bile acid analog
- FXR/TGR5 *in vitro* dual agonist
- Oral administration
- Early development (Phase 1)
- Improves metabolism and fibrosis in animal models

**Liraglutide**
- Acylated Glucagon-like peptide
- GLP-1R agonist class
- Injectable administration (QD)
- Approved for diabetes, obesity
- Under investigation for NASH

Compare efficacious doses head-to-head on histological endpoints in a rodent model of NASH (INT-767 10 mg/kg vs. Liraglutide 0.4 mg/kg; 8 weeks)
Body Weight, Adiposity and Food Intake

Body Weight

Fat Mass

Food Intake

* p<0.05 vs. vehicle; # p<0.05 vs. monotherapy
Glycemic Control

Oral Glucose Tolerance

Area Under Curve

*p<0.05 vs. vehicle; #p<0.05 vs. monotherapy
NAFLD Activity Score

**NAFLD Activity Score**

**Representative H&E Stained Sections**

* *p*<0.05 vs. vehicle; #*p*<0.05 vs. monotherapy
NAS Components

**Steatosis**

<table>
<thead>
<tr>
<th>Chow</th>
<th>Vehicle</th>
<th>INT-767 (10 mg/kg)</th>
<th>Liraglutide (0.4 mg/kg)</th>
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**Inflammation**

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**Ballooning**

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*p<0.05 vs. vehicle; #p<0.05 vs. monotherapy*
Fibrosis Scoring and Quantitation

**Fibrosis Stage**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Chow</th>
<th>Vehicle</th>
<th>INT-767 10 mg/kg</th>
<th>Liraglutide 0.4 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>1</td>
<td>5</td>
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**Fibrosis % Fractional Area**

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<td></td>
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*p<0.05 vs. vehicle; #p<0.05 vs. monotherapy
Fibrosis Stage: Pre- / Post-scores

Pre-Biopsy

Vehicle

INT-767

Liraglutide

Post-Biopsy

Vehicle

INT-767

Liraglutide

Line Graphs

Vehicle

INT-767

Liraglutide

NSD (p=0.99)

p=0.625

*p=0.031
Detailed Analyses of Fibrosis

Vehicle

INT-767

Fiber Density

Analyzed by Genesis Imaging Services
Liraglutide in the C57Bl6 AMLN NASH Model
Body Weight and Glucose

Body Weight

4 h Fasting Blood Glucose

*p<0.05 vs. vehicle; #p<0.05 vs. monotherapy
Liraglutide in the C57Bl6 AMLN NASH Model

Fibrosis

Steatosis

H&E Stained Sections

*\textit{p}<0.05 vs. vehicle; dotted lines are vehicle values in the more severe \textit{Lep}^{ob/ob} model
Summary and Conclusions

- INT-767 alleviated histological NASH in AMLN diet-fed $Lep^{ob/ob}$ mice
  - ↓ Steatosis by 27%, inflammation by 45%, ballooning by 80%
  - ↓ Fibrosis score by 29% and percent fractional area by 24%

- Despite expected GLP-1R pharmacological effects to reduce body weight and glucose, liraglutide did not improve histological NASH in AMLN diet-fed $Lep^{ob/ob}$ mice

- In a follow-up study in AMLN diet-fed C57Bl6 mice, Liraglutide improved NAS due to a reduction in steatosis (only)

- In models of AMLN diet-induced NASH, INT-767 does not require intact leptin signaling to improve NASH, whereas Liraglutide improved only steatosis, in a leptin-dependent manner
Acknowledgements

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- Mathieu Petitjean, Li Chen – Genesis Imaging Services (Pharmanest)