A New Therapy for Nonalcoholic Fatty Liver Disease and Diabetes?  
INT-747 - the First FXR Hepatic Therapeutic Study.

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7. Siemens Healthcare Diagnostics, Tarrytown, NY, USA.

Presented at AASLD 2009, Boston – Hepatology 2009; 50(S4): A183
Bile Acids: from Simple Detergents to Homeostatic Metabolic Mediators

- **Detergents - Gut**
  - Solubilize fats in intestine $\rightarrow$ absorption

- **Farnesoid-X Receptor** – Liver, bile ducts, fat
  - Nuclear receptor for bile acid signaling
    - **Makishima Science** 1999; 284: 1362
  - Natural ligand: Chenodeoxycholic acid
  - Feedback via FGF-19 & SHP
  - $\downarrow$ Hepatic Triglyceride, VLDL Synthesis
    - **Wanatabe JCI** 2004; 113: 1408-1411
  - Modulation of insulin sensitivity & adiposity
    - **Cariou J Biolog Chem** 2006; 281:11039–11049

- **TGR-5** – Liver, fat, enteroendocrine cells
  - G Protein Coupled Receptor - cell membrane
  - Mediates intracellular conversion of T4 to T3
    - **Wanatabe Nature** 2006; 439: 484-489
  - $\uparrow$ GLP-1 & Insulin
    - **Thomas Cell Metabolism** 2009; 10: 167-177
6α-Ethyl Chenodeoxycholic Acid - INT-747
Semi-Synthetic Derivative of Chenodeoxycholic Acid

CDCA
chenodeoxycholic acid

INT-747
6α-ethyl chenodeoxycholic acid

FXR EC_{50} (agonism) 8.66 µM → 0.099 µM

~ 2 log ↑ FXR agonism

Pelliciari R. J.Med.Chem 2002
The Enhanced Potency of 6ECDCA Results from the Filling of a Hydrophobic Pocket by the 6α-Ethyl Moiety

INT-747: Potent and Selective FXR Agonist


- No meaningful activity vs. other Nuclear Receptors
- EC50 for TGR5: 20 µM
- No effects + broad enzyme & receptor screen (at 10 µM)
- Extensively metabolized to glycine and taurine conjugates
  - Equipotent FXR agonism
  - Enterohepatic recirculation
Normal Volunteers – Plasma Concentrations

Post dose: Day 12
Preclinical Studies Overview

• Numerous animal models evaluated
  - BDL, estrogen, litho-cholic acid, CCl₄, ANIT, thioacetamide injury
  - Effects consistent with FXR agonism
    • Induced FXR target genes
    • SHP induction and Cyp7α1 and Cyp8β1 repression
  - Cholerectic
• Anti-fibrotic
  - α1 collagen, αSMA, TGFβ1, MMP-2, TIMP-1, and TIMP-2 mRNA
  - Histology - ↓ fibrosis, reversal of cirrhosis, ↓ Portal hypertension
INT-747 Reverses Fibrosis & Cirrhosis

Thioacetamide (TAA) rat liver fibrosis model

TAA rat model of fibrosis, control vs. INT-747 5mg/kg ip daily begun 4 weeks post-injury in cirrhotic animals for 4 weeks

INT-747 reverses established fibrosis/cirrhosis in validated animal models

Friedman S. et al.,  AASLD Presentation, 2005
Type 2 Diabetes + NAFLD Exploratory Study

Baseline

- Placebo
- INT-747 25mg
- INT-747 50mg

Euglycemic Clamp - 2 Stage

0 1 2 4 6

Baseline
2 weeks

Double Blind Phase
6 weeks
Principal Entry Criteria

• **Inclusion**
  - **Type 2 diabetes** history – ADA criteria:
  - **NAFLD**, defined by ≥ 1 of:
    - **Liver Enzymes**↑
      - **ALT** ≥47 U/L (females), ≥56 U/L (males)
      - **AST** ≥47 U/L (females), ≥60 U/L (males)
    - **Ultrasound/Imaging consistent + NAFLD**
    - **Liver biopsy** (past 5 yr).

• **Exclusion**
  - **Bilirubin** >2 × ULN.
  - **ALT** >155 U/L (females), >185 U/L (males).
  - **AST** >155 U/L (females), >200 U/L (males)
  - **Anti-diabetic medications, except metformin, glyburide or incretins.**
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo - n</th>
<th>25mg - n</th>
<th>50mg - n</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10</td>
<td>14</td>
<td>9</td>
<td>33</td>
<td>52%</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>6</td>
<td>12</td>
<td>31</td>
<td>48%</td>
</tr>
<tr>
<td>Age - y</td>
<td>53</td>
<td>53</td>
<td>51</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Efficacy N</th>
<th>BMI</th>
<th>Wt kg</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>23</td>
<td>17</td>
<td>36.1</td>
<td>104.2</td>
</tr>
<tr>
<td>25mg</td>
<td>20</td>
<td>15</td>
<td>36.5</td>
<td>108.6</td>
</tr>
<tr>
<td>50mg</td>
<td>21</td>
<td>12</td>
<td>36.5</td>
<td>106.4</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>44</td>
<td></td>
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</table>
## NAFLD Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>ALT Increased</td>
<td>20</td>
</tr>
<tr>
<td>AST Increased</td>
<td>13</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>84</td>
</tr>
<tr>
<td>Histology</td>
<td>3</td>
</tr>
</tbody>
</table>

≥ 1 criteria to qualify
# Concomitant Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>83</td>
</tr>
<tr>
<td>Sulfonylureas (glyburide)</td>
<td>25</td>
</tr>
<tr>
<td>Other diabetes Rx (not insulin)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Lipid Lowering</strong></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>43</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Renin Angiotensin Agents</td>
<td>45</td>
</tr>
<tr>
<td>Other anti-HTN</td>
<td>46</td>
</tr>
<tr>
<td><strong>Other drug(s)</strong></td>
<td>97</td>
</tr>
</tbody>
</table>
Results
Glucose Disposal Rate: Low Dose Insulin
60 mU x m² body surface area/min

Day 0
Day 43

Placebo (N=17)
25 mg (N=15)
50 mg (N=12)

Combined doses vs placebo: p=0.048
Glucose Disposal Rate: High Dose Insulin

120 mU x m² body surface area/min

Combined doses vs placebo: p=0.022

Placebo (N=17)
25 mg (N= 15)
50 mg (N=12)

GDR (mg/kg/min)

Day 0
Day 43
% Δ Weight – All Patients

- Placebo
  - N=21
- 25 mg
  - N=20
- 50 mg
  - N=18

p = 0.008
# Clinical AEs in >1 Patient & Significant AEs

<table>
<thead>
<tr>
<th></th>
<th>Pbo</th>
<th>25mg</th>
<th>50mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/group</td>
<td>23</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Any AE</td>
<td>14</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>ALT/AST Increase*</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

* Only severe AE – all others mild or moderate
Gamma-Glutamyl Transpeptidase

ULN range: 39 to 65 U/L

- Placebo (N=23)
- 25 mg (N=20)
- 50 mg (N=18-21)

*p = 0.001
*p = 0.0005
Liver Enzymes

**ALT**
- ULN range: 45 to 52 U/L
- Treatment Day
- Graph showing data for Placebo (N=23), 25 mg (N=20), and 50 mg (N=18-21) with a p-value of 0.003

**AST**
- ULN range: 30 to 52 U/L
- Treatment Day
- Graph showing data for Placebo (N=23), 25 mg (N=20), and 50 mg (N=18-21)

**Alkaline Phosphatase**
- ULN range: 104 to 163 U/L
- Treatment Day
- Graph showing data for Placebo (N=23), 25 mg (N=20), and 50 mg (N=18-21)
Lipids

**Triglycerides**
- ULN range: 149 to 250 mg/dl
- Placebo (N=23)
- 25 mg (N=20)
- 50 mg (N=18-21)

**Total Cholesterol**
- ULN range: 199 to 240 mg/dl
- Placebo (N=23)
- 25 mg (N=20)
- 50 mg (N=18-21)

**HDL**
- LLN range: 20 to 40 mg/dl
- Placebo (N=23)
- 25 mg (N=20)
- 50 mg (N=18-21)

**LDL**
- ULN range: 99 to 130 mg/dl
- Placebo (N=23)
- 25 mg (N=20)
- 50 mg (N=18-21)
OTHER ANALYTES
ELF & FGF-19
Enhanced Liver Fibrosis [ELF] Test
NAFLD Validation

• Composite Score:
  ▪ TIMP-1
  ▪ Hyaluronic Acid
  ▪ P3NP (aminoterminal peptide of pro-collagen III)
  ▪ Validated in NAFLD & other diseases

Guha I, Parkes J, Roderick P et al.
Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology. 2008; 47:455-60
## ELF Test

<table>
<thead>
<tr>
<th>Class</th>
<th>ELF Range</th>
<th>All Patients - %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>&gt; 12.00</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>10.25 - 12.00</td>
<td>5</td>
</tr>
<tr>
<td>Mild to Moderate</td>
<td>7.40 - 10.25</td>
<td>76</td>
</tr>
<tr>
<td>Mild</td>
<td>6.60 - 7.40</td>
<td>14</td>
</tr>
<tr>
<td>None to Mild</td>
<td>&lt; 6.60</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td></td>
</tr>
</tbody>
</table>

Analysis: P. Dillon, PhD Siemens Healthcare Diagnostics

Note: **Not** FDA cleared for use in USA; available in Europe (iQur)
Change in ELF Test Score – Day 0 to 43

- **25 mg (N = 20)**
- **Placebo (N = 23)**
- **50 mg (N = 20)**

- **p = 0.0037**

25mg vs Placebo

- Hyaluronic acid: p=0.05
- P3NP: p=0.01
- TIMP1: p=0.03
FGF-19 – Day 0 and 43

Mean values + SEM

- Placebo (N = 9)
- 25 mg (N = 21)
- 50 mg (N = 21)
Percentage Change in FGF-19
Day 0 to 43

Mean values + SEM

p < 0.001

-100
0
100
200
300
400
500

% Change in FGF-19

Placebo (N = 9)
25 mg (N = 21)
50 mg (N = 21)
Total Bile Acids
Day 0 and 43

Mean values + SEM
Enrichment of INT-747 within Total Bile Acid Pool – Day 43

Total bile acids (μmol/L)

- Placebo
- 25 mg
- 50 mg

Bile acids other than INT-747
INT-747+ Conjugates
Conclusions: INT-747 in DM & NAFLD

- Improves GIR at low & high dose insulin infusions
  - Consistent with hepatic & peripheral effects
- Decreases body weight
  - Possibly related to ↑ in FGF-19
- ↓ in γ-Glutamyl Transpeptidase
- Improvement in ELF fibrosis score – at 25mg
- Well tolerated
  - Not clearly different to Placebo
- Merits further study