Current and Emerging Therapies for Non-Alcohol Steatohepatitis (NASH)

CDDW 2018

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McMaster University
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Conflict of Interest Disclosure
(over the past 24 months)

<table>
<thead>
<tr>
<th>Commercial or Non-Profit Interest</th>
<th>Relationship</th>
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<tbody>
<tr>
<td>Gilead, Merck, Abbvie</td>
<td>Advisory Board</td>
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<tr>
<td>Gilead, Merck, Abbvie, Lupin, Intercept, Janssen</td>
<td>Speaker/Honoraria</td>
</tr>
<tr>
<td>Gilead, Merck, Abbvie, Intercept, NovoNordisk</td>
<td>Research Investigator</td>
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</tbody>
</table>
**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.)

**Communicator** (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)

**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)

**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)

**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)

**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)

**Professional** (as *Professionals*, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)
Outline

- Current best practices in management of NASH
  - Non-pharmacotherapy
  - Currently available pharmacotherapies
  - Emerging / Investigational therapies
NAFLD vs NASH: Prognostic Implications of Steatohepatitis & Fibrosis

- **NAFLD**:
  - > 10 years: 3% Cirrhosis

- **NASH**:
  - 5-10 years: 10-30% Fibrosis Progression or Cirrhosis

References:
- Pais, Gastroenterol Clin Biol 2011
- Wong, Gut 2010
- Fassio, Hepatol 2004
- Harrison Am J Gastroenterol 2003
NAFLD: Mortality

- Long-term follow-up of pts with biopsy-confirmed NAFLD

Survival

\[ \text{Survival} = f(\text{Yrs}) \]

\[
\begin{array}{c|c|c|c}
\text{Yrs} & 0 & 5 & 10 \\
\hline
\text{Survival} & 1.0 & 0.7 & 0.5 \\
\end{array}
\]

Population of Interest for Pharmacotherapies

- **Treat NASH**
  - NASH with fibrosis
  - Advanced fibrosis
  - NASH-related cirrhosis

- **Do Not Treat NAFLD**
  - Pt without biopsy-confirmed NASH
  - Steatosis alone
    - Focus on CVD risk factor modification (weight loss, exercise, aggressive management of metabolic syndrome)
How Much Weight Loss Is Needed for Improvement in NASH?

- **≥ 10% Weight Loss[^3]**
  - Improvement in fibrosis stage (45% of pts)
  - NASH resolution (90% of pts)

- **7% to 10% Weight Loss[^2]**
  - Improvement in NASH Activity Score

- **5% Weight Loss[^1]**
  - Improvement in liver fat and liver stiffness

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What to tell patients……

• Most effective diet is unknown
  • Reduce daily calorie intake by 500-1000
• Involve dietician / weight loss clinic if resources available
• Diet
  • Avoid high Fructose foods/beverages
  • Reduce carbohydrate intake
  • Portion control, lean protein and fibre for satiety
• Exercise
  • 30-60min 3-5 d/wk, moderate to vigorous exercise

Kistler, Am J Gastroenterol 2011
Abdelmalek, Hepatol 2010
Keating, J Hepatol 2012
AASLD guideline, 2018
Lack of RCT data but several cohort studies, 2 large single-centre studies with biopsy followup and a meta-analysis

- Significant improvement in liver histology
  - Improvements in NASH and fibrosis seen
  - Maximal benefit seen 1y post-op
  - Benefit maintained at 5y

- Cannot recommend bariatric surgery specifically for NASH treatment

- Safety and efficacy of bariatric surgery in those with compensated cirrhosis has not been clearly established

Mummadi, CGH 2008
Mathurin, Gastro, 2009
Chalasani, Hepatol, 2012
AASLD guideline, Hepatology, 2018
Lassailly, Gastro, 2015
Bower, Obes Surg, 2015
Why do we need pharmacotherapy for NASH

- Lifestyle changes are difficult to achieve and even more difficult to sustain

Currently Approved Pharmacologic Agents for NASH in Canada

None  Zero  Zilch
Current Status of Pharmacologic Treatments for NASH

- No Health Canada approved therapies specifically for NASH

- Currently available therapeutics with proven efficacy (NASH is an off-label indication)
  - Vitamin E
  - Pioglitazone
PIVENS: Histologic Resolution of NASH at Wk 96 With Vitamin E or Pioglitazone vs. Placebo

- Double-blind, placebo-controlled, randomized, phase III trial in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)

PIVENS: No Significant Improvement in Fibrosis at Wk 96 for Vitamin E or Pioglitazone vs. Placebo

Why Not Empirically Treat Suspected NASH With Vitamin E?

- Not studied in those with diabetes and cirrhosis
- Increased risk of hemorrhagic stroke\textsuperscript{[1,2]}
- Prostate cancer risk?
  - Especially in older men\textsuperscript{[3]}
- Long-term safety?
  - Remains unknown?
  - Doses > 400 IU/day may be associated with increased mortality
    but data limited by small biased studies\textsuperscript{[4]}

\textsuperscript{2} Schürks M, et al. BMJ. 2010;341:c5702.
Pioglitazone in NASH: Is it safe?

- PIVENS - Weight gain avg 3-5kg, nonreversible when drug stopped
  
- Increased risk of CHF in diabetic patients on pioglitazone

- Pioglitazone associated with increase risk of bladder cancer

1. Sanyal, NEJM 2010
2. Lincoff, JAMA, 2007
3. Tuccori, BMJ 2016
Pharmacologic Treatment Options for NASH – AASLD Guidelines 2018

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>NASH without diabetes</td>
<td>NASH with diabetes or cirrhosis</td>
<td>NASH without diabetes</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>NASH with or without diabetes</td>
<td>NASH with cirrhosis</td>
<td>NASH +/- diabetes</td>
</tr>
<tr>
<td>Liraglutide (LEAN trial)</td>
<td>Resolution of NASH vs placebo but premature to recommend for specific treatment of NAFLD/NASH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin, URSO, omega-3 FA</td>
<td>Not recommended</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lipid Lowering Agents

• Statins, Fibrates & Ezetimibe all safe in NASH & may improve steatosis & transaminases

• Statins presently recommended to treat associated dyslipidemia but not specifically for treatment of NAFLD/NASH

1Nseir W, Dig Dis Sci 2012
2Chalasani, Hepatol 2012 and 2018
Multiple targets for new investigational products for future NASH treatments
# Emerging Treatments in NASH: Phase III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Population</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elafibranor</td>
<td>PPAR α/δ agonist</td>
<td>NASH with fibrosis (stage 1-3)</td>
<td>RESOLVE-IT</td>
<td>NASH resolution without fibrosis worsening; long-term composite of all-cause mortality, cirrhosis, and liver-related outcomes</td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>FXR agonist</td>
<td>NASH with fibrosis (stage 1-3)</td>
<td>REGENERATE</td>
<td>Fibrosis improvement without NASH worsening; NASH resolution without fibrosis worsening; all-cause mortality and liver-related outcomes</td>
</tr>
<tr>
<td>Selonsertib</td>
<td>ASK1 inhibitor</td>
<td>NASH with fibrosis (stage 3)</td>
<td>STELLAR 3</td>
<td>Fibrosis improvement without NASH worsening, EFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NASH with compensated cirrhosis</td>
<td>STELLAR 4</td>
<td></td>
</tr>
<tr>
<td>Cenicriviroc</td>
<td>CCR2/5 antagonist</td>
<td>NASH with fibrosis (stage 2/3)</td>
<td>AURORA</td>
<td>Fibrosis improvement without NASH worsening; composite of progression to cirrhosis, liver-related outcomes, and all-cause mortality</td>
</tr>
</tbody>
</table>
Obeticholic Acid: FXR Agonist and Bile Acid Analogue

CDCA
chenodeoxycholic acid

OCA (6-ECDCA)
obeticholic acid

~ 90 x increased potency

FXR EC$_{50}$ = 8.7 µM

6α ethyl substitution

FXR EC$_{50}$ = 99 nM

FXR Central to a Multitude of Key Pathways

Multiple mechanisms

↑ Glucose tolerance

↓ Portal pressure via ↑ iNOS

↓ Inflammation

↓ Fibrosis

↓ stellate cell activation

FXR agonist (eg, obeticholic acid)

↓ Bile acids

↓ Hepatic triglycerides via ↓ SREBP-1C via ↑ β-oxidation

↑ Cholesterol
**FLINT: Obeticholic Acid in Noncirrhotic Pts With NASH**

- Double-blind, placebo-controlled, randomized, multicenter phase IIb trial

Pts with NASH or borderline NASH confirmed by entry biopsy, NAS ≥ 4 (individual scores each ≥ 1), no cirrhosis (N = 283)

- Obeticholic acid 25 mg PO QD (n = 141)
  - Wk 72 Improvement in NAS ≥ 2 Points: 45% (50/110)
  - Wk 72 Improvement in Fibrosis: 35% (36/102)
  - P = .0002

- Placebo (n = 142)
  - Wk 72 Improvement in NAS ≥ 2 Points: 21% (23/109)
  - Wk 72 Improvement in Fibrosis: 19% (19/98)
  - P = .004

Primary Endpoint: Wk 72 Improvement in NAS ≥ 2 Points With No Worsening of Fibrosis

REGENERATE: Long-term Evaluation of Obeticholic Acid for NASH and Fibrosis

- Double-blind, placebo-controlled, randomized, multicenter phase III trial

Pts with biopsy-confirmed NASH, stage 2-3 fibrosis (Planned N = 2065)

Obeticholic acid 25 mg/day

Obeticholic acid 10 mg/day

Placebo

Until accrued 264 outcome events in OCA 25 mg/day and placebo treatment arms (estimated 6 yrs)

Mo 18 interim analysis
Mo 48 interim analysis
Final analysis (~ 6 yrs)

Dual PPARα/δ Agonist

Elafibranor

PPARα

- Fatty acid oxidation
- TG lowering
- HDL raising
- Inflammation

PPARδ

- Lipoprotein metabolism
- Glucose homeostasis
- Energy metabolism
- Inflammation

Liver

Slide courtesy of Bart Staels, MD.
GOLDEN-505: Elafibranor for 52 Wks

- Double-blind, placebo-controlled, randomized, international phase IIb trial

### Protocol-Defined Primary Outcome*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Wk 52</th>
<th>Modified Definition of Response†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elafibranor 80 mg PO QD (n = 93)</td>
<td>23% (21/93)</td>
<td>13% (12/93)</td>
</tr>
<tr>
<td>Elafibranor 120 mg PO QD (n = 91)</td>
<td>21% (19/91)</td>
<td>19% (17/89)</td>
</tr>
<tr>
<td>Placebo (n = 92)</td>
<td>17% (16/92)</td>
<td>12% (11/92)</td>
</tr>
</tbody>
</table>

*Disappearance of steatosis, ballooning, or lobular inflammation.
†Disappearance of ballooning and disappearance or mild persistence of lobular inflammation.

GOLDEN-505: Elafibranor for 52 Wks

RESOLVE-IT: Long-term Evaluation of Elafibranor for NASH

- Randomized, placebo-controlled, double-blind, multicenter phase III study in pts with NASH and fibrosis

- Primary endpoints
  - Resolution of NASH w/o fibrosis worsening at Wk 72
  - Composite of all-cause mortality, cirrhosis, liver-related clinical outcomes at ~ 4 yrs

ClinicalTrials.gov. NCT02704403.
ASK1 Inhibition in NASH: Selonsertib

- ASK1 pathway activated in NASH and correlates with fibrosis stage
- In rodent models, ASK1 inhibition improves steatosis, inflammation and fibrosis
- Selonsertib is a selective, potent, small molecule inhibitor of ASK1

ASK1, apoptosis signal-regulating kinase 1. Trx, thioredoxin.

Progression to Cirrhosis

- Open-label, randomized phase II trial of pts with biopsy-confirmed NASH, NAS ≥ 5, F2-F3 liver fibrosis (N = 72)

Selonsertib: Phase 2 Short-term (24-Wk) Results

Phase 3 Selonsertib vs Placebo
STELLAR-3 (F3) and STELLAR-4 (F4)

- **Week 48 Primary Endpoint**
  - ≥ 1 stage decrease in fibrosis, with no worsening of ballooning or inflammation

- **Clinical Endpoint at Yr5**
  - Reduction in events of clinical decompensation, transplant, death (F3 and F4 study)
  - Reduction in rates of progression to cirrhosis (F3 study)

Liver biopsy, histological analysis, clinical endpoint, and various dosages and numbers of participants are also mentioned.

ClinicalTrials.gov
CENTAUR: Cenicriviroc Results at 52 Wks

- Randomized, double-blind phase IIb trial of pts with NASH, NAS ≥ 4, liver fibrosis, and diabetes or metabolic syndrome (N = 289)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cenicriviroc 150 mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in NAS ≥ 2 Points With No Worsening of Fibrosis</td>
<td>16/145 (11.1%)</td>
<td>23/145 (16.0%)</td>
</tr>
<tr>
<td>Resolution of NASH</td>
<td>11/145 (7.6%)</td>
<td>8/144 (5.5%)</td>
</tr>
<tr>
<td>Improvement in Fibrosis</td>
<td>20/145 (13.8%)</td>
<td>29/145 (20.1%)</td>
</tr>
</tbody>
</table>

P-values:
- Improvement in NAS: P = .52
- Resolution of NASH: P = .49
- Improvement in Fibrosis: P = .02

**Key NASH Therapies: Resolution of NASH**

- Results from separate studies, not head to head
  - Time points and populations may differ between studies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Active therapy</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E 800 IU/day</td>
<td>36/21</td>
<td>15/72</td>
</tr>
<tr>
<td>Pioglitazone 30 mg/day</td>
<td>47</td>
<td>33/70</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg/day</td>
<td>P = .001</td>
<td>P = .019</td>
</tr>
<tr>
<td>Obeticholic Acid 25 mg/day</td>
<td>P = .08</td>
<td>P = .01</td>
</tr>
<tr>
<td>Elafibranor 120 mg/day</td>
<td>P = .05</td>
<td>P = .49</td>
</tr>
<tr>
<td>Cenicriviroc 150 mg/day</td>
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<td></td>
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</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n/N</th>
<th></th>
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<tbody>
<tr>
<td>Vitamin E 800 IU/day</td>
<td>29/15</td>
<td>80/72</td>
</tr>
<tr>
<td>Pioglitazone 30 mg/day</td>
<td>15/72</td>
<td>103/144</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg/day</td>
<td>9/23</td>
<td>2/39</td>
</tr>
<tr>
<td>Obeticholic Acid 25 mg/day</td>
<td>22/102</td>
<td>9/31</td>
</tr>
<tr>
<td>Elafibranor 120 mg/day</td>
<td>13/98</td>
<td>2/39</td>
</tr>
<tr>
<td>Cenicriviroc 150 mg/day</td>
<td>8/145</td>
<td>6/144</td>
</tr>
</tbody>
</table>

- Results from separate studies, not head to head
  - Time points and populations may differ between studies
### Key NASH Therapies: Improvement in Fibrosis

- Results from separate studies, not head to head
  - Time points and populations may differ among studies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose</th>
<th>Pts (%)</th>
<th>n/N</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>800 IU/day</td>
<td>41</td>
<td>33/80</td>
<td>.24</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>30 mg/day</td>
<td>31</td>
<td>31/70</td>
<td>.12</td>
</tr>
<tr>
<td>Obeticholic Acid</td>
<td>25 mg/day</td>
<td>35</td>
<td>36/102</td>
<td>.004</td>
</tr>
<tr>
<td>Elafibranor</td>
<td>120 mg/day</td>
<td>20</td>
<td>29/145</td>
<td>.02</td>
</tr>
<tr>
<td>Cenicriviroc</td>
<td>150 mg/day</td>
<td>20</td>
<td>21/57</td>
<td>NS</td>
</tr>
<tr>
<td>Selonsertib</td>
<td>6 or 18 mg/day</td>
<td>37</td>
<td>22/72</td>
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</tbody>
</table>

*Calculated from publication, which reported separate results for each dose.
References in slidenotes.
# Emerging Treatments in NASH: Phase IIb

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Population</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aramchol</td>
<td>Synthetic fatty acid/bile acid conjugate</td>
<td>NASH</td>
<td>Aramchol_005[1]</td>
<td>Percent change in liver triglycerides</td>
</tr>
<tr>
<td>Emricasan</td>
<td>Pan-caspase inhibitor</td>
<td>NASH with fibrosis (stage 1-3)</td>
<td>ENCORE-NF[2]</td>
<td>Fibrosis improvement without NASH worsening</td>
</tr>
</tbody>
</table>

**Emerging Treatments in NASH: Phase II**

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Mechanism of Action</th>
<th>Study Population[1]</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>LJN452</td>
<td>FXR agonist</td>
<td>NASH (fibrosis stage 0-3), elevated ALT or PDFF &gt; 10%, obesity, T2DM</td>
<td>FLIGHT-FXR[2]</td>
<td>Adverse event profile; change in transaminases</td>
</tr>
<tr>
<td>LMB763</td>
<td>FXR agonist</td>
<td>NASH (fibrosis stage 0-3), elevated ALT or PDFF &gt; 10%, obesity, T2DM</td>
<td>CLMB763X2201 [3]</td>
<td>Adverse event profile and safety; change in transaminases</td>
</tr>
<tr>
<td>GS-9674 + GS-0976</td>
<td>FXR agonist + ACC inhibitor</td>
<td>NASH (fibrosis stage 2-3) or MRE &gt; 2.88 kPa, PDFF ≥ 10% or MRE &gt; 4.67 kPa, not compensated</td>
<td>GS-US-384-3914[5]</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>GS-0976</td>
<td>ACC inhibitor</td>
<td>NAFLD or NASH without cirrhosis</td>
<td>GS-US-426-3989[6]</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>PF-05221304</td>
<td>ACC inhibitor</td>
<td>NASH (fibrosis stage 1-3), MRE ≥ 2.5 kPa, PDFF ≥ 8%</td>
<td>C1171002[7]</td>
<td>Dose-response effect on liver fat</td>
</tr>
</tbody>
</table>
# Emerging Treatments in NASH: Phase II

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Population[1]</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saroglitazar</td>
<td>PPAR α/γ agonist</td>
<td>NAFLD (fibrosis stage 0-3), ALT &gt; 1.5 ULN</td>
<td>EVIDENCES II[2]</td>
<td>Change in ALT</td>
</tr>
<tr>
<td>IVA337</td>
<td>PPAR α/δ/γ agonist</td>
<td>NASH, SAF fibrosis score &lt; 4</td>
<td>NATIVE[3]</td>
<td>Improvement of SAF activity score</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 analogue</td>
<td>NASH (fibrosis stage 1-4), compensated cirrhosis</td>
<td>LEAN[4,5]</td>
<td>Liver histological improvement</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>GLP-1 analogue</td>
<td>NASH (fibrosis stage 2-3)</td>
<td>NN9931-4296[6]</td>
<td>NASH resolution without worsening of fibrosis</td>
</tr>
<tr>
<td>JKB-121</td>
<td>TLR-4 antagonist</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>Pro00062677[7]</td>
<td>Safety and tolerability; change in ALT, hepatic fat; TTR</td>
</tr>
<tr>
<td>NGM282</td>
<td>FGF19 agonist</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>15-0105[8]</td>
<td>Change in hepatic fat</td>
</tr>
<tr>
<td>BMS-986036</td>
<td>Pegylated FGF21</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>MB130-045[9]</td>
<td>Safety and tolerability; change in hepatic fat</td>
</tr>
<tr>
<td>MGL-3196</td>
<td>THR-β agonist</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>MGL-3196-05[10]</td>
<td>Change in hepatic fat</td>
</tr>
<tr>
<td>Volixibat</td>
<td>ASBT inhibitor</td>
<td>NASH (fibrosis stage 0-3)</td>
<td>SHP626-201[11]</td>
<td>Improvement in NAS without fibrosis worsening</td>
</tr>
</tbody>
</table>
Take-Home Points

- NASH increases risk of liver disease progression and poor outcomes vs NAFLD
- Lifestyle interventions are important but often not sufficient to treat NASH
- Bariatric surgery effective but not specifically indicated for Rx of NASH
- Vitamin E and pioglitazone have the best evidence for treatment of NASH currently but clearly these are not the answer
- Statins are safe in NAFLD/NASH
- Multiple investigational agents in phase 3 trials with promising results
- Deep pipeline of agents in earlier phases of clinical trials so future looks bright??
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