Identifying High Risk NASH Patients Using Noninvasive Techniques (NITs)

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Disclosures

- Principal Investigator for a Drug Study: Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Shire, Viking and Zydus
- Consultant: 89BIO, Gilead, Intercept, Pfizer, Novartis, Novo Nordisk, Allergan, Blade, EchoSens, Fractyl, Terns, OWL, Siemens, Roche diagnostic and Abbott
- Advisory Board Membership: 89BIO, Gilead, Intercept, Pfizer, Novartis, Novo Nordisk, Allergan, Blade, EchoSens, Fractyl, Terns, OWL, Siemens, Roche diagnostic and Abbott
- Stockholder: Anaetos, Rivus Pharma and Viking
- Editorial Board Involvement: Clinical Gastroenterology and Hepatology
Hemoglobin A1c

- Monitor long term glycemic control
- Adjust therapy
- Assess the quality of diabetes care
- Predict the risk for the development of complications
NAFL → Early NASH ↔ Fibrotic (F2-F3) → NASH Cirrhosis

NAFL Rules: Natural History

- Steatosis
- Neutrophils
- Mallory hyaline
- Ballooned hepatocytes

C

D
NASH Rules: Baseline Fibrosis Stage Predicted Mortality and Time to Development of Severe Liver Disease

NASH Rules: FDA: Liver Histologic Improvement Endpoints

**NASH Resolution**
- Resolution of steatohepatitis and
- No worsening of liver fibrosis

**Fibrosis Improvement**
- Improvement ≥ 1 fibrosis stage and
- No worsening of steatohepatitis

### Semaglutide

**Patients with fibrosis stage 2 or 3 at baseline and all randomized patients**

- **Semaglutide 0.1 mg**
- **Semaglutide 0.2 mg**
- **Semaglutide 0.4 mg**
- **Placebo**

<table>
<thead>
<tr>
<th>Patients with fibrosis stage 2 or 3 at baseline</th>
<th>All randomized patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.4</td>
<td>100</td>
</tr>
<tr>
<td>35.6</td>
<td>80</td>
</tr>
<tr>
<td>38.5</td>
<td>60</td>
</tr>
<tr>
<td>58.9</td>
<td>40</td>
</tr>
<tr>
<td>56.1</td>
<td>20</td>
</tr>
</tbody>
</table>

- **Resolution of NASH and no worsening of fibrosis**:
  - **Semaglutide 0.1 mg**: 19%
  - **Semaglutide 0.2 mg**: 33%
  - **Semaglutide 0.4 mg**: 45%
  - **Placebo**: 0.043

- **Improvement of fibrosis by at least one stage and no worsening of NASH**:
  - **Semaglutide 0.1 mg**: 24%
  - **Semaglutide 0.2 mg**: 28%
  - **Semaglutide 0.4 mg**: 42%
  - **Placebo**: 0.53

### Lanifibranor

**FAS (N=247)**

<table>
<thead>
<tr>
<th>Placebo (N=81)</th>
<th>800 mg (N=83)</th>
<th>1200 mg (N=83)</th>
</tr>
</thead>
</table>
| Resolution of NASH and no worsening of fibrosis:
  - **Placebo**: 19%
  - **800 mg**: 33%
  - **1200 mg**: 45%
| Improvement of fibrosis by at least one stage and no worsening of NASH:
  - **Placebo**: 24%
  - **800 mg**: 28%
  - **1200 mg**: 42%

What We Know Today About NITs

- Assess Severity
- Assess changes longitudinally
- Correlate with Clinical Liver Events

**Serum**
- Fib-4
- NFS
- Pro-C3
- ELF
- ALT
“Simple Scores” for Predicting Presence of Advanced (F3/4) Fibrosis

<table>
<thead>
<tr>
<th>NAFLD Fibrosis Score</th>
<th>FIB-4 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>• = -1.675 + 0.037 x Age + 0.094 x BMI + 1.13 x IFG/diabetes + 0.99 x AST/ALT ratio - 0.013 x Platelets - 0.66 x Albumin.</td>
<td>• = (Age * AST) / (Platelets * Sqrt (ALT))</td>
</tr>
<tr>
<td>• A score of less than -1.455 excludes fibrosis (NPV 88-93%).</td>
<td>• A score of less than 1.3 excludes fibrosis (NPV 95%)</td>
</tr>
</tbody>
</table>
| • A score of greater than 0.676 predicts fibrosis (PPV 82-90%). | • A score greater than 3.25 predicts fibrosis (PPV ~70%)

Low Cutoff (NPV) | High Cutoff (PPV)
Low Probability of F3/4 | Indeterminate | High Probability of F3/4

PRO-C3

Collagen PRO-C3

Neo-epitope specific antibody bind to protease specific cleavage site measuring Active fibrogenesis

Type-III collagen maturation

N-terminal Pro-peptide

Specific N-Proteases (ADAMTS2, Procollagen C N-Proteinase)

ABC3D/FIBC3

Boyle et al. J Hep Reports. 2019;

<table>
<thead>
<tr>
<th></th>
<th>FIBC3</th>
<th>FIB4</th>
<th>ABC3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC</td>
<td>0.83</td>
<td>0.76</td>
<td>0.81</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>75.00</td>
<td>21.00</td>
<td>66.00</td>
</tr>
<tr>
<td>Specificity</td>
<td>75.00</td>
<td>94.00</td>
<td>75.00</td>
</tr>
</tbody>
</table>
Hyaluronic acid (HA)
Procollagen III amino terminal peptide (PIIINP)
Tissue inhibitor of metalloproteinase 1 (TIMP-1)

- Meta-analysis of 11 studies
- ELF test had a sensitivity of >0.90 for excluding fibrosis at a threshold of 7.7
- To achieve a specificity of 0.90 for advanced and significant fibrosis, thresholds of 10.18 (sensitivity: 0.57) and 9.86 (sensitivity: 0.55) were required, respectively

The Use of Sequential NITs

NIT #1
Absence of advanced fibrosis  Indeterminate  Presence of advanced fibrosis

NIT #2
Absence of advanced fibrosis  Indeterminate  Presence of advanced fibrosis

NIT #3
Absence of advanced fibrosis  Indeterminate  Presence of advanced fibrosis

NIT, non-invasive test.
Factors Associated With Histologic Response in Adult Patients With Nonalcoholic Steatohepatitis in the FLINT trial

FIB-4 Scores and VCTE Over Time
(ITT Population)

Anstee et al. AASLD. 2019.
**Pro-C3 & ELF Longitudinal data**

### MGL-3196

<table>
<thead>
<tr>
<th></th>
<th>Pro-C3 (ng/ml)</th>
<th>ELF (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elevated BL Pro-C3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGL-3196</td>
<td>0.057</td>
<td>0.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.0019</td>
<td>P=0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>p=0.08</th>
<th>p=0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0.08</th>
<th>0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NGM-282

<table>
<thead>
<tr>
<th></th>
<th>1 mg (ng/ml)</th>
<th>3 mg (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>P=0.004</td>
<td>P=0.005</td>
</tr>
<tr>
<td><strong>Elevated BL ELF</strong></td>
<td>P=0.005</td>
<td>P=0.001</td>
</tr>
<tr>
<td>MGL-3196</td>
<td>P=0.005</td>
<td>P=0.005</td>
</tr>
</tbody>
</table>

In the cross-sectional study, FIB-4 and NFS outperformed other NITs to detect advanced fibrosis.

- C-statistics were 0.80 for FIB-4 and 0.78 for NFS.
- A unit change in APRI, FIB-4, or NFS was associated with changes in fibrosis stage of 0.33 (95% CI, 0.20–0.45; P<.001), 0.26 (95% CI, 0.15–0.37; P<.001), and 0.19 (95% CI, 0.07–0.31; P<.002), respectively.
- The cross-validated C-statistic for detecting progression to advanced fibrosis for
  - APRI was 0.82 (95% CI, 0.74–0.89),
  - FIB-4 was 0.81 (95% CI, 0.73–0.81),
  - NFS was 0.80 (95% CI, 0.71–0.88).

FIB-4 Longitudinal data

ELF Predicts Progression to Cirrhosis and Clinical Events

**Progression to Cirrhosis by Baseline ELF Score**

- **ELF < 9.76**
- **ELF ≥ 9.76**

Log-rank $P < 0.001$

HR 4.52 (95% CI 2.30, 8.88)

**Progression to Liver-Related Events by Baseline ELF Score**

- **ELF < 11.27**
- **ELF ≥ 11.27**

Log-rank $P < 0.001$

HR 2.93 (95% CI 1.64, 5.23)

NITs as Predictors of Clinical Outcomes

Kaplan-Meier curve for event-free survival of clinical events stratified by blood biomarker/score
(n=1021 NASH with ≥F3, median follow-up period: 16 months)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELF ≥ 11.3</td>
<td>0.28</td>
<td>0.94</td>
<td>0.48</td>
<td>0.87</td>
<td>2.5 (2.1, 2.9)</td>
</tr>
<tr>
<td>NFS ≥ 0.67</td>
<td>0.59</td>
<td>0.76</td>
<td>0.16</td>
<td>0.96</td>
<td>1.8 (1.6, 2.1)</td>
</tr>
<tr>
<td>FIB-4 ≥ 3.25</td>
<td>0.59</td>
<td>0.76</td>
<td>0.16</td>
<td>0.96</td>
<td>1.5 (1.4, 1.6)</td>
</tr>
<tr>
<td>VCTE ≥ 13.5 kpa</td>
<td>0.59</td>
<td>0.76</td>
<td>0.16</td>
<td>0.96</td>
<td>1.1 (1.1, 1.1)</td>
</tr>
</tbody>
</table>

Advanced fibrosis - NAS ≥4 and F ≥3, CC - compensated cirrhosis; HR- Hazard ratio Adjusted for Age, Sex, Race, Type 2 Diabetes, BMI, and Baseline NAFLD fibrosis score; PPV - Positive predictive value, NPV - Negative predictive value, *n~ 612.

What We Know Today About NITs

- Assess Severity
- Assess changes longitudinally
- Correlate with Clinical Liver Events

Serum:
- Fib-4
- NFS
- Pro-C3
- ELF
- ALT
What We Know Today About NITs

- Imaging
  - Assess Severity
  - Assess changes longitudinally
  - Correlate with Clinical Liver Events

- VCTE
- MRE
- cT1
- MRI-PDFF
# VCTE: Youden’s Index Based Fibrosis Assessment

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Youden’s Threshold (kPa)</th>
<th>AUROC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F1 vs ≥ F2</td>
<td>8.2</td>
<td>0.77</td>
<td>0.71</td>
<td>0.70</td>
<td>0.78</td>
<td>0.61</td>
</tr>
<tr>
<td>F0-F2 vs ≥ F3</td>
<td>9.7</td>
<td>0.80</td>
<td>0.71</td>
<td>0.75</td>
<td>0.63</td>
<td>0.81</td>
</tr>
<tr>
<td>F0-F3 vs F4</td>
<td>13.6</td>
<td>0.89</td>
<td>0.85</td>
<td>0.79</td>
<td>0.29</td>
<td>0.98</td>
</tr>
</tbody>
</table>

The above threshold values are from the cited peer review publication. Clinical usage of threshold values are determined by the provider based on their preferred threshold value reference.

Modified phase-contrast pulse sequence to visualize rapidly propagating mechanical shear waves (~60 Hz)

### Cutoff for Detecting Advanced Fibrosis

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRE stiffness ≥ 3.64 kPa</td>
<td>0.86 (0.65-0.97)</td>
<td>0.91 (0.83-0.96)</td>
<td>0.68 (0.48-0.84)</td>
<td>0.97 (0.91-0.99)</td>
</tr>
</tbody>
</table>

**AUC for diagnosis of advanced fibrosis: 0.924**

A 30% relative reduction in PDFF corresponds to a two-point reduction in the NAS.

cT1 and PDFF were both correlated with all features of the NAFLD activity score (NAS); cT1 was also correlated with fibrosis.

MRI-PDFF responders had significantly higher odds of histologic response, ballooning with OR 2.9 (95% CI, 1-8.2, p-value 0.05)

FIB-4 Scores and VCTE Over Time (ITT Population)

Anstee et al. AASLD. 2019.
LiverMultiScan®: Measuring response

NITs Predict Survival

MRE Stiffness Correlates With Clinical Liver Events

MRE Stiffness kPa

Disease Progression

Cirrhosis

Decompensation

Ascites

HE

EVB

LTX

Death

Odds of Decompensation increase as liver stiffness increase (OR 3.28)

Han MAT, Loomba, Alkhouri A, Noureddin M. *Liver Int.* 2020.
MRE Stiffness Predicts Stiffness and Clinical Liver Events

LiverMultiScan® in Prediction of Clinical Outcomes
cT1 Can Be Used to Identify CLD Patients at Greatest Risk of Poor Outcomes

Kaplan-Meier curve for event-free survival of clinical events stratified by liver cT1
(n=197, 41% NAFLD, median follow-up period: 42 months)

Example cT1 maps
Liver cT1 > 825ms correctly identified 13/14 of clinical events and 9/10 deaths in 197 CLD patients.

Hazard ratio for cT1 9.9 vs 4.1 for FIB-4
VCTE prediction not statistically significant (p=0.4)

LiverMultiScan® outperformed FibroScan® VCTE and FIB-4 blood test, with similar performance to liver biopsy.

CLD, chronic liver disease.
What we know today about NITs

- Imaging
  - Assess Severity
  - Assess changes longitudinally
  - Correlate with Clinical Liver Events

- VCTE
  - ✓ ✓ ✓

- MRE
  - ✓ ✓ ✓

- cT1
  - ✓ ✓ ✓

- MRI-PDFF
  - ? ✓ ✓ ✓
What We Know Today About NITs

NASH with NAS $\geq 4$ and $\geq F2$

Assess Severity

Assess changes longitudinally

Correlate with Clinical Liver Events

FAST
NIS-4
MAST
MASEF
# FAST: For NASH With NAS ≥ 4 and ≥ F2

**AUROC (95% CI)** | **n** | **Prevalence of NASH+NAS≥4+F≥2** | **Rule-out zone (FAST≤0.35)** | **Grey zone (FAST 0.35-0.67), n(%)** | **Rule-in zone (FAST≥0.67)** |
<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation cohort</strong></td>
<td>0.80 (0.76-0.85)</td>
<td>350</td>
<td>174 (50%)</td>
<td>113 (32%)</td>
<td>101 (29%)</td>
</tr>
<tr>
<td><strong>French bariatric surgery cohort</strong></td>
<td>0.95 (0.91-0.99)</td>
<td>110</td>
<td>16 (15%)</td>
<td>69 (63%)</td>
<td>19 (17%)</td>
</tr>
<tr>
<td><strong>USA screening cohort</strong></td>
<td>0.86 (0.80-0.93)</td>
<td>242</td>
<td>28 (12%)</td>
<td>194 (80%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td><strong>China Hong-Kong NAFLD cohort</strong></td>
<td>0.85 (0.76-0.93)</td>
<td>83</td>
<td>36 (43%)</td>
<td>28 (34%)</td>
<td>26 (31%)</td>
</tr>
<tr>
<td><strong>China Wenzhou NAFLD cohort</strong></td>
<td>0.84 (0.73-0.95)</td>
<td>104</td>
<td>9 (9%)</td>
<td>55 (53%)</td>
<td>12 (11%)</td>
</tr>
<tr>
<td><strong>French NAFLD cohort</strong></td>
<td>0.80 (0.73-0.86)</td>
<td>182</td>
<td>78 (43%)</td>
<td>67 (37%)</td>
<td>46 (24%)</td>
</tr>
<tr>
<td><strong>Malaysia NAFLD cohort</strong></td>
<td>0.85 (0.78-0.91)</td>
<td>176</td>
<td>36 (20%)</td>
<td>78 (44%)</td>
<td>39 (22%)</td>
</tr>
<tr>
<td><strong>Turkish NAFLD cohort</strong></td>
<td>0.74 (0.65-0.82)</td>
<td>129</td>
<td>74 (57%)</td>
<td>26 (20%)</td>
<td>46 (36%)</td>
</tr>
<tr>
<td><strong>Pooled external patients cohort</strong></td>
<td>0.85 (0.83-0.87)</td>
<td>1026</td>
<td>277 (27%)</td>
<td>517 (51%)</td>
<td>197 (19%)</td>
</tr>
</tbody>
</table>

## NIS4 Score: NASH With NAS ≥ 4 and ≥ F2

<table>
<thead>
<tr>
<th></th>
<th>Discovery cohort (n=239)</th>
<th>RESOLVE-IT diag validation cohort (n=475)</th>
<th>Angers validation cohort (n=227)</th>
<th>Pooled validation cohort (n=702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of at-risk NASH*</td>
<td>104 (44%)</td>
<td>260 (55%)</td>
<td>85 (37%)</td>
<td>345 (49%)</td>
</tr>
<tr>
<td>AUROC (95% CI)</td>
<td>0.80 (0.73-0.85)</td>
<td>0.83 (0.79-0.86)</td>
<td>0.76 (0.69-0.82)</td>
<td>0.80 (0.77-0.84)</td>
</tr>
<tr>
<td><strong>Rule-out</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low cutoff</td>
<td>&lt;0.36</td>
<td>&lt;0.36</td>
<td>&lt;0.36</td>
<td>&lt;0.36</td>
</tr>
<tr>
<td>n</td>
<td>108 (45%)</td>
<td>175 (37%)</td>
<td>114 (50%)</td>
<td>289 (41%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>80.8% (71.6-87.6)</td>
<td>83.5% (78.3-87.7)</td>
<td>75.3% (64.5-83.7)</td>
<td>81.5% (76.9-85.3)</td>
</tr>
<tr>
<td>Specificity</td>
<td>65.2% (56.5-73.0)</td>
<td>61.4% (54.5-67.9)</td>
<td>65.5 (57.0-73.1)</td>
<td>63.0% (57.8-68.0)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>81.5% (72.6-88.1)</td>
<td>75.4% (68.3-81.5)</td>
<td>81.6% (73.0-88.0)</td>
<td>77.9% (72.5-82.4)</td>
</tr>
<tr>
<td>Indeterminate n</td>
<td>71 (30%)</td>
<td>143 (30%)</td>
<td>49 (22%)</td>
<td>192 (27%)</td>
</tr>
<tr>
<td><strong>Rule in</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High cutoff</td>
<td>≥0.63</td>
<td>≥0.63</td>
<td>≥0.63</td>
<td>≥0.63</td>
</tr>
<tr>
<td>n</td>
<td>60 (25%)</td>
<td>157 (33%)</td>
<td>64 (28%)</td>
<td>221 (31%)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>45.2% (35.5-55.2)</td>
<td>51.5% (45.3-57.7)</td>
<td>48.2% (37.4-59.3)</td>
<td>50.7% (45.3-56.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>90.4% (83.8-94.6)</td>
<td>89.3% (84.2-93.0)</td>
<td>83.8% (76.5-89.3)</td>
<td>87.1% (83.1-90.3)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>78.3% (65.5-87.5)</td>
<td>85.4% (78.6-90.3)</td>
<td>64.1% (51.0-75.4)</td>
<td>79.2% (73.1-84.2)</td>
</tr>
</tbody>
</table>


- **Golden Trial**
- (miR-34a, Alpha2 macroglobulin/A2M, YKL-40 and HbA1C)
MAST: For NASH With NAS ≥ 4 and ≥ F2

- Derivation (103 patients, 17.5% with fibrotic NASH)/ Validation (244, 11.5%)

### ROC curves - validation data

#### MRI-PDFF + MRE + AST

<table>
<thead>
<tr>
<th></th>
<th>AUROC (95% CI)</th>
<th>Rule-out zone MAST &lt; 0.165</th>
<th>Rule-in zone MAST &gt; 0.242</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation</strong></td>
<td>0.943 (0.901-0.984)</td>
<td>89.3% 73.6% 98.3%</td>
<td>82.1% 90.3% 51.6%</td>
</tr>
<tr>
<td><strong>Validation</strong></td>
<td>0.860 (0.781-0.939)</td>
<td>88.9% 63.5% 96.8%</td>
<td>50.0% 90.6% 51.4%</td>
</tr>
</tbody>
</table>

MASEF: For NASH With NAS ≥ 4 and ≥ F2

- The serum-based Metabolomics Advanced Steatohepatitis Fibrosis Score (MASEF) for the non-invasive identification of patients with NASH and significant fibrosis
- The final MASEF score included only 12 lipids, body mass index (BMI), aspartate aminotransferase (AST) and alanine aminotransferase (ALT)

ROC ANALYSIS

<table>
<thead>
<tr>
<th>Cohort</th>
<th>AUC</th>
<th>sens</th>
<th>spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>0.81</td>
<td>0.36</td>
<td>0.96</td>
<td>0.86</td>
<td>0.62</td>
</tr>
<tr>
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<td>0.95</td>
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</table>

What we know today about NITs

- NASH with NAS ≥ 4 and ≥ F2
- Assess Severity
- Assess changes longitudinally
- Correlate with Clinical Liver Events

FAST
NIS-4
MAST
MASEF
NASH Rules: Liver Histologic Improvement Endpoints

NASH Resolution

- Resolution of steatohepatitis and
- No worsening of liver fibrosis

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage and
- No worsening of steatohepatitis

Semaglutide

<table>
<thead>
<tr>
<th>Proportion of patients (%)</th>
<th>Patients with fibrosis stage 2 or 3 at baseline and all randomized patients</th>
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<tr>
<td>Semaglutide 0.1 mg</td>
<td>40.4</td>
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<tr>
<td>Semaglutide 0.2 mg</td>
<td>35.6</td>
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<td>58.9</td>
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<td>Placebo</td>
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<table>
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<th>Proportion of patients (%)</th>
<th>Patients with fibrosis stage 2 or 3 at baseline and all randomized patients</th>
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<tbody>
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<td>FAS (N=247)*</td>
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<td>56.1</td>
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<tr>
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</table>

Patients with clinical suspicion of NASH with significant or advance Fibrosis

Assess for fibrosis using:

- **VCTE** (consider combining with other tests, e.g., ELF, ProC3 and ALT)

Or consider the following tests:

- **FAST** (consider combining with other tests, e.g., ELF)
- **NIS-4** (consider combining with other tests, e.g., VCTE or ELF)

Or:

- **MRI-PDFF** (consider combining with other tests, e.g., VCTE or ELF)
  - Or:
    - **cT1** (consider combining with other tests, e.g., VCTE or ELF)

NASH with significant or advanced fibrosis - Treatment -

Consider Monitoring with (consider at least 2):

- ALT decline
- Changes in VCTE (e.g., 25% reduction in stiffness)
- MRI-PDFF changes (along with ALT and/or VCTE)

Evolving data:

- FAST, cT1

Waiting for more data:

- Pro-C3, ELF

Reassess every 6-12 months
In Summary

• NITs can
  – Assess disease severity
  – Monitor disease changes longitudinally
  – Correlate with liver related events
• Use of liver biopsy can be reduced
• Waiting for phase 3 trials using NITs as primary end points in the near future