Safe Harbor Statement

This presentation contains "forward-looking" statements that involve risks, uncertainties and assumptions, and actual results may differ substantially from those projected or expected in the forward-looking statements. Forward-looking statements include, but are not limited to: any projections of financial information; any statements about future development, clinical or regulatory events; any statements concerning CymaBay's plans, strategies or objectives; and any other statements of expectation or belief regarding future events. These statements are based on estimates and information available to CymaBay at the time of this presentation and are not guarantees of future performance. Actual results could differ materially from CymaBay's current expectations as a result of many factors including, but not limited to: CymaBay's ability to obtain additional financing to fund its operations; unexpected delays or results in clinical trials; uncertainties regarding obtaining regulatory approvals; uncertainties regarding the ability to protect CymaBay's intellectual property; uncertainties regarding market acceptance of any products for which CymaBay is able to obtain regulatory approval; the effects of competition; and other market and general economic conditions. Additional risks relating to CymaBay are contained in CymaBay's filings with the SEC, including without limitation its most recent Quarterly Report on form 10-Q, Annual Report on form 10-K and other documents subsequently filed or furnished to the SEC, especially under the caption “Risk Factors,” which are available on the SEC web site at http://www.sec.gov, for a fuller discussion of these and other risks relating to an investment in CymaBay's common stock. CymaBay assumes no obligation for and does not intend to update these forward-looking statements, except as required by law.
# CymaBay Highlights

**Differentiated program with two late-stage opportunities**

<table>
<thead>
<tr>
<th><strong>Seladelpar</strong></th>
<th>Selective, potent PPARδ agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 3 PBC</strong></td>
<td>Robust anti-cholestatic &amp; anti-inflammatory activity</td>
</tr>
<tr>
<td><strong>Phase 2b NASH</strong></td>
<td>Potential benefits in liver fat, inflammation and pathology</td>
</tr>
<tr>
<td><strong>Strong balance sheet</strong></td>
<td>Current operating plan funded into 2021</td>
</tr>
</tbody>
</table>
### CymaBay Pipeline

*Increasing focus in liver diseases*

<table>
<thead>
<tr>
<th>Internal Programs</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seladelpar</td>
<td>Primary Biliary Cholangitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seladelpar</td>
<td>Non-alcoholic Steatohepatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBX-2982</td>
<td>Undisclosed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(GPR 119 agonist)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB-001</td>
<td>Undisclosed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(GPR 120 agonist)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Licensed Programs</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arhalofenate</td>
<td>Gout</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(U.S.)
CymaBay Analyst & Investor Day
Agenda

PBC
- Disease, current treatment options and unmet medical need – Dr. Bowlus
- Seladelpar Phase 2 data in PBC (ILC 2018) – Dr. Hirschfield
- Phase 3 study – Dr. Boudes

NASH
- Disease and current approaches in development – Dr. Harrison
- Mechanism and rationale for development in NASH – Dr. McWherter
- Phase 2b study – Dr. Boudes

Summary, Key Upcoming Catalysts, Q&A
Primary Biliary Cholangitis (PBC)

Dr. Christopher Bowlus, UC Davis Health
Primary Biliary Cholangitis
Current Treatments and Unmet Needs

Christopher L. Bowlus, MD
Lena Valente Professor and Chief
Division of Gastroenterology and Hepatology
University of California Davis
PBC: A Progressive, Debilitating Liver Disease

• Most common autoimmune liver disease\(^a\)

• Chronic, slowly progressive\(^b\)

• Inflammation and destruction of the biliary epithelial cells of intrahepatic bile ducts

• Obstruction of bile flow (cholestasis)

• Ultimately causes cirrhosis\(^b\)

Micrograph of PBC showing bile duct inflammation and injury.

---

PBC Diagnostic Criteria

1. Persistently elevated alkaline phosphatase
2. Anti-mitochondrial antibody
3. Liver biopsy consistent with PBC

Presence of at least 2 of 3 criteria

No true population-based studies

**Incidence**
0.33 – 5.8*

**Prevalence**
1.91 – 40.2*

Prevalence appears to be increasing

Possible increasing case identification

AMA prevalence 430 – 1,000*

Higher prevalence in women (10:1)

1 in 1,000 women older than 40 years

Described in most ethnic groups

Possibly more severe in Latinos³

Increasing identification in China⁴

*Per 100,000 person years¹

Pathogenic Model of PBC

**Host Susceptibility**
- Female sex
- MHC
- IL-12A
- 1L-12RB2

**Environmental Exposures**
- Micro-organisms
- Xenobiotics

**PDC-E2 Tolerance Breakdown**
- Regulatory T Cells
- AMA
- CD4/CD8 T Cells

**Bile Duct Damage**
- Bile Duct Apoptotic
- Bleb
- AMA
- PBC Macrophage

---

Clinical Endpoints

- AMA
  - Loss of tolerance to PDC-E2

- Elevated ALP
  - Immune-mediated cholangitis

- Cholestasis
  - Ductopenia

- Portal Hypertension

- Variceal Bleeding
  - Cirrhosis

- Liver-related Death/Liver Transplantation

- IMPAIRED Quality of Life
  - Fatigue
  - Pruritus
Defining Response to UDCA

• Barcelona
  - Decrease in ALP level > 40% of baseline level or a normal level

Paris I (all criteria met)
  - ALP level ≤ 3 X ULN
  - AST level ≤ 2 X ULN
  - Normal bilirubin level

• Paris II (all criteria met)
  - ALP level ≤ 1.5 X ULN
  - AST level ≤ 1.5 X ULN
  - Normal bilirubin level

• Toronto
  - ALP level < 1.67 × ULN

Effect of ALP at 12 months on overall transplantation free survival

Total Global PBC population (90% treated UDCA)

Follow up after 1 year (years)

Cum Survival

<1xULN
1-1.67xULN
>1.67xULN

B. Hansen (personal communication used with permission)
Pruritus Is Common In Patients With PBC

• Prevalence as high as 69%[a]

• Unknown etiology
  • Suspected pruritogens: bile salts, endogenous opioids, histamine, serotonin, progesterone/estrogen, and autotaxin/lysophosphatidic acid[a,b]

• Diurnal variation: most intense itching in the late evening[b]

• Localization reported: limbs (soles of feet, palms of hands)[b]

• Exacerbated by pregnancy or contact with wool/heat[c]

POISE Primary Endpoint

- Composite Endpoint
  - ALP < 1.67 X ULN
  - >15% Reduction in ALP
  - Normal total bilirubin

- Primary Endpoint at Month 12
  - 5–10-mg group (46%)
  - 10-mg group (47%)
  - Placebo group (10%)
  - P<0.001 for both comparisons

Long-Term Obeticholic Acid Treatment Associated with Reversal or Stabilization of Fibrosis/Cirrhosis in Patients with Primary Biliary Cholangitis

Demographics and PBC Disease Characteristics Biopsy Cohort (N=13)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biopsy Cohort (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58 (46, 76)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Duration PBC, years</td>
<td>9.4 (1.7, 21.3)</td>
</tr>
<tr>
<td>History of PBC-related pruritus, n (%)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>UDCA Usage, n (Dose, mg/kg)</td>
<td>13 (13.5)</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>322 (213, 530)</td>
</tr>
<tr>
<td>Total Bilirubin, µmol/L</td>
<td>6.2 (3.9, 15.1)</td>
</tr>
<tr>
<td>Direct Bilirubin, µmol/L</td>
<td>1.5 (1.5, 10.5)</td>
</tr>
<tr>
<td>Fibrosis Stage (F1/F2/F3/F4/F5)</td>
<td>1/3/5/2/2</td>
</tr>
</tbody>
</table>

**Biopsy Timing (years, range)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First Dose of OCA to follow-up biopsy, years</td>
<td>3.0 (2.9-3.0)</td>
</tr>
<tr>
<td>Baseline biopsy to follow-up biopsy, years</td>
<td>3.8 (2.9-4.1)</td>
</tr>
</tbody>
</table>

Data are Median (Min, Max) unless otherwise indicated.

The Majority of Patients had Improvement or No Worsening in Fibrosis Stage after 3 Years of OCA Treatment

- Six patients (46%) showed reversal in fibrosis (1 stage, n=4; 2 stages, n=2), while 2 patients (15%) showed fibrosis worsening by 1 stage
- All 4 patients with baseline cirrhosis showed reversal of fibrosis by at least 1 stage and 3 (75%) improved to fibrosis without cirrhosis

F0=no fibrosis; F1=periportal fibrosis; F2=bridging fibrosis with rare septa; F3=bridging fibrosis with many septa; F4= incomplete cirrhosis; F5=cirrhosis
OCA Limitations

• Pruritus

• Lipid Changes

• FDA Post-Marketing Letter
  • 19 deaths, 8 with reported causes
    • 7 cases of Child B or C cirrhosis and receiving 5 mg *daily*
    • 8 additional cases of serious liver injury without death
      • 3 cases of Child B or C cirrhosis and receiving 5 mg *daily*
      • 5 cases with Child A or no reported liver dysfunction
BEZURSO - Bezaﬁbrate

Recruiting centers: 21
Recruiting period: 2012/10/22 - 2014/12/22

Inadequate biochemical response to UDCA (Paris-2 criteria)

Randomization N=100

M0 M3 M6 M9 M12 M15 M18 M21 M24

Placebo N=50
Placebo N=46
Placebo N=44

Bezaﬁbrate 400 mg/d N=50
Bezaﬁbrate 400 mg/d N=50
Bezaﬁbrate 400 mg/d N=48

Premature termination N=4
Premature termination N=2
Premature termination N=2

UDCA 13-15 mg/kg/d

M24 complete biochemical response

**Primary endpoint**

![Bar chart showing the number of patients with complete response over months for Placebo and Bezafibrate groups.](chart.png)

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo</th>
<th>Bezafibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Bezafrirate</td>
</tr>
<tr>
<td>46</td>
</tr>
<tr>
<td>41</td>
</tr>
<tr>
<td>41</td>
</tr>
<tr>
<td>39</td>
</tr>
<tr>
<td>41</td>
</tr>
<tr>
<td>41</td>
</tr>
<tr>
<td>36</td>
</tr>
<tr>
<td>36</td>
</tr>
<tr>
<td>36</td>
</tr>
<tr>
<td>39</td>
</tr>
</tbody>
</table>

Normalization of alkaline phosphatase level

Changes in itch score (VAS)

Bezafibrate safety reports

• Transaminases > 5 xULN:
  • 1 under placebo
  • 3 under bezafibrate, treatment discontinuation in 2, resolved in all

• CPK > 5 xULN:
  • 1 under bezafibrate (statin not discontinued), resolved after discontinuation

• Serum creatinine:
  • +5% under bezafibrate vs. -3% under placebo at M24 (p<.01)
  • Median (IQR) at M24 (µmole/L): 65.5 (58 – 71) vs. 61.0 (55 – 70)
UDCA: EASL Treatment Guidelines 2017

Stratify Risk and Treat
UDCA for all (13 to 15 mg/kg/day)
Assess Biochemical Response at 1 Year
Goal: Identification of low- and high-risk patients
UDCA responder (low-risk disease)
Inadequate UDCA responder
Individualized Follow-up
According to symptom burden and disease stage
Add Second-Line Therapy
- Licensed: OCA
- Off-label: fibrates, budesonide
- Clinical trials
Monitoring Based On
Bilirubin, ALP, AST, albumin, platelet count, and elastography
Features of AIH?
Seladelpar Phase 2 Data in PBC
Presented at ILC/EASL 2018, Paris

Dr. Gideon Hirschfield, University of Birmingham, UK
Phase 2 Low Dose Study in PBC

Key Observations

- Potent and clinically significant anti-cholestatic activity
- Rapid and sustained anti-inflammatory effects
- No signal for drug-induced itch
## Phase 2 Low Dose Study in PBC – As Amended

**Open label, dose ranging, stable UDCA dose* or intolerant to UDCA**

### AP ≥ 1.67 x ULN; ALT/AST ≤ 3 x ULN; Total Bilirubin ≤ 2 x ULN

<table>
<thead>
<tr>
<th>Main</th>
<th>Extension (Option for Dose Adjustment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seladelpar 5 mg qd (n = 49)</td>
<td>Seladelpar (5 or 10 mg)</td>
</tr>
<tr>
<td>Seladelpar 10 mg qd (n = 49)</td>
<td>Seladelpar (5 or 10 mg)</td>
</tr>
<tr>
<td>Seladelpar 2 mg qd (n = 18)</td>
<td>Seladelpar (2, 5 or 10 mg)</td>
</tr>
</tbody>
</table>

52 weeks

---

* UDCA therapy for prior 12 months
### Phase 2 Low Dose Study in PBC

#### Baseline characteristics

<table>
<thead>
<tr>
<th>CB8025-21629 Study</th>
<th>Seladelpar 2 mg</th>
<th>Seladelpar 5 mg</th>
<th>Seladelpar 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Age, years</td>
<td>55 (10)</td>
<td>57 (8)</td>
<td>56 (9)</td>
</tr>
<tr>
<td>Female/Male</td>
<td>11/0</td>
<td>30/0</td>
<td>27/3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (7)</td>
<td>27 (7)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>History of Pruritus</td>
<td>7 (65%)</td>
<td>19 (63%)</td>
<td>22 (73%)</td>
</tr>
<tr>
<td>AP, U/L</td>
<td>300 (121)</td>
<td>310 (152)</td>
<td>265 (83)</td>
</tr>
<tr>
<td>GGT, U/L</td>
<td>255 (143)</td>
<td>201 (141)</td>
<td>254 (185)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>54 (25)</td>
<td>40 (22)</td>
<td>49 (25)</td>
</tr>
<tr>
<td>Total Bilirubin, mg/dL</td>
<td>0.60 (0.12)</td>
<td>0.68 (0.35)</td>
<td>0.84 (0.34)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.1 (0.2)</td>
<td>4.0 (0.4)</td>
<td>4.1 (0.3)</td>
</tr>
<tr>
<td>UDCA Dose, mg/kg</td>
<td>14 (4)</td>
<td>15 (3)</td>
<td>17 (6)</td>
</tr>
</tbody>
</table>

Safety population as of January 8, 2018. Mean (SD), Baseline: mean of screening(s) and Day 1
### Phase 2 Low Dose Study in PBC

#### Safety, Week 12 and Week 26 cohorts

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Dose Through Week 12</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg</td>
<td>5 mg</td>
<td>10 mg</td>
<td></td>
</tr>
<tr>
<td>Safety Population*</td>
<td>11</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Week 12 Cohort</td>
<td>6</td>
<td>25</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Dose Week 12 Through Week 26</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 or 2 to 5 mg</td>
<td>5 mg</td>
<td>5 to 10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Week 26 Cohort</td>
<td>4</td>
<td>13</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

* As of January 8, 2018.
Phase 2 Low Dose Study in PBC
Dose response and clinical activity with robust decreases in AP

Mean percent AP change from baseline to Week 12
Phase 2 Low Dose Study in PBC
Sustained anti-cholestatic activity to Week 26

AP changes from baseline to Week 26

AP % Change from Baseline

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 10 mg, n=6</td>
<td>-43%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg, n=13</td>
<td>-45%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg, n=19</td>
<td>-43%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Titration allowed
### Phase 2 Low Dose Study in PBC
**AP responders from baseline to Week 26**

<table>
<thead>
<tr>
<th>At Week 26 n (%)</th>
<th>Seladelpar Titration 5 mg or 5 to 10 mg n=19</th>
<th>Seladelpar 10 mg n=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline AP (U/L)</td>
<td>348</td>
<td>272</td>
</tr>
<tr>
<td><strong>Primary Composite Endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder Rate</td>
<td>13 (68%)</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>AP &lt; 1.67 x ULN</td>
<td>13 (68%)</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>AP decrease ≥ 15%</td>
<td>18 (95%)</td>
<td>17 (89%)</td>
</tr>
<tr>
<td>Total bilirubin ≤ ULN</td>
<td>18 (95%)</td>
<td>17 (89%)</td>
</tr>
<tr>
<td><strong>AP Normalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP ≤ ULN at Week 26</td>
<td>5 (26%)</td>
<td>6 (32%)</td>
</tr>
</tbody>
</table>
Week 12 Cohort

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Median ALT</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-50</td>
<td>-50%</td>
</tr>
<tr>
<td>2</td>
<td>-40</td>
<td>-40%</td>
</tr>
<tr>
<td>4</td>
<td>-30</td>
<td>-30%</td>
</tr>
<tr>
<td>6</td>
<td>-20</td>
<td>-20%</td>
</tr>
<tr>
<td>8</td>
<td>-10</td>
<td>-10%</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>5 m g, n=25</td>
<td>-28%</td>
</tr>
<tr>
<td></td>
<td>2 m g, n=6</td>
<td>-9%</td>
</tr>
</tbody>
</table>

Week 26 Cohort

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Median ALT</th>
<th>% Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-50</td>
<td>-50%</td>
</tr>
<tr>
<td>2</td>
<td>-40</td>
<td>-40%</td>
</tr>
<tr>
<td>4</td>
<td>-30</td>
<td>-30%</td>
</tr>
<tr>
<td>6</td>
<td>-20</td>
<td>-20%</td>
</tr>
<tr>
<td>8</td>
<td>-10</td>
<td>-10%</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>10 m g, n=22</td>
<td>-35%</td>
</tr>
<tr>
<td>14</td>
<td>5 m g, n=19</td>
<td>-40%</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Phase 2 Low Dose Study in PBC
Changes in self reported symptom scores: Pruritus

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Seladelpar Titration 5 mg or 5 to 10 mg</th>
<th>Seladelpar 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS (0-100)</td>
<td>19</td>
<td>37</td>
</tr>
</tbody>
</table>

Week 26 Cohort
Phase 2 Low Dose Study in PBC
Changes in self reported symptom scores: PBC-40 QoL

Week 26 Cohort

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Seladelpar Titration 5 mg or 5 to 10 mg</th>
<th>Seladelpar 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBC-40, Total (34-200)</td>
<td>108</td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>PBC-40, Fatigue (11-55)</td>
<td>31</td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>

Total Score

Fatigue

Weeks

Median PBC-40

% Change from Baseline

5 mg, n=19

10 mg, n=19
Six SAEs, all deemed unrelated to seladelpar

Two AEs leading to seladelpar discontinuation, both unrelated to seladelpar

No transaminase safety signal

No signal for drug-induced pruritus
Seladelpar for PBC

Conclusions

Potent and clinically significant anti-cholestatic and anti-inflammatory activity at 5 and 10 mg / day

No signal for drug-induced itch

Ongoing Phase 2 study now fully enrolled

Preparing for Phase 3 in 2018
Seladelpar Planned Phase 3 Study - PBC

Dr. Pol Boudes, Chief Medical Officer
Seladelpar for PBC
Phase 3 program objectives

- Obtain conditional US/EU approval for the treatment of PBC in patients that are not responding adequately to UDCA or are intolerant to UDCA
  - Improved target label compared to Ocaliva
  - Superior activity on markers of cholestasis
  - No drug-induced pruritus

- Potential to improve PBC-associated pruritus as an additional upside

- PBC patients with advanced disease to be evaluated in a separate study
### Population
- PBC with intolerance or inadequate response to UDCA
- AP > 1.67 x ULN, bilirubin ≤ 2 x ULN (mild and moderate PBC)
- Includes patients with severe pruritus

### Design
- Double blind, 52-weeks, placebo controlled (N=240)
- Seladelpar 5/10 mg titration and 10 mg vs. placebo (1:1:1 randomization)
- Stratified by AP and pruritus
- Pruritus evaluated with Numerical Rating Scale (0 to 10) using e-diary

**Phase 3 Pivotal Study – CB8025-31735**

*Planned for 2H 2018*
Phase 3 Pivotal Study – CB8025-31735
More than 100 centers in North America, EU and beyond

Study Diagram – Clinical Study
n=240

- (n=80) Seladelpar 5 mg
- (n=80) Seladelpar 10 mg
- (n=80) Seladelpar 5 mg
- (n=80) Seladelpar 10 mg
- (n=80) Placebo

Long Term Safety Study (CB8025-31731)

Screening  Run-In  Treatment
0 M1 M3 M6 M9 M12
Randomization
Primary Objective:

- To evaluate the safety and effect on cholestasis of two seladelpar regimens (5 mg/day possibly titrated to 10 mg/day and 10 mg/day) over 52 weeks of treatment compared to placebo

Primary Outcome Measures:

- Response on the validated composite endpoint at 12 months:
  - \( AP < 1.67 \times \text{upper limit of normal (ULN)}, \) and
  - \( \geq 15\% \) decrease in AP, and
  - Total Bilirubin \( \leq \) ULN

- Adverse events, routine biochemistry and hematology
Key Secondary Objectives:

- To evaluate the effect of seladelpar on normalization of AP levels
- To evaluate the effect of seladelpar on pruritus

Key Secondary Outcome Measures:

- Proportion of patients with AP < 1.0 × ULN at 6 and 12 months
- Change from baseline in pruritus Numerical Rating Scale at 6 months
Objective: To evaluate seladelpar long term safety and efficacy

Duration: until seladelpar is commercially available or program is discontinued

Design: Open label, non-controlled, seladelpar dose continued (5 or 10 mg/day)

Participants: Any subject enrolled in low dose PBC study or in any new seladelpar study will be eligible
- Low dose study fully enrolled (N>100)
- 32/32 (100%) of patients who reached 52 weeks elected to enroll (6/11)
Non-Alcoholic Steatohepatitis (NASH)

Dr. Stephen Harrison, Pinnacle Clinical Research
The Burden of NASH and Emerging Pharmacologic Treatment

Stephen A. Harrison, MD, FACP, FAASLD
COL (ret.), USA, MC
Visiting Professor of Hepatology
Radcliffe Department of Medicine, University of Oxford
Medical Director, Pinnacle Clinical Research
What is NAFLD?

- Spectrum of liver disease characterised by:
  - Hepatic steatosis
  - No significant alcohol consumption or competing aetiologies for hepatic steatosis
- Most common cause of liver disease in Western countries
- Predicted to become a leading cause of end stage liver disease, hepatocellular carcinoma and indication for liver transplantation

NAFLD, non-alcoholic fatty liver disease
Townsend SA and Newsome PN. Aliment Pharmacol Ther. 2017;46:494–507;
Bertot LC et al. Int J Mol Sci
NASH is distinguished by its histologic patterns

NASH is part of the broader Non-Alcoholic Fatty Liver Disease (NAFLD) spectrum

- **Non-Alcoholic Fatty Liver (NAFL)**
  - Steatosis in >5% of hepatocytes

- **Non-Alcoholic Steatohepatitis (NASH)**
  - Steatosis
  - Lobular Inflammation
  - Hepatocellular ballooning

NASH with Fibrosis

- NASH can be accompanied by varying levels of fibrosis from stage 0 (none) to 4 (cirrhosis)^

Diagnostic criteria for NASH is not uniform, but commonly includes at least 3 key histologic markers

- **Steatosis**: retention of triglycerides and other fats in liver cells
- **Hepatocellular ballooning**: a form of cell death, where cells are enlarged or “ballooned”
- **Lobular inflammation**: infiltration of the tissue with immune cells due to liver injury

Fibrosis is an important histologic pattern, but is not required for NASH diagnosis

- **Fibrosis**: accumulation of extracellular matrix proteins manifesting as tissue scarring; other histologic markers of NASH may dissipate with onset of cirrhosis

*Patients have varying rates of progression and regression

^ Fibrosis stage based on Brunt Kleiner system
Epidemiology and Natural History
Portion size escalation and obesity

Cheeseburgers:

20 yrs ago

333 cal
(regular Hardee’s Cheeseburger still 350 cal)

Now

1300 cal

Obesity:

1990

2015

www.nhlbi.nih.gov and CDC
The disease burden of NASH on the population is expected to increase over time

NASH prevalence could grow along with the rapid increase in diabetes and obesity

Conservative

Aggressive


Global prevalence of NAFLD

NAFLD, non-alcoholic fatty liver disease
Prevalence of NAFLD/NASH in South Texas

771 patients in DB lock

9 patients with CLD

198 patients that didn’t have all 4 exams (MRI-PDFF, MRE, LIF and FS)

93 patients should have had a LB (FS≥7 | MRE≥3 | mean LIF≥2 | MRI-PDFF≥5)

6 patients had a LB but no reading yet (Beaujon)

465 patients OK for analysis including 198 with LB

The 267/465 patients with no LB will be considered as “normal liver” since they all have all imaging modalities “normal”
Prevalence of NAFLD/NASH in South Texas

NAFLD prevalence (%)

- All: 32% (N=65)
- DM: 71% (N=243)
- Caucasian - non hispanic: 29% (N=89)
- Caucasian - hispanic: 57% (N=93)
- African-American: 20% (N=20)
- Asian: 30% (N=89)
- Other: 28% (N=14)

Data on file
Natural History of NAFLD

NAFLD

- Isolated Fatty Liver
  - >80%
  - None to very minimal progression to fibrosis
  - No ↑ risk of death compared with the general population

- Fatty Liver with Mild Inflammation
  - Possible sampling variability with some risk of progression

NASH

- ↑ risk of death compared with general population
  - Cardiovascular, malignancy, liver-related
- NASH with fibrosis portends worse prognosis
  - Fibrosis progression associated with diabetes, severe IR, weight gain >5 kg, rising ALT, AST

- ~11% over 15 years, but significant variability

NASH Cirrhosis

- ~7% over 6.5 years

HCC

- ~31% over 8 years

Decompensation

### Heirarchy of Mortality Risk

1. Fibrosis
2. Portal inflammation
3. Diagnosis of NASH
4. Ballooning degeneration

### Mortality/Liver Transplant Risk by Fibrosis Stage (95% CI of HR)

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>1.18–2.81</td>
</tr>
<tr>
<td>Stage 2</td>
<td>1.20–3.03</td>
</tr>
<tr>
<td>Stage 3</td>
<td>1.16–3.12</td>
</tr>
<tr>
<td>Stage 4</td>
<td>3.35–12.04</td>
</tr>
</tbody>
</table>

### Liver-Related Events Risk by Fibrosis Stage (95% CI of HR)

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>0.63–8.91</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2.26–24.94</td>
</tr>
<tr>
<td>Stage 3</td>
<td>4.35–43.65</td>
</tr>
<tr>
<td>Stage 4</td>
<td>11.94–188.61</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; NASH, nonalcoholic steatohepatitis.

Treatment of NASH

Lifestyle Modification
Pharmacotherapy
Weight Loss Pyramid

- Weight Loss ≥10%<sup>1</sup>
- Weight Loss ≥7%<sup>1</sup>
- Weight Loss ≥5%<sup>1</sup>-3
- Weight Loss ≥3%<sup>1</sup>-4

 Patients achieving:

- Fibrosis (45%)
  - <10% in 1 year<sup>1</sup>

- NASH Resolution (64–90%)*
  - 18% in 1 year<sup>1</sup>

- Ballooning / inflammation (41–100%)*
  - 30% in 1 year<sup>1</sup>

- Steatosis (35–100%)*
  - Depending on degree of weight loss

<sup>1</sup> Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78  
Pharmacotherapy for NASH
Pathogenesis of NAFLD/NASH
Agents in development for NASH

*FDA fast track status; **FDA breakthrough designation.

- PPAR modulators
  - selonsertib
  - **obeticholic acid
  - *cenicriviroc
  - saroglitazar
  - IVA337
  - MT-3995
  - IMM-124E
  - **elafibranor
  - *emricasan
  - *tipelukast
  - sotagliflozin
  - remogliflozin
  - sotagliflozin
  - GRI-0621
  - CER-002
  - NC101

- RAAS modulators
  - seladelpAR
  - BI 1467335/B1
  - BMS-986036
  - GS-9674
  - GS-0976
  - MSDC-0602K
  - LMB763
  - *NS-0200
  - **obeticholic acid
  - BMS-986171
  - JKB 121
  - *EDP-305
  - PF-05221304
  - NGM313, NGM386, NGM395
  - NGM282
  - O304
  - INT-767
  - KBP-042

- Metabolism modulators
  - norursodeoxycholic acid
  - *aramchol
  - VK2809
  - *EDP-305
  - INT-767
  - A4250
  - IONIS-DGAT2Rx
  - KIB-042

- Neurotransmitter modulators
  - semaglutide
  - MGL-3196
  - RG-125
  - DS102
  - PF-06835919

- Incretins
  - **elafibranor
  - *emricasan
  - *tipelukast
  - MSDC-0602K
  - LMB763
  - *NS-0200

- Immune modulators
  - GRI-0621
  - DUR-928
  - JKB 121
  - *EDP-305

- Antifibrotic/anti-inflammatory
  - bertilumab
  - *ND-102-s201
  - VBY-376

- Apoptosis inhibitors
  - seladelpAR
  - *GR-MD-02
  - solithromycin
  - *emricasan
  - *tipelukast

- Glucose pathway modulators
  - ertugliflozin
  - rastagliflozin
  - sotagliflozin
  - GRI-0621
  - CER-002

- Immune modulators
  - GRI-0621
  - DUR-928
  - JKB 121
  - *EDP-305

- Lipid modulators
  - norursodeoxycholic acid
  - *aramchol
  - VK2809
  - *EDP-305
  - INT-767
  - A4250
  - IONIS-DGAT2Rx

*FDA fast track status; **FDA breakthrough designation.

FDA, Food and Drug Administration; IV, intravenous; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; RAAS, renin-angiotensin-aldosterone system.
NASH Ongoing Phase 3 trials

• **REGENERATE & REVERSE** with Obeticholic Acid ( Intercept )
• **RESOLVE -IT** with Elafibranor (Genfit)
• ** STELLAR 3 & STELLAR 4** with Selonsertib (Gilead)
• **AURORA** with cenicriviroc (Allergan)

*All are Phase3/4 adaptive design with histological end points for Subpart H conditional approval followed by clinical end points for full approval*
Key NASH Therapies: Resolution of NASH

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

Key NASH Therapies: Improvement in Fibrosis

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

*Calculated from publication, which reported separate results for each dose.*
SELECT COMPOUNDS IN PHASE 2 DEVELOPMENT
Data Comparison: Change in Absolute Liver Fat Content

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in Absolute Liver Fat Content (MRI-PDFF; %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM282 (12W)</td>
<td>-9.7</td>
</tr>
<tr>
<td>GS-0976 (ACC)² (12W)</td>
<td>-11.9</td>
</tr>
<tr>
<td>BMS-986036 (16W)</td>
<td>-0.9</td>
</tr>
<tr>
<td>GS-4997 (ASK1)² (24W)</td>
<td>-1.0</td>
</tr>
<tr>
<td>Aramchol™4 (52W)</td>
<td>-3.4</td>
</tr>
<tr>
<td>OCA¹ (72W)</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

1 Selonsertib (SEL) +/- Simtuzumab (SIM) open label pooled study data; simtuzumab data used as proxy for placebo data
2 Placebo-subtracted data; secondary analysis of OCA FLINT trial
3 Absolute changes in LFC for GS-0976 and GS-4997 calculated from baseline values and relative median change values
4 LFC assessed by MRS

Sources: BMS-986036 (EASL 2017); Galmed (Press release June 12, 2018); GS-0976 (AASLD 2017); GS-4997 (Loomba et al, Hepatology 2017); OCA (AASLD 2017); NGM282 (Harrison et al. The Lancet 2018)
Data Comparison: Change in Relative Liver Fat Content

Change in relative liver fat content (MRI-PDFF; %)

<table>
<thead>
<tr>
<th></th>
<th>PBO 3 mg</th>
<th>PBO 10 mg QD</th>
<th>PBO 20 mg QW</th>
<th>PBO 5 mg 20 mg</th>
<th>SIM 1 6 mg 18 mg</th>
<th>PBO All 1 4</th>
<th>SIM 1 6 mg 18 mg</th>
<th>MGL-3196 25 mg</th>
<th>MGL-3196 36 mg</th>
<th>OCA 2 72W</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM282 (12W)</td>
<td>-1</td>
<td>-6</td>
<td>-27</td>
<td>-29</td>
<td>-13</td>
<td>-13</td>
<td>-10</td>
<td>-36</td>
<td>-42</td>
<td>-17</td>
</tr>
<tr>
<td>BMS-986036 3 (16W)</td>
<td>-47 *</td>
<td>-38</td>
<td>-27</td>
<td>-29</td>
<td>-13</td>
<td>-13</td>
<td>-10</td>
<td>-36</td>
<td>-42</td>
<td>-17</td>
</tr>
<tr>
<td>GS-0976 (ACC) (12W)</td>
<td>-61 *</td>
<td>-38</td>
<td>-27</td>
<td>-29</td>
<td>-13</td>
<td>-13</td>
<td>-10</td>
<td>-36</td>
<td>-42</td>
<td>-17</td>
</tr>
<tr>
<td>MGL-3196 (12W)</td>
<td>-13</td>
<td>-7</td>
<td>-5</td>
<td>-13</td>
<td>-10</td>
<td>-10</td>
<td>-10</td>
<td>-36</td>
<td>-42</td>
<td>-17</td>
</tr>
<tr>
<td>MGL-3196 (36W)</td>
<td>-13</td>
<td>-7</td>
<td>-5</td>
<td>-10</td>
<td>-36</td>
<td>-36</td>
<td>-36</td>
<td>-42</td>
<td>-37 *</td>
<td>-17</td>
</tr>
<tr>
<td>OCA 2 (72W)</td>
<td>-13</td>
<td>-7</td>
<td>-5</td>
<td>-10</td>
<td>-36</td>
<td>-36</td>
<td>-36</td>
<td>-42</td>
<td>-37 *</td>
<td>-17</td>
</tr>
<tr>
<td>% pts. w/ ≥30% LFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-986036 3 (16W)</td>
<td>7</td>
<td>85</td>
<td>92</td>
<td>25</td>
<td>57</td>
<td>52</td>
<td>15</td>
<td>23</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>GS-0976 (ACC) (12W)</td>
<td>25</td>
<td>57</td>
<td>52</td>
<td>15</td>
<td>23</td>
<td>48</td>
<td>10</td>
<td>13</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>GS-4997 (ASK1) (24W)</td>
<td>10</td>
<td>13</td>
<td>26</td>
<td>18</td>
<td>60</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGL-3196 (36W)</td>
<td>18</td>
<td>60</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Selonsertib (SEL) +/- Simtuzumab (SIM) open label pooled study data; simtuzumab data used as proxy for placebo data
2 Placebo-subtracted data; secondary analysis of OCA FLINT trial
3 Relative change in LFC for BMS-986036 calculated from reported baseline values and absolute changes
4 Absolute change in LFC for MGL-3196 calculated from baseline value (across entire study) and relative median change from baseline; data from ongoing blinded study where “High MGL-3196” was a pre-specified group of patients with relatively higher drug levels as measured by sex hormone binding globulin (marker of MGL-3196 hepatic level and activity) and “All MGL-3196” include low and high levels as measured by sex hormone binding globulin

Sources: BMS-986036 (EASL 2017); GS-0976 (AASLD 2017); GS-4997 (Loomba et al, Hepatology 2017); OCA (AASLD 2017); MGL-3196 (Press release Dec. 6, 2017 and transcript of webcast, and Press release June 12, 2018)

*Statistically significant
Data Comparison: Change in ALT

Change in ALT from baseline (U/L)

<table>
<thead>
<tr>
<th>Drug</th>
<th>PBO 3mg</th>
<th>10 mg QD</th>
<th>20 mg QW</th>
<th>PBO 5 mg</th>
<th>20 mg</th>
<th>SIM 1 mg</th>
<th>6 mg</th>
<th>18 mg</th>
<th>Not reported</th>
<th>Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM282 (12W)</td>
<td>-2</td>
<td>-4</td>
<td>-16</td>
<td>-3</td>
<td>-6</td>
<td>-3</td>
<td>-6</td>
<td>-8</td>
<td>-12</td>
<td>-17</td>
</tr>
<tr>
<td>BMS-986036 (16W)</td>
<td>-33</td>
<td>-25</td>
<td>-15</td>
<td>-5</td>
<td>-15</td>
<td>-5</td>
<td>-11</td>
<td>-12</td>
<td>-5</td>
<td>-12</td>
</tr>
<tr>
<td>GS-0976 (ACC) (12W)</td>
<td>-22</td>
<td>-16</td>
<td>-11</td>
<td>-10</td>
<td>-20.5</td>
<td>-11</td>
<td>-12</td>
<td>-24</td>
<td>-24</td>
<td>-24</td>
</tr>
<tr>
<td>GS-4997 (ASK1) (24W)</td>
<td>-43</td>
<td>-33</td>
<td>-24</td>
<td>-7</td>
<td>-10</td>
<td>-5</td>
<td>-11</td>
<td>-12</td>
<td>-20.5</td>
<td>-20.5</td>
</tr>
<tr>
<td>Aramchol (52W)</td>
<td>-33</td>
<td>-24</td>
<td>-11</td>
<td>-10</td>
<td>-20.5</td>
<td>-11</td>
<td>-12</td>
<td>-20.5</td>
<td>-12</td>
<td>-17</td>
</tr>
<tr>
<td>OCA (72W)</td>
<td>-33</td>
<td>-24</td>
<td>-11</td>
<td>-10</td>
<td>-20.5</td>
<td>-11</td>
<td>-12</td>
<td>-20.5</td>
<td>-12</td>
<td>-17</td>
</tr>
</tbody>
</table>

Sources: BMS-986036 (EASL 2017); Galmed (Press release June 12, 2018); GS-0976 (AASLD 2017); GS-4997 (Loomba et al, Hepatology 2017); OCA (AASLD 2017)

1 Selonsertib (SEL) +/- Simtuzumab (SIM) open label pooled study data; simtuzumab data used as proxy for placebo data
2 Placebo-subtracted data; secondary analysis of OCA FLINT trial
3 Absolute change in ALT for BMS-986036 and GS-0976 calculated from reported baseline values and relative changes
4 Relative change in ALT for GS-4997 calculated from reported baseline values and relative changes

*Statistically significant
Resolution of NASH\(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of patients</th>
<th># pts. with paired biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E(^2)</td>
<td>36</td>
<td>80</td>
</tr>
<tr>
<td>Pioglitazone(^2)</td>
<td>21</td>
<td>72</td>
</tr>
<tr>
<td>OCA(^3)</td>
<td>22</td>
<td>70</td>
</tr>
<tr>
<td>Elafibranor(^4)</td>
<td>19*</td>
<td>98</td>
</tr>
<tr>
<td>Cenicriviroc(^5)</td>
<td>8</td>
<td>126</td>
</tr>
<tr>
<td>Liraglutide(^6)</td>
<td>39*</td>
<td>102</td>
</tr>
<tr>
<td>Aramchol(^7)</td>
<td>19*</td>
<td>126</td>
</tr>
<tr>
<td>MGL-3196 (36W)</td>
<td>27*</td>
<td>73</td>
</tr>
</tbody>
</table>

\(^1\) Resolution of NASH as defined by each study below
\(^2\) PIVENS (Resolution of definite NASH); FLINT (Not NAFLD, or NAFLD but not NASH at 72W biopsy; no requirement for absence of worsening of fibrosis); GOLDEN-505 modified definition (Ballooning score = 0 together with lobular inflammation score = 0 or 1 and resulting in an overall pathologic diagnosis of steatosis alone or steatosis with mild inflammation, without worsening of fibrosis (any stage increase in fibrosis is considered fibrosis progression)); ITT population
\(^3\) CENTAUR study 1Y data (Complete resolution of NASH and no worsening of fibrosis stage)
\(^4\) ARREST (Ballooning score = 0 and lobular inflammation score = 0 or 1)
\(^5\) 600mg dose vs placebo

Sources: Sanyal et al, NEJM 2010 (PIVENS); Armstrong et al, Lancet 2016 (LEAN); Neuschwander-Tetri et al, Lancet 2014 (FLINT); Ratziu et al, Gastro 2016 (GOLDEN-505); Friedman et al, Hepatology 2017 (CENTAUR); MGL-3196 (Press release June 12, 2018); Galmed (Press release June 12, 2018)
SELECTING THE RIGHT PATIENTS FOR NASH CLINICAL TRIALS
Current Requirement for NASH Patients in Phase 2 & 3 Clinical Trials

Ph 3 trials: 7600 Subjects
Ph 2 trials: 2400 Subjects

Likely 1-2000 more NASH subjects required in 2018 for new phase 2 and 3 studies starting

Majority F2/3 Fibrosis
Screen Fail Rates for Current and Recently Completed NASH Trials

~55-60%
Number of NAFLD Patients Required to Screen for Current NASH Studies Given Screen Fail Rate

22,225 NAFLD Subjects Screened

55% Screen Fail Rate

~ cost per SF:
- $2000 w/o MRI or bx
- $5000 w/MRI, but no bx
- $8000 w/MRI and bx

10,000 NASH Subjects Randomized

*Also includes indirect CRO costs (logistics, central reading, monitoring of screening visits, etc
* Historical biopsies are still being utilized in about 1/3 of cases. This would bring the cost down some
Histological Reasons for Screen Failing in a Large Phase 2 Trial

- **54%**
- **Stage 0, NAS <4**
- **18%**
- **Stage 0, NAS >/= 4**
- **11%**
- **Stage 1, no NASH**
- **7%**
- **Stage 2/3, No NASH**
- **10%**
- **Cirrhosis**
Pre-screening criteria for NASH clinical trials

High likelihood of NASH and fibrosis
- Age >50, Hispanic, DM, obesity, HTN, FS kPa >8.5, AST >40, AST/ALT ratio ≥1, NFS >0.676, FIB-4 >2.67

Intermediate likelihood of NASH and fibrosis
- Age >40, well-controlled DM, obesity, HTN, FS kPa >7.0, AST >20

Low likelihood of NASH and fibrosis
- Age <40, non-DM, non-obese, FS kPa <7, AST <20, NFS <=1.455, FIB-4 <1.30

Konerman et al, J Hepatol 2018
Number of NAFLD Patients Required to Screen for Current NASH Studies Given Screen Fail Rate

18,180 NAFLD Subjects Screened

~ cost per SF:
- $2000 w/o MRI or bx
- $5000 w/MRI, but no bx
- $8000 w/MRI and bx

45% Screen Fail Rate

10,000 NASH Subjects Randomized

Dropping SF rate from 55% to 45%, reduced the number needed to screen by 4,045 subjects. Assuming all made it to liver biopsy, this would be a cost savings of 20 to 30 million US dollars.
Seladelpar Clinical and Preclinical Rationale for NASH

Dr. Charles McWherter, Chief Scientific Officer
Seladelpar
Once daily oral PPAR\(\delta\) agonist for inflammatory liver diseases

Human PPAR\(\delta\) EC\(_{50}\) = 2 nM
630-Fold Selective Over PPAR\(\alpha\)
Inactive Against PPAR\(\gamma\)

Bile Acid Homeostasis
- Cholesterol synthesis ↓
- Bile acid synthesis (C4) ↓
- Transport ↑

Inflammation
- NF\(\kappa\)B-dependent gene activation ↓
- Inflammatory cytokines ↓
- hs-C-Reactive Protein ↓

Fibrosis
- Connective Tissue Growth Factor ↓
- Stellate cell activation ↓
- Collagen deposition ↓

Metabolic Effects
- Cholesterol/LDL-C ↓
- Fatty acid oxidation ↑
- Insulin sensitivity ↑

Gene Activation or Repression

PPAR\(\delta\) and RXR
Seladelpar in an 8-Week Ph 2 Study in Mixed Dyslipidemia
Cardiovascular, metabolic and anti-inflammatory activity

- Obese patients with elevated TG and LDL-C (“NAFLD overlap”)
- Decreases in hs-CRP, Free FA, small dense LDL, HOMA-IR

**Serum Triglycerides**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from Day 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 28)</td>
<td>-10.00 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Seladelpar 50 mg (N = 28)</td>
<td>-30.00 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Seladelpar 100 mg (N = 32)</td>
<td>-40.00 (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

**LDL-C**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change from Day 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N = 28)</td>
<td>-20.00 (p &lt; 0.001)</td>
</tr>
<tr>
<td>Seladelpar 50 mg (N = 28)</td>
<td>-30.00 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Seladelpar 100 mg (N = 32)</td>
<td>-40.00 (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

Obese Diabetic & Dyslipidemic foz/foz Mouse Model of NASH

- Collaboration with Geoff Farrell at the Australian National University & Matthew Yeh, UW Seattle
- Loss of function mutation in alms1 gene produces hyperphagic mice
- Mouse characteristics
  - Obese
  - Insulin resistant and diabetic
  - Hyperlipidemic
  - Hepatic steatosis and lipotoxicity
  - Inflammation and ballooning
  - NASH established by 20 weeks
  - Liver fibrosis
- Groups (n=8): Seladelpar and Vehicle dosed in foz/foz and wild type mice

Reductions in Serum Triglyceride and Cholesterol
**Seladelpar effects similar to those seen in mixed dyslipidemic patients**

* p < .05 seladelpar vs. vehicle

<table>
<thead>
<tr>
<th>Serum Triglyceride</th>
<th>mmol/L (at 28 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1.5</td>
</tr>
<tr>
<td>Seladelpar</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum Cholesterol</th>
<th>mmol/L (at 28 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>8</td>
</tr>
<tr>
<td>Seladelpar</td>
<td>4</td>
</tr>
</tbody>
</table>

* p < .05 seladelpar vs. vehicle
Seladelpar Reduced ALT and Improved Liver Pathology
Effect consistent with reduction in hepatocellular stress

Seladelpar treatment improves liver pathology which is accompanied by a 48% decrease in serum ALT

* p < .05 seladelpar vs. vehicle
Seladelpar Reduced Hepatic Steatosis

Reductions in all sub-types of hepatic lipids and cholesterol

* p < .05 seladelpar vs. vehicle
Seladelpar Reversed Ballooning and Reduced Macrophage Content
Decreases likely linked to decreased lipotoxic lipids and cholesterol

****p<.0001 seladelpar vs. vehicle
*p<.05 seladelpar vs. vehicle
Decreased Liver Injury was Accompanied by Lower Fibrosis
Reduced collagen levels and fibrosis related genes

* p < .05 seladelpar vs. vehicle
Seladelpar Resulted in Weight Independent Metabolic Effects

Improvements in Glycemic Control

* p < .05 seladelpar vs. vehicle
Seladelpar for NASH
Potential role for PPARδ agonists in the treatment of NASH

Pathological Progression from NAFLD to NASH

- Steatosis
- Insulin resistance
- Free Cholesterol
- Lipotoxic lipids
- ER stress/ROS
- Inflammatory mediators
- Activation & recruitment
  - Kupffer cells
  - macrophages
  - neutrophils
- Cell death
- Stellate cell activation
- Extracellular matrix deposition & remodeling

Seladelpar (PPARδ) Pharmacology
Seladelpar Phase 2b Study - NASH

Dr. Pol Boudes, Chief Medical Officer
## Seladelpar Phase 2b Study in NASH

*Initiated in 2Q 2018*

### Population
- NASH proven by baseline biopsy
- Liver fat ≥10%, F1 to F3
- Includes diabetics

### Design
- Double blind, 52-week, placebo controlled (N=175)
- 10, 20 and 50 mg of seladelpar vs. placebo (2:2:2:1 randomization)
- Primary: 12-week change from baseline in liver fat (MRI-PDFF)
- Secondary: 52-week histological improvement in NAS and fibrosis
## Phase 2b Dose Ranging Study in NASH

### 52-Week Study in Biopsy-Confirmed NASH Patients

**Enrollment target of 175 patients**
*Baseline: MRI-PDFF Liver Fat ≥ 10% and Biopsy NAS ≥ 4, F1 to F3*

<table>
<thead>
<tr>
<th>Dose</th>
<th>Participants (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seladelpar 10 mg</td>
<td>50</td>
</tr>
<tr>
<td>Seladelpar 20 mg</td>
<td>50</td>
</tr>
<tr>
<td>Seladelpar 50 mg</td>
<td>50</td>
</tr>
<tr>
<td>Placebo</td>
<td>25</td>
</tr>
</tbody>
</table>

### Primary outcome:
- Safety & Tolerability
- Decrease in liver fat at 12 weeks

### Secondary outcomes:
- NASH histology at 52 weeks
- Liver fat at 26 and 52 weeks
- MRE at 52 weeks
- Biomarkers at 12, 26, & 52 weeks

**Timeline:**
- **Baseline:** Biopsy, MRI-PDFF, Biomarkers
- **12 weeks:** MRI-PDFF, Biomarkers
- **26 weeks:** MRI-PDFF, Biomarkers
- **52 weeks:** Biopsy, MRI-PDFF, MRE, Biomarkers
Phase 2b Dose Ranging Study in NASH

**Dose ranging and primary efficacy**

- **Dose Range**
  - 10 mg, highest dose tested in ongoing PBC study: safe, active on hepatic inflammation, and cholestasis
  - 50 mg, lowest dose tested in obese with mixed dyslipidemia: safe, effective to lower triglycerides, fatty acids, and LDL-C
  - 20 mg, completes dose range

- **Primary outcome: Proton Density Fat Fraction by MRI (MRI-PDFF)**
  - Perspectum Diagnostics technology
  - Central reading
  - Quality assurance and quality control
  - Qualified US investigational sites
Seladelpar Phase 2b Study in NASH
LiverMultiScan™ (Perspectum Diagnostics)

Screening Report from CB8025-21730 Patient

T2* map
MR relaxation time
Shown to decrease with increased hepatic iron overload‡

MRI-PDFF
Primary endpoint of study
Shown to correspond to histological measures of steatosis†

Corrected T1 Exploratory endpoint in study
Free-water content in tissue
Shown to increase in inflammation and fibrosis•

†Idilman et al., 2013; Reeder et al., 2017
‡Wood et al., 2005; Hoad et al., 2015
•Banerjee et al, 2014; Pavlides et al, 2015; Pavlides et al. 2016

Statistics Summary
Region 1
Fat: 21.6 %
Iron: 1.3 mg/g dry weight liver
cT1: 1046 ms

Normal range: <5.6% ¹
Normal range: <1.8mg/g ²
Reference interval: 632ms - 795ms ³

T1 image quality: Satisfactory
T2* image quality: Satisfactory
Fat image quality: Satisfactory
Phase 2b Dose Ranging Study in NASH
Secondary outcomes as proofs of activity

- MRI-PDFF at week 26 and 52
- Magnetic Resonance Elastography: better technique than ultrasound
- Liver biopsy
  - Double-blind reading, with sequence blinding and efficacy reading
  - Two highly qualified readers, with proven track records, and adjudication in case of discrepancy
  - Exploratory methods: digitization and artificial intelligence reads
- Additional promising biochemical (e.g. ELF, Pro-C3) and imaging markers (e.g. cT1)
CymaBay Key Projected Milestones
*Multiple catalysts in 2018*

| 1H 2018 | ✓ 26-week Ph 2 PBC data – Late Breaker at EASL ILC 2018  
|         | ✓ Initiation of Ph 2b NASH study  
|         | ✓ FDA End of Phase 2 and EMA Scientific Advice meetings  |
| 2H 2018 | § Initiation of Ph 3 PBC study  
|         | § 52-week Ph 2 PBC data |

*Improving the lives of patients with liver diseases*