Disclaimer

Some of the statements contained in this presentation constitute forward-looking statements. Statements that are not historical facts are forward-looking statements. Forward-looking statements generally can be identified by the use of forward-looking terminology such as “may”, “will”, “expect”, “intend”, “estimate”, “anticipate”, “believe”, “continue” or similar terminology. These statements are based on the Company’s current strategy, plans, objectives, assumptions, estimates and projections. Investors should therefore not place undue reliance on those statements. The Company makes no representation, warranty or prediction that the results anticipated by such forward-looking statements will be achieved, and such forward-looking statements represent, in each case, only one of many possible scenarios and should not be viewed as the most likely or standard scenario. Forward-looking statements speak only as of the date that they are made and the Company does not undertake to update any forward-looking statements in light of new information or future events. Forward-looking statements involve inherent risks and uncertainties. The Company cautions that a number of important factors could cause actual results to differ materially from those contained in any forward-looking statement.
Well Diversified Mid-to-Late Stage Metabolic Pipeline for Large Market Opportunities

Global partnerships secured for late stage clinical program in type 2 diabetes

- **Imeglimin:** First in class oral drug candidate targeting mitochondrial dysfunction
  - Partnered with Sumitomo Dainippon Pharma and Roivant Sciences
  - Phase 3 results for TIMES 1 in Japan met primary and key secondary endpoints; U.S. trial in T2D patients with CKD 3b/4 ongoing
  - Total potential deal value >$900M plus royalties; partners funding Ph 3 & commercialization

Two clinical stage NASH programs targeting underlying root cause of disease which can be developed as monotherapy and/or as combination therapy

- **PXL770:** Direct AMPK activator for NASH
  - Pathway targeting steatosis, inflammation, and fibrosis
  - Phase 2a program underway

- **PXL065:** MPC inhibitor for NASH
  - Deuterium-stabilized R-pioglitazone
  - Pioglitazone (racemate) demonstrated resolution of NASH without worsening of fibrosis
  - Phase 1b planned initiation Q2 19; Pivotal Ph 2 program initiation expected Q4 19/ Q1 20

- Preclinical studies underway for additional metabolic and rare diseases
- Euronext listed (POXEL); strong cash position
  - EUR 59.0 million (USD 66.3 million) cash & equiv. 3/31/19; runway into 2021
Leadership Team
Highly Experienced Management Team

Thomas Kuhn (Pharm D, MBA)
CEO and Co-founder

Anne Renevot
Chief Financial Officer

Noah Beerman (MBA)
Executive VP, Business Development and President, US Operations

Christophe Arbet-Engels (MD, PhD, MBA)
CMO and EVP Late Development & Medical Affairs

Sébastien Bolze (Pharm D, PhD)
Executive Vice President, Non-Clinical Development, Co-founder

Sophie Bozec (PhD)
Senior Vice President, R&D Pharmacology, Co-founder

Pascale Fouqueray (MD, PhD)
Executive Vice President, Early Development & Translational Medicine, Co-founder

Jonae Barnes
Senior Vice President, Investor Relations & Public Relations
# Metabolic Pipeline

**Well-diversified Pipeline with Mid-to-late-stage Programs**

<table>
<thead>
<tr>
<th>Indication</th>
<th>MOA</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Partner/ Rights</th>
<th>Next Steps</th>
</tr>
</thead>
</table>
| **Imeglimin**               |                            |             |         |         | *Ph 3*  | Sumitomo Dainippon Pharma                                                          | • Phase 3 TIMES completion  
| Japan/Asia*                 | Type 2 Diabetes            | Mitochondrial Bioenergetics |         |         |         |                                                                                  | • Target JNDA submission 2020                                              |
| **Imeglimin**               |                            |             |         |         | *Ph 3*  | **ROIVANT SCIENCES**                                                              | • Manufacturing drug for Phase 3  
| US/ EU/Other**              | Type 2 Diabetes            | Mitochondrial Bioenergetics |         |         |         |                                                                                  | • Study in T2D patients w/ CKD                                           |
| **PXL770**                  | NASH/ metabolic diseases   | Direct AMPK activator     |         |         | *Ph 2*  | **Poxel/DeuteRx programs**                                                        | • Complete Phase 2a program in NASH                                       |
| **PXL007** (EYP001)         | Hepatitis B NASH           | FXR agonist              |         |         | *Ph 2*  | **Enyo Pharma**                                                                   | • Complete Phase 1 program by Enyo Pharma                                 |
| **PXL065** (formerly DRX-065)| NASH                      | MPC Inhibitor            |         |         | *Ph 2*  | **Poxel/DeuteRx programs**                                                        | • Complete Phase 1, tox, CMC  
|                             |                            |                         |         |         |         |                                                                                  | • Initiate Pivotal Phase 2 study                                         |

- **Open arrow designates expected development status in 2019**

*including: China, South Korea, Taiwan, Indonesia, Vietnam, Thailand, Malaysia, the Philippines, Singapore, Myanmar, Cambodia, and Laos.

**countries not covered in the Sumitomo Dainippon Pharma agreement**
**Key Value Drivers**

**Imeglimin**
- Japan is a ~$5B+ market opportunity for T2D with strong growth
- Approx. 2.4 million patients in the US with T2D have CKD stages 3b/4
- Unique opportunity for NASH and other chronic metabolic diseases

**PXL770**
- Study in T2D patients with CKD and manufacturing drug for Phase 3 program ongoing
- PXL770 direct AMPK activator Phase 2a program underway
- Complete Phase 2a PoC program in NASH expected 1H 2020

**PXL065**
- PXL065 (d-R-pioglitazone) a potent MPC inhibitor advancing to Phase 1b
- Potential for expedited development in NASH and orphan metabolic diseases
- Initiation of pivotal Phase 2 study in NASH expected Q4 19/1Q 20

**Predlin**
- Focus on metabolic diseases; specialty and orphan indications
- Conducting preclinical studies in metabolic and rare diseases
- Additional metabolic and rare opportunities

---

*Decision Resources, September 2014*
Imeglimin

First in a New Class of Potential Anti-diabetic Treatments with a Differentiated Mechanism of Action
## Imeglimin Global Partnerships

**Combined Potential Total Deal Value >$900 Million**

<table>
<thead>
<tr>
<th>Partner</th>
<th>Imeglimin Rights</th>
<th>Deal Value</th>
<th>Development Status</th>
</tr>
</thead>
</table>
| **Sumitomo Dainippon Pharma** | Development and commercialization rights in Japan, China, South Korea, Taiwan and 9 other Southeast Asian countries* | • Upfront payment: $42M  
• Future potential development milestone payments and sales-based payments of up to approx. $257M  
• Double digit escalating royalties | • Phase 3 TIMES program (TIMES 1, TIMES 2 and TIMES 3) in T2D patients  
• Target JNDA submission in Japan 2020 |

| **ROIVANT SCIENCES** | Development and commercialization in the U.S., Europe, and other countries** | • Upfront payment: $35M¹  
Equity Investment: $15M at €8.5/share  
• Future potential development and regulatory milestone payments and sales-based payments of up to $600M  
• Double digit escalating royalties | • Ongoing study in T2D patients with CKD  
• Pending successful completion and post-FDA meeting, goal is to initiate Phase 3 |

---

*including: Indonesia, Vietnam, Thailand, Malaysia, the Philippines, Singapore, Myanmar, Cambodia, and Laos. **countries not covered in the Sumitomo Dainippon Pharma agreement

1. Poxel contributing $25M (~€20M) to development program over a 2-year period
Imeglimin Development Strategy for Japan

Targeting a JNDA Submission in 2020 for T2D

Mechanism of action relevant for Asian T2D patients

Phase 3 TIMES program fully enrolled with over 1,100 patients

Phase 3 TIMES 1 trial met its primary and key secondary endpoints

<table>
<thead>
<tr>
<th>Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Phase 1**
  - 2016: Phase 2b
    - N=300
  - 2018: TIMES 1: Monotherapy vs placebo
    - N= ~200; 6-month treatment
  - 2019: JNDA Subm.

- **Phase 2b**
  - N=300

- **TIMES 1**
  - Monotherapy vs placebo
  - N= ~200; 6-month treatment

- **TIMES 2**
  - Long term safety Mono & Add-on to oral therapy (Open label)
  - N=~700; 12 months

- **TIMES 3**
  - Long term safety add-on to insulin
  - N=~200; 12 months

- Non-pivotal trials in renal impaired population

Sumitomo Dainippon Pharma is development and commercialization partner for Japan
Phase 3 TIMES 1 Trial in Japan Met Primary and Key Secondary Endpoints (n=213)

A 24-week Phase 3, randomized, double-blind, placebo-controlled, monotherapy trial to assess the efficacy, safety and tolerability of Imeglimin administered orally in Japanese patients with type 2 diabetes

- TIMES 1 trial in Japan met its primary endpoint of a reduction in HbA1c and secondary endpoints, including fasting plasma glucose
- Similar tolerability profile observed compared to placebo
- TIMES 1 results are consistent with the Phase 2b results observed in Japan
TIMES 1 Trial Met Primary Endpoint of HbA1c Reduction

<table>
<thead>
<tr>
<th>Change in HbA1c - 24 weeks</th>
<th>Placebo</th>
<th>Imeglimin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>107</td>
<td>106</td>
</tr>
<tr>
<td>HbA1c (%), mean (SD)</td>
<td>7.93 (0.684)</td>
<td>7.99 (0.764)</td>
</tr>
</tbody>
</table>

- **LS mean (SE) = -0.87% (0.09)**

- Statistically significant HbA1c reduction with demonstrated efficacy and an observed tolerability profile similar to placebo (n=213)

- TIMES 1 results are consistent with Phase 2b results observed in Japan

\[ p < 0.0001 \]
Japan: Accessible T2D Market with Solid Growth $5B+ Anticipated to Grow to $6B in 2020

- 2nd largest diabetes market outside of US/EU
- ~$5B+ (/year)
- Estimated sales in Japan expected to grow to $6B by 2020; Imeglimin’s target date for JNDA submission
- Sitagliptin: ~$1.1B+ annual sales in 3 years*
- We believe there is clear development path defined by PMDA: all recent new agents approved with ~1,000 patients in Phase 3
- Asia: significant opportunity in China

* Decision Resources, 2015 Report

Source: Oppenheimer & Co. estimates
Roivant Development Focus for Imeglimin

• Roivant to develop Imeglimin first specifically to treat patients with type 2 diabetes with chronic kidney disease (CKD) stages 3b/4\(^1\)
  – Opportunity to study Imeglimin in broader T2D population
• Diabetes is the most common cause of chronic kidney disease
• Patients with type 2 diabetes and CKD stages 3b/4
  – Approximately 2.4 million adults in the US\(^2\)
  – Patients have increased cardiovascular risk
  – Challenging glucose management
• Underserved population
  – Many approved therapies require dose reduction or are not recommended in the presence of kidney disease
  – Insulin and insulin secretagogues are the most commonly used therapies at suboptimal doses to prevent risk of hypoglycemia
  – We believe there is a need for a new treatment at optimal dose, providing a strong efficacy and safety profile with no hypoglycemia risk
• Imeglimin Phase 2 data (Japan & US) was observed to be well tolerated and demonstrated similar efficacy in patients with impaired renal function compared to patients with normal renal function

---

1 CKD stage 3b= eGFR 30-44 ml/min/1.73 m2 inclusive; CKD stage 4 = 15-29 ml/min/1.73m2 inclusive
PXL770 and PXL065

Two Differentiated Drug Candidates with Complementary Mechanisms of Action for the Treatment of NASH
Progression of Non-alcoholic Fatty Liver Disease (NAFLD)

- Excessive caloric intake
  - Sedentary lifestyle

- Metabolic syndrome
- Dyslipidemia
- Type II diabetes
- Obesity

NAFLD
- 25% of the general population
- >70% in diabetic & obese patients

NASH
- 12% of the general population
- 25-70% in diabetic and obese patients ≥ 50

Cirrhosis

- High morbidity
- Cardiovascular events
  - (leading cause of death)
- Hepatic impairment
- Hepatocellular carcinoma

Excessive caloric intake
Sedentary lifestyle
Metabolic syndrome
Dyslipidemia
Type II diabetes
Obesity
NAFLD
25% of the general population
>70% in diabetic & obese patients
NASH
12% of the general population
25-70% in diabetic and obese patients ≥ 50
Cirrhosis

Steatosis
Fat Deposition > Lipotoxicity > Collagen Deposition
Inflammation Fibrosis

J. Hepatology 2018, 68, 362-375
NASH: A Multifactorial Metabolic Disease

Adipose Tissue
- Lipolysis 70%
- Low grade inflammation

Liver
- STEATOSIS
- INFLAMMATION
- FIBROSIS

Muscle
- Peripheral
- Insulin Resistance

Hepatocytes
- De Novo Lipogenesis 20%

Hepatic Stellate Cells
- Activation and collagen deposition

Mitochondria
- Impaired mitochondrial integrity and functions

Sugar
- FFA
- TG

FFA
Why Activating AMP Kinase is Important for Managing Metabolic Disorders

AMPK is an heterotrimeric enzyme with an $\alpha_{(1,2)}$ catalytic and $\beta_{(1,2)}$/
$\gamma_{(1,2,3)}$ regulatory subunits

- **Steatosis**: AMPK is an energy sensor, regulating energy homeostasis and adjusting cell activities to the level of energy available
  - By triggering reactions leading to energy production (FA oxidation, glucose uptake)
  - By reducing reactions requiring energy consumption (FA synthesis / DNL, protein and cholesterol synthesis)

- **Inflammation**: AMPK switches macrophages polarization decreasing cytokine secretion and reduces inflammation processes both in liver and adipose tissue

- **Ballooning**: AMPK improves mitochondrial function and integrity, restoring better cell function and survival

- **Fibrosis**: AMPK reduces hepatic stellate cell activation and ECM secretion in the liver
PXL770: a Differentiated Profile for NASH

- PXL770 allosterically activates the 12 AMPK heterotrimeric complexes and protects the AMPK against dephosphorylation.
- By targeting the master regulator of cellular energy, we believe PXL770 has a unique and differentiated profile for the treatment of NASH:
  - Improves insulin sensitivity
  - Inhibits the two main sources of steatosis
  - Reduces adipose tissue and liver inflammation
  - Decreases profibrogenic pathways
  - Improves CV risk factors
- In addition to monotherapy, PXL770 has the potential to be combined with all other products in development for NASH, targeting other pathways (incl. MPC inhibitor, FXR agonist, THRb, ...).
Expected Effects of PXL770 for NASH

*a Direct AMPK Activator*

**Effects in Adipose Tissue**
- Low grade inflammation
- Lipolysis
- Peripheral insulin resistance

**Effects in Muscle**
- De novo lipogenesis

**Effects in Hepatocytes**

**Effects in Liver**
- Steatosis
- Chronic inflammation
- Effects in Hepatic Stellate Cells
- Fibrogenesis
- Hepatic stellate cell activation

**Effects in Mitochondria**
- Mitochondrial integrity
- Mitochondrial functions
PXL770 Observed to Improve Liver Steatosis and NAS in a Diet induced Obesity Biopsy-Proven NASH Mouse Model

**Male C57BL/6J** were fed a diet high in trans fat (40%), fructose (20%) and cholesterol (2%) for a total of 41 weeks and treated during 8-week treatment.

PXL770 was observed to improve steatosis, hepatocytes ballooning and inflammation scores.

Elafibranor (30 mg/kg)
PXL770 Observed to Decrease Adipose Tissue & Liver Inflammation, Markers in a Diet Induced Obesity Biopsy-Proven NASH Mouse Model

**Male C57BL/6J** were fed a diet high in trans fat (40%), fructose (20%) and cholesterol (2%) for a total of 41 weeks and treated during an 8-week treatment.

### Adipose Tissue Gene Expression

- **DIO-NASH vehicle**
- **DIO-NASH PXL770 35mg/kg bid**
- **DIO-NASH PXL770 75mg/kg bid**
- **DIO-NASH Elafibranor 30mg/kg od**

### Liver Gene Expression

- **DIO-NASH vehicle**
- **DIO-NASH PXL770 35mg/kg bid**
- **DIO-NASH PXL770 75mg/kg bid**
- **DIO-NASH Elafibranor 30mg/kg od**

- *: p< 0.05, **: p< 0.01, ***: p< 0.001 compared to DIO-NASH vehicle
PXL770 Observed to Improve Fibrogenic Gene Expression in a Diet Induced Obesity Biopsy-Proven NASH Mouse Model

**Male C57BL/6J** were fed a diet high in trans fat (40%), fructose (20%) and cholesterol (2%) for a total of 41 weeks and treated during an 8-week treatment.

- PXL770 observed to decrease profibrogenic mediators
- PXL770 observed to decrease stellate cells activation
- PXL770 observed to decrease fibrotic fiber formation and increase ECM breakdown

---

**Graphs**:

- **TGFβ**
- **α-Smooth Muscle Actin**
- **PDGF**
- **COL1A1**
- **MMP2**
- **COL3A1**

**Legend**:

- LEAN- Chow vehicle
- DIO-NASH vehicle
- DIO-NASH PXL770 75mg/kg bid
- DIO-NASH PXL770 35mg/kg bid
- DIO-NASH Elafibranor 30mg/kg od

*: p< 0.05, **: p< 0.01, ***: p< 0.001 compared to DIO-NASH vehicle
PXL770 Observed to Improve the Main CV Risk Factors Associated with NASH

- PXL770 observed to improve CV risk factors in several metabolic rodent models:
  - Insulin sensitivity
  - Glycemic control: basal glycemia, glucose tolerance and HbA1c
  - Circulating lipids (TGs, cholesterol)
  - Fat mass and body weight
PXL770 Development Strategy to PoC for NASH

**Phase 1 Favorable Results**
- Observed to be well tolerated with a favorable pharmacokinetics profile after single and multiple ascending administration up to the highest dose tested of 500 mg (n=124)
- No drug-drug interaction with rosvastatin (statin drug) observed
- No observed cardiac toxicity

**Phase 2 Program**
- Phase 2a efficacy and safety trial
  - ~100 patients with NAFLD (likely NASH)
  - 12-week treatment
  - Primary endpoint: change in liver fat mass based on MRI-PDFF
  - Assessment of effect on inhibition of lipolysis and hepatic *de novo* lipogenesis and safety
- PK/PD trial to assess PK profile and effects on hepatic and metabolic parameters
- Phase 2b/3 in biopsy proven NASH patients
- Considering additional PoC studies in other metabolic indications
PXL770 Phase 2a PoC Underway (n=~100)

**Trial Design:**
US multicenter, double-blind, placebo-controlled, randomized trial with 4 parallel groups

- **Screening**
  - 2 weeks

- **Placebo Run-In**
  - 4 weeks

- **Double-blind treatment period**
  - 12 weeks
  - PXL770 250 mg QD
  - PXL770 250 mg BID
  - PXL770 500 mg QD
  - Placebo BID

- **Follow-up**
  - 1 week
  - MRI-PDFF
  - MRI-PDFF
PXL065 - Potentially Compelling Product Opportunity

Chiral switch of pioglitazone (pio), observed to be efficacious for the treatment of NASH

Pioglitazone (pio)  \[ \leftrightarrow \]  PXL065 (d-R-pio)

- Inhibitor of mitochondrial pyruvate carrier (MPC)
  - MPC identified as non-PPAR\(\gamma\) target of thiazolidinediones (TZDs), including pio & rosiglitazone
  - MPC modulates pyruvate flux into mitochondria to affect glucose, lipid, amino acid homeostasis
  - MPC knockdown / inhibitor increases glycolysis, glutaminolysis, and \(\beta\)-oxidation, which can lead to decreased glucose production and anti-inflammatory effects
- Preclin & clin data show potential for efficacy with reduced PPAR\(\gamma\)-related side effects
  - Phase 1 observed to be well tolerated
  - 15 mg PXL065 predicted similar exposure to R-pio as 45 mg pio (Actos\textsuperscript{®})
- We believe there is a commercially compelling strategy for competitive NASH landscape
  - NCE via 505(b)(2), new IP, opportunity for both mono- and combination therapies
- Wholly-owned and expansive IP portfolio for metabolic & specialty indications
Thiazolidinediones (TZDs), Pioglitazone, and NASH

- TZDs are interconverting mixtures of stereoisomers
  - Includes pioglitazone, rosiglitazone, troglitazone, lobeglitazone, MIN-102, MSDC-0602
  - PK and PD of stereoisomers mostly unknown
  - MoA includes PPARγ agonism and mitochondrial pyruvate carrier (MPC) inhibition

- Pioglitazone is approved since 1999
  - >30 million patient years of exposure\(^1\)

- Pioglitazone has been extensively studied and is efficacious for NASH
  - Achieved “Resolution of NASH without worsening of fibrosis” in Phase 4 trial\(^2\)
  - Only drug recommended for biopsy-proven NASH by AASLD & EASL Practice Guidelines\(^3\)
  - Currently prescribed by ~14% of physicians for biopsy-proven NASH patients\(^4\)
  - Limited use due to PPARγ-related side effects: weight gain, fluid retention, bone loss

---

4. Therap Adv Gastroenterol. 2016, 9(1), 4-12
Pio Cusi Phase 4 trial (45 mg, 18 mos) - Ann Intern Med. 2016, 165(5), 305-315 (only completers with definite NASH at baseline). Patients on placebo benefited from 4% weight loss due to hypocaloric diet.

Ocaliva REGENERATE Phase 3 trial (25 mg, 18 mos), Intercept press release Feb 19, 2019

CVC (Cenicriviroc) CENTAUR Phase 2b trial (150 mg, 1 yr/12 mos) – Hepatology 2017 (doi: 10.1002/hep.29477)

Elafibranor Phase 2 trial (120 mg, 52 wks/12 mos) - Gastroenterology. 2016, 150(5), 1147-1159

Liraglutide Phase 2 trial (0.6 increased to 1.8 mg sc weekly 48 wks) - The Lancet, 2016, 387(10019), 679–690

MGL-3196 Phase 2 trial (36 wks/8 mos) – press release May 31, 2018. Results from per protocol, not intent to treat (ITT) population.

Aramchol Phase 2 trial (600 mg, 52 wks) – press release June 12, 2018. No effect on "Fibrosis without worsening of NASH".

**Pio Observed to be Efficacious for NASH**

**Use Limited by Weight Gain**

**Resolution of NASH**

**without worsening of fibrosis**

Patients with Improvement, %

Pio Ocaliva Intercept Elafibranor CVC Liraglutide MGL-3196 Aramchol

- **Pio Observed to be Efficacious for NASH**
- **Use Limited by Weight Gain**

Pio Cusi Phase 4 trial (45 mg, 18 mos) - Ann Intern Med. 2016, 165(5), 305-315 (only completers with definite NASH at baseline). Patients on placebo benefited from 4% weight loss due to hypocaloric diet.

Ocaliva REGENERATE Phase 3 trial (25 mg, 18 mos), Intercept press release Feb 19, 2019

CVC (Cenicriviroc) CENTAUR Phase 2b trial (150 mg, 1 yr/12 mos) – Hepatology 2017 (doi: 10.1002/hep.29477)

Elafibranor Phase 2 trial (120 mg, 52 wks/12 mos) - Gastroenterology. 2016, 150(5), 1147-1159

Liraglutide Phase 2 trial (0.6 increased to 1.8 mg sc weekly 48 wks) - The Lancet, 2016, 387(10019), 679–690

MGL-3196 Phase 2 trial (36 wks/8 mos) – press release May 31, 2018. Results from per protocol, not intent to treat (ITT) population.

Aramchol Phase 2 trial (600 mg, 52 wks) – press release June 12, 2018. No effect on "Fibrosis without worsening of NASH".
PXL065 Characterization & Target Profile: Benefits of Pio for NASH with Reduced PPARγ Side Effects

Pio is mixture of 2 stereoisomers with dramatically different properties

S-Pio (stabilized)
- MPC inhibitor
- PPARγ agonist

Undesired side effects:
- Weight gain
- Fluid retention

PXL065 (stabilized R-pio)
- MPC inhibitor
- Very weak PPARγ agonist

Anti-inflammatory
NASH efficacy

MOA – mechanism of action, MPC – mitochondrial pyruvate carrier
Expected Effects of PXL065 for NASH

a Mitochondrial Pyruvate Carrier (MPC) Inhibitor

Effects in Adipose Tissue

Peripheral insulin resistance

Effects in Muscle

Effects in Liver

Steatosis
Chronic inflammation
Fibrosis
Neoglucogenesis

Mitochondrial integrity
Mitochondrial functions

Effects in Mitochondria

NASH
PXL065 Inhibits Mitochondrial Pyruvate Carrier (MPC) Without PPARγ Agonist Activity from S-Stereoisomer

**MPC Inhibition in HepG2 Cells**

![Graph showing MPC inhibition in HepG2 cells with different concentrations of PXL065 (R-Pio), d-S-Pio, and Pioglitazone.](image)

**PPARγ Agonist Activity**

![Graph showing PPARγ agonist activity with different concentrations of PXL065 (R-Pio), d-S-Pio, and Pioglitazone.](image)

- **IC$_{50}$**
  - PXL065 (R-Pio): 6.5 µM
  - d-S-Pio: 8.5 µM
  - Pioglitazone: 6.8 µM

- **EC$_{50}$**
  - PXL065 (R-Pio): >100 µM
  - d-S-Pio: 3.5 µM
  - Pioglitazone: 4.6 µM

*Results are expressed as % of response of positive control (10µM rosiglitazone).*
Liver histopathology on day 43 in mice fed a Choline Deficient (CD) or an Methionine/Choline Deficient (MCD) diet, Pioglitazone (30 mg/kg/day) or PXL065 (15 mg/kg/day), Wilcoxon rank sum test vs vehicle; *p < 0.05, **p < 0.005, ***p < 0.001
PXL065 Phase 1a Part 1 Results

Favorable Tolerability and Pharmacokinetics (PK)

- Single oral dose of PXL065 (22.5mg) or Actos® (45mg) in healthy subjects, 18-40 yrs

- Tolerability
  - PXL065 was observed to be well-tolerated

- PK Results
  - Observed stabilization of d-R-pio with limited interconversion to S-pio
  - Relative exposure (AUC) to R-pio/S-pio increased ~3x
  - PKPD simulation predicts 15 mg PXL065 ≥ efficacy as 45 mg pio without weight gain
Phases of Development:

**Phase I SAD**
- NASH efficacy demonstrated without PPARγ effects
- Observed to be well tolerated and PK after single 22.5 mg PXL065 vs 45 mg Actos®
- Abbreviated tox due to 505(b)(2) path
- 2H 18 – Q3 19
  - SAD study completed
  - Favorable safety & tolerability profile
  - Stabilization of R-pioglitazone confirmed at all doses tested
- Completion of MAD

**Phase I MAD**
- Safety, PK

**Pivotal Phase 2 Program**
- Expedited development program using 505(b)(2) regulatory path
  - Pivotal phase 2
    - ~350 biopsy proven NASH patients
    - 52wk treatment: 2 or 3 doses vs placebo
    - Primary endpoint: NASH resolution and / or fibrosis improvement
    - Initiation: Expected in Q4 19 / Q1 20
  - Confirmatory program under assessment based use of Actos® data for 505(b)(2)
# PXL770 and PXL065 Differentiated in NASH

## Comparison of Hepatic Effects Across Key Measures

<table>
<thead>
<tr>
<th>Target MoA</th>
<th>Agents</th>
<th>Current Phase</th>
<th>Results in Animal</th>
<th>Results in Human</th>
<th>Reduction of Hepatic Parameters</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARγ, MPC</td>
<td>Pioglitazone¹</td>
<td>generic</td>
<td>●</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FXR</td>
<td>OCA²</td>
<td>3</td>
<td>●</td>
<td>limited</td>
<td>limited</td>
<td>limited</td>
</tr>
<tr>
<td>PPARαδ</td>
<td>Elafibranor³</td>
<td>3</td>
<td>●</td>
<td>limited</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CCR2,5</td>
<td>CVC⁴</td>
<td>3</td>
<td>●</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ASK1</td>
<td>Selonsertib⁵</td>
<td>3</td>
<td>●</td>
<td>limited</td>
<td>X</td>
<td>limited</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Liraglutide⁶</td>
<td>2</td>
<td>●</td>
<td>limited</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>THRβ</td>
<td>MGL-3196⁷</td>
<td>3</td>
<td>●</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>AMPK</td>
<td>PXL770</td>
<td>2</td>
<td>●</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>MPC</td>
<td>PXL065</td>
<td>1</td>
<td>●</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ statistically significant
X no effect
"limited" some effect

2. REGENERATE Phase 3 trial, Intercept press release Feb 19, 2019
6. The Lancet, 2016, 387(10019), 679–690
7. Madrigal press release May 31, 2018
Expected Effects of PXL770 and PXL065 for NASH

- **Effects in Adipose Tissue**
  - Low grade inflammation
  - Lipolysis
  - Peripheral insulin resistance

- **Effects in Muscle**
  - De novo lipogenesis

- **Effects in Hepatocytes**
  - Neoglucogenesis

- **Effects in Liver**
  - Steatosis
  - Chronic inflammation
  - Fibrosis
  - Neoglucogenesis

- **Effects in Hepatic Stellate Cells**
  - Fibrogenesis
  - Hepatic stellate cell activation

- **Effects in Mitochondria**
Summary
Significant Upcoming Milestones for 2019/2020

• Imeglimin
  – Phase 3 TIMES 3 16-week, double-blind, placebo-controlled part (Mid-19)
  – Phase 3 TIMES 2 and full results from TIMES 3 (Q4 19)
  – Imeglimin manuscripts published related to efficacy, safety and PK (2019)
  – Metavant completion of study in T2D patients with CKD 3b/4 (mid-year) pending successful completion and post-FDA meeting, initiate Phase 3
  – NDA submission in Japan (2020)
  – Imeglimin target launch in Japan (2021)

• PXL770
  – PK/PD study initiation (Q2 19)
  – PK/PD data results (2H 2019)
  – Phase 2a data results (1H 20)

• PXL065
  – Initiate Phase 1b multiple ascending dose study (Q2 19)
  – Completion of Phase 1 program (Mid-year to Q3 19)
  – Pivotal Phase 2 initiation in NASH (Q4 19 / Q1 20)
  – Pivotal Phase 2 readout (2022)

• Additional preclinical data on other metabolic and rare diseases (2019)
Appendix
Imeglimin
Imeglimin treatment: Restored normal mitochondrial function

• Glucose lowering related benefits:
  – Improve β-cells function and survival
  – Increase glucose dependent insulin secretion from pancreas
  – Improve insulin sensitivity in liver and muscles
• Beyond Glucose lowering related benefits:
  – Improve endothelial dysfunction
  – Improve diastolic dysfunction

Diabetic state: Impaired mitochondrial function leading to

• Insufficient insulin secretion from pancreas
• Insulin resistance in liver and muscles
• β-cells dysfunction and death
• Endothelial cell dysfunction and death

Imeglimin: A Differentiated Mechanism of Action in the Mitochondria Enabling ‘Glucose-plus’ Benefits
Imeglimin Phase 2b Trial In Japan Met Primary and Secondary Endpoints (N=299)

Full Phase 2b data presented at the European Association of the Study of Diabetes, in Lisbon (Sept. 2017)

- Phase 2b trial in Japan met primary HbA1c endpoint and secondary endpoints
- Demonstrated efficacy in chronic kidney disease patients was similar to patients with normal renal function
- Observed to be well tolerated:
  - Rate of observed adverse events similar to placebo at 500 mg and 1000 mg. Slightly higher rate of GI events at 1500 mg (no adverse event greater than 10%)
  - No serious adverse events related to Imeglimin
- No weight gain
Imeglimin Phase 2b Trial in Japan Met Primary Endpoint in Reduction of HbA1c vs. Placebo (N=299)

Change in HbA1c from baseline

- ** p < 0.0001
Phase 2b Trial In Japan: Similar Efficacy Demonstrated in T2D Patients with Renal Impairment vs with Normal Kidney Function

Change in HbA1c - 24 weeks

- 500 mg: N = 24 (eGFR ≥ 80; -0.53%), N = 51 (eGFR < 80; -0.44%)
- 1000 mg: N = 24 (eGFR ≥ 80; -0.92%), N = 49 (eGFR < 80; -0.83%)
- 1500 mg: N = 23 (eGFR ≥ 80; -0.89%), N = 50 (eGFR < 80; -0.92%)