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Corporate Presentation

October 2020

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.

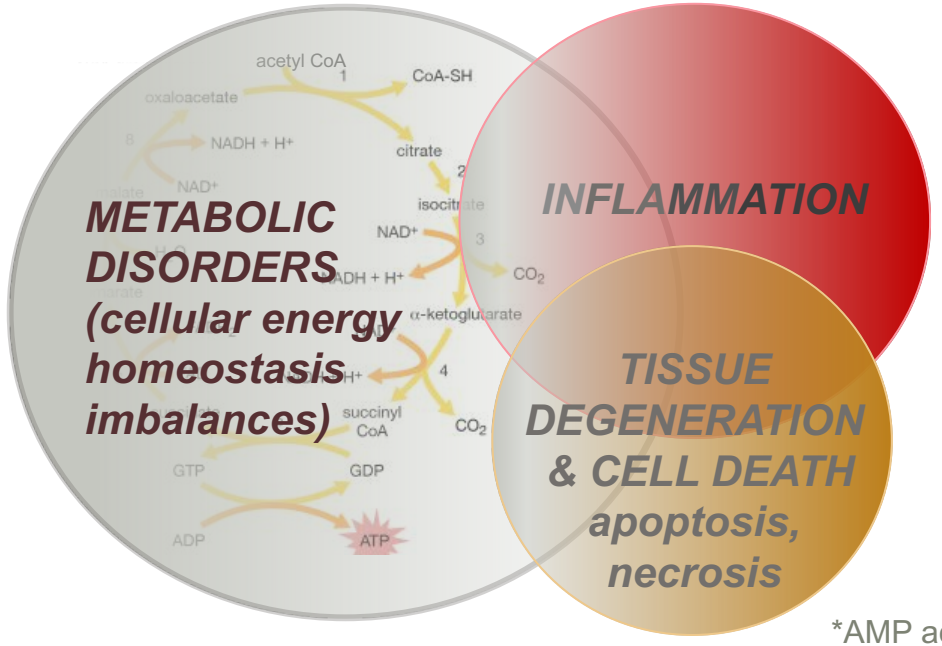
In the context of the COVID-19 outbreak, which was declared a pandemic by the World Health Organization (WHO) on March 12, 2020, the Company is regularly reviewing the impact of the outbreak on its business. As of the date of this presentation, and based on publicly available information, the Company has not identified the occurrence of any material negative effect on its business due to the COVID-19 pandemic that remains unresolved. However, the Company anticipates that the COVID-19 pandemic could have further material negative impact on its business operations. The worldwide impact of COVID-19 may notably affect the Company’s internal organization and efficiency, particularly in countries where it operates and where confinement measures are implemented by the authorities. In addition, COVID-19 may impact market conditions and the Company’s ability to seek additional funding or enter into partnerships. Particularly, delays in the supply of drug substance or drug products, in the initiation or the timing of results of preclinical and/or clinical trials, as well as delays linked to the responsiveness of regulatory authorities could occur, which could potentially have an impact on the Company’s development programs and partnered programs. The Company will continue to actively monitor the situation.

Mission and Vision

To discover, develop and commercialize innovative therapies for patients suffering from *serious chronic diseases* with underlying *metabolic pathophysiology*

- Mid-to-late stage first-in-class pipeline: Type 2 diabetes (globally partnered) and NASH
- Pipeline expansion in chronic and rare metabolic indications
  - Internal AMPK* and D-TZD# Platforms
  - External Opportunities

Targeting Defects in Cellular Metabolism

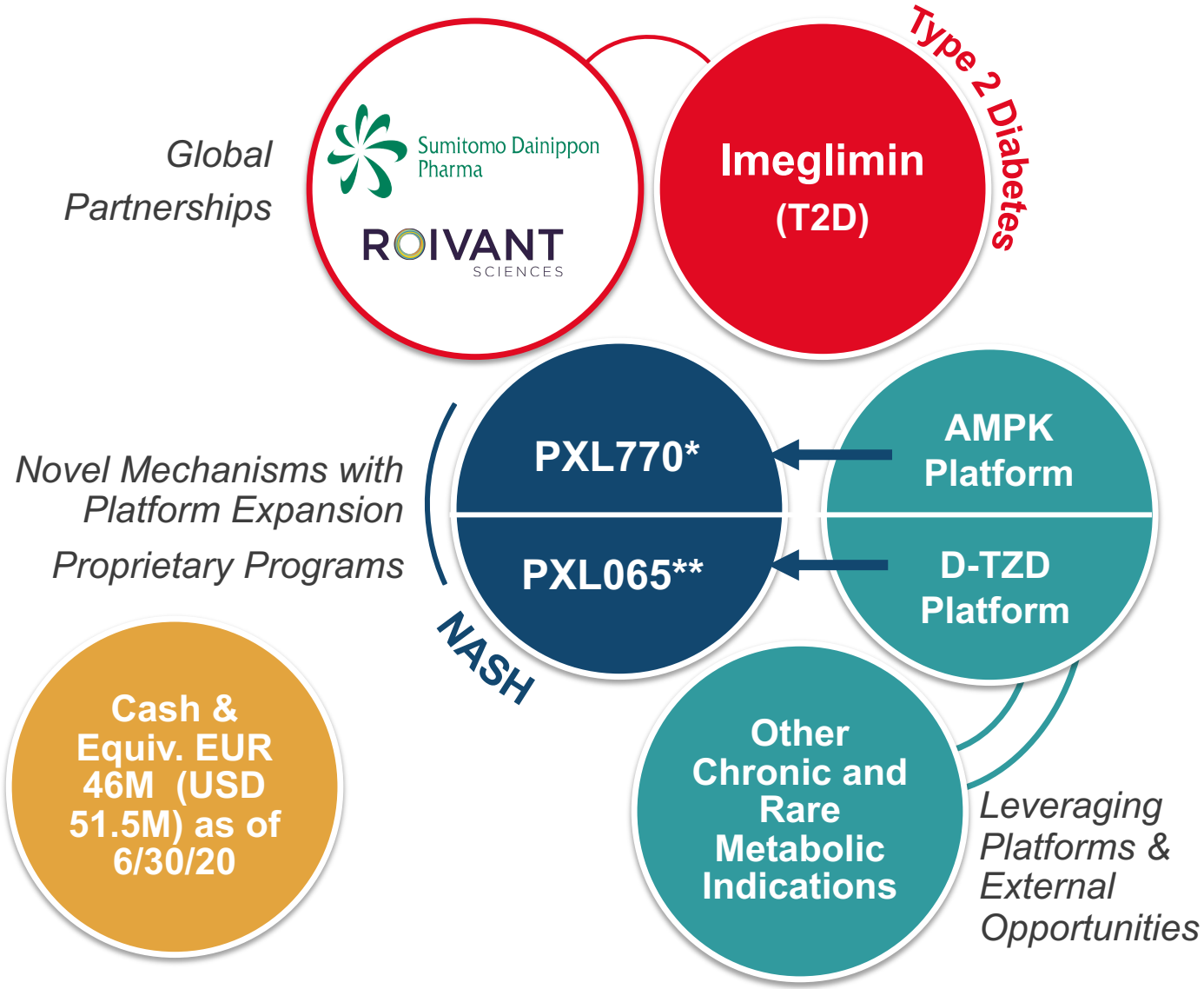


Leveraging AMPK & D-TZD Platforms Metabolic Component + Unmet Medical Need

- ***Hereditary Metabolic Disorders:***
  e.g. adrenoleukodystrophy
- ***Endocrinopathies***
- ***Renal Diseases:***
  e.g. diabetic nephropathy, polycystic kidney disease, others
- ***Other: rare, orphan indications***

*AMP activated protein kinase; # Deuterium-stabilized thiazolidinediones

Three Mid-to-Late Stage First-in-Class Drug Candidates with Novel Mechanisms and Differentiated Strategies



Anticipated first product launch in Japan in 2021 through **Imeglimin partnership** with Sumitomo Dainippon Pharma

Several significant milestones in 2020 including results in **NASH & other metabolic indications**

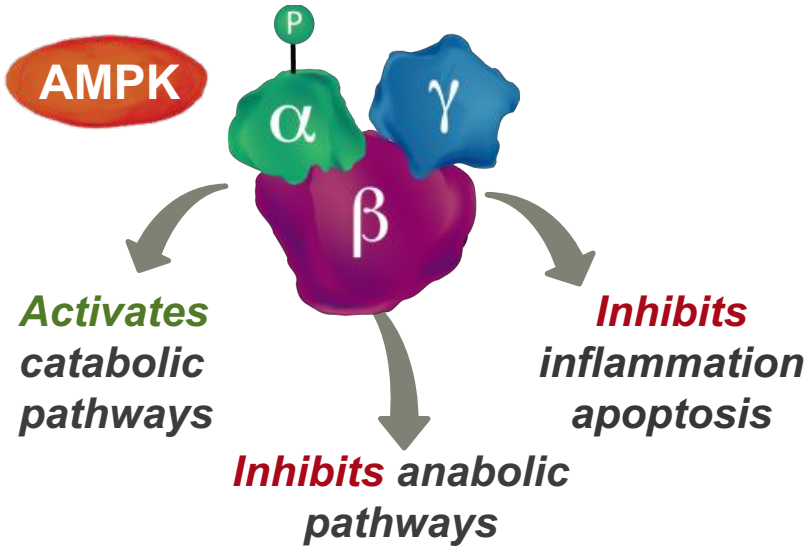
Highly experienced management team; extensive **metabolic R&D expertise** & track record in **US, EU and Japan**

Global company with presence in 3 countries (France, US and Japan); listed on **Euronext Paris**

*PLX770 direct AMP-kinase activator (AMPK) from platform **PXL065 deuterium-stabilized R-pioglitazone (mitochondrial pyruvate inhibitor) from D-TZD (deuterated thiazolidinediones) platform

Poxel Targets Key Mechanisms that have Distinct Roles in Regulating Cellular Energy Homeostasis

Multiple Entry Points Available to Intervene in Metabolic Diseases



NASH Other

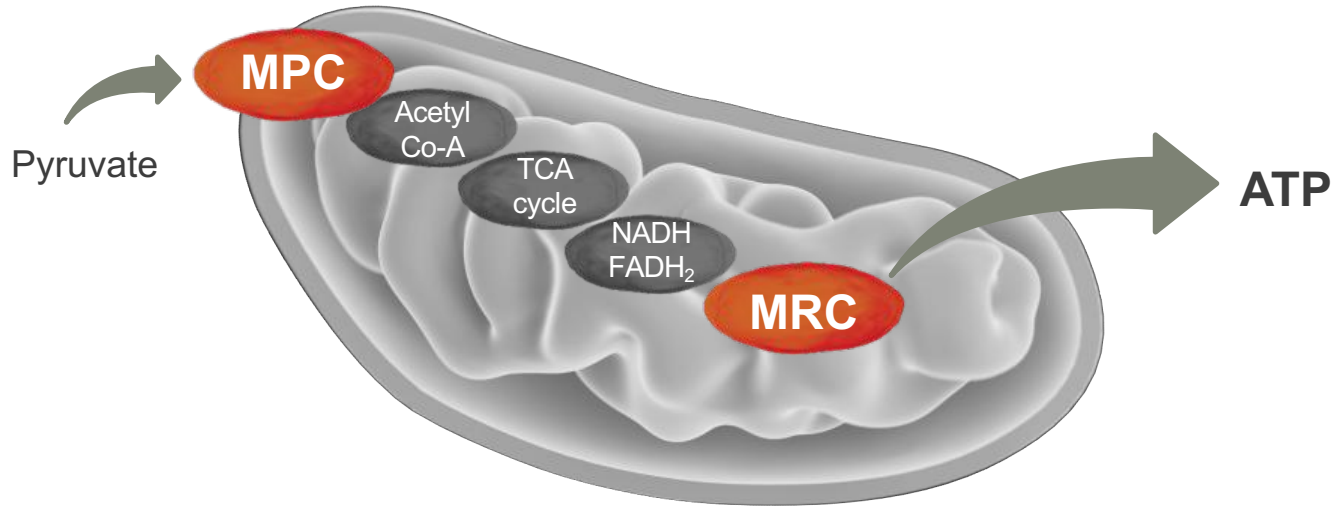
AMP-activated Protein Kinase (AMPK), cellular *energy sensor* - activation: reduces liver fat, increases insulin sensitivity, decreases inflammation

NASH Other

Mitochondrial Pyruvate Carrier (MPC), fuel *gate-keeper* – inhibition: promotes fat utilization, increases insulin sensitivity, decreases inflammation

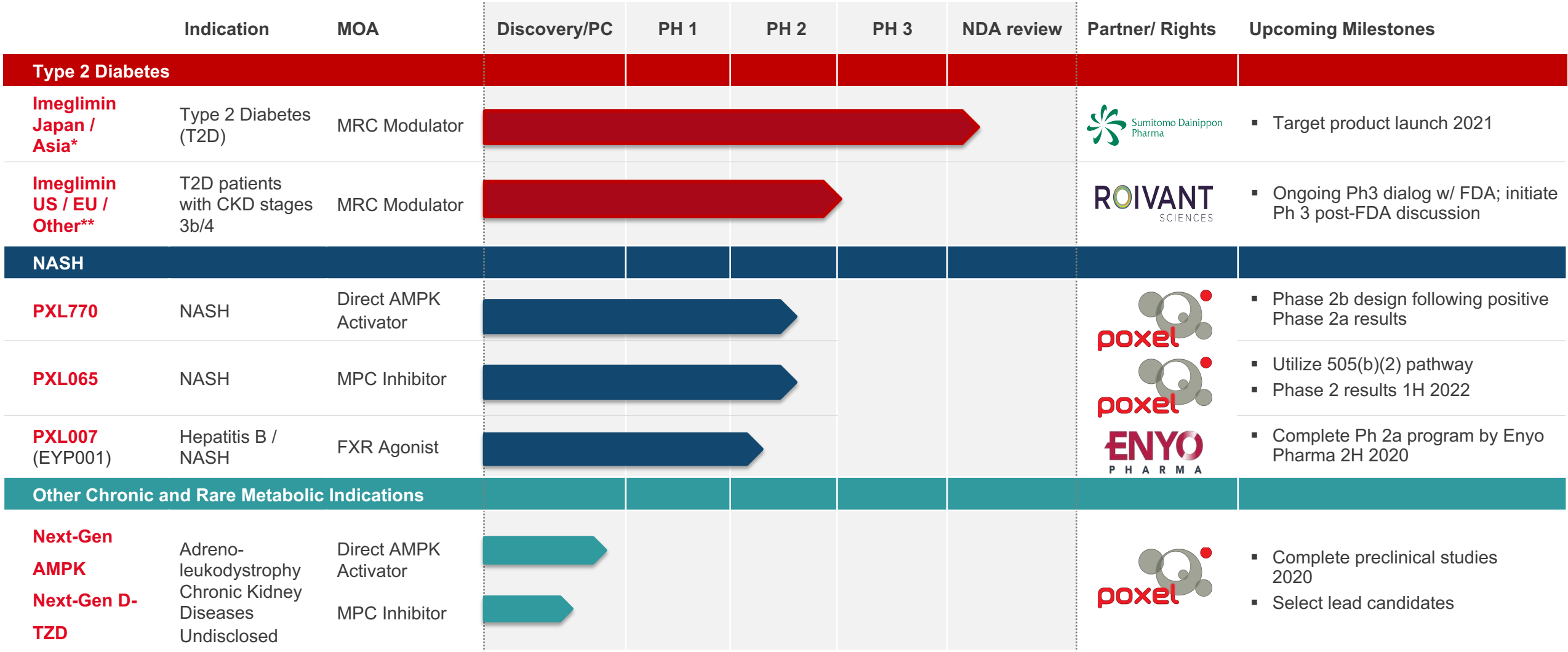
T2D

Mitochondrial Respiratory Chain (MRC), cell's *energy producing* machine – potential to **modulate** function**:** improves β-cell function, increases insulin sensitivity, improves endothelial and diastolic dysfunction



Poxel Mid-to-Late Stage Metabolic Pipeline

Due to COVID-19, the Company Continues to Monitor All Developments that Might Impact the Timelines for Achievement of our Corporate Objectives



*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.

Leadership Team

Highly Experienced Management Team; Extensive R&D and Metabolic Expertise

Thomas Kuhn (Pharm D, MBA)

Chief Executive Officer (CEO) and Co-founder

MERCK

Anne Renevot

Chief Financial Officer (CFO)

Cartier · EOS imaging · EY Building a better working world

Noah Beerman (MBA)

Executive Vice President, Business Development & President, US Operations

coronado BIOSCIENCES · GALENA BIOPHARMA · Indevus Pharmaceuticals, Inc.

David Moller (MD)

Executive Vice President, Chief Scientific Officer (CSO)

MERCK · Lilly

Jonae Barnes

Senior Vice President, Investor Relations, Corporate Communications & Public Relations

SEPRACOR · agenus · Vision MEDICINES

Sébastien Bolze (Pharm D, PhD)

Executive Vice President, Chief Operating Officer (COO), Co-founder

FOURNIER PHARMA · MERCK · SOLVAY PHARMA

Sophie Bozec (PhD)

Senior Vice President, R&D Pharmacology, Co-founder

MERCK

Quentin Durand

Chief Legal Officer

AMF · Davis Polk · Dechert LLP

Pascale Fouqueray (MD, PhD)

Executive Vice President, Clinical Development & Regulatory Affairs, Co-founder

MERCK

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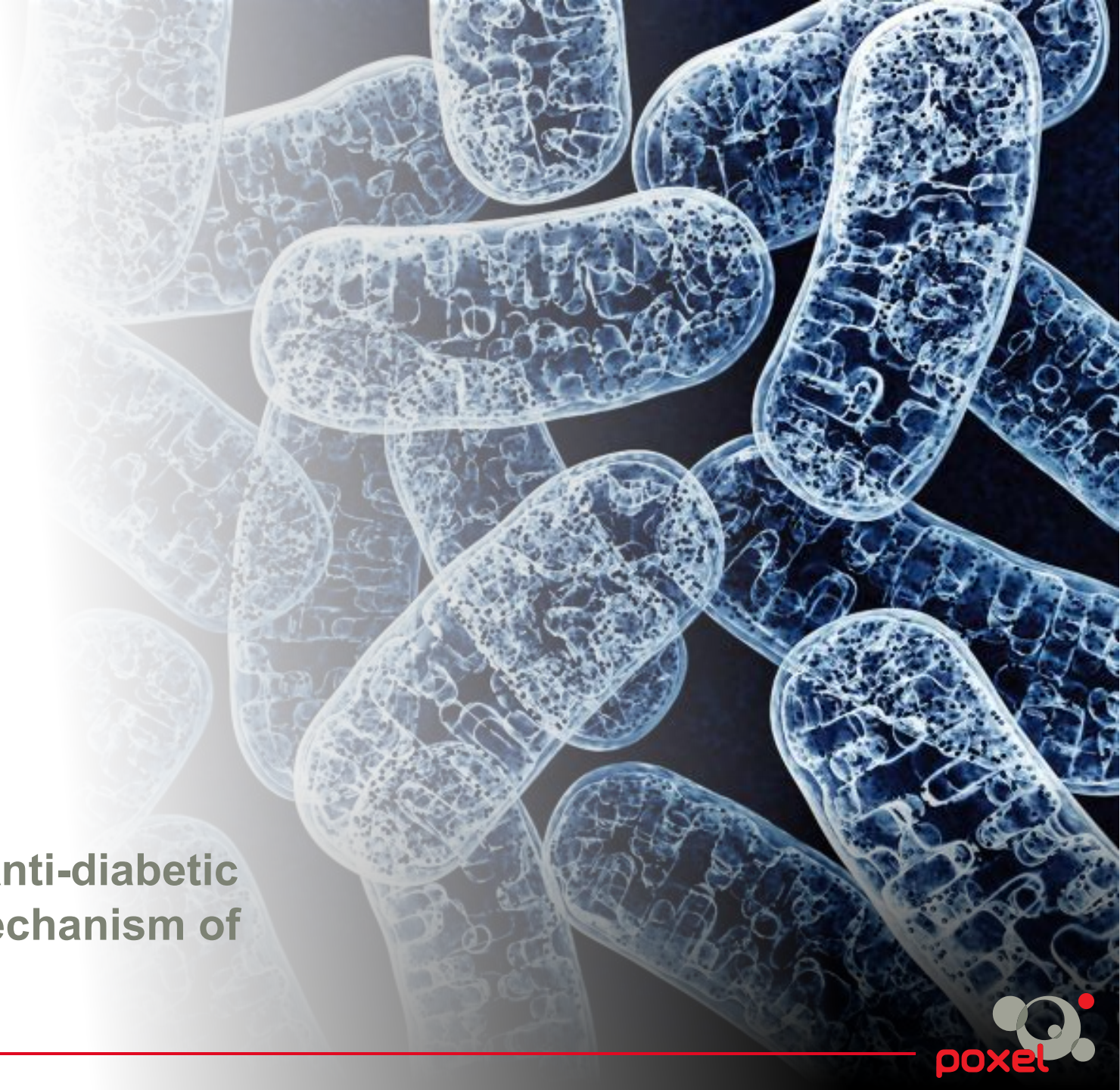
Type-2-Diabetes



Imeglimin

Global Partnerships

Sumitomo Dainippon Pharma

ROIVANT SCIENCES

First in a New Class of Potential Anti-diabetic Therapies with a Differentiated Mechanism of Action

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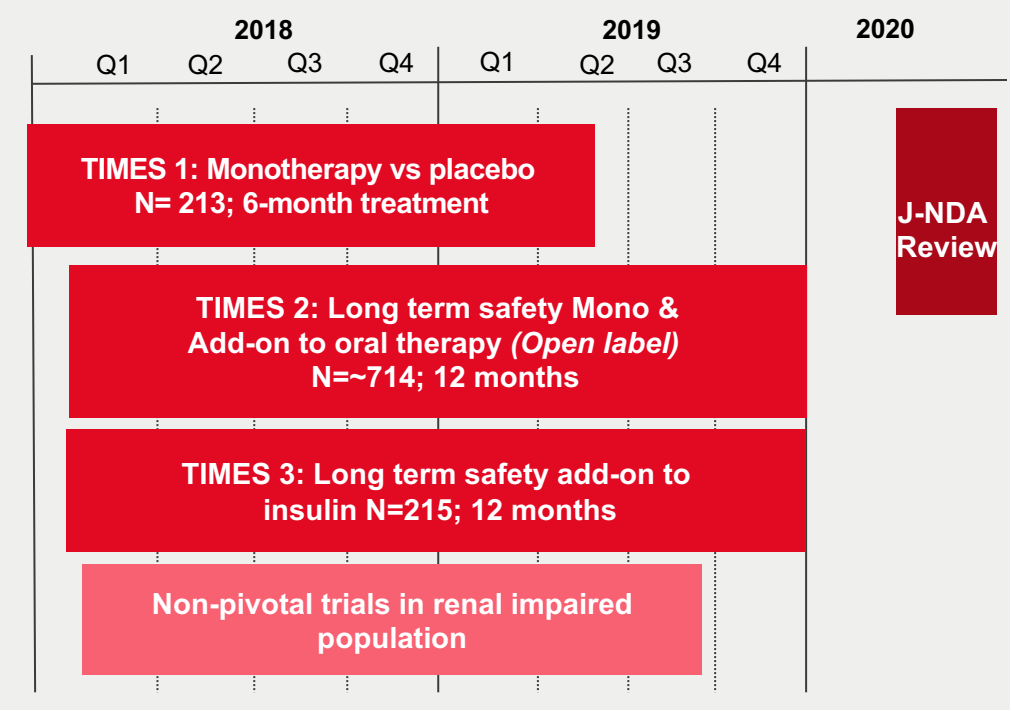
Successful Completion of Phase 3 Program in Japan

JNDA Under Review; Target Launch 2021[1]

Sumitomo Dainippon Pharma

Poxel led Phase 3 TIMES program in >1,100 T2D patients; met endpoints and objectives and observed to be safe and well-tolerated



Partnership Details

- Sumitomo commercialization partner for Japan, China and 11 other East and Southeast Asian countries[2]
- Future potential development milestone payments and sales-based payments of up to **approx. $253M**[3]
- Double-digit escalating royalties
- J-NDA approval triggers **milestone payment of ~€14.2M ($16.6M)**[4] and ability to draw down **EUR 13.5M** from IPF loan

Business Opportunity Japan: Maximize Product Profile

- Sumitomo #1 diabetes franchise; Guidance **FY20 $900M**[1]
- DPP4i's are prescribed to 80% T2D patients[5]
- Limited treatment options for selected populations, including elderly and patients with renal impairment
  - *elderly patients account for ~60% of T2D in Japan*
- TIMES program observed to show ***robust efficacy with favorable safety and tolerability profile***

1. Sumitomo fiscal year April-March .
2. Including: South Korea, Taiwan, Indonesia, Vietnam, Thailand, Malaysia, the Philippines, Singapore, Myanmar, Cambodia, and Laos.
3. Currency exchange rate is at the date of the agreement.
4. Converted at the exchange rate as of July 28, 2020.
5. IQVIA data FY2016 and NDB data FY2016.

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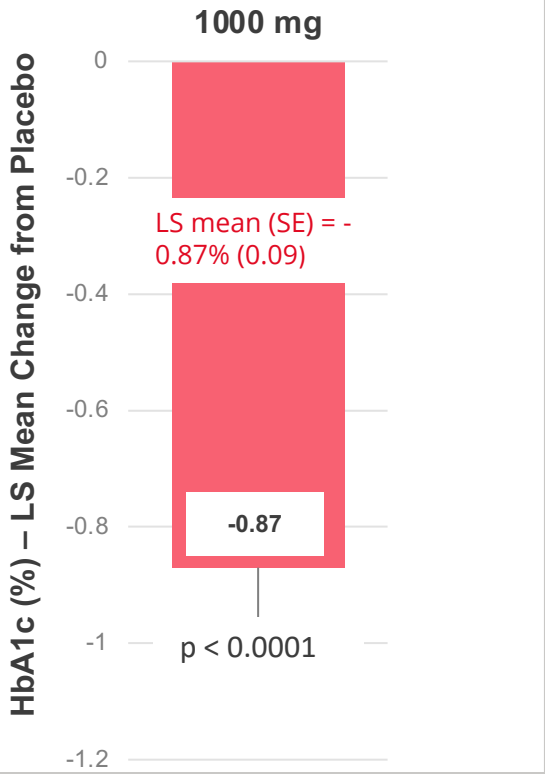
Imeglimin Phase 3 TIMES Program Overview (N=1,142)

Robust and Consistent Efficacy in Monotherapy and as an Add-on Therapy

TIMES 1* Monotherapy

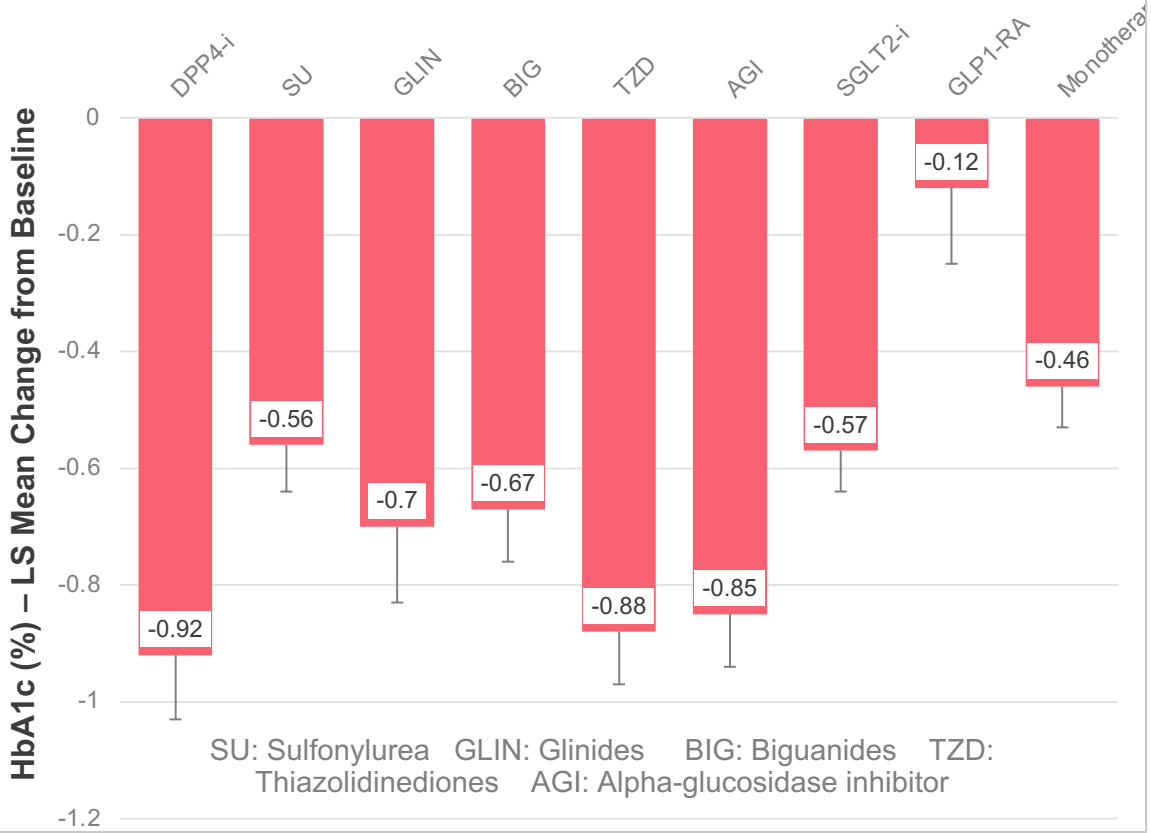
Change in HbA1c – 24 Weeks

Patients (n)	Placebo (N=107)	Imeglimin (N=106)
HbA1c (%), mean (SD)	7.93 (0.684)	7.99 (0.764)



TIMES 2 As an Add-on to Standard of Care

Change in HbA1c (vs baseline) – 52 Weeks

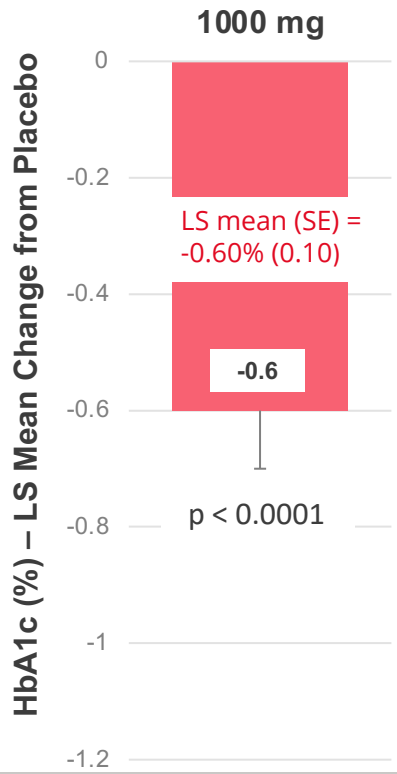


SU: Sulfonylurea GLIN: Glinides BIG: Biguanides TZD: Thiazolidinediones AGI: Alpha-glucosidase inhibitor

TIMES 3 Combination with Insulin

Change in HbA1c – 16 Weeks

Patients (n)	Placebo (N=107)	Imeglimin (N=108)
HbA1c (%), mean (SD)	8.8 (0.8)	8.7 (0.7)



*European Association for the Study of Diabetes meeting 2019.

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Imeglimin Development Strategy for the US & EU

Targeting Type 2 Diabetes Patients with Chronic Kidney Disease (CKD) Stages 3b/4

ROIVANT SCIENCES METAVANT

- **Development and commercialization partner in the US, Europe**, and other countries*
- Poxel and Roivant will decide on a potential co-promotion prior to commercialization

Partnership Details

- Upfront payment: **$35M**[1]
- 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

Initial Development Focus: T2D patients with CKD stages 3b/4[2]

- Demonstrated similar efficacy and was well-tolerated in renally impaired patients (TIMES 1 & Phase 2 data; Japan, US and Europe)
- PK/PD trial met primary objective in this patient population
  - Favorable safety and tolerability profile observed
  - PK/PD data consistent with previous Poxel data
- Given FDA feedback and new draft guidance in March 2020, Metavant is adjusting its Phase 3 plan
- New FDA interactions planned for 2H 2020

*countries not covered in the Sumitomo Dainippon Pharma agreement

1. Poxel contributed $25M (~€20M) to development program over a 2-year period.
2. CKD stage 3b= eGFR 30-44 ml/min/1.73 m2 inclusive; CKD stage 4 = 15-29 ml/min/1.73m2 inclusive.

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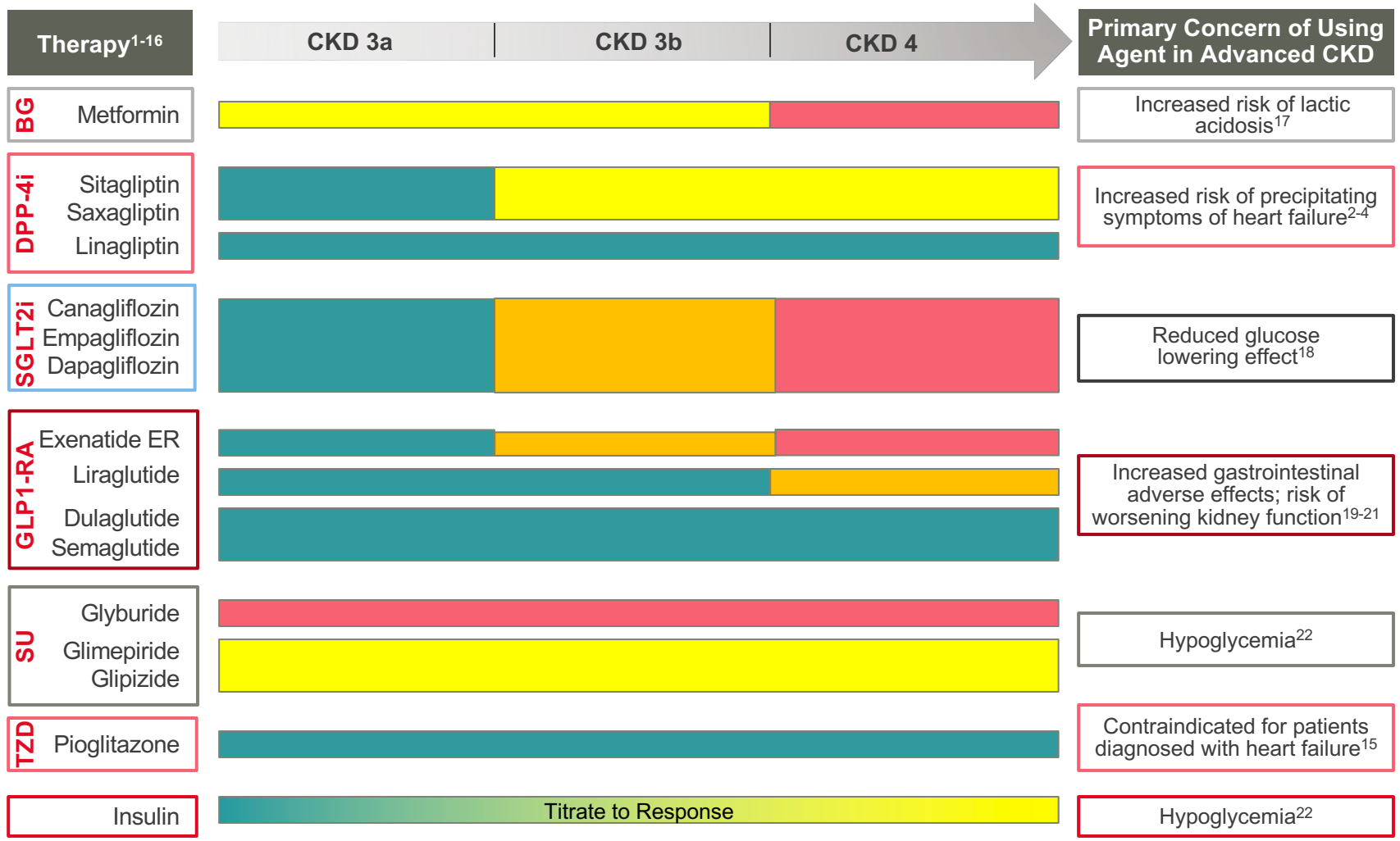
Limitations of Current Therapies to Treat T2D by Kidney Disease Stage Drives Metavant Focus for Imeglimin

T2D patients with CKD stages 3b/4

- Diabetes is the most common cause of CKD
- ~ 2.4 million adults in the US[2]
- Increased cardiovascular risk and challenging glucose management

Underserved patient population

- Many therapies require dose reduction or not recommended in the presence of kidney disease
- Insulin and insulin secretagogues most commonly used at suboptimal doses to prevent hypoglycemia risk
- We believe there is a need for a new treatment with robust efficacy and safety profile with no hypoglycemia risk



Please note that references for this slide are in the Appendix section.

= no dose reduction = use with caution = dose reduction = should not be used/contraindicated

NASH

PXL770
Proprietary Program

Direct AMPK Activator for the Treatment of NASH

Progression of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)

Excessive caloric intake
Sedentary lifestyle

Metabolic syndrome
Dyslipidemia
Type 2 diabetes
Obesity

High Morbidity

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

Normal

NAFLD

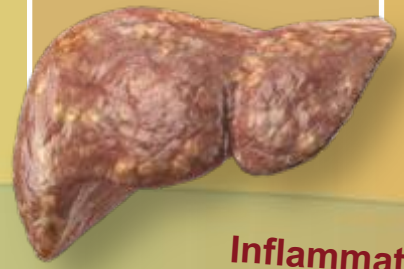
25% of the general population

>70% in diabetic & obese patients

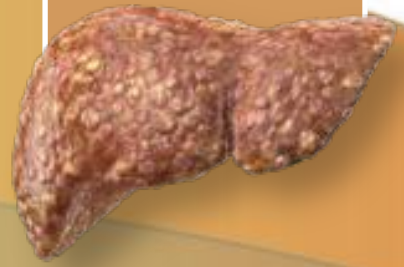
NASH

12% of the general population

25-70% in diabetic and obese patients ≥ 50



Cirrhosis



Fat Deposition › **Steatosis** **Lipotoxicity** › **Inflammation** **Fibrosis** **Collagen Deposition**

Estimated Market Opportunity: >$20B by 2025

J.Hepatology 2018, 68, 362-375. Market Research Engine, Jan. 2020.

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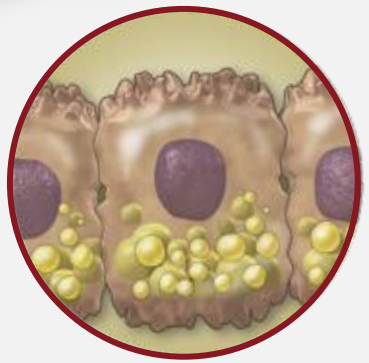
PXL770 & PXL065 Aim to Address Hallmarks of NASH Pathology

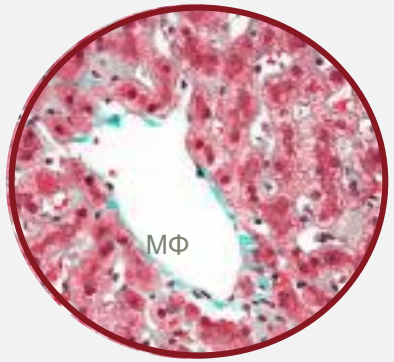
NASH is a Complex, Multifactorial Disease

HALLMARKS OF NASH



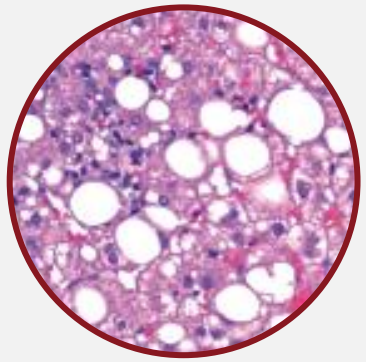
Fat gets released from the adipose tissue and accumulates in the liver cells and stays stored there

Steatosis



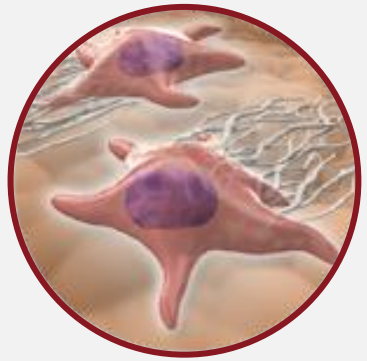
Macrophages (MΦ) become activated and lead to inflammation in the liver

Inflammation



Fat accumulation and inflammation cause degenerative structural changes; ballooning is a sign of cell damage & suffering

Ballooning



Hepatic stellate cells become activated and create scar tissue

Fibrosis

There are no currently approved drugs that treat symptoms & complications across all four categories

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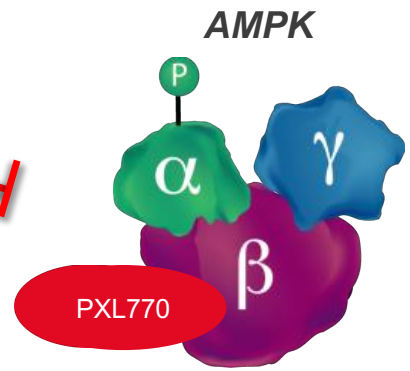
PXL770 is a Direct AMP Kinase Activator

AMPK Activation Restores Metabolic Balance & Inhibits Inflammation



Overnutrition (metabolic syndrome, NASH, Type 2 Diabetes)

Caloric Restriction, Exercise

1) Activates catabolic pathways

- Fatty acid oxidation
- Glucose uptake
- Glycolysis

2) Inhibits anabolic pathways

- Fatty acid & triglyceride synthesis
- Cholesterol synthesis
- Protein synthesis
- Mitochondrial biogenesis

3) Other benefits

- Reduces inflammation
  - ↓macrophage and dendritic cell activation
  - ↓ pro-inflammatory cytokines
  - ↓ Nf-κB plus many others
- Reduces tissue damage (*e.g.* apoptosis via Caspase 6)
- Inhibits lipolysis in adipose

AMPK activation - potential to target core drivers of NASH and to improve key cardiometabolic risk factors

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Preclinical Efficacy Profile – Improvements in all Core NASH Features

Data Observed in Multiple Rodent Models Supports Potential for PXL770's Beneficial Clinical Effects

A. Improved liver steatosis

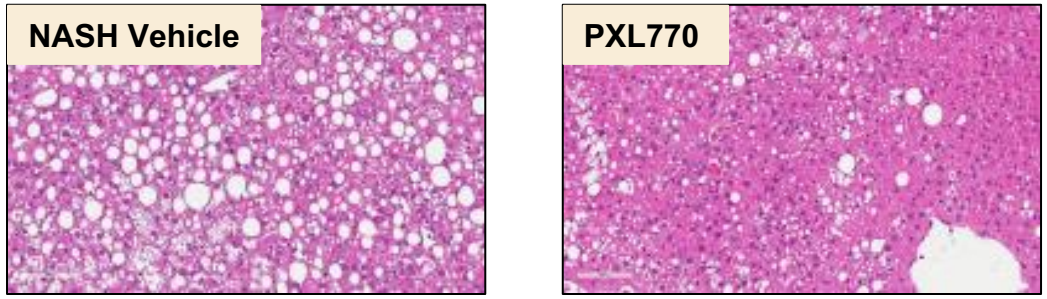
B. Decreased liver (and adipose tissue) inflammation

C. Decreased profibrogenic pathways in liver

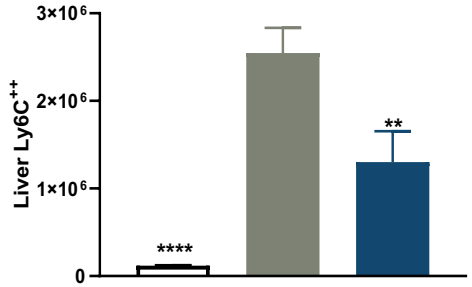
D. Improved plasma liver enzymes (ALT and AST)

E. Improved NAFLD Activity Score (NAS)

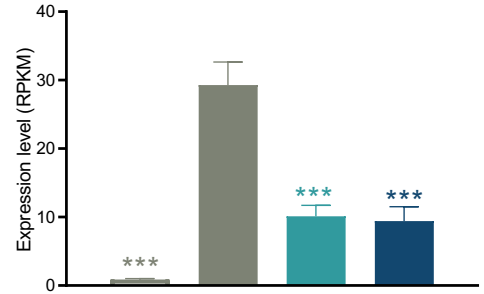
A.



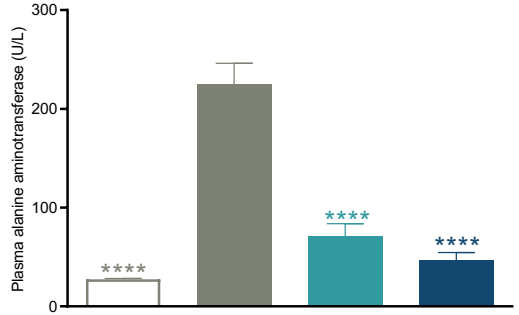
B. Total Liver Macrophages



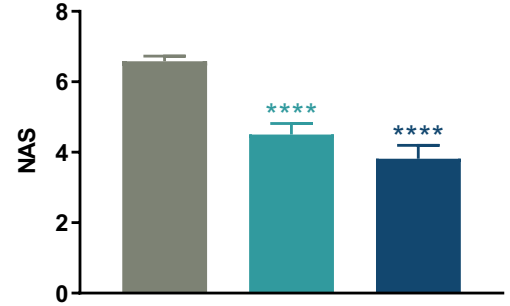
C. Collagen 1A1 (Liver)



D. Plasma ALT



E. NAS Score



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

**: p< 0.01, ***: p< 0.001; **** p<0.0001 compared to DIO-NASH vehicle. n=11-12/group

Poster#4, Global NASH Congress, 26th–27th February 2018, London, UK.

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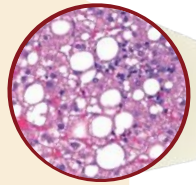
Pre-Clinical Data Demonstrate Potential Synergy of PXL770/AMPK Activation with Other Agents in Development

PXL770

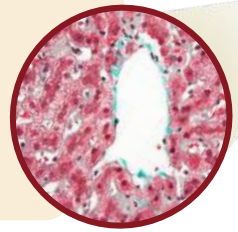
Effects in Adipose Tissue

- Low grade inflammation
- Lipolysis

Effects in Liver



- *De novo* lipogenesis / Steatosis
- Chronic inflammation
- Stellate cell activation / Fibrosis



- Apoptosis / cell death

Effects in Muscle

- Peripheral insulin resistance

Other Mechanisms

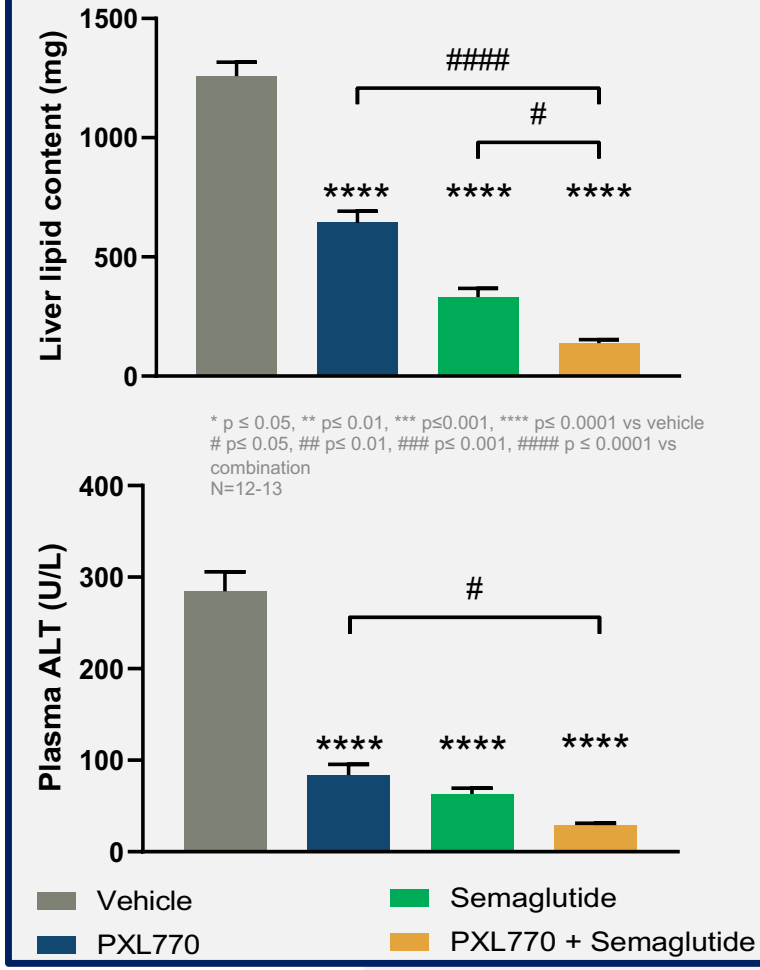
GLP-1

FXR

THRβ

MPC

PXL770 / Semaglutide (GLP-1) Mouse NASH Model



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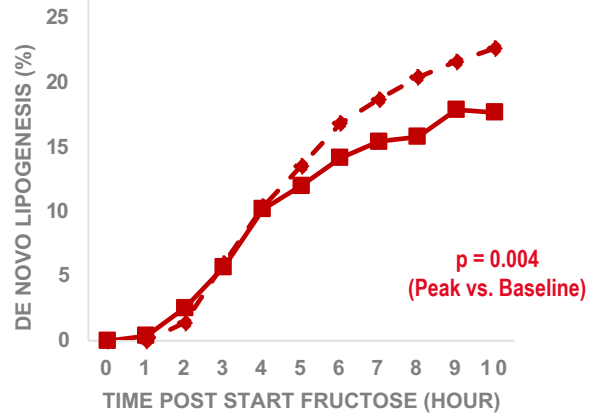
Phase I Program Summary

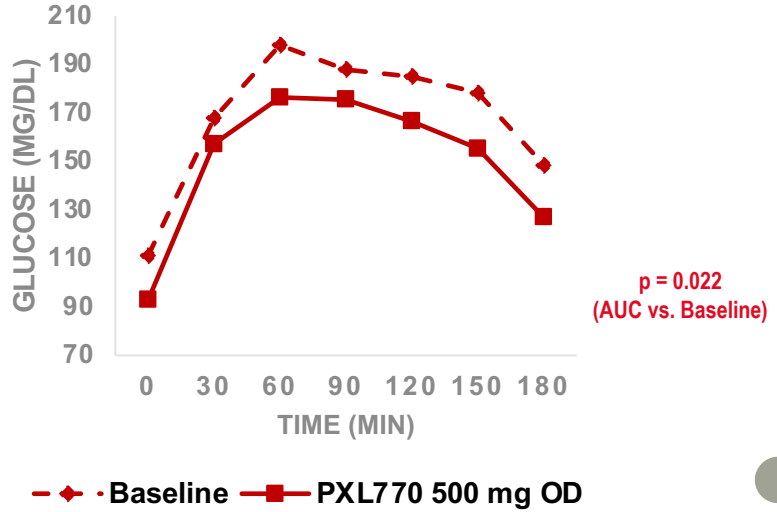
Favorable PK, Safety, Target Engagement, Efficacy Signals

- **Healthy Subjects (Single & Multiple Dose Studies)**
  - 132 subjects
  - linear, dose-proportional exposure
  - terminal $T_{1/2}$ 25 hour
  - no statin interaction; no QT/ECG signals
  - good tolerability; low placebo-like incidence of TAE events
- **Four Week PKPD Trial**
  - 16 non-diabetic NAFLD subjects with insulin resistance (12 active; 4 placebo)
  - suppressed de-novo lipogenesis◊
  - improved glycemia - total and incremental glucose AUC
  - improved insulin sensitivity - *HOMA-IR (p=0.013); Matsuda# (p=0.014); OGIS$^{\Delta}$ (p=0.012)
- **AMPK activation demonstrated:** beneficial impact on key pathways of liver injury and NASH

Fructose-stimulated de novo lipogenesis Versus baseline (at week 4) (N=12)



Oral glucose tolerance Versus baseline (at week 4) (N=12)



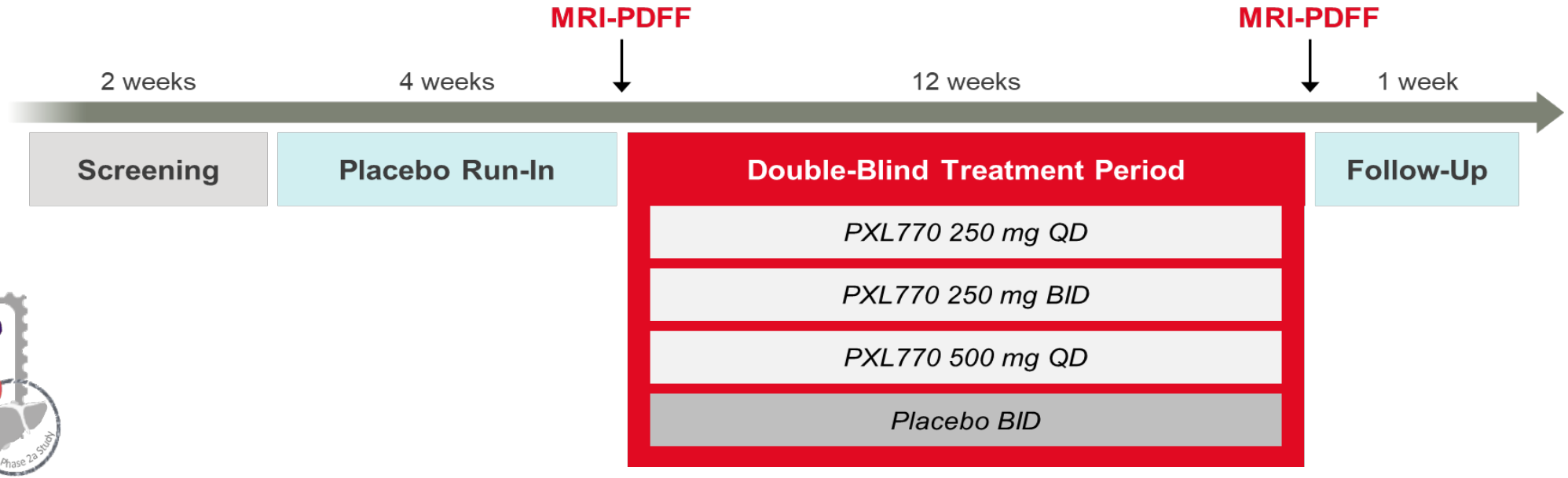
◊ Versus baseline; no effect in Placebo group; *responsible for ~25% of liver fat accumulation*

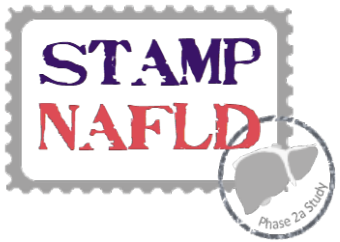
*Homeostatic Model Assessment of Insulin Resistance; # Diabetes Care 1999; **22**: 1462–1470; Δ Oral glucose insulin sensitivity index

PXL770: Phase 2a Study Design

Phase 2a 12-week, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Trial

- N = 120 presumed NASH patients with and without Type 2 diabetes
- Inclusion criteria: increased hepatic fat (assessed via CAP and MRI-PDFF)
- Trial assessed efficacy and safety
- Primary endpoint: relative change in % liver fat mass (MRI-PDFF) from baseline





PXL770 Phase 2a Baseline Characteristics

	Placebo	PXL770 250 mg QD	PXL770 250 mg BID	PXL770 500 mg QD
N	31	30	30	29
Age, mean (SD)	51.5 (12.17)	52.5 (12.93)	50.6 (12.26)	55.7 (12.63)
Male, N (%)	15 (48.4%)	13 (43.3%)	7 (23.3%)	7 (24.1%)
BMI (kg/m^2), mean (SD)	35.4 (5.9)	35.2 (6.3)	36.6 (6.3)	35.1 (4.95)
T2DM, N(%)	14 (45.2%)	13 (43.3%)	14 (46.7%)	12 (41.4%)
Therapy for T2DM, N (%)	9 (69.2%)	11 (84.6%)	14 (93.3%)	11 (91.7%)
HbA1c (%)*, mean (SD)	6.03 (1.095)	6.29 (1.093)	6.19 (0.837)	6.11 (0.762)
FPG (%)*, mean (SD)	117.2 (34.78)	120.2 (35.07)	117.2 (27.00)	112.7 (20.60)
Liver fat content (%), mean (SD)	21.8 (8.4)	16.0 (4.6)	20.3 (7.6)	18.7 (6.5)
ALT* (UI/L), mean (SD)	37.2 (19)	37.2 (22)	37.8 (37)	41.3 (35)

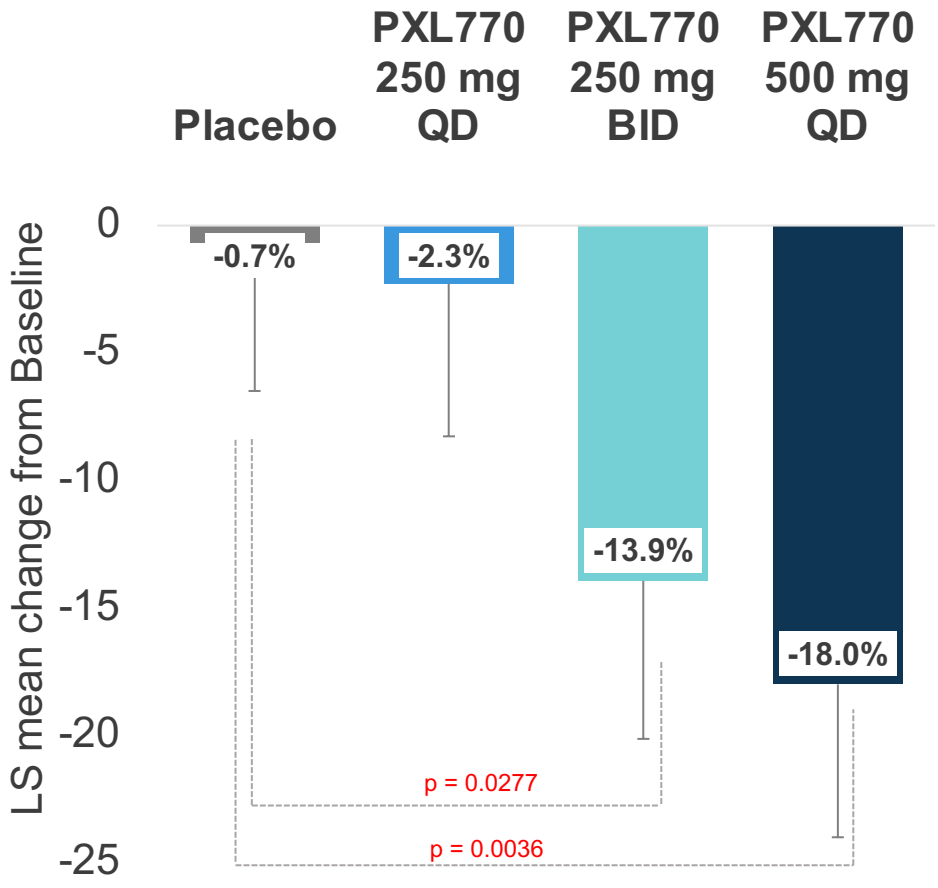
*Normal range:

- ALT : 6 – 41 UI/L
- FPG < 126 mg/dL
- HbA1c < 6.5% (non-diabetic)

Significant Relative Decrease in Liver Fat Mass & ALT

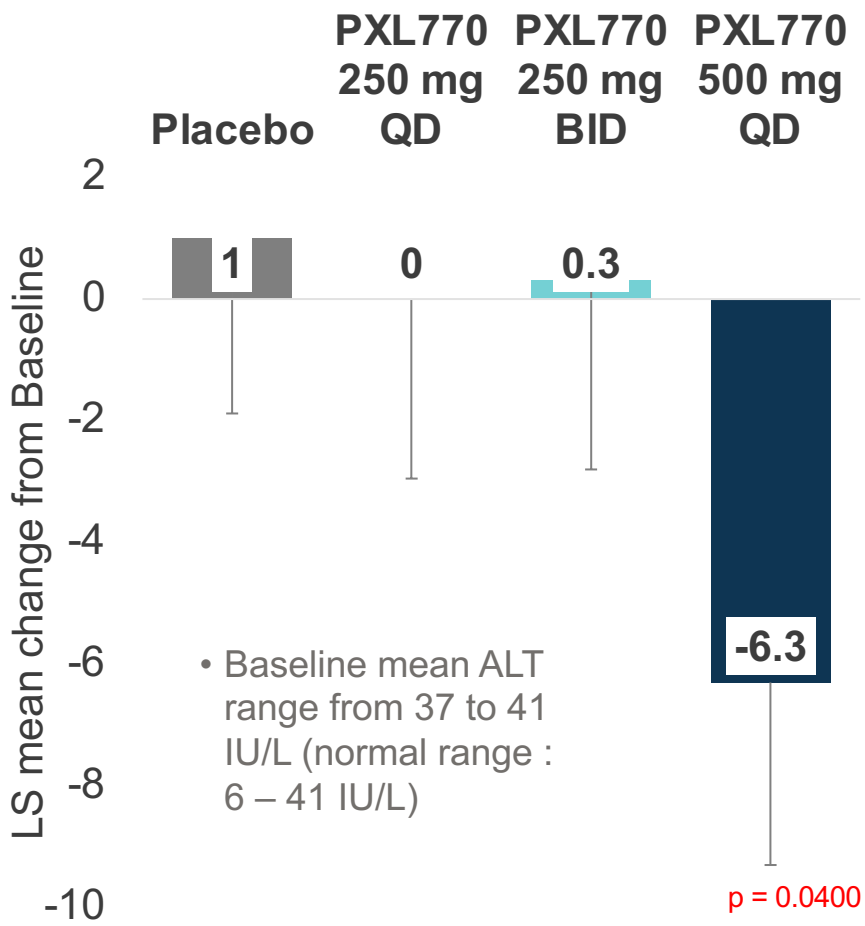
Changes from Baseline vs. Placebo

Liver Fat Content (% Change)



- Proportion achieving ≥ 30 % reduction in liver fat mass: 27.6% in 500 mg QD group vs. 6.5% Placebo group (p= 0.0501)
- Greater relative liver fat mass reduction (up to 85%) observed in more responsive patients

ALT (IU/L)



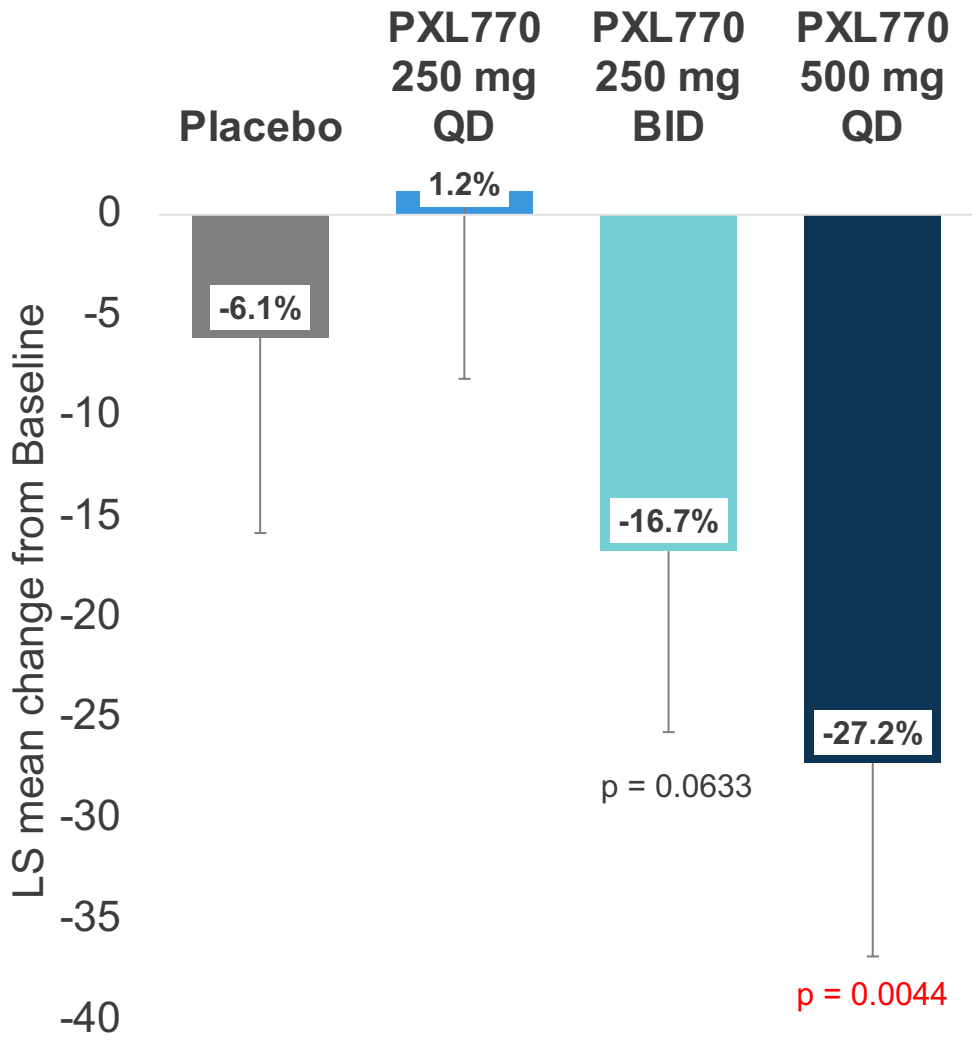
- Baseline mean ALT range from 37 to 41 IU/L (normal range : 6 – 41 IU/L)

ANCOVA on PP set

More Pronounced Effect on Relative Decrease in Liver Fat Mass (MRI-PDFF) in Patient Subgroup with Type 2 Diabetes

Changes from Baseline and vs. Placebo

- Approximately 47% of patients with NASH also have Type 2 diabetes[1]
- Patients with Type 2 diabetes at higher risk of progression to fibrosis – end stage liver disease[2]



41-47% of patients in each group with diagnosis of Type 2 diabetes

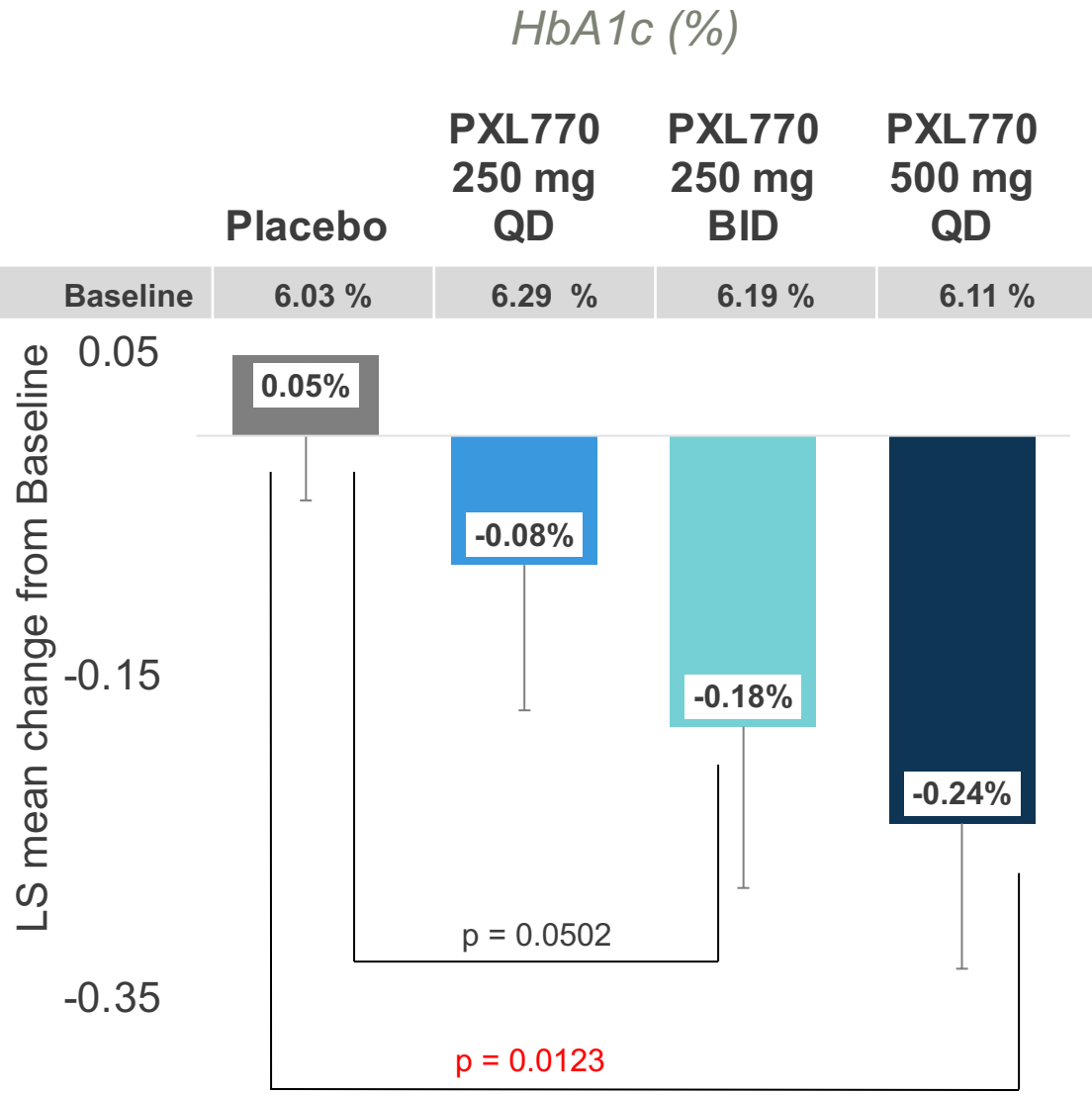
1. Marchisello S et al In J Mol Sci 20:1948-, 2019; Younossi ZM, Hepatology 64:73-84, 2016

2. Gastaldelli A & Cusi K, JHEP Reports 1:312-328, 2019

Significantly Improved Glycemia - Despite Low Baseline HbA1c

Changes from Baseline vs. Placebo

- Baseline HbA1c range from 6 to 6.3 % (non-diabetic range < 6.5%)
- Greater effect in subgroup with Type 2 diabetes
- Similar (or greater) than effects observed with approved anti-diabetic medications in non-diabetic subjects with impaired glucose tolerance



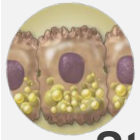
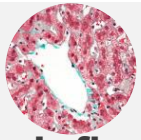
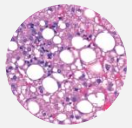
PXL770 Phase 2a Safety Summary

- Well tolerated in all three treatment groups
- Total number of patients experiencing treatment emergent adverse events in each PXL770-treated group (20-23) similar to placebo (21)
- TEAE's mainly mild to moderate; AE's relating to GI organ class most common
- Serious Adverse Events
  - 500 mg once-daily group: 1 unrelated (sick sinus syndrome)
  - 250 mg twice-daily group: 1 unrelated (sepsis) and 1 possibly related (ALT increase)
- Overall safety profile consistent with Phase 1 program

PXL770 Phase 2a Results Summary

- Oral first-in-class agent observed to produce statistically significant efficacy
  - reduction in liver fat mass
  - observed to improve other key measures of ALT and HbA1c
- Greater response observed in patients with type 2 diabetes – higher risk and substantial sized subpopulation
- Results support potential in NASH – plans for Ph2b under discussion; goals - confirm safety and evaluate important histological endpoints – *e.g.* inflammation and fibrosis, and key subpopulations (*e.g.* T2DM)
- Based on distinct mechanism and preclinical combination results, either monotherapy or co-administration with other agents could provide broad treatment for NASH
- Results also support potential for PXL770 and the AMPK platform in other chronic and rare metabolic diseases

PXL770 - Translation of NASH Efficacy Parameters

	Rodent (*in vivo*)	Human Cells (*in vitro*)	NASH/NAFLD Patient
 **Steatosis**	✓ ↓ steatosis score; ↓ liver lipids; ↓ de novo lipogenesis	✓ ↓ de novo lipogenesis	✓ ↓ de novo lipogenesis; ↓ liver fat mass
 **Inflammation**	✓ ↓ inflammation score; ↓ liver leukocytes; MCP1 (+ other)	✓ ↓ cytokine secretion (macrophage)	***Pending Phase IIb***
 **Ballooning**	✓ ↓ ballooning score	no model	✓ ↓ ALT ***Pending Phase IIb***
Fibrosis	✓ ↓ fibrogenesis	✓ ↓ stellate cell activation	***Pending Phase IIb***
↓ Insulin Resistance	✓ improved OGTT; ↑ glucose utilization (clamp) ↓ HbA1c	✓ ↑ glucose uptake (muscle cells)	✓ improved OGTT, HOMA-IR, Matsuda; ✓ ↓ HbA1c

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PXL065

Proprietary Program

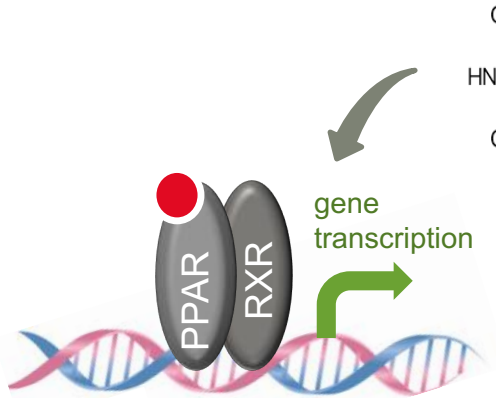
MPC Inhibitor for the Treatment of NASH Utilizing the 505(b)(2) Regulatory Pathway

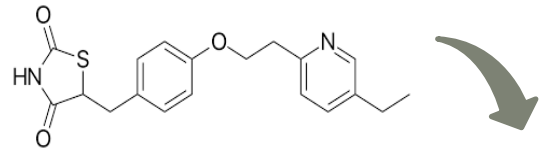
PXL065: Leveraging the Benefits of Pioglitazone

With Reduced PPARγ Activity

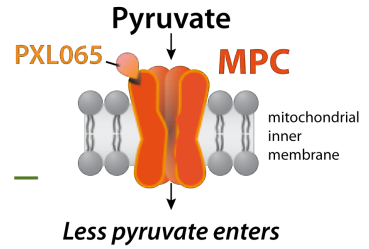
- **Pioglitazone used in T2D for > 20 years**
  - >30 million patient-years of exposure[1]
  - Established CV outcomes benefit[2]
- **Pioglitazone extensively studied and has demonstrated resolution of NASH**
  - Demonstrated "Resolution of NASH without worsening of fibrosis" in Phase 4 trial[3]
  - Only drug recommended for biopsy-proven NASH by AASLD & EASL Practice Guidelines[4]
  - Currently prescribed by ~14% of physicians for biopsy-proven NASH patients[5]
  - Limited use due to *PPARγ-related side effects*: weight gain, fluid retention, bone loss

- **Pioglitazone, TZDs: both genomic (PPAR) and non-genomic mechanisms**
- **PXL065 is an NCE which *selectively mediates non-PPAR* effects of Pioglitazone**





Non-Genomic Mechanisms (MPC)



- Regulation of fuel selection – modified cell signaling
- Enhanced lipid metabolism
- Anti-inflammatory
- Contributes to glucose lowering

1. Takeda 2014. https://www.takeda.com/newsroom/newsreleases/2014
2. Diab & Vascular Disease Res 2018; 16:133-143
3. Ann Intern Med. 2016, 165(5), 305-315
4. J Hepatol. 2016, 64(6),1388-402; Hepatology 2018, 67, 328-357
5. Therap Adv Gastroenterol. 2016, 9(1), 4-12

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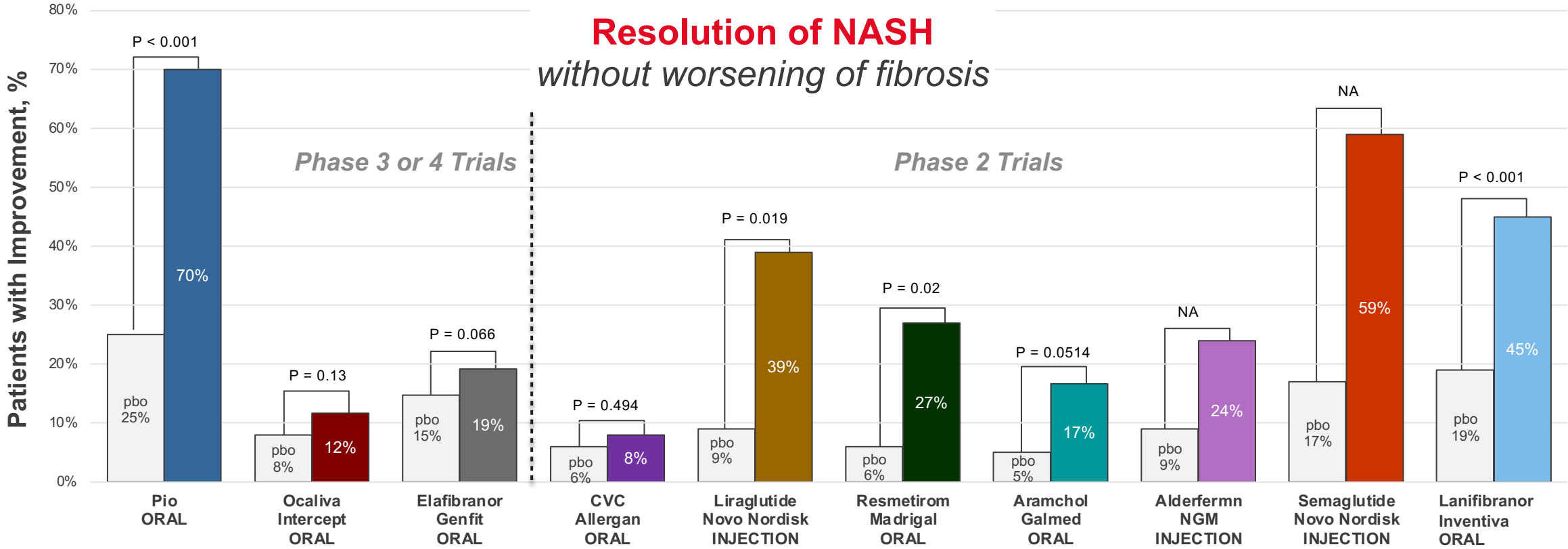
Pioglitazone has Demonstrated Resolution of NASH

Largest Effect of Oral Agents - Use Limited by Weight Gain



Pio Cusi Phase 4 trial (30→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) - Lancet. 2019, 394(10215), 2184-2196

Elafibranor RESOLV-IT Phase 3 trial (120 mg, 52 wks/) – Press release May 11, 2020

CVC (Cenicriviroc) CENTAUR Phase 2 trial (150 mg, 2 yrs) – Hepatology 2020, Jan 13 epub

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

Resmetirom (MGL-3196) Phase 2 trial (80 mg +/- 20 mg, 36 wks) – Lancet 2019 394:2012-24. 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".

Aldaferin (NGM282) Phase 2 trial (1 mg, 24 wks, cohort 4) - Press release Feb 25, 2020. P value not disclosed.

Semaglutide Phase 2 trial (0.4 mg, 72 wks) – Press release May 6, 2020. P value not disclosed.

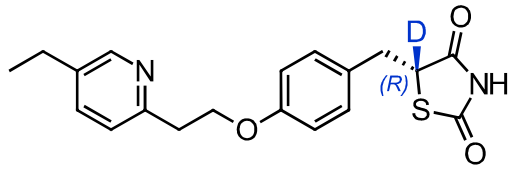
Lanafibranor Phase 2 trial (1200 mg, 24 wks, ITT population) – Press release Jun 15, 2020 (also at 800 mg 33% pts met endpoint, p=0,043)

No head-to-head trials have been conducted. Data derived from different clinical trials with potentially different designs, patient populations, and definition of NASH resolution.

PXL065: A Single Stabilized Stereoisomer of Pioglitazone

Benefits of Pioglitazone for NASH with Reduced PPARγ Side Effects

- **Pioglitazone is a mixture of 2 stereoisomers with dramatically different properties**
- **PXL065 is the deuterium-stabilized R-stereoisomer**



S-Pioglitazone (stabilized)

- MPC inhibitor
- Strong PPARγ agonist
- **Undesired side effects:**
  - **Weight gain**
  - **Fluid retention**

PXL065 (stabilized R-pio)

- MPC inhibitor
- Very weak PPARγ agonism
- **Anti-inflammatory**
- **Activity in NASH**

Composition of Matter IP

505(b)(2) Regulatory Path

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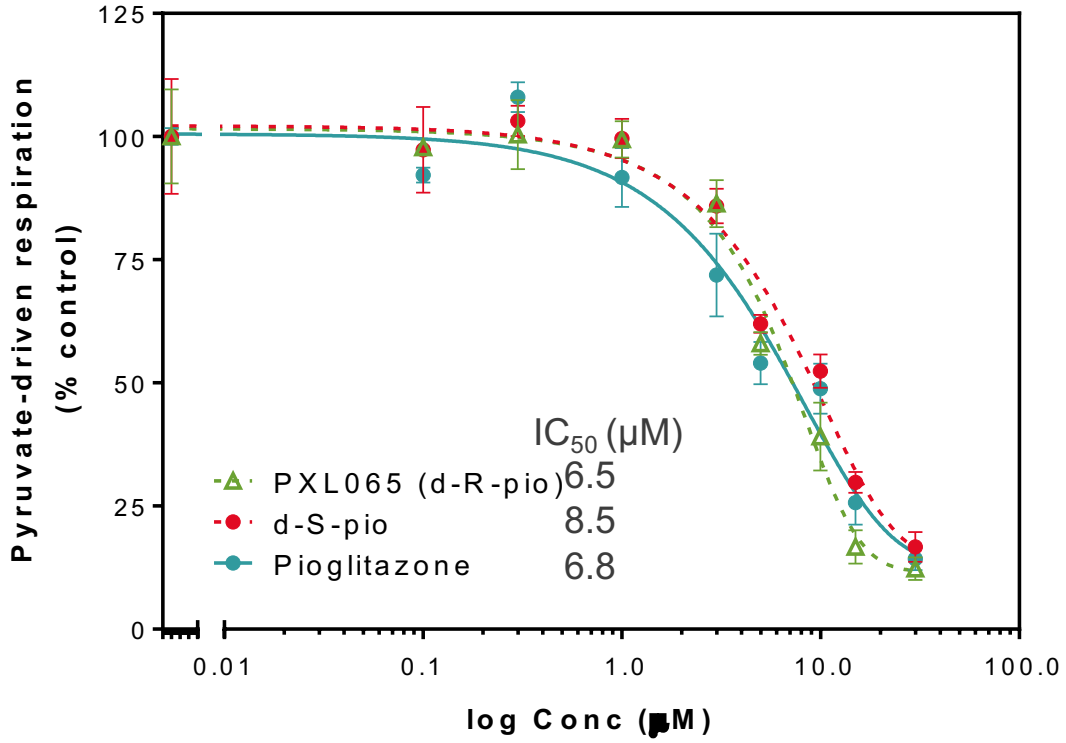
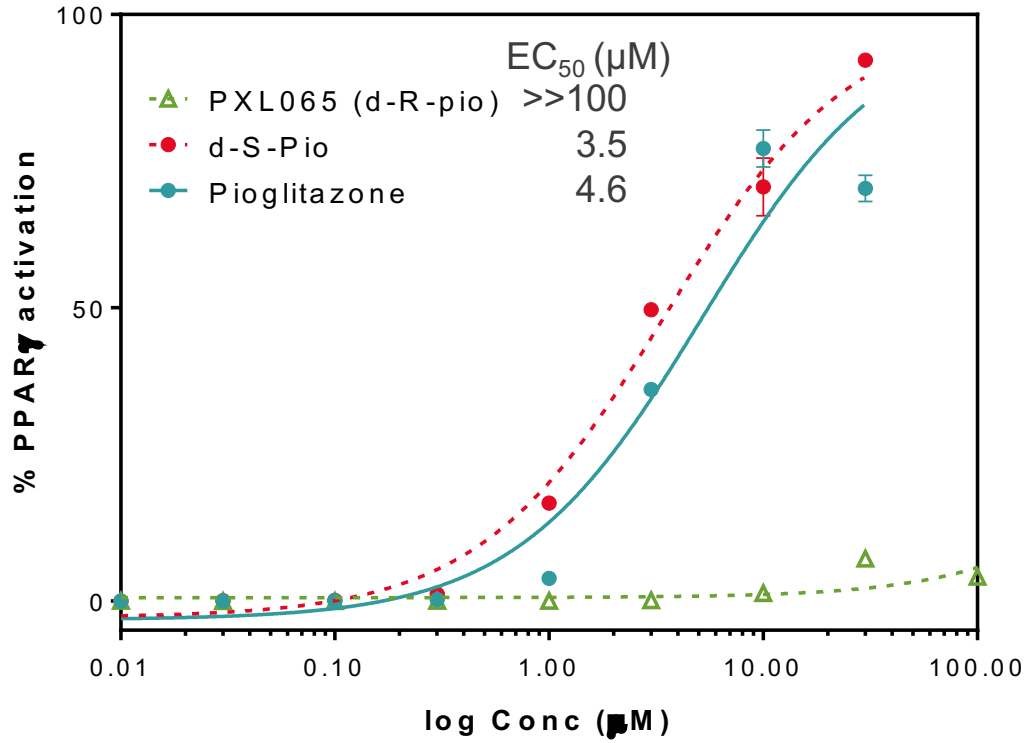
PXL065 Targets Inhibition of MPC

Without PPARγ Agonist Activity from S-Stereoisomer

MPC Inhibition in HepG2 Cells



PPARγ Agonist Activity

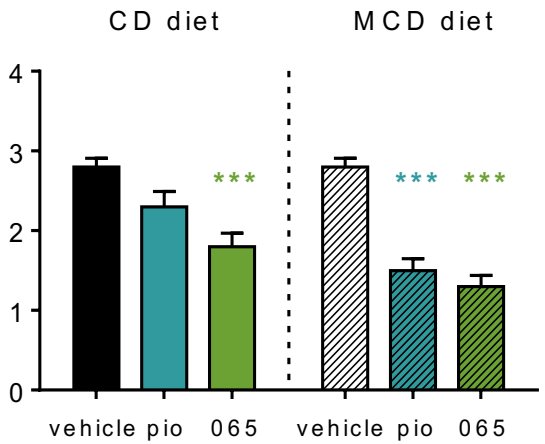


PPARγ activation in fluorescence-based TRAP220 coactivator recruitment assay
Results are expressed as % of response of positive control (10μM rosiglitazone)

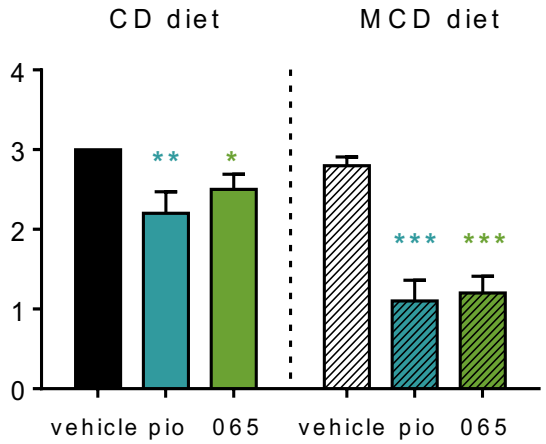
PXL065: Similar Activity to Pioglitazone in NASH Mouse Models

Results Consistent with Potential Beneficial Clinical Effects

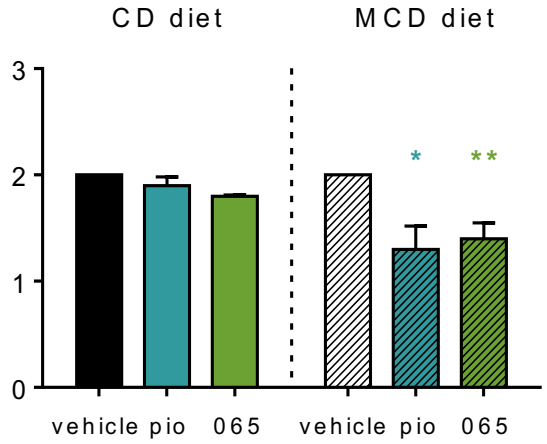
Steatosis



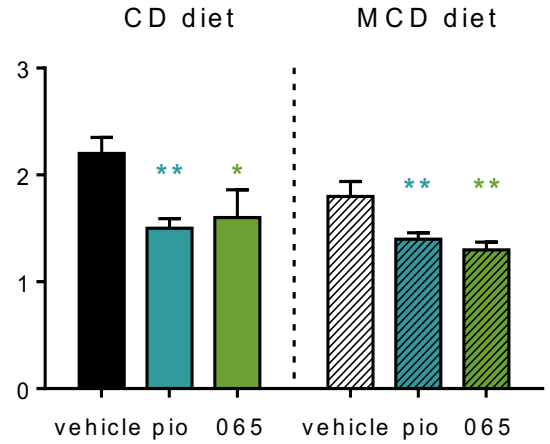
Inflammation



Ballooning



Fibrosis

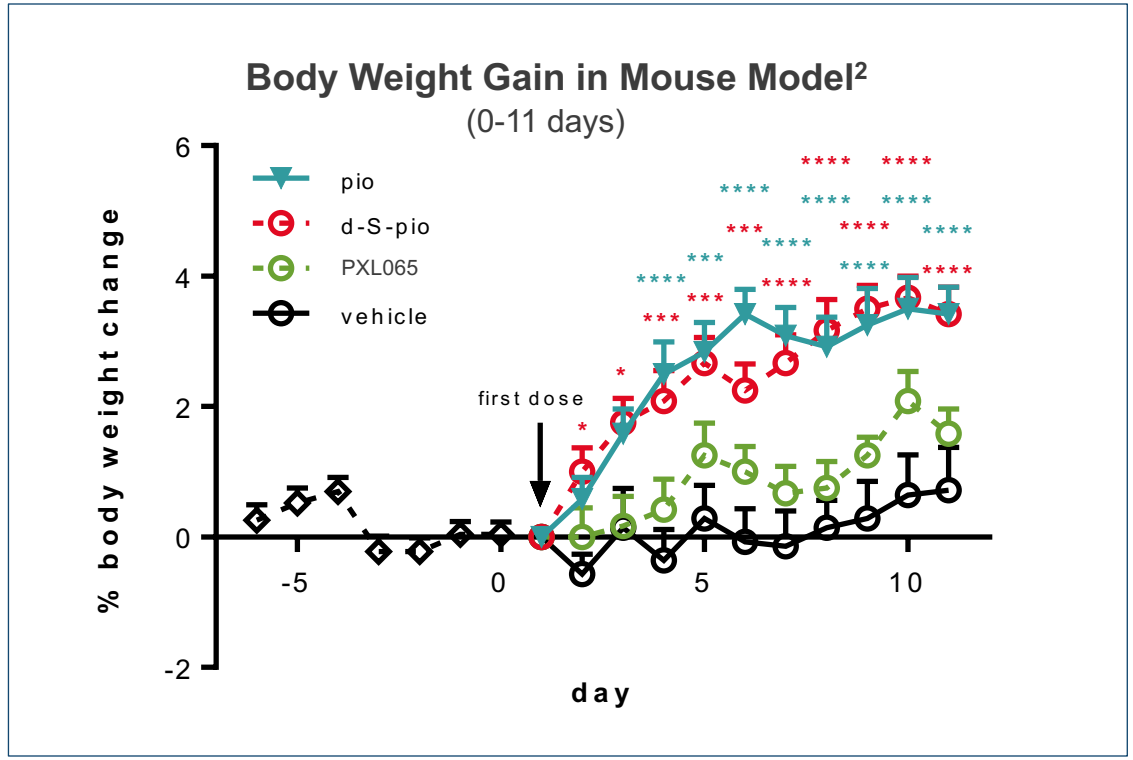


- Liver histopathology on day 43 in mice fed a Choline Deficient (CD) or a Methionine/Choline Deficient (MCD) diet
- Pioglitazone (30 mg/kg/day) or PXL065 (15 mg/kg/day), Wilcoxon rank sum test vs vehicle; *p < 0.05, **p < 0.005, ***p < 0.001

Summary of PXL065 Benefits in NASH

PXL065 (R-Pio) Retains Benefits of Pio; S-Pio Drives Weight Gain in Mouse Model

NASH Rodent Models[1] Functional Parameters	Pio	PXL-065
⬇ Hepatic Triglycerides	✓	✓
⬇ Hepatic Free Fatty Acids	✓	✓
⬇ Hepatic Cholesterol	✓	✓
⬇ Hepatic Steatosis	✓	✓
⬇ Hepatic Inflammation	✓	✓
⬇ Hepatic Ballooning	✓	✓
⬇ Hepatic Fibrosis	✓	✓
⬆ Weight Gain	✓	-
⬆ Fluid Retention	✓	-

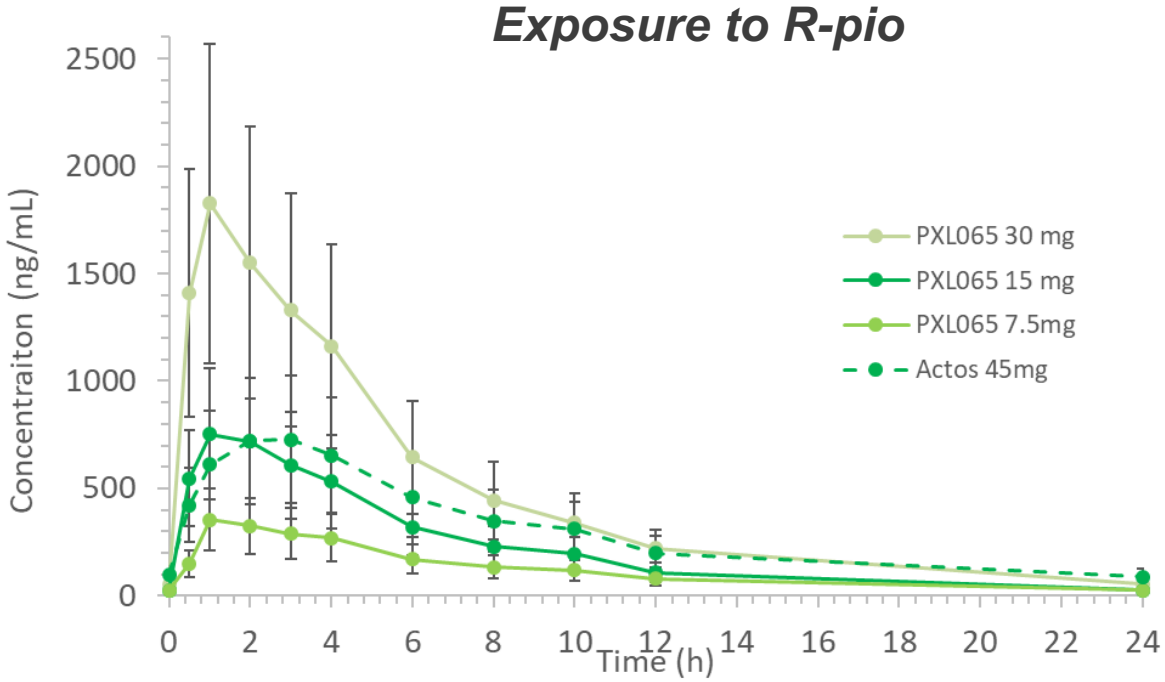


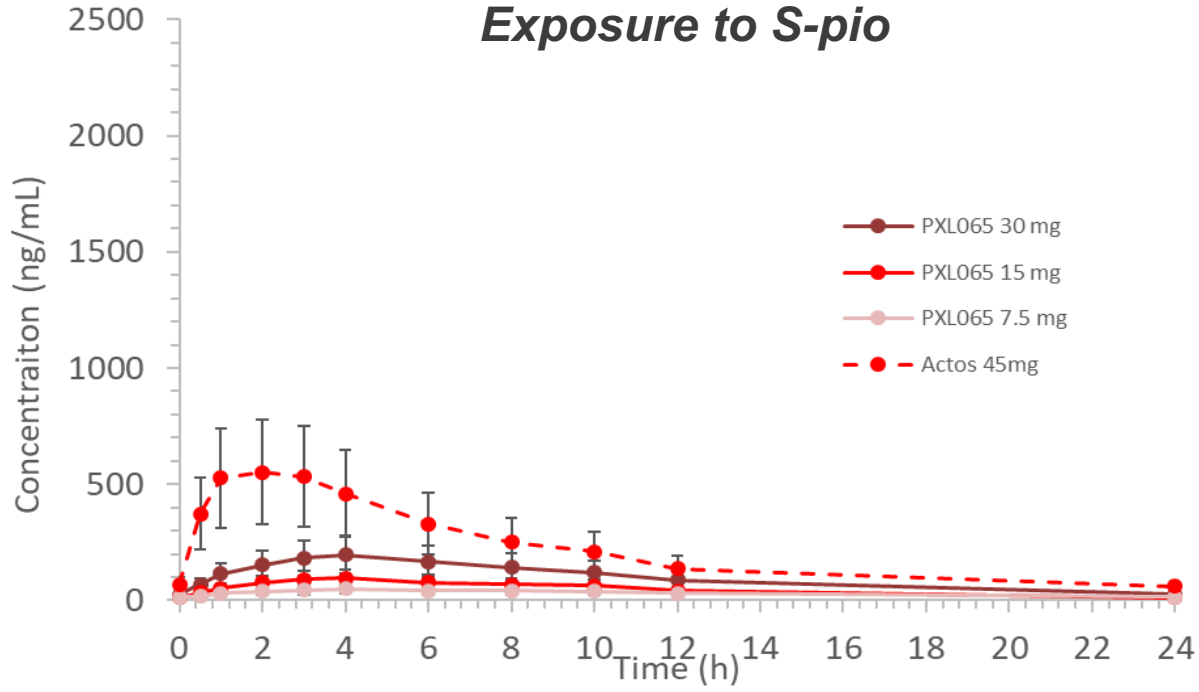
NASH rodent models selected based on literature: *C57BL/6J mouse model of weight gain & edema* (Nat Med 2005, 11, 861-866) and methionine-choline deficient (MCD) model of NASH (Lab Investig. 2007, 87, 56-65). Additional choline deficient (CD) model of NASH was validated with RenaSci. In MCD model both pio and PXL065 reduced ballooning. d-S-pio was only run in the CD model where no effect on ballooning with any compound was observed.

*Weight gain measured in C57BL/6J mouse model. Pioglitazone dosed at 30 mg/kg, d-S-pio and PXL065 dosed at 15 mg/kg. Statistical significance determined by 1-way (total day 11) or 2-way (% by day) ANOVA with Dunnett's post-test average ± SEM; * p < 0.05, ** p < 0.01, *** p < 0.001, **** P < 0.0001*

PXL065: Phase 1 Study Results

15 mg PXL065 vs. 45 mg Actos®[1]: Similar R-Pio Exposure; S-Pio Exposure Decreased ~5-fold



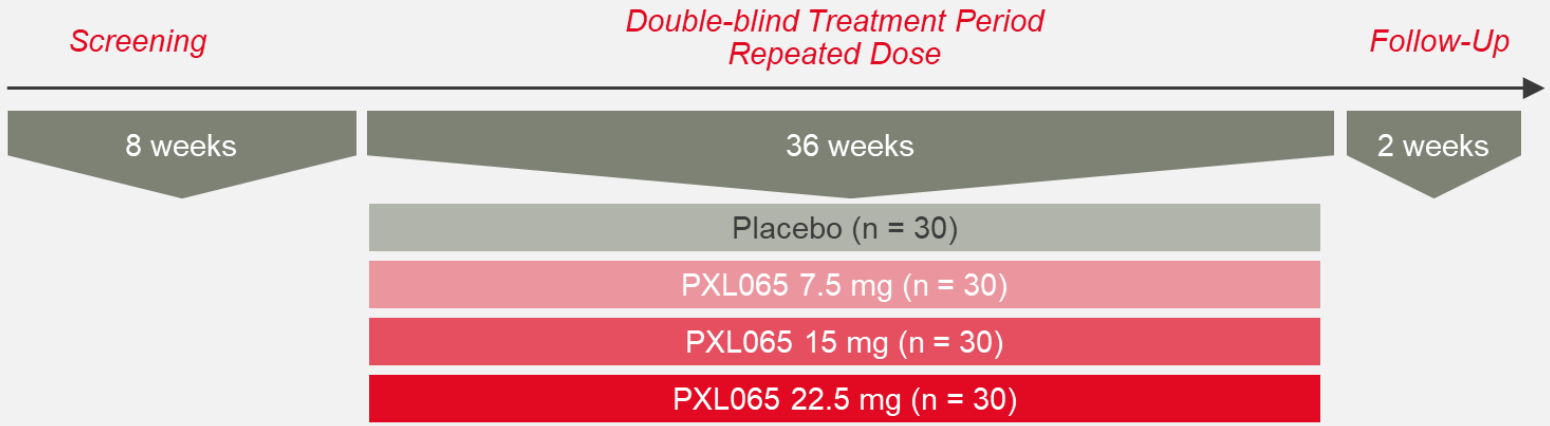


- Single (SAD) and repeated (Ph1b) oral dose studies completed
- Stabilization and sustained higher exposure to R-pio (limited conversion to S-pio)
  - PK dose proportionality; no food effect
  - tablet formulation qualified in Ph1b study
- Well tolerated at all doses tested

Actos is the branded version of pioglitazone and a registered trademark of Takeda Chemical Industries, Ltd.

PXL065: One Phase 2 Trial in Biopsy-Proven NASH Patients; Leveraging 505(b)(2) Pathway

A 36-week multicenter, double-blind, placebo-controlled, parallel group, randomized trial to evaluate the safety and efficacy of PXL065 at 3 doses in 120 noncirrhotic biopsy-proven NASH patients



DESTINY 1

Deuterium-stabilized R-pio (PXL065) Efficacy and Safety Trial In NASH'

- Phase 2 will seek to identify one or two doses for the Phase 3 registration trial
- Primary objective: Assess efficacy of escalating doses of PXL065 by relative change in liver fat (MRI-PDFF)
- Secondary objectives:
  - Assess other efficacy parameters of PXL065 (e.g. ALT, liver histology)
  - Assess safety and tolerability of PXL065 (e.g. body weight gain)
  - Assess pharmacokinetics of PXL065 at pre-specified timepoints and PK/PD correlation

Additional Opportunities

Pipeline Expansion

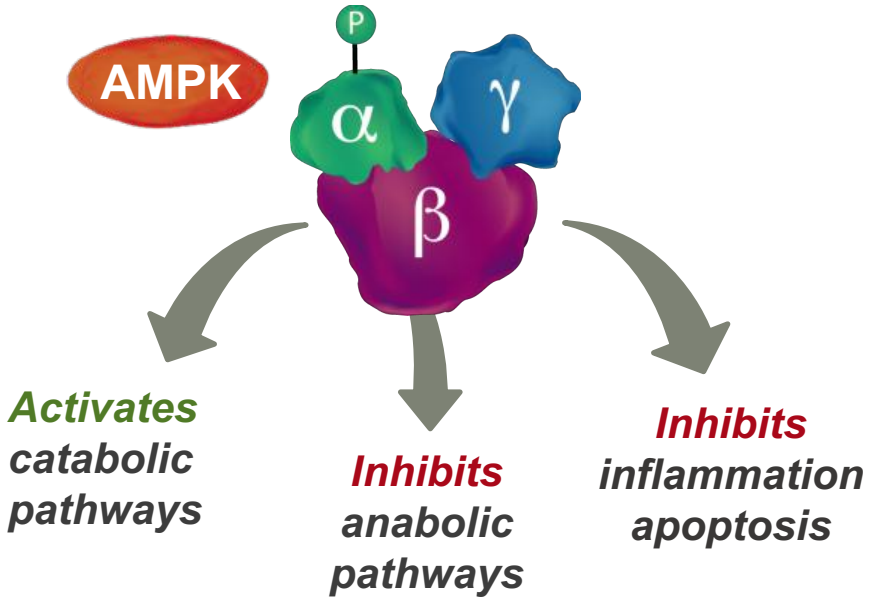
Chronic and Rare Metabolic Indications

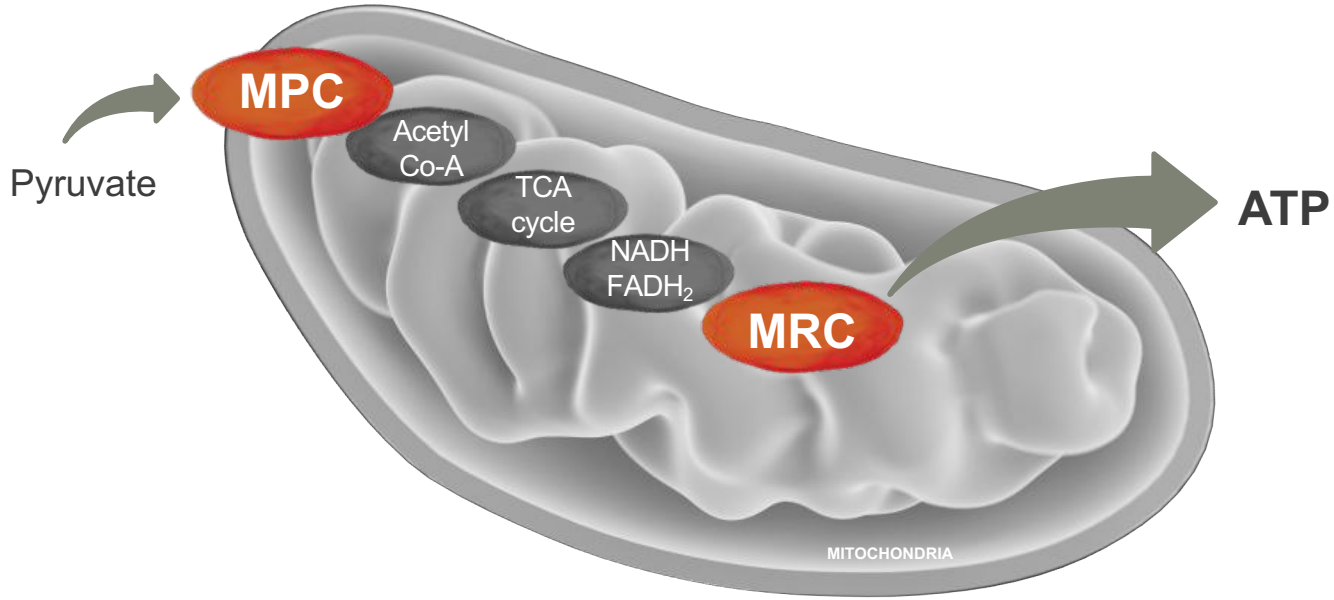
Next Generation AMPK Activators

Next Generation D-TZD's*

*Deuterium-modified thiazolidinediones.

AMPK and MPC Dysregulation are Implicated in the Biology of Various Metabolic Diseases





Exploring applications of current and next generation AMPK activators and MPC inhibitors in biologically relevant metabolic diseases

Rare Metabolic

Adrenoleukodystrophy (ALD; AMN)

Mitochondrial disorders

Renal

Diabetic kidney disease

Polycystic kidney disease

Endocrine

Type 2 diabetes

Polycystic ovary syndrome

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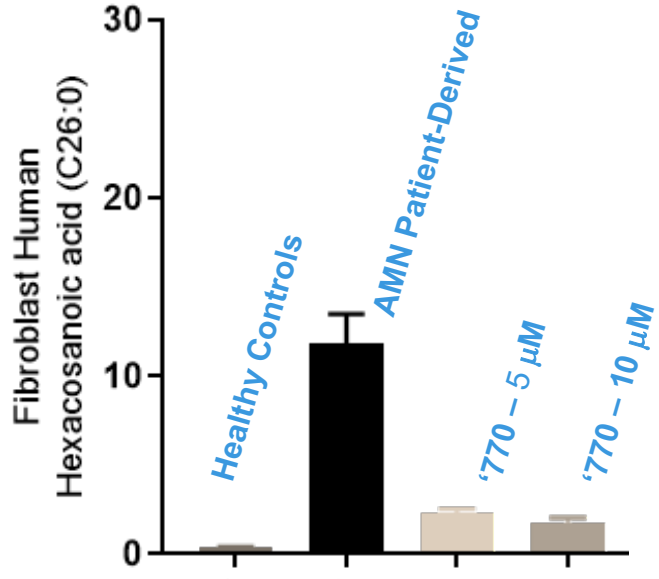
Potential of AMPK Activation to Treat Adrenoleukodystrophy

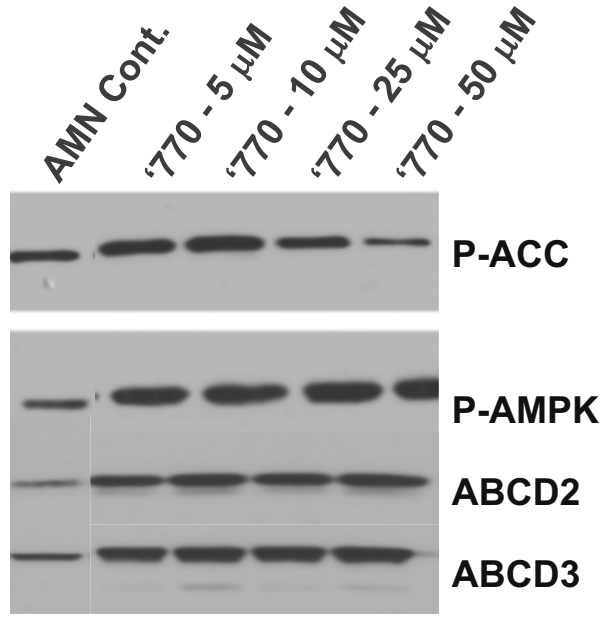
ALD AMN

Why AMPK ?

- AMPK is ***suppressed*** in brain from ALD patients[1]
- ***ABCD2/3 could replace*** function of missing ABCD1; AMPK activation with metformin elevates ABCD2 levels in patient cell lines and ABCD1-KO mice[1]
- Deletion of AMPKα1 in glial cells of ABCD1-null mice (AMN model) → mitochondrial dysfunction/low ATP [2]

PXL770 reduces VLCFA & induces ABCD2/ABCD3 in cells from human AMN-ALD patients





1. J Neurochem 138:86-, 2016.
2. Singh J, Med Inflamm, 2015.

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Potential for AMPK Activation to Treat Renal Diseases

DKD

Diabetic Kidney Disease

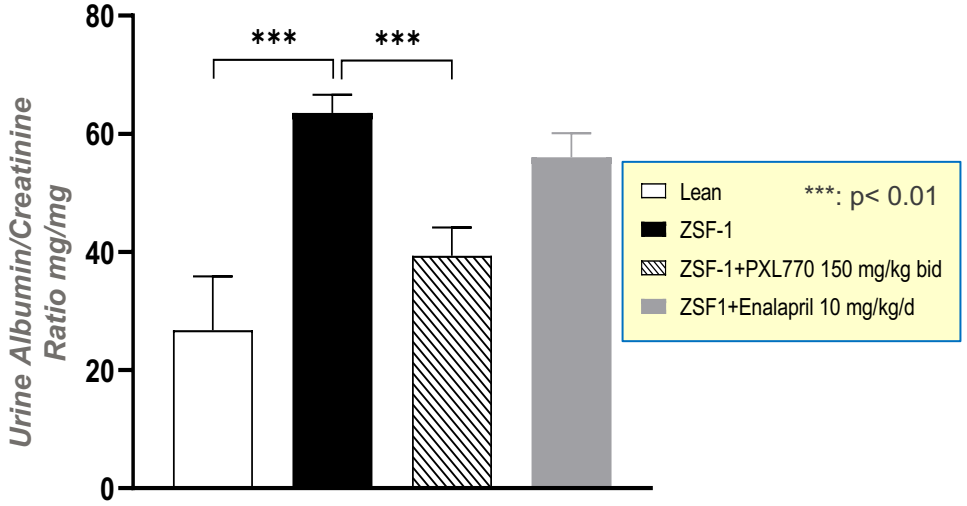
- Multiple pathways engaged; anti-inflammatory, anti-apoptotic, anti-fibrotic effects of AMPK[1]
- AMPK activity is ***reduced*** in human/rodent DKD tissue samples[2]
- ***Preclinical efficacy*** reported with indirect and direct AMPK activation[3]

PKD

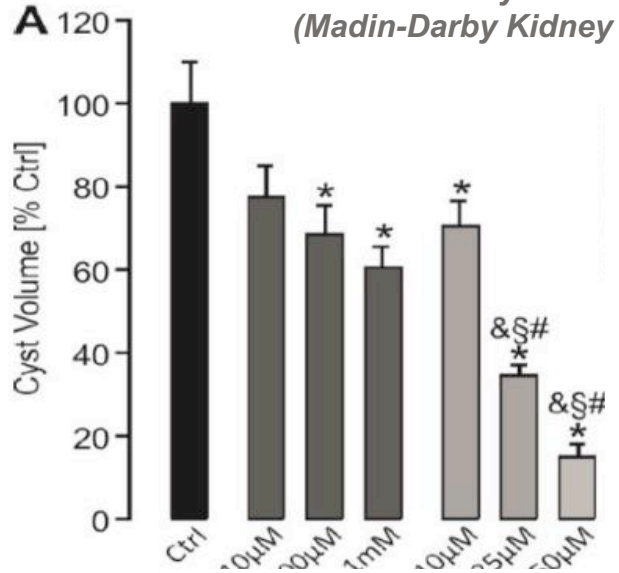
Polycystic Kidney Disease

- Autosomal dominant; fourth leading cause of CKD
- Significant unmet medical need
- ***AMPK activation validation***:
  - AMPK pathways linked to pathophysiology (*eg* mTOR[4]; CFTR[5])
  - *In vivo* efficacy with both indirect and direct AMPK activators[6]

PXL770 Improves Kidney Function in ZSF1 Rat Model of DKD



PXL770 Reduces Cyst Volume in vitro (Madin-Darby Kidney cells)



Significant:
*vs control, & vs. metformin 10 µm (&), vs. metformin 100 µM (§) and 1 mM (#)

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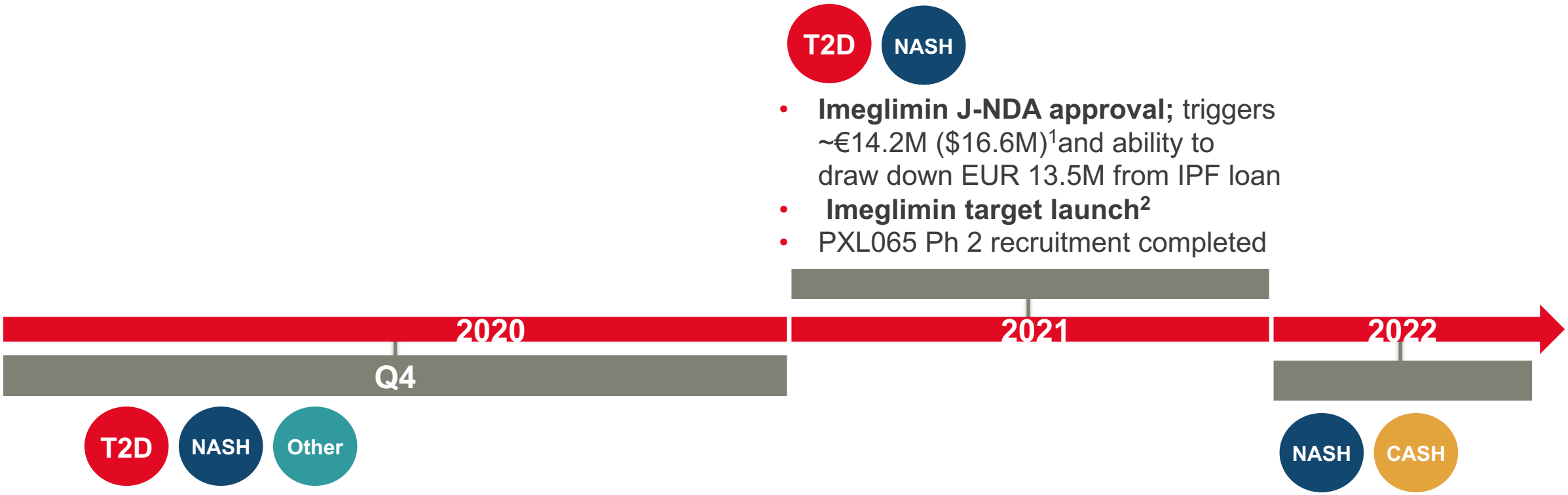
poxel

Upcoming Milestones

Cash Runway Through Significant Milestones in 2022



- **Imeglimin J-NDA approval;** triggers ~€14.2M ($16.6M)[1] and ability to draw down EUR 13.5M from IPF loan
- **Imeglimin target launch[2]**
- PXL065 Ph 2 recruitment completed

- Finalization of PXL770 **Phase 2b clinical trial design**
- Imeglimin: presentations at Japanese Diabetes Society mtg PXL770 and PXL065: **presentations at AASLD and NASH Summit**
- Imeglimin, PXL770 and PXL065 data published
- **Additional preclinical results in rare diseases for AMPK and D-TZD platforms**
- Metavant interactions w/FDA for Imeglimin Ph 3 plan

- **PXL065 Ph 2 results**
- As of 6/30/20 cash & cash equivalents: EUR 46.0 million (USD 51.5 million)
- **Cash runway through 2022 with current business plan**

1. 1. Converted at the exchange rate as of July 28, 2020 2. Sumitomo fiscal year April-March

Appendix

Key Financial & Shareholder Information

Market data

Ticker: POXEL

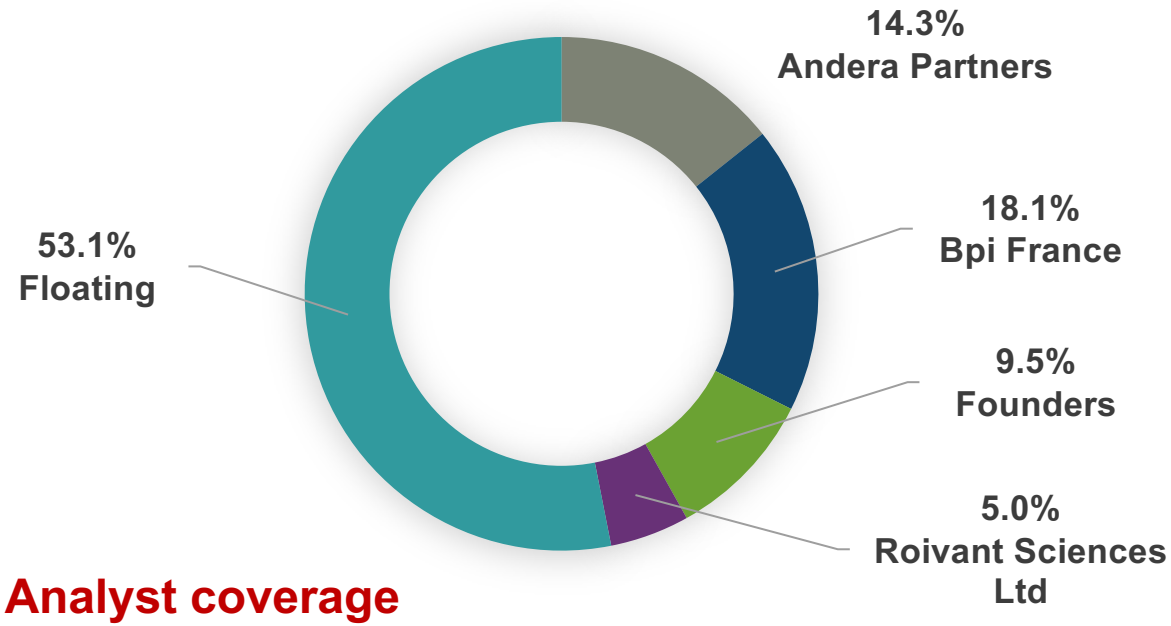
ISIN: FR0012432516

Number of shares: 28,495,523*

Key financials

- As of 6/30/20 cash & cash equivalents: EUR 46.0 million (USD 51.5 million)
- Cash runway extends through 2022 based on our current business plan

Shareholder ownership**



Analyst coverage

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JMP Securities	Jason Butler
Kepler Cheuvreux	Arsene Guekam
Oddo	Martial Descoutures

*at August-end 2020.

**at the date of the presentation, based on the Company's knowledge.

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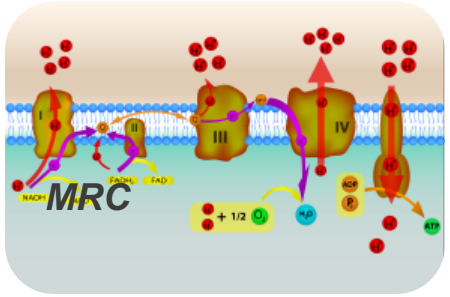
Imeglimin Observed to Restore Normal Mitochondrial Function in Type 2 Diabetes (T2D)

Diabetic state is caused by an impaired mitochondrial state



Mitochondrial Respiratory Chain (MRC) becomes activated

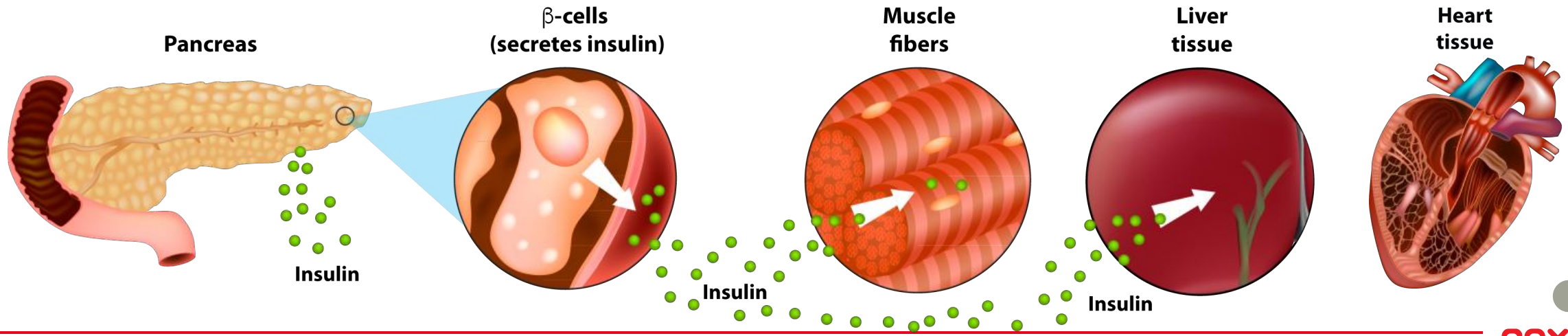
Activating the MRC has these desirable downstream effects in T2D:

Increases glucose-dependent insulin secretion from pancreas

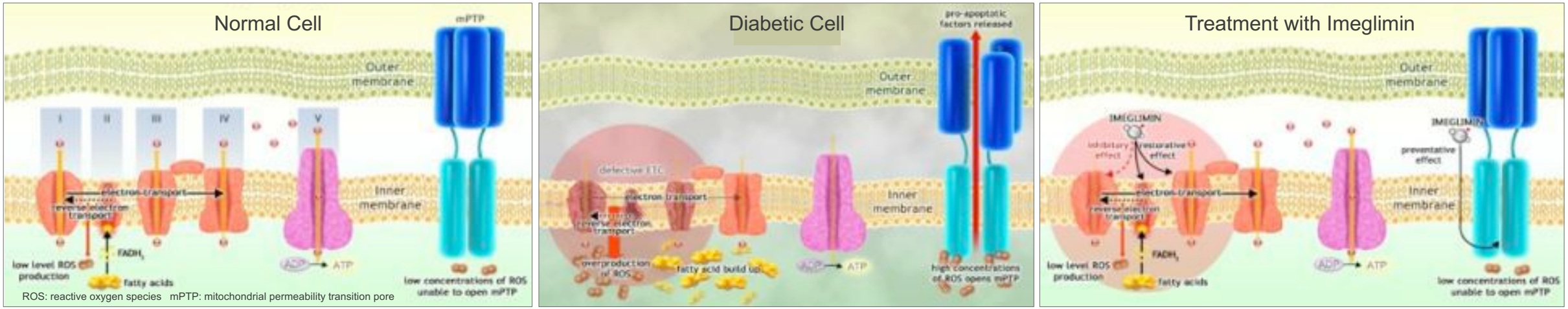
Improves β-cell dysfunction and survival

Improves insulin sensitivity in muscle cells and liver cells

Improves endothelial and diastolic dysfunction



Imeglimin: A Differentiated Mechanism of Action in the Mitochondria Enabling 'Glucose-plus' Benefits



ROS: reactive oxygen species mPTP: mitochondrial permeability transition pore

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 treatment: Restored normal mitochondrial function

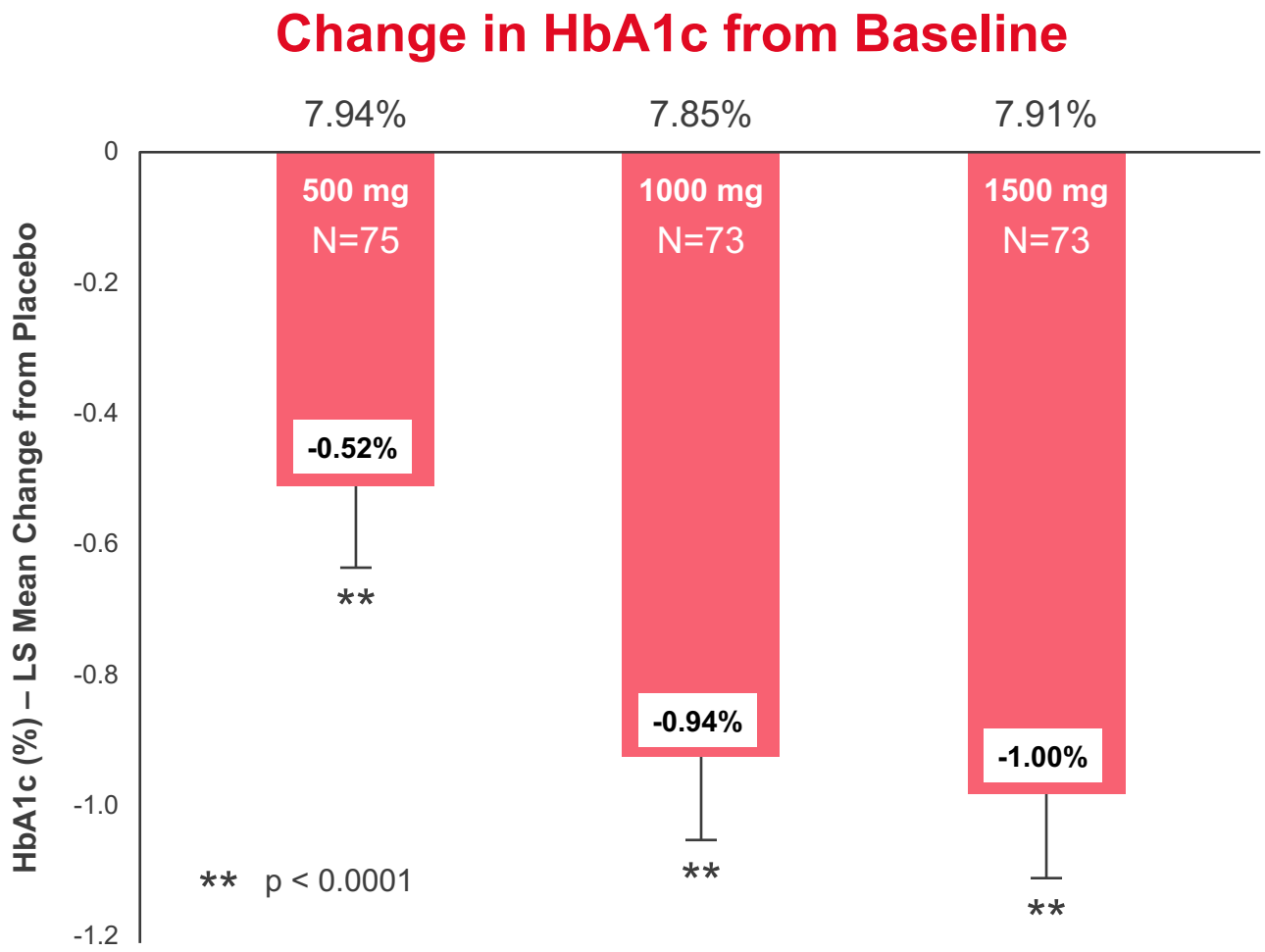
- Glucose-lowering related benefits:
  - Improve β-cells function and survival
  - Increase glucose dependent insulin secretion from pancreas
  - Improve insulin sensitivity in liver and muscles
- Beyond glucose-lowering related benefits:
  - Improve endothelial dysfunction
  - Improve diastolic dysfunction

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, Lisbon (Sept. 2017)

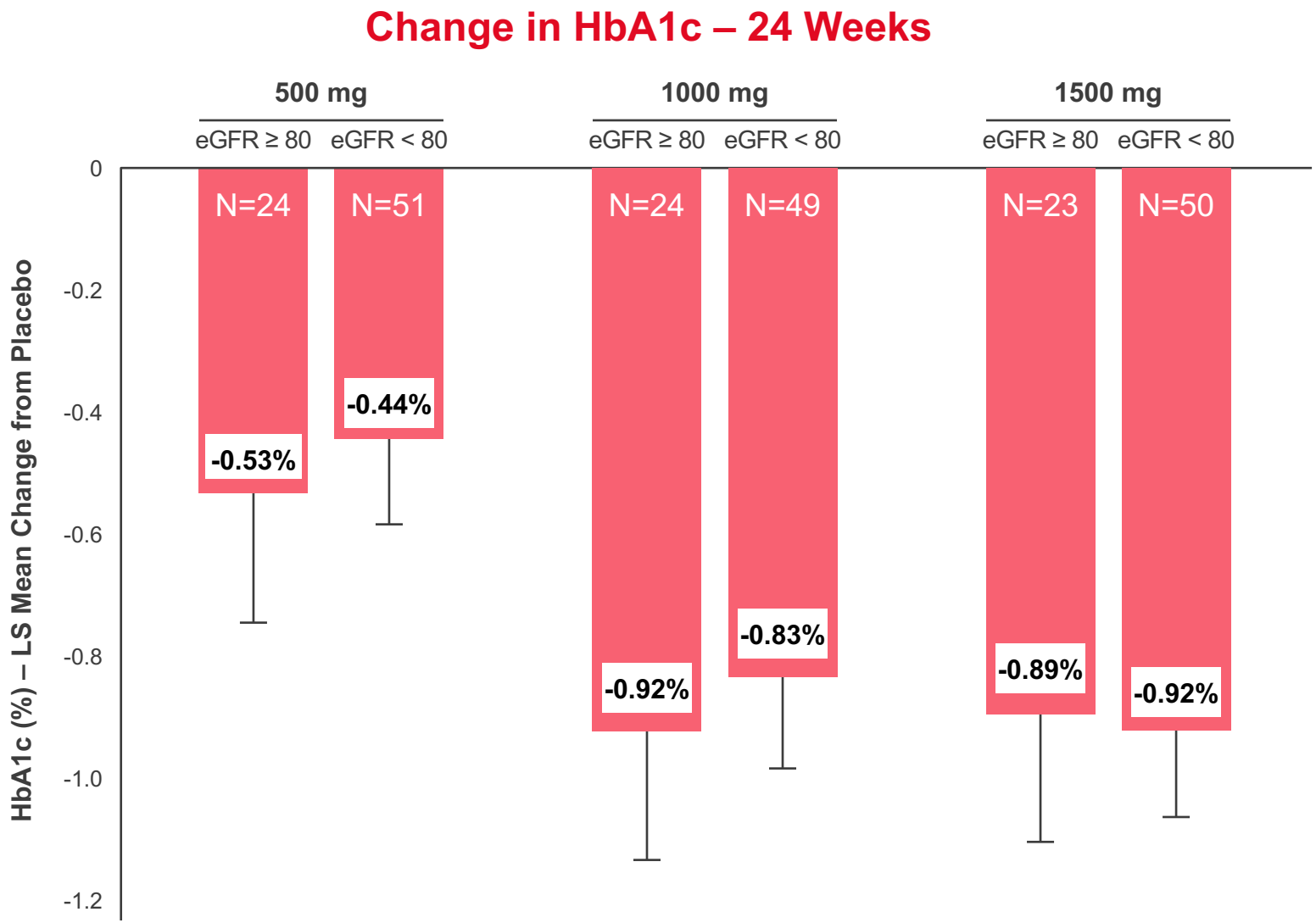
- Phase 2b trial in Japan met primary HbA1c endpoint and secondary endpoints
- Demonstrated efficacy in chronic kidney disease patients was similar to patients with normal renal function
- Observed to be well tolerated:
  - Rate of observed adverse events similar to placebo at 500 mg and 1000 mg. Slightly higher rate of GI events at 1500 mg (no adverse event greater than 10%)
  - No serious adverse events related to Imeglimin
- No weight gain
- Optimal dose for Phase 3 program in Japan is 1000 mg

Imeglimin Phase 2b Trial in Japan Met Primary Endpoint in Reduction of HbA1c vs. Placebo (N=299)



European Association of the Study of Diabetes, in Lisbon (Sept. 2017)

Phase 2b Trial in Japan: Similar Efficacy Demonstrated in T2D Patients with Renal Impairment vs with Normal Kidney Function



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