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Corporate Presentation

November 2023

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.

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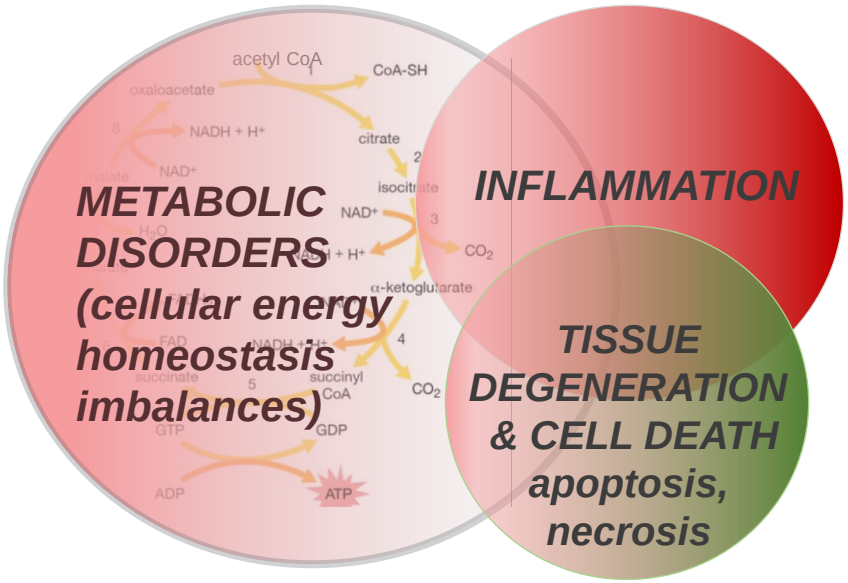
Poxel's Mission & Key Investment Highlights

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



- Strategic focus on **rare metabolic diseases** and **NASH**
- **Royalties** from TWYMEEG® (Imeglimin), approved and launched in Japan in 2021 for Type 2 Diabetes
- Proven capabilities to **build solid partnerships** and to **lead drug development**
- Highly **Experienced Management Team** in Metabolic Diseases
- **Cash & cash equivalents**: EUR 5,3 million as of 9/30/2023; **cash runway through Q2 2025**[1]

1. Assuming full IRIS equity-linked financing facility drawdown.

Key Financial & Shareholder Information

Market data

Ticker: POXEL

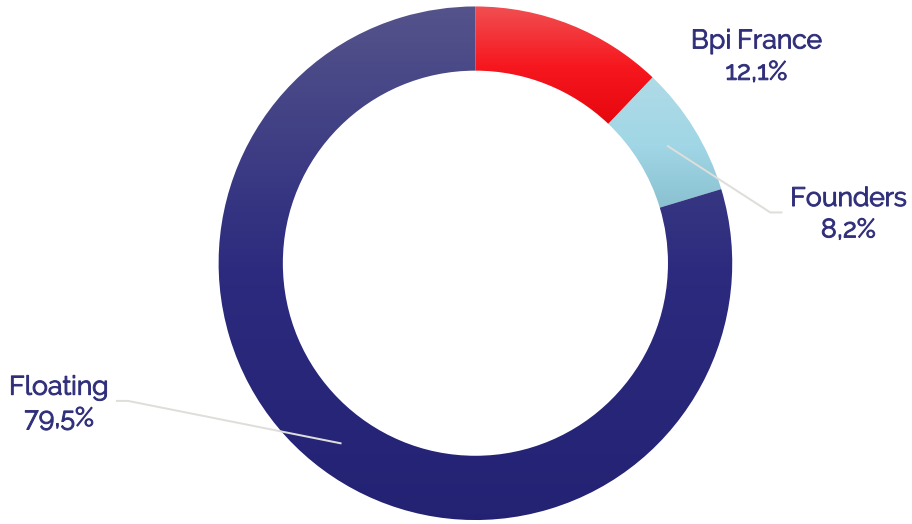
ISIN: FR0012432516

Number of shares: 35,698,701[1]

Key financials

- As of 9/30/23 cash & cash equivalents: **EUR 5.3 million**

Shareholder ownership[1]



Analyst coverage

Degroof Petercam	David Seynnaeve

1. As of October 31, 2023. For the most up to date share count, please refer to the website: Regulatory Documentation | Poxel SA (poxelpharma.com)

Leadership Team

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

Thomas Kuhn (Pharm D, MBA)

Chief Executive Officer and Co-founder

MERCK

Sébastien Bolze (Pharm D, PhD)

EVP, Chief Operating Officer (COO), Co-founder

FOURNIER PHARMA MERCK SOLVAY PHARMA

Pascale Fouqueray (MD, PhD)

EVP, Clinical Development & Regulatory Affairs, Co-founder

MERCK

Sophie Bozec (PhD)

EVP, R&D Pharmacology & Scientific Communication, Co-founder

MERCK

Sylvie Bertrand

Vice President, Human Resources

ThermoFisher SCIENTIFIC Sabert

Quentin Durand

EVP, Chief Legal Officer and Head of CSR Corporate Social Responsibility

AMF Dechert LLP

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Strategic Focus On Rare Metabolic Indications And NASH

Proprietary program

Rare Diseases

Focus of PXL770, based on potential in multiple rare metabolic indications and given MoA

ALD[1]: **Fast track and Orphan drug designations (ODD)** ✓

➡ Next step: Phase 2 study to confirm potential in ALD patients, subject to financing

ADPKD[2]: **Orphan Drug Designation (ODD);** Completed preclinical ✓

➡ Next step: Phase 2 ready, developing clinical strategy

Partnership opportunity

NASH

PXL065 as oral, first-in-class, addressing large market opportunity

Phase 2 DESTINY-1: primary efficacy endpoint met; strong improvement in fibrosis observed ✓

Active partnering discussions for a potential pivotal program initiation

Ongoing partnership

Type-2-Diabetes

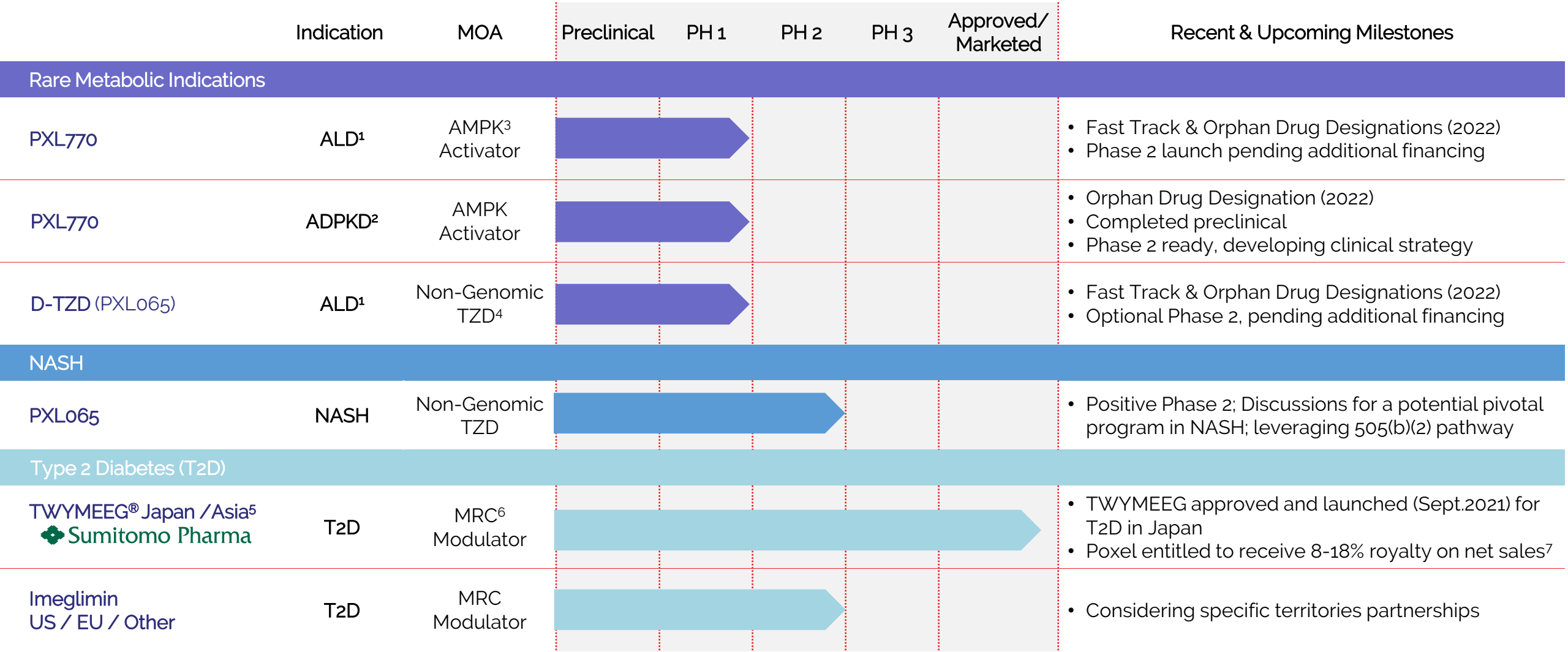
TWYMEEG (Imeglimin) **marketed by Sumitomo Pharma**, #1 diabetes company in Japan

- **Strong sales momentum thanks to combination potential: Sumitomo FY2022 forecast increased by 20%**
- Poxel entitled to receive escalating 8-18% royalties on net sales[3] and potential sales-based payments up to JPY 26.5B (EUR 200M, 1st payment expected YE2024, followed by next payments)
- Royalties and sales-based payments to repay debt through Q2 2029 at latest

1. X-linked adrenoleukodystrophy.
2. Autosomal dominant polycystic kidney disease.
3. 8% royalties expected through Sumitomo Pharma FY22 (to March 2023). First 8% of royalties on net sales of Imeglimin paid to Merck Serono. Net royalties above 8% retained by Poxel.

Robust Mid-to-Late Stage Metabolic Pipeline

Focus on Rare Metabolic Diseases and NASH



1. Adrenoleukodystrophy.
2. Autosomal dominant polycystic kidney disease.
3. AMP-kinase.
4. Deuterium-modified thiazolidinedione.
5. Includes: China, South Korea, Taiwan, Indonesia, Vietnam, Thailand, Malaysia, Philippines, Singapore, Myanmar, Cambodia, Laos.
6. Mitochondrial Respiratory Chain.
7. First 8% royalty of Imeglimin net sales paid to Merck.

Rare Diseases

Accelerating & Expanding Rare Metabolic Disease Programs

PXL770

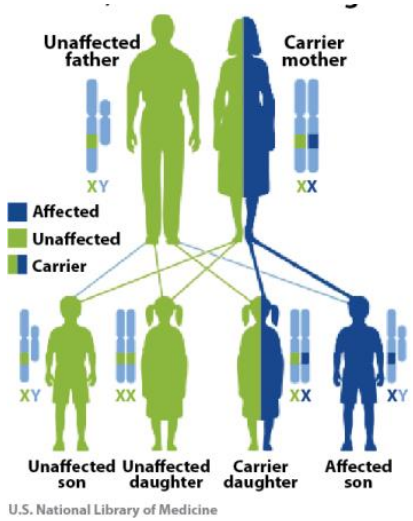
- AMPK Activator in Adrenoleukodystrophy (ALD) - Fast Track & Orphan Drug
- Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Adrenoleukodystrophy

A Not-so-Rare Orphan Neurometabolic Disease

Genetics

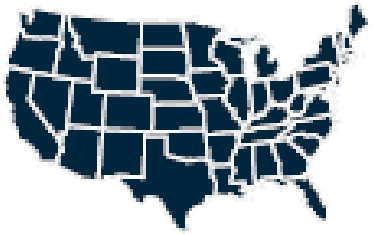
- Monogenic, X-linked mutations in ABCD1 gene
- Gene encodes a transporter present in peroxisomes required for metabolism of very long chain fatty acids (VLCFA)
- *Males more severely affected*



Prevalence

Estimated US Prevalence[1]

20,000 – 29,000



Estimated Global Prevalence[1]

444,000 – 644,000

Diagnosis & Clinical Features

- <u>Diagnosis</u>
  - newborn screening – increasingly common (now >60% of newborns in US)
  - clinical presentation followed by measurement of VLCFA and genotyping
- <u>Clinical</u>
  - spinal cord degeneration - adrenomyeloneuropathy (AMN) - Slowly progressive; impaired gait-balance-movement; bladder-bowel dysfunction; in ≈100% of males with adult onset, also affects women
  - cerebral lesions – Damage to brain white matter; cognitive impairment; loss of vision/hearing; impaired balance-movement; death - up to ~60% lifetime risk – both children and adults
  - adrenal insufficiency

1. Based on published and newborn screening incidence rates of 1/12,000-1/17,000; Bezman L, Ann Neurol 2001; 49:512-17; Kemper AR, Genet Med. 2017; 19:121-26; Schmidt JL, Am J Med Genet 2020; 182A:1906-12; https://rarediseases.org/rare-diseases/adrenoleukodystrophy.

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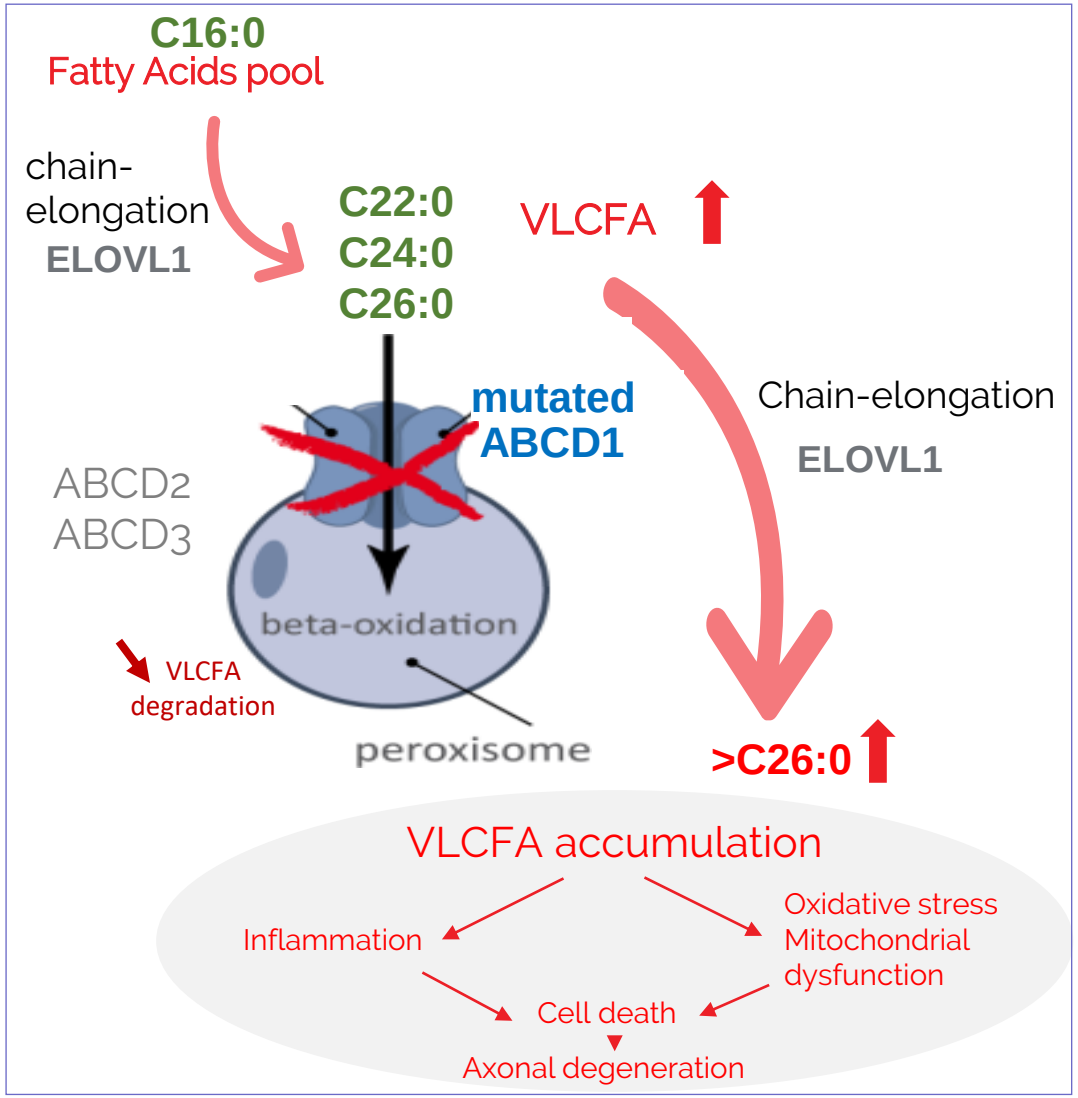
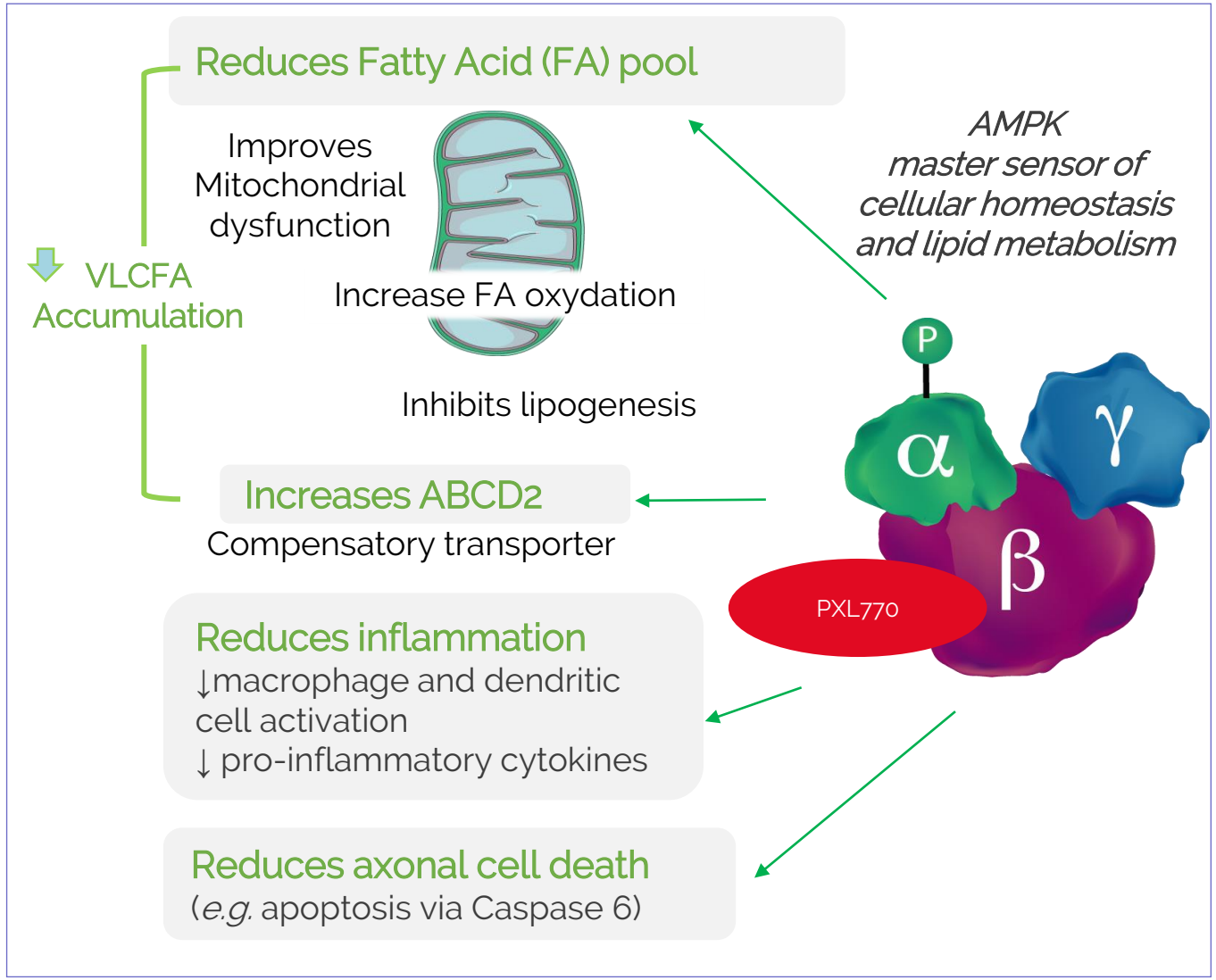
AMP Kinase Activation

Beneficial Role in ALD Pathophysiology





ALD pathophysiology

PXL770/AMPK activation beneficial effects

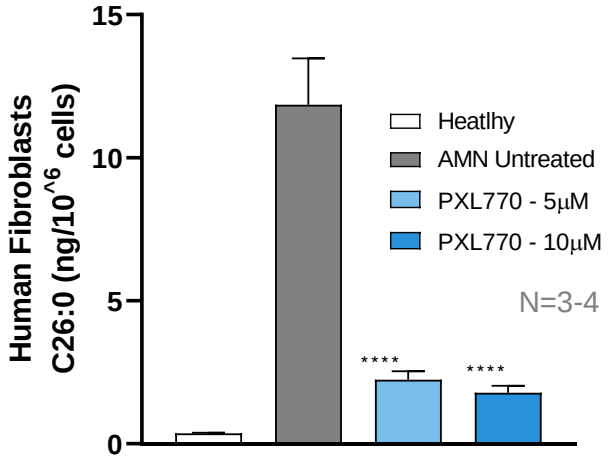
PXL770: Strong Preclinical Data

- PXL770 is active in patient-derived cells and in the classical animal model
- Sufficient brain and spinal cord penetration expected in human to trigger similar VLCFA[1] reduction as observed in animal models in these tissues

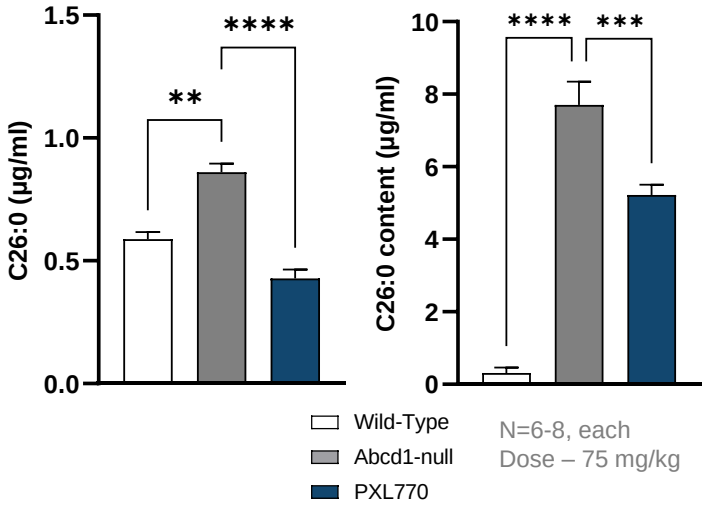
ASPET | The Journal of Pharmacology and Experimental Therapeutics

Full preclinical package available in Journal of Pharmacology and Experimental Therapeutics June 28, 2022,
DOI: https://doi.org/10.1124/jpet.122.001208

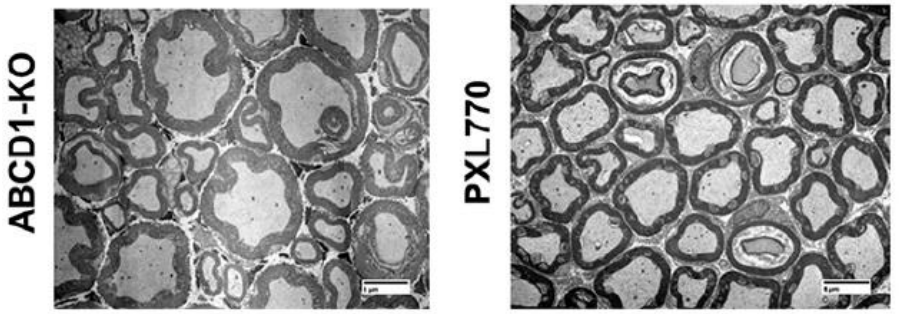
AMN - Fibroblasts
Supression of Elevated VLCFA



Lowered VLCFA in Abcd1 Null Mice
Plasma ***Spinal Cord***



Improved Neural Histology
(&Locomotor Function) in Abcd1 Null Mice



Beneficial Effects of the Direct AMP-Kinase Activator PXL770 in In Vitro and In Vivo Models of X-Linked Adrenoleukodystrophy[S]

Phase 2 study as next step

1. VLCFA: very long chain fatty acids.

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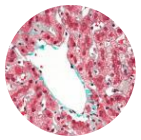
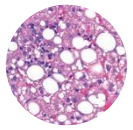
PXL770 - Phase 2 Ready Molecule with Demonstrated Human Target Engagement and Translation

Established Human Safety (> 200 Subjects; up to 12 Weeks)

	Rodent (*in vivo*)	Human Cells (*in vitro*)	Human 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) ✓ ↓ inflammation signature in ALD cells	*Not assessed in NASH* *Pending in ALD*
 Hepatocyte Cell Damage/ Death	✓ ↓ hepatocyte ballooning	*no model*	✓ ↓ ALT / AST (NAFLD)
Insulin Resistance Hyperglycemia	✓ ↑ glucose infusion rate (clamp) ✓ ↓ HbA1c	✓ ↑ glucose uptake (muscle cells)	✓ improved OGTT, HOMA-IR, Matsuda ✓ ↓ HbA1c
Neurodegeneration	✓ restores axonal morphology ✓ improves mobility	✓ improved mitochondrial function	*Pending in ALD*

Translation of multiple effects from preclinical-clinical indicates higher probability in ALD

PXL770 vs. Other ALD Compounds

Advanced Drug Candidates with Potential for Superior Clinical Results

		PXL770[1]	PXL065[2]	Leriglitazone[3,4]	VK0214[5]
	Mechanism	AMPK activator	Non-genomic D-TZD	PPARγ	Thyroid receptor β
	Stage	Ph 2a – Ready	Ph2a – Ready	Ph 2b/3	Ph 1b
Human	ALD Cells	⇩⇩⇩ VLCFA ⇧ ABCD2 ⇧ mitochondrial respiration	⇩⇩⇩VLCFA ⇧ ABCD2 ⇧ mitochondrial respiration	*No VLCFA or ABCD2 effects reported*	*VLCFA not reported* ⇧ ABCD2
In Vivo Abcd1 Null Mice	Biomarker Signal	⇩⇩ VLCFA - plasma, brain, spinal cord	⇩⇩ VLCFA - plasma, brain, spinal cord	⇩ VLCFA spinal cord (*plasma not reported*)	⇩ VLCFA plasma, spinal cord
	Neuro Histology	Improved	Improved	Improved	*Not reported*
	Neuro-Behavior	Improved	Improved	Improved	*Not reported*
	Other Comments	Clinical safety: (>200 exposures)	Clinical safety: >130 exposures plus 505(b)(2)	Missed primary endpoint in Ph 2b/3 *weight gain, edema*	Phase 1 completed

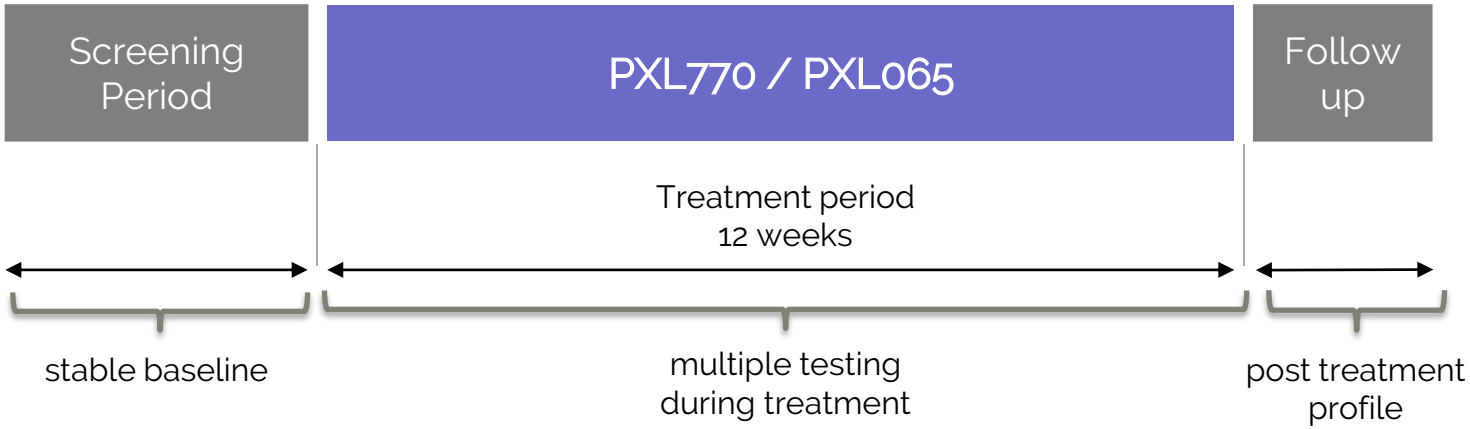
1. J Pharmacol Exp Ther 2022 doi.org/10.1124/jpet.122.001208.
2. J Pharmacol Exp Ther 2022 doi.org/10.1124/jpet.122.001208 .
3. Rodriquez-Pascau Science Trans Med 2021; Am Acad Neuro (AAN) oral presentation 2021.
4. Minoryx 2021 press release.
5. Viking corporate presentation 2021.

Planned Phase 2 Studies in ALD/AMN

Preparation Underway

Key inclusion criteria

- Males with adrenomyeloneuropathy (AMN)
- No active cerebral disease
- 2 cohorts of 12 patients for PXL770



Endpoints

- VLCFA[1] – biomarker and hallmark of disease – drives pathology
- Neurofilament light chain (NfL) – validated biomarker of neuronal damage
- Other exploratory biomarkers
- Safety
- PK

Preparation of Study Launch

- Granted Fast Track and Orphan Drug Designations
- Community Engagement
  - Established relationships with Key Opinion Leaders
  - Collaborations with important patient advocacy groups

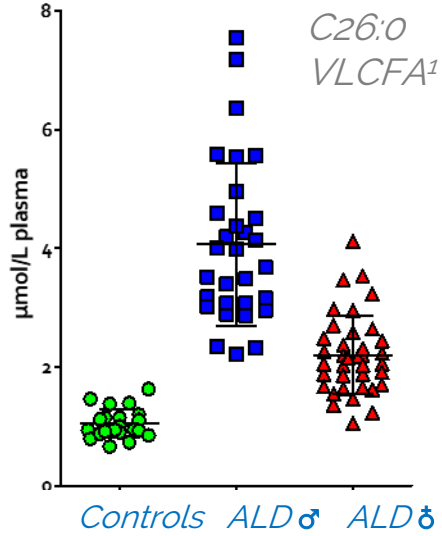
Subject to financing, Phase 2a planned to initiate as soon as possible

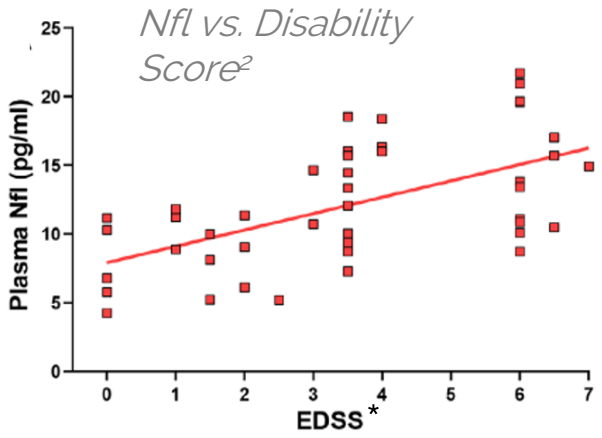
1. VLCFA: very long chain fatty acids.

Phase 2 Expected Outcomes

Assessment of Several Parameters Will Inform Phase 3 Decision

- VLCFA[1] lowering – proximal driver of disease pathophysiology
  - reduction in mean and/or in individual patients vs. baseline – c26:0 and C24:0
  - consistent intra-patient profiles based on repeated measures at several time points
  - lower C26:0 / C22:0 ratio – indicative of a specific disease-modifying effect
  - reductions in C26:0 lysophosphatidylcholine (Lyso-PC) – more stable form of VLCFA; recently shown to better correlate with disease severity vs C26:0 (Marc Engelen, unpublished)
- Reduction in Neurofilament Light Chain (NfL) – well validated biomarker of axonal degeneration; moderately elevated in AMN vs. healthy; correlated with disease severity
- Other (exploratory) biomarkers (e.g. MMP9, microRNAs)
- Confirm Safety
- PK – confirm plasma exposure profile is similar to healthy subjects with tablet formulation





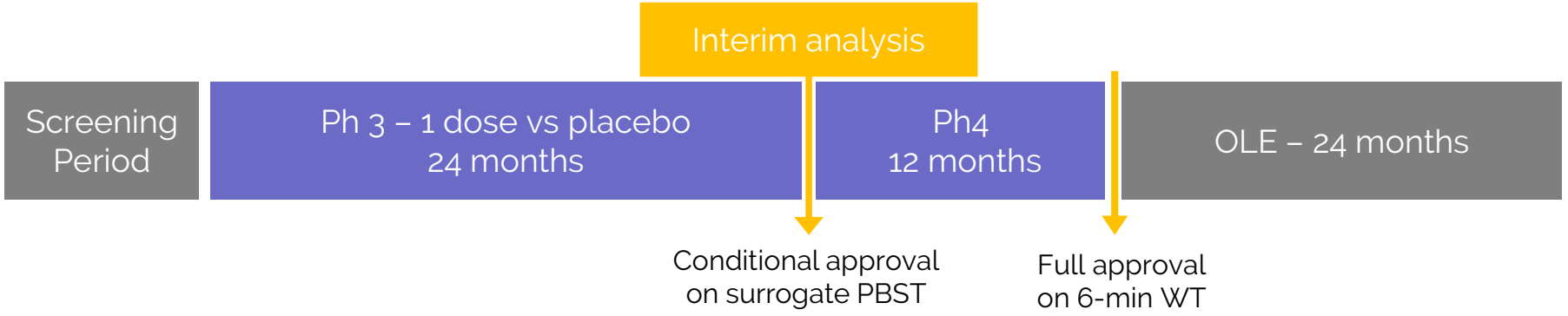
1. VLCFA: very long chain fatty acids.
2. Huffnagel et al. 2017 Mol Genet Metab; 122:209-

*Engelen et al. 2020 Ann Clin Trans Neurol; 7:2127-; *Expanded Disability Status Scale

Pivotal Program

Key inclusion criteria

- Males with AMN
- No active cerebral disease
- ~150 patients randomized 2:1 active-placebo



Endpoints

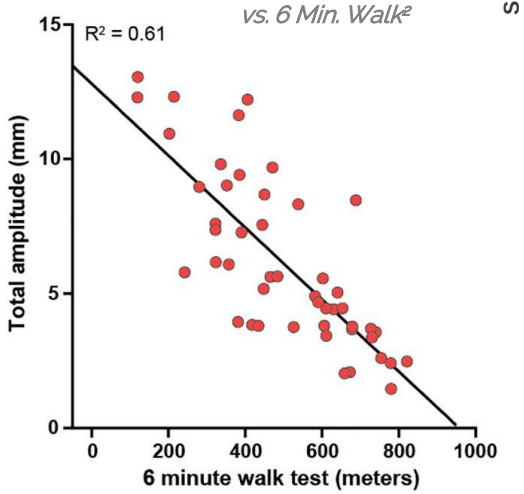
- Surrogate endpoint for conditional approval
  - Postural Body Sway Test at 24 months
- Primary endpoint for full approval
  - 6 Minute Walk Test at 36 months
- Secondary
  - Neurofilament light chain (validated biomarker of neuronal damage)
  - Neurological scores (SSPROM – EDSS)
  - VLCFA C26-LPC (biomarker– drives pathology)
  - MRI – Loes score
  - Falls and other patient-reported outcomes
  - PK
- Safety

Potential pivotal program initiation: H2 2025
Potential phase 3 read-out: 2028 - conditional approval: 2029

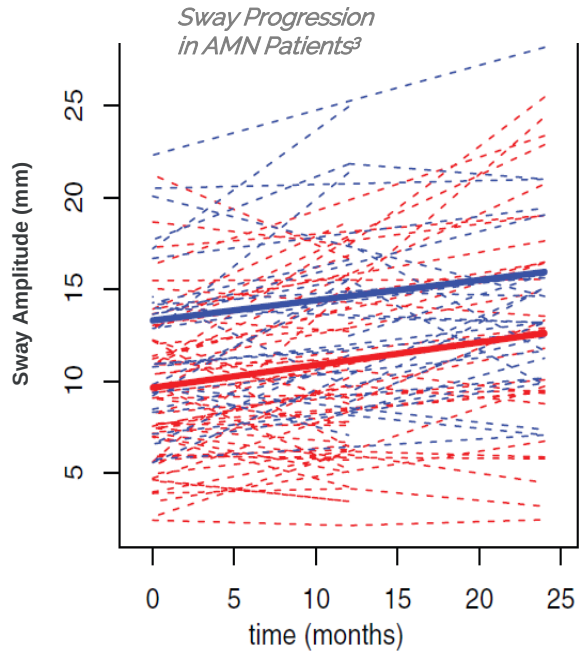
Rationale for Phase 3 Endpoints

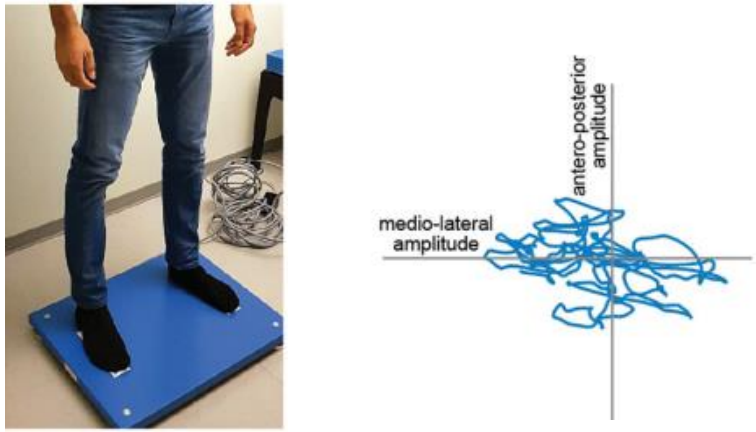
- **Postural Body Sway**
  - accurate/validated measurement of balance [most common AMN symptom is loss of balance[1]]; facilitated by APDM Opal home wearable sensor system
  - highly correlated with disease severity [EDSS, 6-min walk][2]
  - progression demonstrated over 18-24 months[3]
- **6-min. Walk Test**
  - classical mobility test; acceptable as final approval endpoint
  - progression in AMN demonstrated over 24 months[3]
- **Important Secondary Endpoints**
  - NfL
  - cerebral disease – Loes (MRI lesion) score plus incidence of new onset C-ALD diagnosis
  - disability scores (EDSS, SSPROM)
  - incidence of falls
  - other quality of life measures

Body Sway vs. 6 Min. Walk[2]

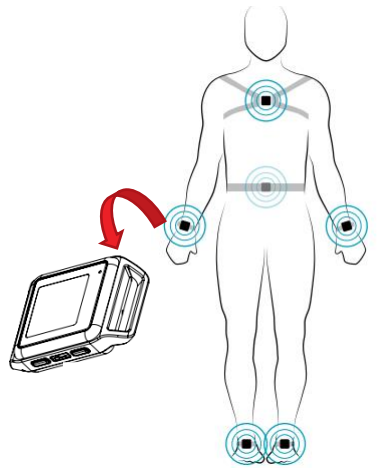


Sway Progression in AMN Patients[3]





APDM



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1. ALD Connect-FDA Patient Focused Drug Development workshop; July 2022.
2. Frontiers Physiol 2020; DOI: 10.3389/phys.2020.00786.
3. J Inher Metab Dis 2021; DOI: 10.1002/jimd.12457 [p=0.0011]; male and female.

ALD Opportunity Summary

High Unmet Needs, Blockbuster Market Potential

Blockbuster Market Opportunity

- **Global prevalence of 444,000 – 644,000**
  - US prevalence of 20,000-29,000;
  - EU prevalence of ~26, 000
- Ability for **premium pricing** based upon other orphan drugs with similar prevalence (>$ 150k/year)

Expedited Clinical Development

- **Established safety profile** of PXL770 mitigates risk & may **reduce clinical development timelines**
- Data from ALD preclinical models suggest **potential for significant impact on key biomarkers**, such as VLCFA (very long chain fatty acids)
- **Regulatory designations for PXL770**:
  - US: **Orphan** (7 years exclusivity) & **Fast Track granted**. Potential for Breakthrough & Priority Review
  - EU: **Orphan** (10 years exclusivity) **granted**. Potential for PRIME

Most Advanced Oral Product After Leriglitazone[1]

- **Few active competitors**
- PXL770 would be **the 2nd oral compound to be evaluated in a Phase 2**
- PXL770 has a **differentiated MoA**

Strong Value Generation

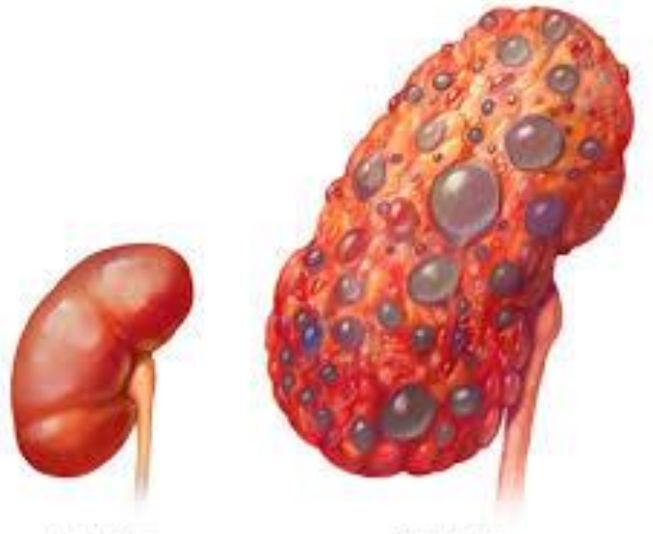
- Opportunity to develop PXL770 through **commercialization**
- **Limited commercial investment to target blockbuster opportunity**

1. A Marketing Authorization Application for the Minoryx candidate leriglitazone is currently under review by the European Medicines Agency for the treatment of adult male patients with X-linked adrenoleukodystrophy (X-ALD).

ADPKD and PXL770 as AMPK

ADPKD

- Autosomal-dominant genetic form of chronic kidney disease (CKD)
- 140,000 patients in US; fourth leading cause of CKD
- >50% develop renal failure by age 50 → dialysis, transplant
- 1 drug approved - tolvaptan - used to attenuate progression; severe liver AE's and poor tolerability (polyuria)



Normal Kidney Polycystic Kidney

Why AMPK?

- AMPK activity lower in kidney of rodents & humans with CKD[1]
- Metabolic status influences clinical disease progression[2-4]
- Food restriction attenuates/reverses PKD in animals[3-5]; AMPK activation mimics effects of food restriction[2,5]
- mTOR*, CFTR** & cAMP drive PKD pathology; AMPK: inhibits mTOR, suppresses CFTR, lowers cAMP[3,7]
- Inflammation, fibrosis increased in ADPKD; AMPK suppresses[3,8]
- Indirect AMPK activation (metformin; high concentration) suppresses cyst growth *in vitro* & *in vivo*[9]
- *In vivo* (mouse) efficacy with direct AMPK activation (salsalate)[10]

*mammalian target of Rapamycin
**cystic fibrosis transmembrane conductance regulator

1. *Am J Physiol Renal Physiol* 309: F414–, 2015; J Clin Invest 123: 4888-, 2013.
2. Nat Rev Nephrol 14: 678–687, 2018; Nat Rev Nephrol 15: 735– 749, 2019.
3. Front Med 2022 doi: 10.3389/fmed.2022.753418.
4. CJASN 2020 doi: 10.2215/CJN.13291019.
5. J Am Soc Nephrol 27:1437– 1447, 2016.
6. Nature 493: 346-55, 2013; Cell 178:1102-14, 2019.
7. Nephrol Dial Trans 21:598–604, 2006. PNAS 108: 2462–2467, 2011; J Clin Invest 105:1711–1721, 2000.
8. Hepatol Commun, 2022. 6: 101-119.
9. J Clin Invest 108:1167-74, 2001; PNAS 108: 2462–2467, 2011; Sci Rep 7: 7161, 2017; Am J Renal Physiol 322: F27-, 2022.
10. EBioMedicine 47:436-445, 2019.

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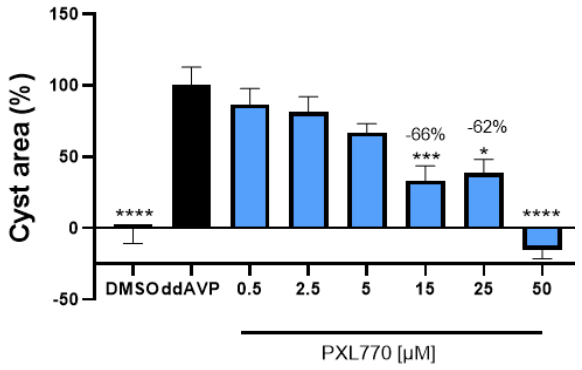
PXL770 Opportunity in ADPKD

Phase 2-Ready Asset with Orphan Drug Designation (ODD)

- Robust efficacy profile with target engagement in established ADPKD model systems:
  - reduced cyst growth in human and canine assays
  - in inducible kidney epithelium-specific Pkd1 knockout mouse: normalized kidney function (urea), improved kidney weight (2KW/BW) and histology – immunohistochemistry (cyst index, proliferation, inflammation, fibrosis)
- Additional efficacy also demonstrated in diabetic kidney disease model

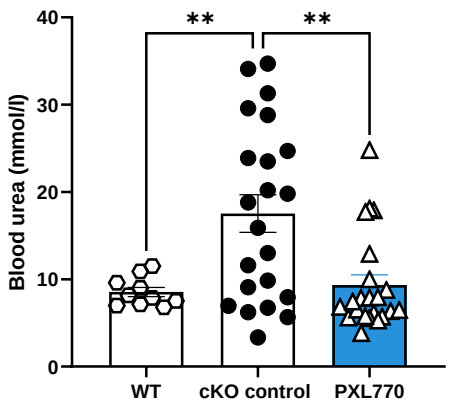
Full preclinical package available in Kidney International (2023) 103, 917–929; https://doi.org/10.1016/ j.kint.2023.01.026

Reduced Human Cyst Growth

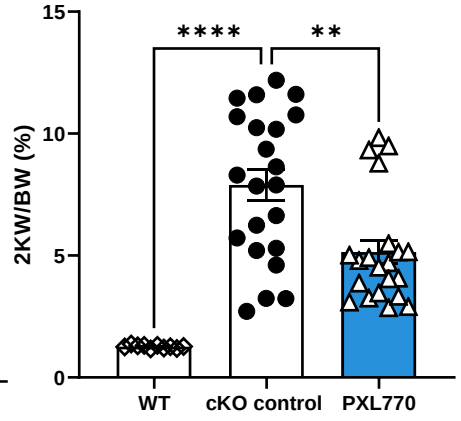


Efficacy Profile in ADPKD Mouse Model (62 Days)

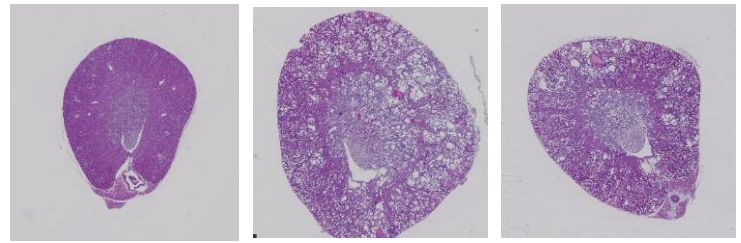
Normalizes Kidney Function



Reduces Kidney Weight



Improves Multiple Histology Parameters



Wild Type | ADPKD Control | PXL770

Development program prepared - Regulatory interactions ongoing

NASH

PXL065 – Partnership Opportunity

Non-Genomic Pathway D-TZD Modulator for Treatment of NASH Utilizing the 505(b)(2) Regulatory Pathway

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Non-Alcoholic Steatohepatitis (NASH)

No Approved Medicines – PXL065 as First-in-Class Oral Therapy

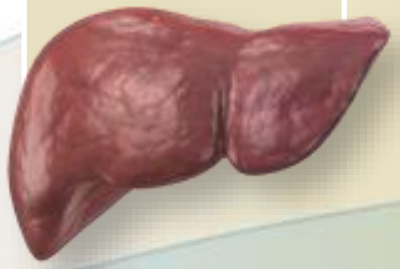
Excessive caloric intake
Sedentary lifestyle

Metabolic syndrome
Dyslipidemia
Type 2 diabetes
Obesity

High Morbidity

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

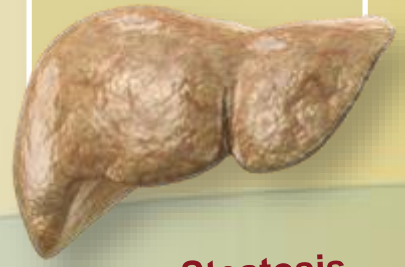
Normal



NAFLD

25% of the general population

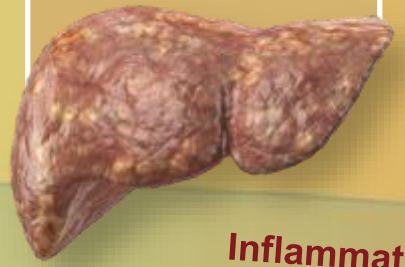
>70% in diabetic & obese patients



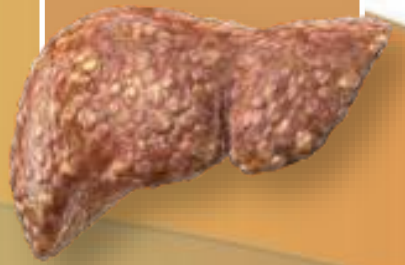
NASH

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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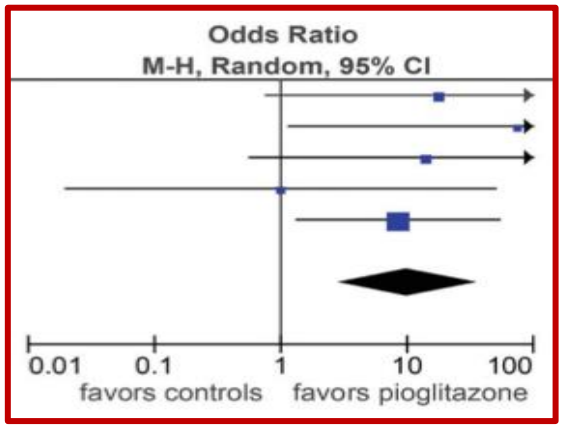
Pioglitazone Extensively Studied and Effective in NASH

Recommended Use by AASLD-EASL - not Prescribed due to Common AE's

	Study	N	Duration	Improvements in NASH			
				ALT/AST	Steatosis	Inflammation	Fibrosis
6 Biopsy Trials	Promrat 2004[1]	18	48 wks	✓	✓	✓	✓
	Belfort 2006[2], Gastaldelli 2021[3]	55	6 mos	✓	✓	✓	✓
	Aithal 2008[4]	74	12 mos	✓			✓
	Sanyal 2010[5] (PIVENS)	247	96 wks	✓	✓	✓	
	Cusi 2016[6]	101	18 mos		✓	✓	✓
	Huang 2021[7]	90	24 wks	✓	✓	✓	
	Meta-analysis (Musso 2017[8])	392	6-24 mos	-	-	-	✓
	Meta-analysis (Boettcher 2012[9])	271	6-24 mos	-	✓	✓	✓

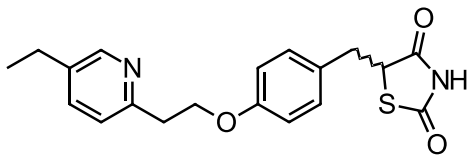
- Fibrosis meta-analysis[7]: OR for improvement in advanced (F3-F4) fibrosis in NASH patients
- Network *meta-analysis* of 48 NASH trials (data through 2019) – pioglitazone was the most effective therapeutic agent[10]



1. Promrat 2004 - Hepatology 39: 188-196. 2. Belfort 2006 - N Engl J Med 355: 2297-2307 3. Gastaldelli A 2021 Liver Interntl DOI: 10.1111/liv.15005; 4. Aithal 2008 - Gastroenterology 135: 1176-1184 5. Sanyal 2010 - NEJM 362, 1675-1685 (post hoc analysis of in Therapeutic Advances in Gastroenterology 2011, 4, 249-263) 6. Cusi 2016 – Ann Intern Med. 165, 305-315 (also Resolution of NASH). 7.Huang J-F 2021 Hepatol Interntl doi/10.1007/s12072-021-10242-2 (also Resolution of NASH) 8. Musso 2017 - Hepatology 2017, epub. (efficacy in advanced fibrosis). 9. Boettcher 2012 - Aliment Pharmacol Ther 35, 66-75 (includes reanalysis of PIVENS data) 10. Panunzi S 2021 Diabetes Obes Metab doi/10.1111/dom.14304

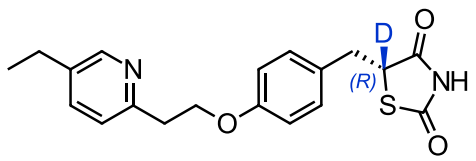
PXL065: Oral NCE* Derived from Pioglitazone

- Pioglitazone, TZDs[1]: 2 enantiomers that rapidly interconvert; both genomic (PPARγ) and non-genomic mechanisms
- PXL065 is deuterium-stabilized single stereoisomer (NCE); selectively mediates non-PPARγ effects of pioglitazone[2,3] – retains efficacy in preclinical NASH models with no significant weight gain-fluid retention[2]

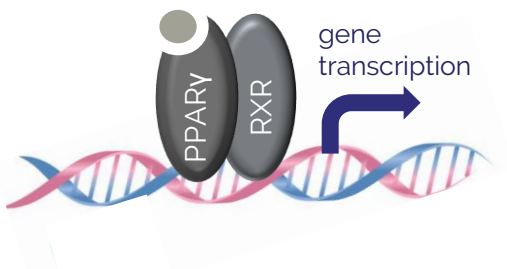


Pioglitazone
(*S* + *R* enantiomers)

PXL065
(stabilized *R* enantiomer)



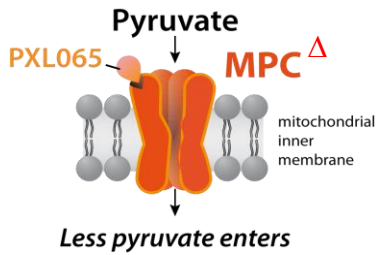
Genomic Pathway



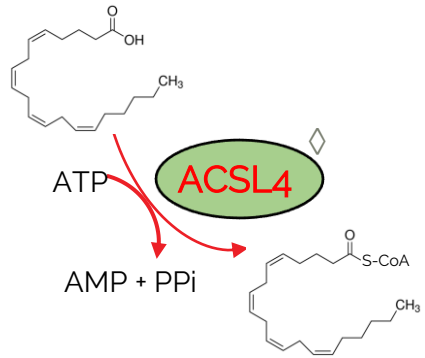
- Weight gain
- Fluid retention

Non-Genomic Pathways

- Regulation of fuel selection – modified cell signaling
- Enhanced lipid metabolism
- Anti-inflammatory; anti-fibrotic; cell protective
- Both MPC and ACSL4 are implicated as NASH targets[4]



Less pyruvate enters



Lipid peroxidation
Ferroptosis

*NCE: New Chemical Entity.

1. TZD - thiazolidinedione; MPC - mitochondrial pyruvate carrier; ◊ ACSL4 - acyl-CoA synthetase long chain member 4.
2. Hepatol Comm 2021 DOI 10.1002/hep4.1723.
3. J Inherit Met Dis 2022 DOI: 10.1002/jimd.12510.
4. Cell Metab 2015; 22:682-94;. Hepatology 2017; 65:1543-56; Mol Metab 2017; 6:1468-79; Nat Chem Biol 2017; 13:91-98; Mol Metab 2018; 9:43-56; Diabetes 2007; 56:2759-65; Am J Physiol 2016; 310:G117-27; Cell Death Dis 2019; 10:449; Am J Pathol 2020; 190:68-81; Int J Mol Sci 2019; 20:4968; Hepatol Comm 2021 DOI 10.1002/hep4.1723.

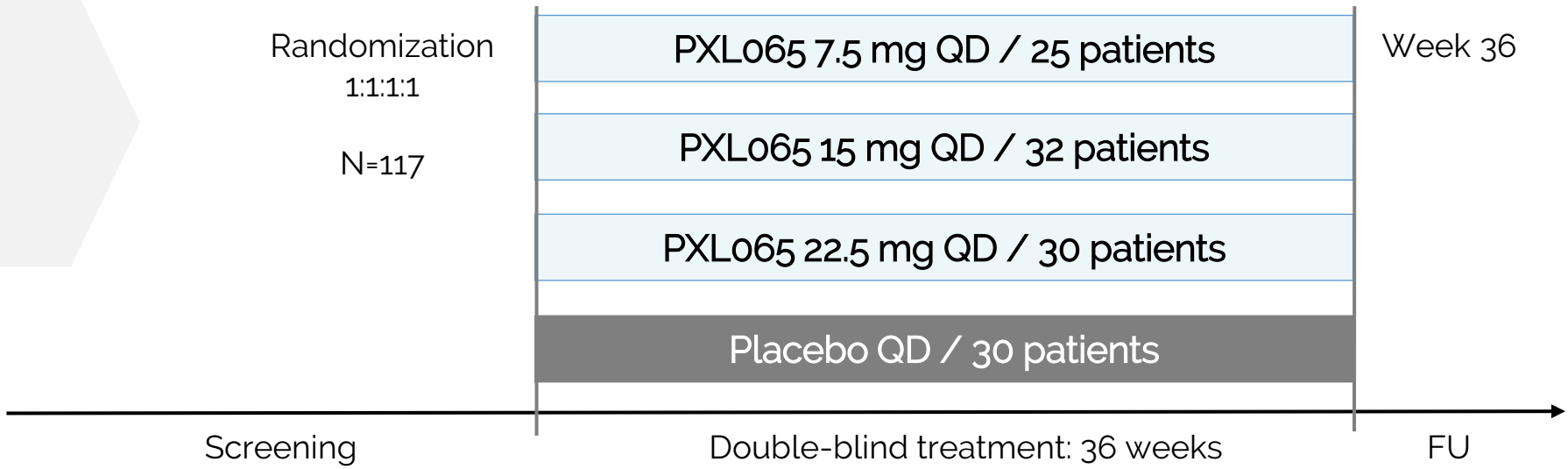
PXL065 Phase 2 Trial Design

Single Streamlined Study - 505(b)(2) Pathway

DESTINY 1

Key inclusion criteria

- Biopsy-proven NASH patients
- Liver fat content (MRI-PDFF) ≥ 8%



Primary Endpoint

- Relative change in liver fat content (MRI-PDFF)

Secondary Endpoints

- Liver histology
- Non-invasive NASH-related tests
- Metabolic parameters
- Safety, PK

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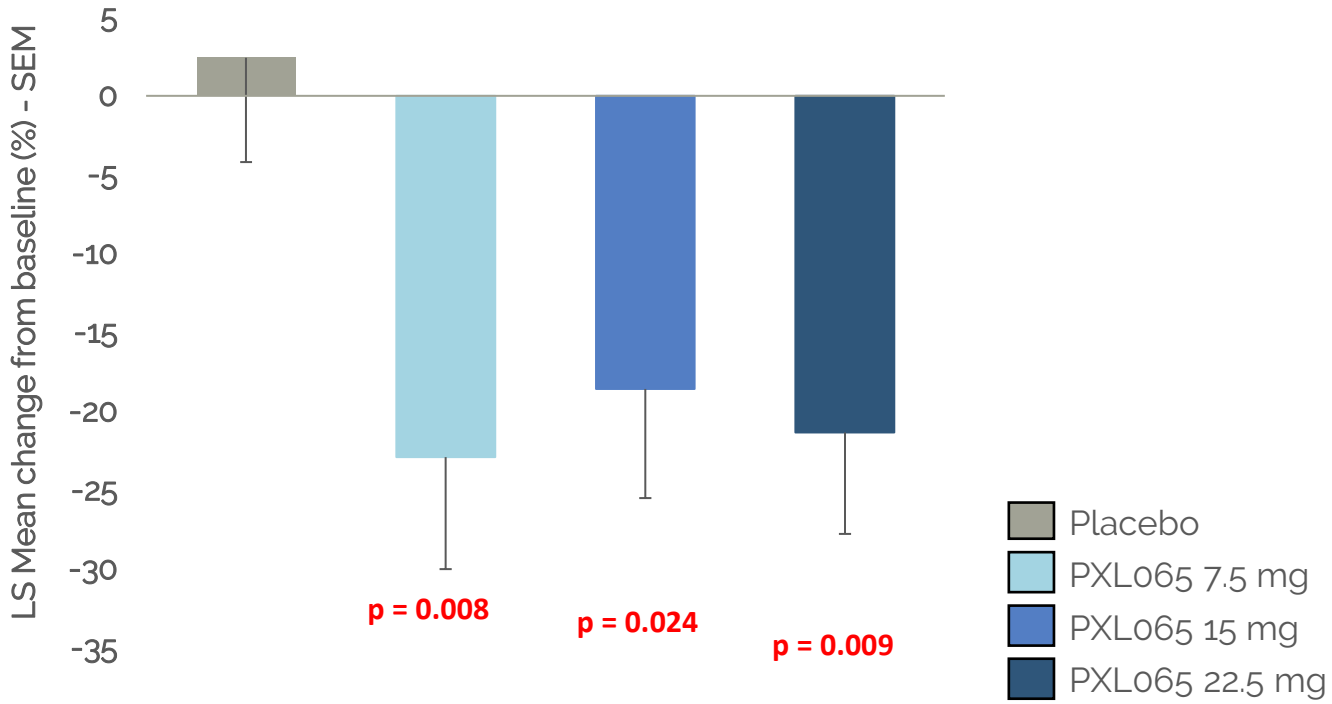
Relative Change in LFC (%) from Baseline to Week 36

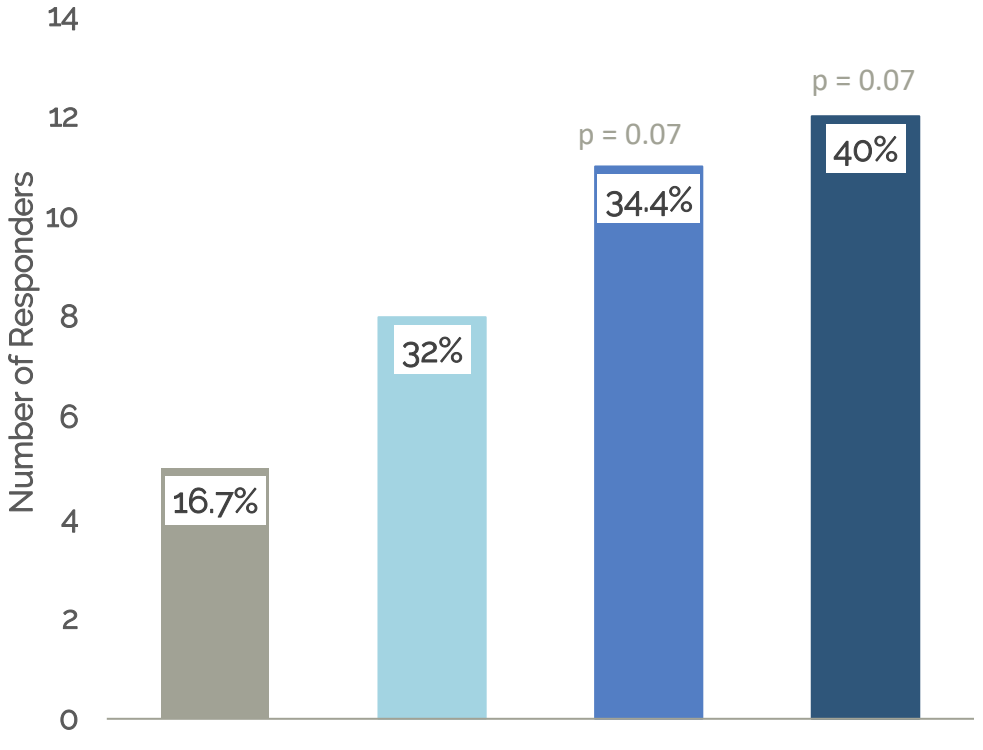
Primary Efficacy Endpoint - Primary Analysis - ITT Set

DESTINY 1

Relative Change in LFC (%) from Baseline to Week 36[1]



Relative Reduction in LFC (%) ≥ 30% from Baseline to Week 36[2]



Improvement (21-25% vs. placebo) in LFC (primary endpoint) achieved in all PXL065 groups

[1] ANCOVA model adjusting for treatment and for randomization stratification factors and baseline LFC as a continuous covariate.
[2] Cochran-Mantel-Haenszel test stratified according to T2DM status and NASH CRN fibrosis scoring system. P-value obtained from Cochran-Mantel-Haenszel test of general association. Missing Week 36 assessments were imputed using a multivariate imputation approach by fully conditional specification regression method assuming missing at random mechanism. Results were combined across imputed sets of data using Rubin's rule.
p-values shown for comparisons versus placebo.

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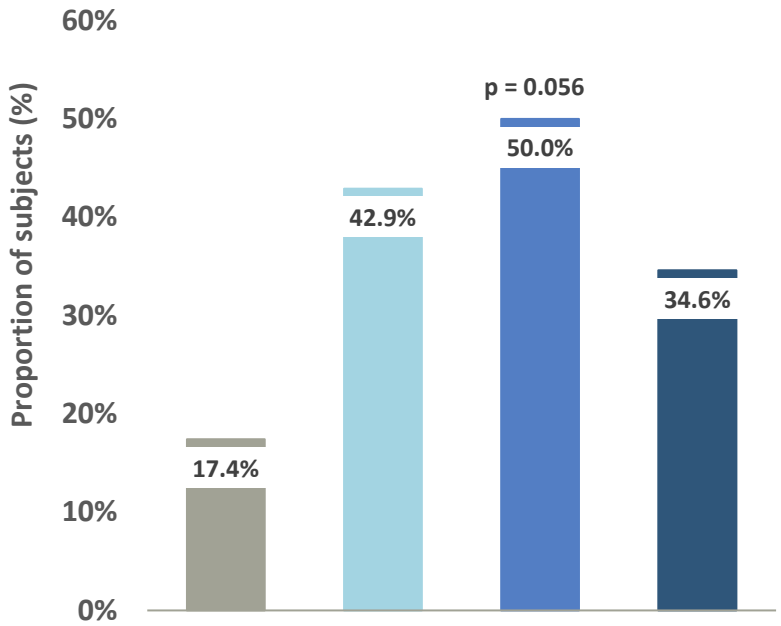
Responses in Liver Histology – Fibrosis

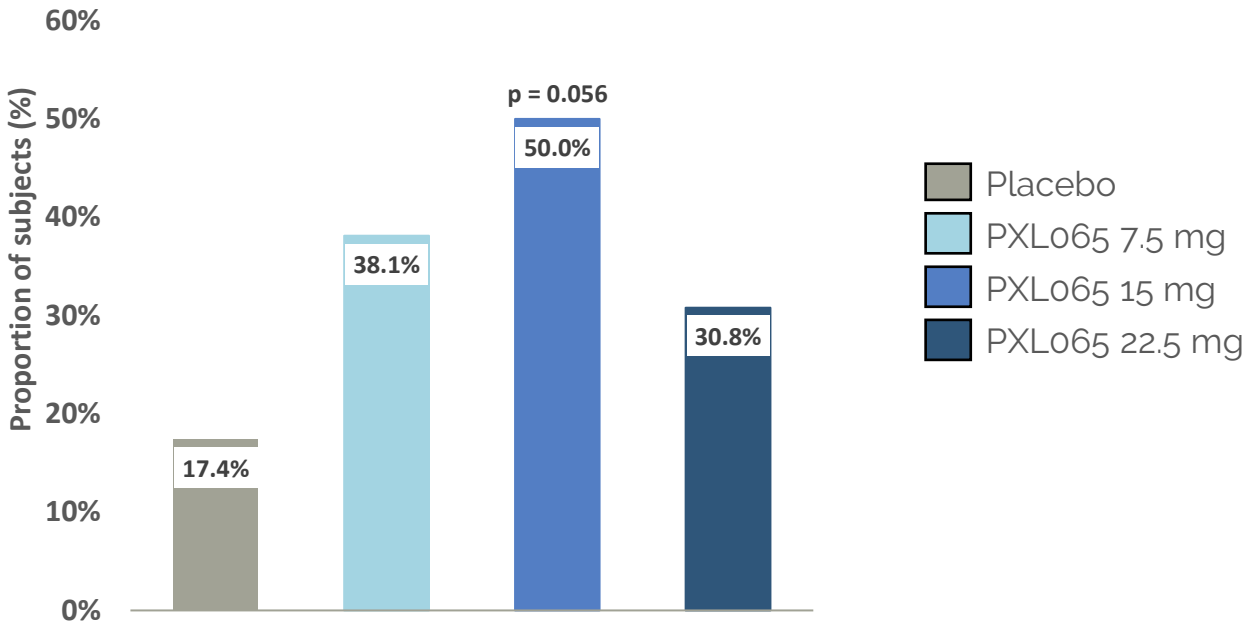
*Exploratory Efficacy Endpoint– Completers with Biopsy**

DESTINY 1

≥ 1 point improvement in NASH CRN fibrosis score



≥ 1 point improvement in fibrosis without worsening of NASH



Strong improvement in fibrosis without worsening of NASH
(FDA approval endpoint) achieved with PXL065 (close to significance)

*92 patients; study not powered for biopsy significance. Cochran-Mantel-Haenszel test stratified according to T2DM status and NASH CRN fibrosis scoring system. P-value obtained from Cochran-Mantel-Haenszel test of general association.

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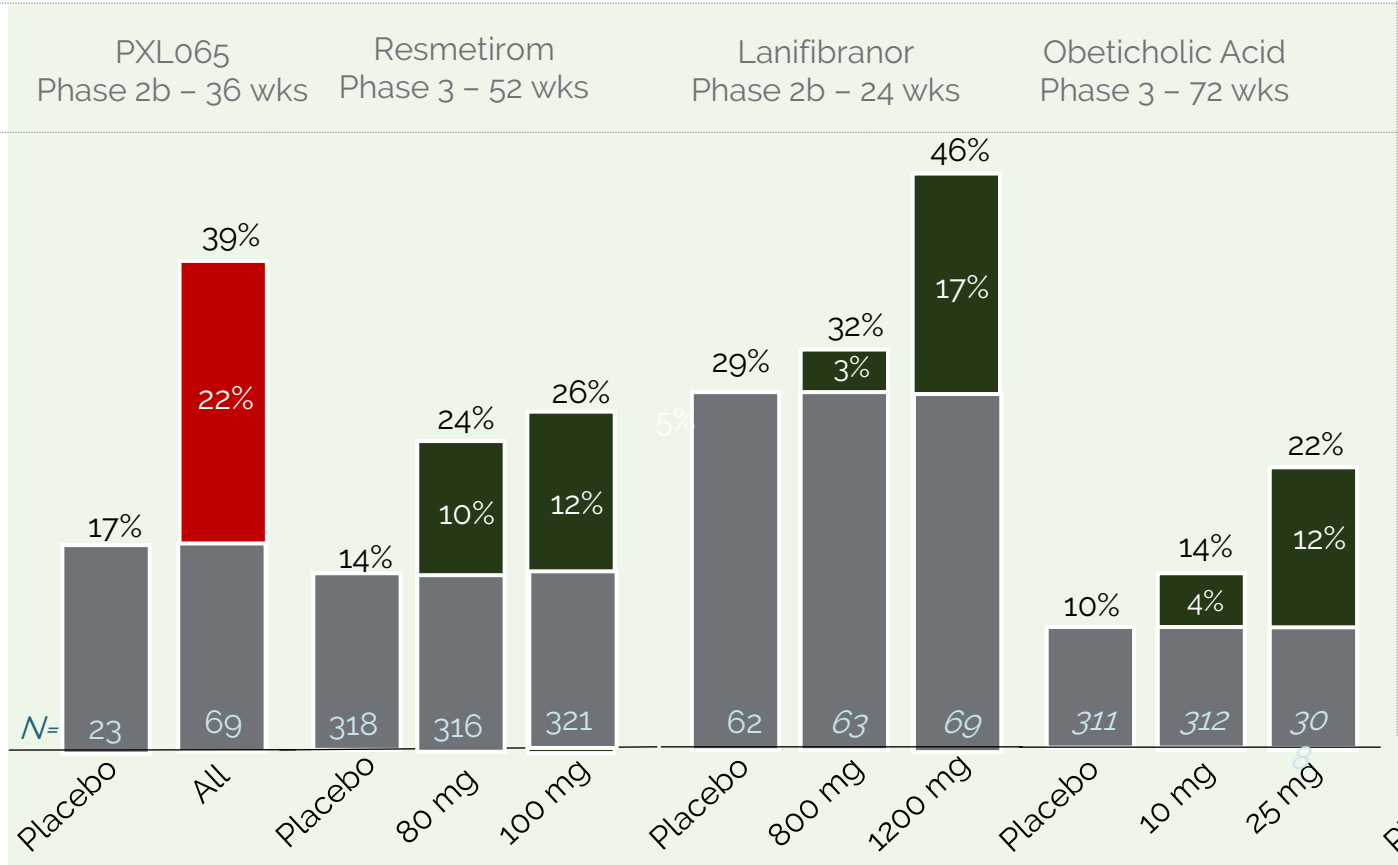
PXL065 Fibrosis Response Comparison to Other Candidates

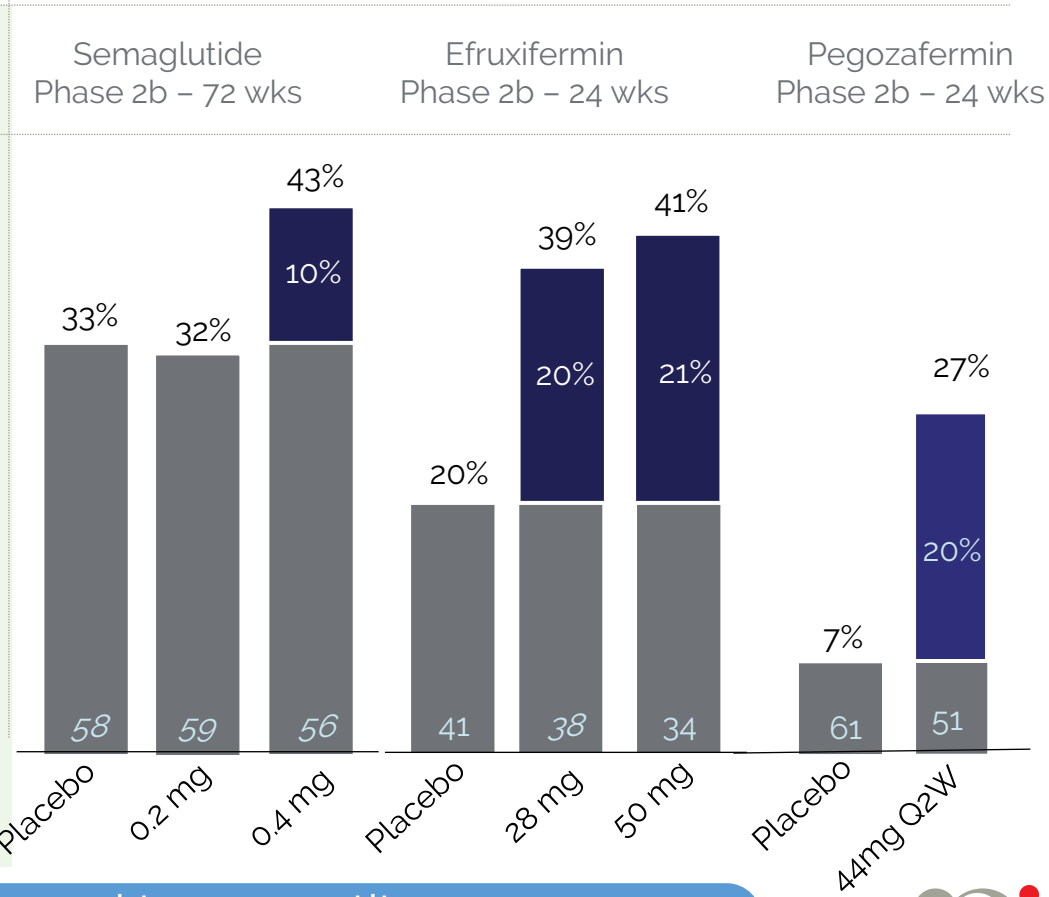
≥1 Stage Fibrosis Improvement with no Worsening of NASH (FDA Approval Endpoint)

poxel | Madrigal Pharmaceuticals | inventiva | Intercept | novo nordisk | akero | 89bio

Orals



Injectables



Effect on fibrosis well positioned compared to competitors

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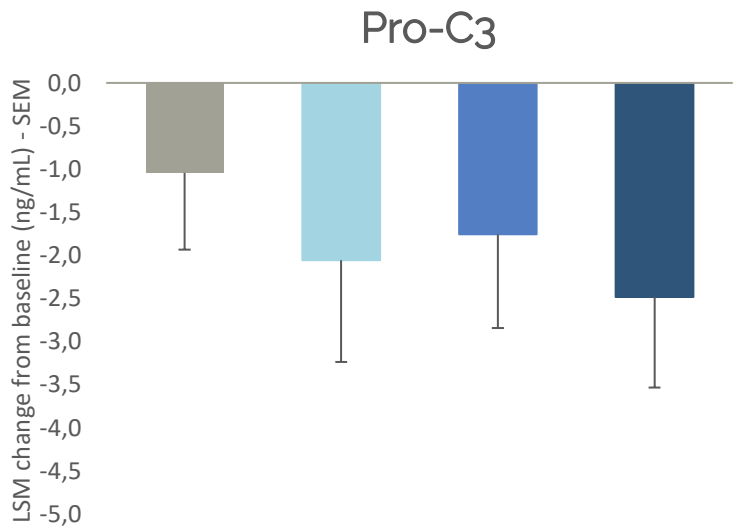
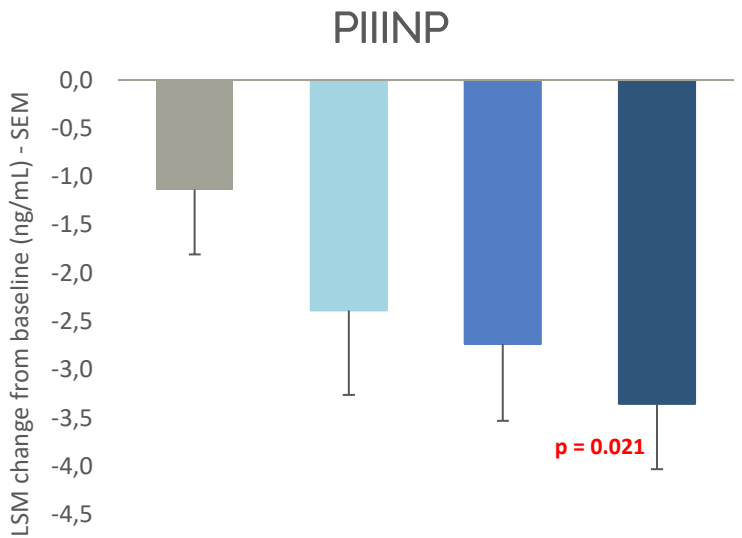
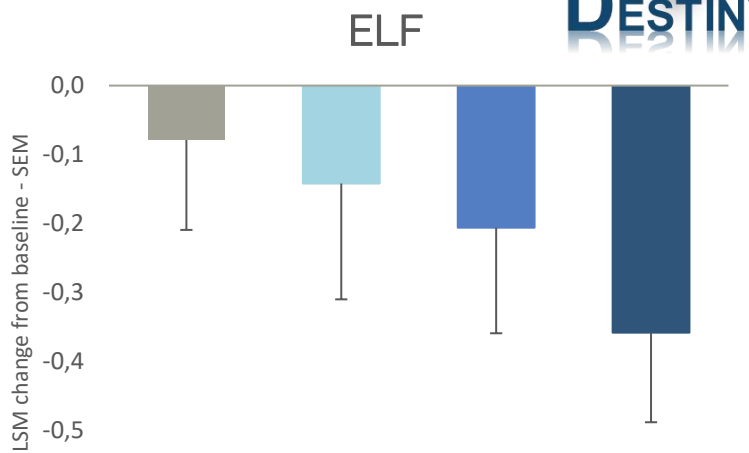
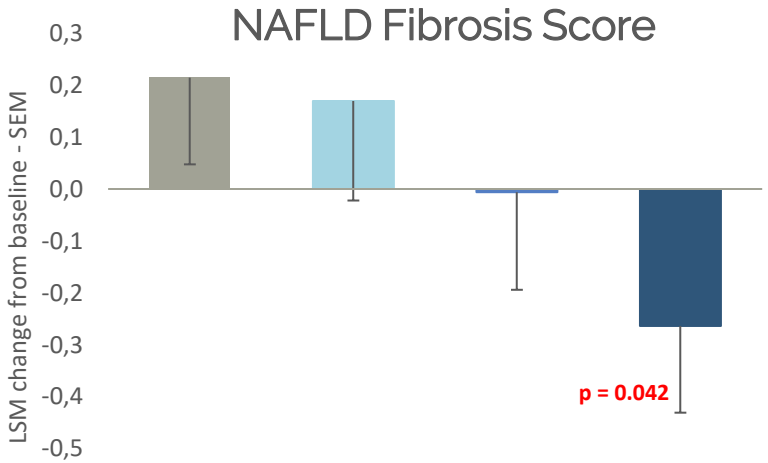
Improved Biomarkers of Fibrogenesis - Fibrosis Risk Scores

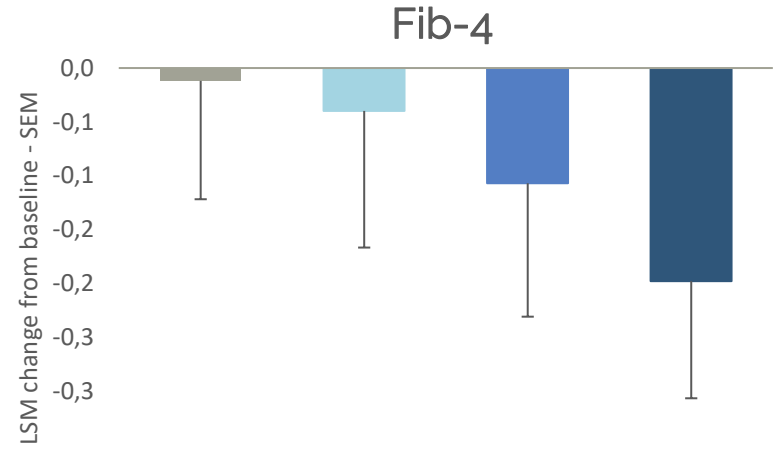
Exploratory Efficacy Endpoints - ITT Set

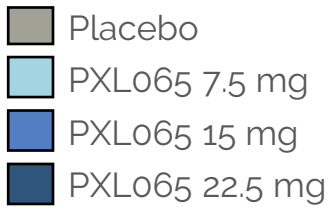










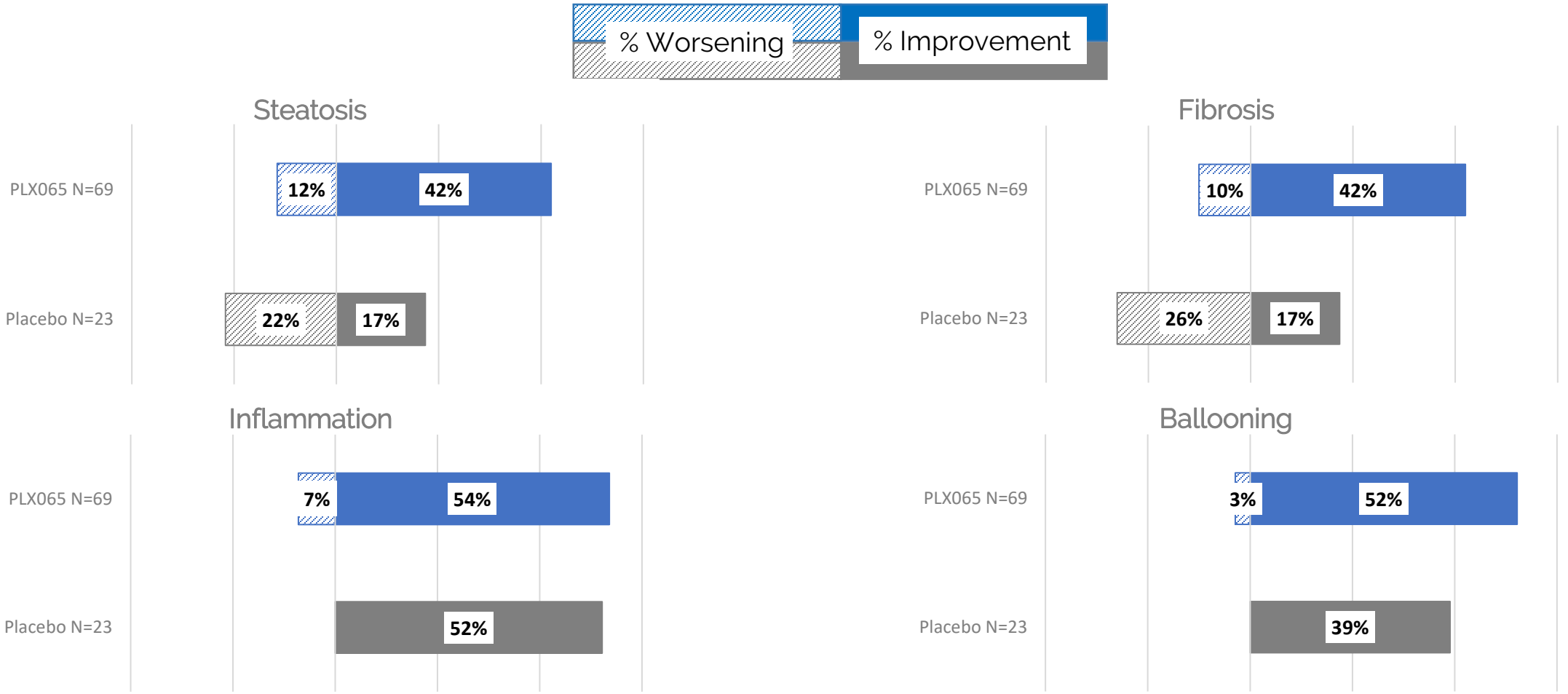


Positive effects on all measured parameters, consistent across biomarkers

Linear regression with following covariates treatment group, stratification factors, i.e. T2DM status and NASH CRN fibrosis scoring system and baseline Pro-C3 / PIIINP / ELF / NFS / Fib-4 as a covariate. p-values shown for comparisons versus placebo.

Responses in Liver Histology – Pooled PXL065

Post Hoc Analysis – Completers with Biopsy



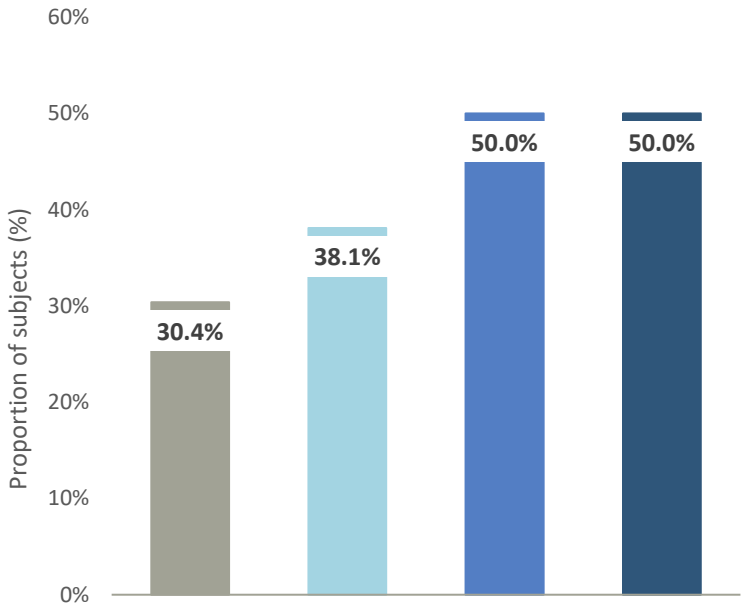
PXL065 improves steatosis and fibrosis *and* prevents worsening in fibrosis
~50% improvement in inflammation and ballooning with PXL065 but unexpected high response in placebo

Responses in Liver Histology - NASH

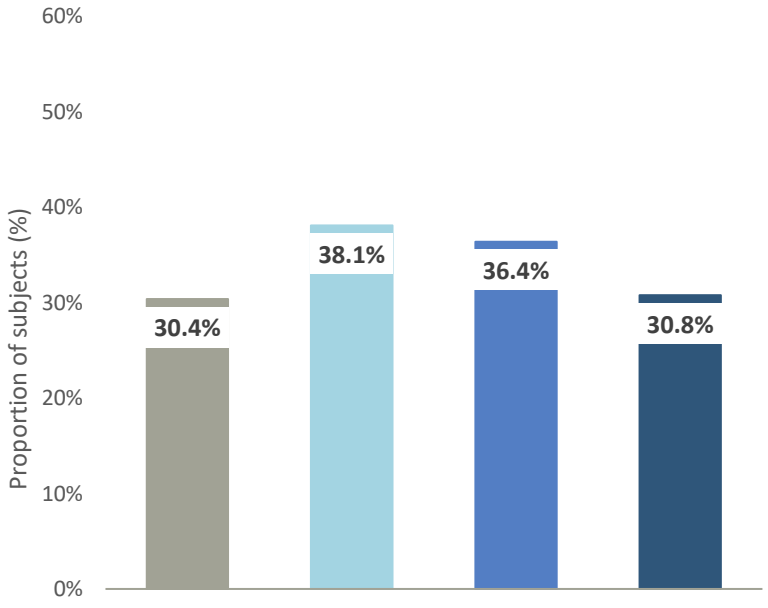
Exploratory efficacy endpoint – Completers with Biopsy

DESTINY 1

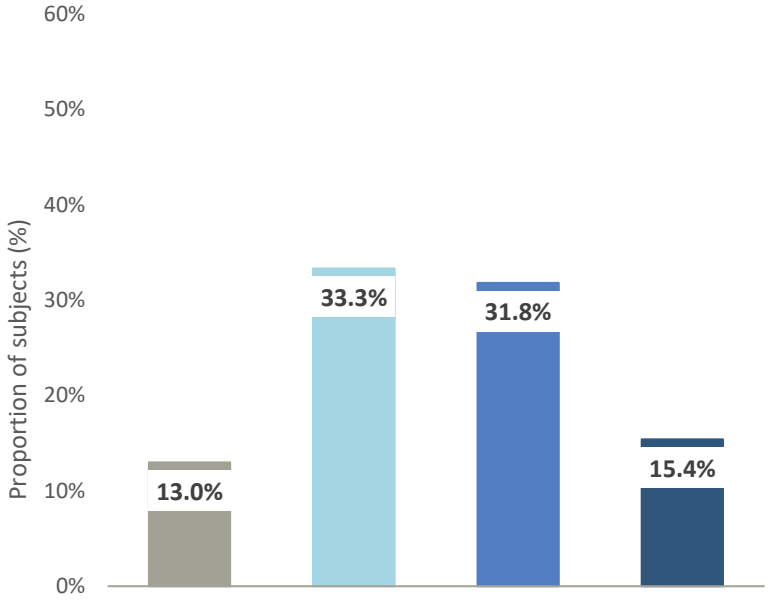
≥ 2-point improvement in NAS without worsening of fibrosis score



NASH resolution with no worsening in fibrosis score



NASH resolution with ≥ 1 point improvement in fibrosis score



Placebo
PXL065 7.5 mg
PXL065 15 mg
PXL065 22.5 mg

Higher number of PXL065 patients improved NAS and reached NASH resolution *and* improvement in fibrosis by at least 1 stage

Cochran-Mantel-Haenszel test stratified according to T2DM status and NASH CRN fibrosis scoring system. P-value obtained from Cochran-Mantel-Haenszel test of general association.

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Results Published in Journal of Hepatology

Nature Review: "Safer pioglitazone alternative is effective"

JOURNAL OF HEPATOLOGY
The Home of Liver Research
EASL
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NASH Patients: a Phase 2 randomized placebo-controlled trial (DESTINY-1)

Stephen A. Harrison • Carole Thang • Sébastien Bolze • ... Jean-Marie Grouin • David E. Moller • Pascale Fouqueray • Show all authors • Show footnotes

Open Access • Published: February 17, 2023 • DOI: https://doi.org/10.1016/j.jhep.2023.02.004

Highlights
Abstract
Graphical abstract
Keywords
Impact and implications
Introduction

Highlights

- Pioglitazone is used in NASH but has side effects
- PXL065 is a novel stabilized R-Pioglitazone enantiomer which lacks PPARγ activity
- PXL065 reduced liver fat; improved - non-invasive tests, histology, glycemia-insulin sensitivity
- PXL065 reduced potential PPARγ-driven side effects of weight gain and oedema
- PXL065 is a new oral approach to NASH which merits further study in a pivotal trial

Research highlights

NASH

Safer pioglitazone alternative is effective

A deuterium-stabilized enantiomer of pioglitazone known as PXL065 has greater clinical potential than pioglitazone itself for the treatment of nonalcoholic steatohepatitis (NASH), results of a phase II trial suggest. Previous evidence indicates that pioglitazone is effective in NASH but has adverse effects owing to its activation of peroxisome proliferator-activated receptor-γ (PPARγ). The placebo-controlled trial of PXL065 indicated that it has a similar efficacy profile to pioglitazone, but this molecule does not activate PPARγ so is potentially safer. The investigators conclude that a pivotal clinical trial of PXL065 is justified.

Ian Fyfe

Original article: Harrison, S. A. et al. Evaluation of PXL065 – deuterium-stabilized (R)-pioglitazone in NASH patients: a phase 2 randomized placebo-controlled trial (DESTINY-1). *J. Hepatol.* https://doi.org/10.1016/j.jhep.2023.02.004 (2023)

Safety Summary

- Good safety-tolerability
- No dose dependent weight gain
- No increase in edema
- Summary of Treatment Emergent Adverse Events (TEAEs)
  - **No relevant difference** in the incidence of subjects presenting with TEAE (60 to 80%), mainly from grade 1 or grade 2 severity
  - Low incidence in subjects presenting with related TEAE (12 to 27%)
  - One death (placebo); only one TEAE leading to discontinuation at the dose of 22.5 mg*
  - Similar incidence in Serious TEAE (3 to 9%) , all considered non-related to the drug (no SUSAR)
- No other AE of specific interest
  - Except one case of increase liver enzyme in the placebo group

*agranulocytosis.

Phase 2 PXL065 Summary & Next Steps

- Primary efficacy endpoint met
- Strong improvement in fibrosis observed (FDA approval endpoint) - effect size as good or better than leading competitors' results
  - PXL065 has potential for better fibrosis benefit than Resmetirom (Phase 2 vs Phase 3 data), which remains the key unmet need in NASH
- Metabolic benefits – significant HbA1c and insulin sensitivity effect
- Safe and well tolerated without PPARγ – driven AE's
- PXL065 is a differentiated NASH development candidate
  - Results confirm potential to retain beneficial hepatic and metabolic effects of pioglitazone with reduced PPARγ-driven side effects; consistent PK profile
  - Strong potential of PXL065 in combination with Resmetirom as the MOA's and profiles are highly complementary (NASH resolution / Fibrosis and Glycemic plus Lipid benefits)
- Scientific presentations and publications
  - Phase 2 results oral presentation at AASLD (Nov. 2022)
  - Publication in Journal of Hepatology (Feb. 2023)

Ongoing discussions with potential partners for a pivotal program in NASH

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TWYMEEG® (Imeglimin) – Ongoing Partnership

Approved in Japan and
Marketed by Sumitomo Pharma

TWYMEEG® (Imeglimin): Strong Growth Trajectory

Partnered in Asia[1] with Diabetes Market Leader, Sumitomo Pharma

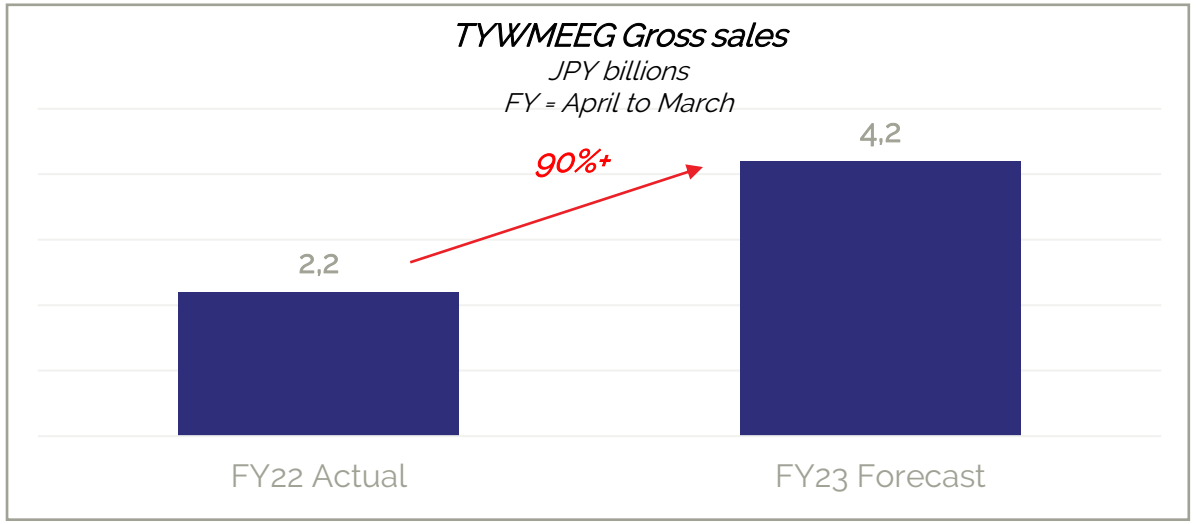
Commercial Strategy

Sumitomo Pharma

- Sumitomo #1 diabetes franchise
- Positioning: TWYMEEG can be prescribed as monotherapy and as add-on to any therapy; **Increasing combination use** with DPP4 (prescribed to 80% T2D patients[2]) and also SGLT2 inhibitors
- Extensive medical affairs & clinical activities
- Patent estate extends to 2036 (incl. potential 5-year patent term extension), with other applications ongoing

TWYMEEG Revenue Trends

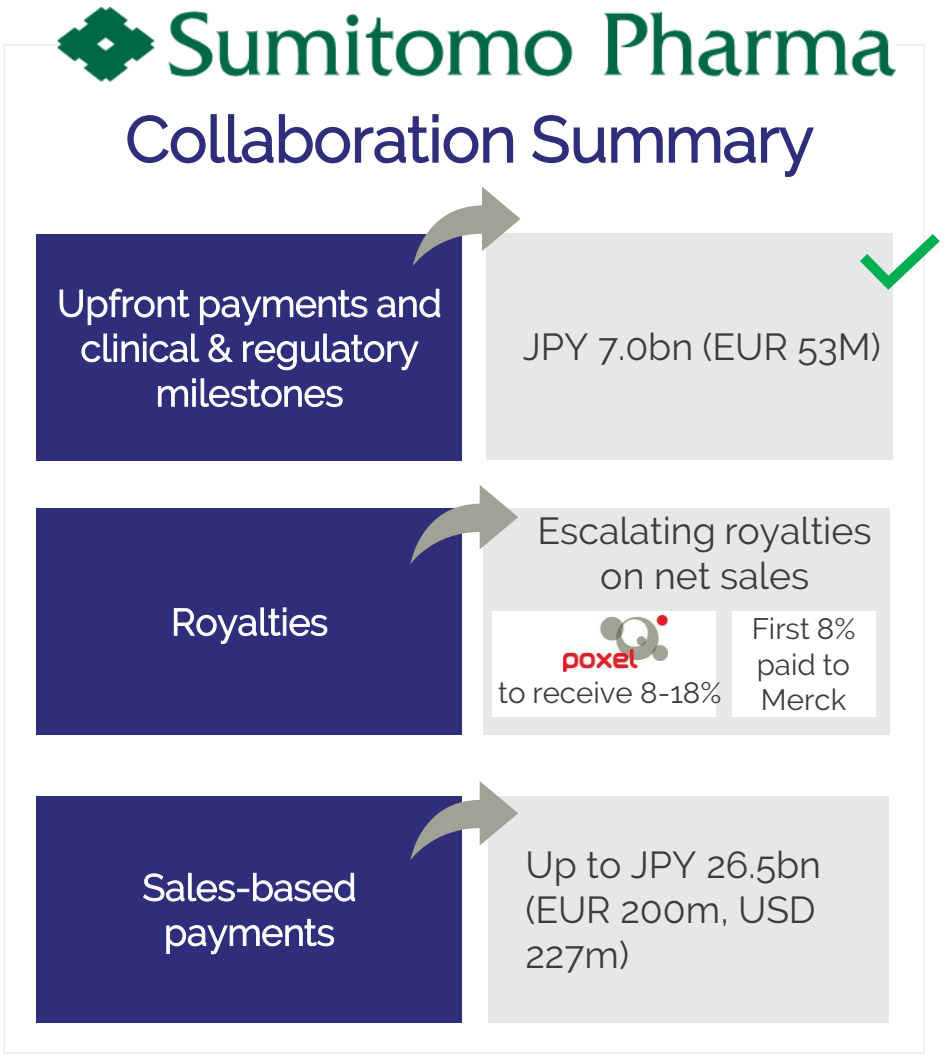
- Sales in Japan for FY22 (JPY 2.2B, EUR 15.0M) exceeded prior guidance by more than 20%
- Sumitomo **FY23 forecast** (JPY4.2B, EUR 28.9M) = **90% growth** vs. FY22; Poxel expects 8% royalty on net sales (conservative assumption)
- During Sumitomo FY24, upon reaching JPY5B (EUR 34.4M) threshold, Poxel expects 10% royalty on net sales & sales-based payment (JPY 500M, EUR 3.4M)



1. Including: Japan, China, South Korea, Taiwan, Indonesia, Vietnam, Thailand, Malaysia, the Philippines, Singapore, Myanmar, Cambodia, and Laos.
2. IQVIA data FY2016 and NDB data FY2016.
3. Currency exchange as of March 31, 2023

TWYMEEG® Collaboration Economics

Future Royalties and Sales-Based Payments to Cover Full Debt Reimbursement



- **Debt repayments to be repaid with positive net TWYMEEG royalties[1]**
  - Debt Restructuring agreements with lenders postpone initiation of repayments to Q1 2025 at latest, under conservative forecast
  - Before the end of Sumitomo fiscal year 2024[2], Poxel expects TWYMEEG net sales in Japan to reach JPY 5 billion, entitling Poxel to receive 10% royalties on all TWYMEEG net sales and a sales-based payment of JPY 500 million (EUR 3.6 million)[3]
  - Full repayment of all debts expected by Q2 2029
  - After this time, subsequent net royalties and sales-based payments will revert back to Poxel
- **Active ongoing partnership discussions for specific territories**

1. First 8% of royalties on net sales of Imeglimin paid to Merck Serono.
2. Sumitomo Pharma fiscal year April-March.
3. Currency exchange as of December 31, 2022.

Conclusion

Strategic Focus on Rare Diseases

Targeting Indications with High Unmet Needs

RARE DISEASES

- PXL770 development focused on rare diseases
  - subject to additional financing, launch of a Phase 2 clinical trial in ALD
- Potential to advance PXL770 into Phase 2 for ADPKD
  - significant opportunity addressing underlying pathology
- D-TZD platform potential in rare diseases to be assessed
  - through Phase 2 clinical trial in AMN-ALD with PXL065

PARTNERSHIPS OPPORTUNITIES

- PXL065 prioritized to advance in NASH as a partnered program
  - discussions for a potential pivotal program in NASH initiated
- Additional partnerships for Imeglimin in specific territories
  - ongoing active discussions

FINANCIAL VISIBILITY

- Cash & cash equivalents: EUR 5.3 million as of 9/30/2023
- Cash runway extended through Q2 2025[1]

1. Based upon debt restructuring and full equity-linked financing facility with IRIS up to EUR 15 million, in the form of bonds redeemable into new or existing shares.

Contact

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