New Strategic Direction: Increasing Focus on Rare Metabolic Diseases

12 July 2021

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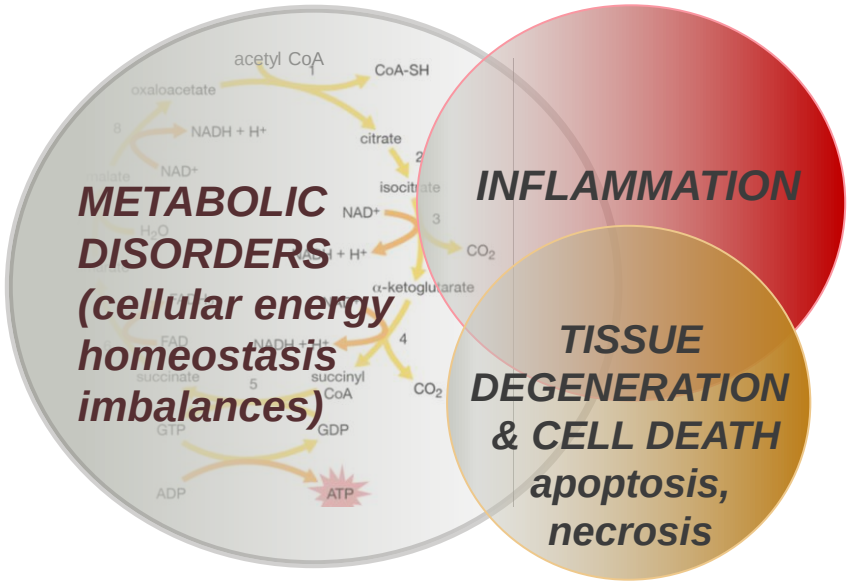
Agenda

Topic	Speaker
Introduction & Strategy	Thomas Kuhn, Poxel CEO
Adrenoleukodystrophy (ALD) Overview	Marc Engelen, MD, PhD *(English)* (Pediatric) Neurologist Department of Neurology and Pediatrics Amsterdam University Medical Centers Amsterdam Leukodystrophy Center Ben Lenail *(French)* Co-founder and Board member of ALD Connect
Patient Perspective	Ben Lenail *(French and English)* Co-founder and Board member of ALD Connect
Scientific Rationale, Data for '065/'770 Development Plan for ALD	David Moller, MD, Poxel CSO Pascale Fouqueray, MD, PhD, Poxel EVP Clinical Development and Regulatory Affairs
Closing Remarks	Thomas Kuhn, Poxel CEO
Q&A	All, joined by: Noah Beerman, Poxel EVP, BD, President US Anne Renevot, Poxel CFO

Poxel's Mission and Vision

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



Poxel's Increasing Focus on Rare Metabolic Diseases

A New Strategic Direction Building upon Recent Achievements

- **Following the recent approval of TWYMEEG® (Imeglimin) in Japan and associated potential future revenues, Poxel to accelerate and expand rare metabolic disease programs**
- **In rare metabolic diseases, first leveraging our internal platforms: dTZD and direct AMPK activators**
  - Plan to advance 1 program in ALD into a pivotal study
  - Initiating PXL065 and PXL770 Phase 2a clinical Proof-of-Concept (POC) studies in adrenoleukodystrophy (ALD) in early 2022; Data expected Q4 2022
  - Faster-to-market strategy with goal to launch an additional rare disease development program in 2022
- **Continued commitment to non-alcoholic steatohepatitis (NASH)**
  - Plan to advance 1 program in NASH into a pivotal study
  - Patient screening is finished and enrollment in DESTINY Phase 2 trial with PXL065 is now expected to complete Q3 2021; Results anticipated Q3 2022
  - Future development of PXL770 in NASH to be evaluated pending PXL065 DESTINY Phase 2 data in NASH and Phase 2 POC results in ALD

TWYMEEG® (Imeglimin): Approved in Japan

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

- **June 23rd Approval in Japan triggered:**
  - 3rd and final tranche of **EUR 13.5 million** from IPF loan received June 30, 2021
  - Milestone payment of **~EUR 13.2 million (USD 15.8 million)**[2] from Sumitomo in Q3
- **Target launch expected in 2021**
- Future potential development milestone payments and sales-based payments of up to **approx. EUR 200 million** (USD 230 million) [3], and double-digit **escalating royalties**

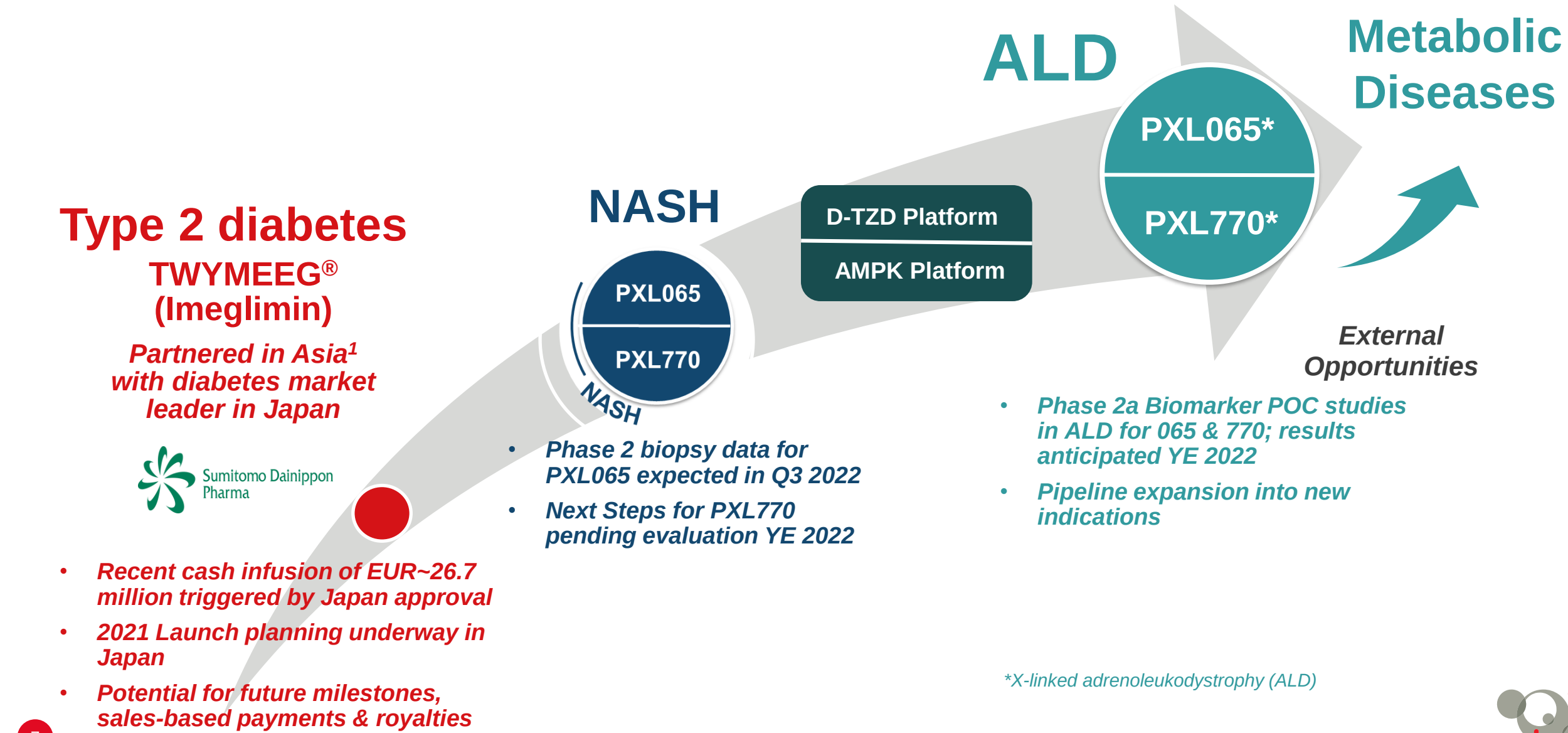
Business Opportunity Japan: Maximize Product Profile

- Sumitomo #1 diabetes franchise; Guidance **FY20 USD 900 million**[4]
- 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***
  - *as Monotherapy and as an Add-on Therapy*

1. Including: Japan, China, South Korea, Taiwan, Indonesia, Vietnam, Thailand, Malaysia, the Philippines, Singapore, Myanmar, Cambodia, and Laos
2. Currency exchange rate at the date of the approval (23 June 2021)
3. Currency exchange rate at the date of the agreement (30 Oct 2017)
4. Sumitomo fiscal year April-March.
5. IQVIA data FY2016 and NDB data FY2016.

A New Chapter to Drive Shareholder Value

Focus on Rare Metabolic Diseases and NASH



- ***Recent cash infusion of EUR~26.7 million triggered by Japan approval***
- ***2021 Launch planning underway in Japan***
- ***Potential for future milestones, sales-based payments & royalties***

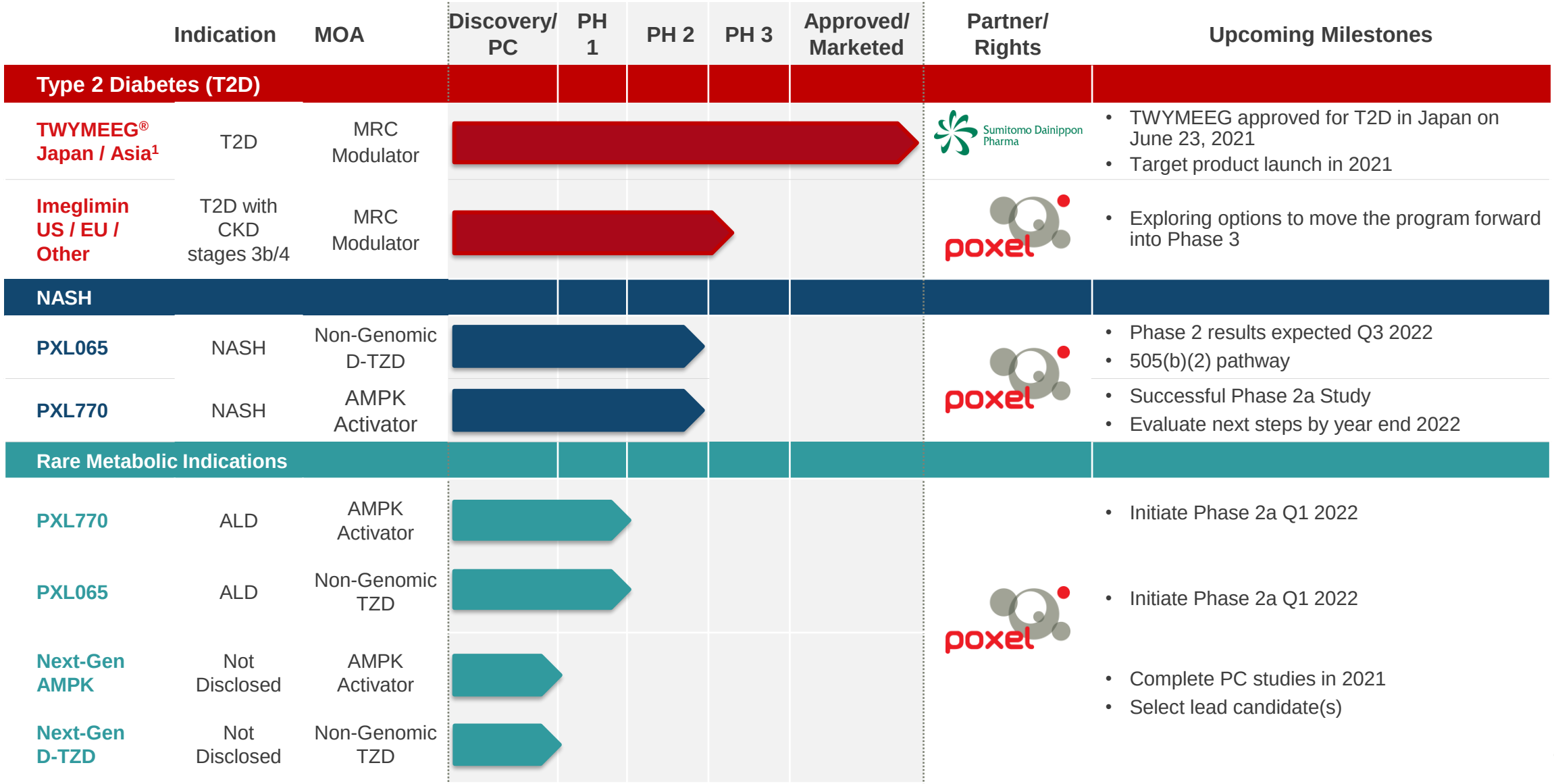
- ***Phase 2 biopsy data for PXL065 expected in Q3 2022***
- ***Next Steps for PXL770 pending evaluation YE 2022***

- ***Phase 2a Biomarker POC studies in ALD for 065 & 770; results anticipated YE 2022***
- ***Pipeline expansion into new indications***

**X-linked adrenoleukodystrophy (ALD)*

Robust Mid-to-Late Stage Metabolic Pipeline

Focus on Rare Metabolic Diseases and NASH



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

X-linked adrenoleukodystrophy (ALD): pathophysiology and clinical features

Marc Engelen, MD, PhD
(Pediatric) Neurologist
Department of Neurology and Pediatrics
Amsterdam University Medical Centers

Amsterdam Leukodystrophy Center

July 2021

X-linked adrenoleukodystrophy (ALD): a not so rare orphan disease

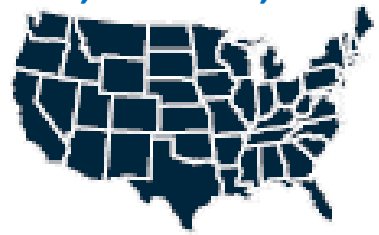
Genetics

- Monogenic, mutations in *ABCD1* gene on the X-chromosome
- Gene encodes ALD protein, a transporter present in peroxisomes required for metabolism of very long chain fatty acids (VLCFA)
- Men and women are affected, but clear differences in symptomatology and disease progression

Prevalence

Estimated US Prevalence*

20,000 – 29,000

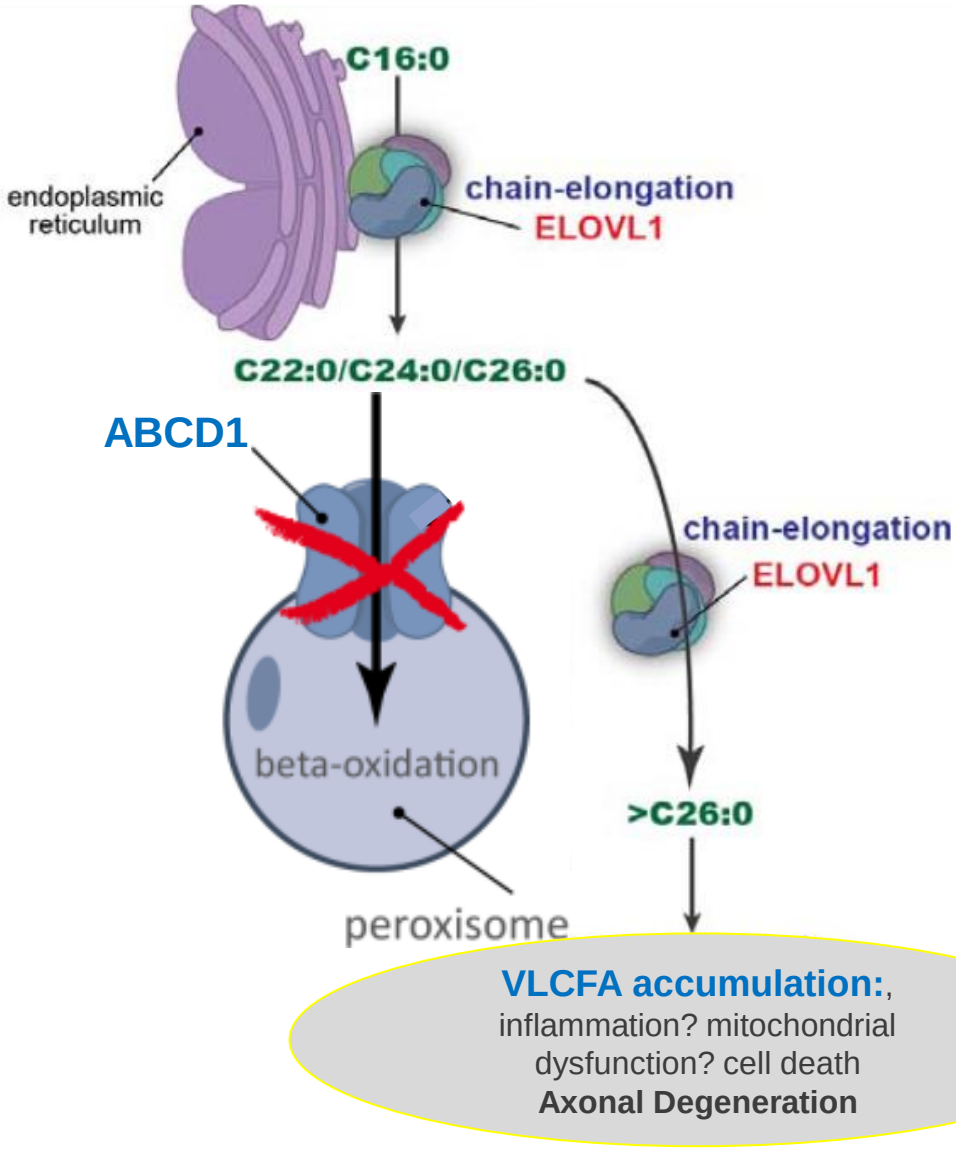


Estimated Global Prevalence*

444,000 – 644,000

* Moser 1993
Bezman 2001
Kemper 2017
Schmidt 2020

ALD: pathophysiology



ABCD1: Transports VLCFA into peroxisome for degradation (ABCD2 can serve as an alternative peroxisomal transporter)

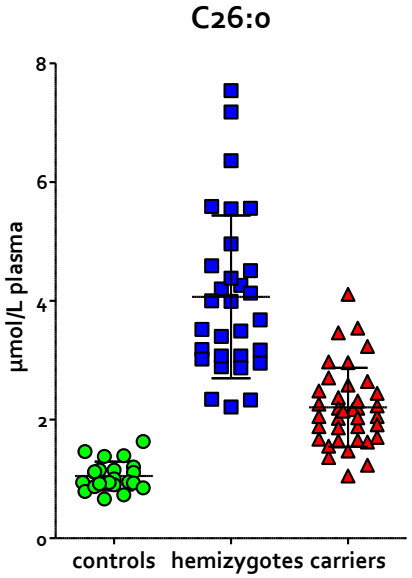
Defective ABCD1 leads to accumulation of VLCFA in tissues

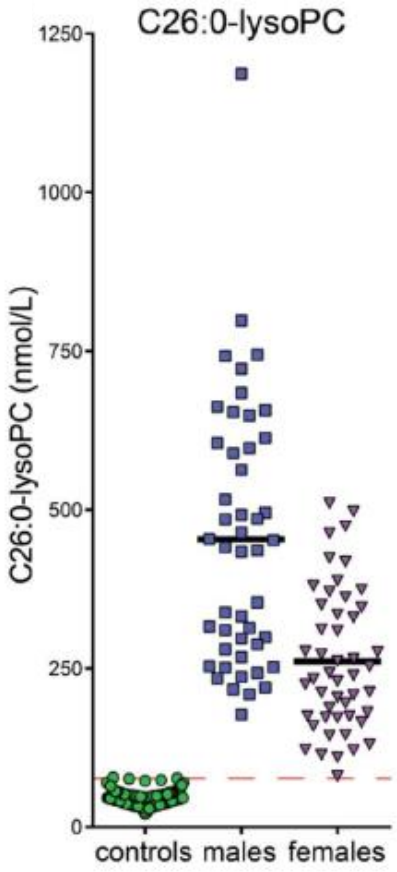
VLCFA cause axonal degeneration and secondary demyelination

Pujol et al. Hum Mol Genet 2004
Foucade et al. Am J Physiol Endo Metab 2009
Kemp & Wanders Mol Genet Metab 2007
Bergner et al. Glia 2021

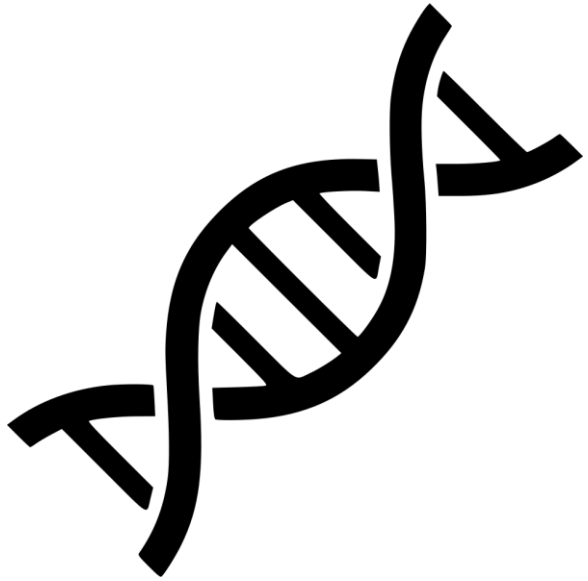
ALD: diagnosis

VLCFA levels

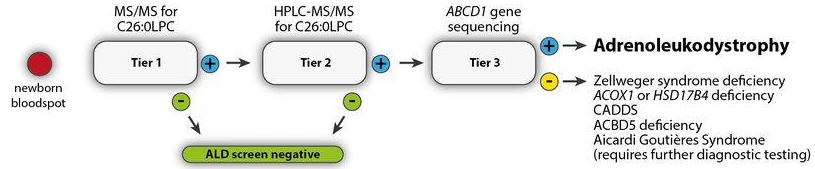




ABCD1 mutation analysis



Newborn screening



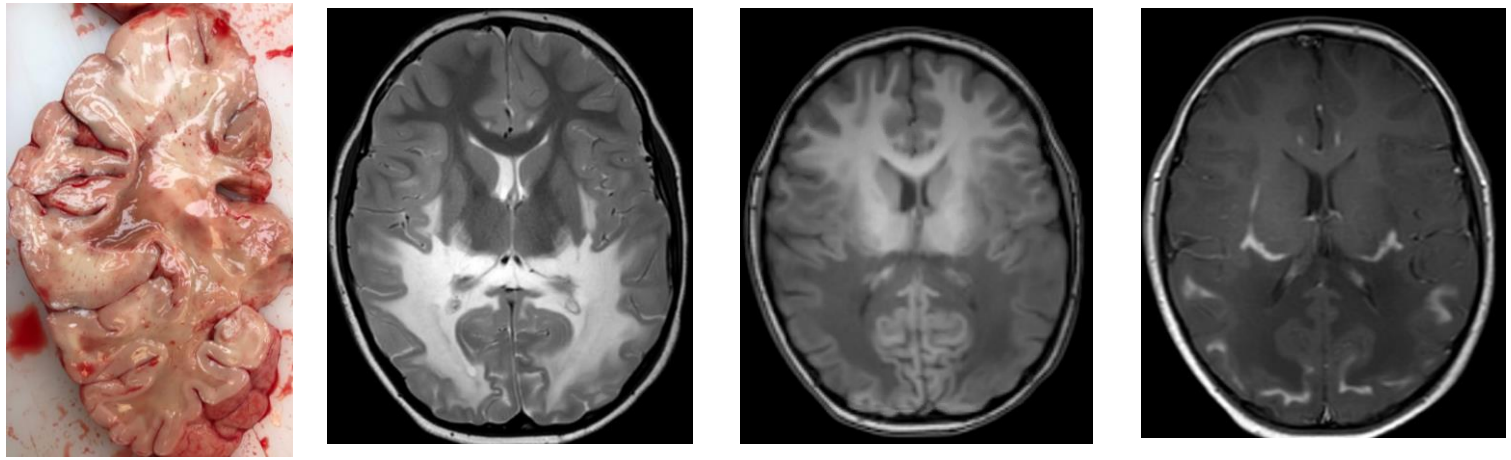
In the U.S. > 60% of newborns screened

Netherlands started in 2021

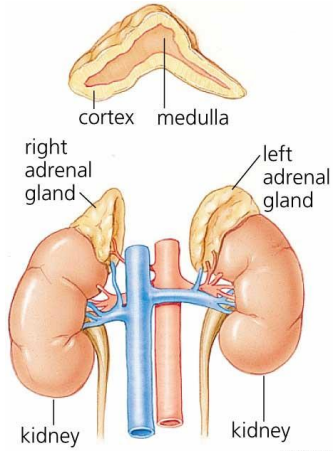
Kemp et al, Nature Reviews Endo, 2016
Huffnagel et al, Mol Genet Metab, 2017

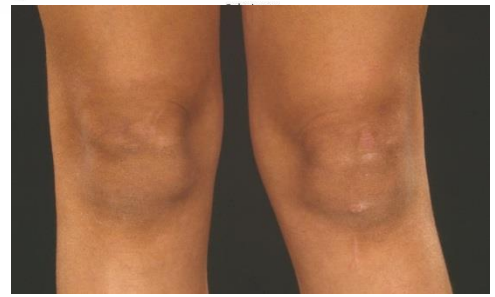
ALD: clinical features

Leukodystrophy: Cerebral ALD (C-ALD)

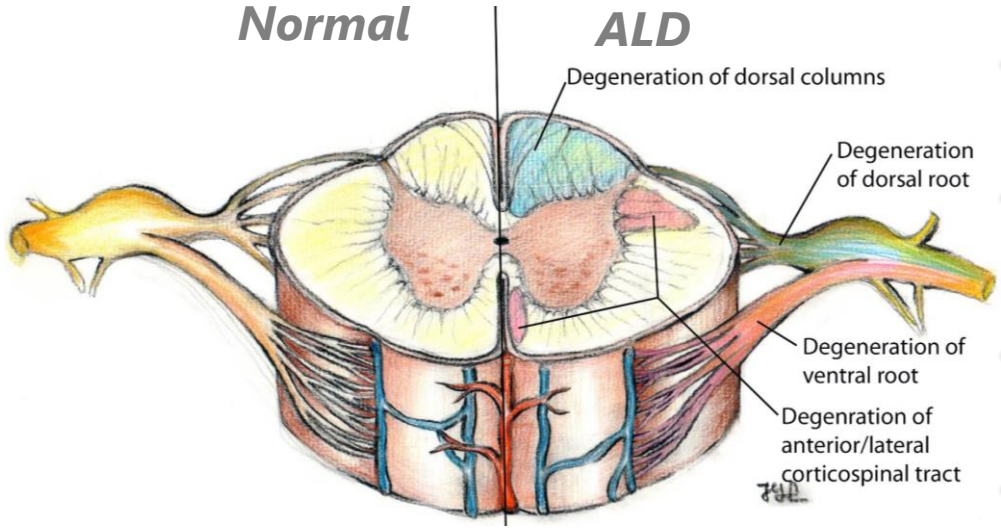


Adrenal Insufficiency





Spinal cord disease : adrenomyeloneuropathy (AMN)



Sensory ataxia

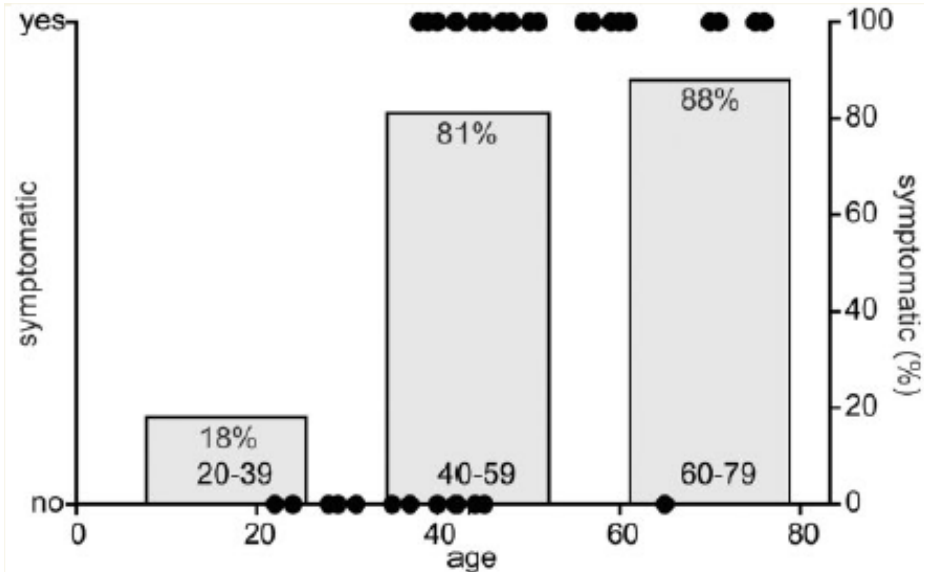
Spasticity

Gait disorder

Powers et al, 2000
Huffnagel et al, 2019

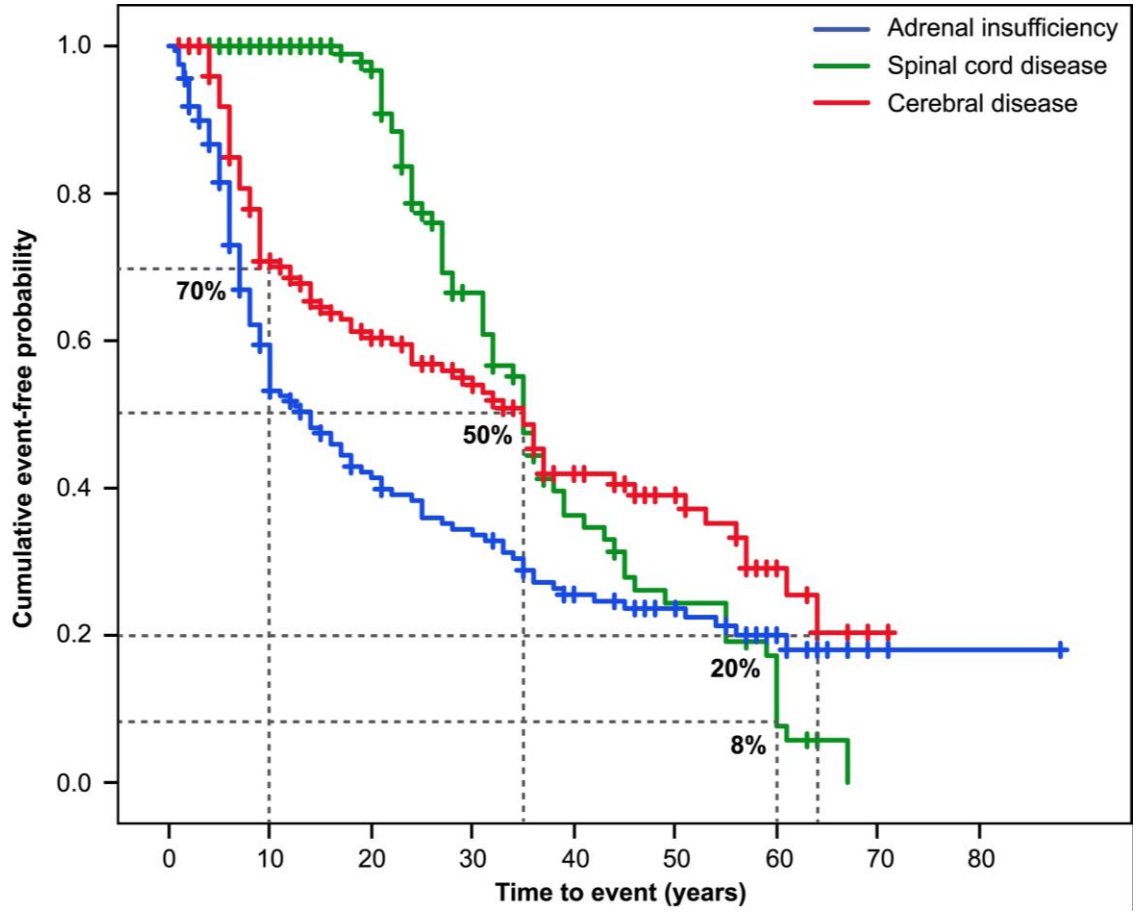
ALD: clinical features

- Women – by > 60:
  - ~90% have spinal cord disease
  - adrenal failure and cerebral disease are very rare

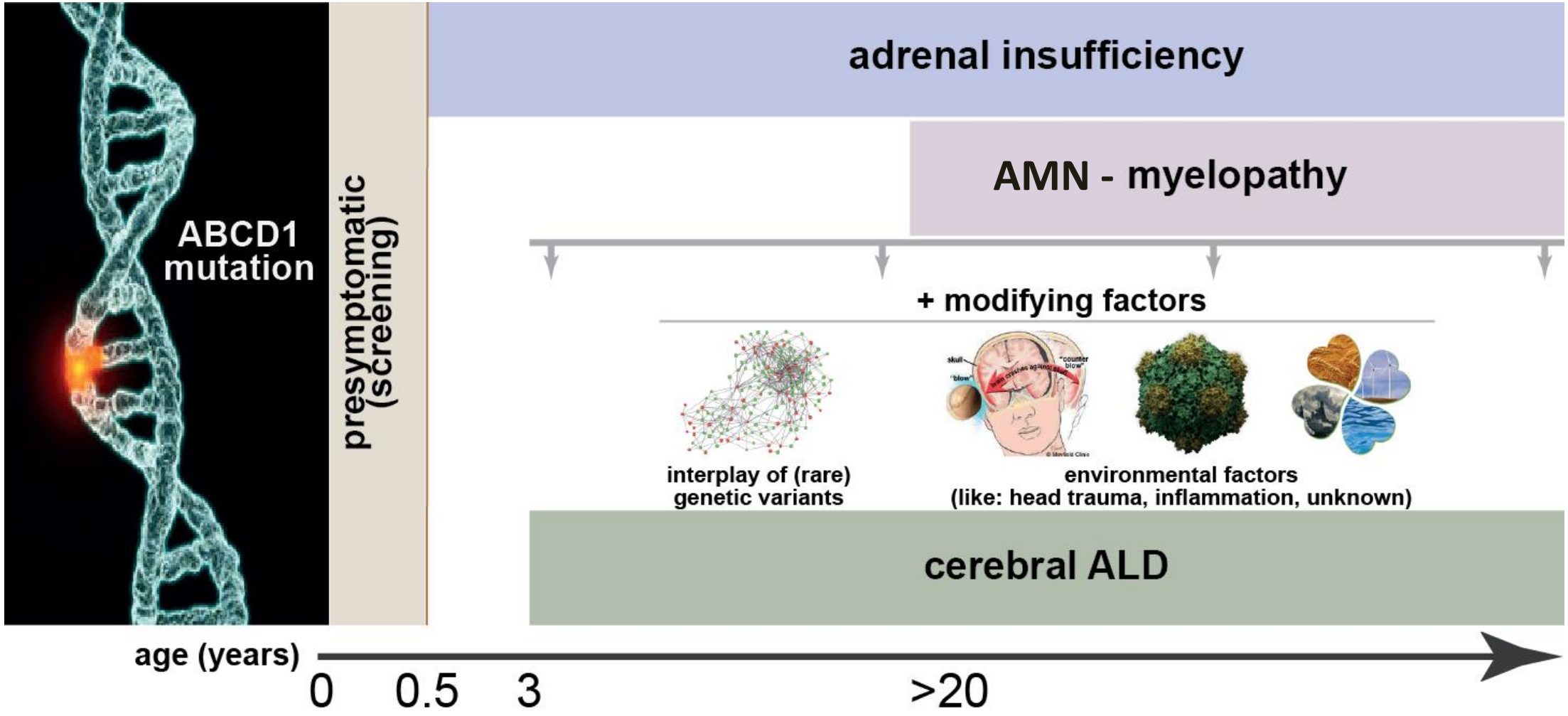


Engelen et al, Brain, 2014
Huffnagel et al, J Clin Endocrinol Metab 2019

- Men – by age 65:
  - >90% have spinal cord disease
  - 80% have developed cerebral disease



Adrenoleukodystrophy: clinical features

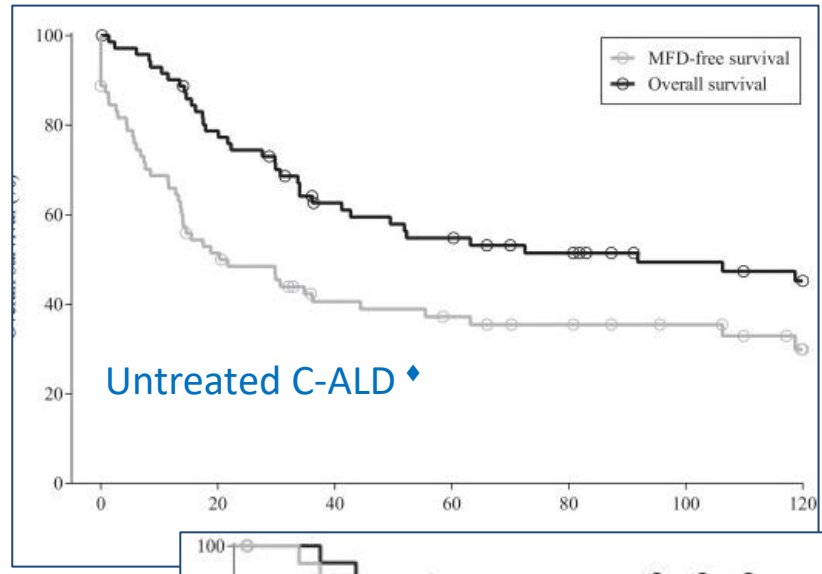


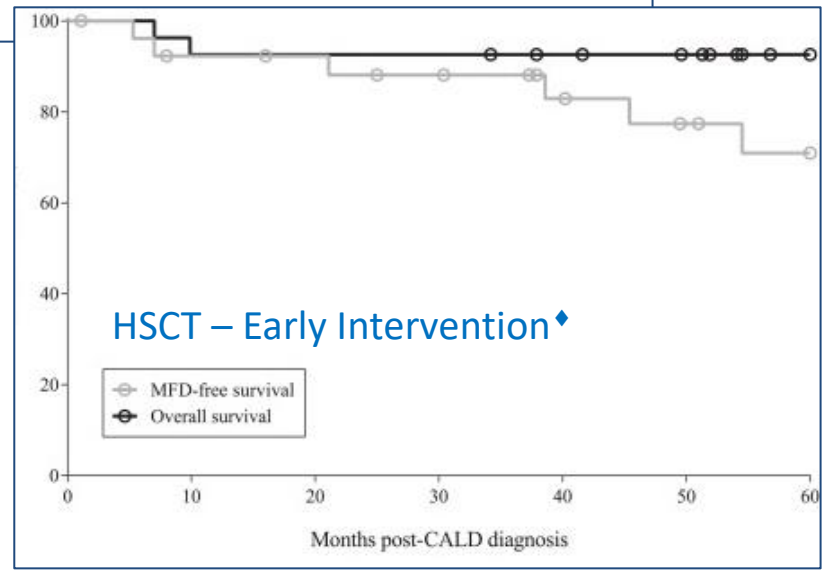
Kemp et al, Nature Reviews Endo, 2016

ALD: treatment

- Adrenal insufficiency → glucocorticoid replacement therapy
- Early stage (early onset) C-ALD → HSCT or *ex-vivo* Lenti-viral gene therapy (SKYSONA™ Bluebird Bio$^{\Delta}$)

  HSCT does not prevent spinal cord disease ("AMN")
- Advanced or later onset C-ALD → only supportive care
- AMN:
  - supportive care only
  - *major target for future therapies*





$^{\Delta}$ Positive EMA-CHMP opinion May 2021
https://bluebirdbio.com/news-releases

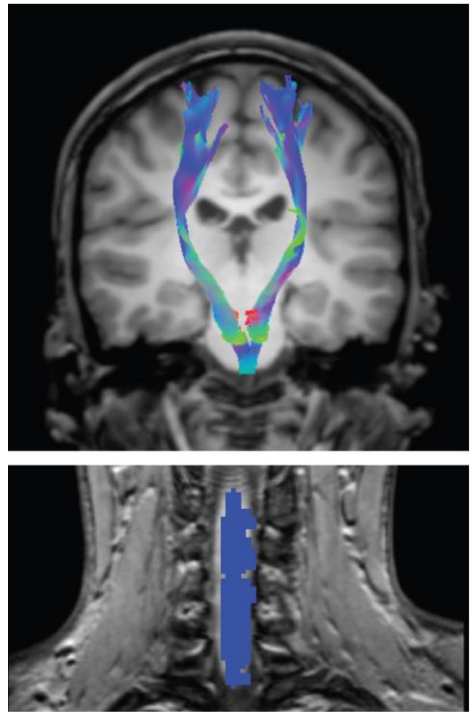
♦HSCT Data from Raymond GV. Biol Blood Marrow Trans 2019; 25:538-48. Early intervention = Neuro function score <1; LOES score 0.5-9

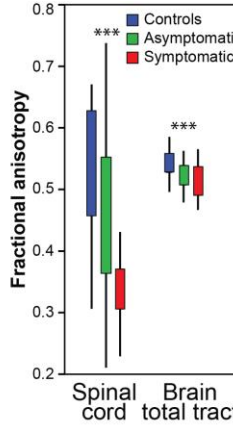
Towards objective outcome measures for clinical trials

Non-Invasive Biomarkers

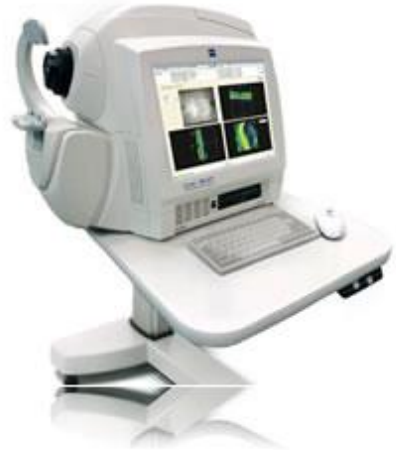
- VLCFA
- Neurofilament Light Chain
- Others

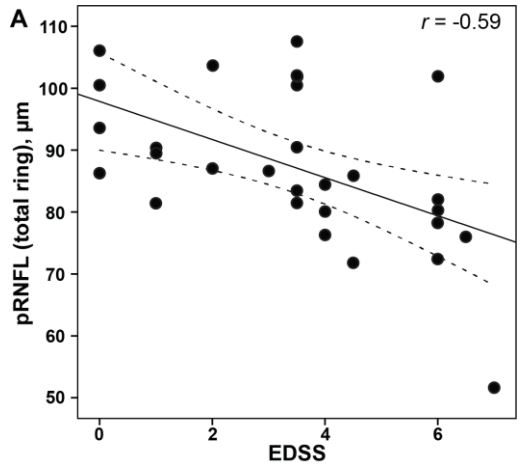
qMRI (like DTI and CSA)



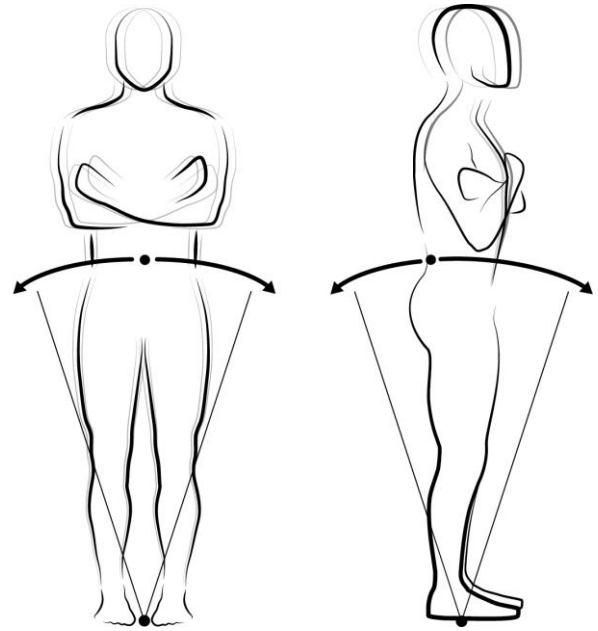


Optical coherence tomography





Postural Body Sway



Huffnagal et al. Neurology 2019
van Ballegoij et al. Front Physiol 2020
van Ballegoij et al. Ann Clin Trans Neurol 2020
van der Stadt et al. J Inherit Metab Dis 2020
van Ballegoij et al. Ann Clin Trans Neurol 2021

ALD: treatment development and unmet needs

- AMN:
  - Slowly progressive – severe and disabling disease; no disease modifying therapy available
  - Delay progression of spinal cord disease
  - Prevent loss of mobility, bladder and bowel dysfunction
  - Improve quality of life
  - *Both* men and women
- Cerebral ALD:
  - Faster progression; causes disability and death 2 – 3 years after onset in most cases; in many cases diagnosis too late for HSCT
  - Prevent onset and progression in adults
  - Delay or obviate need for HSCT (or gene therapy) in childhood new onset C-ALD

ALD –

A Patient Perspective

Ben Lenail

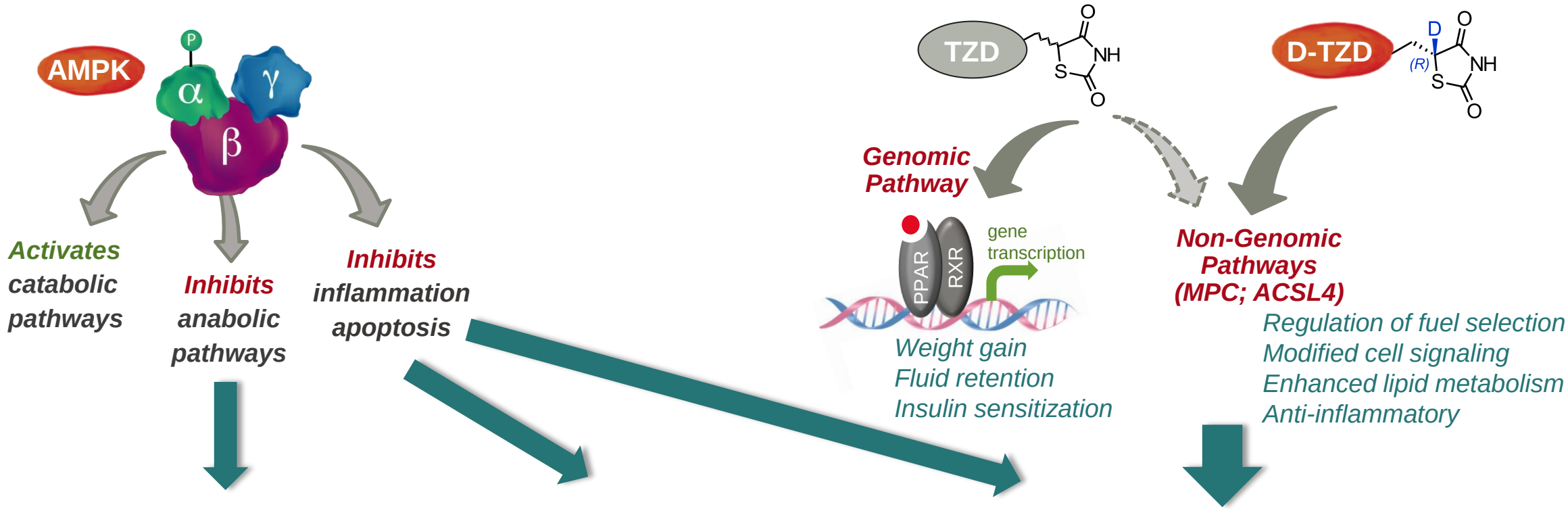
Poxel ALD Program

David E. Moller, MD – Chief Scientific Officer

Pascale Fouqueray, MD, PhD, EVP Clinical Development and Regulatory Affairs

Harnessing AMPK and D-TZD Platforms to Address Rare Diseases with Metabolic Pathophysiology

Two Programs Approaching Clinical Development for ALD



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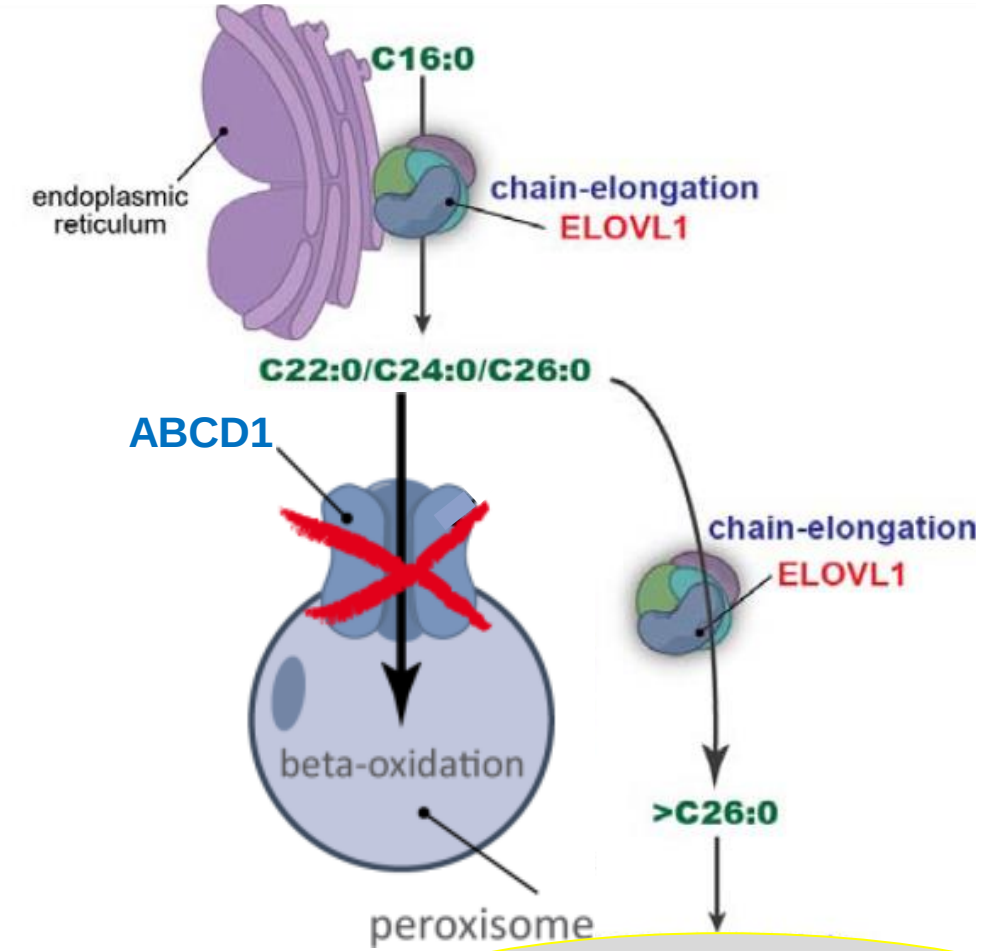
Poxel Platforms – Potential to Target ALD Pathophysiology



VLCFA accumulation:, inflammation? mitochondrial dysfunction? cell death
Axonal Degeneration

ABCD1: Transports VLCFA into peroxisome for degradation (ABCD2 can serve as an alternative peroxisomal transporter)

Defective ABCD1 leads to accumulation of VLCFA in tissues

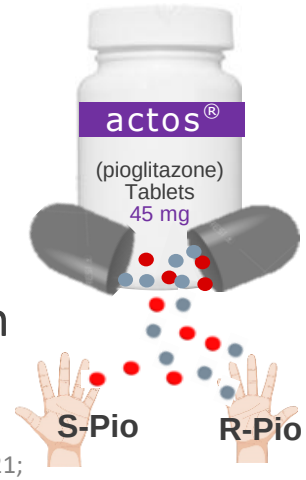
VLCFA cause axonal degeneration and secondary demyelination

D-TZD's and AMPK activators: modulate lipid metabolism and mitochondrial function, mediate anti-inflammatory effects; inhibit apoptosis

Two First-in-Class Advanced Lead Molecules

PXL065

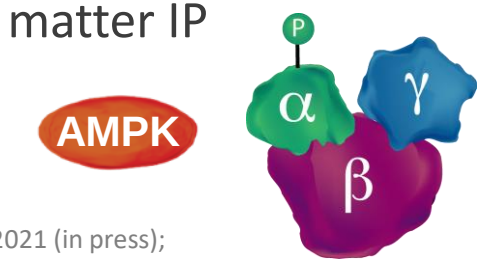
- Deuterium stabilized *R*-stereoisomer of pioglitazone*
- Preclinical:
  - no (PPARγ –driven) weight gain/fluid retention
  - metabolic and anti-inflammatory efficacy
- Clinical
  - completed Phase I
  - confirmed selective *R*-pio exposure
  - good safety profile in >130 human exposures (Phase I plus ongoing Destiny 1 NASH trial)
- Composition of matter IP
- 505(b)(2) regulatory path; open IND in ALD/AMN



*approved Type 2 diabetes therapy (Actos); Jacques V et al. Hep Comm 2021; implicated in ALD - Brain 2013;136:2432-43

PXL770

- Proprietary direct allosteric AMPK activator♦
- Preclinical:
  - Metabolic, anti-inflammatory, cytoprotective efficacy in NASH, diabetes, kidney, CV models
- Clinical
  - orally bioavailable; once daily PK profile
  - human target engagement and efficacy demonstrated (diabetes and NAFLD)
  - >200 human exposures for up to 12 weeks
  - well tolerated with favorable safety profile
- Composition of matter IP



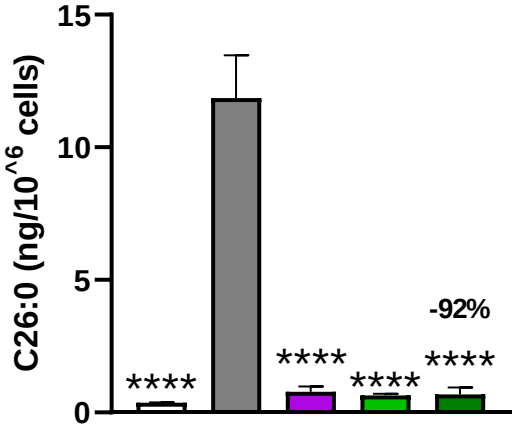
♦ Gluais-Dagorn et al. Hep Comm 2021 (in press); implicated in ALD – Weidling I J Neurochem 2016

D-TZD's: Rationale and Strong Preclinical Data

- Pioglitazone attenuates neuroinflammation and confers neuroprotection:
  - non-human primates with Parkinson's disease[1]
  - rodent acute brain ischemia[2], spinal cord injury[3]
- Pioglitazone efficacy achieved in ABCD1-null mice[4]
- MPC inhibition implicated as a therapeutic approach in neurodegeneration5,6
- PXL065 is active in ALD/AMN patient-derived cells and in ABCD1 null mice:

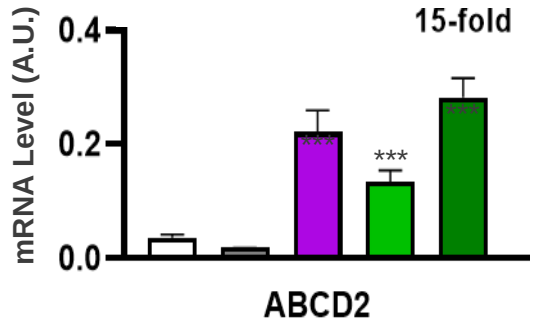
J Neuroinflamm 2011; 8:91
Exp Neurol 2009; 216:321-
Exp Neurol 2017; 293:74-
4. Brain 2013;136:2432-43
5. Sci Trans Med 2016; 8:368ra174
6. Neural Regen Res 2017;12:1807-8

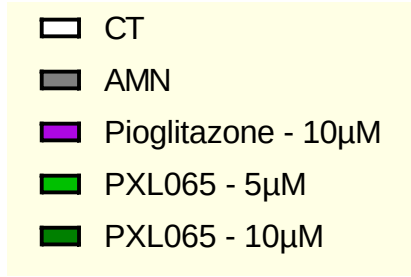
AMN – Fibroblasts Suppression of Elevated VLCFA



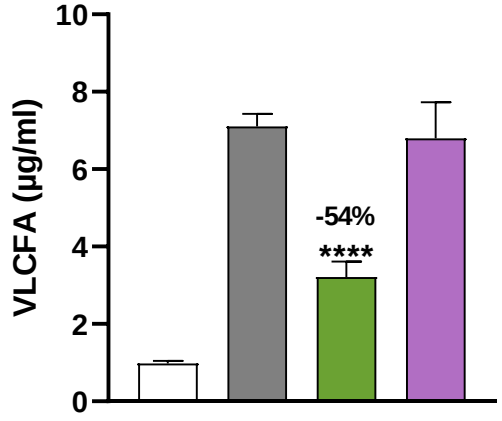
N=3-4

AMN – Fibroblasts Compensatory Transporter Gene Expression





ABCD1 Null Mouse Model Spinal Cord Suppression of Elevated VLCFA (C26:0)



***p<0.01, ****p<0.001

N=12-15; Dose =15 mg/kg QD

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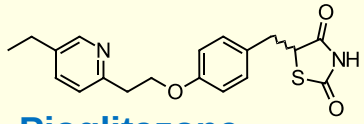
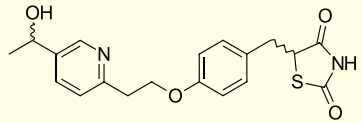
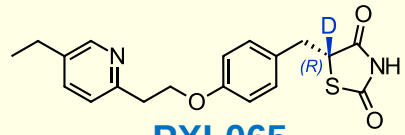
D-TZD's: Clinical Results Support Pursuit of ALD/AMN

Leriglitazone - Human PoC with PPARγ - Related AEs

- Phase 2/3 trial in adult AMN patients (n=116; 96 week)[Δ]
- Primary Endpoint: 6 min walk test - *Failed (*differences "observed in early symptomatic pts")
- Secondary / Exploratory: Body Sway - *Significant (p=0.036; p=0.003) improvements*

  SSPROM & EDSS – *Positive effect*

  Cerebral ALD - *Positive effect*

	 **Pioglitazone**	 **Leriglitazone (M-IV Pio Metabolite)**	 **PXL065**
MoA	PPARγ agonist & Non-genomic effects (MPC, other)*	PPARγ agonist & MPC inhibition**	Minimal PPARγ activity Non-genomic effects (MPC, other)*
Relationship to Pio	Parent molecule	M-IV metabolite of Pio	R-Pio (1/2 of pio mixture)
Known or expected side effects (PPARγ)	weight gain (≈3 kg), edema, & risk of bone fracture	weight gain (5.8 kg[Δ]), edema[Δ]	No significant PPARγ–related side effects expected

PXL065 and other D-TZD's:
Potential for superior efficacy with reduced side effects

[Δ]Minoryx press release Feb. 2021; Am Acad Neurology 2021 presentation; *Both Pio isomers have similar mitochondrial pyruvate carrier (MPC) activity; **in-house data and results reported in Minoryx patent WO 2019/234690

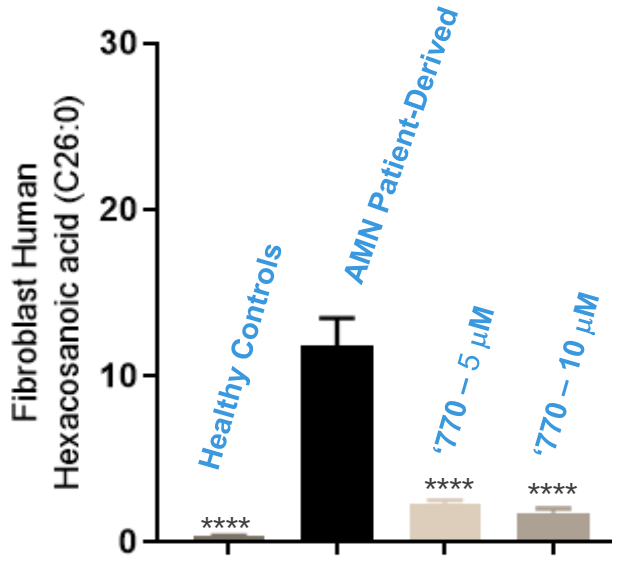
AMPK: Scientific Rationale and Strong Preclinical Data

- Deletion of AMPK in glial cells of ABCD1-null mice → mitochondrial dysfunction / low ATP[1]
- Reduced AMPK in patient-derived cells and brain tissue from ALD patients[2,3]
- AMPK activation with metformin* elevates ABCD2 levels in patient cell lines and ABCD1-null mice[3,4]
- *PXL770 is active in ALD/AMN patient-derived cells and in ABCD1 null mice:*

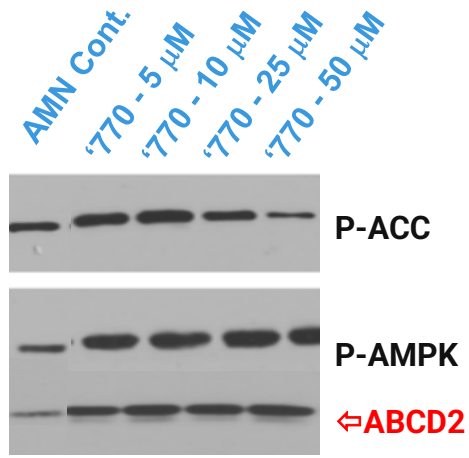
J Neurochem. 2016 Jul; 138(1): 10–13. PMID
Published online 2016 Mar 15. doi: 10.1111/jnc.13594

The ABCD's of 5′-Adenosine Monophosphate-activated Protein Kinase and Adrenoleukodystrophy

AMN – Fibroblasts Suppression of Elevated VLCFA

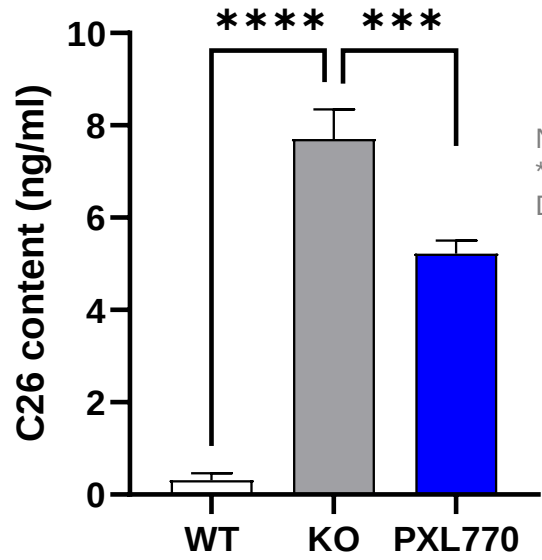


AMN – Fibroblasts Compensatory Transporter Protein Expression



N=3-4

ABCD1 Null (KO) Mouse Model Spinal Cord Suppression of Elevated VLCFA (C26:0)



N=6-8, each
****p<0.001
Dose – 75 mg/kg BID

1. Mediators Inflamm 2015; 176983
2. Biochem Biophys Res Comm 2014;445:126-
3. J Neurochem 2016; 138:86-
4. J Neurochem 2016; 138:10-

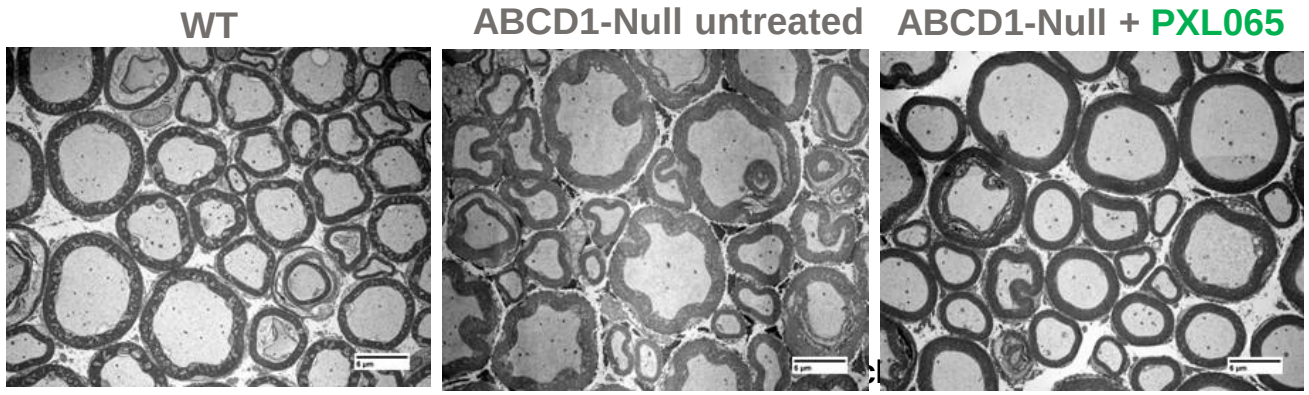
* well accepted indirect AMPK activator; requires metformin concentrations >> clinical exposure levels

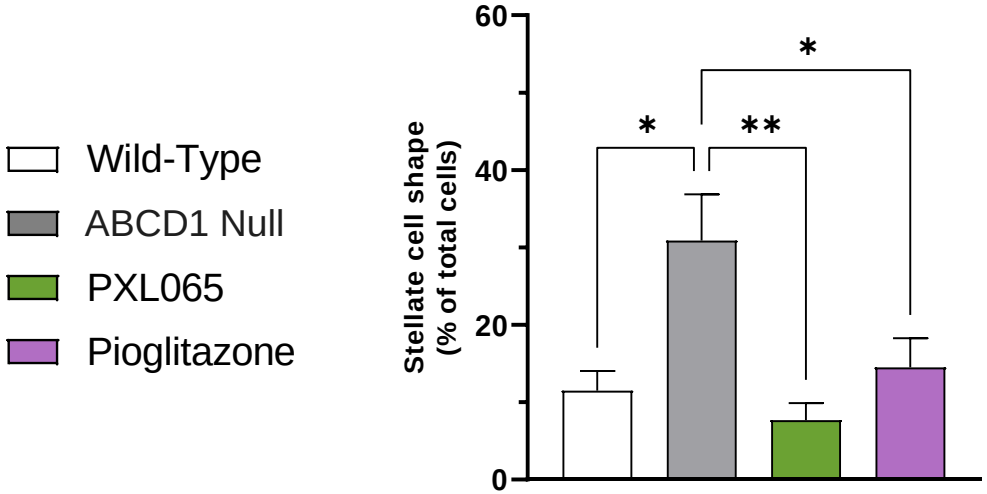
poxel

Both PXL065 and PXL770 Mediate Neurologic Benefits

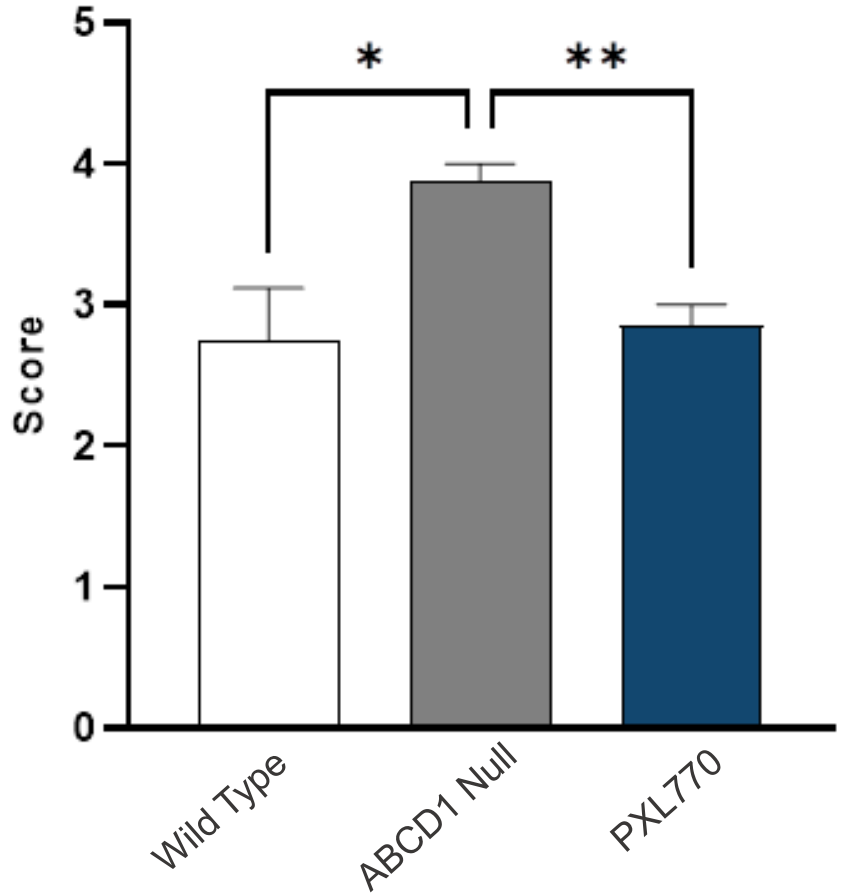
ABCD1-Null Mouse (12 wk Treatment)

Electronic Microscopy of Sciatic Nerve





Neurologic Tests (Balance Beam)



*p<0.05; **p<0.01

Poxel Lead Molecules vs. Selected Competitors

Advanced Drug Candidates with Potential for Superior Clinical Results

	PXL065	PXL770	Leriglitazone*	VK0214▽	ABX-002♦
Mechanism	Non-genomic D-TZD	AMPK activator	PPARγ (+ other TZD)	Thyroid receptor β	Thyroid receptor β
Stage	Ph2a – Ready	Ph 2a – Ready	Ph 2b/3	Ph 1b	*Preclinical*
Human ALD Cells	⇩⇩⇩VLCFA ⇧ ABCD2 ⇧ mitochondrial respiration	⇩⇩⇩ VLCFA ⇧ ABCD2 ⇧ mitochondrial respiration	*No VLCFA or ABCD2 effects reported*	*VLCFA not reported* ⇧ ABCD2	*Not reported*
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	⇩ VLCFA plasma, brain; *spinal cord not reported*
Neuro Histology	Improved	Improved	Improved	*Not reported*	*Not reported*
Neuro-Behavior	Improved	Improved	Improved	*Not reported*	*Not reported*
Other Comments	Clinical safety: >130 exposures plus 505(b)(2)	Clinical safety: (>200 exposures)	+ results in Ph2b/3 *weight gain, edema*	Phase I completed	*No clinical experience*

* Rodriquez-Pascau Science Trans Med 2021; Am Acad Neuro (AAN) oral presentation 2021; Minoryx 2021 press release

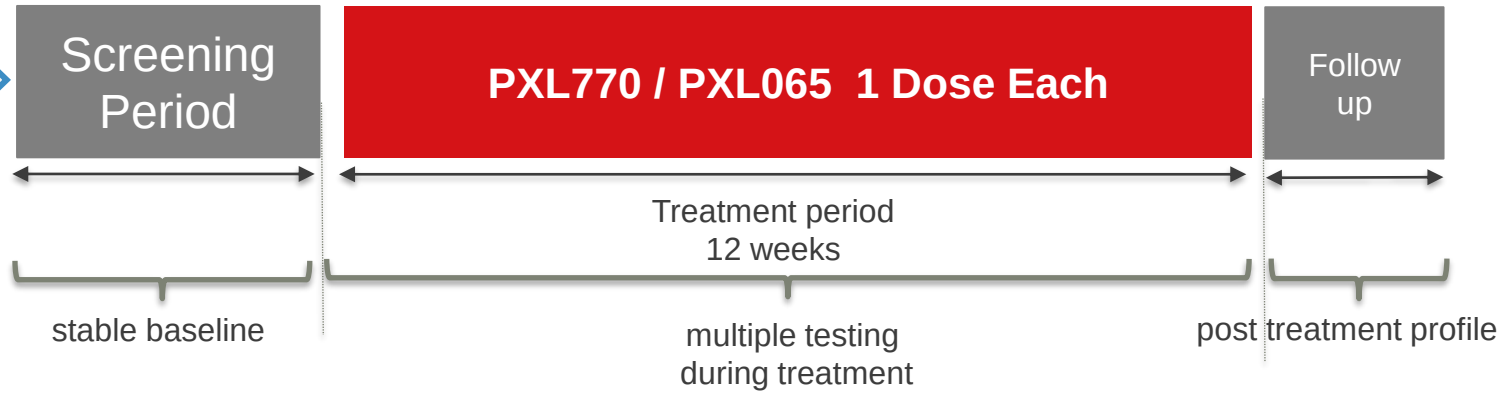
▽ Viking corporate presentation 2021; ♦Autobahn AAN Poster 2021

Planned Phase 2A Studies in ALD/AMN

PXL770 and PXL065 in Two Separate Identical Studies

Key inclusion criteria

- Males with AMN
- Age 18-65
- No active cerebral disease
- 12 patients each



Endpoints

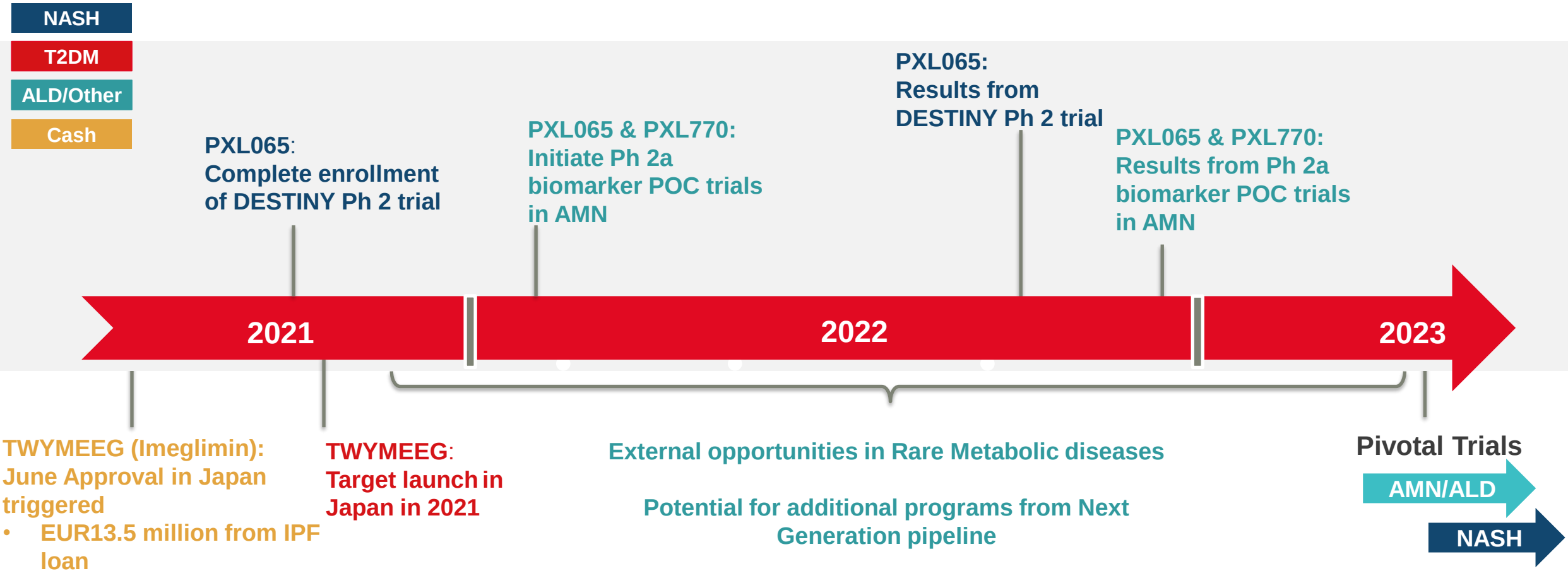
- VLCFA – biomarker and hallmark of disease – drives pathology
- Neurofilament light chain – validated biomarker of neuronal damage
- Other / exploratory biomarkers
- PK
- Safety

Phase 2A initiation 1Q22 – completion 4Q22
Phase 3 Pivotal trial(s) to begin in 2023

Upcoming Milestones

Thomas Kuhn, CEO

Near-Term Milestones to Drive Poxel's Growth



1 Currency exchange rate at the date of the approval (23 June 2021)

Summary and Investment Highlights

- **Strategic Focus on rare metabolic indications and NASH**
  - ALD: PXL065 and PXL770 Phase 2a biomarker Proof-of-Concept results by year end 2022; potential to advance into pivotal trial
  - NASH: PXL065 Phase 2 results anticipated Q3 2022; option to advance either PXL065 or PXL770 as oral, first-in-class addressing large market opportunity
- **TWYMEEG® (Imeglimin) Approved** for T2D in Japan
  - Sumitomo, #1 diabetes company in Japan, expecting to launch 2021
  - Up to EUR 200 million (~USD 230 million)[1] in future potential milestone and sales-based payments and double-digit escalating royalties
  - US/Europe: exploring options to move the program forward into Phase 3
- **Cash & Cash Equivalents: EUR 32.8 million (USD 38.4 million) as of 3/31/2021**
  - Additional EUR 13.5 million from IPF Loan in June and EUR 13.2 million[2] approval milestone in Q3 from Sumitomo
- **Highly Experienced Management Team** with extensive metabolic R&D and business expertise & track record in US, EU and Japan

1. Currency exchange rate at the date of the agreement (30 Oct 2017) 2. Currency exchange rate at the date of the approval (23 June 2021)

Question & Answer Session

Concluding Remarks