Investor and Analyst Event

April 8, 2024

Callum
Living with
ENPP1 Deficiency

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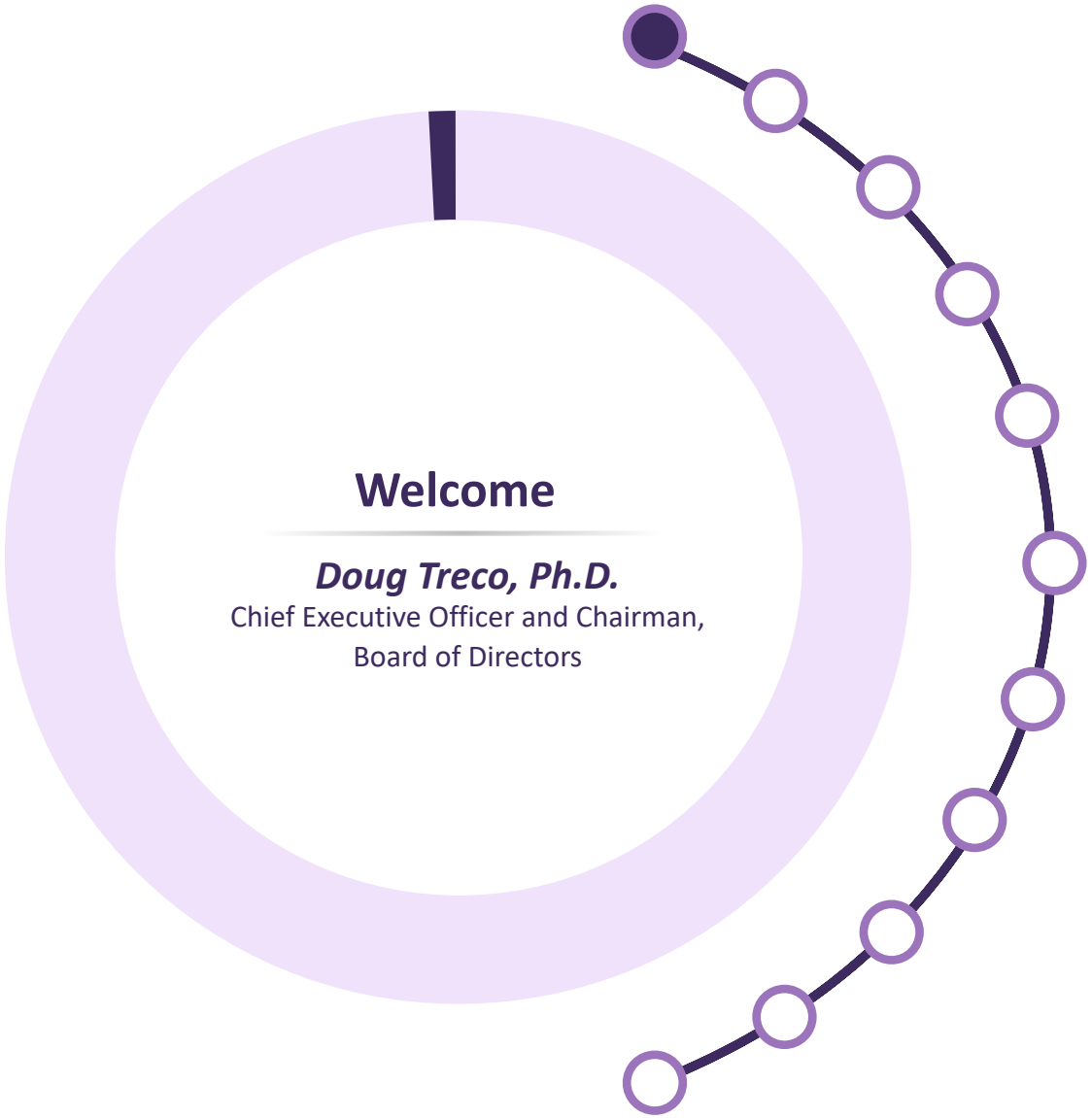
In addition, the forward-looking statements included in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

Event agenda



Welcome

ABCC6 Deficiency: Disease Overview

Topline Data: ABCC6 Deficiency Phase 1/2 Trial

Retinal Disease in ABCC6 Deficiency

ABCC6 Pediatric Disease – A Critical Unmet Need

- Early-Onset ABCC6 Deficiency – Natural History Study
- Pediatric Stroke – Case Study
- Market Overview

ABCC6 Deficiency Regulatory Strategy

Topline Data: ENPP1 Deficiency Phase 1/2 Trial

Key Takeaways

Question and Answer

Phase 1/2 trial of INZ-701 in adults with ABCC6 Deficiency successfully met all study objectives

Safety

- ✓ INZ-701 demonstrated a **favorable safety profile**
- ✓ No serious or severe adverse events
- ✓ Low/moderate, sometimes transient, ADA titers

PK/PD

- ✓ **Rapid** and **sustained increase in PPi** observed in highest dose cohort (1.8 mg/kg)

Clinical

- ✓ **Positive changes** in carotid intima-media (cIMT) thickness and choroidal layer of eye support **improvements in vascular health**
- ✓ Improvement in visual function (VFQ-25) and multiple PROs observed

VFQ-25: Visual Function Questionnaire; PRO: Patient Reported Outcomes; ADA: Anti-drug antibodies

Focused on pediatric population with ABCC6 Deficiency

Unmet Need

- ✓ Retrospective natural history study (early-onset) and interventional study (adults) identified **risk of stroke** and **retinal disease** as consistent presentation in ABCC6 Deficiency

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Market

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Market

- ✓ Market research identified **substantial pediatric population** that represents the most important unmet need in ABCC6 Deficiency

Regulatory

- ✓ Phase 3 trial design planning in progress
- ✓ Plan to seek **accelerated approval** based on imaging metric predictive of ischemic stroke

Phase 1/2 trial of INZ-701 in adults with ENPP1 Deficiency successfully met all study objectives

Safety

- ✓ **Favorable safety profile** was maintained
- ✓ Low/moderate, sometimes transient, ADA titers

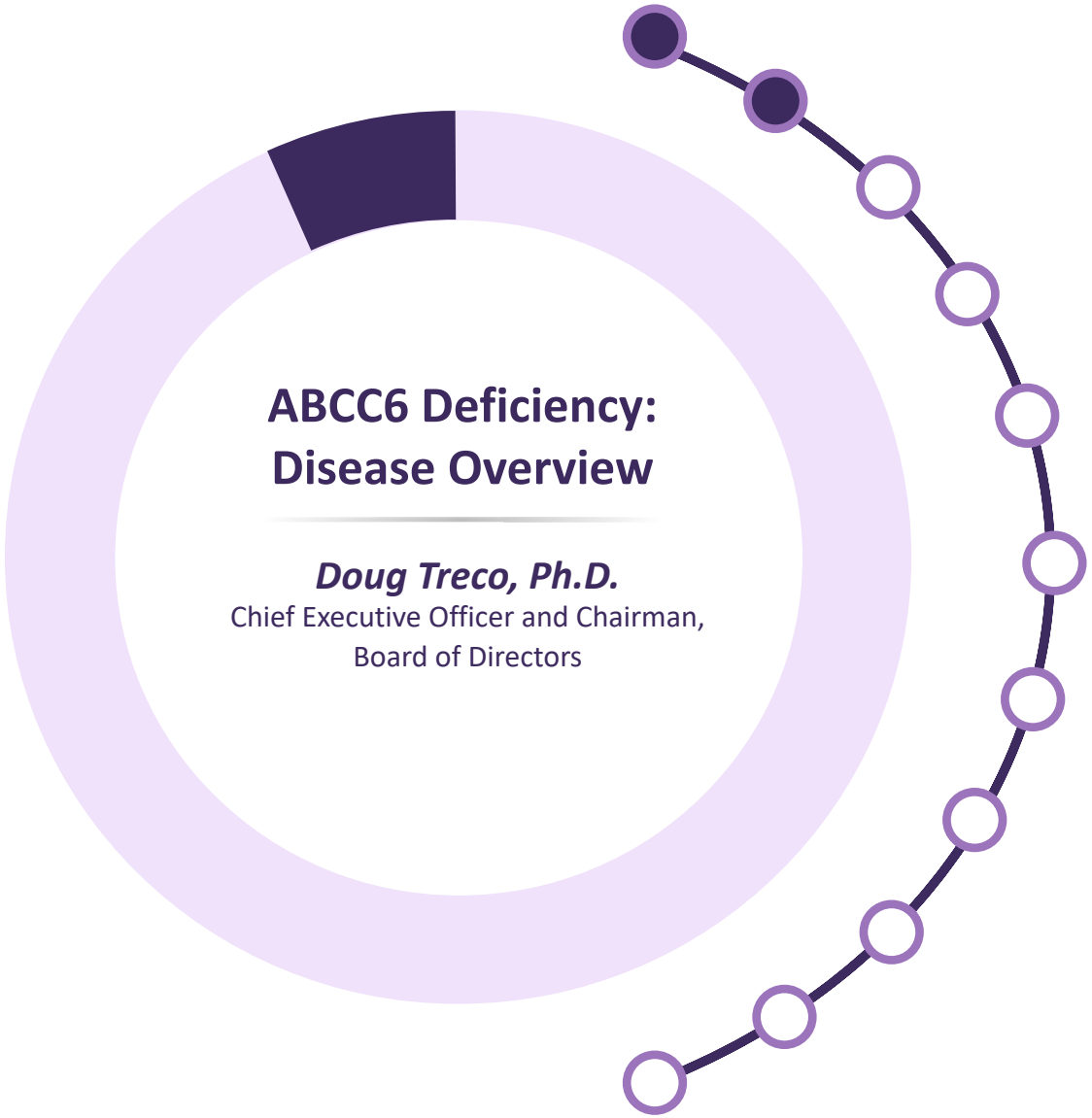
PK/PD

- ✓ **PK data** from cohort 4 **support once-weekly dosing**
- ✓ **PPi remained elevated** with long-term treatment

Clinical

- ✓ Favorable response on **clinical outcomes** (PROs and 6MWT) was **maintained**
- ✓ Bone biomarker response consistent with restoring proper bone mineralization

Event agenda



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ABCC6 Deficiency is a multisystem, rare genetic disease: High morbidity and a continuum of effects across age groups

PXE
18+ Years

Blindness, cardiovascular disease and mobility impairment [3-7]

Progressive arterial calcification

Increased incidence of stroke and dementia

Retinal calcification – Angioid streaks, atrophy

Progressive calcification and fragmentation of elastic fibers

Genetic Prevalence: 1:25,000 - 1:50,000 [8-9]

Sources: *1. Ferreira et al. JBMR 2021; 2. Grossi et al, Eur J Med Genet, 63 2020; 3. Shimada et al. Int.J.Mol.Sci. 2021; 4.Risseeuw et al. Retina, 2019; 5. Leftheriotis et al. J Vasc Surg, 2011; 6. Vanakker et al. Hum Mutat. 2008; 7. Van den Berg et al. Cerebrovasc Dis, 2000; 8. Internal, Unpublished Data; 9. Ferreira et al. Genet Med, 2021*

ABCC6 Deficiency is a multisystem, rare genetic disease: High morbidity and a continuum of effects across age groups

GACI-2
0-1 Years

~10% mortality within 12 months of birth [1]

Severe cardiovascular complications and pulmonary hypertension

PXE
18+ Years

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ABCC6 Deficiency is a multisystem, rare genetic disease: High morbidity and a continuum of effects across age groups

GACI-2
0-1 Years

~10% mortality within 12 months of birth [1]

- Severe cardiovascular complications and pulmonary hypertension

Pediatric
1 to <18 years

Multisystem vasculopathy and strokes [2]

- Progressive cardiovascular calcification/stenosis of major arteries
- Cerebrovascular calcification -including stroke
- Initial retinal calcification

PXE
18+ Years

Blindness, cardiovascular disease and mobility impairment [3-7]

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- Increased incidence of stroke and dementia
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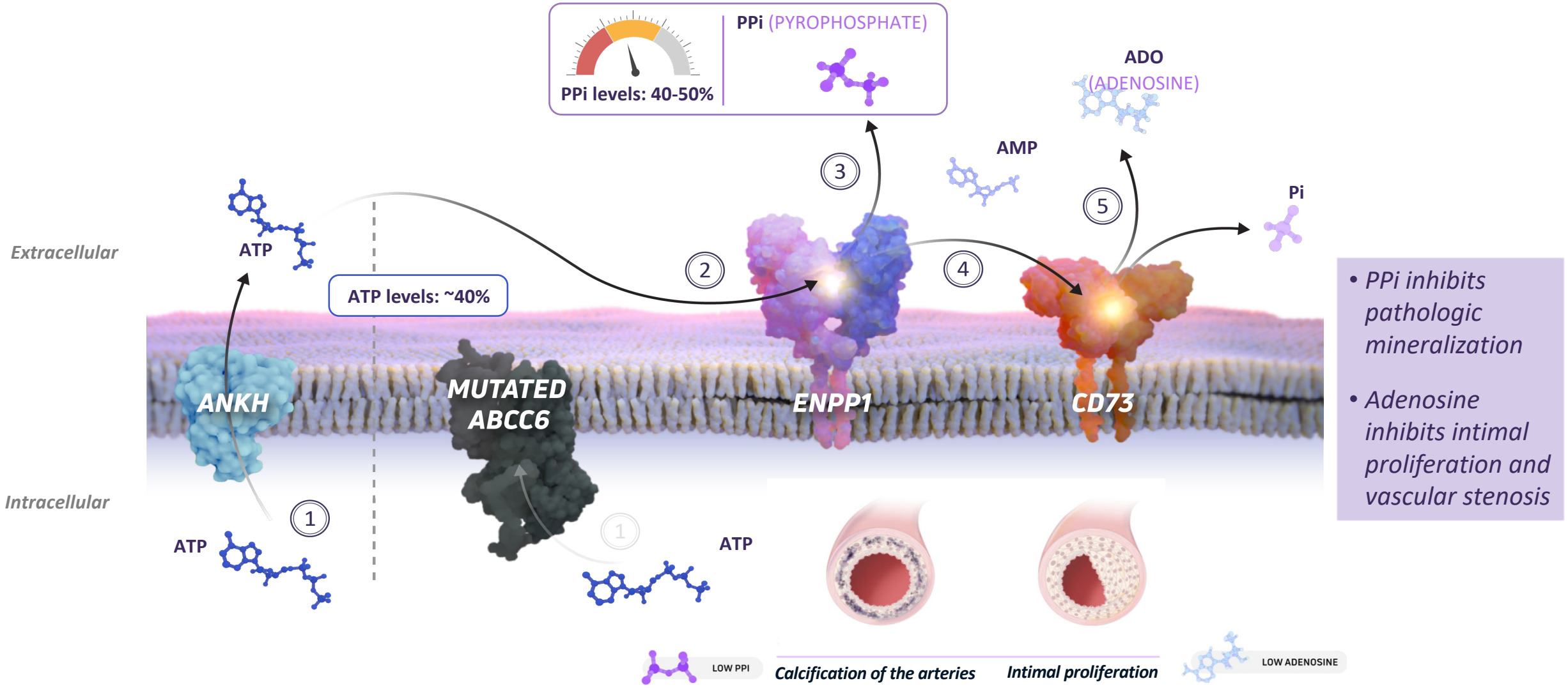
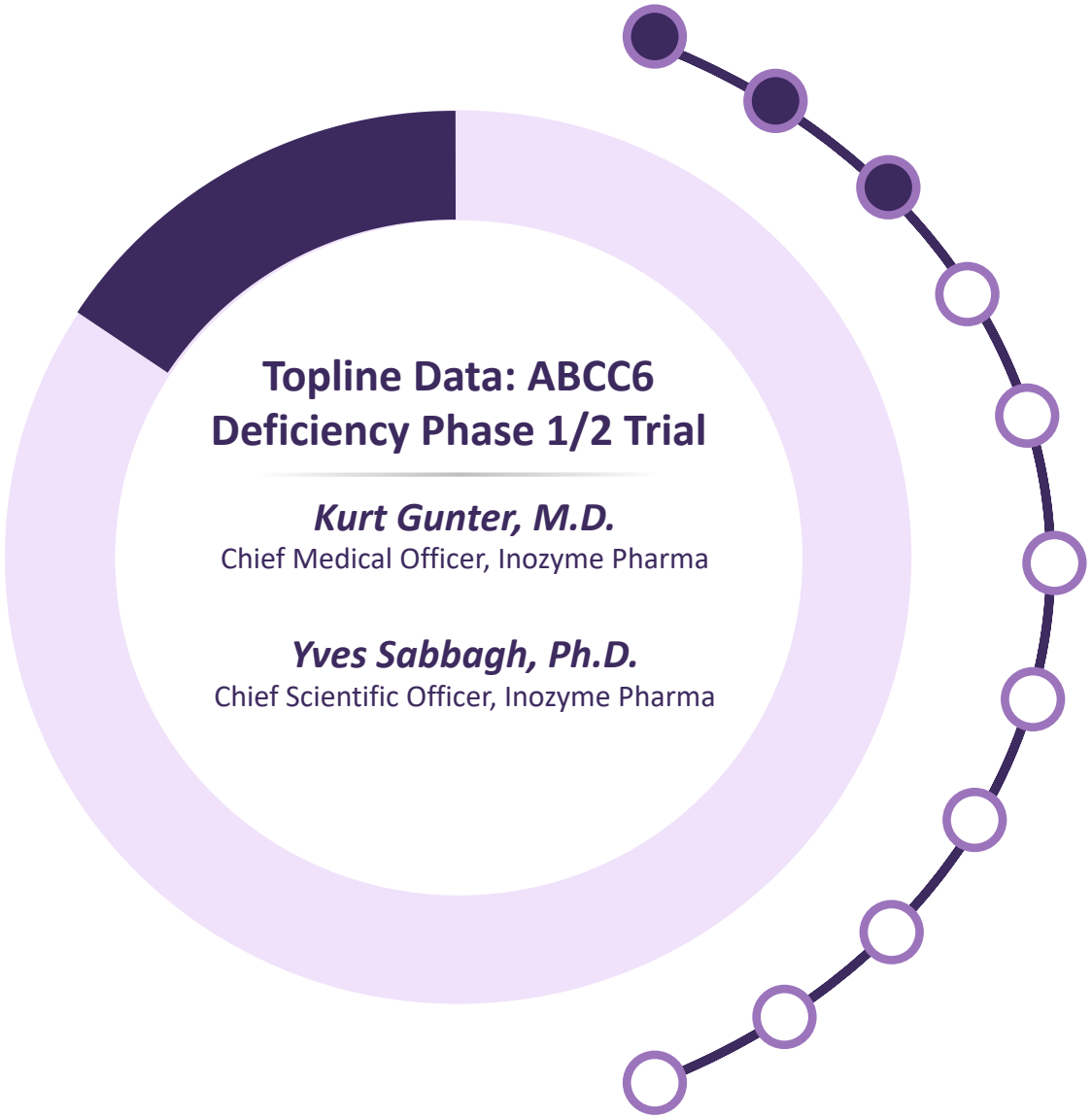
Mutations in the *ABCC6* gene leads to reduced ATP levels, resulting in low levels of PPi and adenosine



- *PPi inhibits pathologic mineralization*
- *Adenosine inhibits intimal proliferation and vascular stenosis*

Event agenda



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Adult ABCC6 Deficiency (PXE) Phase 1/2 trial

A Phase 1/2, open-label, multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of INZ-701 followed by an open-label long-term extension period in adults with ABCC6 Deficiency

Study Population:
Adults

Eligibility Criteria:

- Age 18-69 years
- Confirmed clinical and genetic diagnosis

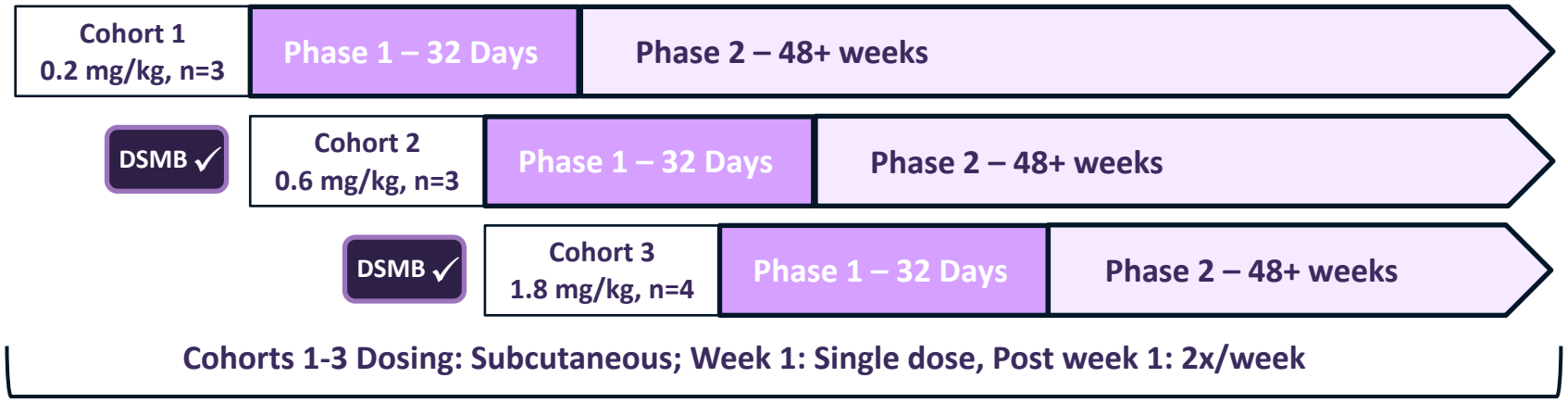
Primary Goals

- **Safety** and **tolerability**
- **Immunogenicity**
- **Pharmacokinetic properties**
- **Pharmacodynamics (PPi)**

Secondary Goal

Evaluate potential endpoints for pivotal study

Study Design:



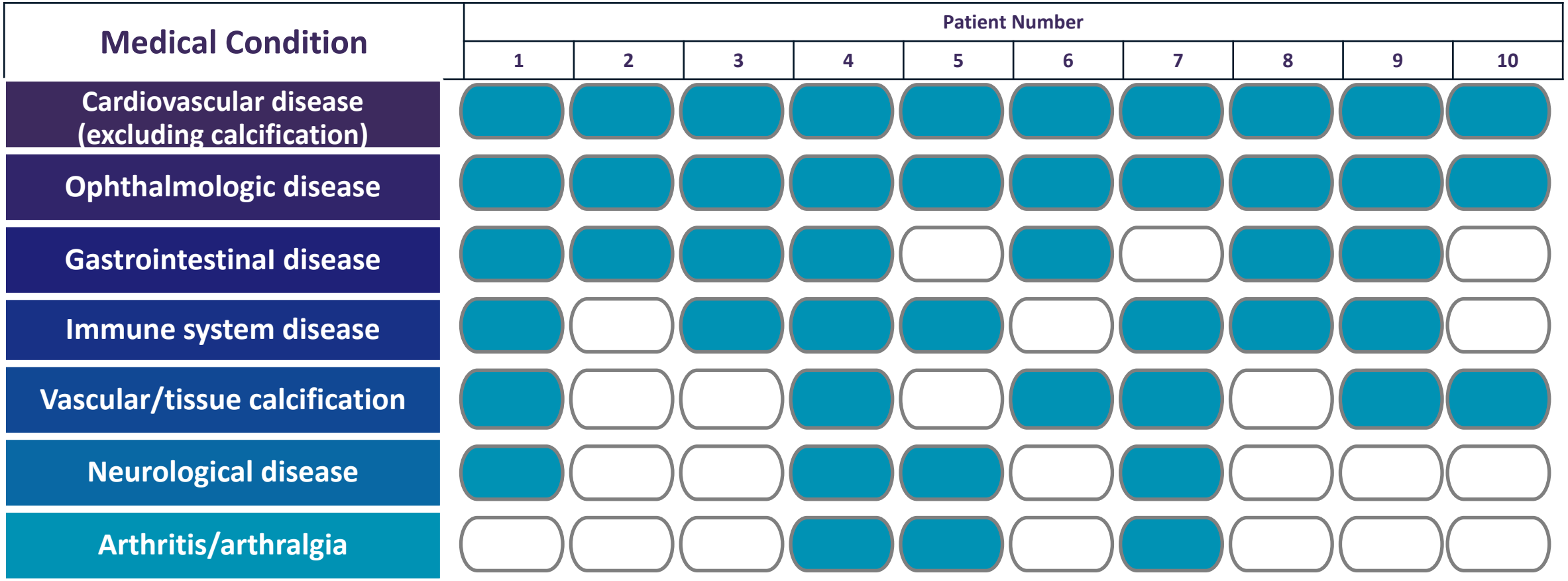
DSMB = Data Safety Monitoring Board. clinicaltrials.gov: NCT04686175

Patient demographics

Parameter	Statistic	INZ-701 Dose Cohort		
		0.2 mg/kg (n=3)	0.6 mg/kg (n=3)	1.8 mg/kg (n=4)
Age	Median	40	63	49
	Range	29-56	52-67	48-55
Gender	Male (n=4)	2	0	2
	Female (n=6)	1	3	2
Race	White (n=10)	3	3	4

Data cut – 10 Jan 2024

Adults enrolled had significant disease burden



Cardiovascular disease: abnormal carotid intima-media thickness (cIMT), aneurysm, arrhythmia, cardiac murmur, carotid arteriopathy, carotid plaque, claudication, hypertension, myocardial infarction, peripheral vascular disease, vascular malformation

Ophthalmologic disease: angioid streaks, blindness, cataract, choroidal neovascularization, chorioretinal atrophy, eyelid ptosis, macular degeneration, optic disc drusen, retinal degeneration, retinal hemorrhage, retinopathy, visual field defect, vitreous detachment

Gastrointestinal disease: arterial-venous malformation, constipation, gastric antral vascular ectasia, hemorrhage, inguinal hernia, irritable bowel syndrome, oromaxillary fistula, reflux, umbilical hernia

Neurological disease: chronic headache, migraine, neuralgia

Immune system disease: drug hypersensitivity, food allergy, seasonal atopy

Data cut – 10 Jan 2024

INZ-701 exhibited a favorable safety profile

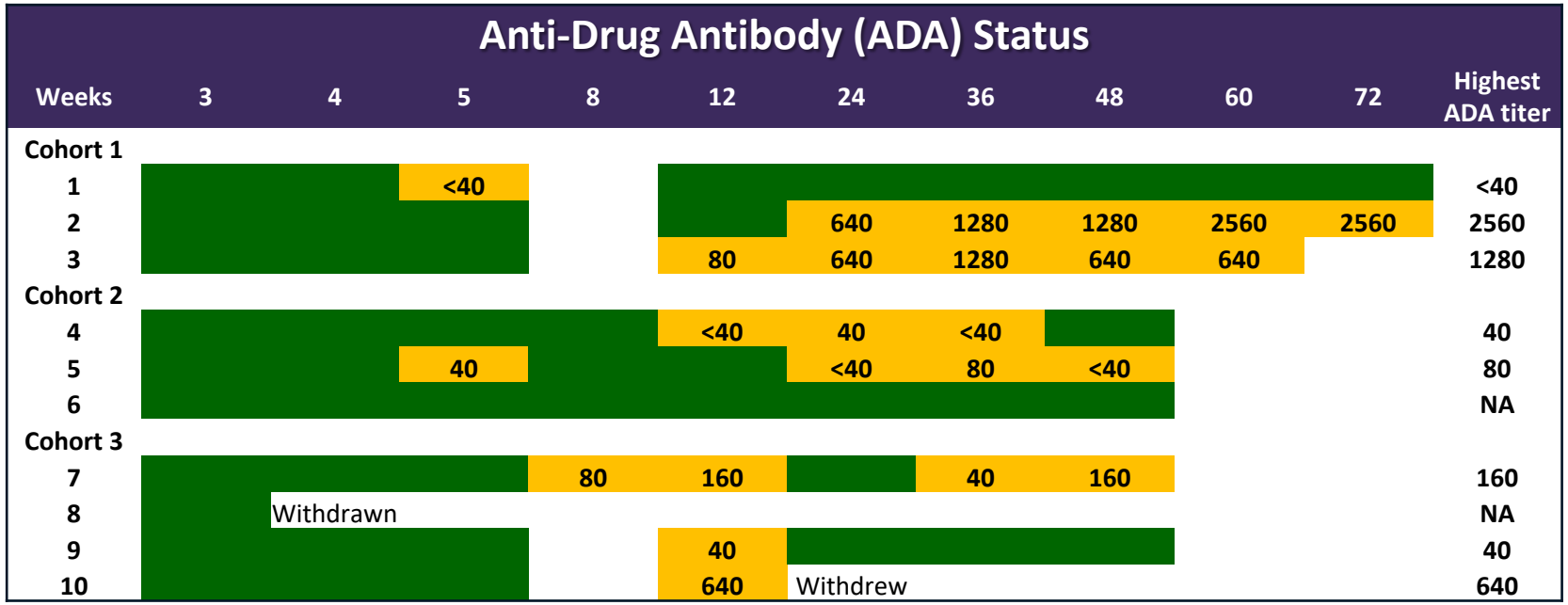
Events	INZ-701 dose cohort – No. of patients with at least one event			All patients (n=10)
	0.2 mg/kg biweekly n=3	0.6 mg/kg biweekly n=3	1.8 mg/kg biweekly n=4	
Adverse Event	3	3	4	10
Adverse Event Related to INZ-701	1	3	3	7
Serious Adverse Event	0	0	0	0

- **All adverse events were mild or moderate in severity**
  - 7/10 patients experienced mild to moderate adverse events related to INZ-701
    - Injection site reactions occurred in 7/10 patients and were all mild
    - Others included fatigue, erythema, night sweats and urticaria
- **No serious or severe (> grade 2) adverse events**
- **1 adverse event led to discontinuation of INZ-701 by 1 patient during Phase 1**
  - Moderate urticaria in one patient in 1.8 mg/kg cohort
- **1 patient from 1.8 mg/kg cohort withdrew from the study during Phase 2; not related to an adverse event**
- **8 patients remain on treatment and 7 continue with self-administration (1 patient receiving home injections by a nursing service)**
- **Time on study range: 45-631+ days; 12+ patient-years**

Data cut – 10 Jan 2024

Favorable immunogenicity profile observed

Low/moderate, non-neutralizing ADA titers detected; Transient in 3 of 8 patients



ADA titers for other drugs were observed in previously conducted trials by other companies

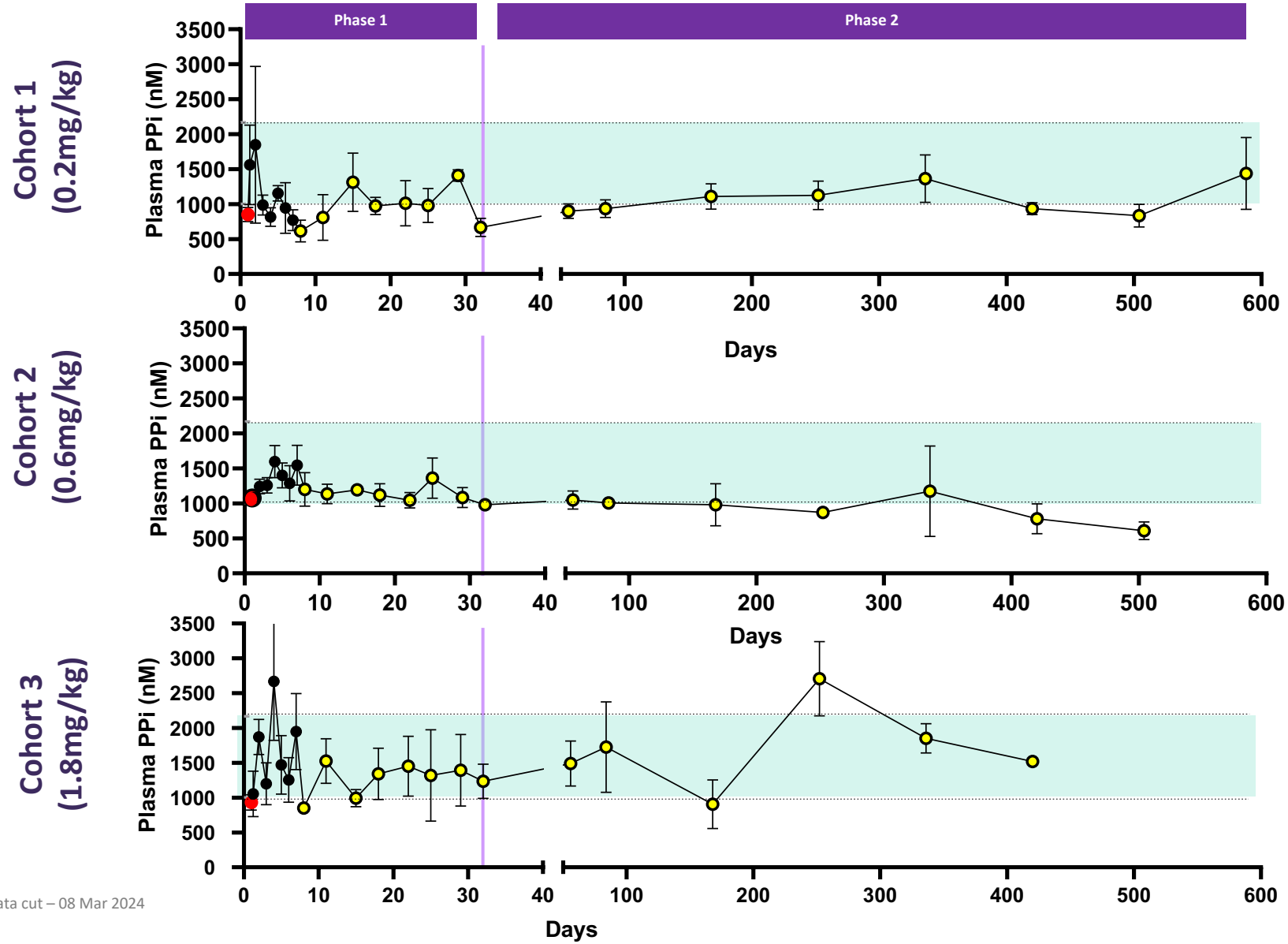
STRENSIQ® ADA titers: 2,048[1]; patients with ADA: 89%[4]

ALDURAZYME® ADA titers: 31,972[2]; patients with ADA: 97%[4]

LUMIZYME® ADA titers: >51,200[3]; patients with ADA: 89%[4]

Data cut – 10 Jan 2024; ***Sources:*** *1. Hofmann et al, JCEM 2019; 2. Xue et al, Mol Genet Metab 2016; 3.Kazi et al, JCI 2017; 4. Product USPI 23*

Rapid and sustained increase in PPi observed at 1.8 mg/kg dose through 420+ days



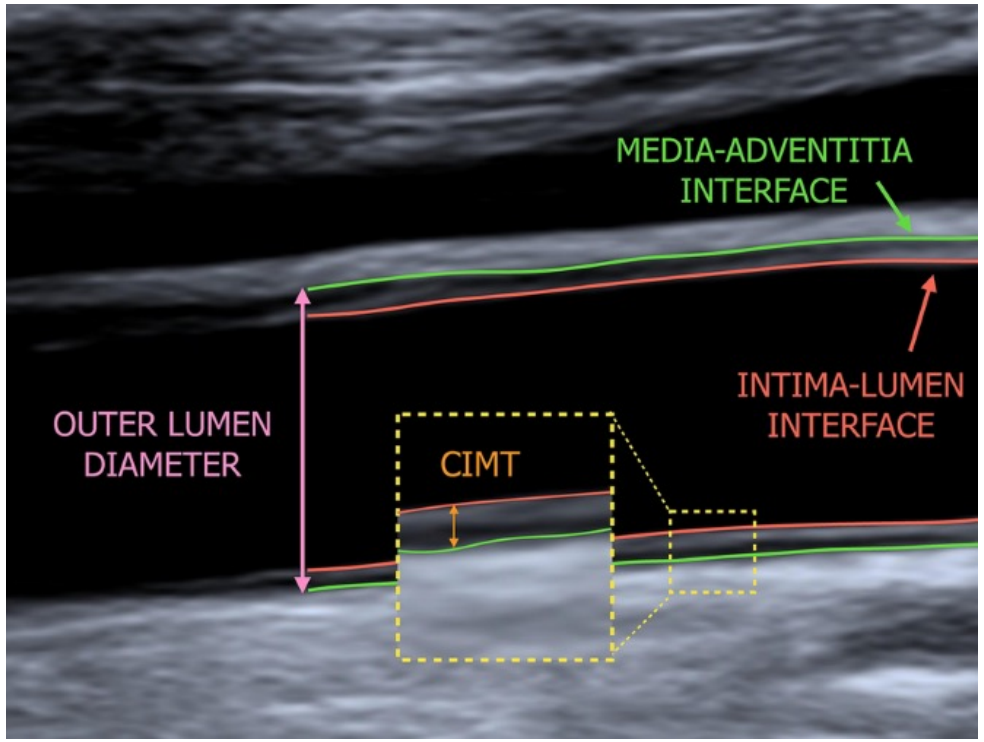
- Rapid increase observed after the 1st dose
- PPi levels reached the healthy volunteer range after the 1st dose

Baseline PPi (pre-dose) + 1st INZ-701 dose
PPi measurement (post-dose)
PPi measurement (pre-dose)
Healthy subject PPi levels; n=10
Data presented as mean ± SEM

Data cut – 08 Mar 2024

cIMT (carotid intima-media thickness) is a predictive marker for cardiovascular disease and stroke

Carotid ultrasound measuring cIMT



General Population Meta-analysis [1]

International collaboration
119 RCTs
100,667 participants
12,038 incident CVD events

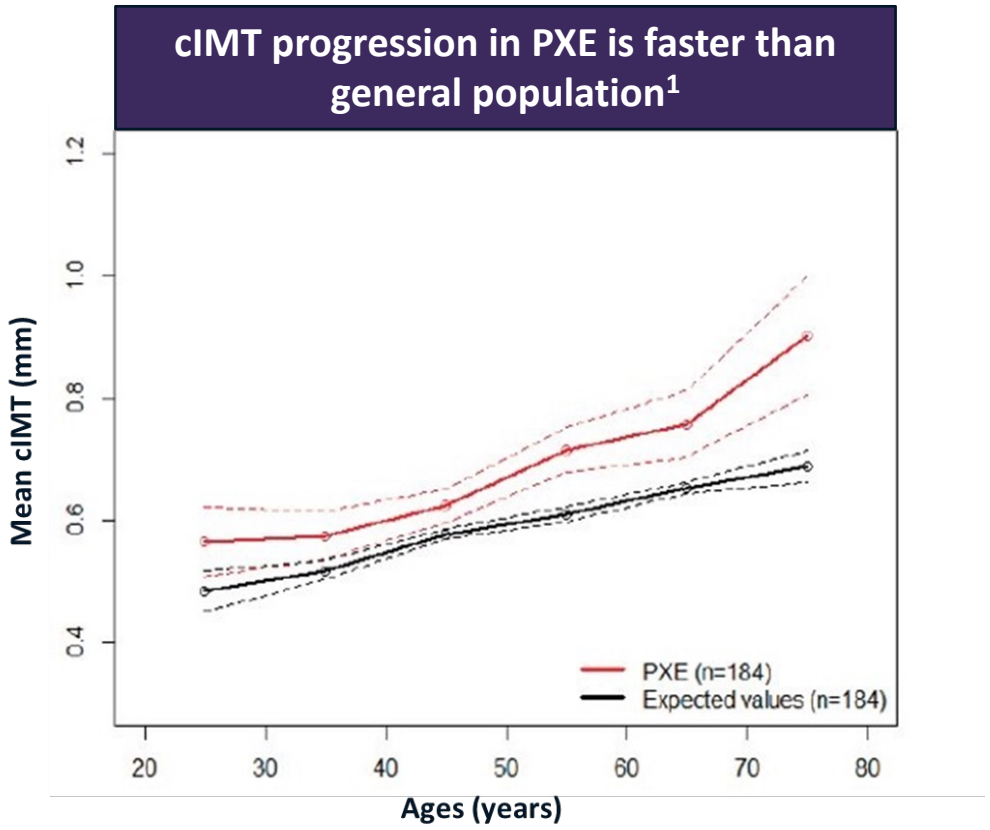
Mean age: 62 years

42% female

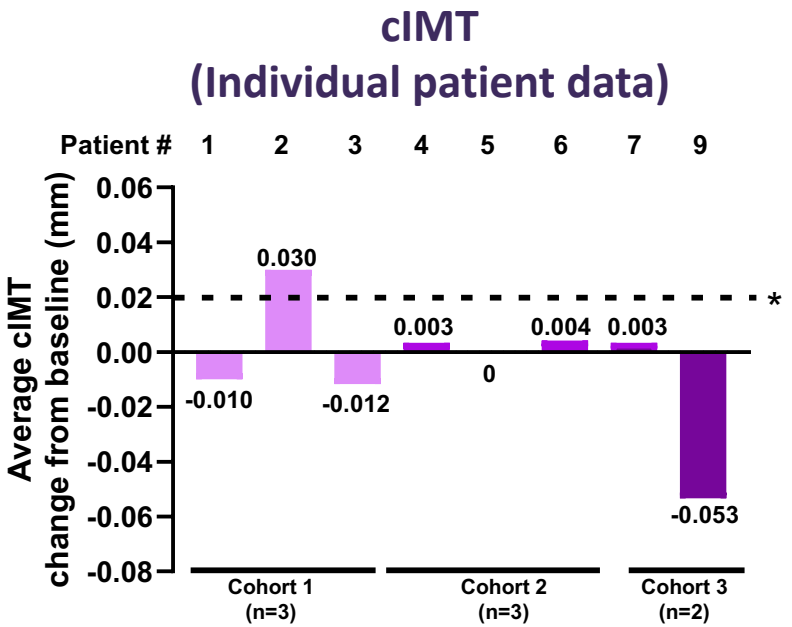
- Key finding: cIMT progression increases risk of cardiovascular disease (CVD) and stroke
- Relative risk for CVD (MI, stroke, revascularization or CV mortality): 0.91 per each 0.01 mm/year reduction of cIMT progression (p< 0.001)
- Relative risk for stroke: 0.92 per each 0.01 mm/year reduction of cIMT progression (p=0.039)

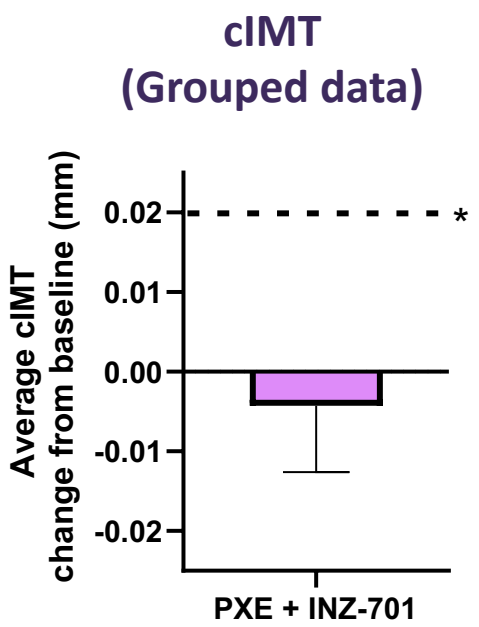
Source: *1. Willeit et al, Circulation, 2020; MI – myocardial infarction*

cIMT decreased on average with INZ-701 treatment



Dashed lines represent 95% confidence intervals





*** Change observed in untreated PXE patients [2]**

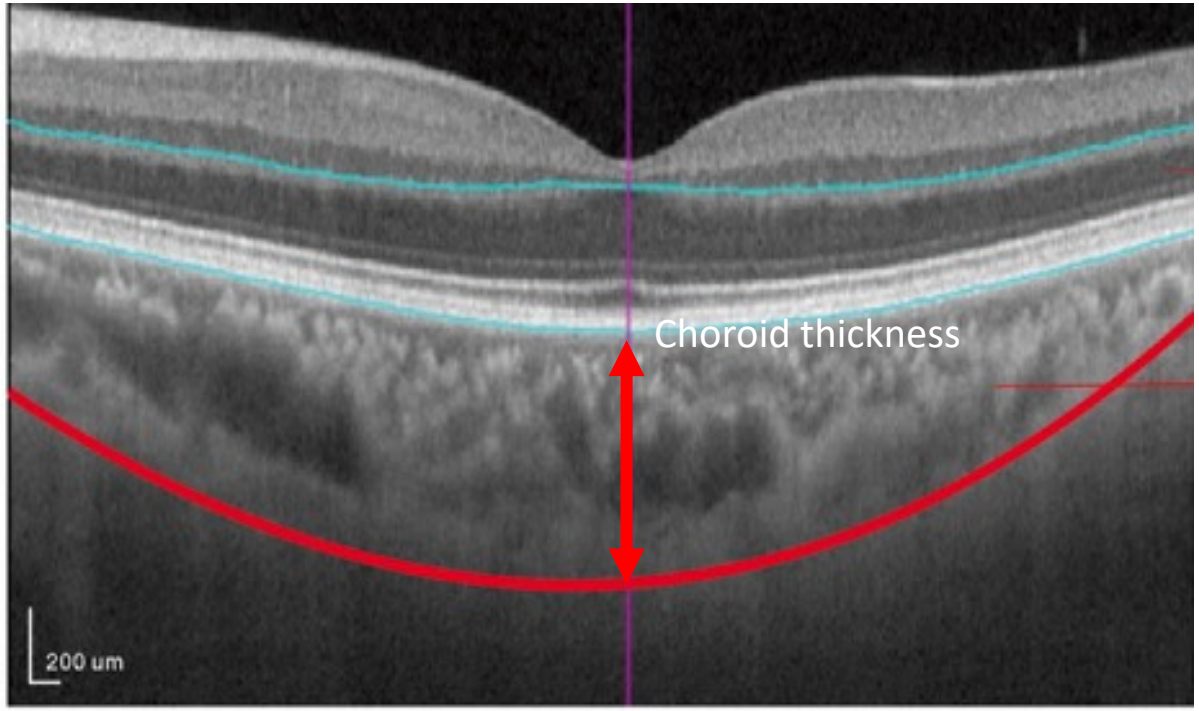
- 7 of 8 evaluable patients had reductions or stabilization in cIMT
- Greatest individual mean increase in cIMT was 0.03 mm
- In the UMC Utrecht TEMP study of etidronate vs. placebo in PXE patients, placebo patients showed a mean cIMT increase of 0.02 mm/year[2]

Data cut – 10 Jan 2024; Data presented as mean ± SEM; ***Sources:*** *1. Kranenburg, UMC Repository (Dissertation), 2018; 2. Kranenburg et al. JACC, 2018*

Choroidal defects are associated with neovascularization and degenerative changes in eye

Optical coherence tomography (OCT) offers a non-invasive, highly quantifiable view of retinal pathology

Retinal cross section by OCT



Choroid biology

- Layer of tissue that is part of the middle layer of the wall of the eye, between the sclera and the retina
- Consists primarily of blood vessels which supply oxygen and nutrients to the retina

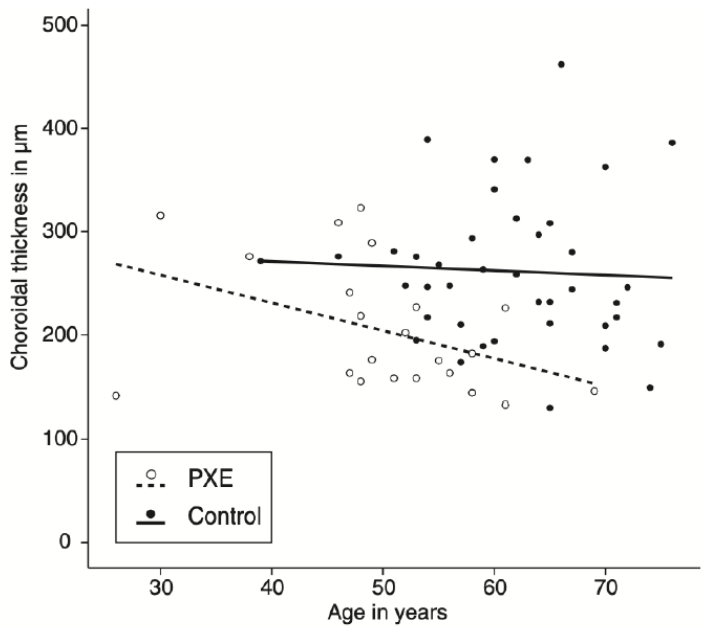
OCT

- Produces a cross sectional image of the retina
- Used to measure choroid thickness and other retinal structures
- Choroid thickness is measured using a standardized protocol by 2 different readers and results averaged

Sources: *Kwapong et al, Brain Behav 2021*

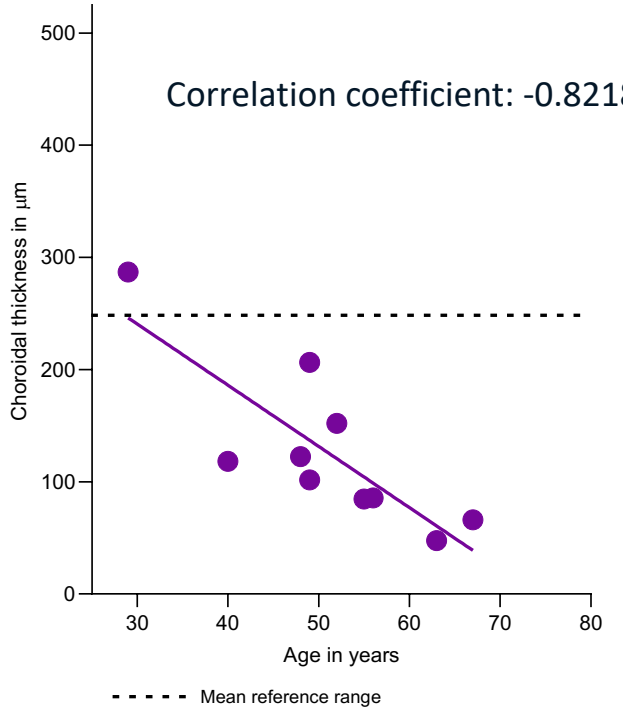
Choroidal thickness is low in adults with ABCC6 Deficiency and decreases with age

Choroidal thickness is lower in ABCC6 Deficient (PXE) patients compared to controls and decreased with age



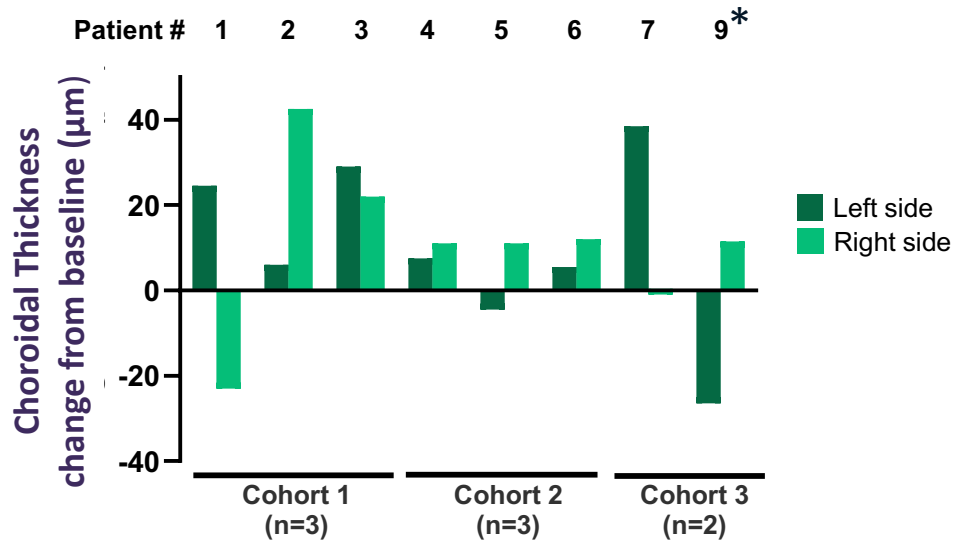
***Source**: Risseeuw et al, Acta Ophth, 2020*

Baseline data from Inozyme trial showed choroidal thickness decreased with age



Choroidal thickness increased with INZ-701 treatment

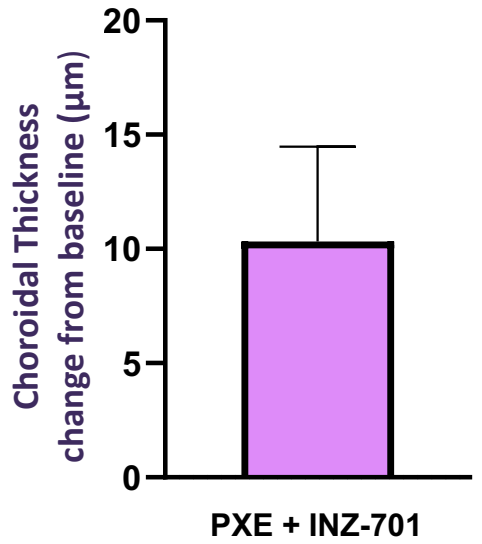
Choroidal thickness (Individual eye data)



- 12/16 eyes in evaluable patients had increases in choroidal thickness
- No effect of anti-VEGF treatment

**Patient experienced grade 2 vitreous hemorrhage on study; not considered drug-related*

Choroidal thickness (Grouped data)



- 7/8 evaluable patients had increases in choroidal thickness
- No effect of anti-VEGF treatment

Data presented as mean ± SEM

Visual Function Questionnaire (VFQ-25)

VFQ-25	• Developed by US National Eye Institute • Designed for patients with chronic eye disease • VFQ-25 global score in an unselected population without eye disease was approximately 91[1]

Consists of 25 vision-targeted questions which generate subscores

- Difficulty with near vision activities
- Difficulty with distance vision activities
- Limitations to social function due to vision
- Role limitations due to vision
- Dependency on others due to vision
- Mental health symptoms due to vision
- Driving difficulties
- Limitations with peripheral vision
- Limitations with color vision
- Ocular pain
- General health

Subscores are averaged to generate a composite score

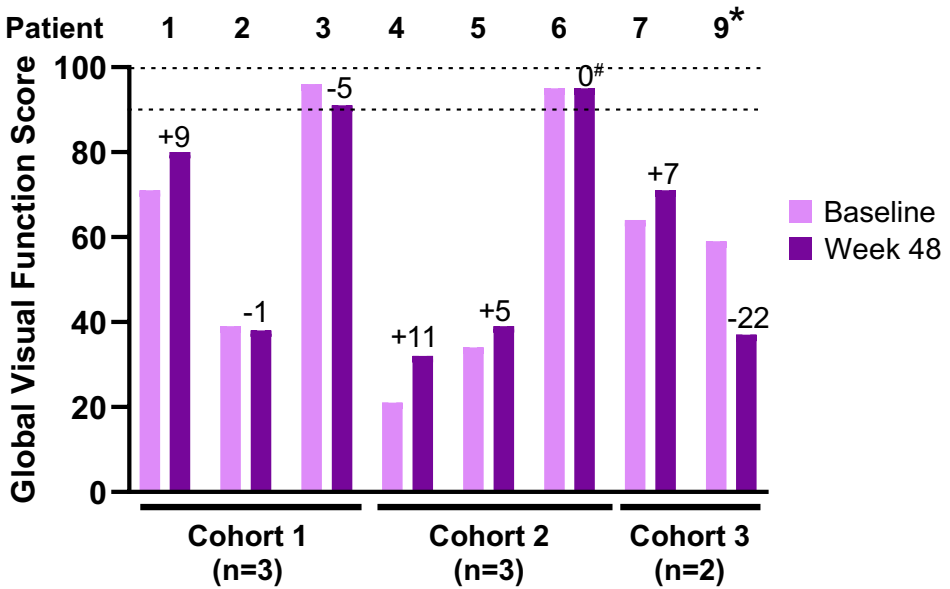
VFQ-25 validated in the following chronic diseases

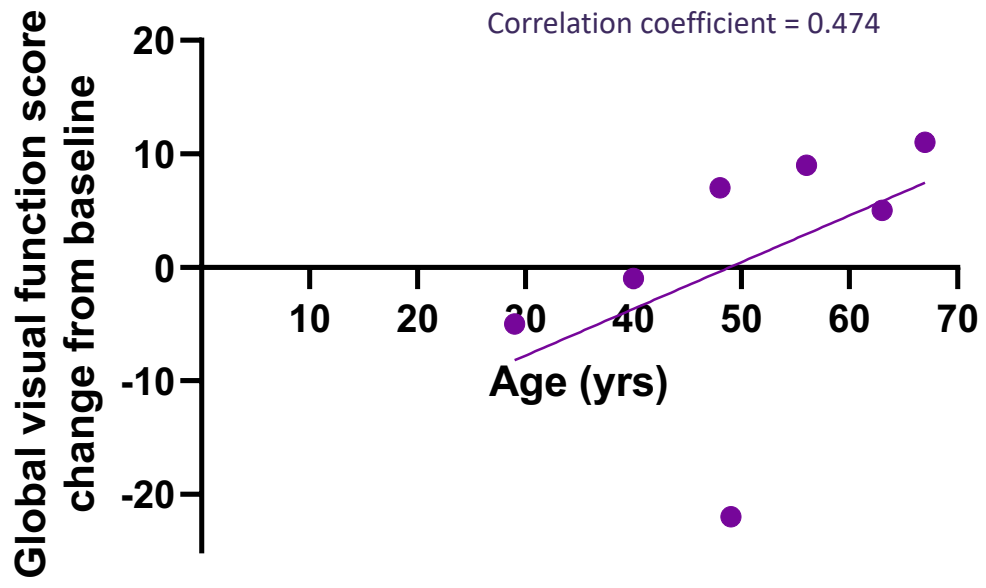
- Age related macular degeneration
- Cataracts
- Diabetic macular edema
- Diabetic retinopathy
- Multiple sclerosis
- Ocular hypertension/glaucoma
- Stargardt disease

Source : 1. Hirneiss et al, Graefes Arch Clin Exp Ophthalmol, 2010

VFQ-25 scores indicated preservation and improvement of visual function over 48 weeks

4 of 6 evaluable patients with VFQ-25 scores below normal at baseline improved over 48 weeks





 # Data available up to week 24 only

**Patient experienced grade 2 vitreous hemorrhage on study; not considered drug-related*

Improvement in visual function was greater in older patients

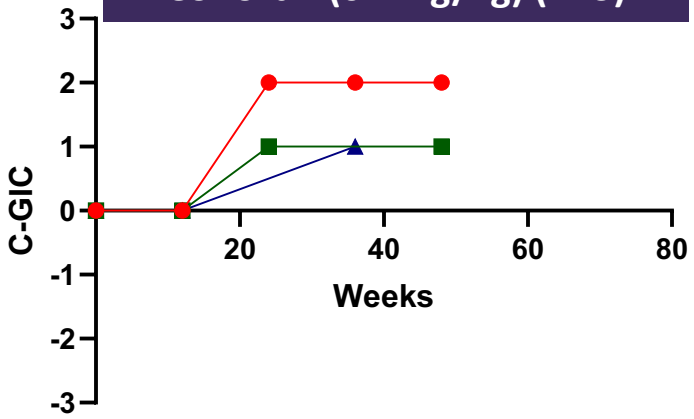
- 4/7 improved on both choroidal thickness and VFQ-25
- 6/7 improved on choroidal thickness
- 4/7 improved on VFQ-25

Data cut – 10 Jan 2024; ***Source :*** *1. Hirneiss et al, Graefes Arch Clin Exp Ophthalmol, 2010*

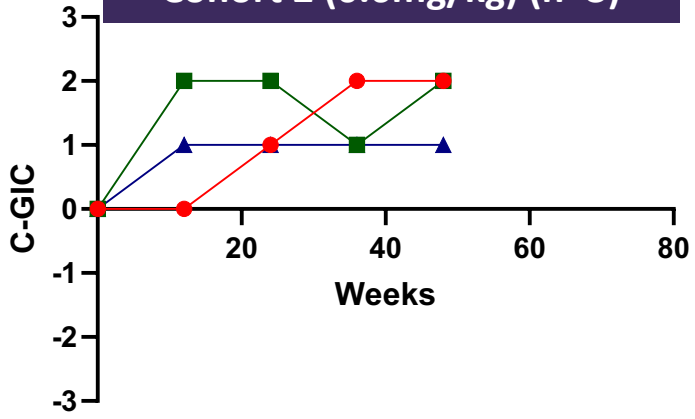
Global Impression of Change Scale: Concordant improvement in C-GIC and P-GIC in all three dose cohorts

Clinician's Global Impression

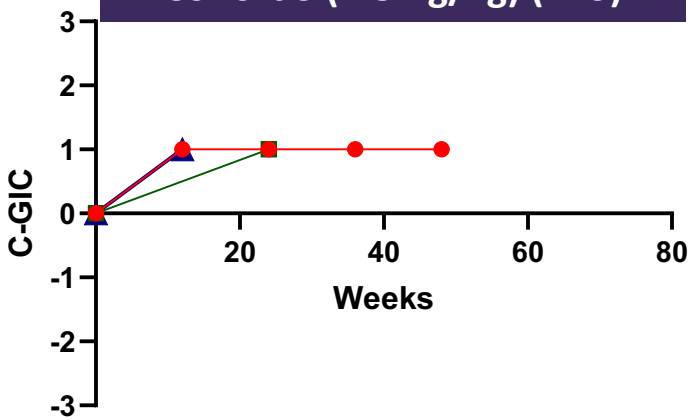
Cohort 1 (0.2mg/kg) (n=3)



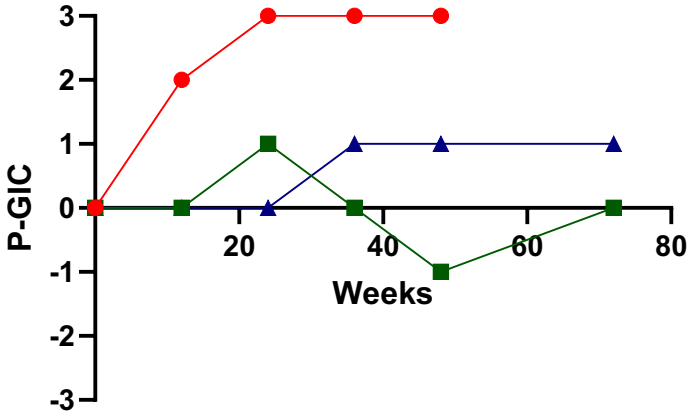
Cohort 2 (0.6mg/kg) (n=3)

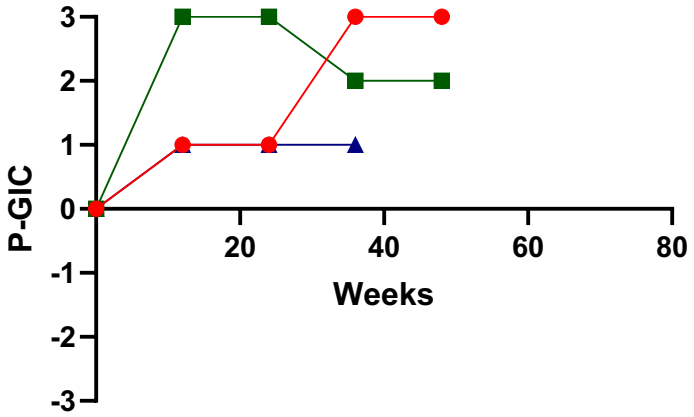


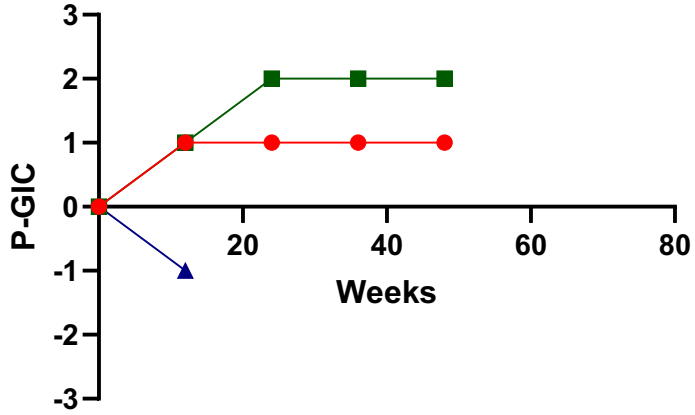
Cohort 3 (1.8mg/kg) (n=3)

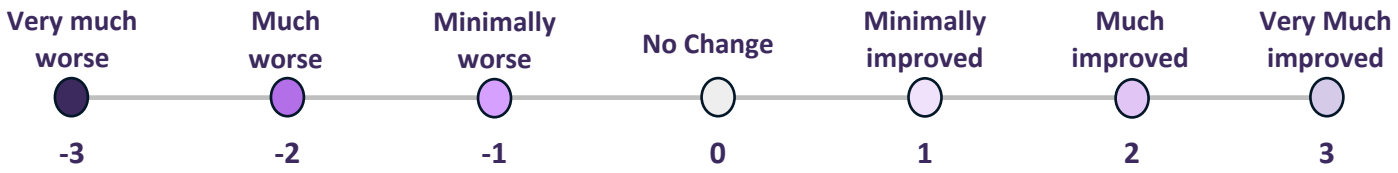


Patient's Global Impression









Data cut – 10 Jan 2024
Colors represent individual patients in respective cohorts

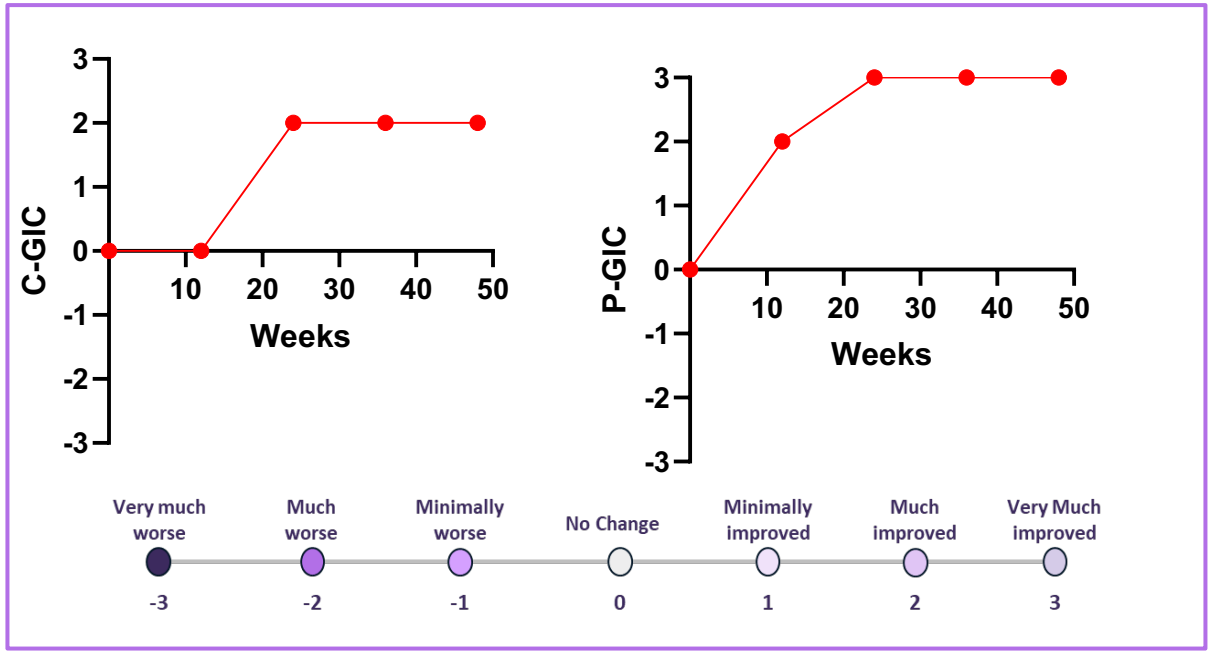
Case Study: Concordant changes across multiple domains

Clinical findings

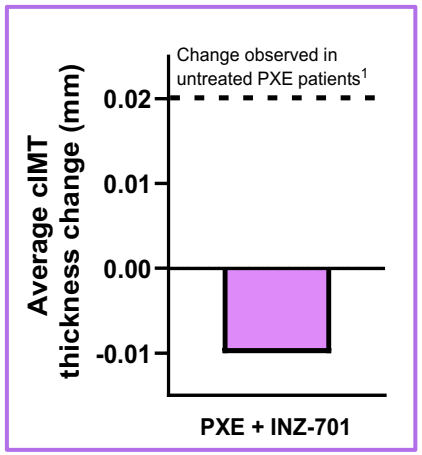
- PPi Baseline: 804 nM; Mean PPi Day 11- 504: 1117 nM (mean increase 39% from baseline)
- P-GIC and C-GIC scores of much to very much improved
- cIMT decreased a mean of 0.01 mm from baseline at week 48
- Average choroid thickness increased 0.75 µm at week 48
- Improvement on PROMIS PRO: fatigue: 38 to 30 (wk 48); cognitive function: 55 to 63 (wk 12)
- VFQ-25 improved from 71 to 80 at week 48
- Stable arterial calcification over 48 weeks by low dose CT
- Nephrocalcinosis stable over 48 weeks (data not shown)

Data cut – 10 Jan 2024; **Source:** 1 *Kranenburg et al, JACC, 2018*

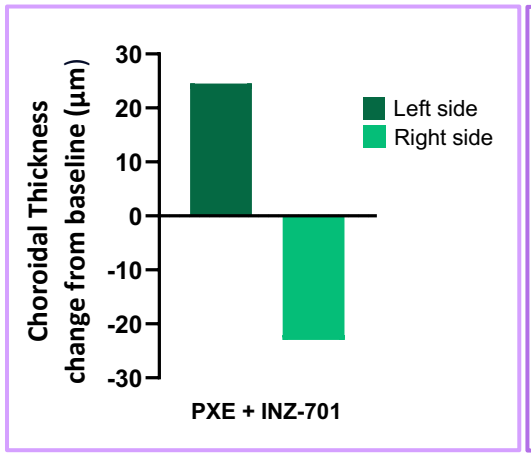
Clinician's and Patient's Global Impression of Change (C-GIC, P-GIC)



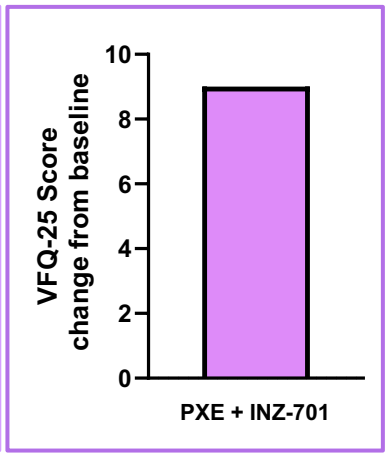
cIMT



Choroidal thickness



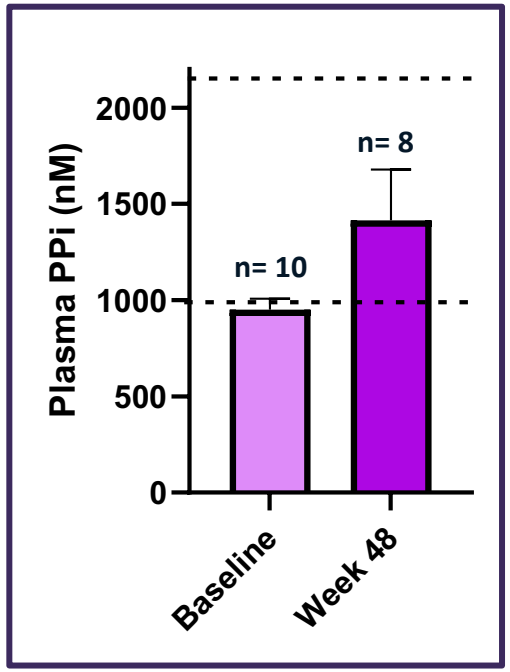
VFQ-25



INZ-701 showed benefit across multiple domains relevant for future pivotal trial

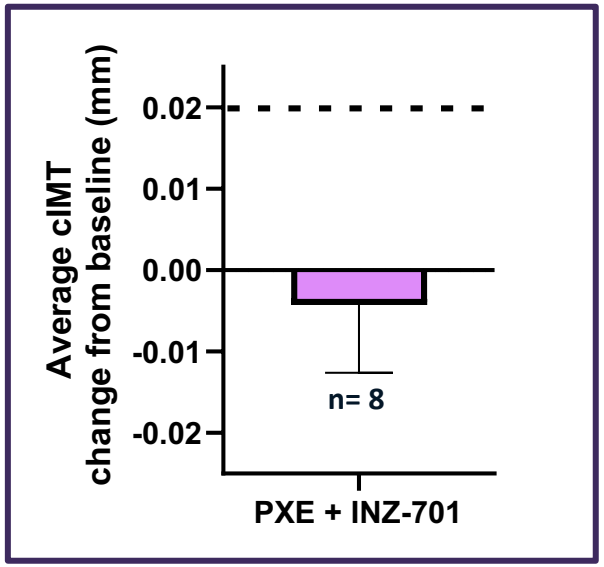
Combined cohort 1-3 data comparing baseline to week 48

PPi increased



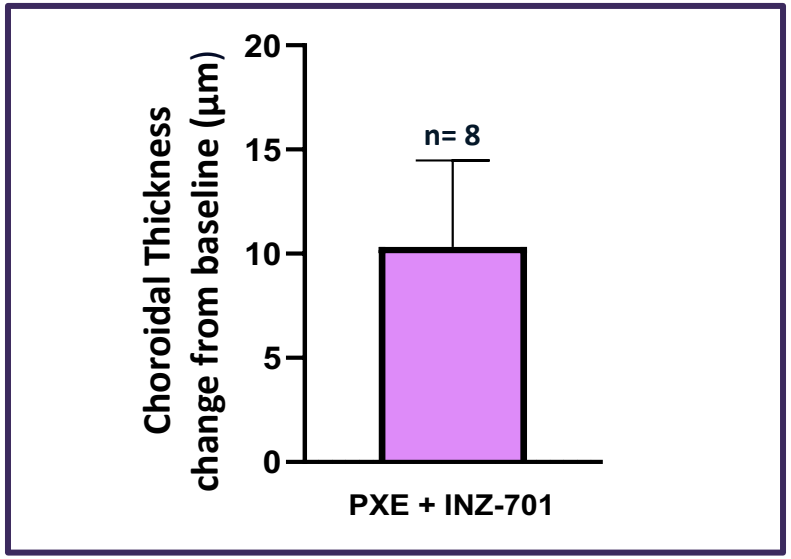
Normal range

cIMT decreased



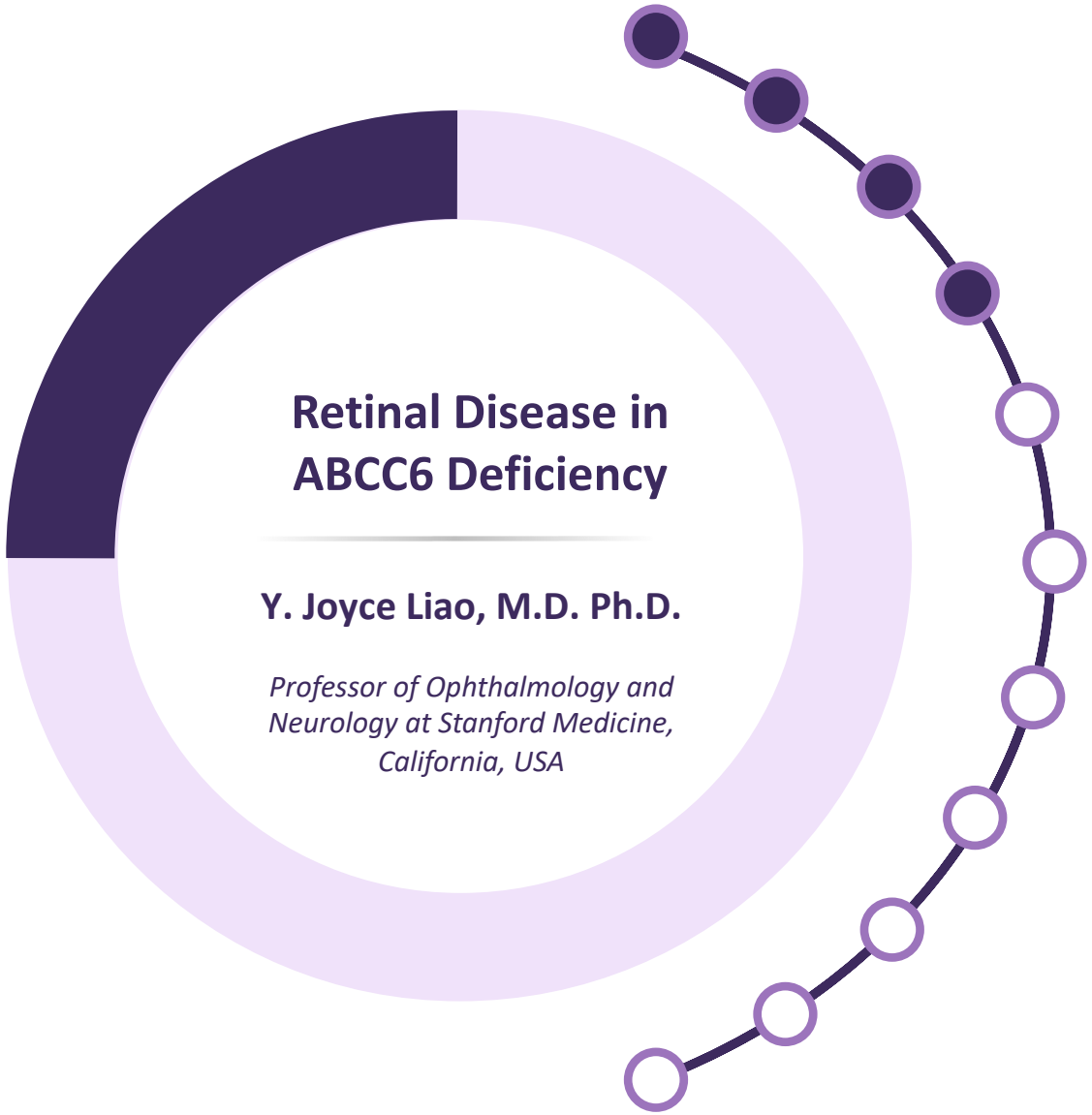
Mean annual cIMT change in TEMP study[1]

Choroidal thickness increased



Data cut – 10 Jan 2024; Data presented as mean ± SEM **Source:** 1. *Kranenburg et al, JACC, 2018*

Event agenda



Welcome

ABCC6 Deficiency: Disease Overview

Topline Data: ABCC6 Deficiency Phase 1/2 Trial

Retinal Disease in ABCC6 Deficiency

ABCC6 Pediatric Disease – A Critical Unmet Need

- Early-Onset ABCC6 Deficiency – Natural History Study
- Pediatric Stroke – Case Study
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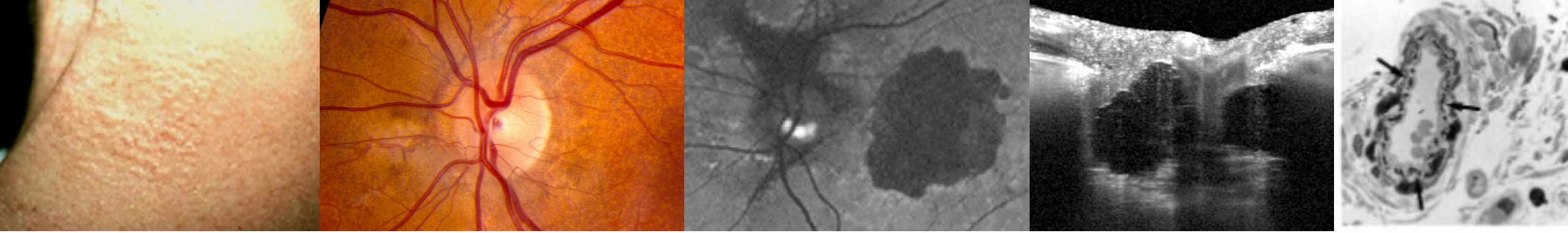
Topline Data: ENPP1 Deficiency Phase 1/2 Trial

Key Takeaways

Question and Answer



Pseudoxanthoma Elasticum (PXE): Ocular manifestations and vision loss

Joyce Liao, MD PhD

Stanford Medicine Professor of Ophthalmology and Professor of Neurology

Director of Neuro-Ophthalmology

Stanford University School of Medicine

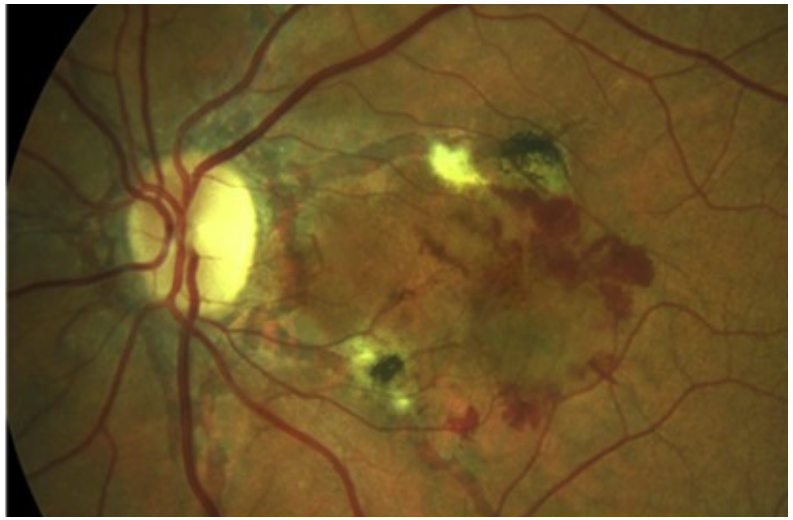
inozyme pharma

April 2024

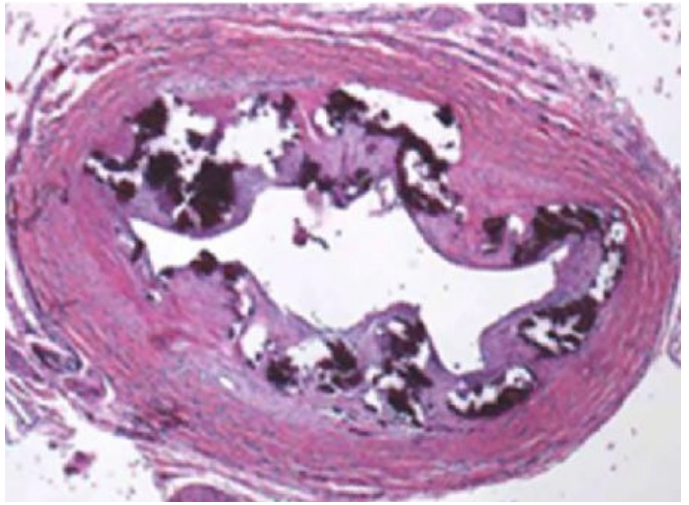
Pseudoxanthoma Elasticum (PXE)

- Multi-organ involvement, especially eye, blood vessels, and skin
- Skin most obviously involved early; ***vision loss impacts patients most***
- Disease progression:
  - Starts in early childhood (1st decade)
  - *Everyone progresses over time*
- Eye involvement in 100% of patients, leading to visual disability, blindness

Vision Loss

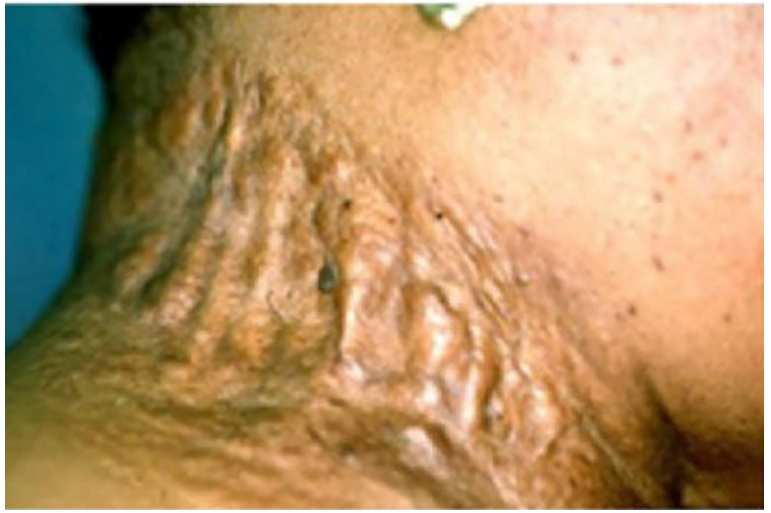


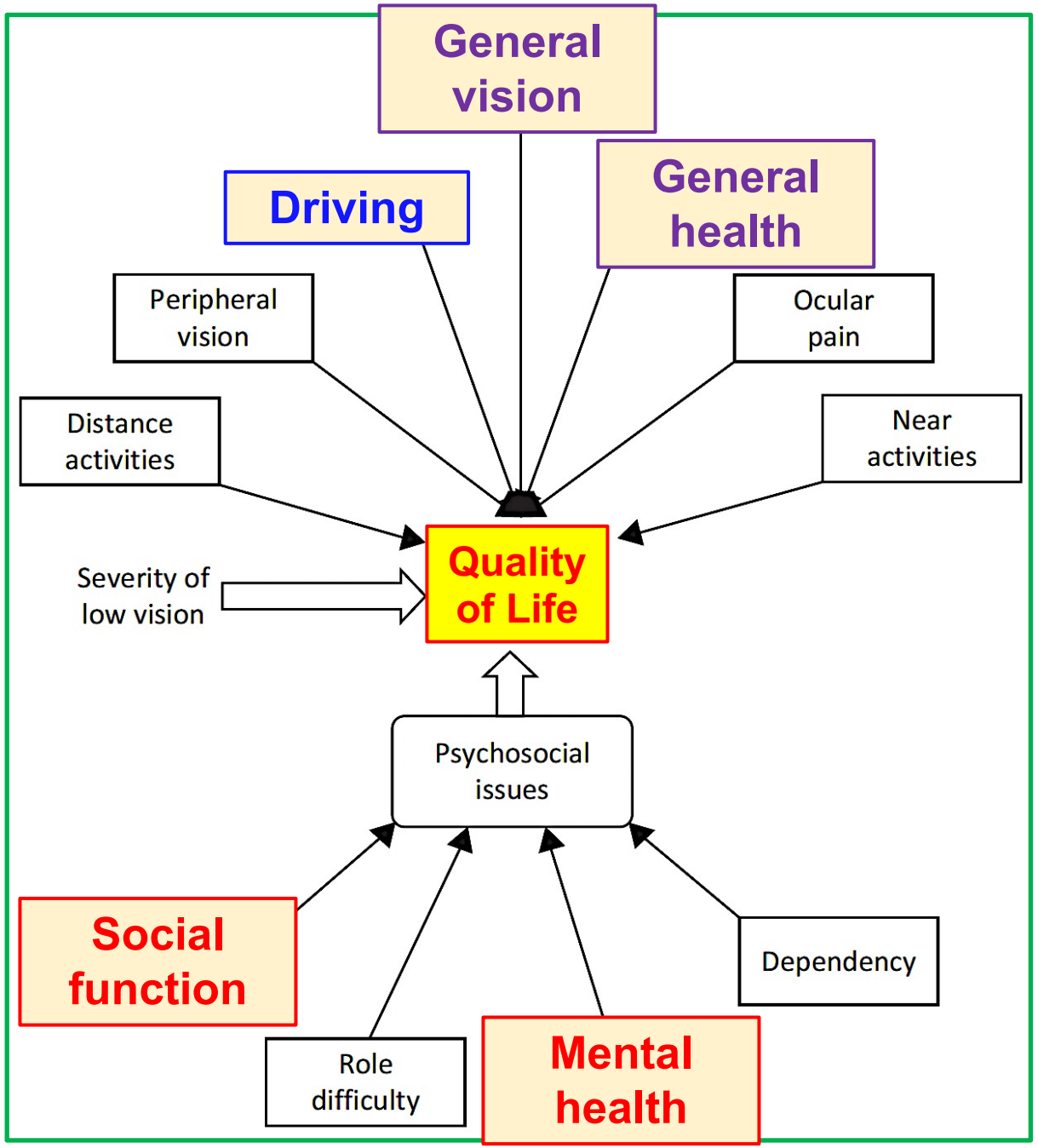
Vascular Complications



PMC6412714

Skin Abnormalities





Adamptey et al. https://doi. org/10.4102/aveh.v77i1.401

Severity of visual impairment and psychological impact are measured using NEI VFQ-25

https://www.spectrumeyecarenc.com/wp-content/uploads/2020/06/file-980x735.jpg

Devastating Impact of Visual Impairment in Children

- **In children, visual impairment is particularly devastating, and have significant impact beyond vision**
  - ↓ Education
  - ↓ Psycho-social well-being
  - ↓ Future potential and ↑ morbidity and mortality

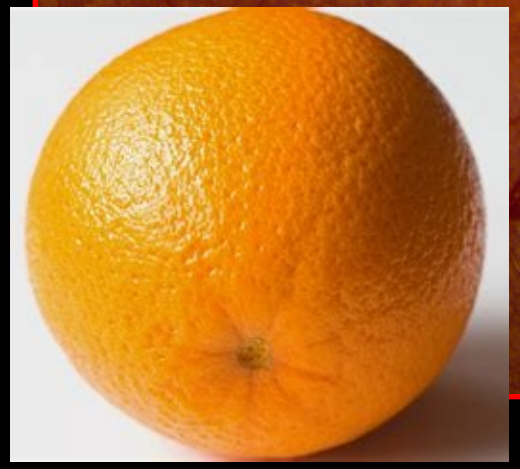
PMC8196425, PMC10946163, PMC10653485

Different eye findings in PXE

Stage 1: peau d'orange appearance of retina

PXE

Orange peel like appearance of the back of the eye due to calcium deposition

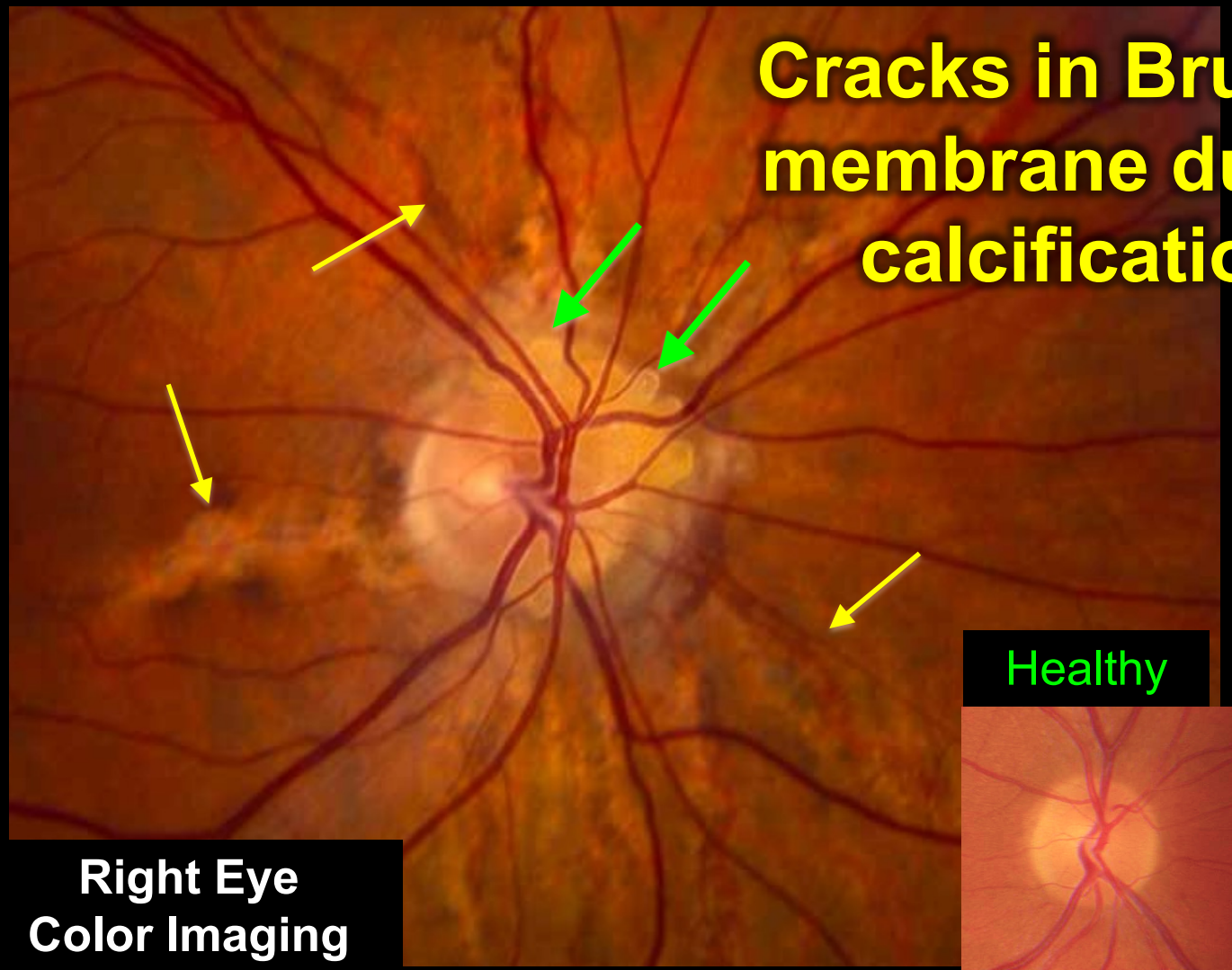


Healthy

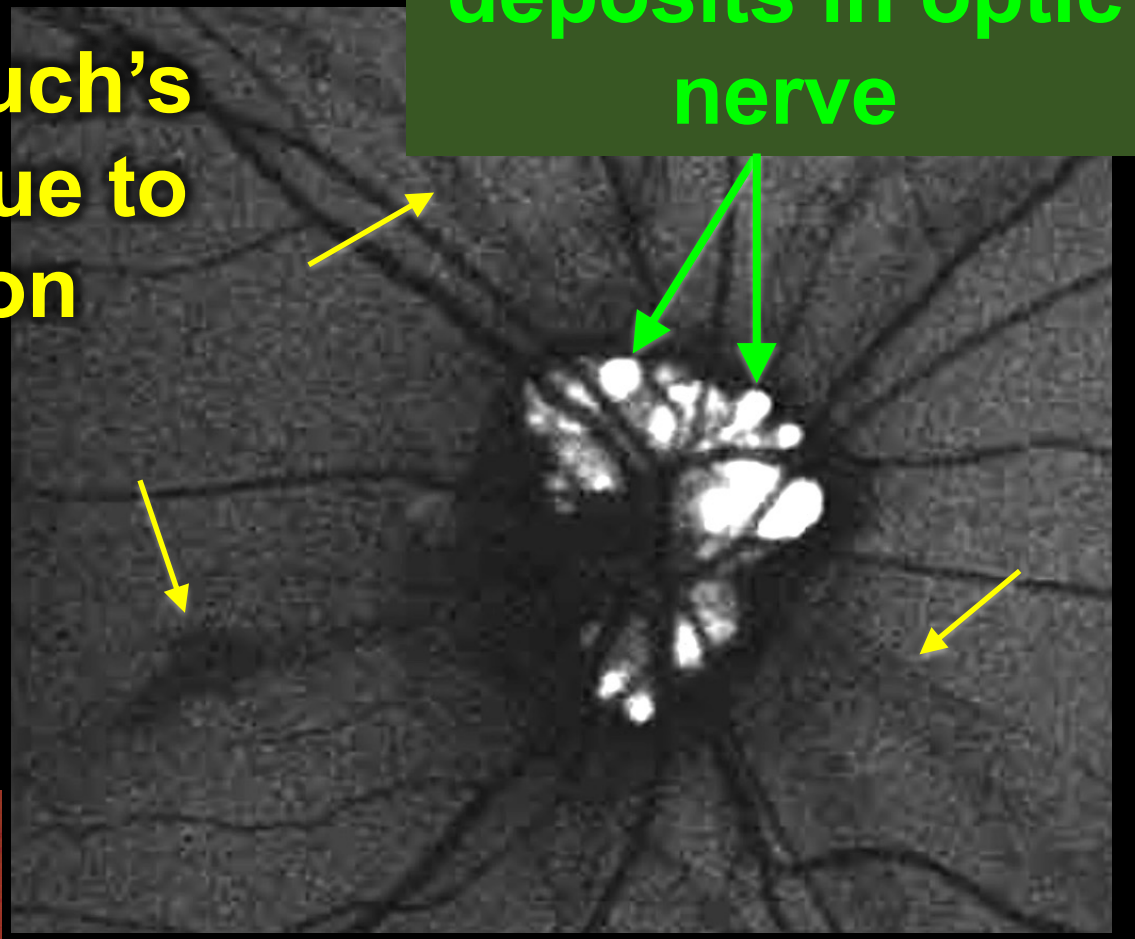
Fundus Color Imaging

http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/pxe.htm

Stage 2: Angioid Streaks



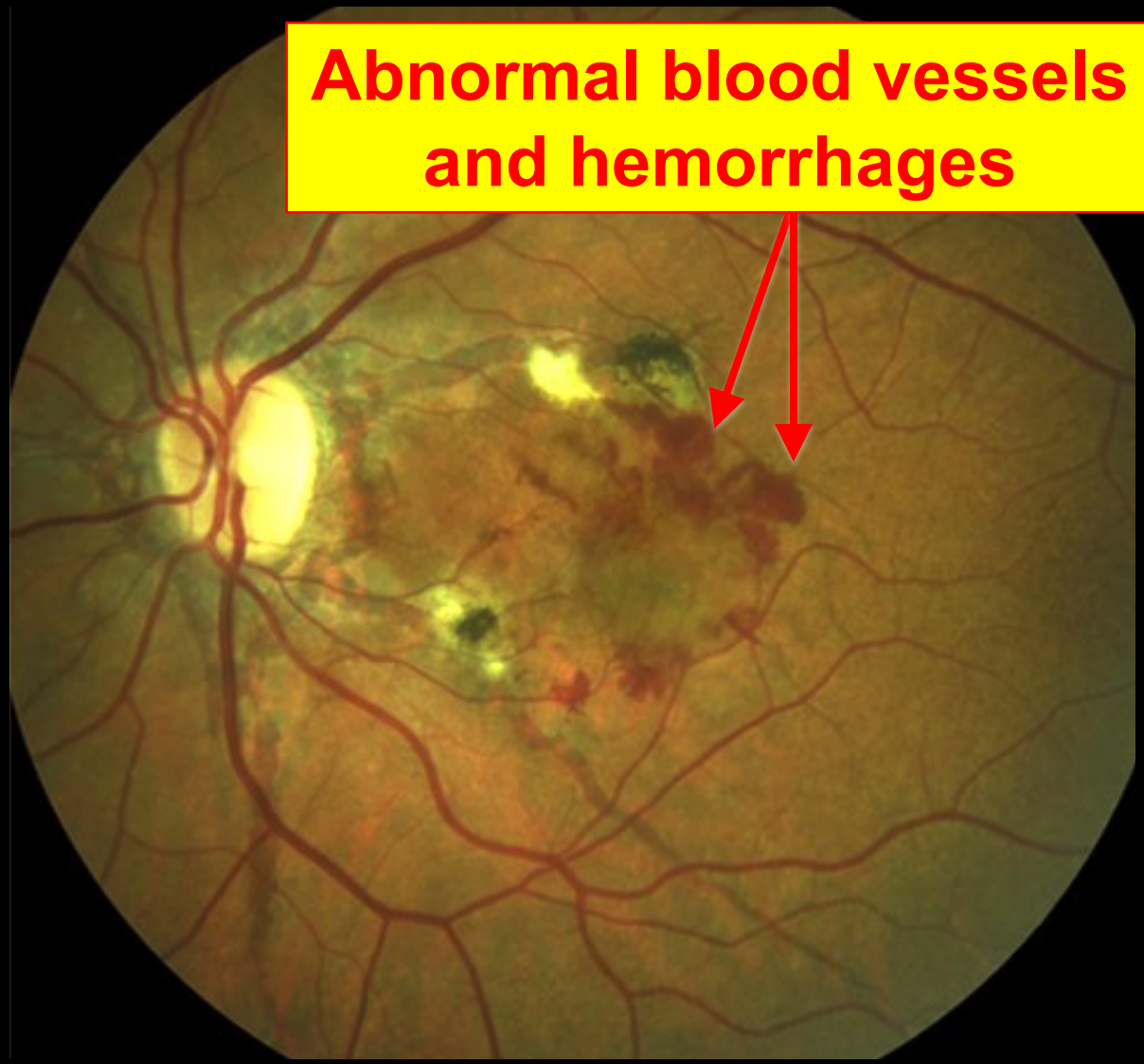
Right Eye
Color Imaging

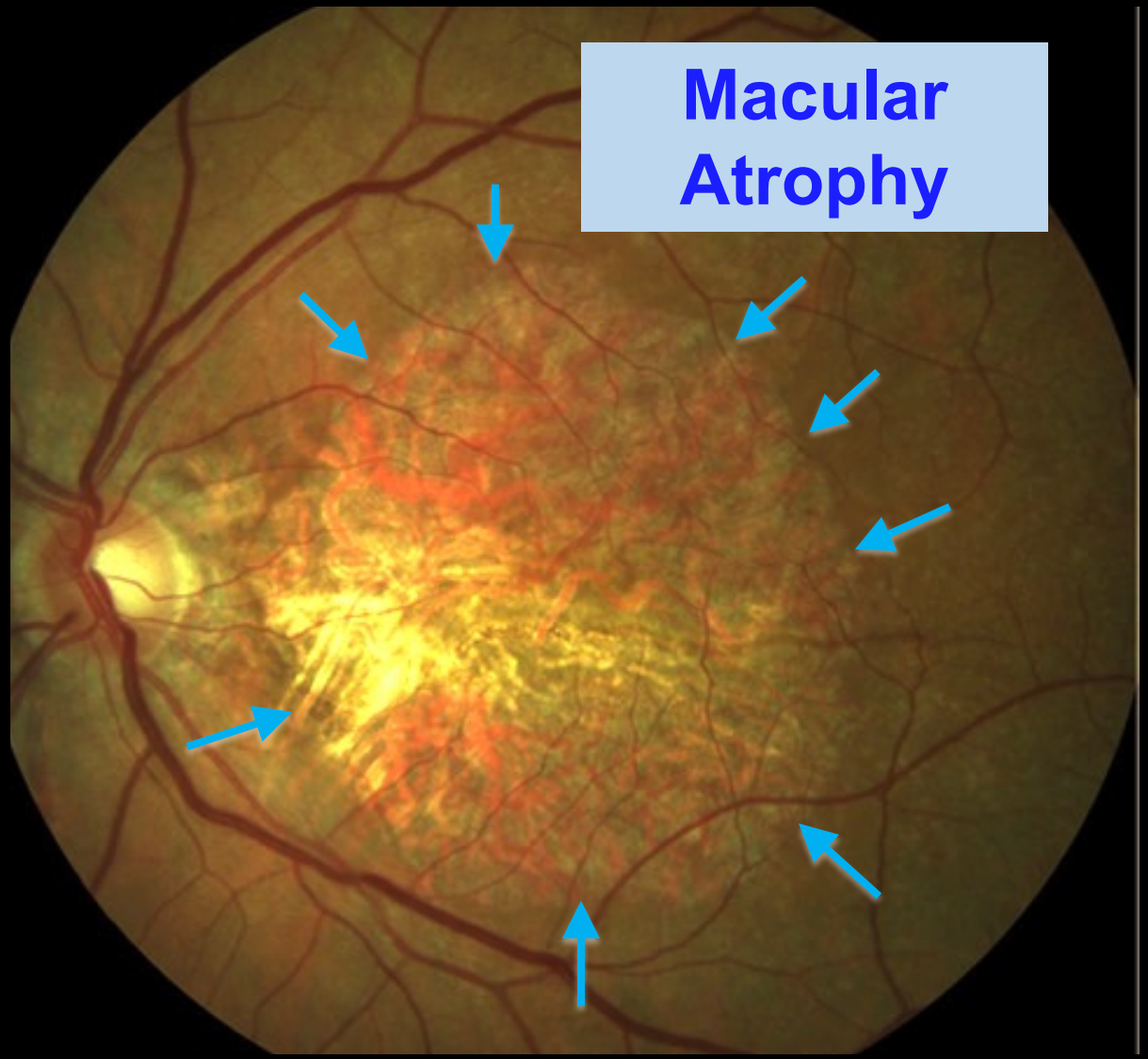


Same Eye
Autofluorescence Imaging

https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/angioid-streaks-optic-disc-drusen-pseudoxanthoma-elasticum.htm

Stages 3/4: Neovascularization, hemorrhage, atrophy

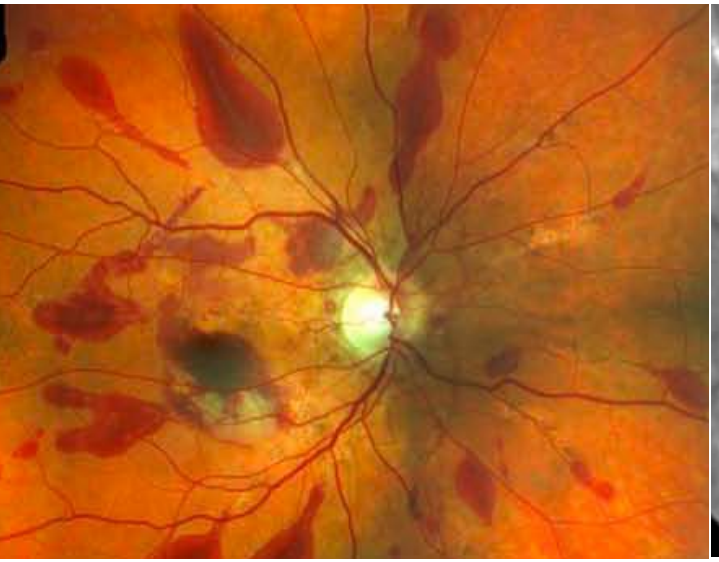
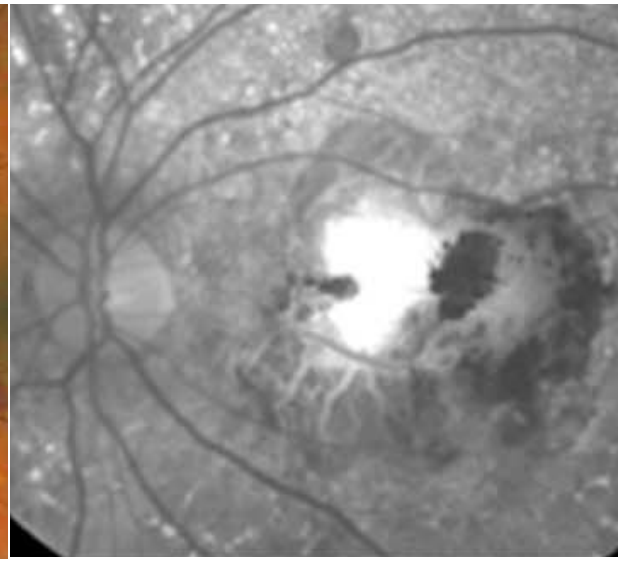
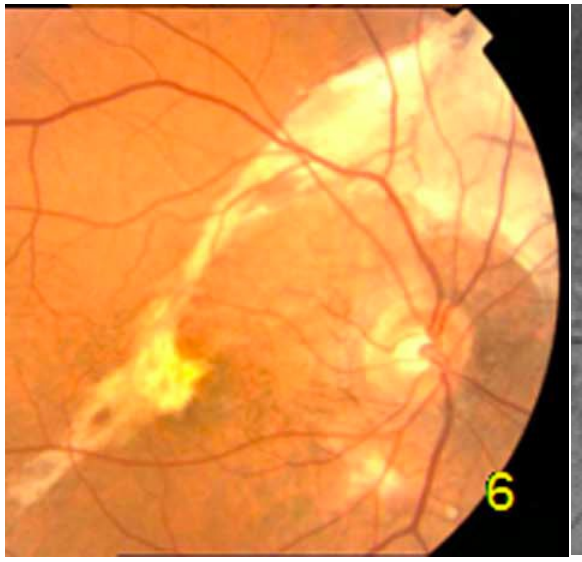


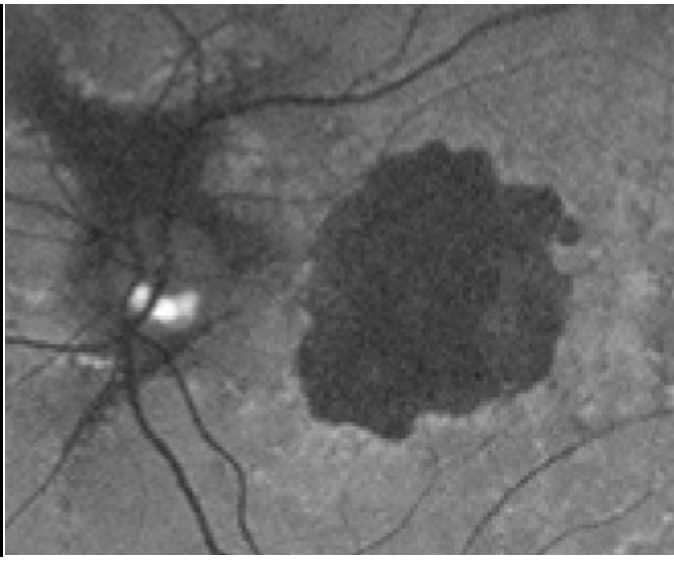


Gliem M, *et al*: Choroidal changes associated with Bruch membrane pathology in pseudoxanthoma elasticum. Am J Ophthalmol 2014, 158(1):198-207 e193.

PXE: Different stages of eye severity

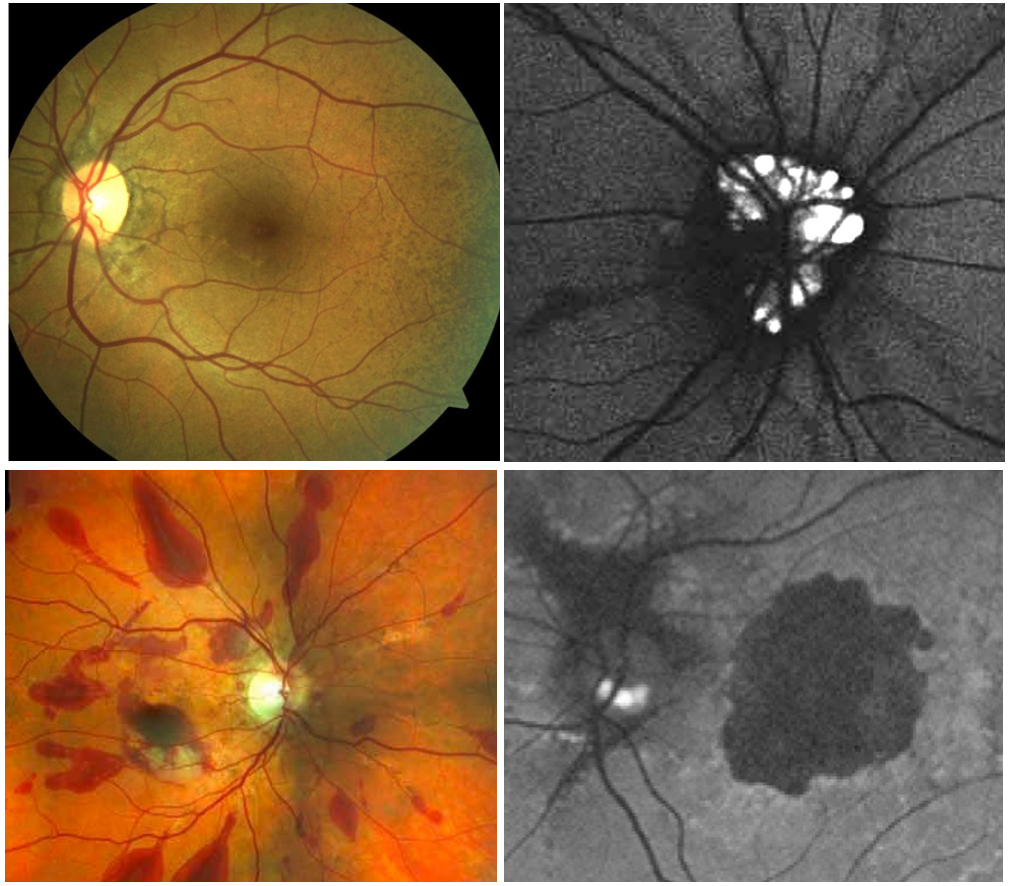
Phenodex-index		Phenodex-FlorMore index	
Eye		**Eye**	
E0	No sign	**E0**	No sign
E1	*Peau d'orange*	**E1**	*Peau d'orange* and/or *Coquille d'oeuf*
E2	Angioid streaks	**E2**	Angioid streaks and/or comet lesion with or without comet tail
E3	Bleeding and/or scarring	**E3**	Bleeding and/or scarring and/or pattern dystrophy-like changes
		E4	Extensive atrophy involving the entire posterior pole



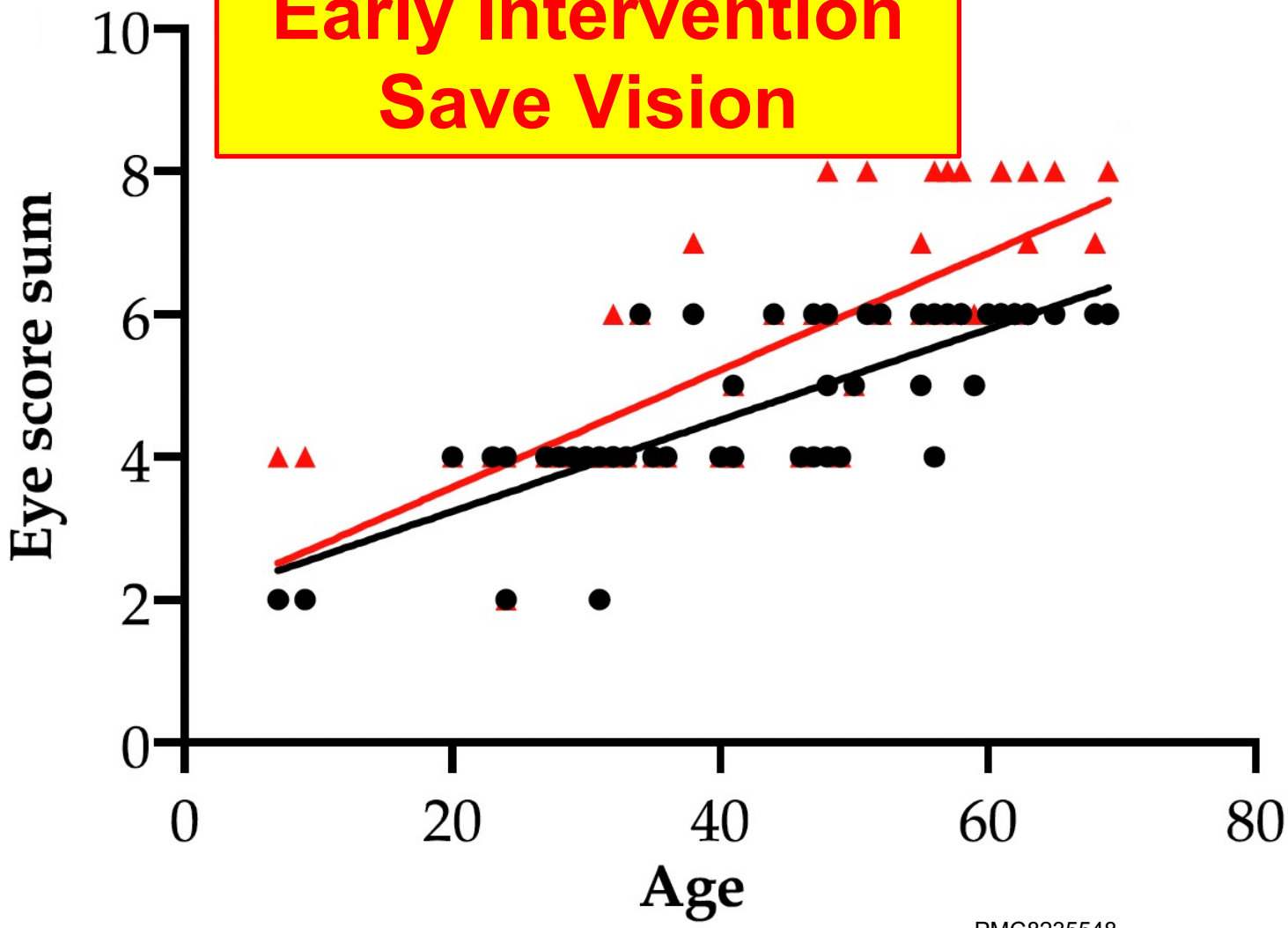
PMC3617449, PMC8235548, https://www.ncbi.nlm.nih.gov/pubmed/20189652

PXE: Eye severity worsens with age



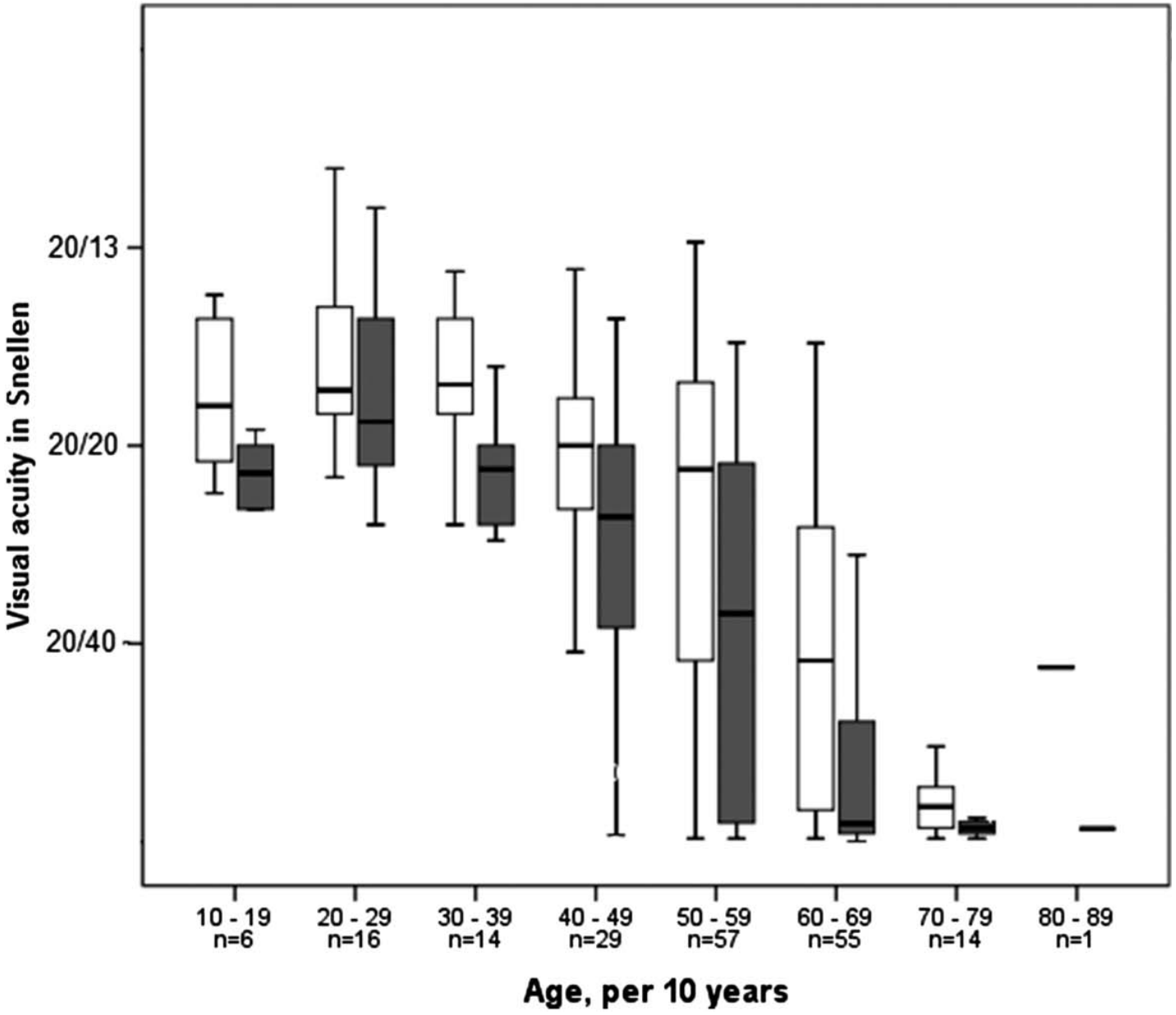
Phenodex-index		Phenodex-FlorMore index	
Eye		**Eye**	
E0	No sign	**E0**	No sign
E1	*Peau d'orange*	**E1**	*Peau d'orange* and/or *Coquille d'oeuf*
E2	Angioid streaks	**E2**	Angioid streaks and/or comet lesion with or without comet tail
E3	Bleeding and/or scarring	**E3**	Bleeding and/or scarring and/or pattern dystrophy-like changes
		E4	Extensive atrophy involving the entire posterior pole

Early Detection
Early Intervention
Save Vision



PMC8235548

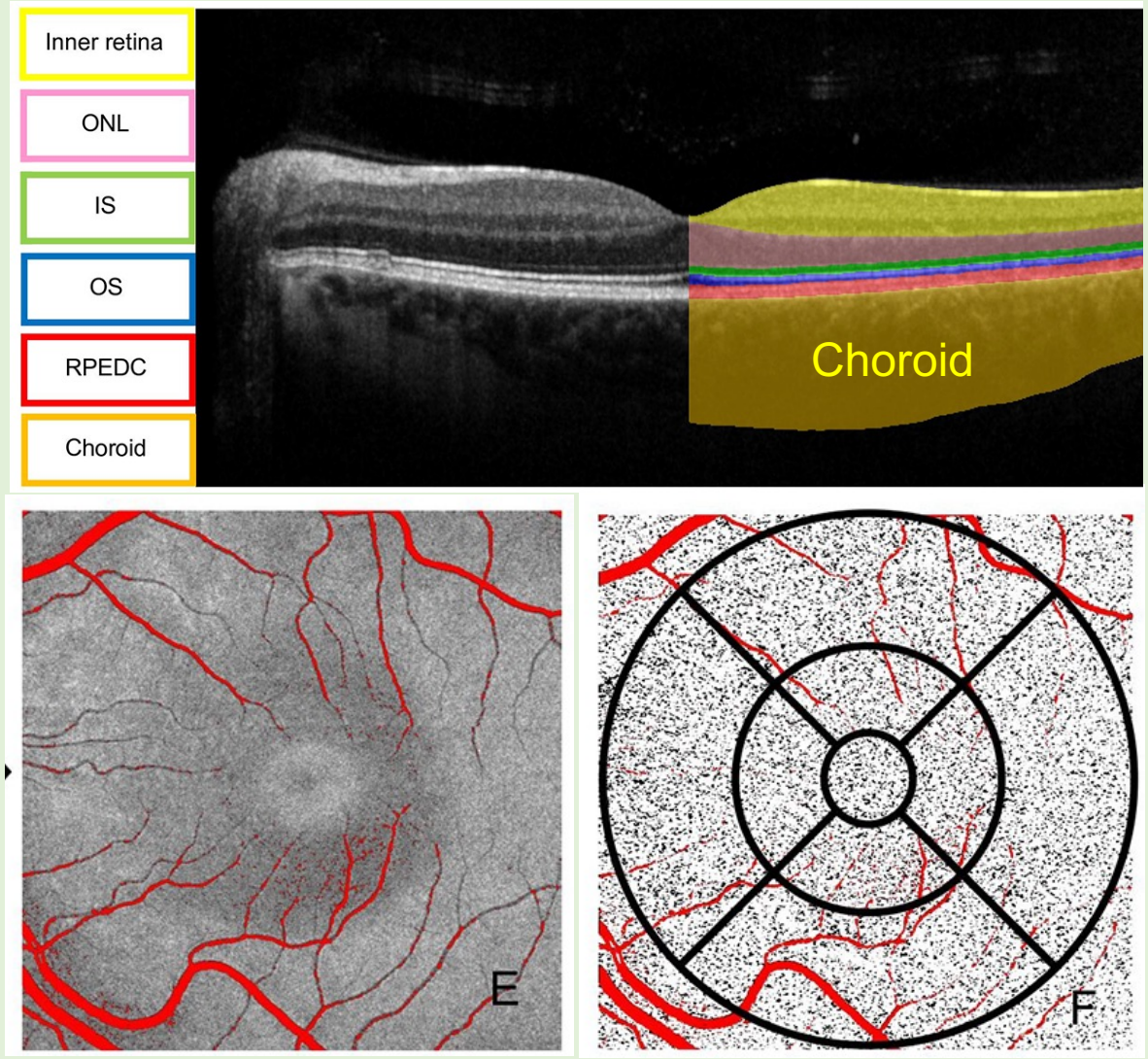
Decrease visual acuity with age



Vision loss **or even the** ***possibility*** **of vision loss has a huge impact on the quality of life and emotional well-being of PXE patients**

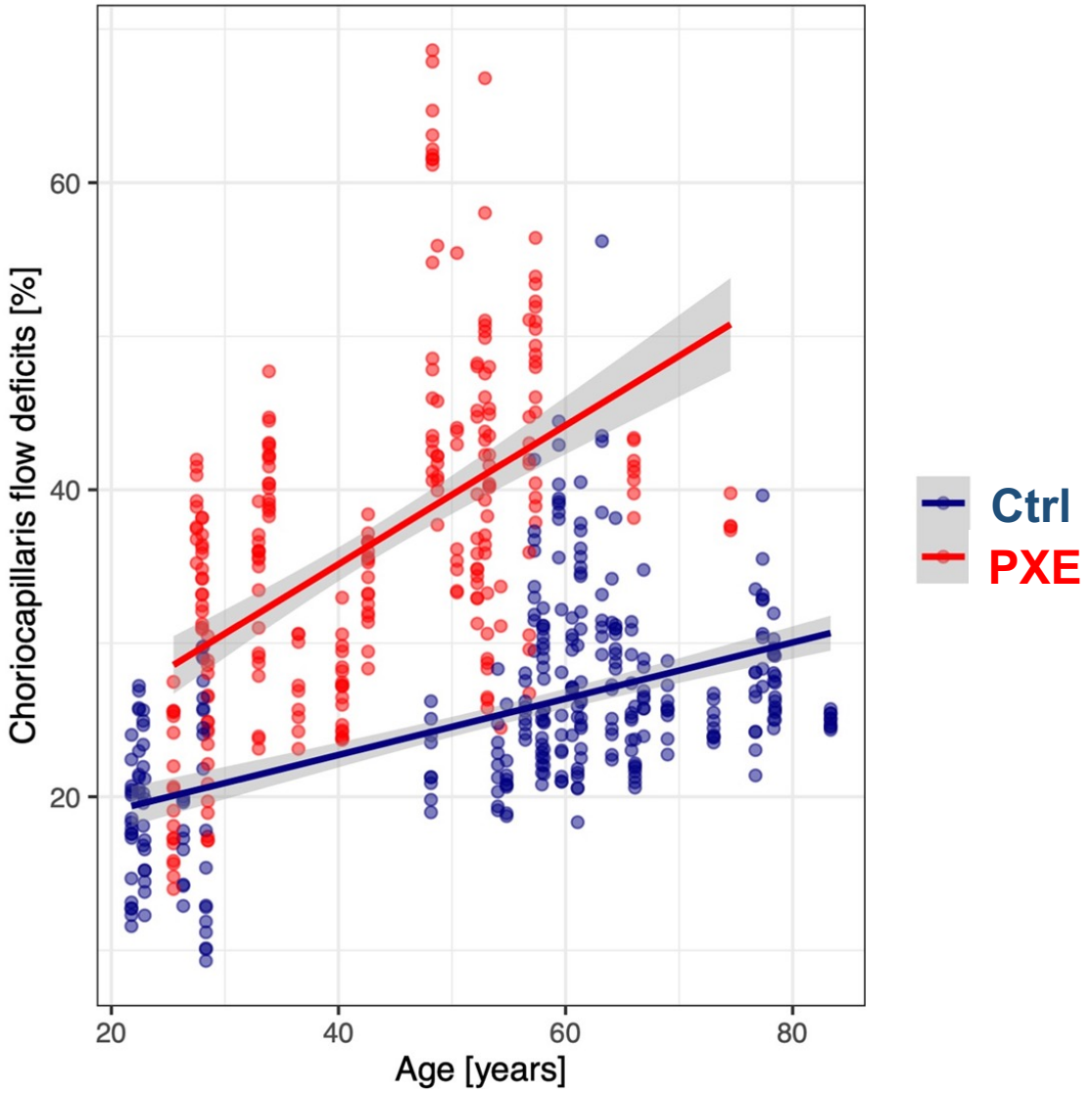
Risseeuw S, et al. Visual Acuity in Pseudoxanthoma Elasticum. *Retina* 2019;39:1580-1587.

Segmentation of the Choroid and Blood Flow as Biomarker of PXE



PMC9946047

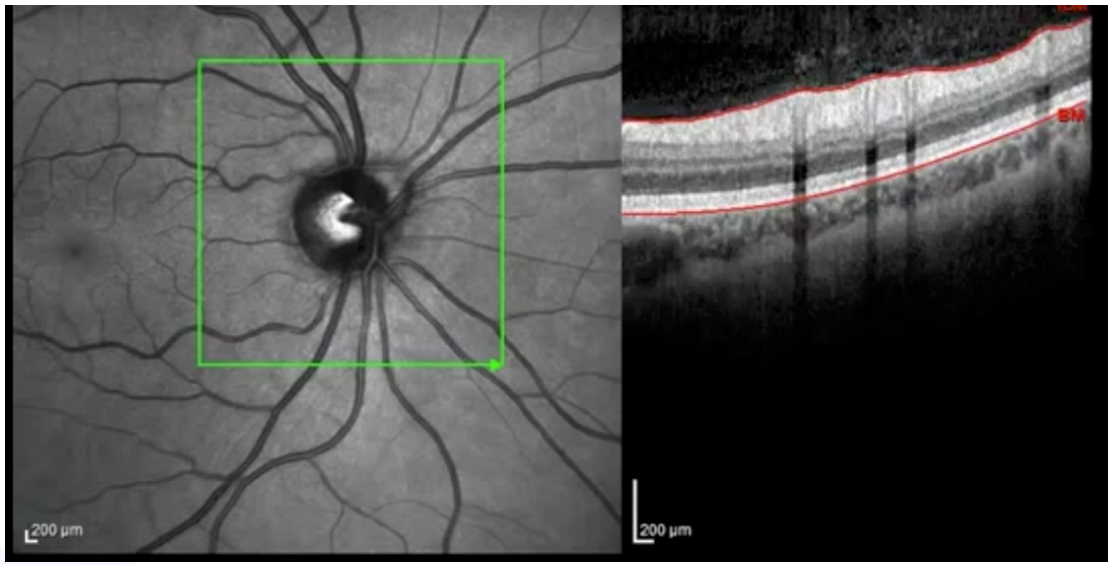
PXE: Severe thinning of choroid over time



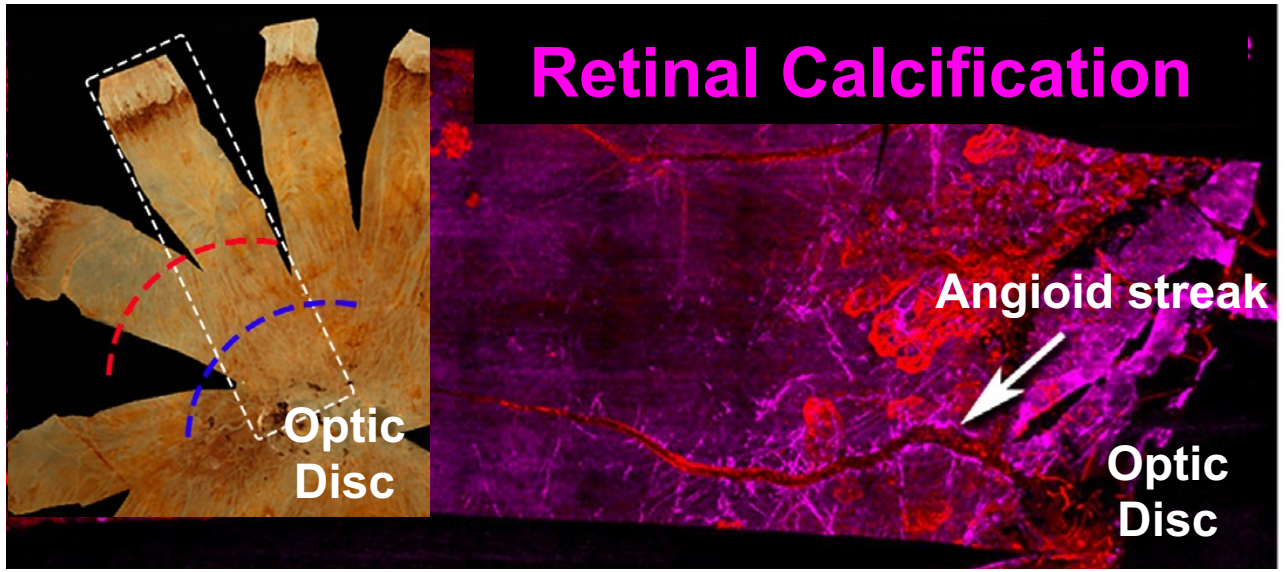
Summary: Eye biomarkers to monitor Rx effects of INZ-701

- **PXE eye changes occur in the 1st decade of life; progress in 100%**
- **Early diagnosis:** eye imaging is noninvasive, directly visualizes disease
- **Early Rx: INZ-701 → ↑ pyrophosphate (PPi) level → ↓calcification**
- **Goals: save vision and ↓ devastating effects of visual impairment**

Optical Coherence Tomography (OCT)



PXE human retina stained for calcium



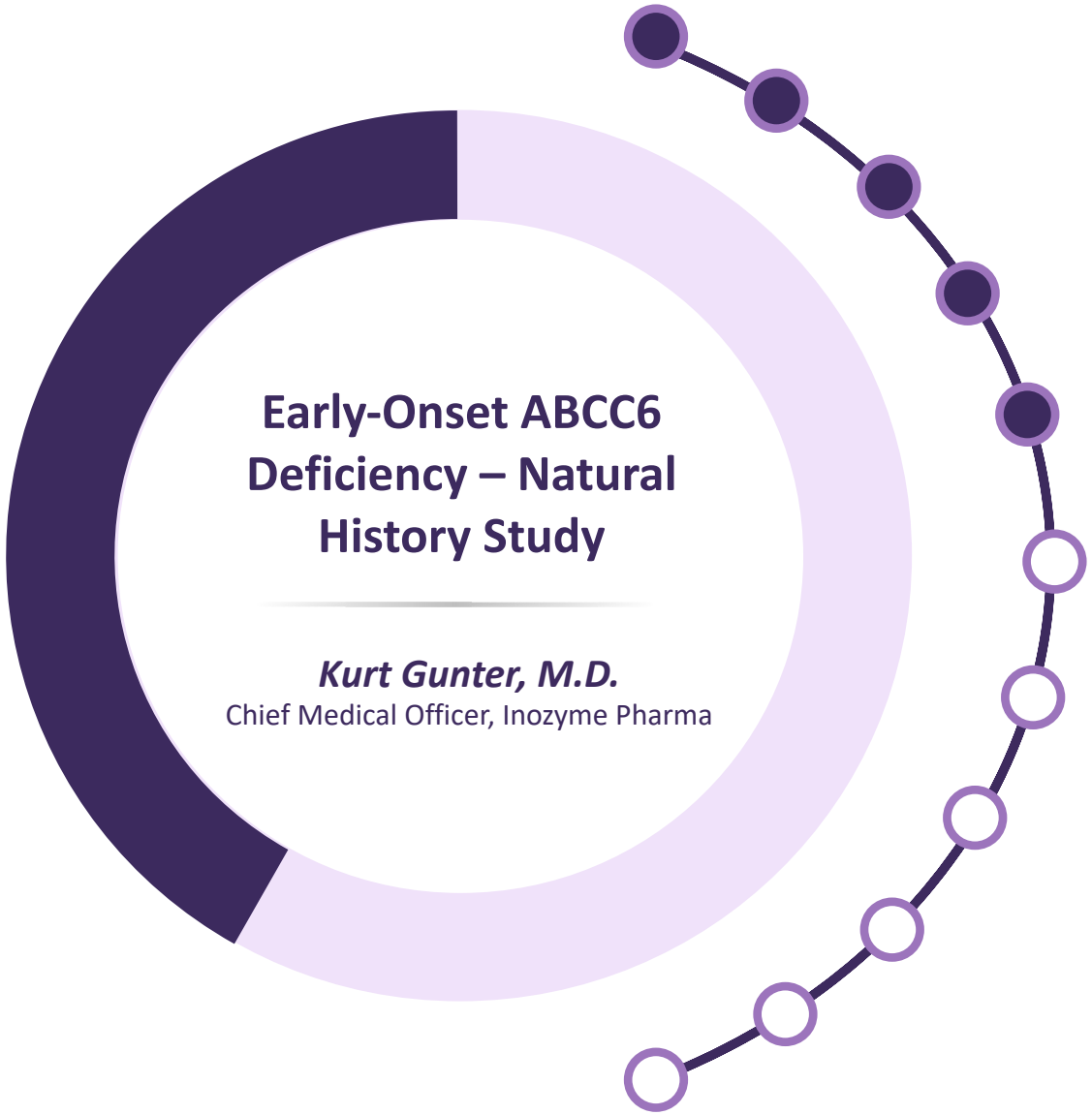
inozyme pharma

PMC10758992

Thank you for your attention!

Joyce Liao
yjliao@stanford.edu

Event agenda



Welcome

ABCC6 Deficiency: Disease Overview

Topline Data: ABCC6 Deficiency Phase 1/2 Trial

Retinal Disease in ABCC6 Deficiency

ABCC6 Pediatric Disease – A Critical Unmet Need

- **Early-Onset ABCC6 Deficiency – Natural History Study**
- Pediatric Stroke – Case Study
- Market Overview

ABCC6 Deficiency Regulatory Strategy

Topline Data: ENPP1 Deficiency Phase 1/2 Trial

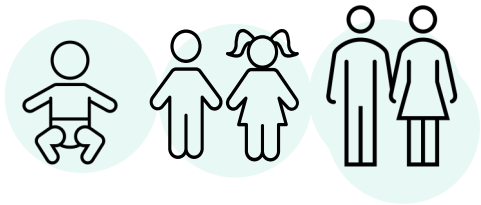
Key Takeaways

Question and Answer

ABCC6 Deficiency retrospective natural history study design (INZ701-006)

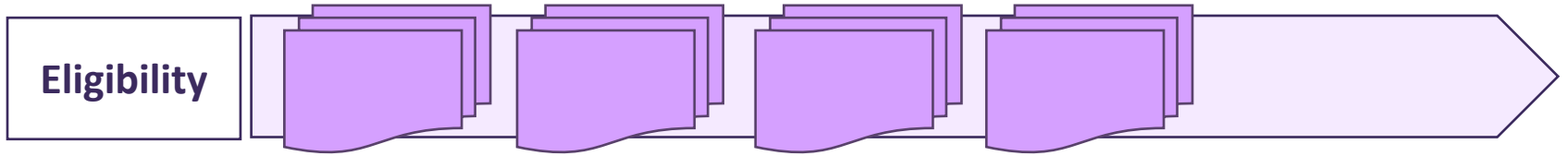
A retrospective, longitudinal natural history study of subjects with ENPP1 Deficiency of Early-Onset ABCC6 Deficiency

Population:
All ages



- Subjects with ENPP1 Deficiency and early onset ABCC6 Deficiency (GACI Type-2)
- Biallelic mutations

Design: Multiple center, longitudinal review of medical records



Performed as a GCP compliant study with informed consent and pre-specified case report form

Multicenter, Multinational (France, Germany, UK and US)

Objectives:

Primary

- Support future study design for the early-onset form of ABCC6 Deficiency

Data collection

- Genetics
- Demographics and medical history
- Perinatal information
- Growth rates, developmental milestones
- Imaging (prenatal US, CT, renal US, carotid US, standard x-ray)
- Laboratory results
- Surgical procedures

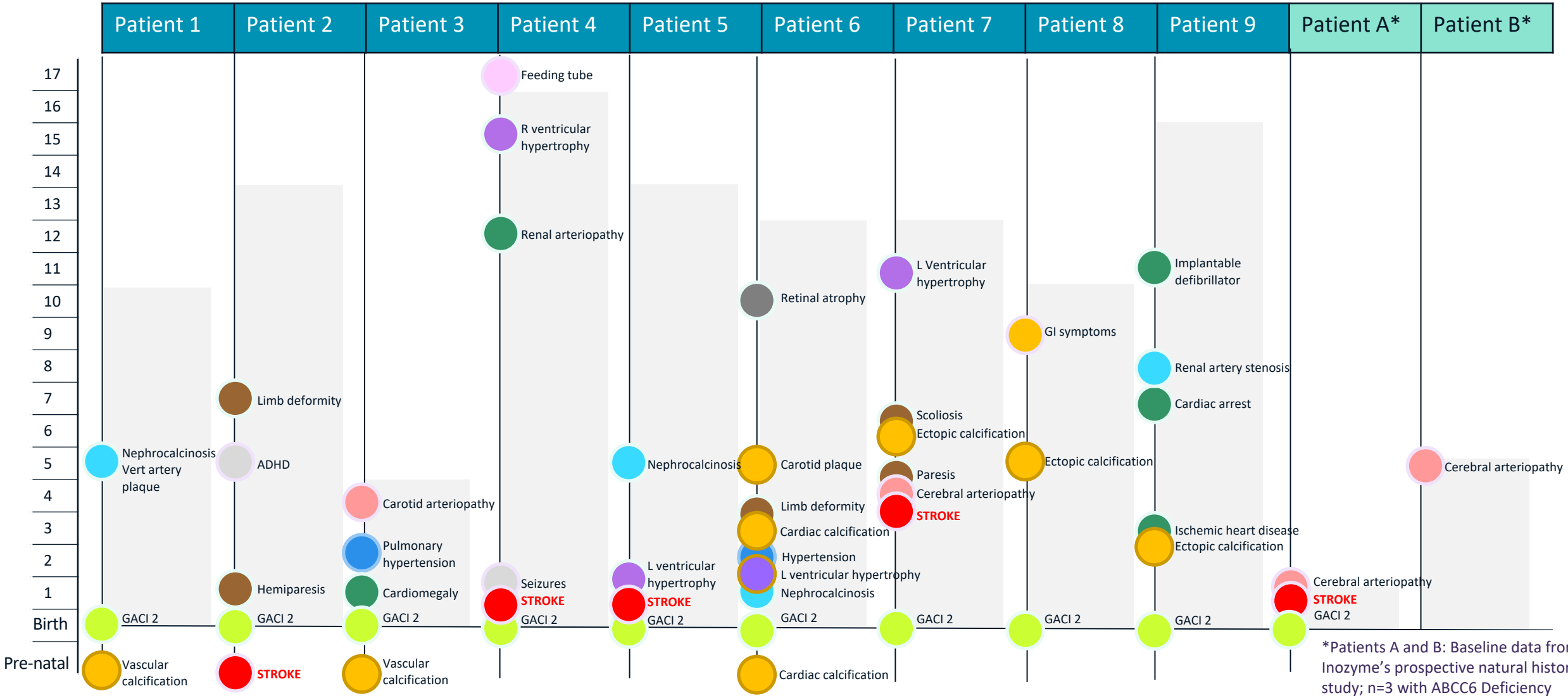
clinicaltrials.gov: NCT05734196

Retrospective natural history study: ABCC6 Deficiency patient demographics

Parameter	Statistic	Result (n=9)
Age at study entry (years)	Median	12.5
	Range	4-16
Gender	Male	5
	Female	4
Race	White	4
	Not provided	3
	Black or African American	2

Data cut – 10 Jan 2024

Retrospective Natural History Study: ABCC6 Deficiency patients had a heavy disease burden



*Patients A and B: Baseline data from Inozyme's prospective natural history study; n=3 with ABCC6 Deficiency

Data cut – 10 Jan 2024

Shaded area indicates age at time of informed consent

ABCC6 Deficiency Natural History study conclusions

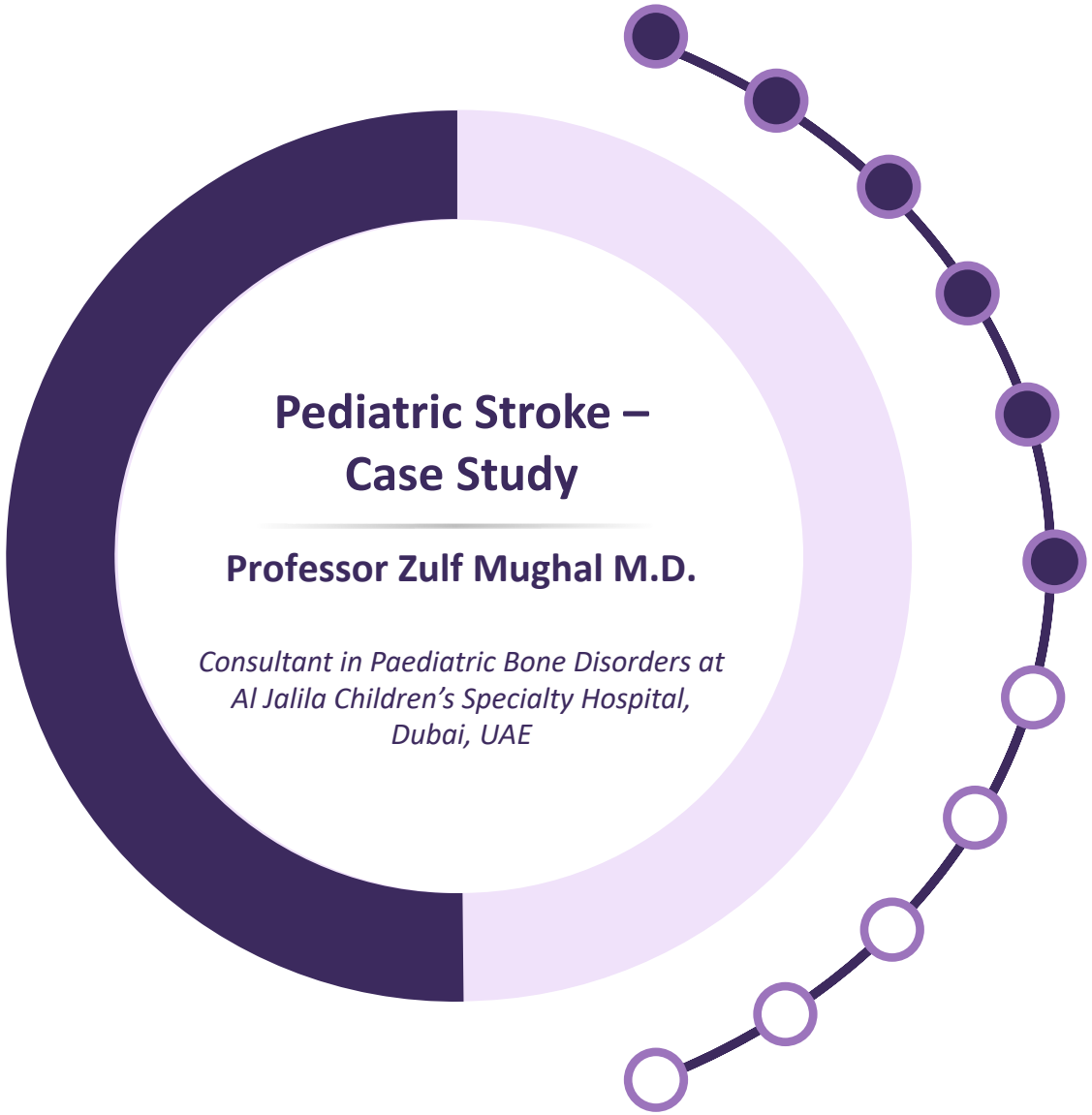
- Pediatric patients with ABCC6 Deficiency suffer from a heavy disease burden
- High rates of disabling stroke and cardiovascular disease
  - Stroke may occur very early in life, even prenatally
  - Cardiovascular disease is severe, considering the young age of the patients
  - Renal disease occurs secondary to arterial stenosis and nephrocalcinosis
    - May contribute to the relatively high incidence of hypertension
  - Retinal disease occurs but was not systematically screened for in this population
- Planning interventional studies in pediatric patients with ABCC6 Deficiency, given the medical need and lack of treatment options

The presentation of neurological symptoms in pediatric ABCC6 deficient patients is documented in several published case studies

Reference	Patient Age (Sex)	Symptoms		Evidence of Vascular	
		Cardiovascular	Neurologic	Calcification	Stenosis
Nitschke Y, 2012	5 (M)*	Cardiac dysfunction, HTN	Diffuse white matter disease	X	
	3 (M)**	Severe HTN, cardiomegaly	Psychomotor retardation	X	
	2.5# (F)	HTN, cardiac failure		X	
Li Q, 2013	8	Murmur, decreased pulses		X	
Dibi A, 2017	6 (F)	HTN, LV hypertrophy, cardiomyopathy		X	
	7 (F)	HTN, cardiomyopathy	Neurological sequelae, convulsions	X	X
	11 (M)	HTN, LV hypertrophy		X	
	2 (F)`	HTN, cardiomegaly, LV hypertrophy, cardiomyopathy			
Bertamino M, 2018	14 (F)		Stroke, seizure, moderate intellectual disability, epilepsy		X
	5 (M)	Severe HTN, LV hypertrophy	Stroke, seizure		X
Grossi A, 2020	Pediatric	Severe HTN	Stroke		X
	Pediatric		Stroke		X
Yao R, 2023	5 (F)	HTN, dyspnea, chest pain		X	

PubMed search completed on March 18, 2024 (not comprehensive; exclusive of GACI-2 only . Nitschke et al. The American Journal of Human Genetics 90, 25-39; 2012 10.1016/j.ajhg.2011.11.020. Li et al. Br J Dermatol: 169(5); 2013 10.1111/bjd.12462. Dibi et al. Journal of Vascular Medicine: 42(6); 2017 10.1016/j.jdmv.2017.09.002. Bertamino et al. European Journal of Paediatric Neurology: 22 (725-728); 2018 10.1016/j.ejpn.2018.04.002.Grossi et al. European Journal of Medical Genetics: 63 (104039); 2020 10.1016/j.ejmg.2020.104030. Yao et al. J Pers. Med: 14 (54); 2023 10.3390/jpm14010054.*Patient #8 in publication; **Patient #10 in publication. #Patient #17 in publication. HTN = hypertension. LV = left ventricle

Event agenda



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Question and Answer

Ischemic Stroke in Children due to Biallelic *ABCC6* Mutations

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Disclosure

Honoraria & consultancy fees from Inozyme

Pediatric ABCC6 Deficiency Case Study: Proband (Female, 14 years of age)

Medical History

- Presented to hospital at 3 ½ yrs of age in 2014
- Parents non consanguineous and different ethnicity
- Uneventful pregnancy, perinatal period & development until presentation
- An upper respiratory tract infection & 4 weeks later developed a right sided “Bells palsy” (LMN facial nerve palsy)
- Progressed to recurrent transient ischaemic attacks & strokes

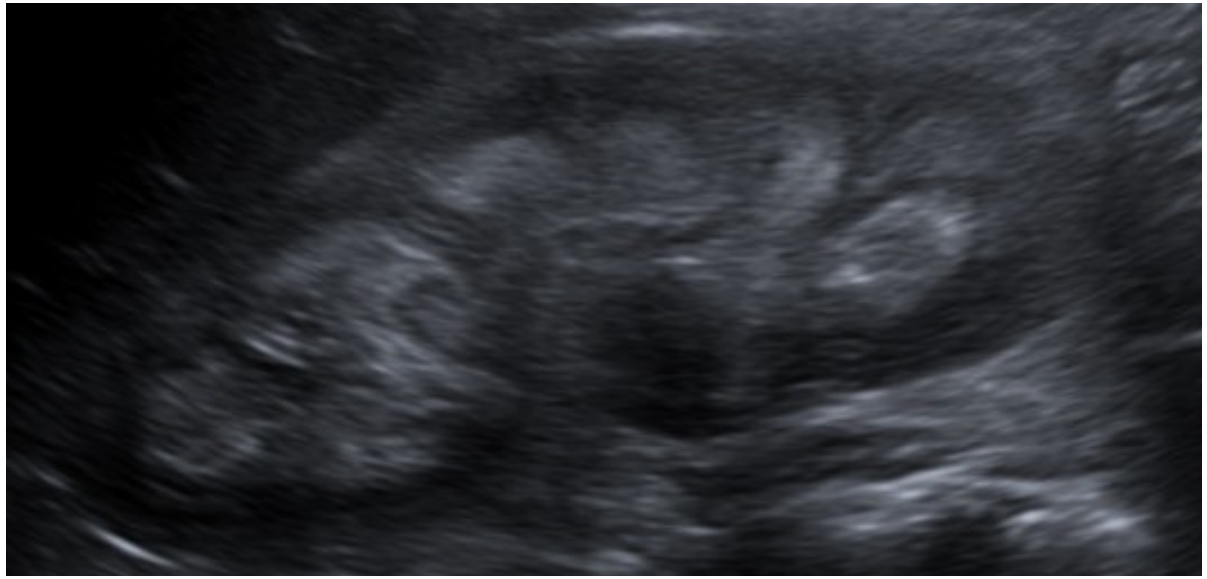
Genetic Analysis

- The NGS Paediatric stroke panel – Negative
- Ectonucleotide pyrophosphatase-phosphodiesterase 1 (*ENPP1*) – No mutations found
- Targeted exome testing detected pathogenic splice site c.2787+1G>T heterozygous mutation in *ABCC6* gene
- Further testing – Deletion of exons 2-4 in *ABCC6* gene
- Both parents were found to carry one of identified mutations

Diagnosis: Generalised arterial calcification of infancy 2 (GACI-2) secondary to compound heterozygous mutation in the *ABCC6* gene

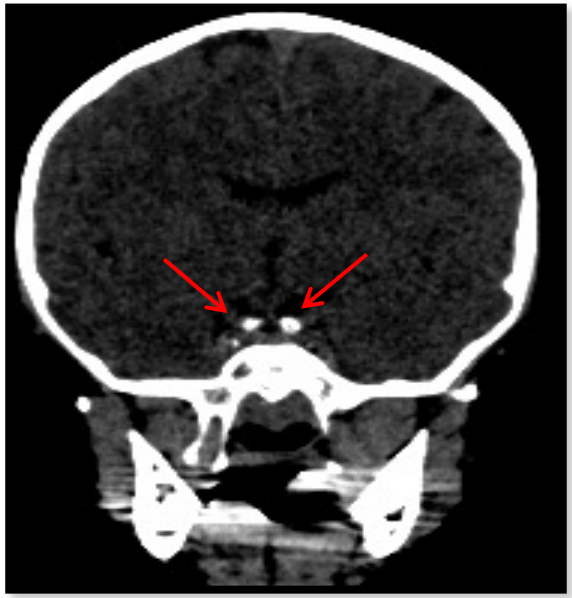
Proband: Clinical presentation (cont.)

- Skin – normal (no plaque like lesions)
- Eyes – Visual impairment (no angioid streaks)
- Blood Pressure – Raised
- Normal cardiac structure with moderate
- Left ventricle hypertrophy
- Kidneys – Bilateral nephrocalcinosis
- Neuroimaging …….

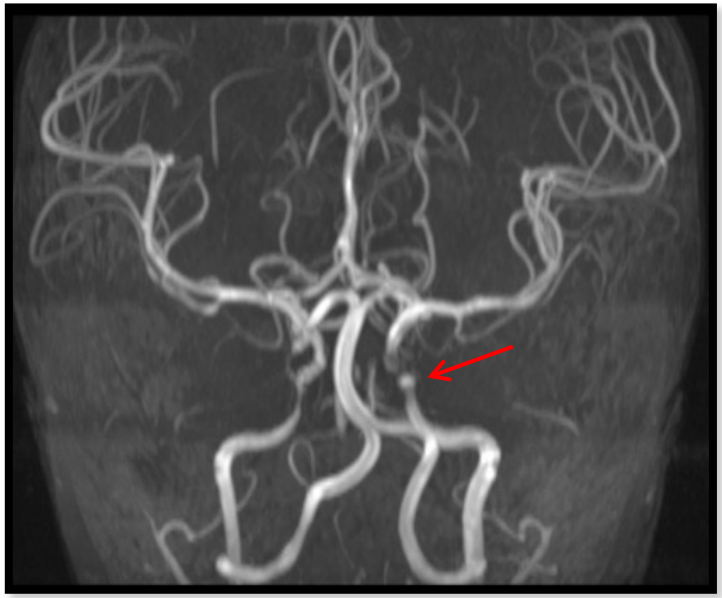


Renal ultrasound scan

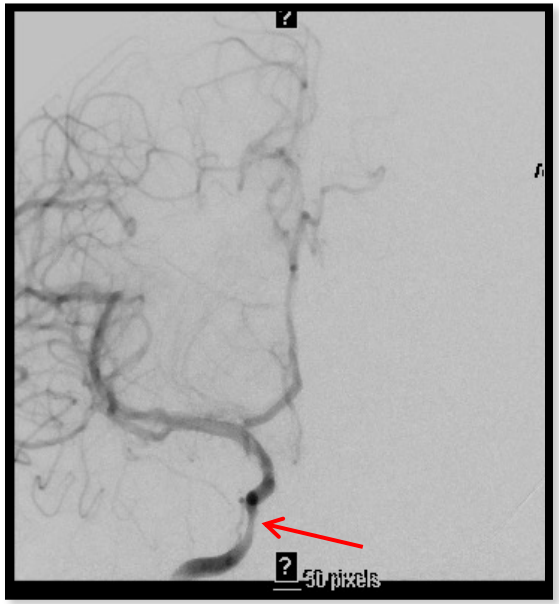
Proband: Neuroimaging

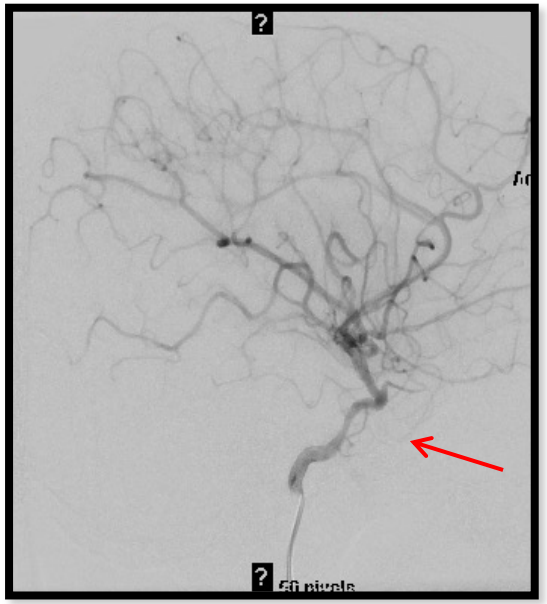


Non contrast CT shows calcification in the right & left internal carotid arteries (ICA)



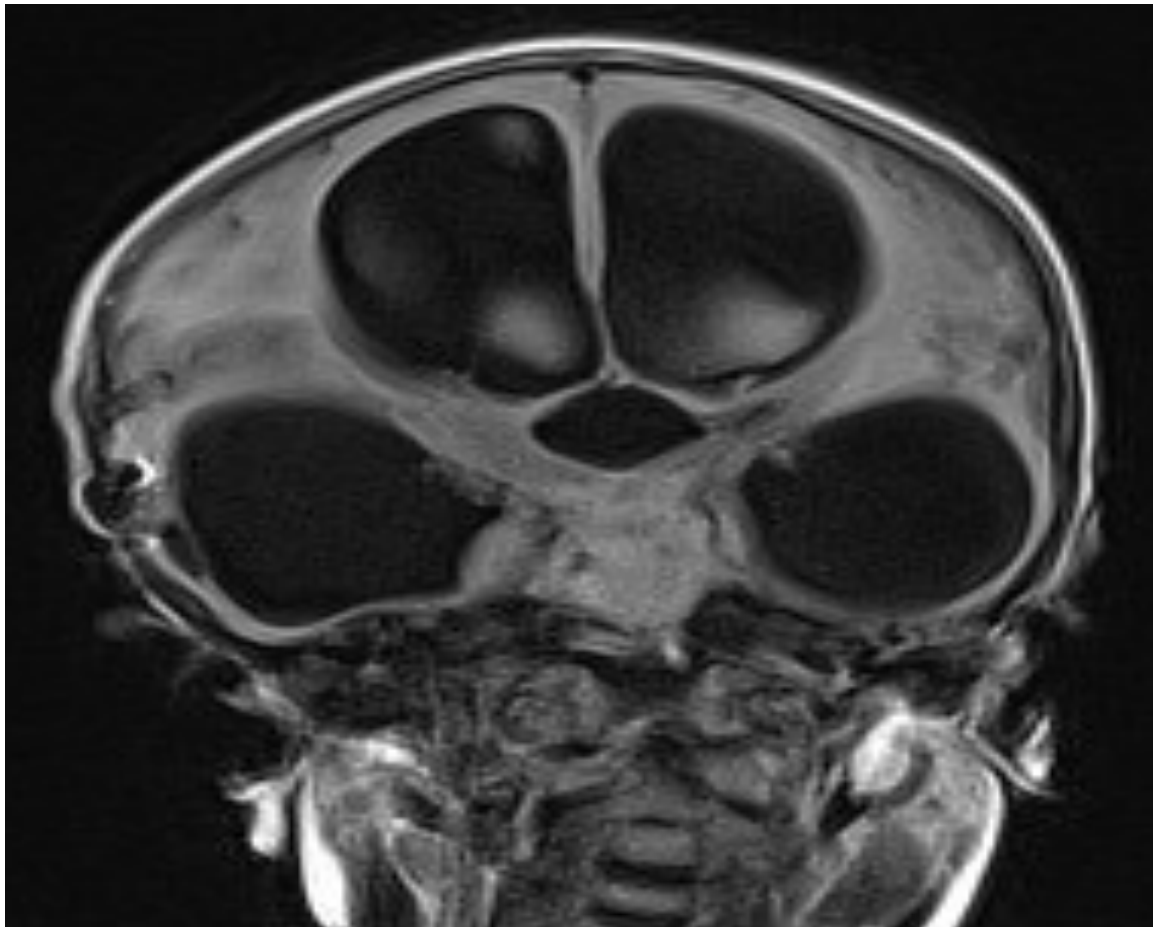
MRI showing narrowing of right & left ICA



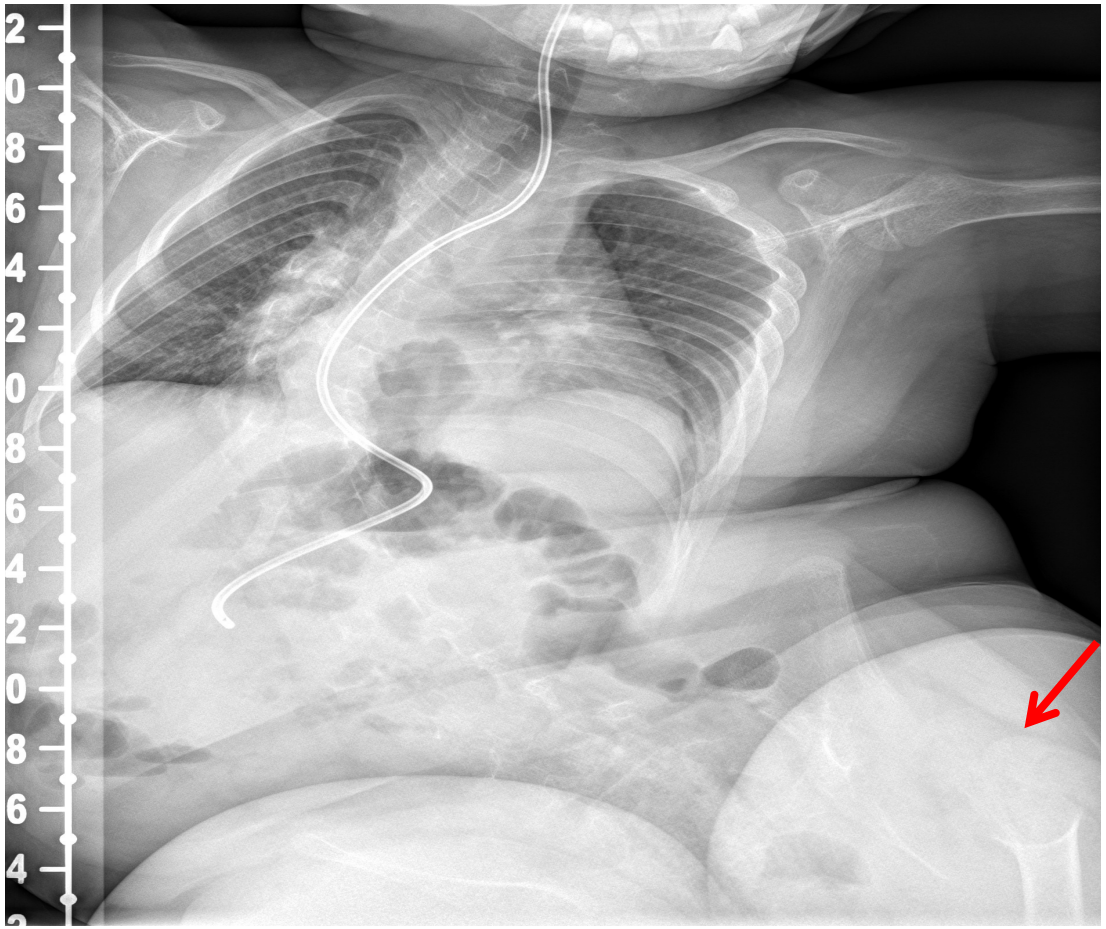


Angiography demonstrating bilateral ICA narrowing

Proband: Neuroimaging (cont.)



2016 – MRI scan of the brain showing encephalomalacic changes and ventriculomegaly



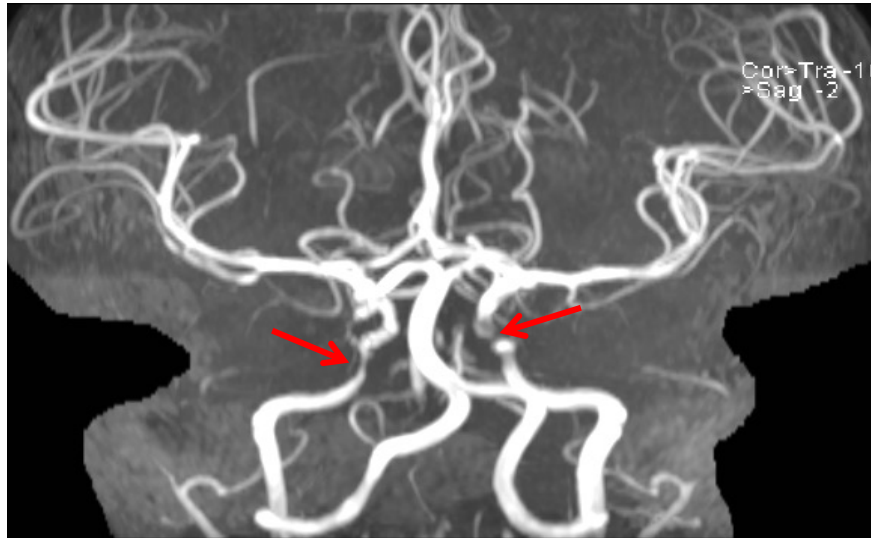
2016 – Scoliosis (arrow shows subluxated left hip)

Proband: Summary of disease consequences

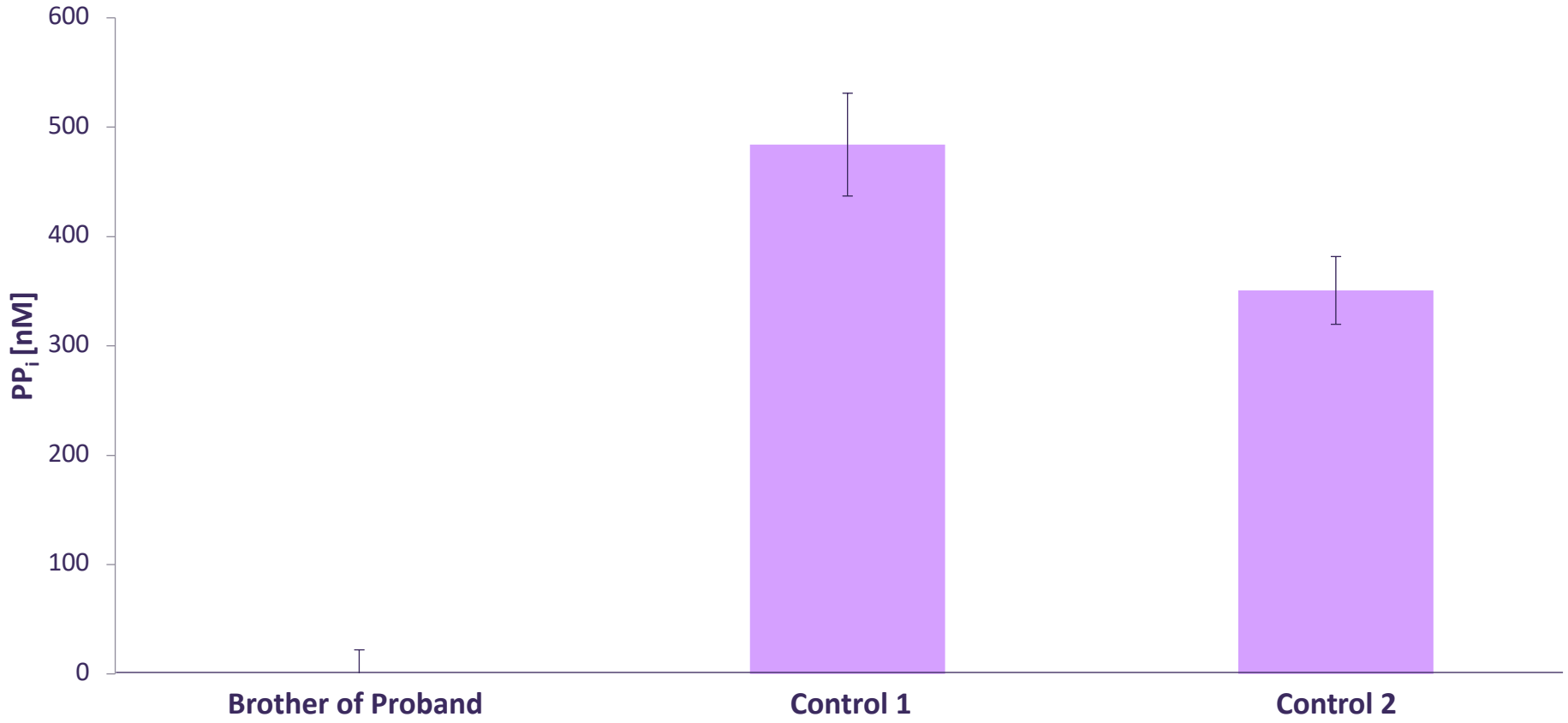
- Severely disabled due to repeated arterial ischemic infarcts
- Severe asymmetrical spastic quadriparesis
- Impairment of safe swallow – Feeding tube
- Blind
- Epilepsy
- Severe scoliosis
- Subluxed left hip
- Chronic pain

Brother of Proband (Male, 12 years of age)

- Inherited both the *ABCC6* mutations
- Stretchy skin but no other features of Pseudoxanthoma elasticum (*plaque like skin changes & angioid streaks in the retina*)
- Imaging of the brain:
  - MRI: Moderate bilateral narrowing of internal carotid arteries & the large posterior communicating artery
  - CT: Calcification of the internal carotid arteries & ophthalmic arteries
- Heart normal
- Renal ultrasound scan:
  - Echogenic areas - ? microcalcifications



Brother of Proband: Plasma PPI analysis



	nM PPi	SEM
Brother of Proband	0	22
Control 1	484	47
Control 2	351	31

Plasma PPi measured by Dr. Rutsch and Dr.Nitschke (Münster University Children's Hospital, Germany)

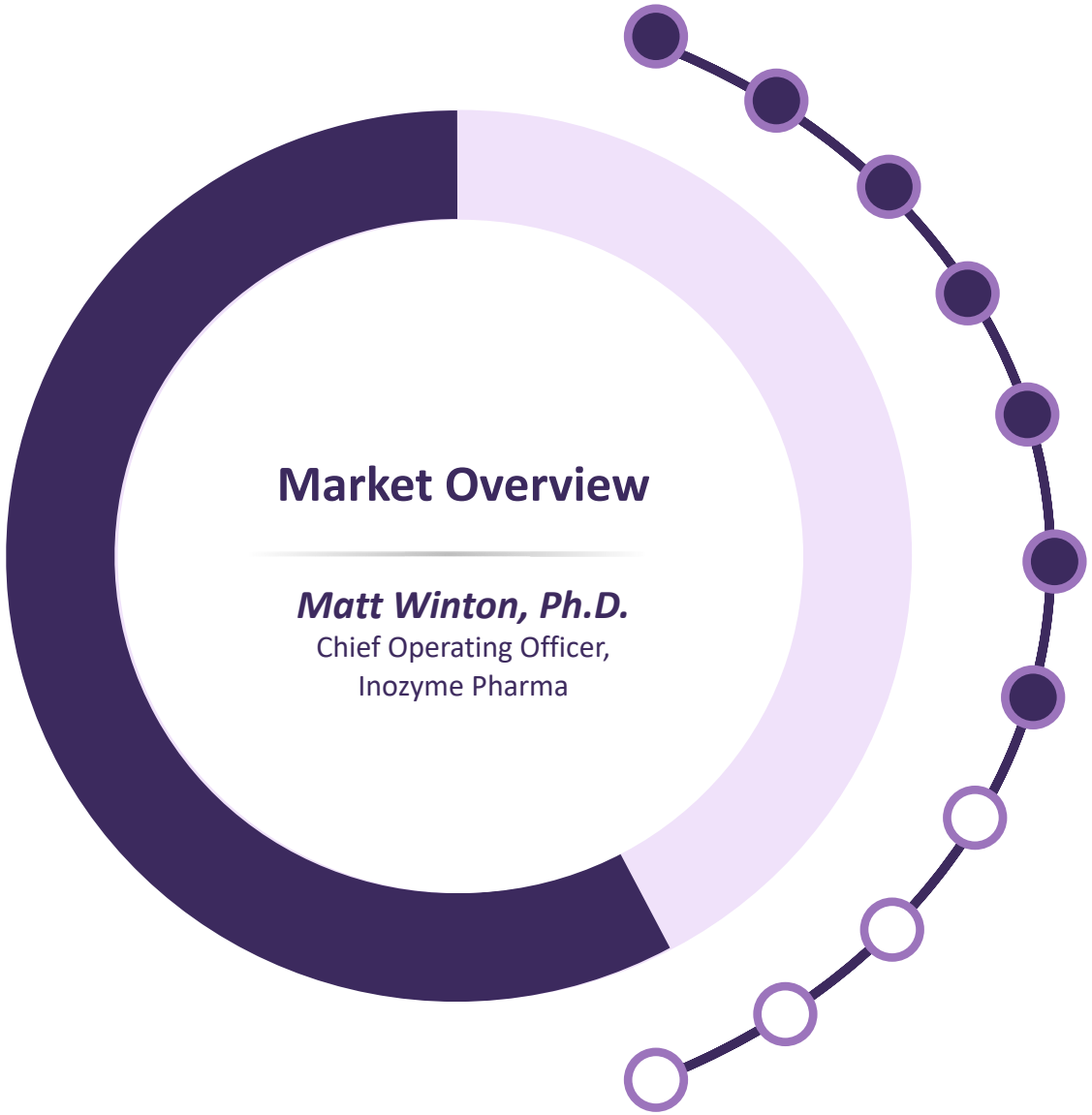
Brother of Proband: Care plan

- Continue careful clinical monitoring in the Neurovascular multidisciplinary clinic and by imaging (MRI of the brain and whole-body CT scans)
- Revascularization surgery if required
- Candidate for treatment and enrollment in ENPP1-Fc replacement clinical trial, with goal of preventing future cerebrovascular events and/or ischemic stroke

Key takeaways

- Mutations in *ABCC6* cause significant morbidity
- Substantial unmet need in this pediatric ABCC6 Deficiency patient population
- *ABCC6* and *ENPP1* should be included in the genetic analysis for children with ischemic stroke and/or severe cardiovascular defects

Event agenda



Welcome

ABCC6 Deficiency: Disease Overview

Topline Data: ABCC6 Deficiency Phase 1/2 Trial

Retinal Disease in ABCC6 Deficiency

ABCC6 Pediatric Disease – A Critical Unmet Need

- Early-Onset ABCC6 Deficiency – Natural History Study
- Pediatric Stroke – Case Study
- **Market Overview**

ABCC6 Deficiency Regulatory Strategy

Topline Data: ENPP1 Deficiency Phase 1/2 Trial

Key Takeaways

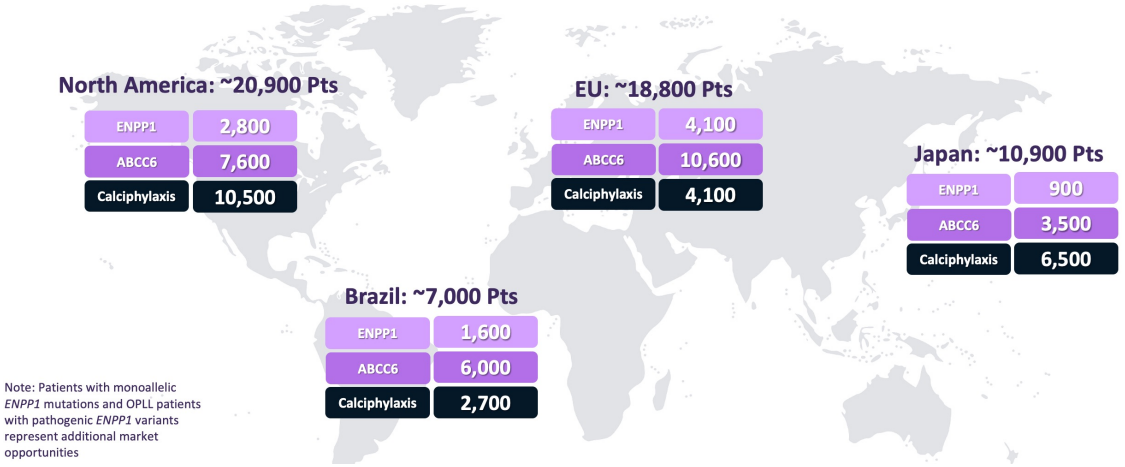
Question and Answer

Evidence of pediatric ABCC6 Deficiency patients generally aligns to published genetic prevalence of 1:25,000-1:50,000

GACI-2	Pediatric	PXE
0-1 Years (1-2%)*	1 to <18 years (25-30%)	18+ Years (70-75%)

Genetic Prevalence: 1:25,000 - 1:50,000 [1,2]

Significant opportunity for INZ-701 across major markets with potential for further geographic and targeted patient expansion



Note: Patients with monoallelic *ENPP1* mutations and OPLL patients with pathogenic *ENPP1* variants represent additional market opportunities

- Based on published genetic prevalence, we estimate **~25,000-30,000 patients** with ABCC6 Deficiency across major markets of interest
- Utilizing 25%[3] as the share of the population between 1 and <18 years of age, suggests **~7,000 pediatric ABCC6 Deficiency patients**
  - North America: ~1,900
  - Brazil: ~1,500
  - EU: ~2,650
  - Japan: ~875

*Estimated percent of total prevalence. PXE, pseudoxanthoma elasticum

Sources: 1. Internal, Unpublished Data; 2. Ferreira et. Al. Genet Med, 2021; 3. Undata - http://data.un.org/Data.aspx?d=POP&f=tableCode%3A22

Understanding and confirming the market opportunity

Prevalence

Diagnosis / Patient Identification

Clinical Presentation / Burden of Disease

EHR Databases Analysis
Investigate medical records mentioning ABCC6, PXE and/or GACI to understand clinical journey of patients

Genetic Testing Companies
Identify pediatric patients that have been genetically confirmed for ABCC6 Deficiency

Genotype - Phenotype Correlation Research
Elucidate pediatric phenotypes of interest and corresponding genotypes

Claims Data Assessment
Use disease codes to elucidate pediatric patient numbers and healthcare events

HCP Outreach
Speak with ~200 pediatric neurologists and ophthalmologists to understand experience with these patients

KOL Discussions and Advisory Board
Gain perspectives of treating physicians and obtain feedback on potential endpoints

Pediatric ABCC6 Deficiency EAP/ISTs

~1,300 likely US pediatric patients with ABCC6 Deficiency were identified, representing ~70% of estimated genetic prevalence

Pediatric ABCC6 Deficiency: US Patient estimates

Ischemic Stroke
940 patients

- *Ischemic stroke between ages 1-18*
- *Genetic panel ordered between ages 1 and <18* ***OR*** *mild neurological symptoms occurred prior to stroke*
- *PXE or a phosphorous disorder diagnosis code in all history*
- *Exclusion of differential diagnoses*

Angioid Streaks
264 patients

- *Angioid streaks between ages 1 and <18*
- *Exclusion of differential diagnoses and eye injuries*

Retinal Imaging/OCT
60 patients

- *Optical coherence tomography (OCT) between ages 1 and <18*
- *Genetic panel ordered* ***AND*** *mild neurological symptoms occurred between ages 1 and <18*
- *PXE or a phosphorous disorder diagnosis code in all history*
- *Exclusion of differential diagnoses*

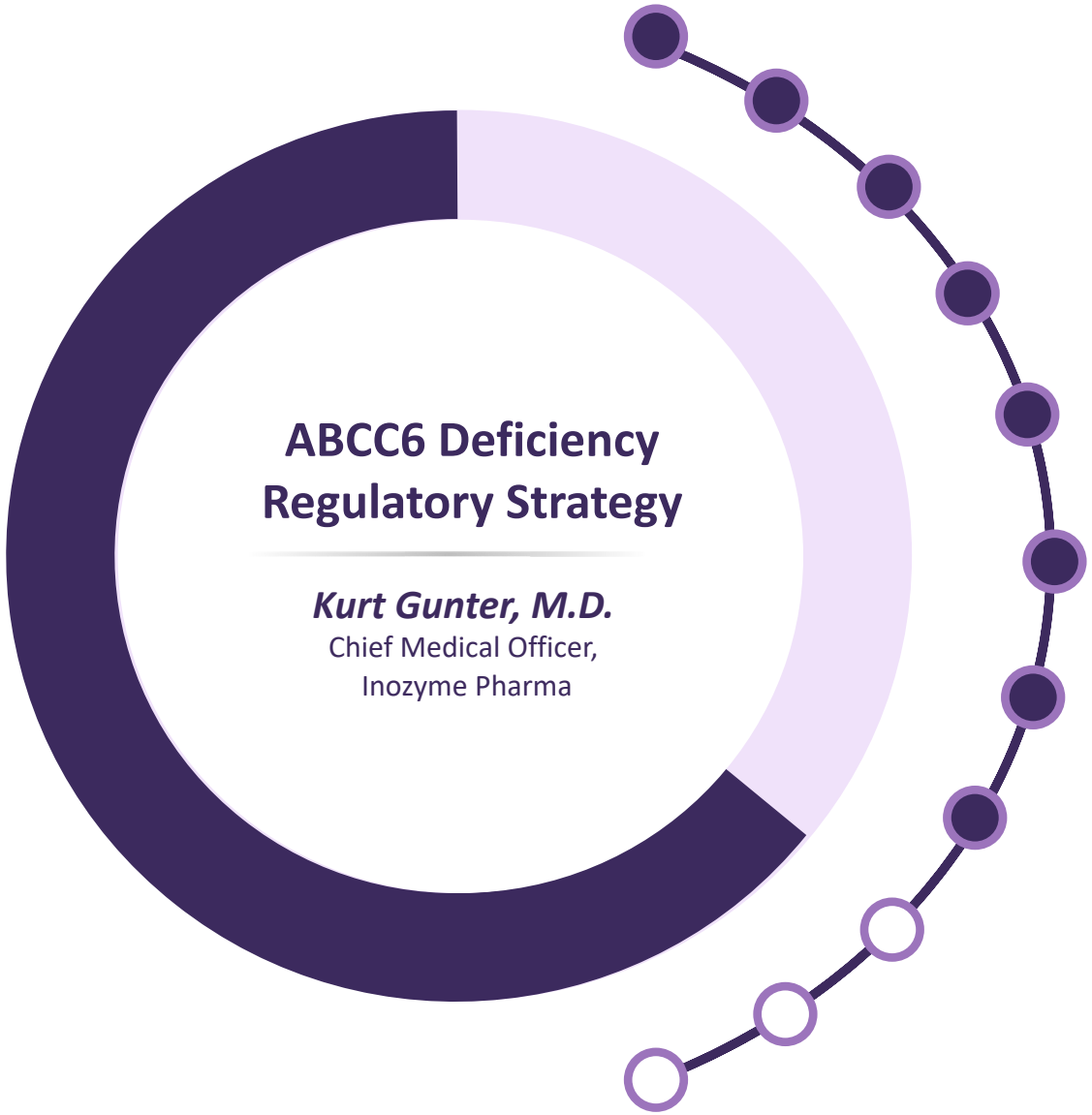
Cardiovascular Anomaly
24 patients

- *Cardiovascular anomaly* ***AND*** *arterial calcification between ages 1-and <18*
- *PXE or a phosphorous disorder diagnosis code in all history*
- *Exclusion of differential diagnoses*

Identified 1,288 likely U.S. pediatric patients with ABCC6 Deficiency

Sources: *IPM Longitudinal claims database An all-history (2009 – present) lookback period was utilized for clinical profiling Patients with 2+ claims for any one differential diagnosis (sickle cell disorders, Ehlers-Danlos syndrome, Paget's disease) were excluded. Based on 65% medical claims capture rate. No projection factor was used for claims coverage.*

Event agenda



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Key Takeaways

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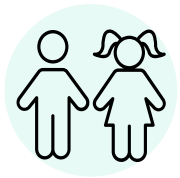
ASPIRE: Pivotal Study Concept in Pediatric Patients with ABCC6 Deficiency

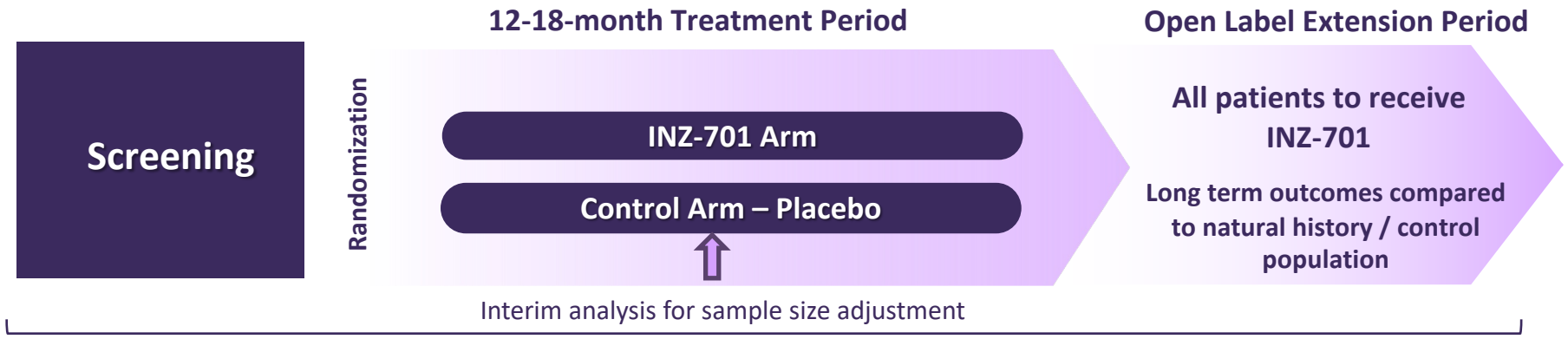
Designed to support Accelerated Approval (US) / Conditional Approval (EU)

Population:
1 to <18 years



- ABCC6 genetic variants
- History of cerebrovascular disease clinically or by imaging

Design: Multicenter, multinational, randomized, double blind, placebo controlled



Potential Endpoints:

Primary

- **Progression of cerebral vasculopathy** by imaging or other endpoint*

*Subject to regulatory agreements

Additional

- **PPi** concentration
- Incidence of **neurological events**
- **Arterial/cerebral calcium** score by CT
- OCT for **choroidal thickness** and other retinal parameters
- **VFQ-25**
- **Pediatric stroke outcome measure (PSOM)**
- PK and enzyme activity
- **Safety**

Planned roadmap for clinical development of INZ-701 in ABCC6 Deficiency

Ongoing Study

ENERGY-1: Infant (0-12 mos.)
Phase 1b
Single arm

- ***Safety*** *and* ***tolerability*** *as primary*
- ***PPi*** *and* ***survival*** *as secondary*

Future Studies

ASPIRE: Pediatric (≥1-<18 yrs.)*
Phase 3
Randomized, controlled

- *Potential accelerated approval based on endpoints predictive of clinical benefit over 12–18-month randomized period*
- *Monitor for* ***cerebrovascular, cardiovascular and ophthalmic*** *outcomes against untreated control population over 3-5 years to support full approval*

Adult – PXE (18+)*
Phase 3
Randomized, controlled

- *Composite endpoint comprised of* ***retinal measurements, peripheral arterial disease outcomes*** *and* ***PPi***

Completed Study

Adult – PXE (18+)
Phase 1/2
Single arm – MAD

- *Generally safe and well tolerated*
- *Consistently elevated PPi at highest dose*
- *Signals of clinical activity on vascular and ophthalmic for retinal endpoints*

*Subject to regulatory discussions and appropriate financial resources

Basis for Potential Accelerated Approval (US) /Conditional Approval (EU)

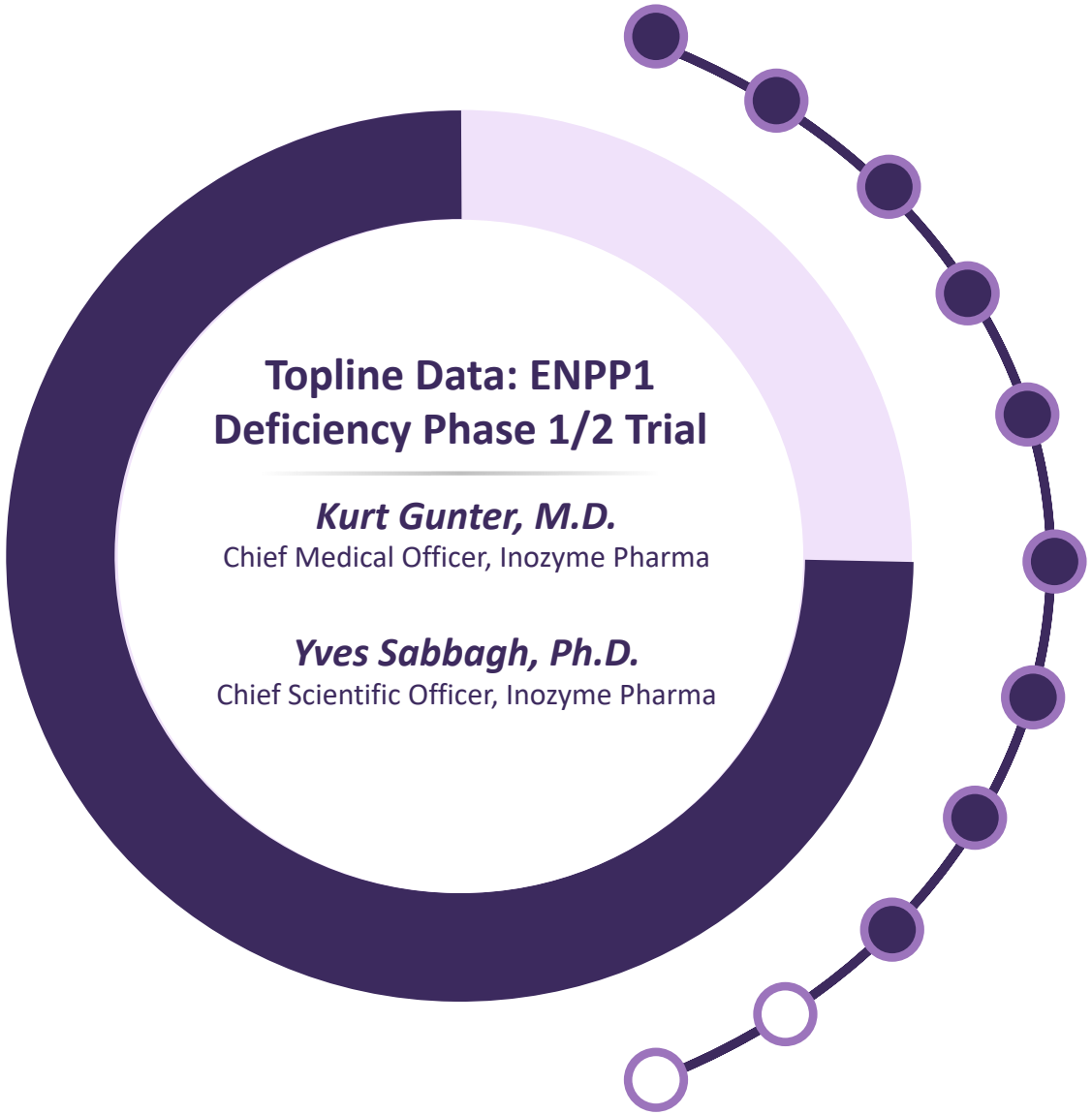
1st BLA/MAA

- Adult Phase 1/2 full data
- ENERGY-1 available data
- ASPIRE - Pediatric Pivotal trial data

Additional filings

- Adult (18+) study (Supplemental BLA/MAA)
- Japan, Brazil, Middle East

Event agenda



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Adult ENPP1 Deficiency Phase 1/2 trial

A Phase 1/2, open-label, multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of INZ-701 followed by an open-label long-term extension period in adults with ENPP1 Deficiency

Study Population:
Adults

Eligibility Criteria:

- Age 18-64 years
- Confirmed clinical and genetic diagnosis

Primary Goals

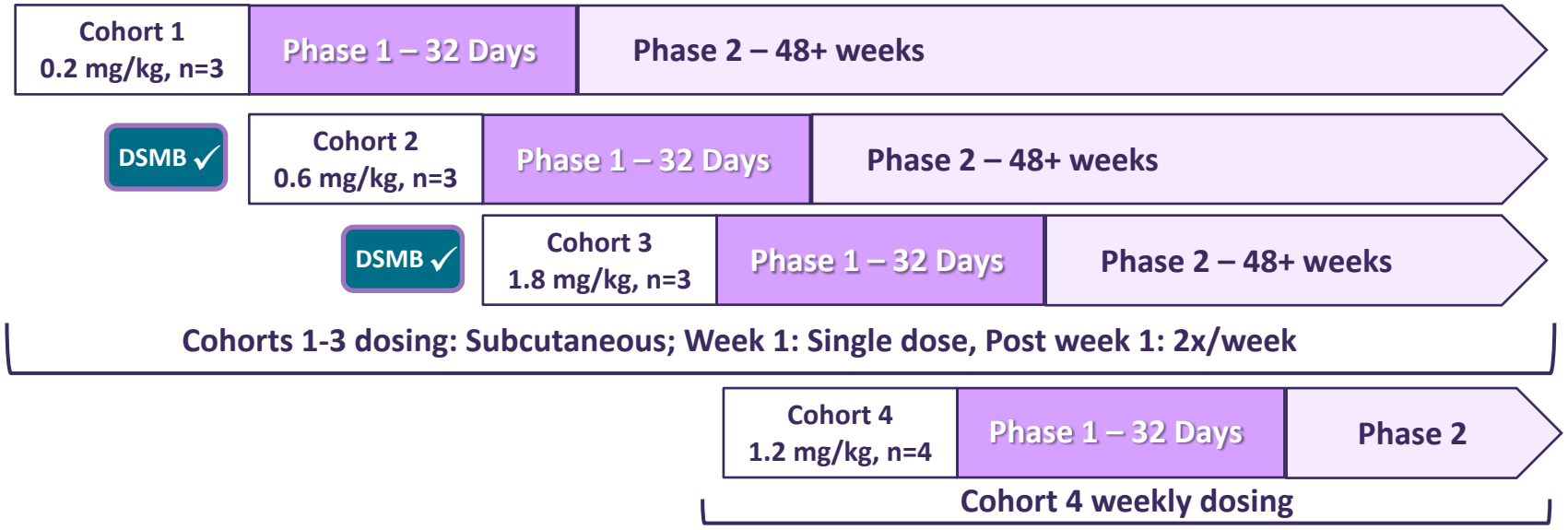
- **Safety** and **tolerability**
- **Immunogenicity**
- **Pharmacokinetic properties**
- **Pharmacodynamics (PPi)**

Secondary Goals

Evaluate potential endpoints for pivotal study

- **Ectopic calcification**, **skeletal**, **vascular** and **physical function**, and **patient reported outcomes**
- Exploratory **biomarkers**

Study Design:



DSMB = Data Safety Monitoring Board. clinicaltrials.gov: NCT04686175

INZ-701 continued to exhibit a favorable safety profile

Event	INZ-701 dose cohort – No. of patients with at least one event				Total patients (n=13)
	0.2 mg/kg biweekly n=3	0.6 mg/kg biweekly n=3	1.8 mg/kg biweekly n=3	1.2 mg/kg weekly n=4	
Adverse event (AE)	3	3	2	3	11
Adverse event related to INZ-701	2	1	1	3	7
Serious adverse event	0	2	0	0	2

Most adverse events were mild or moderate in severity

- 7/13 patients experienced mild adverse events related to INZ-701
  - Injection site reactions occurred in 5 patients
  - Other related adverse events included decreased appetite, extremity pain and fatigue

2 serious adverse events - not related to INZ-701

- Patella fracture (motor vehicle accident), cardiac surgery complication

No adverse events led to discontinuation of INZ-701

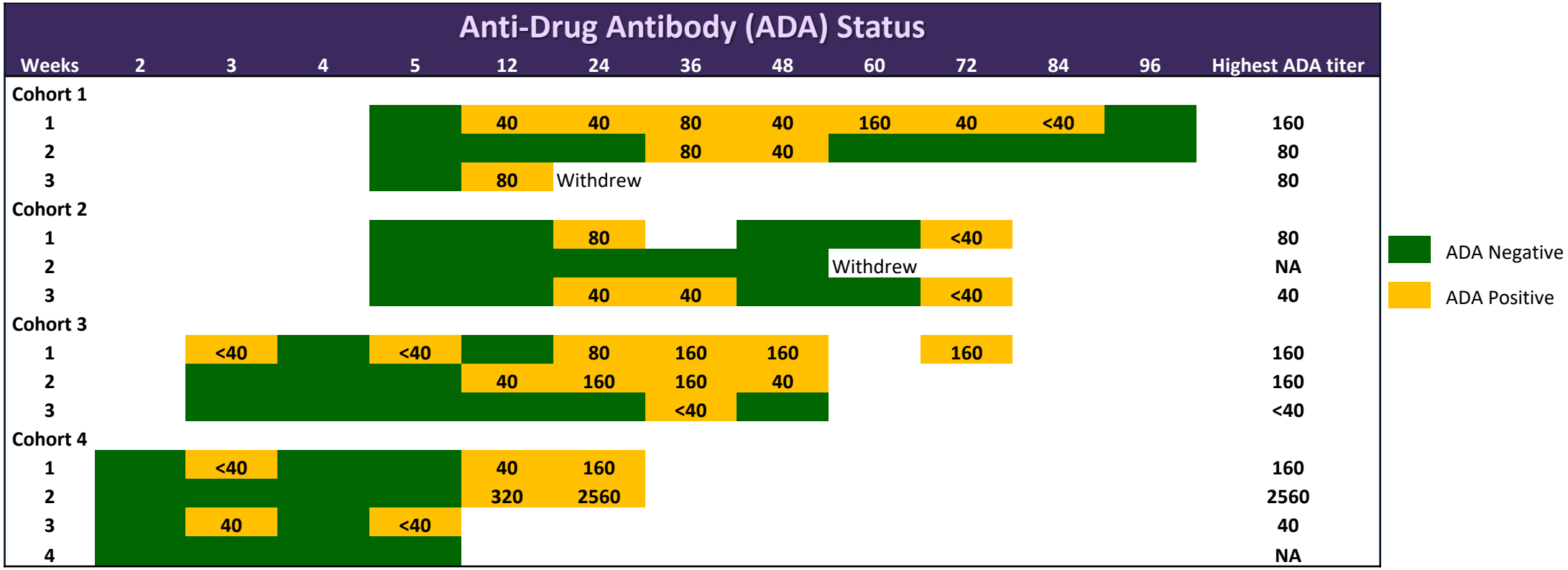
No adverse events led to study withdrawal from Phase 1

- 2 patients withdrew from Phase 2 (1 from cohort 1 and 1 from cohort 2); not related to adverse events
- 11 patients remain on study; 10/11 transitioned to self-administration
- Time on study range: 22-742+ days; 12+ patient-years

Data cut – 4 Jan 2024

Favorable immunogenicity profile observed

Low, non-neutralizing ADA titers detected; Transient in at least 3 of 11 patients



ADA titers for other drugs were observed in previously conducted trials by other companies

STRENSIQ® ADA titers: 2,048[1]; patients with ADA: 89%[4]

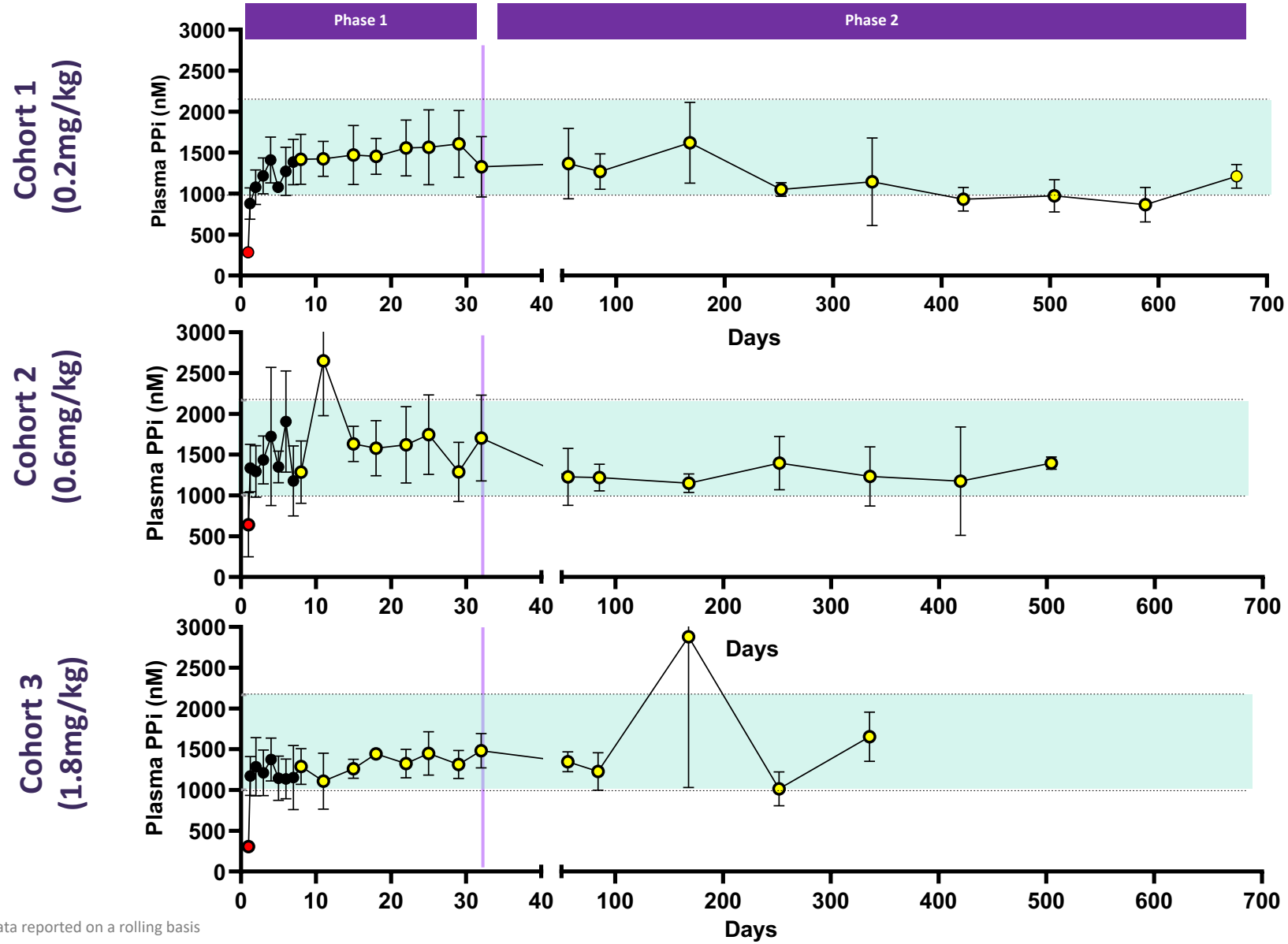
ALDURAZYME® ADA titers: 31,972[2]; patients with ADA: 97%[4]

LUMIZYME® ADA titers: >51,200[3]; patients with ADA: 89%[4]

Data cut – 4 Mar 2024; ADA titer range measured as dilution factor

Sources: *1. Hofmann et al, JCEM 2019; 2. Xue et al, Mol Genet Metab 2016; 3.Kazi et al, JCI 2017; 4. Product USPI 23*

Rapid and sustained increase in PPi observed at all three dose cohorts



- Rapid increase observed after the 1st dose
- PPi levels reached the healthy volunteer range after the 1st dose

Baseline PPi (pre-dose) + 1st INZ-701 dose
PPi measurement (post-dose)
PPi measurement (pre-dose)
Healthy subject PPi levels; n=10
Data presented as mean ± SEM

Data reported on a rolling basis

Long-term data from Cohort 1-3 continued to show PPi correction and positive changes in biomarkers and PROs

- Cohorts 1-3 continued to show sustained levels on PPi in the normal range
  - Cohort 1 through 96 weeks
  - Cohort 2 through 72 weeks
  - Cohort 3 through 48 weeks

- Significant decrease in serum FGF-23 level in Cohort 3 observed through week 48

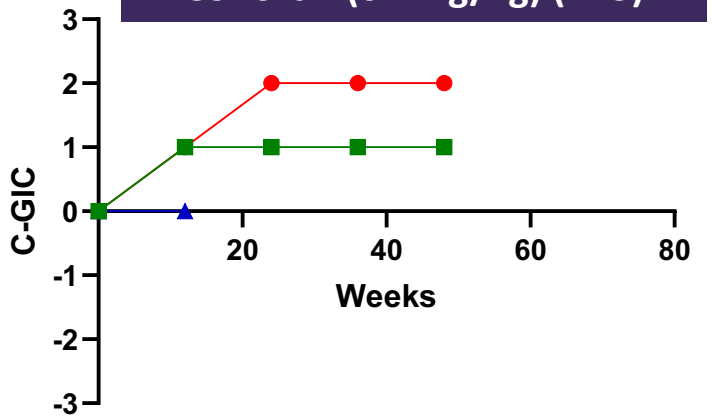
- Bone biomarker response remained consistent with restoring proper bone mineralization to improve bone pathology with data through week 48 in Cohort 3
  - Increase in bone formation marker: Bone-specific alkaline phosphatase (BSAP)
  - Decrease in bone resorption marker: C-telopeptide (CTX)

- Favorable responses on the PROMIS and Global Impression of Change Patient Reported Outcome measures were maintained across cohorts

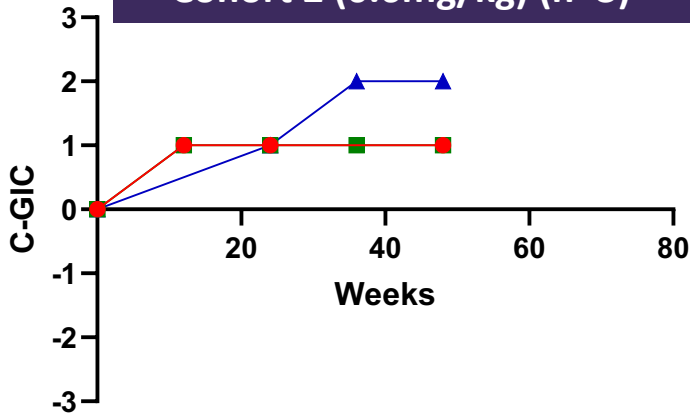
Global Impression of Change Scale: Concordant improvement in C-GIC and P-GIC in all three dose cohorts

Clinician's Global Impression

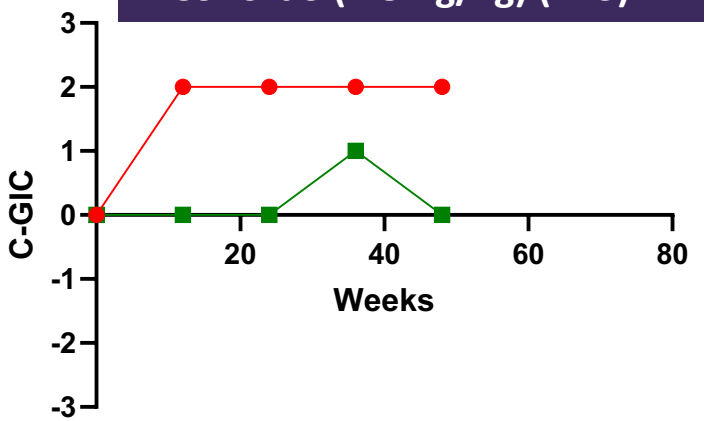
Cohort 1 (0.2mg/kg) (n=3)



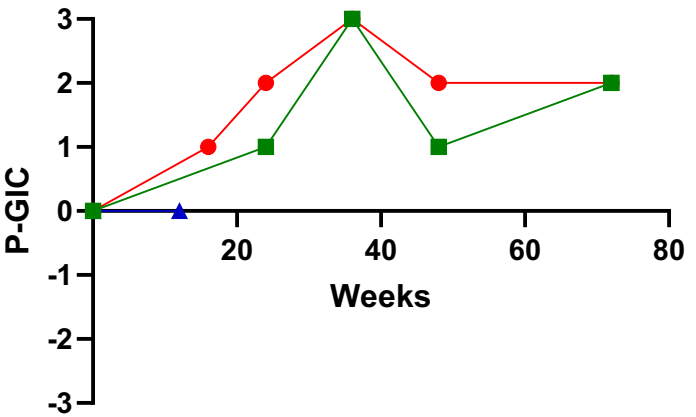
Cohort 2 (0.6mg/kg) (n=3)

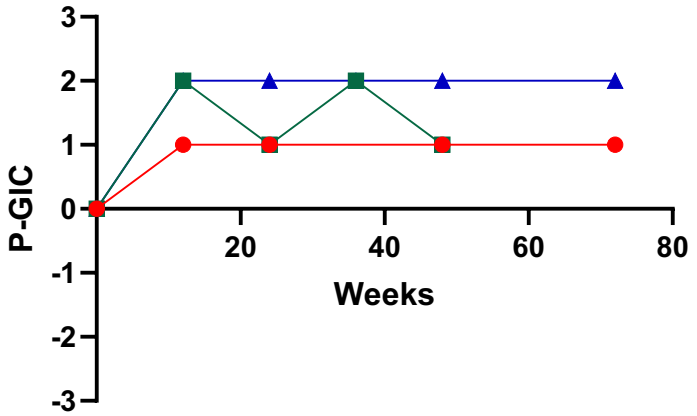


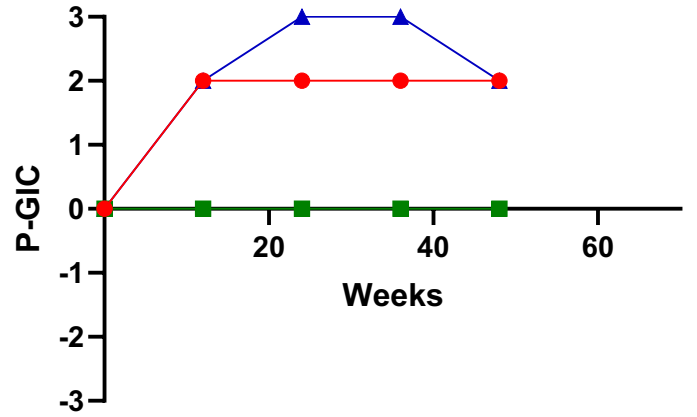
Cohort 3 (1.8mg/kg) (n=3)*

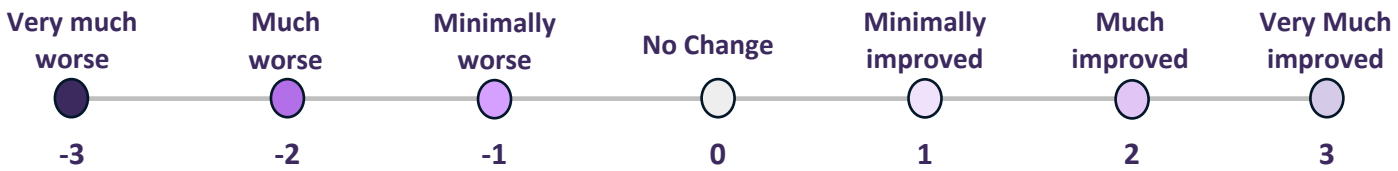


Patient's Global Impression







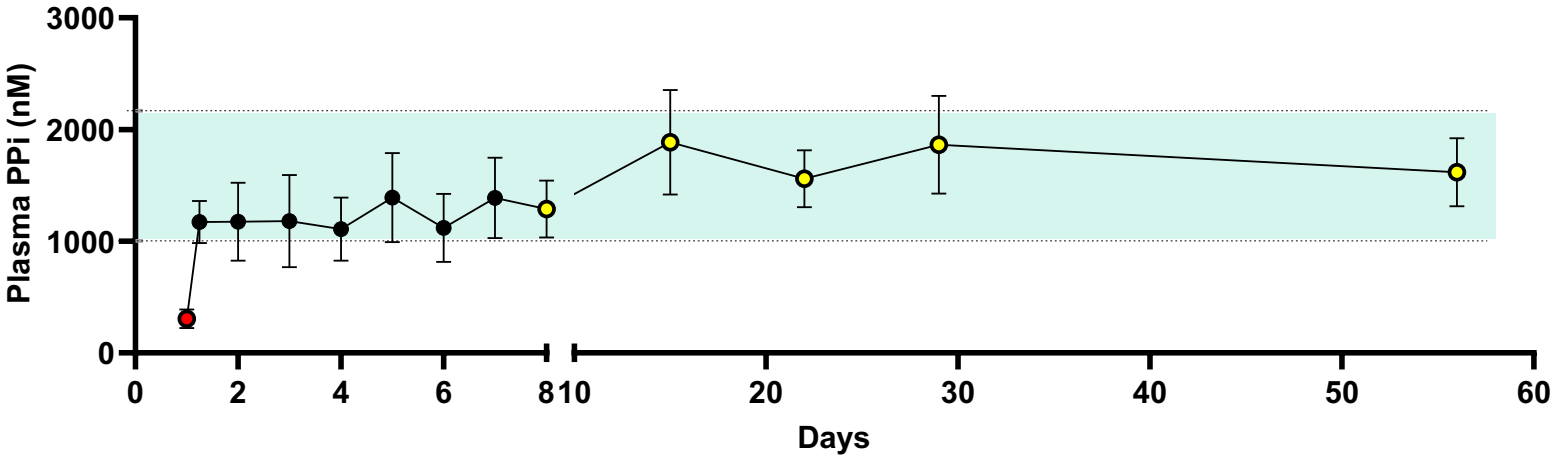


* n=2 for C-GIC

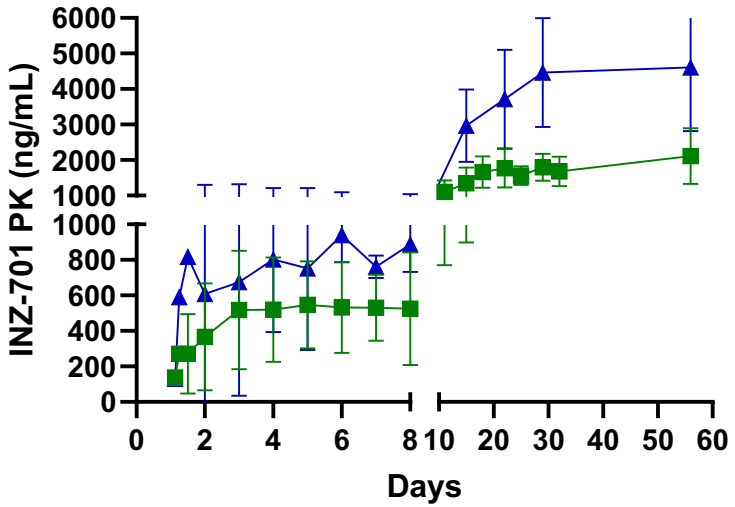
Data cut 25 Jan 24
Colors represent individual patients in respective cohorts

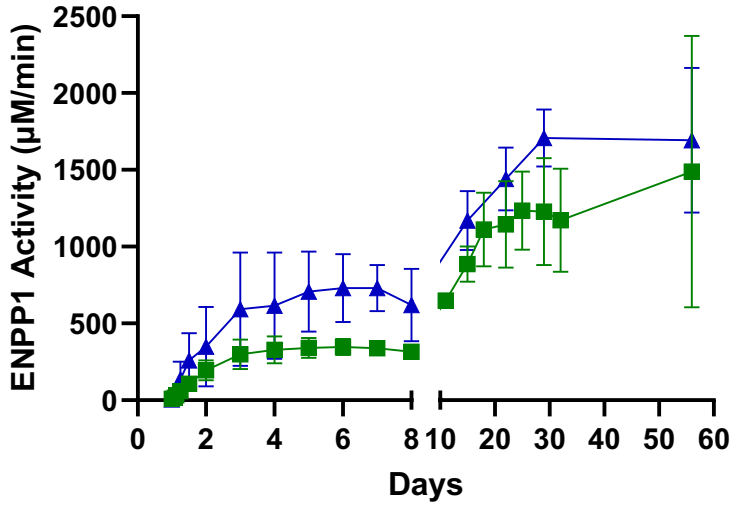
Cohort 4: Once-weekly dosing increased PPi into the normal range and demonstrated consistent drug exposure

Consistent exposure seen with weekly dosing comparing 0.6 mg/kg bi-weekly vs. 1.2 mg/kg once weekly



- Baseline PPi (pre-dose) + 1st INZ-701 dose
- PPi measurement (post-dose)
- PPi measurement (pre-dose)
- Healthy subject PPi levels; n=10
- Data presented as mean ± SEM





- Cohort 2 (0.6 mg/kg; 2x/wk)
- Cohort 4 (1.2 mg/kg; 1x/wk)

PK & ENPP1 Data cut – 4 Mar 2024; PPi reported on a rolling basis

Event agenda

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Topline Data: ENPP1 Deficiency Phase 1/2 Trial

Key Takeaways

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Phase 1/2 trial of INZ-701 in adults with ENPP1 Deficiency successfully met all study objectives

Safety

- ✓ **Favorable safety profile** was maintained
- ✓ Low/moderate, sometimes transient, ADA titers

PK/PD

- ✓ **PK data** from cohort 4 **support once-weekly dosing**
- ✓ **PPi remained elevated** with long-term treatment

Clinical

- ✓ Favorable response on **clinical outcomes** (PROs and 6MWT) was **maintained**
- ✓ Bone biomarker response consistent with restoring proper bone mineralization

Phase 1/2 trial of INZ-701 in adults with ABCC6 Deficiency successfully met all study objectives

Safety

- ✓ INZ-701 demonstrated a **favorable safety profile**
- ✓ No serious or severe adverse events
- ✓ Low/moderate, sometimes transient, ADA titers

PK/PD

- ✓ **Rapid** and **sustained increase in PPi** observed in highest dose cohort (1.8 mg/kg)

Clinical

- ✓ **Positive changes** in carotid intima-media (cIMT) thickness and choroidal layer of eye support **improvements in vascular health**
- ✓ Improvement in visual function (VFQ-25) and multiple PROs observed

VFQ-25: Visual Function Questionnaire; PRO: Patient Reported Outcomes; ADA: Anti-drug antibodies

Focused on pediatric population with ABCC6 Deficiency

Unmet Need

- ✓ Retrospective natural history study (early-onset) and interventional study (adults) identified **risk of stroke** and **retinal disease** as consistent presentation in ABCC6 Deficiency

Market

- ✓ Market research identified **substantial pediatric population** that represents the most important unmet need in ABCC6 Deficiency

Regulatory

- ✓ Phase 3 trial design planning in progress
- ✓ Plan to seek **accelerated approval** based on imaging metric predictive of ischemic stroke

Event agenda

Welcome

ABCC6 Deficiency: Disease Overview

Topline Data: ABCC6 Deficiency Phase 1/2 Trial

Retinal Disease

ABCC6 Pediatric Disease – A Critical Unmet Need

- Early-Onset ABCC6 Deficiency – Natural History Study
- Pediatric Stroke – Case Study
- Market Overview

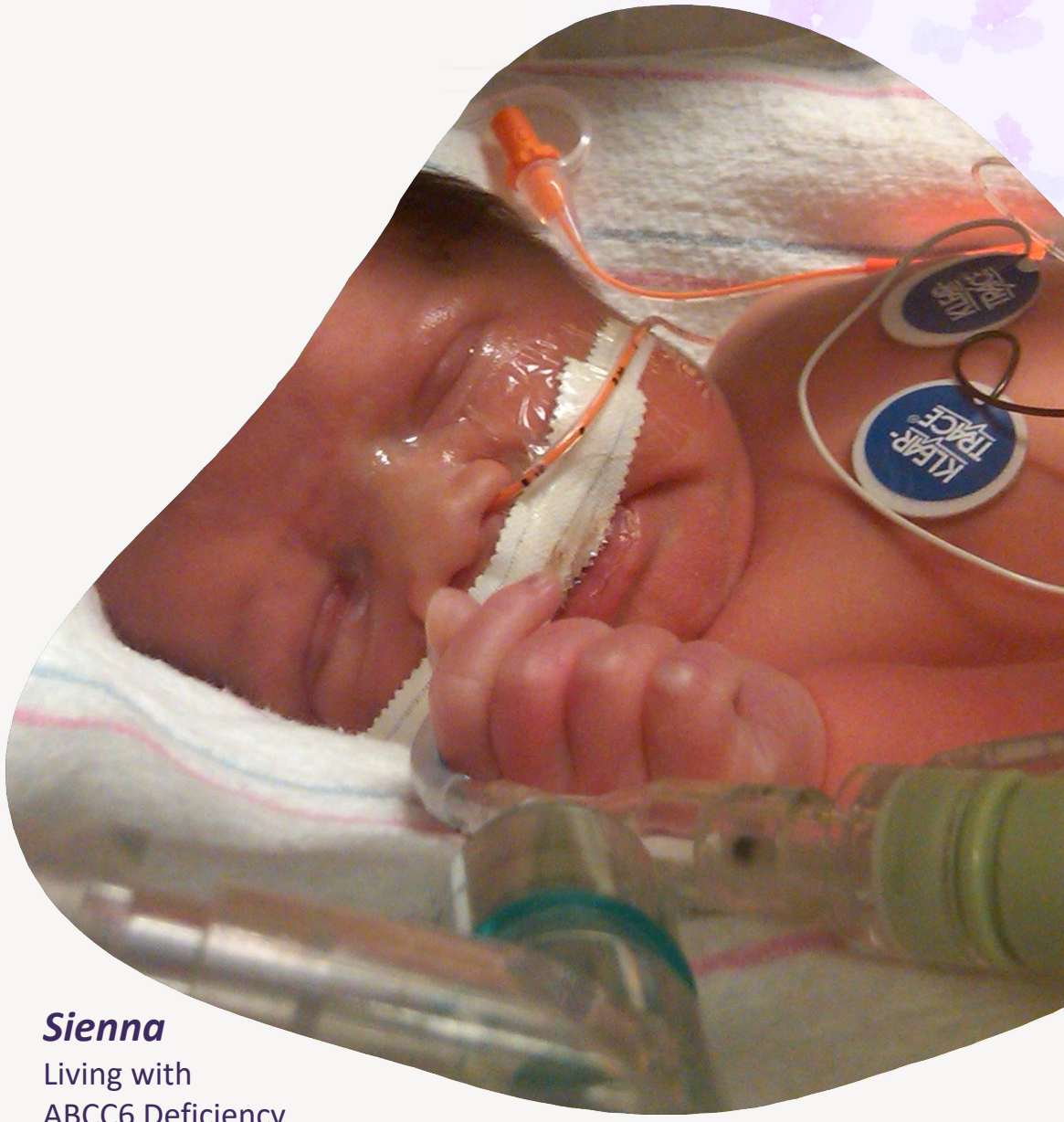
ABCC6 Deficiency Regulatory Strategy

Topline Data: ENPP1 Deficiency Phase 1/2 Trial

Key Takeaways

Question and Answer

Thank you to the patient community, physicians and investigators



Sienna
Living with
ABCC6 Deficiency