Small Molecule Genetic Therapies for Rare Diseases

Corporate Presentation

July 2024

Forward-looking statements

This presentation contains forward-looking statements, which are generally statements that are not historical facts. Forward-looking statements can be identified by the words *"expects," "anticipates," "believes," "intends," "estimates," "plans," "will," "outlook"* and similar expressions. Forward-looking statements are based on management's current plans, estimates, assumptions and projections, and speak only as of the date they are made. We undertake no obligation to update any forward-looking statement in light of new information or future events, except as otherwise required by law. Forward-looking statements involve inherent risks and uncertainties, most of which are difficult to predict and are generally beyond our control. Actual results or outcomes may differ materially from those implied by the forward-looking statements as a result of the impact of a number of factors, including: the development of the Company's readthrough technology; the approval of the Company's patent applications; the Company's ability to successfully defend its intellectual property or obtain necessary licenses at a cost acceptable to the Company, if at all; the successful implementation of the Company's research and development programs and collaborations; the Company's ability to obtain applicable regulatory approvals for its current and future product candidates; the acceptance by the market of the Company's products should they receive regulatory approval; the timing and success of the Company's preliminary studies, preclinical research, clinical trials, and related regulatory filings; the ability of the Company to consummate additional financings as needed; the impact of global health concerns, such as the COVID-19 global pandemic, on our ability to continue our clinical and preclinical programs and otherwise operate our business effectively; including successfully integrating the combined companies; as well as those discussed in more detail in our Annual Report on Form 10-K and our other reports filed with the Securities and Exchange Commission.

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Two clinical stage disease-modifying small molecule therapies supported by global partnership

Small molecule Genetic Premature Termination Codon readthrough therapies

ELX-02 — Pivotal Stage Ready Rare Genetic Kidney Therapy

Alport syndrome nonsense mutation (NMAS) patients

>$5 billion peak sales potential	Disease modifying **MOA validated** in Phase 2 POC study	Orphan Drug Designation
Positive FDA Pre IND feedback	Ready to start trial in the **UK**	

ZKN-013 — Phase 1 Rare Genetic Skin and Colon Disease Therapy

Nonsense Mutation RDEB and FAP

Robust preclinical **efficacy with survival benefit** in FAP

Exclusive global partnership with **Almirall**

- Up to **$470 million** in milestones
- Tiered royalties on global sales with peak sales potential of **>$5 billion**

RDEB: Recessive Dystrophic Epidermolysis Bullosa; FAP: Familial Adenomatous Polyposis

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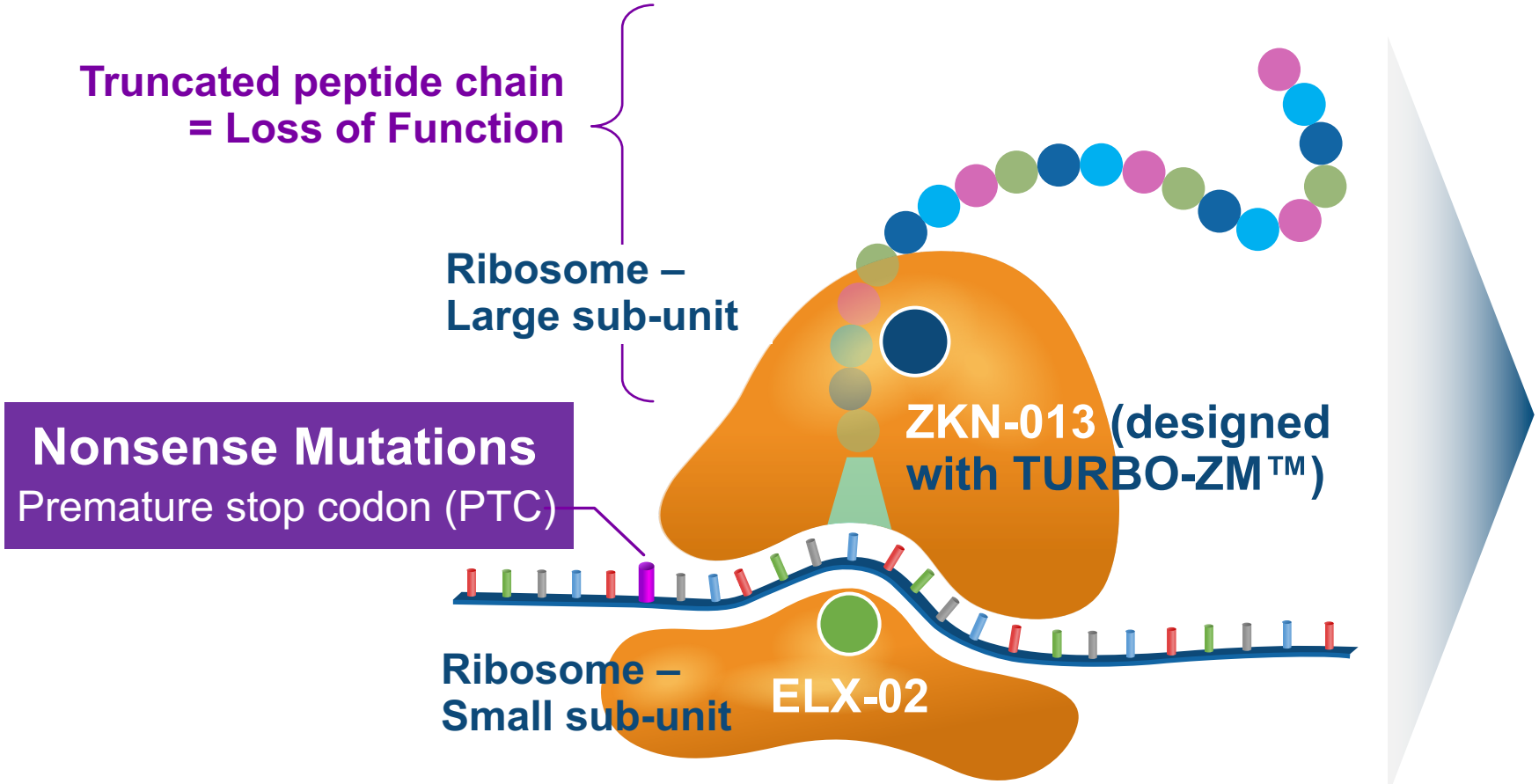
First in class RNA-targeted therapeutics that induce full-length functional proteins

MOA: Restore full-length protein by inducing readthrough of premature stop codon mutations caused by nonsense genetic mutations



ELX-02 and ZKN-013 rationally designed with superior efficacy and safety to gentamicin and erythromycin

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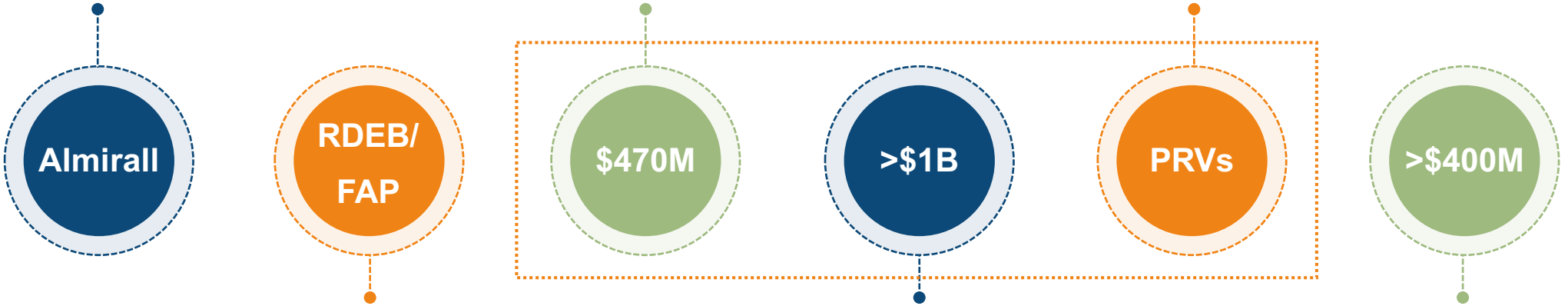
ZKN-013 exclusively licensed to Almirall; unlocks significant value from pipeline validating TURBO-ZM platform

ZKN-013 Global development and commercialization rights to Almirall

Eloxx eligible to receive up to $470 million in development, regulatory and sales milestones

Potential for Priority Review Vouchers (PRVs) for each indication



Provides entry into rare diseases, with initial focus on PTC readthrough in RDEB and FAP

Tiered royalties >$1B on sales with peak sales potential of >$5 billion

Total deal net present value to Eloxx >$400M

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ELX-02: Pivotal stage ready novel genetic therapy to treat Alport patients with nonsense mutations (NMAS)

ELX-02: PTC readthrough for NMAS and other rare genetic kidney diseases

Significant Opportunity

14,000 patients*

No Approved Drugs

Orphan Drug (ODD); Rare disease pricing

Potential for Priority Review Voucher

Robust clinical and non-clinical safety and efficacy validation

ELX-02 reversed structural kidney damage in 3 NMAS patients after only 8 weeks in Phase 2

Protein restoration and function in multiple animal studies

Gene agnostic readthrough

145 subjects treated with 89.4 months exposure; safe in chronic tox studies

Supported Development Plan

FDA supported trial design to validate P2 results

Ready to initiate Study in UK: Supported by RaDaR**

*Developed Markets
** UK Registry of Rare Renal Diseases

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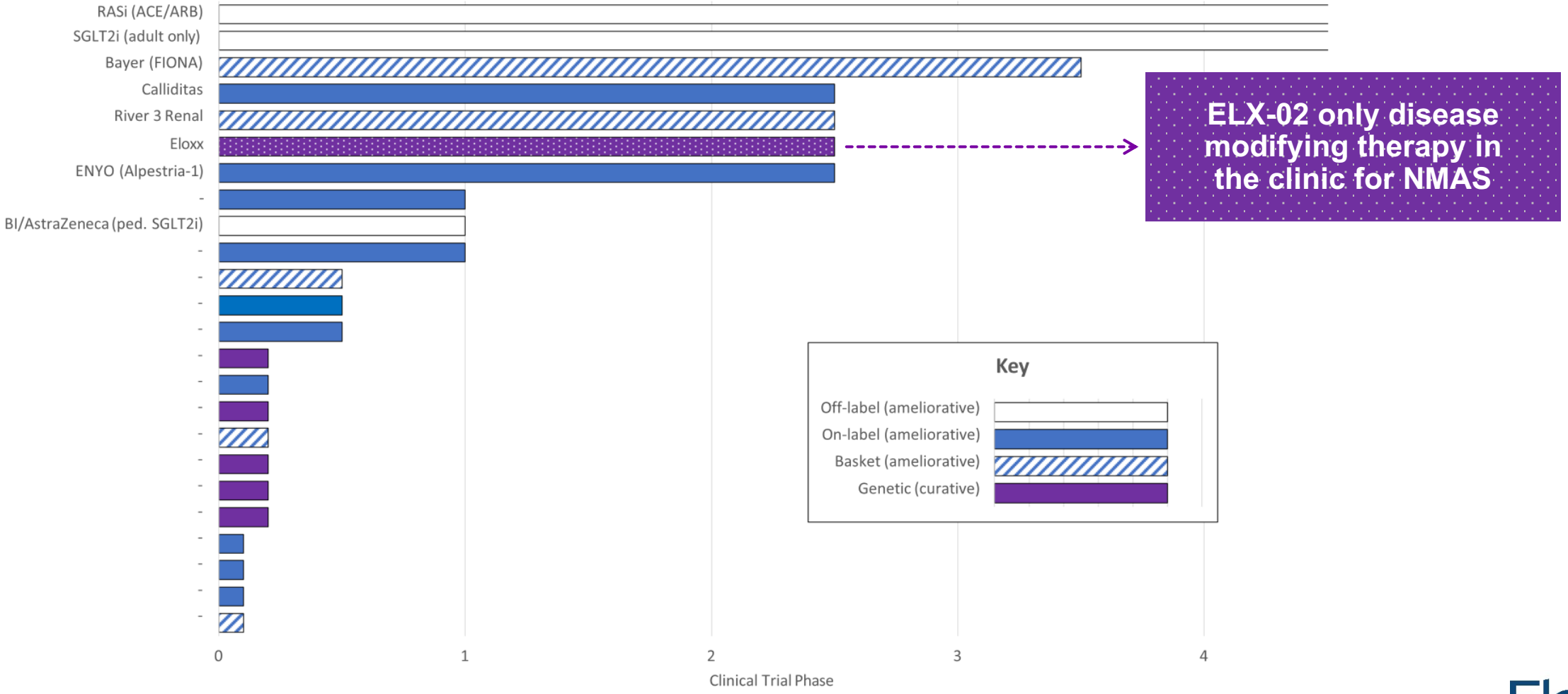
Alport Syndrome Foundation Therapeutic pipeline: ELX-02 only disease modifying therapy in the clinic

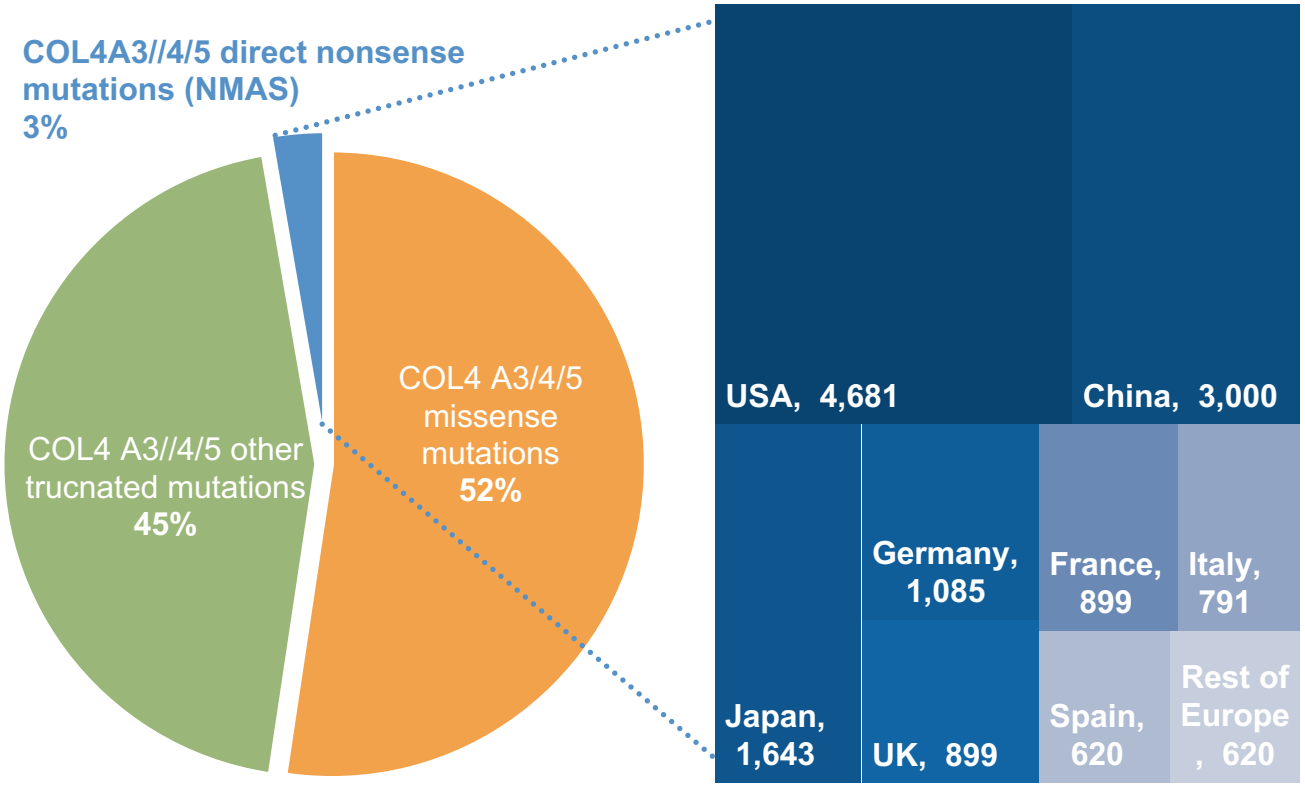
Alport syndrome therapeutic pipeline [June 2024]



NMAS is an ultra-rare, majority pediatric and significantly debilitating genetically driven subset of Alport Syndrome (AS)

Disease prevalence: AS and NMAS

NMAS prevalence N = Approx 14,000



Disease Overview: AS and NMAS

- Truncated collagen 4 alpha proteins result in loss of function in the GBM
- GBM irregularities; podocyte foot process effacement (FPE) and podocyte loss
- No approved therapies
- All patients reach kidney failure and hearing loss before 30 years of age
- High patient dissatisfaction amongst all AS patients with current treatment options*

GBM: Glomerular Basement Membrane

* AS patients as reported in a recent Externally-Led Patient-Focused Drug Development meeting, with 87% of patients either moderately or not at all satisfied (Feldman 2019)

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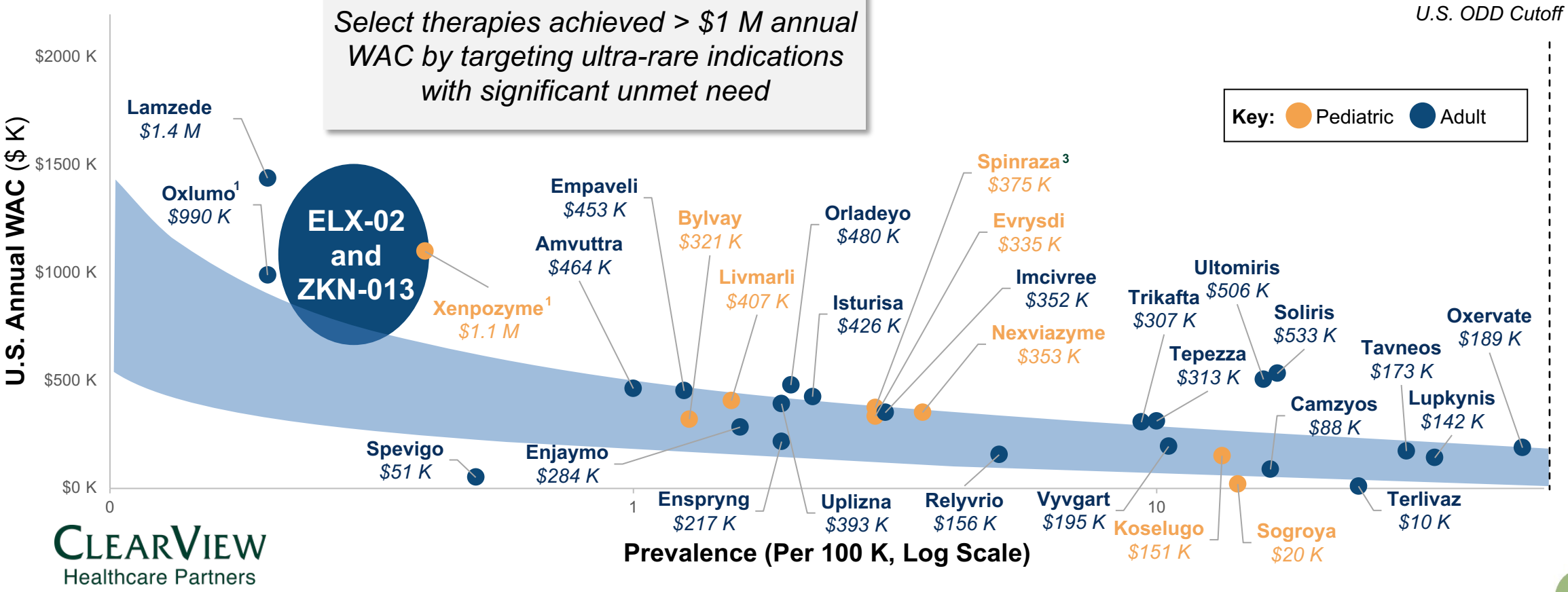
U.S. non-oncology orphan drug pricing supports substantial pricing headroom for ELX-02 and ZKN-013

Prevalence vs. Launch Price for Select Non-Oncology Therapies in the U.S.

NON-EXHAUSTIVE

Illustrative and Selective

Select therapies achieved > $1 M annual WAC by targeting ultra-rare indications with significant unmet need



ClearView Healthcare Partners

1 Represents annual WAC for pediatric population; 2 Evans. BJPsych Bull. 2017; 3 Represents Spinraza's maintenance dose. First year of treatment including initial loading doses and remaining maintenance doses totals to ~$750 K. ODD: Orphan Drug Designation; WAC: Wholesale Acquisition Cost. Source: FDA Labels; Navlin; ClearView Analysis.

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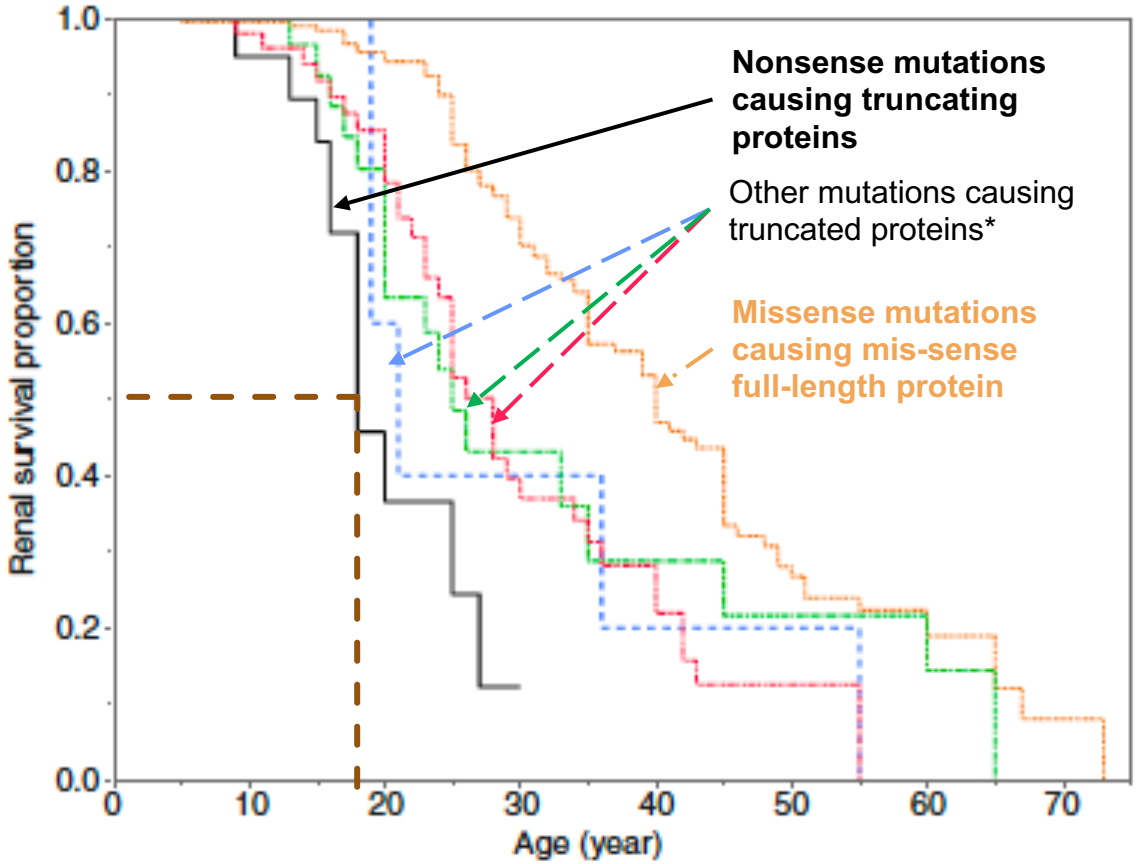
Natural history studies confirm the rapid progression to kidney failure of NMAS patients

Renal survival proportion based on mutation type and transcript variant in 248 Japanese patients with COL4A5 variants and RaDaR natural history



RaDaR Natural History for NMAS patients:

- NMAS patients with COL4A3/4 mutations have even more severe decline in kidney function with mean age at diagnosis of 9.1 years and mean age at kidney failure of 20 year
- eGFR decline of -6.9 (COL4A5) to -22.4 (COL4A3/4) ml/min/1.73m2/year
- *COL4A5* males with all truncating proteins have mean eGFR at diagnosis of 60.1average
- Rapid progression to kidney failure in patients with UPCR >1g/g (RaDaR)

* Yamamura, Horinouchi, Nagano, et al. 2020. Other truncating protein mutations include large rearrangement, splicing variant and small rearrangement

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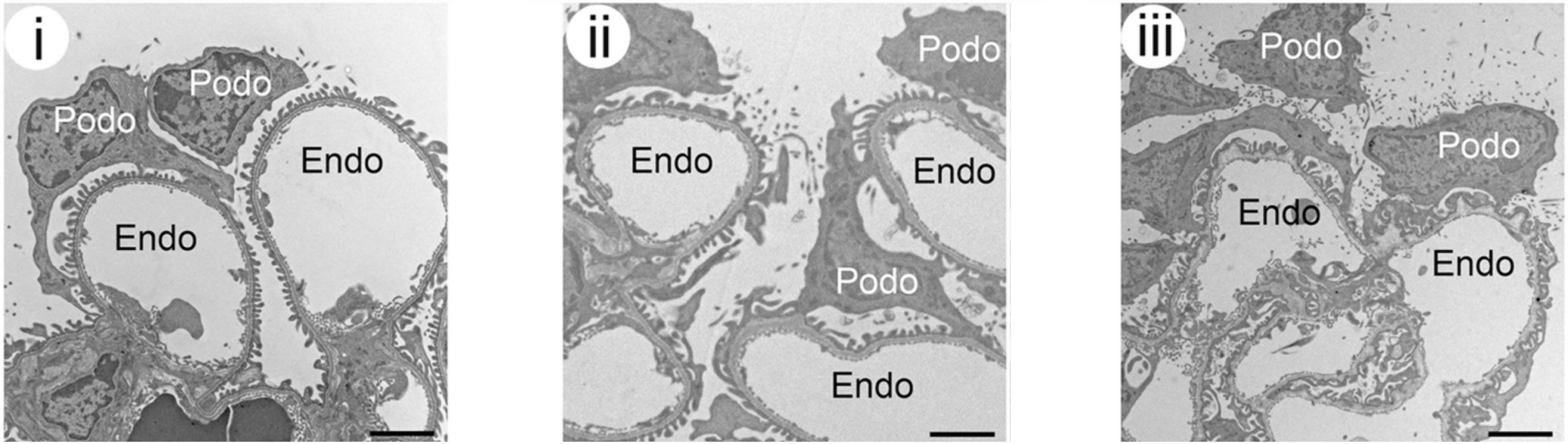
NMAS is a progressive disease characterized foot process effacement (FPE) and podocyte loss

Comparison of glomerular structures between Wt and Col4a3 knockout mice

Wild Type	*Col4a3+/-*	Col4a3-/- (NMAS)



Absence of any one of the Col IV a3, a4 or a5 proteins results in altered GBM morphology and loss of podocyte foot process architecture

Sci Rep **7**, 11696 (2017). https://doi.org/10.1038/s41598-017-12064-5

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ELX-02 induces new collagen 4 by podocytes for treatment benefit in NMAS patients

ELX-02: Small molecule PTC readthrough genetic therapy for protein restoration

Nonsense mutations in COL4A43/4/5

NMAS Disease Pathogenesis → **PTC and loss of functional protein** → **Podocyte injury Podocyte Foot Process Effacement (FPE)** → **Proteinuria** → **Podocyte loss** → **eGFR decline and Kidney failure**

Treatment effect of ELX-02 therapy	**Induces full-length Collagen protein** by podocytes by readthrough of PTC	**Reduces FPE** by regulating integrin signaling pathways in the podocytes resulting in an increase in foot processes and increase in slit diaphragms	Reduced FPE **reduces severity of proteinuria** if podocyte loss is not advanced prior to treatment	**Slows/reduces loss** of post-mitotic podocytes	**Delays progression** to kidney failure

PTC= Premature Termination Codon

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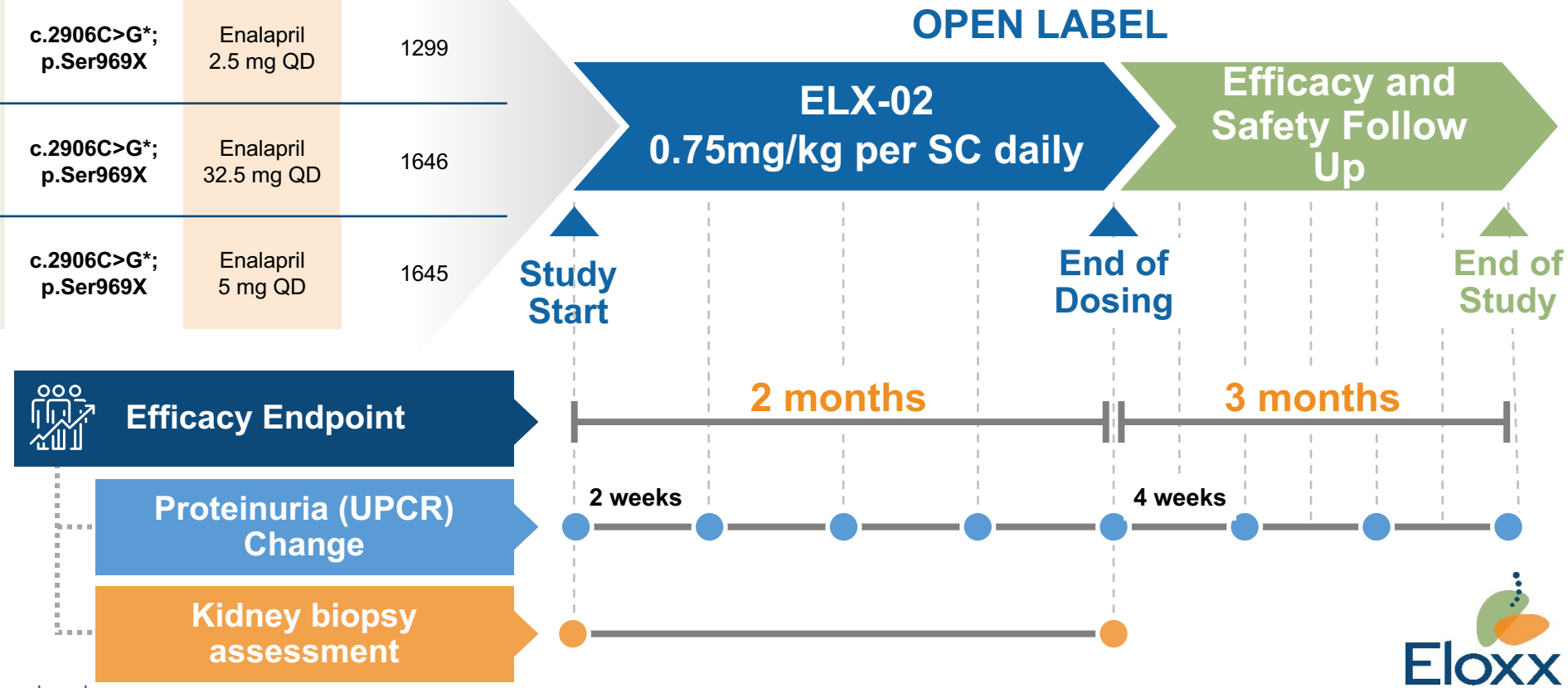
Completed Phase 2 UK study of ELX-02 in Patients with Alport Syndrome

Baseline characteristics of patients and Phase 2 trial design (COL4A5 and COL4A3/4 Nonsense Mutations (NCT05448755)

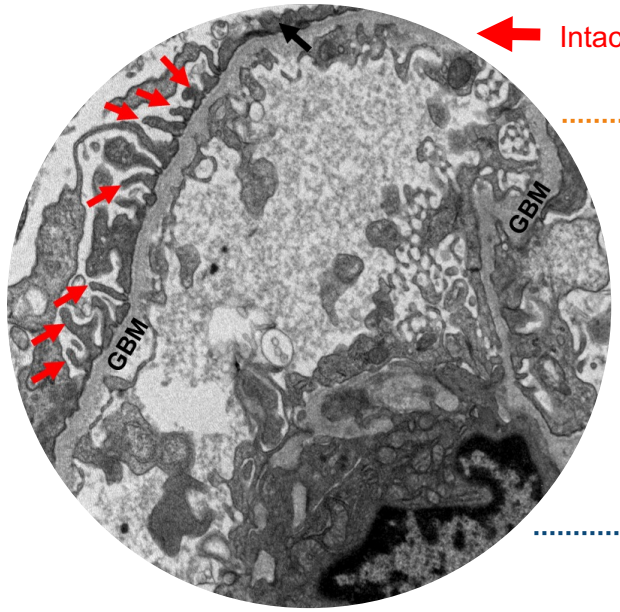
Patient	Age	Sex	COl4 Gene Affected	Nonsense Mutation	RAAS Block dose	Proteinuria (mg/g)
4401-01	12	Male	COL4A4	**c.2906C>G*; p.Ser969X**	Enalapril 2.5 mg QD	1299
4401-02	12	Male	COL4A4	**c.2906C>G*; p.Ser969X**	Enalapril 32.5 mg QD	1646
4402-01	19	Female	COL4A4	**c.2906C>G*; p.Ser969X**	Enalapril 5 mg QD	1645



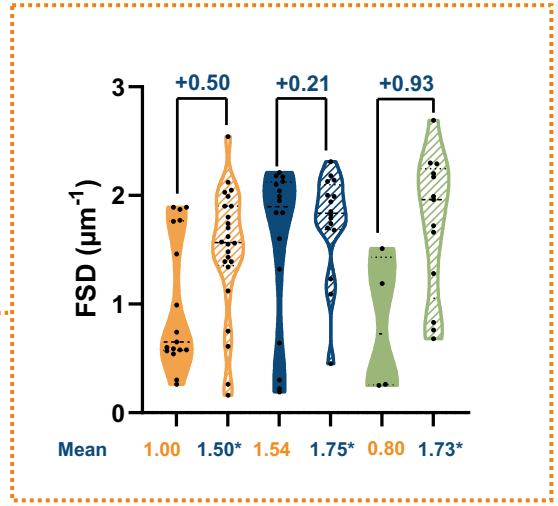
Sponsor: Eloxx Pharmaceuticals, Inc.; www.eloxxpharma.com

Study Results: Treatment with ELX-02 resulted in structural improvement and clinical benefit

Reduction of Foot Process Effacement (FPE) in all 3 patients



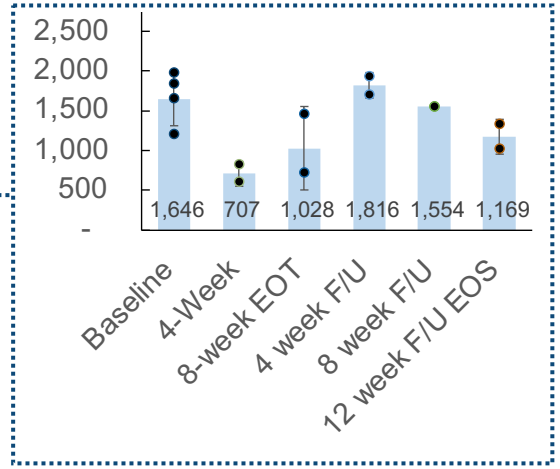
Qualitative assessment by Mayo Clinic and Univ of Washington. Increase in *COL4A5* expression in the GBM



Marginally Significant Increase in Filtration Slit Density (FSD)

Ad hoc p value =0.06 indicates large treatment effect

All patients reached meaningful improvement relative to healthy values



UPCR stable/declining at EOT and up to 8 weeks after treatment

37.8% reduction at EOT in 1 patient that also had FSD increase to 85% of normal at EOT

25% reduction at 4-and 8-weeks post treatment in 2nd patient with FSD increase to 84% of normal

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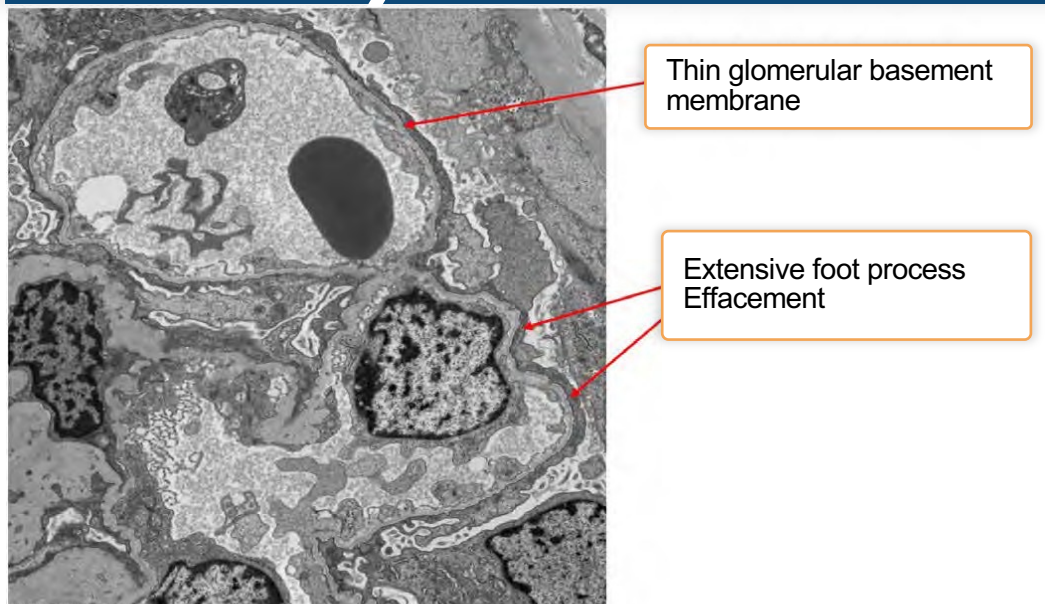
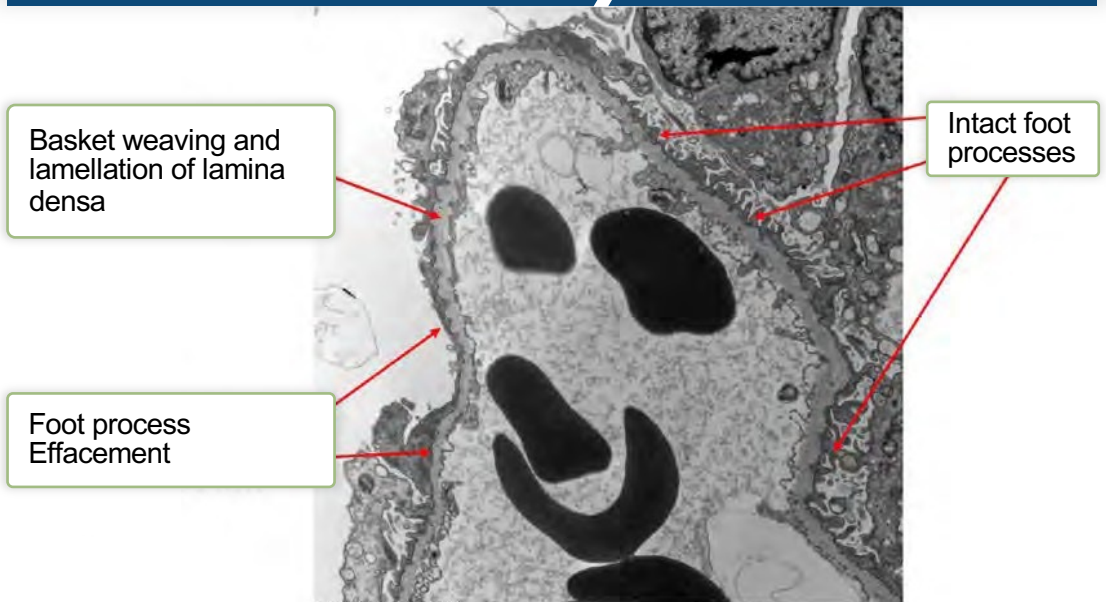
ELX-02 treatment reduced foot process effacement (FPE) in all 3 treated patients after ONLY 8 weeks

Representative TEM images pre-and post treatment in Study EL-014

Pre-treatment: Extensive FPE



Post-treatment (Day 60): Reduced FPE



Original assessment by Mayo Clinic validated and quantified by Dr. Behzad Najafian at Univ Of Washington (leading kidney pathologist and TEM expert)

TEM images and analysis done at Mayo Clinic by kidney pathologist on a blinded basis

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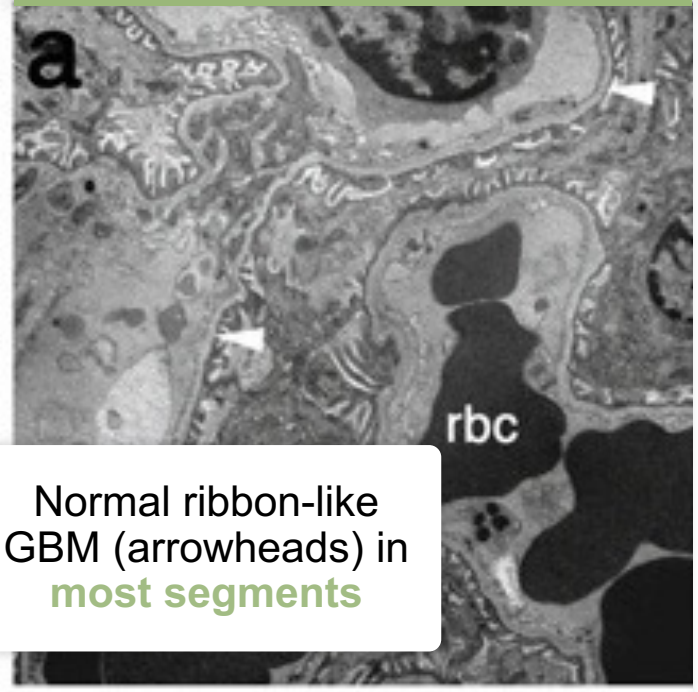
Similar disease regression seen in rescued Col4a3 mutant mice after 20 weeks of treatment

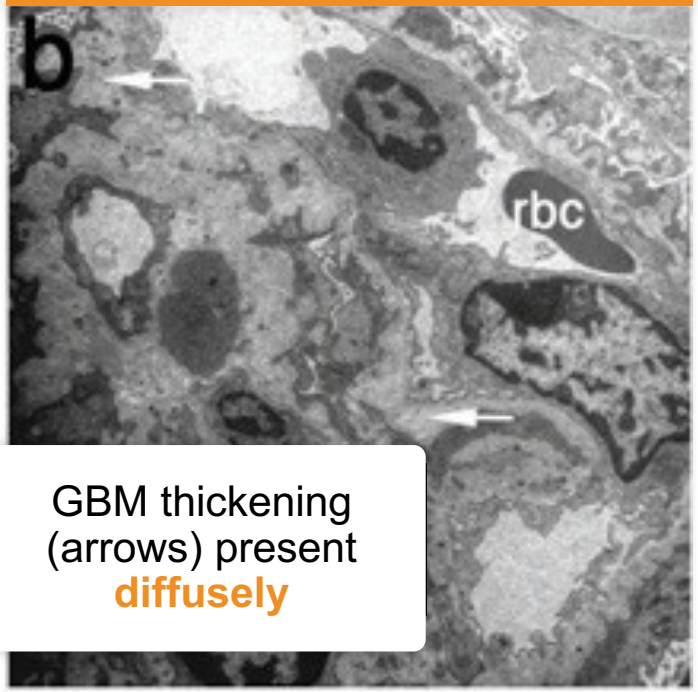
Ultrastructural assessment of glomerular capillary wall and podocyte foot process effacement in wildtype, Alport and rescued mice (at 20 weeks)

Col4a3$^{+/-}$ Mouse at postnatal day 0



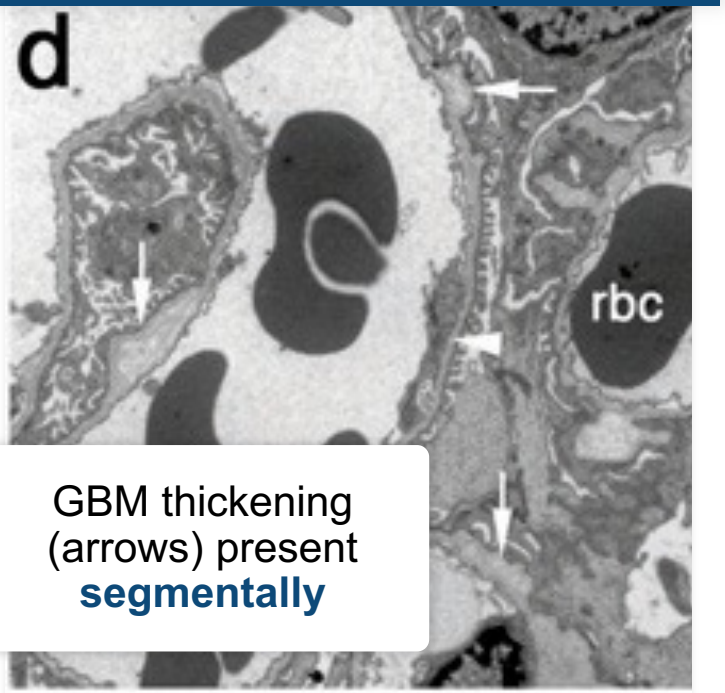
Normal ribbon-like GBM (arrowheads) in **most segments**

Col4a3$^{-/-}$ mutant mouse



GBM thickening (arrows) present **diffusely**

Col4a3$^{-/-}$ Mouse rescued at post natal day 21 for 20 weeks



GBM thickening (arrows) present **segmentally**

Feasibility of Repairing Glomerular Basement Membrane Defects in Alport Syndrome; Jeffrey Miner et al. J Am Soc Nephrol 25: 687–692, 2014. doi: 10.1681/ASN.2013070798

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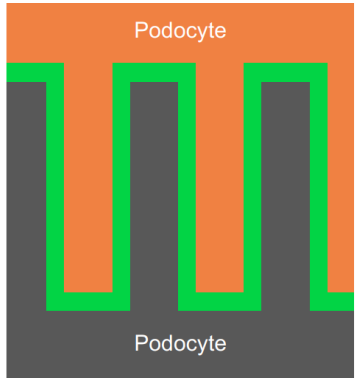
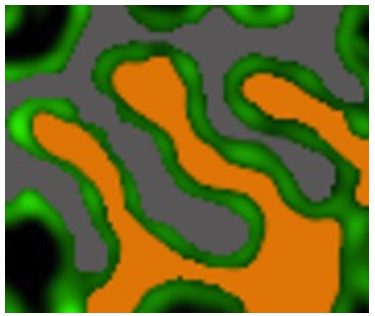
Foot Process Effacement quantified with Filtration Slit Density (FSD)

Unbiased assessment of filtration slit density (FSD)

Healthy foot process (FP)



Apical view



Filtration Slit

Filtration Slit Density (FSD)

Filtration Slit Length over surface area

Correlated to disease severity:
Alport, Fabry nephropathy, diabetic nephropathy, FSGS, and minimal change disease

Method 1: Manual

Transmission Electron Microscopy (TEM)

Unbiased stereology

Filtration slit length over peripheral GBM area
- 2-4 glomeruli assessed
- Diagnosis in glomerular diseases

Method 2: Automated

3D Structured Illumination Microscopy (SIM) In FFPE*

High magnification immunofluorescence

Filtration slit length over foot process area
- Automated glomeruli selection
- Immunostaining with podocin (filtration slits) and synaptopodin (foot process area)
- Differentiate between healthy, treated and diseased in animal and human studies and between primary and secondary FSGS
- Strongly correlated with TEM assessments (Siegrist 2007)

- Developed by Nipoka applied on apical view of podocyte morphology in Formalin Fixed Paraffin embedded (FFPE) biopsies in a 3D- image created by combining 19 “optical sections” into a maximum intensity projection

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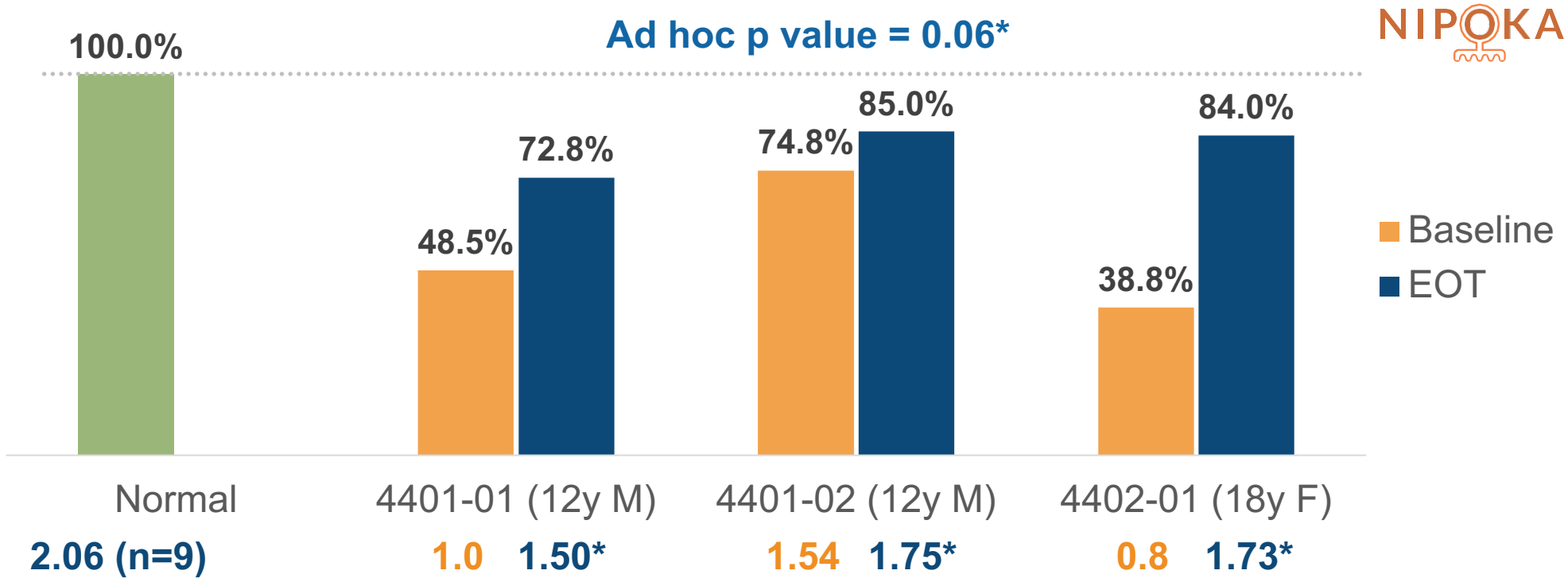
Marginally significant increase in FSD in all 3 NMAS patients with shift to healthy controls supports large treatment effect

FSD (Method 2: 3D-SIM) in NMAS patients in Study EL-014 as percent of healthy subjects in ONLY 8 weeks

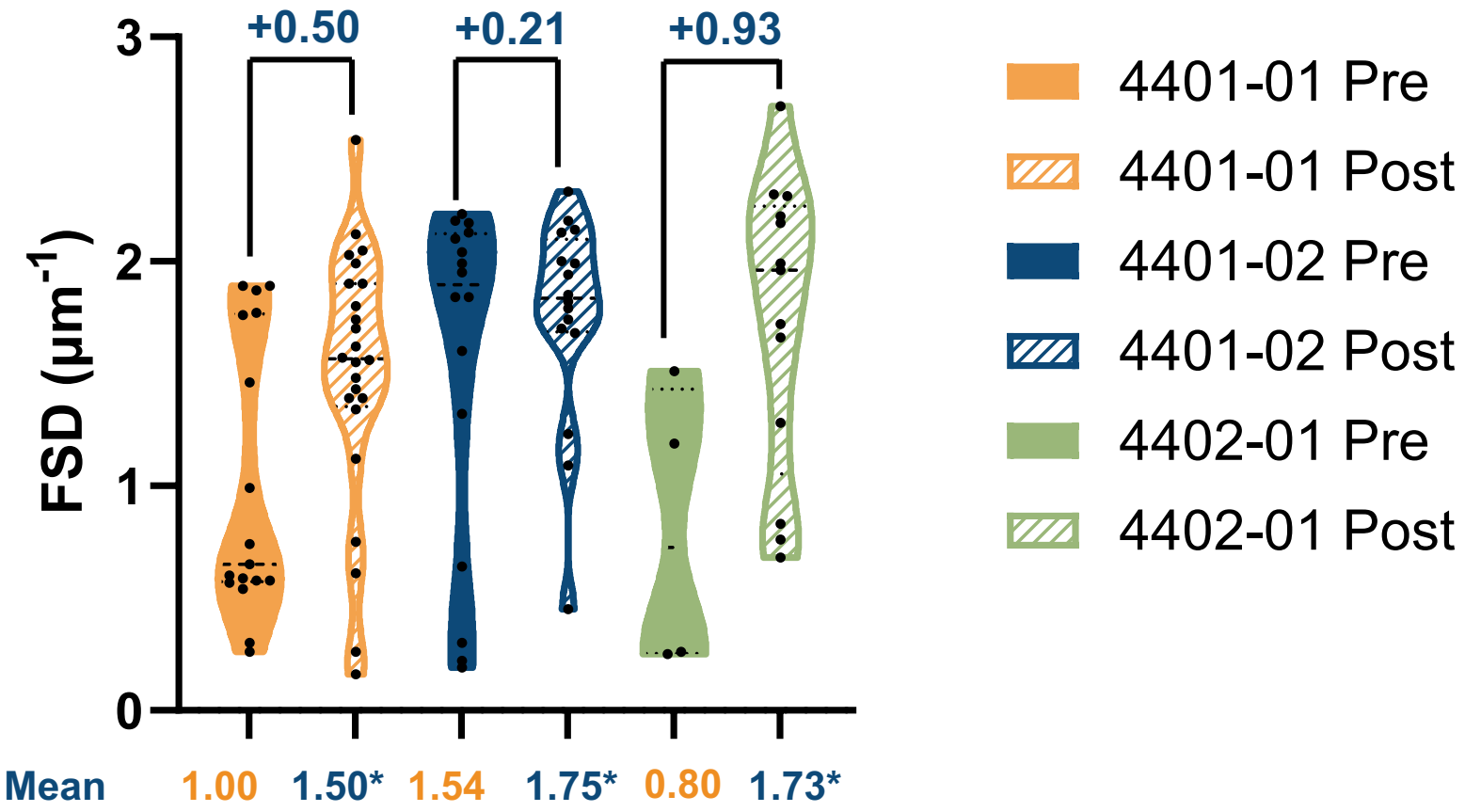


Mean FSD values of 2.06 ± 0.21 μm^{-1} in healthy controls in non-CKD subjects[1].

1 Prospective NURTuRE study (raw data provided by Evotec from TH-PO786 ASN 2023
* Ad hoc p=0.06 based on paired two sample for means t-test (one tail)

Consistent and marginally significant FSD improvement in all 3 NMAS patients after ELX-02 treatment

Distribution of FSD (Method 2) across glomeruli pre and post 8-week ELX-02 treatment in Study EL-014

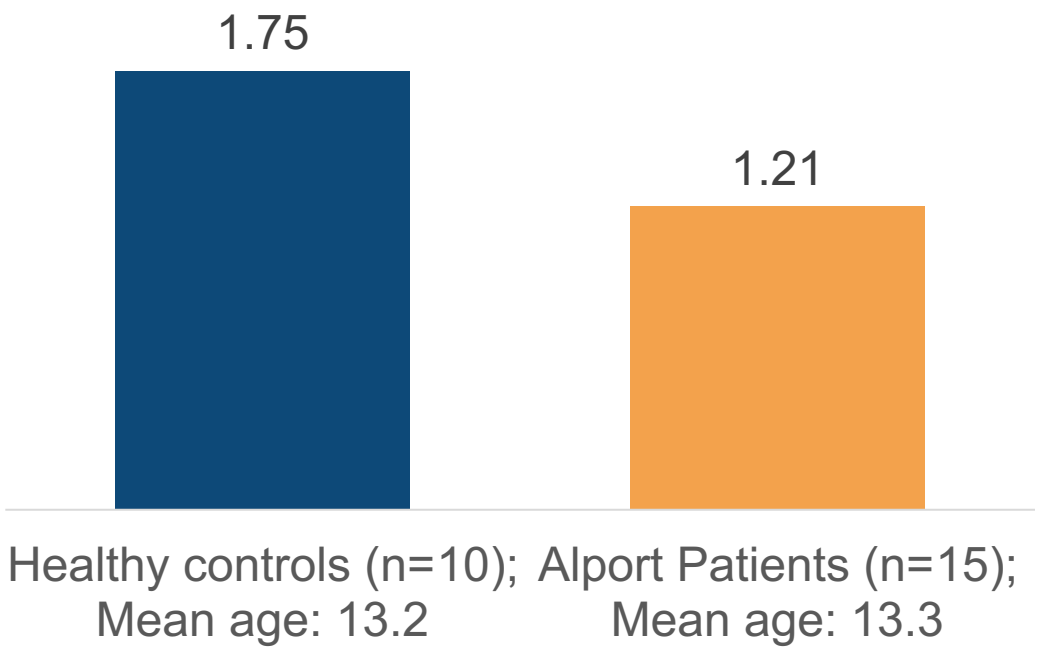


* Ad hoc p value =0.06 based on paired two sample for means t-test (one tail)

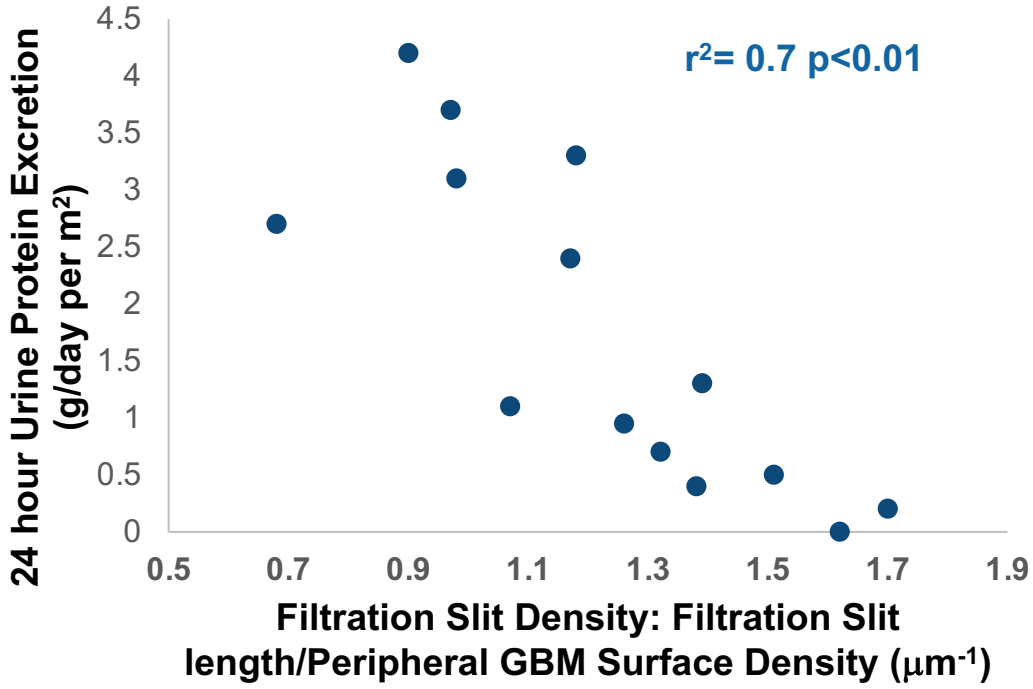
Lower FSD compared to healthy controls in AS patients correlates with higher proteinuria in natural history study

TEM assessment (Method 1) of FSD and function in Alport patients[1]

FSD (TEM based); μm^{-1}



FSD versus 24-hour urine protein excretion (n-=15)



[1] Kim et al J. Am. Soc. Nephrol. 1995; 5: 1659-1668; Data replotted from Kim et al. Age ranges 4- 26 years. FSD assessment using Light microscopy and TEM image analysis of kidney biopsies

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Small FSD changes associated with meaningful changes in UPCR in glomerular diseases

FSD (Method 2) and UPCR in prospective patient kidney biopsies with glomerular diseases

NIPOKA

Disease Type	N	FSD μm^{-1} (%change from normal)	UPCR (mg/g)
Membranous Nephropathy (MN)	10	0.9 (-56%)	6,904
Focal Segmental Glomerulosclerosis (FSGS)	12	1.5 (-27%)	4,430
Minimal Change Disease (MCD)	10	1.4 (-32%)	4,230
IgA Nephropathy	13	1.7 (-18%)	2,841
Healthy controls	**9**	**2.06**	n/a

r^2 of FSD and UPCR = 96.7%

TH-PO786 ASN 2023; Unpublished data provided by Evotec

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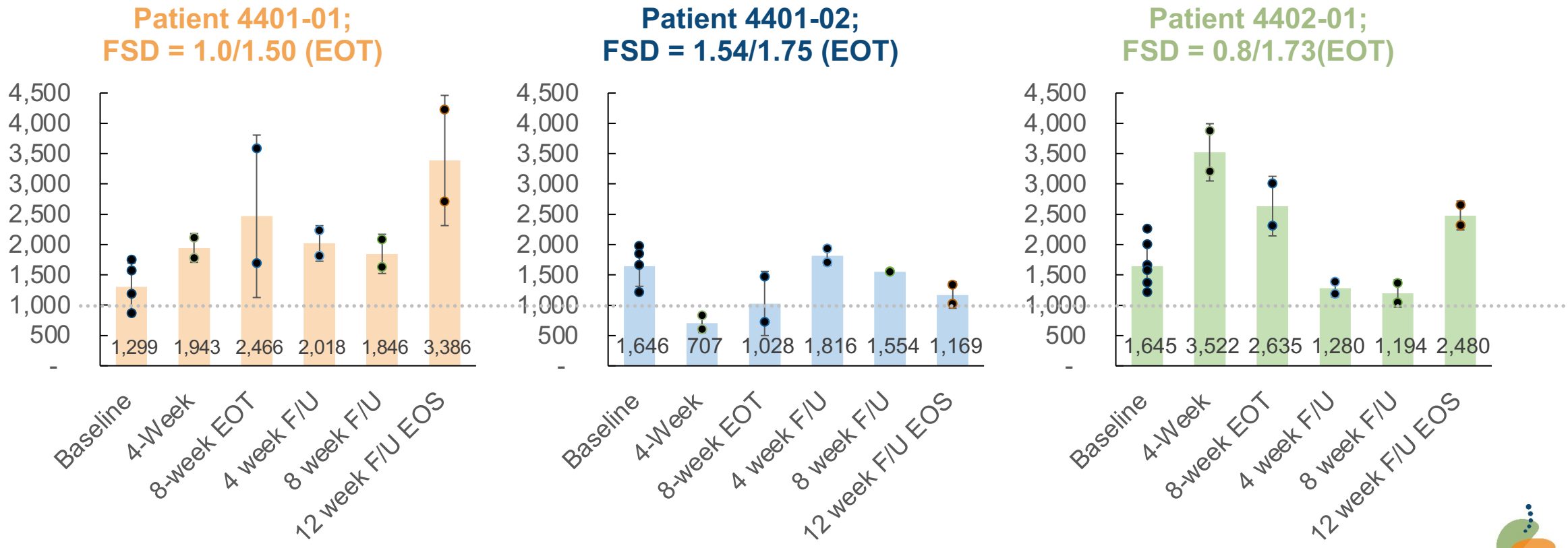
Stable/declining UPCR up to 8-weeks after EOT suggests link to FSD and potential for improvement with longer treatment

UPCR trends in Study EL-014 in 3 NMAS patients, mg/g (geometric means and individual UPCR values from serial measurements*

Stable up to 8-weeks after EOT follow up | Declining/stable | Declining/stable up to 8 weeks after EOT



* Urine sample assessments based on the collection of second void at each day after discarding the first morning void. UPCR measurements taken on 1-day prior to and visit day during study period. Baseline values based on UPCR values from screening, baseline and Day 1 visits. Individual RaDaR natural history studies indicate significant risk reduction at UPCR <= 1000 mg/g

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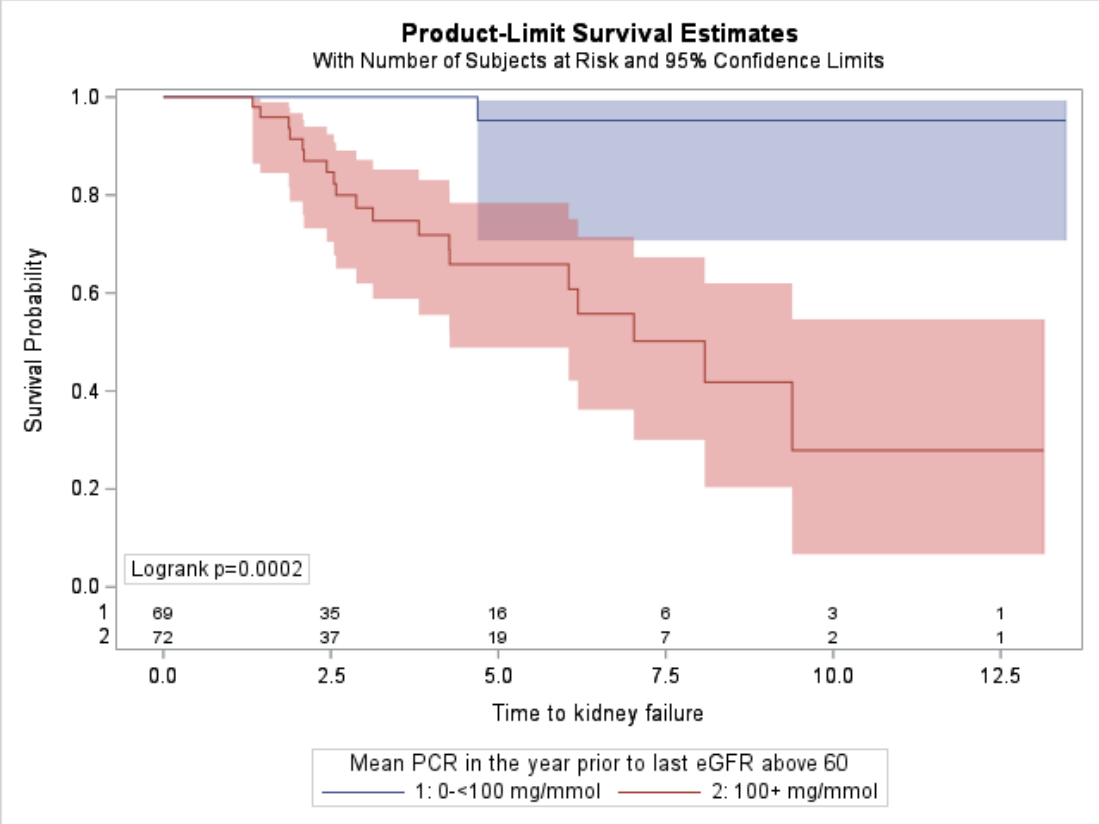
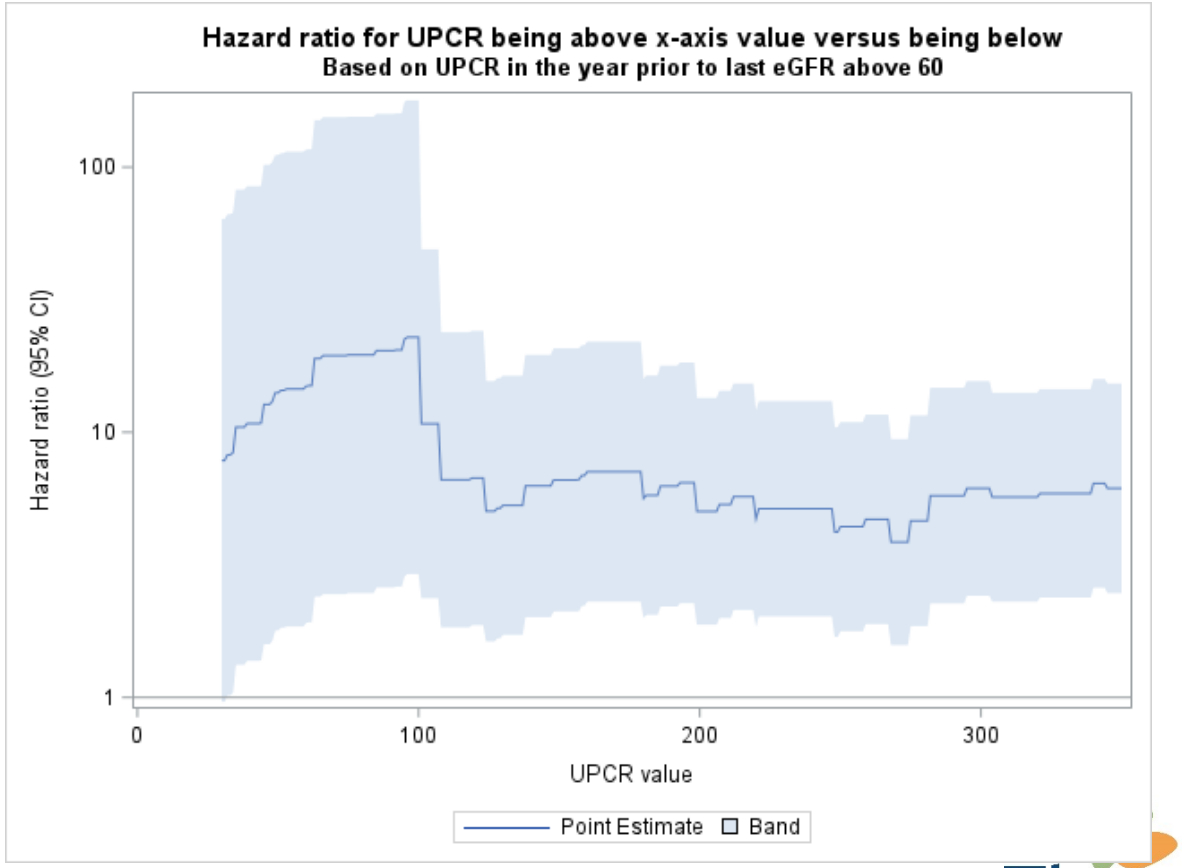
Progression to kidney failure in Alport significantly worse in patients with UPCR >~1g/g at last eGFR above 60

Time to kidney failure based on last eGFR above 60



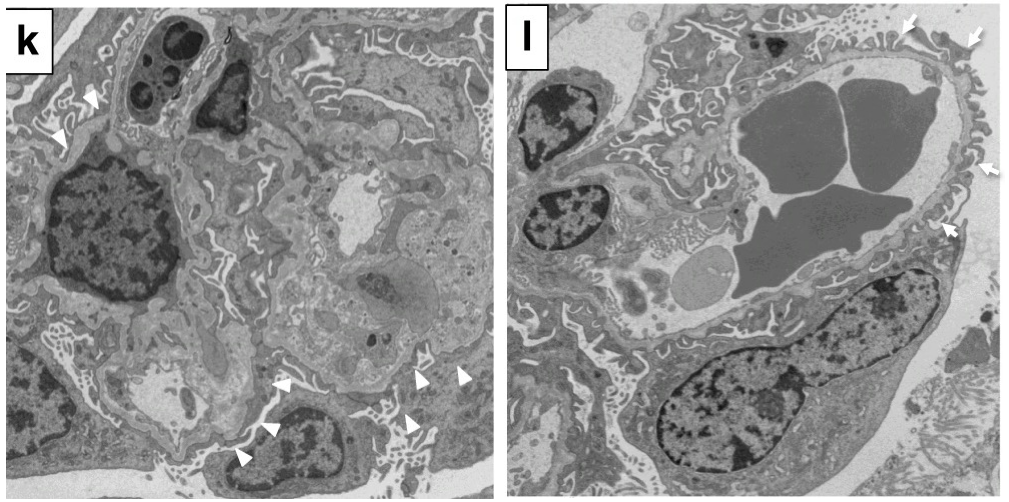
Hazard ratio based on UPCR at last eGFR above 60



Prior mice studies support likely functional benefit with longer treatment duration of ELX-02 in NMAS patients

Exon skipping 16-week treatment in Col4a5 exon 21 frame shift mutation mouse*

Reduction in FPE only observed in treated mouse



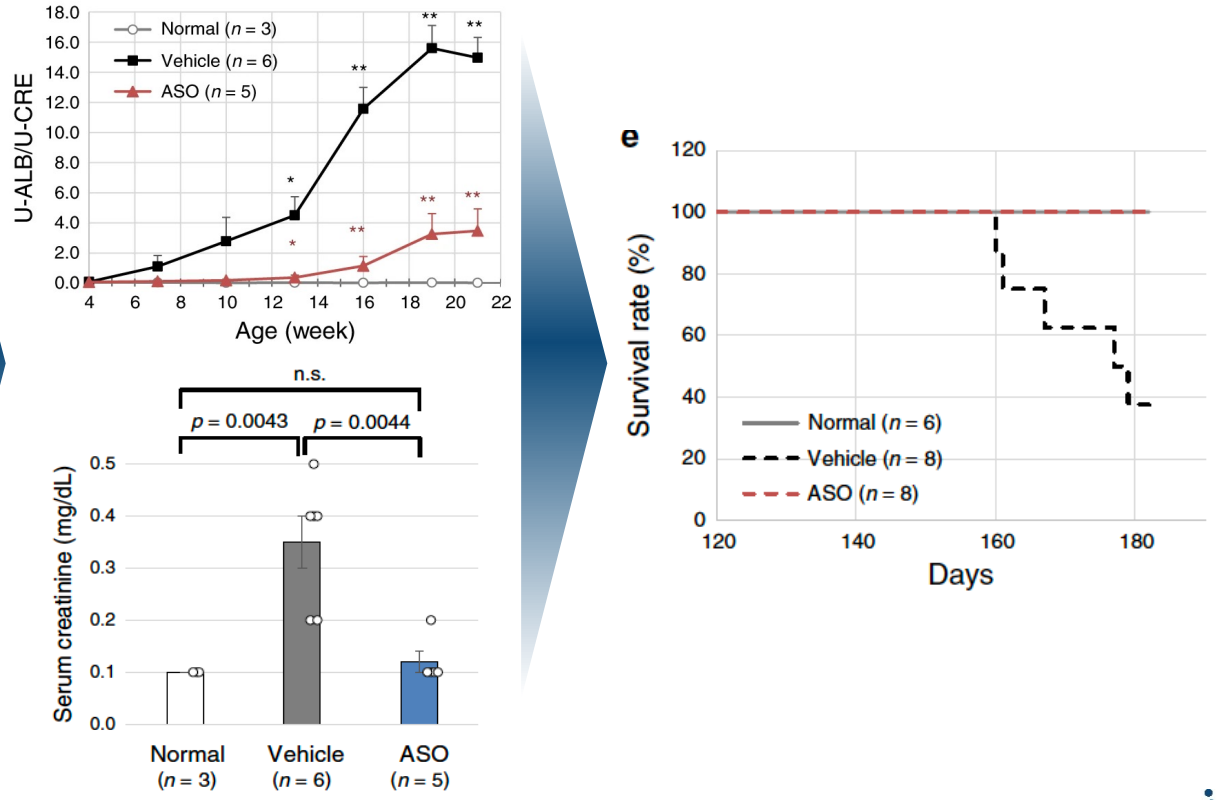
Vehicle treated

Widespread FPE and severe thickening and lamellation of GBM (arrowheads)

ASO treated

Mild irregularity of GBM and reduced FPE (arrows)

Improvement in kidney function and survival



* Col4a5 mutant mouse model with c.1411C > T (p.Arg471*) in exon 21 and this mutation is equivalent to the nonsense mutation of c.1411C > T (p.Gln471*) of human COL4A5

- p<0.05; **p<0.01; ASO: antisense-oligonucleotide

[1] *Nat. Commun.* 11, 2777. Yamamura et. Al 2020https://doi.org/10.1038/s41467-020-16605-x.

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Strong support by Alport community of treating clinicians, KOLs, and patient advocates to proceed

Significant KOL conviction in potential of ELX-02 based on data

- Results consistent with studies of protein restoration in Alport knockout mice (Jeff Miner, Alport Syndrome Foundation (ASF) scientific advisory board member)
- Changes in biopsy consistent with activation of signaling pathways
- UPCR reduction in just 2 months considered impressive given hemodynamic variability

Confirmed interest in clinical trial participation by treating clinicians

- **13 clinicians** in US and Ex-US reviewed data and want to participate
- Several Physicians on ASF medical advisory board (e.g., Dr. Michelle Rheault, Dr. Alessia Fornoni, Dr. Rasheed Gbadegsein and Dr. Moumita Barua)
- Physicians in UK and Australia have identified **12 potential patients**

ASN American Society of Nephrology

Data presented by **Dr. Michelle Rheault** at ASN in November on her own request

ALPORT SYNDROME FOUNDATION Hope | Action | Support

Strong support from Alport Syndrome Foundation: “The AS community needs this to happen”

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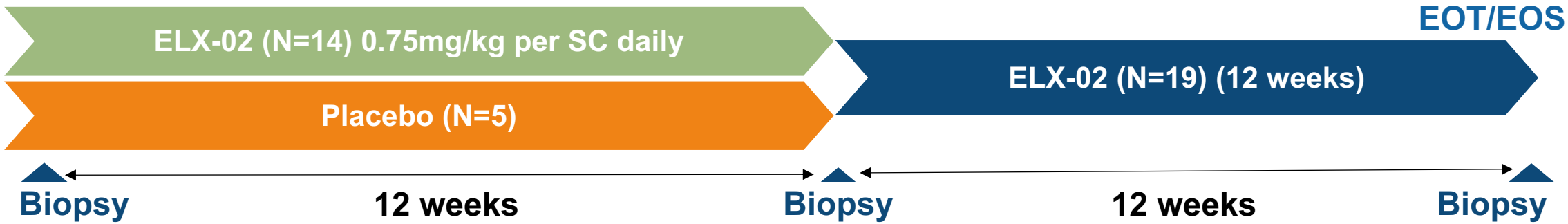
FDA Pre IND Meeting Guidance: Supports modified delayed Start 24-week Phase 2 study with biopsy and UPCR endpoints



Delayed start (instead of open label); NO CHANGE IN TOTAL PATIENTS

- Include 5 patient placebo arm and 14 on drug vs 19 on drug as originally proposed

Duration: **Same treatment duration but no follow up**

- 24-week study without need for follow up due to placebo arm

Patient population: FDA recommended 12-17 enrollment after POC in adult subset

- Age: 12+ ex-US; Start with 18 and older (1-3 patients) then expand to 12 -17 years in the US and older
- eGFR>= 45; UPCR>=300mg/g (**NO CHANGE)**

Primary efficacy end points (NO CHANGE)

- Change in FSD (biopsy)and UPCR compared to placebo at 12 weeks
- Comparison of changes in FSD and UPCR between delayed start and drug arm at 24 weeks

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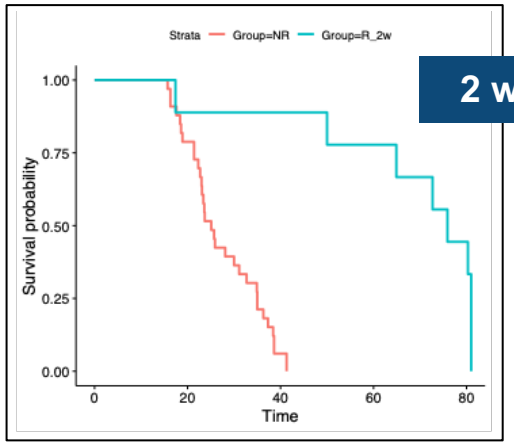
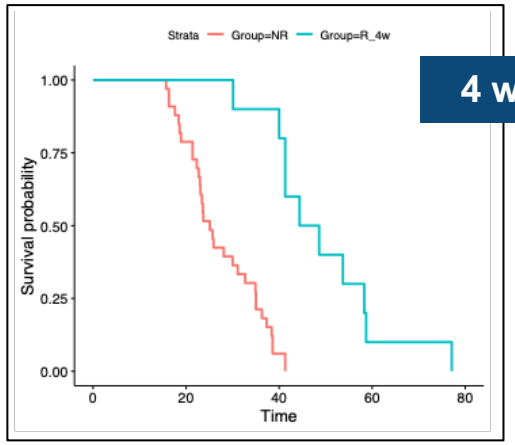
Protein restoration is beneficial even in mid stage of disease

Protein rescue benefit by age at initiation in Alport mice (without ACE-I or ARB treatment)

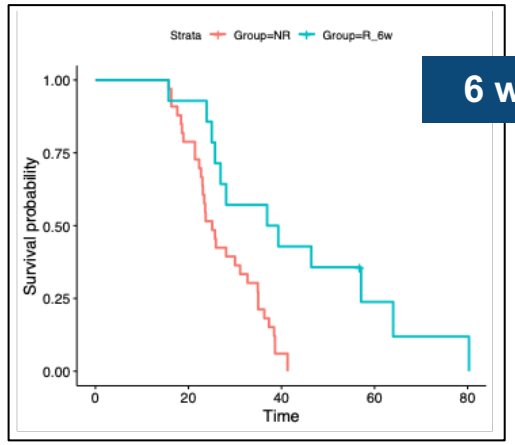
Induce at **2 weeks**



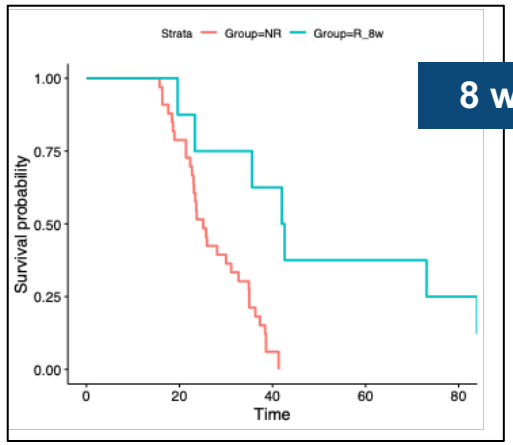
Induce at **4 weeks**



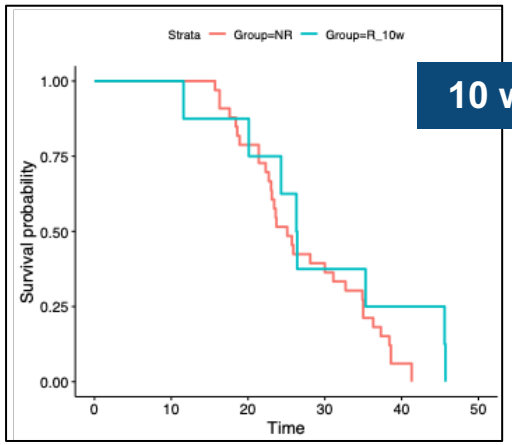
Induce at **6 weeks**



Induce at **8 weeks**



Induce at **10 weeks**



KEY

Red Line:
Dox-induced non-rescuable Alport mice

Blue Line:
Dox-induced rescuable Alport mice

Unpublished research by Dr. Jeff Miner

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FDA agreed in principle to proposed efficacy end points of FSD and UPCR

Proposed safety assessment and endpoints

Key Safety assessments

Kidney

Serum Cr, UACR, UPCR, eGFR, KIM-1, Clusterin, Serum CysC, others (TBD); Kidney Biopsies

Hearing

Audiogram, Tinnitus and Dizziness Handicap Indices (THI and DHI).

Efficacy Endpoints

Biopsy assessments vs. baseline

Change in filtration slit density (FSD) (co-primary)
Change in Foot Process Width (FPW) (secondary)

Functional assessments vs. baseline

Change in UPCR (co-primary)
Change in eGFR, UACR (secondary)

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Summary

01

Positive pre-IND meeting on ELX-02 with FDA

02

Engaged with the FDA and plans to submit an IND for a phase 2 trial tor ELX-02 that could serve as a pivotal study in NMAS

03

Ready to initiate global Phase 2 study based on FDA guidance on Phase 2 study

04

Expect robust enrollment based on Strong KOL and patient advocacy group support

05

Potential for accelerated approval based on 12-week placebo-controlled part of Phase 2 study

06

Secured investment from largest shareholder based on strategic partnership and company drafted FDA minutes

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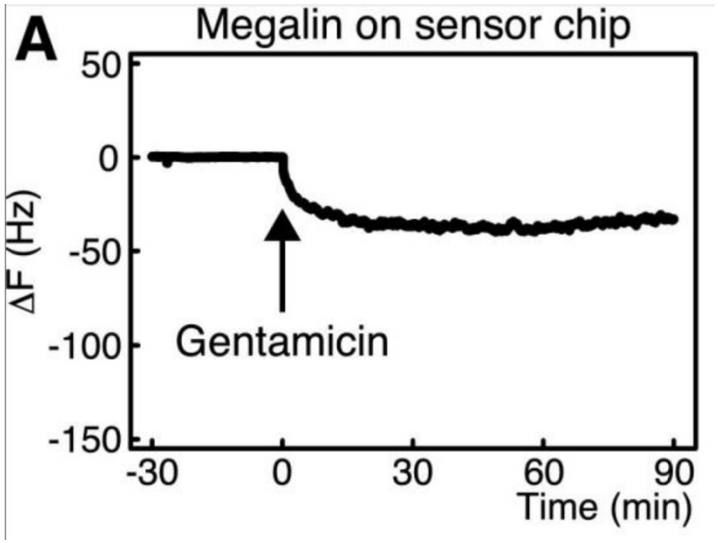
Appendix

ELX-02 uptake by megalin in the kidney expands therapeutic index

Aminoglycosides are taken up megalin present in the kidney, inner ear and eyes

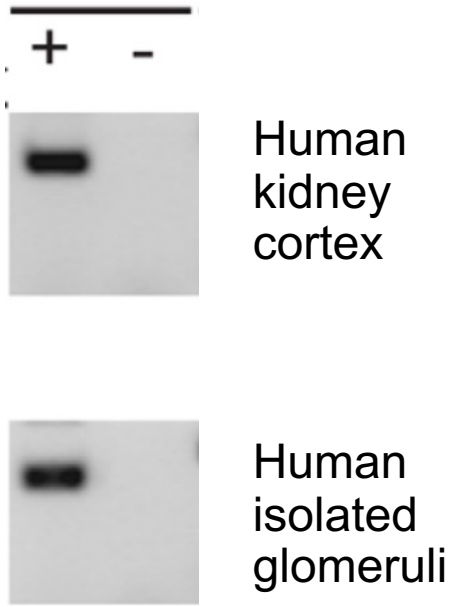
Megalin binding of aminoglycosides[1]

Quartz Crystal Microbalance experiment[1]

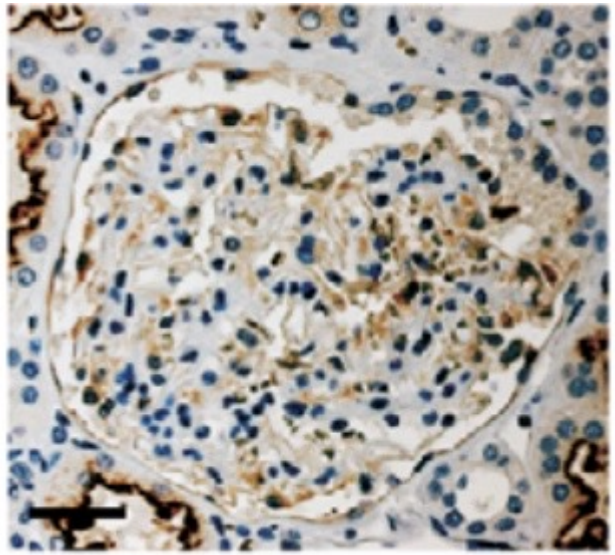


RNA levels for megalin in kidney (RT-PCR)[2]

Reverse transcriptase



Immunohistochemistry* for megalin in Glomeruli[2]



[1] J Am Soc Nephrolv.28(6); 2017 JunPMC5461786
[2] PLoS ONE 6(9): e25065. doi:10.1371/journal.pone.0025065
*DAB staining

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ELX-02: Novel aminoglycoside with gentamicin mechanism of protein induction by premature stop codon readthrough

Gentamicin has demonstrated proof-of mechanism in >36 genetic diseases

Diseases	Evidence	Readthrough Agent(s) Tested	
		Macrolides	Aminoglycosides
Familial Adenomatous Polyposis (FAP)	Clinical[1]	Ery, Tyl	Gen
Cystic Fibrosis Class 1	Clinical[2]	Tyl	Gen, G418
Duchenne Muscular Dystrophy	Clinical[3]		Gen
Dystrophic Epidermolysis Bullosa (RDEB)	Clinical[4]		Gen, G418
Lysosomal Storage Disorders, e.g., MPSI (Hurler), cystinosis	*ex vivo*[5]		Gen, G418
Rett Syndrome	*ex vivo*[5]	Ery	Gen
Spinal Muscular Atrophy (SMA)	*ex vivo*[5]	Azm, Ery	Gen
Ataxia-Telangiectasia (ATM)	*ex vivo*[5]	Ery	Gen
Usher syndrome/retinitis pigmentosa (RP)	*in vivo* Preclinical[6]		Gen, G418

Macrolides: Erythromycin (Ery); Tylosin (Tyl); Azithromycin (Azm)
Aminoglycosides: Gentamicin (Gen); Geneticin (G418)

[1]Kariv, R. Ann. Oncol. 2018, 29, suppl3; [2]Sermet-Gaudelus, I. BMC Med. 2007, 5, 5; [3]Malik, V. Ther. Adv. Neurol. Disord. 2010, 3, 379; [4]Woodley, D. J Clin Invest. 2017;127(8):3028, [5]Caspi, M., J Mol Med (Berl). 2016 Apr;94(4):469-82; [6]Goldmann, T, Hum Gene Ther. 2011 May;22(5):537-47.

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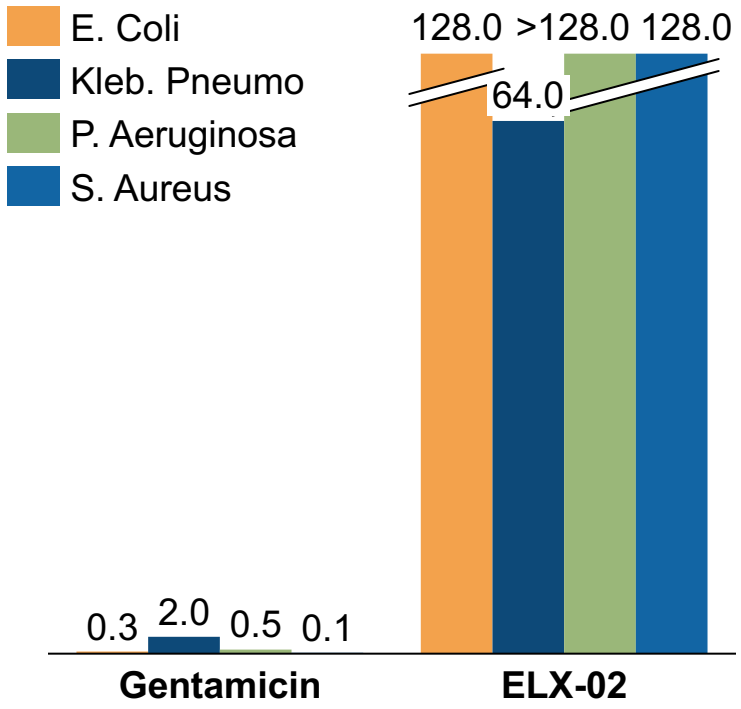
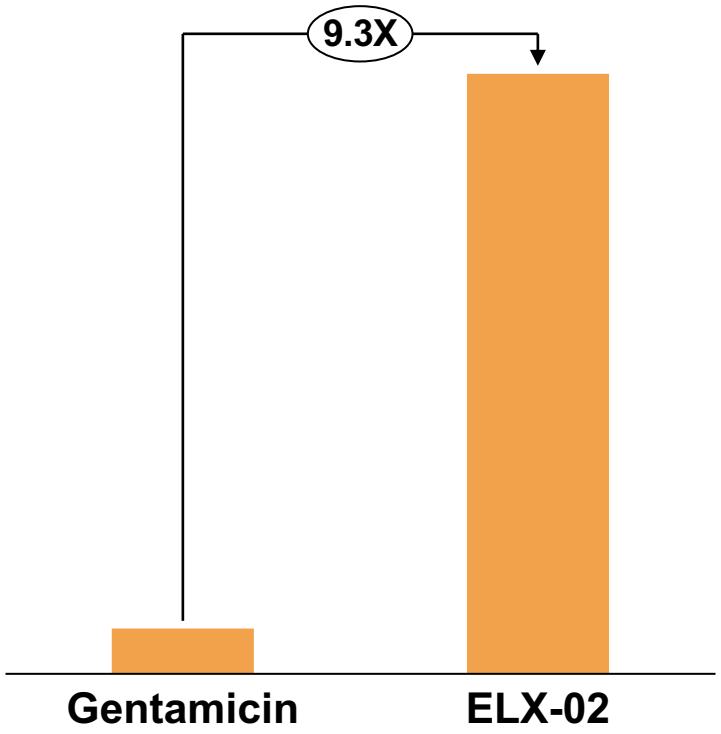
ELX-02 is a novel non-antibiotic readthrough agent designed for superior efficacy and safety

ELX-02's significantly lower anti-mitochondrial activity key for superior safety

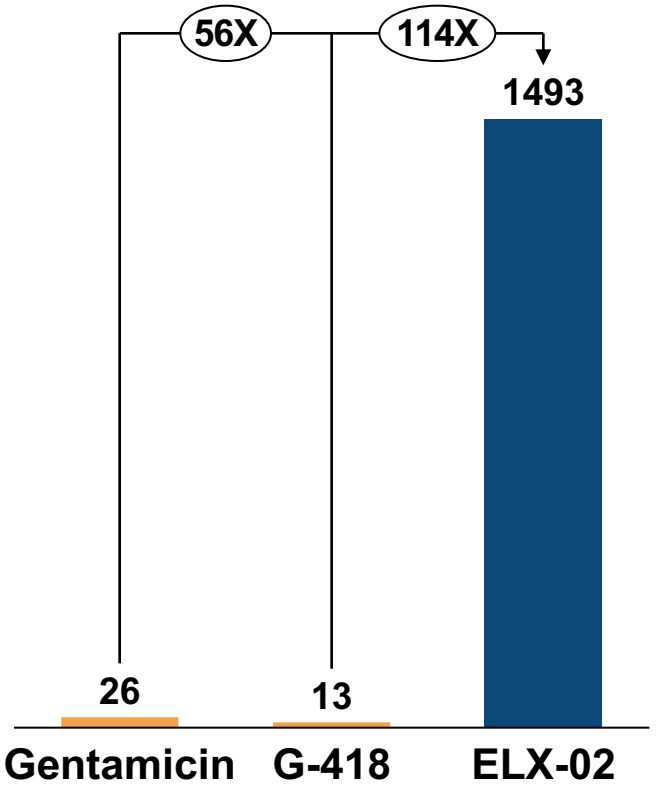
Relative ELX-02 antibiotic activity (MIC μg/mL)



Relative ELX-02 readthrough activity[1]



Relative mitochondrial protein inhibition (IC_{50} μM)[2]



1. Readthrough measured in G542X HE cell Dual Luciferase assay
2. Data adapted from: J Med Chem. 2012 Dec 13;55(23):10630-43; Shhulman,et al 2014.

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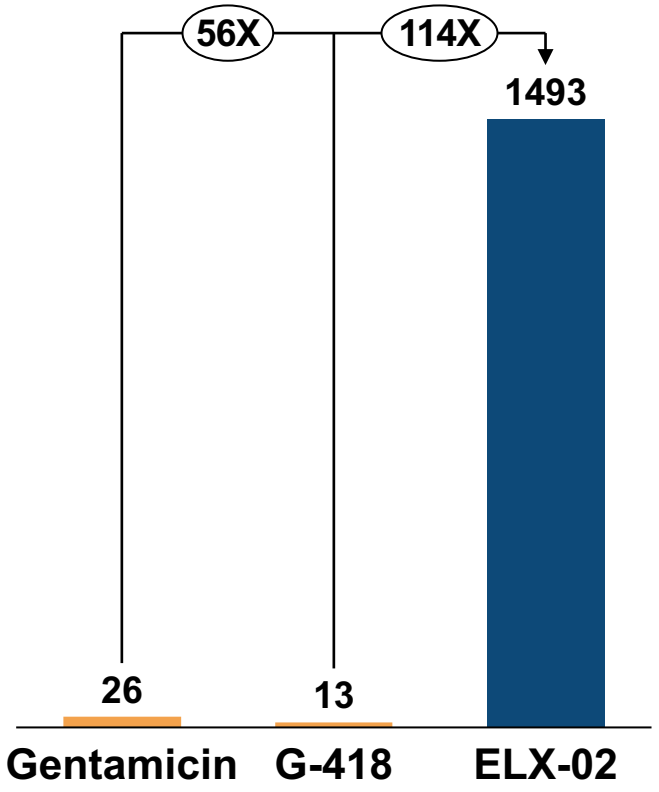
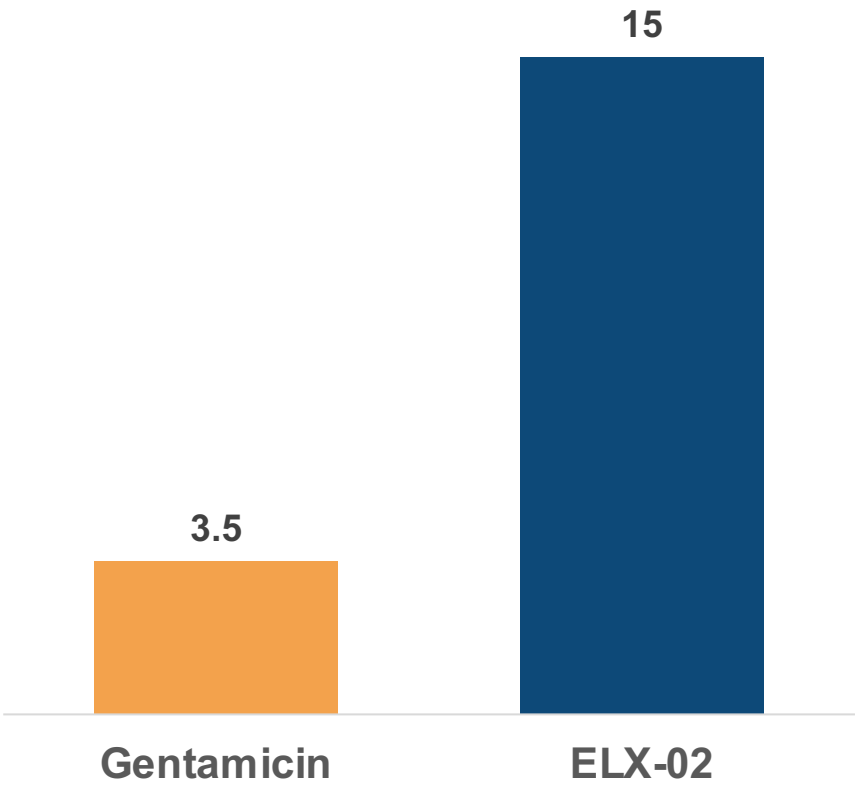
ELX-02 has minimal mitochondrial inhibition and ototoxicity compared to antibiotic aminoglycosides

ELX-02's significantly lower anti-mitochondrial activity for an improved safety profile

Relative mitochondrial protein inhibition (IC_{50} μM)[1]



Loss of cochlear hair cells in mouse cochlear explant assay(IC_{50} μM)[2]



1. Data adapted from: Kandaswamy 2012
2. Data from Xue 2014

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Strong pediatric and adult safety profile confirmed in 8 clinical trials in 145 subjects (89.4 subject-months exposure)

No nephrotoxicity or hearing loss observed in any patients to date

No ELX-02 related SAEs in Phase 1 and 2 studies at doses up to 7.5 mg/kg in 145 subjects (including 2 pediatric) with no nephrotoxicity or hearing loss

ELX-02 was well tolerated up to 3.0 mg/kg dose across Phase 2 patients (n=40)

- Mild to moderate injection site reactions most common adverse events mostly at higher doses (1.5 mg/kg/day)
- No hearing loss in CF trials at 1.5 mg/kg after 5 weeks mild hearing loss in patients at baseline
- No kidney toxicity in cystinosis patients despite eGFR as low as 44
- No kidney toxicity in Alport patients including 2 pediatric (aged 12 years) patients at 0.75 mg/kg/day

SAE: Serious adverse events

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Safety experience supports treatment in adolescents

- ELX-02 has 56-fold lower mitochondrial inhibition and 4.3-fold higher IC50 in 72 hour mouse cochlear explant assay compared to gentamicin
- 13-week juvenile toxicity study supports dosing patients 6 years and older with a 10.9-fold exposure margin at the dose of 0.75mg/kg QD in NMAS patients
- No ELX-02 ototoxicity observed in two 1-month toxicity studies indicate that even at doses at which severe renal toxicity was induced (240 mg/kg/dose)
- No accumulation of kidney toxicity observed in chronic toxicity studies in rats and dogs
- Similar exposure in adolescents (12 year-olds) treated with ELX-02 and adults in clincal studies
- No kidney toxicity or hearing loss in adolescent (12 year olds) NMAS patients observed after 8 weeks of drug exposure at 0.75mg/kg QD dose

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ELX-02 has a gene agnostic PTC readthrough mechanism validated across range of preclinical models

Summary of preclinical evidence of impact of protein restoration with ELX-02

Indication (Gene)	Protein expression	Protein function	NMD rescue	*in vivo* function
CF (CFTR)		✓ (Patient derived organoids)	✓	✓ (Transgenic intestinal mouse model)
RDEB (COL7)	✓ (keratinocytes and fibroblasts)	✓(Skin equivalent model)		
Alport (COL4A5)	✓ (Luciferase assays)			Col4A5 and Col4A3 mice treated with protein restoration (non ELX-02). Alport mice model not suited for ELX-02
ADPKD (PKD1/2)	✓ (hSCPC)	✓ (hSCPC)		
Cystinosis (CTNS)		✓ (W138X)	✓	✓(CTNS Y2266X/Y226X mice)
JEB (LAMB3)	✓ (keratinocytes and fibroblasts)			
Neurofibromatosis (NF1)				✓
MPS I (IDUA)		✓ (Embryonic fibroblasts)		✓ (W392X mouse)
Rett (MeCP2)	✓ (human fibroblasts, neuron cells)	✓		✓ (Ai14 mice, Mecp2 R168X/x mice)
USH 1	✓ (human cells)	✓		✓ (PCDH15 mice)

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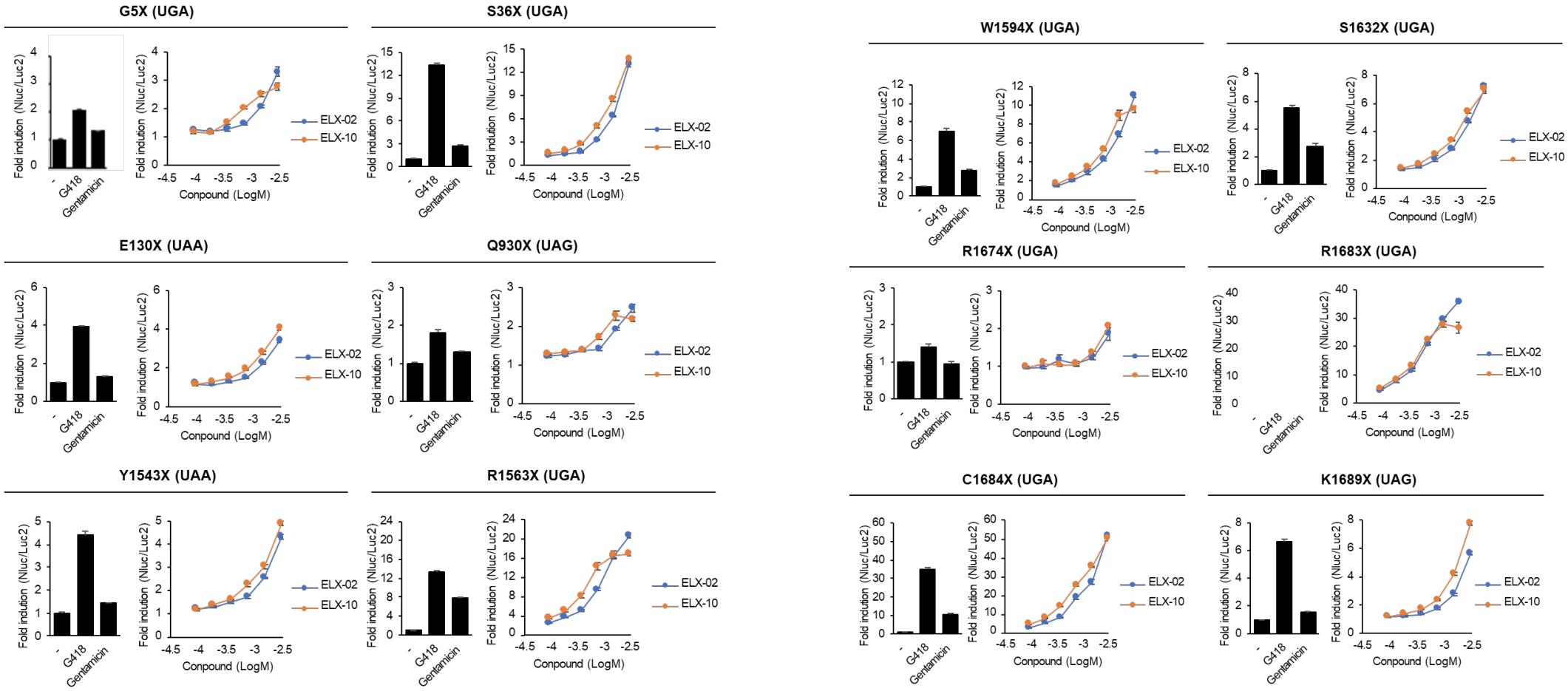
ELX-02 induces significant full length collagen IV across nonsense COL4A5 mutations

ELX-02 readthrough COL4A5 nonsense mutation in HEK293 cells at 24 hours resulted in 6 to 15% full-length collagen IV protein induction



Experiment conducted at Washington University by Dr. Jeff Miner, Poster Presentation at ASN 2022 “Investigational therapy of Alport Syndrome with ELX-02” Hariri, Omachi, Miner et al

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Phase 2 results from Study EL-014 support advancing to larger phase 2 study to validate results

- FPE in NMAS patients is unilaterally and universally progressive, therefore any observed improvement in FPE can only be drug-induced
- All patients reached meaningful improvement in FSD relative to healthy FSD values confirming small changes in FSD can be clinically material
- FSD of healthy controls (1.75) vs. Alport patients (1.21) measured using TEM images was consistent with that in Study EL-014 (1.12) and healthy controls in the the Evotec Nurture Study (2.06)
- Change in FSD was observed in the patient with a reduction in UPCR
- 4-week-old Alport mice with a *Col4a5* exon 21 frame shift mutation treated with vehicle did not have any improvement in FPE or UACR. Mice treated with antisense-oligonucleotide (ASO) had an FPE and UACR improvement after 16 weeks (at week 21)

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Consistent changes in foot process effacement and collagen expression seen in TEM and FFPE biopsy assessments

Summary of Biopsy assessments in ELX-014 in 3 NMAS patients

Patient	Change in Collagen 4 alpha 5 expression in GBM in fresh frozen biopsies	Change in observed foot process effacement in TEM images	Change in FSD in FFPE biopsies
4401-01	**Improvement** post treatment to global or segmental loss of alpha 5 staining of GBMs compared to a global loss pre treatment	**More regions** of GBM in Post-treatment biopsies covered by intact foot processes (19% reduction in Foot Process Width)	**Increase** from 1.0 to 1.5μm^{-1}
4401-02	**Improvement** post treatment to global or segmental loss of alpha 5 staining of GBMs compared to a global loss pre treatment	**More regions** of GBM in Post-treatment biopsies appears to **be covered by intact foot processes** (however, quantifications showed 6% increase)	**Increase** from 1.54 to 1.75μm^{-1}
4402-01	**Improvement** post treatment to segmental from partial loss of alpha 5 staining of GBMs pre treatment.	Post-treatment shows wider areas of intact foot processes. (45% reduction in Foot Process)	**Increase** from 0.8 to 1.73μm^{-1}

TEM: Transmission Electron Microscope ; FFPE: Formalin Fixed Paraffin Embedded;

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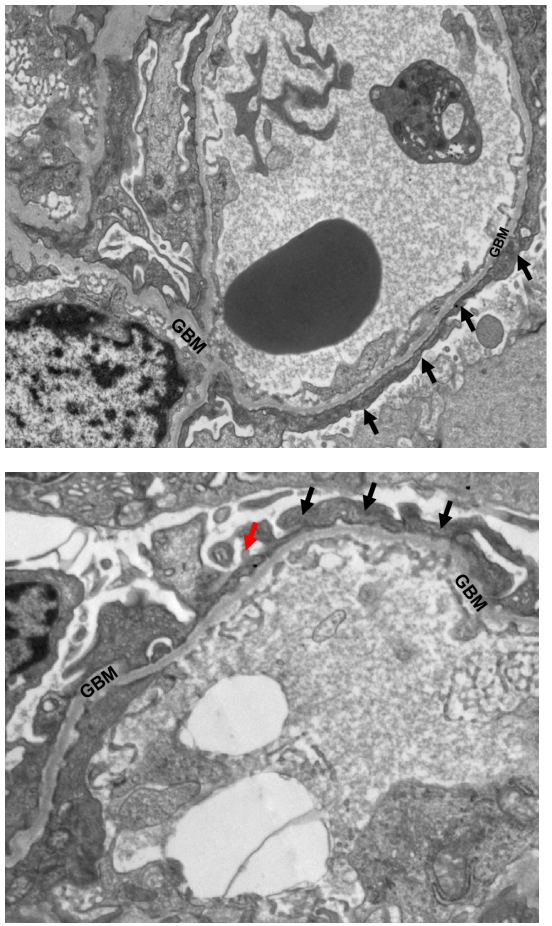
Reduction podocyte foot process effacement in all three Phase 2 ELX-14 patients prior to study start

Pre-Treatment representative TEM images

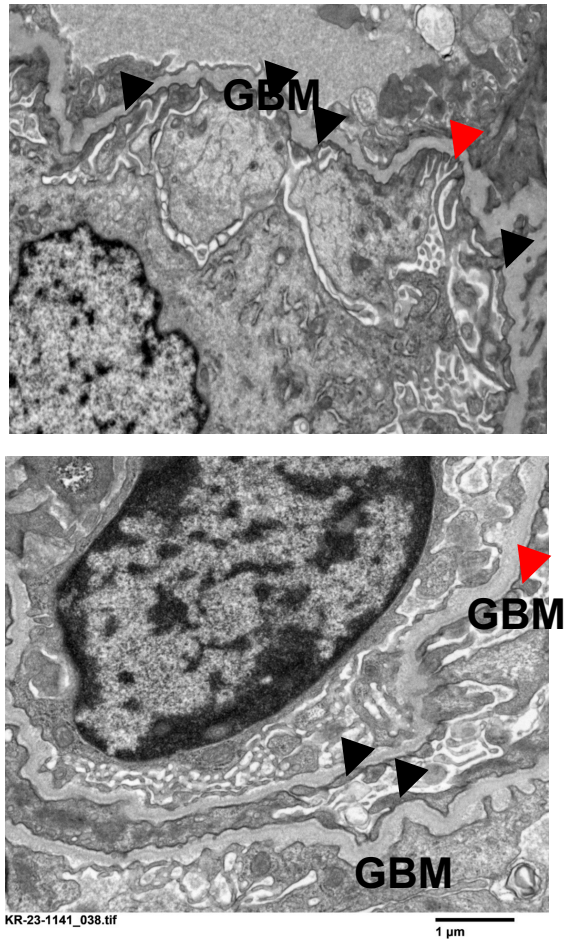
= foot process

= effaced foot process

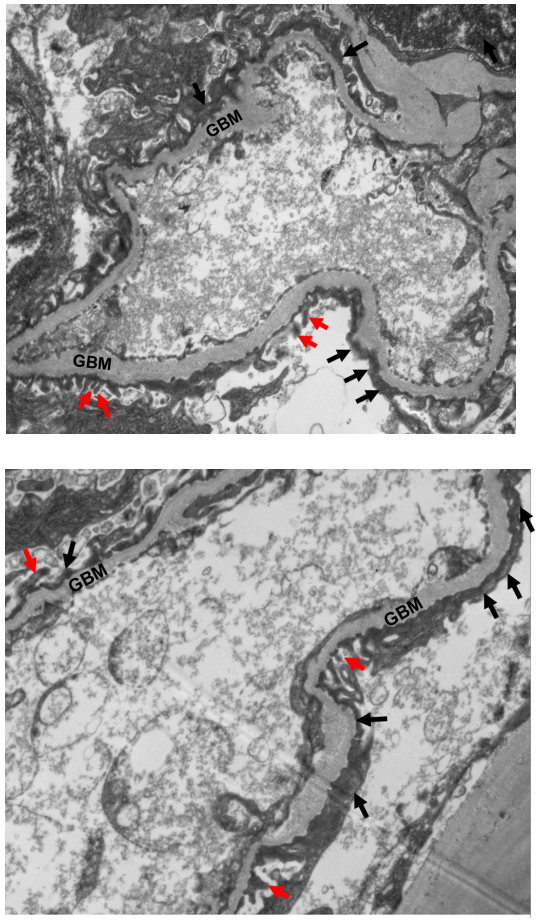
Patient 4401-01



Patient 4401-02



Patient 4402-01



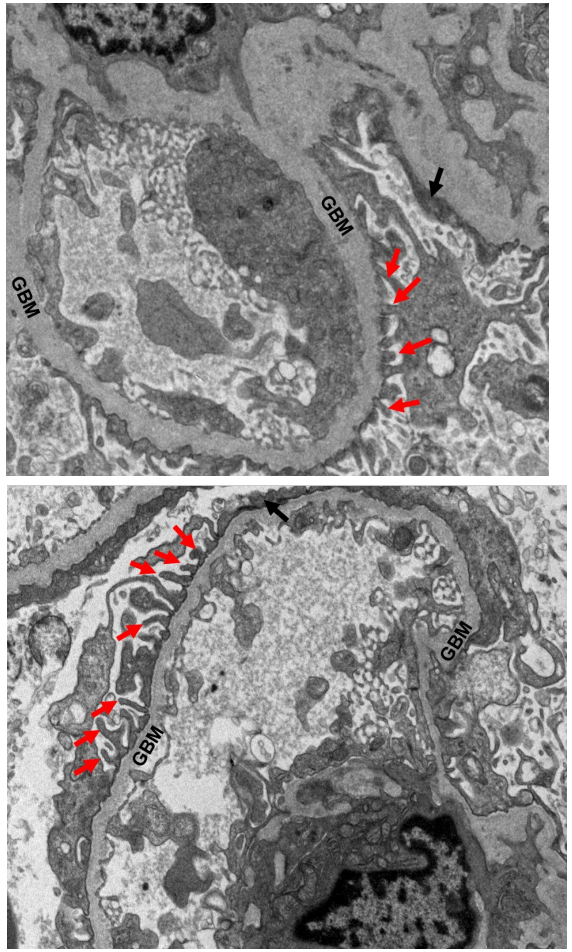
Meaningful reduction in podocyte foot process effacement in all three patients at end of treatment

Post-Treatment representative TEM images

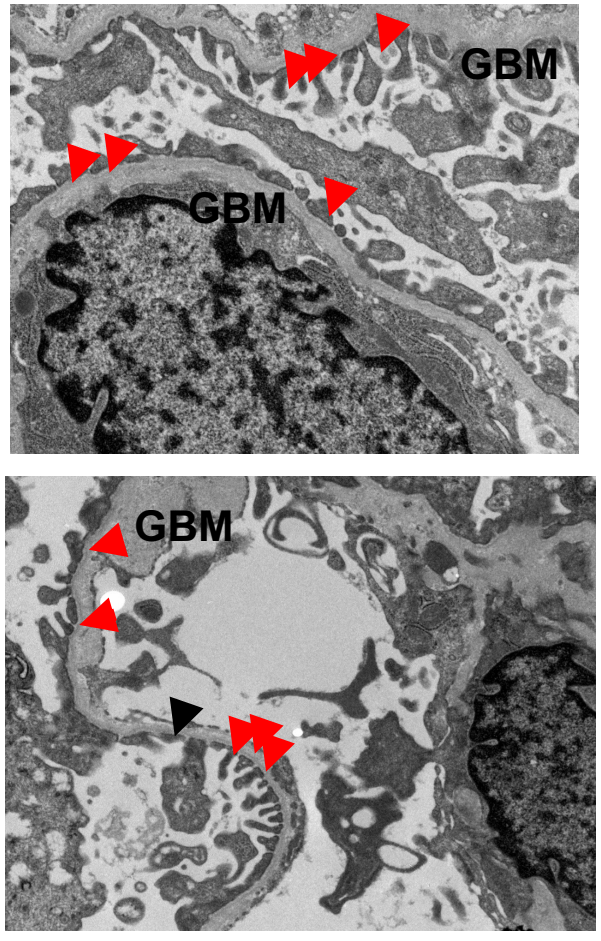
= foot process

= effaced foot process

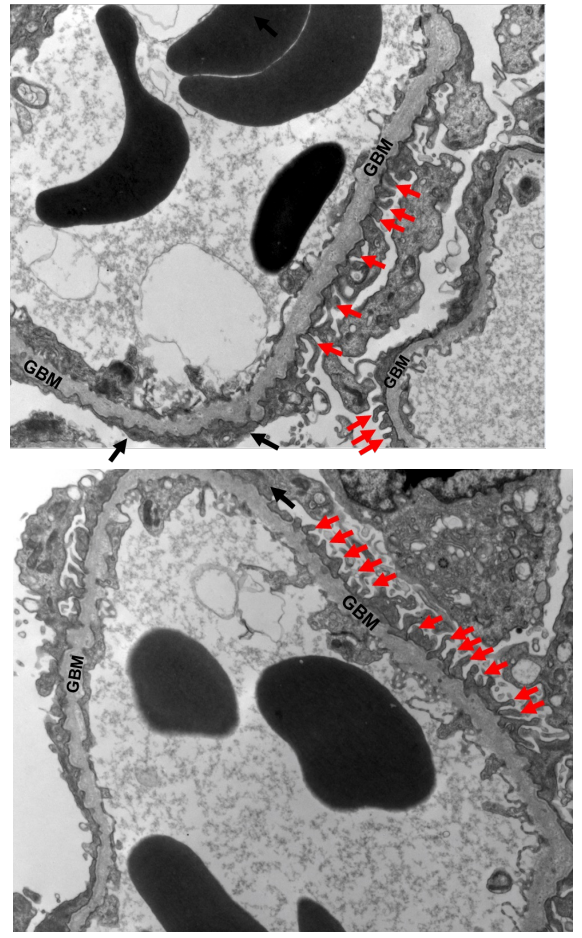
Patient 4401-01



Patient 4401-02



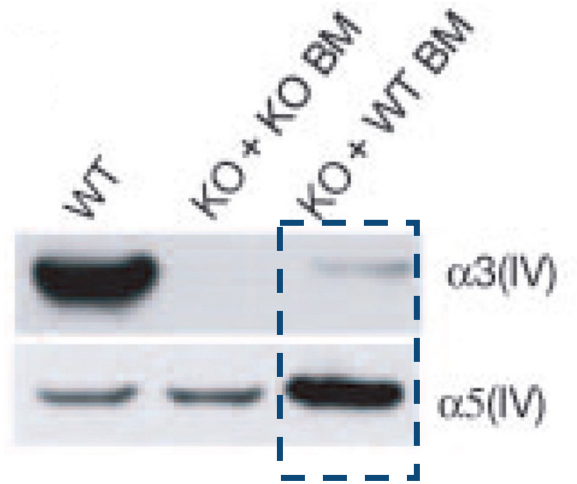
Patient 4402-01



Col4a3 restoration in mice also reduced foot process effacement and lowered albuminuria

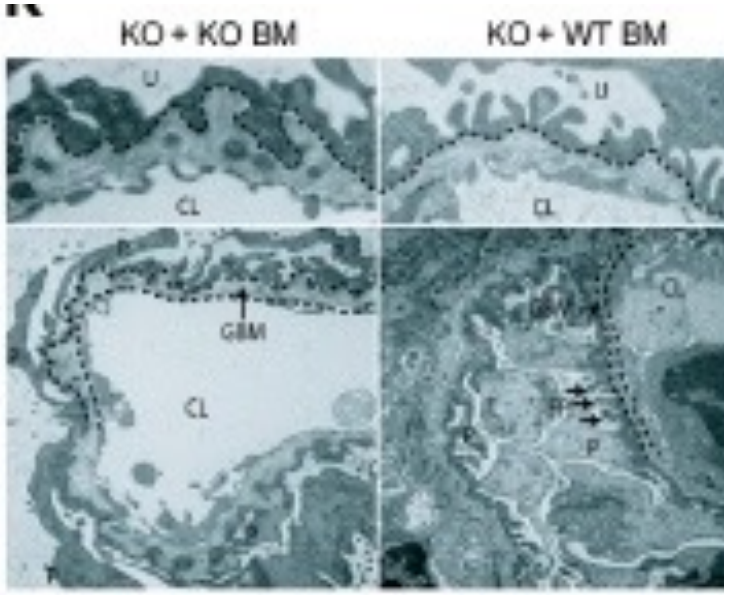
Bi-weekly Col4a3$^{+/-}$ bone marrow (BM) therapy in C57BL/6 Col4a3$^{-/-}$ knockout mice at age 20 weeks for 3 weeks[1]

Western blot of COL4A3[2]

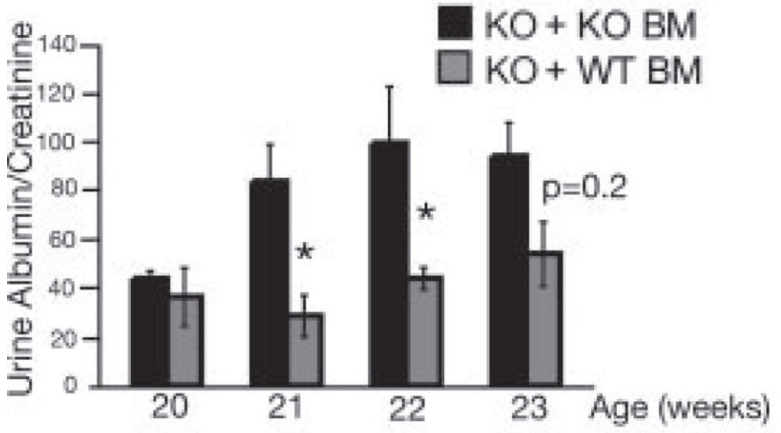


Treatment effect[2]

Change in Podocyte foot process effacement



Change in AUCR



[1].JASN November 2009, 20 (11) 2359-2370.
2 Wild type (WT) COl4A3 treated mice: n=4; Knockout treated mice: n=3
*p<0.05

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Large pediatric population given natural history of early diagnosis and rapid progression

Nonsense mutation Alport syndrome patients with truncating mutations are diagnosed early and progressed rapidly to proteinuria and kidney failure

RaDaR
National Registry of Rare Kidney Diseases

Nonsense mutation Alport Syndrome Type	Median Age at diagnosis (years)	Mean eGFR at diagnosis (ml/min/1.73m2/year)	Median annual eGFR decline (ml/min/1.73m2/year)	Median UPCR, g/g before eGFR>30	Mean age at ESRD (years)
X-linked COL4A5 Males	19.6 years (IQR: 8.7 to 29.6)	61.4±61.1	-6.9 (IQR: -8.7 to -4.2)	1.4 (IQR:0.9 -3.0)	31.9±10.9
Autosomal Recessive COL4A3/4 Males	7.0 years (IQR: 4.6 to 22.9)	nm	-22.4 (IQR: -29.9 to -14.8)	1.9 (IQR:0.9 -3.1)	20.1±3.2
Autosomal Recessive COL4A3/4 Females	4.7 years (IQR: 2.7 to 15.2)	nm	-7.1 (IQR: -10.7 to -3.4)	1.9 (IQR:0.9 -3.1)	23.8±10.9

7x to 22x worse than in healthy subjects; 4x to 7x worse than in IgaN patients

20 to 40 years earlier than missense Alport patients

IQR= Interquartile range
Source: UK Registry of Rare Kidney Diseases (RaDaR)

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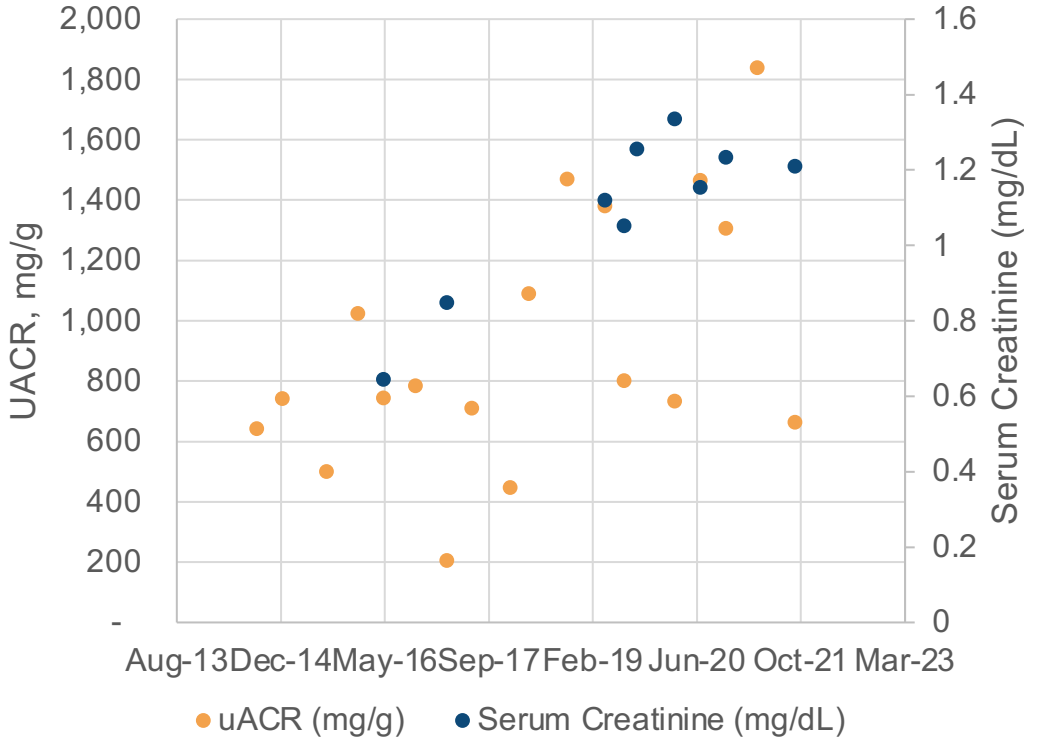
NMAS patients have progressive kidney disease

Serum creatinine changes in AS patients

- 52% of Alport patients in the UK RaDaR Registry had a 0.3mg/dL or more increase in serum creatinine within 6 months
- Patient 4402-01 (Adult 18 years old) had a 0.21 mg/dL from May 2016 to March 2017 and an increase of 0.21mg/dl from July 2019 to September 2019
- UACR in patients 4401-01 and 4401-02 (12 year old) increased by >100% in 12 months prior to treatment
- All three patients enrolled in Study ELX-014 had significant increases in UACR over time

UACR and Serum Creatinine trends for patient 4402-01



Three alport phase 2 studies active evaluating non-disease modifying therapies

Study Name	Drug Name	MOA	Control	Trial size	Duration (weeks)	Age	UACR / UPCR	eGFR	Efficacy endpoint
ALPESTRIA-1	vonafexor	Anti fibrotic: Highly selective FXR agonist	Open label	20 (3 dose cohorts)	24	16-40	n/a	n/a	n/a
R3R01 - ASFFSGS - 201	R3-R01	Reduce the accumulation of toxic lipids in podocytes	Open Label	20	12	18+ (12+ ex US)	UPCR ≥ 1.0 g/g	≥ 45 mL/min/1.73 m2	Change in UPCR
Setanaxib/ Calliditas	Setanaxib	NOX inhibitor – anti fibrotic/anti inflammatory	Placebo	18	24	12-40	UPCR ≥ 0.8 g/g	≥30 ml/min/1.73 m2	% of patients with 25% reductio in UPCR, Change in UPCR vs baseline

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