RARE Thinking for RARE Solutions

Investor and Analyst Webcast:
Alport syndrome and ELX-02 clinical results

June 27, 2023

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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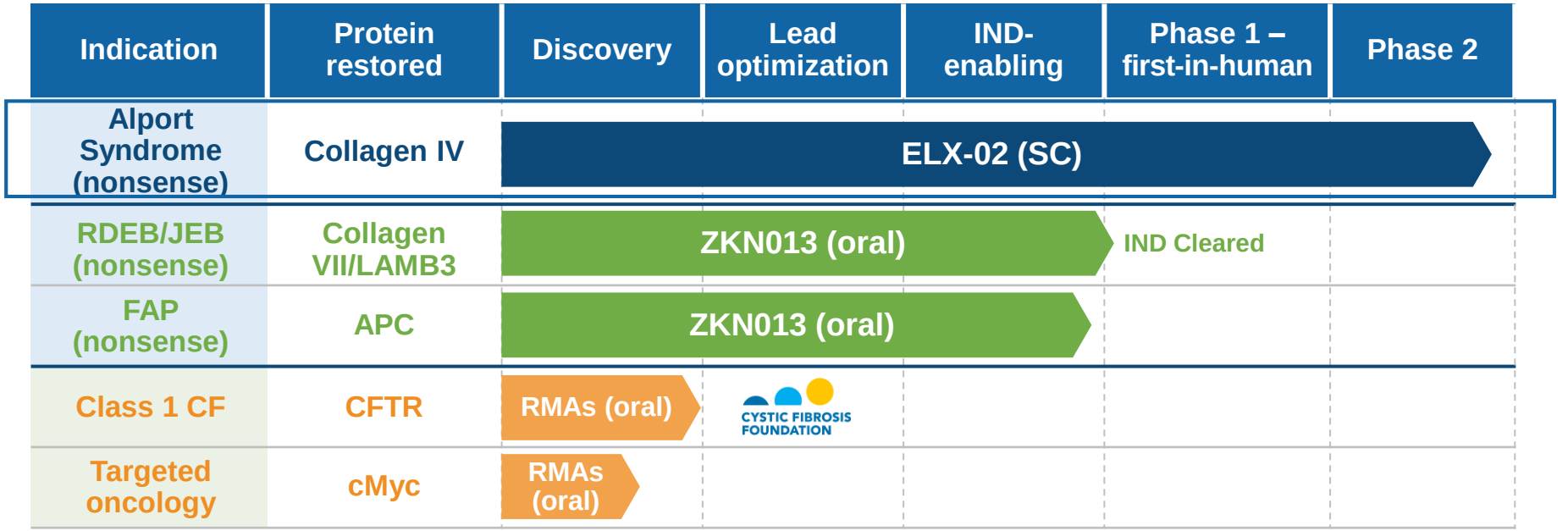
Agenda

Topic	Speaker
Introductory Remarks	Sumit Aggarwal, President and CEO (Eloxx)
Alport Syndrome Overview	Prof. Rachel Lennon
Perspectives on Clinical Development in Alport	Prof. Rachel Lennon
ELX-02 Alport Syndrome Phase 2 Results	Prof. Detlef Bockenhauer
ELX-02 for Alport Syndrome	Dr. Ali Hariri, Chief Medical Officer (Eloxx)
Summary	Sumit Aggarwal, President and CEO (Eloxx)
Q&A	

Pipeline of potential first-in-class gene therapies to treat patients with nonsense mutations



Class 1 CF: Cystic fibrosis patients with class1 mutations; **RDEB/JEB:** Recessive Dystrophic/Junctional Epidermolysis Bullosa; **FAP**: Familial adenomatous polyposis; **PoC**: Proof of concept; SC: Subcutaneous; **IND**: Investigational New Drug

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Professor Rachel Lennon

- Professor of Nephrology
- Consultant Paediatric Nephrologist
- Director of the Wellcome Centre for Cell-Matrix Research
- Director of the Stoneygate & Kidney Research UK Alport Research Hub

Professor Detlef Bockenhauer

- Professor and Chair of Paediatric Nephrology, University Hospital and KU Leuven
- Honorary Consultant at Great Ormond Street Hospital (GOSH) NHS Foundation Trust, London
- Principal Investigator for ELX-02 Phase 2 trial in Alport Syndrome

Leadership team with track record of execution in therapeutics to treat rare diseases

Sumit Aggarwal
President and CEO

- 20+ years investing and transforming healthcare companies
- Raised >$150M
- Biotech Investor

progenity
McKinsey&Company
Adage Capital Management

Dr. Vijay Modur
Head of Research & Development

- 20+ years in translation and drug development
- Led Venglustat ADPKD and Fabry programs at Sanofi

MERCK
NOVARTIS
SANOFI GENZYME

Dr. Ali Hariri
SVP & Chief Medical Officer

- Led Lademirsen program for Alport Syndrome and clinical lead for Venglustat trial for ADPKD
- Secured full approval for Fabryzyme
- Expertise across a range of rare areas

SANOFI GENZYME
IONIS
Takeda

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Alport Syndrome Overview:

Dr. Lennon

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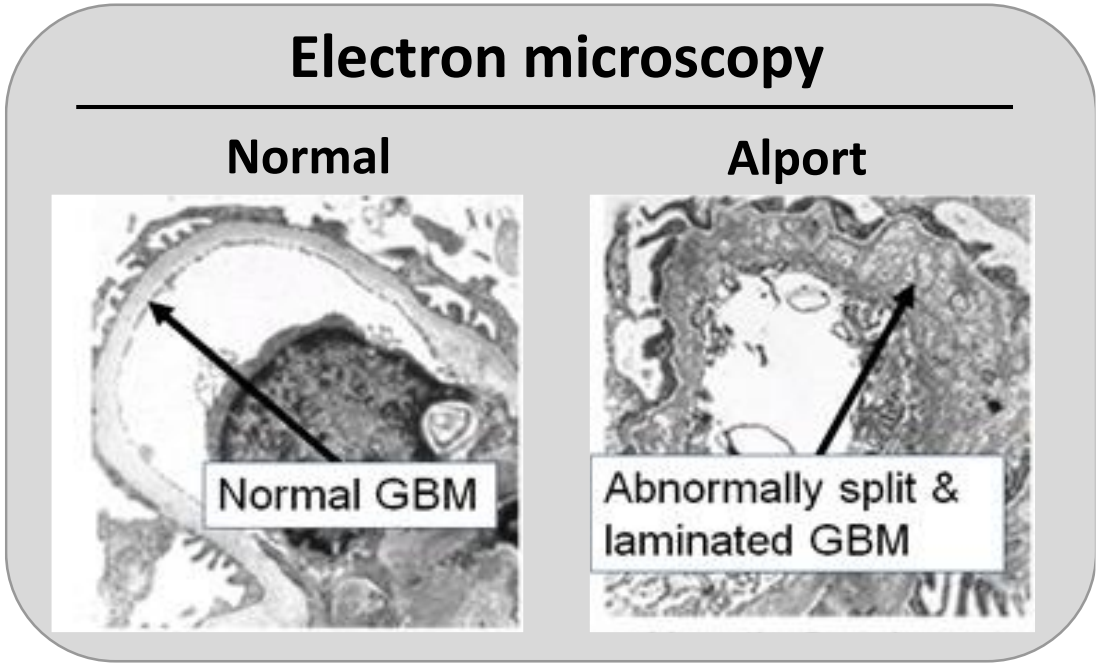
Alport Syndrome (AS) is a rare progressive hereditary glomerular kidney disease caused by variants in *COL4A*

Alport syndrome nonsense mutation disease overview

Alport disease overview[1,2]

- **Defects in *COL4A* genes**
  - X-linked in 85% - *COL4A5* gene
  - Recessive in ~15% - *COL4A3/4* genes
  - **Over 70 nonsense mutations** described
- **Fragile basement membranes**
  - Nonsense mutations result in **truncated proteins**
  - **High proteinuria** and hematuria
  - Leads to kidney disease (CKD and ESKD)
- **Limited therapeutic options (RAAS Blockade)**

Kidney glomerular basement membrane



Abnormal basement membranes

[1]J Am Soc Nephrolv.28(6); 2017 JunPMC5461786
[2]J Clin Invest 1995 Sep;96(3):1404-13

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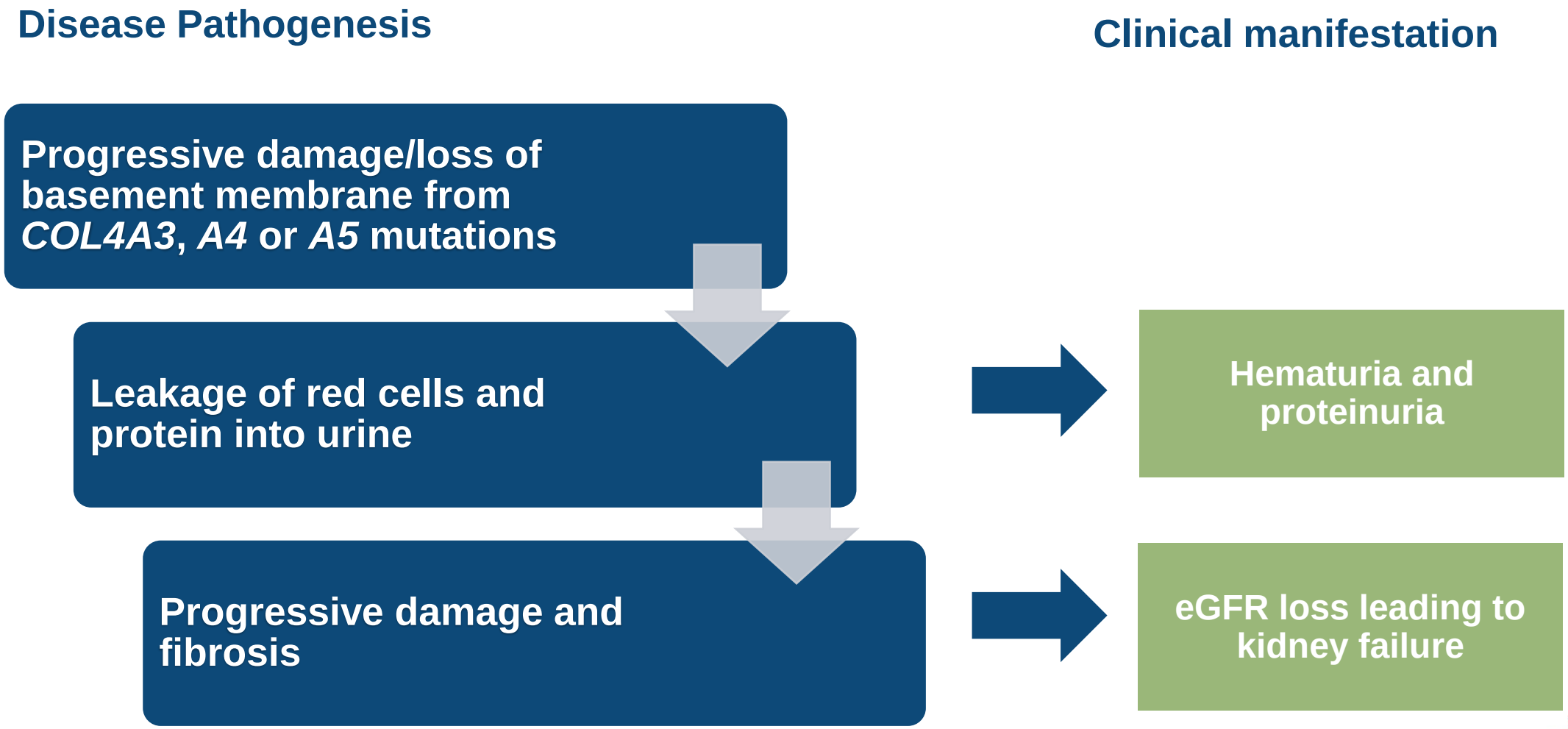
Continuous glomerular damage leads to proteinuria and hematuria resulting in loss of kidney function



*Has only been performed for research purposes

Mutation status of *COL4A3/4/5* genes drives disease severity

Distribution of patients with Alport syndrome by mutation type

Inheritance	Affected gene(s)	Genetic state	Share of Alport syndrome	Estimated risk of ESKD
X-linked	***COL4A5***	**Hemizygous male**	**~32%**	**100%**
		Heterozygous female	~48%	up to 25%
Autosomal	***COL4A3* and *A4***	**Recessive**	**~15%**	**100%**
		Dominant		Up to 20%

Adapted from Kidney International (2018) 93, 1045–1051

Nonsense mutations affect X-linked and autosomal recessive patients at different rates

Nonsense mutation frequency for *COL4A5* vs. *COL4A3/4**

Gene	Inheritance	Prevalence	Nonsense mutation frequency, % of all patients	Nonsense mutation patient prevalence
COL4A5	**X-linked**	**1 in 2,320 to 10,000**	**6.6%**	**1 in 36,000 to 150,000**
COL4A3* or *COL4A4	**Autosomal recessive**	**1 in 40,000**	**10%**	**1 in 400,000**

JASN 32(9):p 2273-2290, September 2021.

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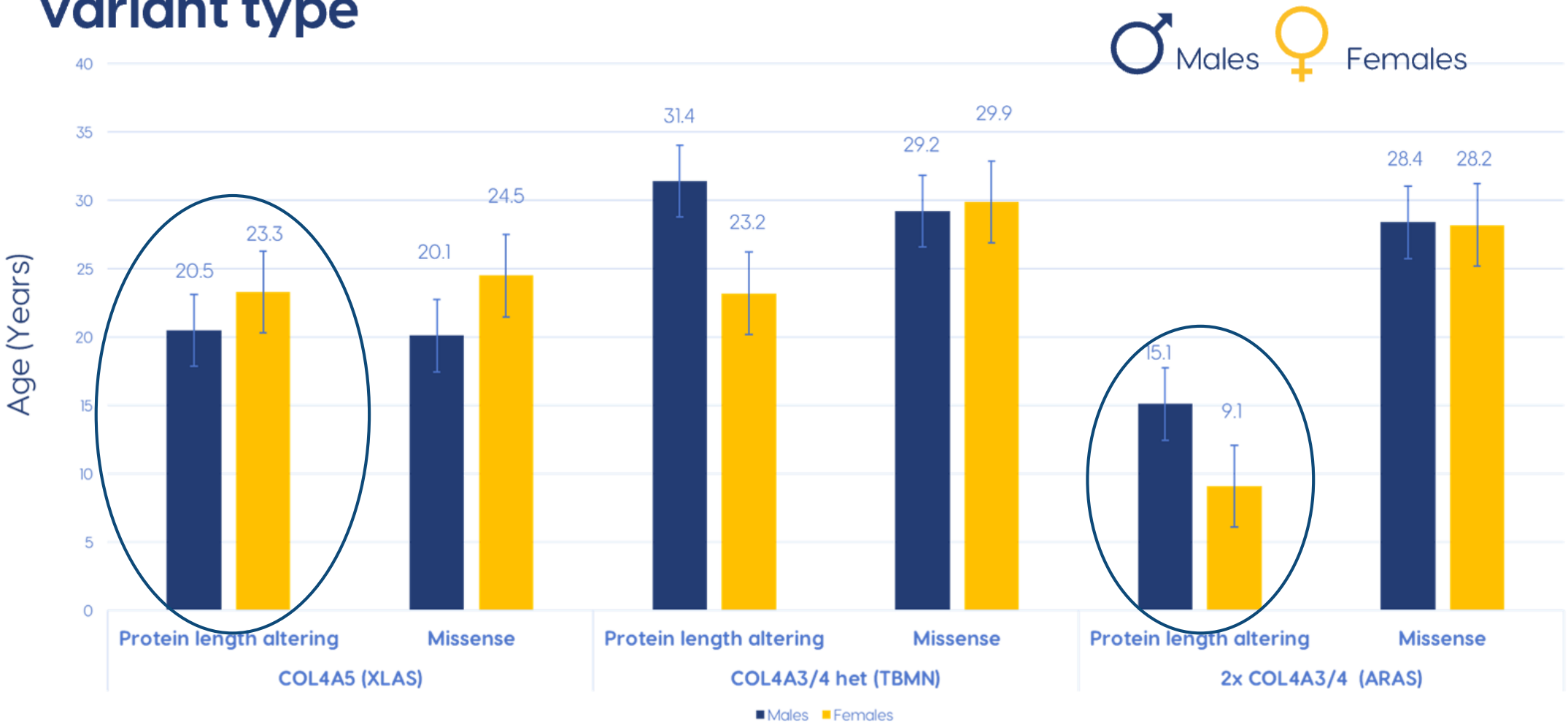
Patients with truncated proteins present earlier due to severity and early disease manifestation

Median age at diagnosis, by genotype, Sex and variant type



Patients with truncated protein reach ESKD at younger ages

Data from National Registry of Rare Kidney Diseases (RaDaR) registry UK

Median Age of End stage Renal Disease (ESRD) in Alport patients

Col4 Gene	Sex	Missense	Truncated
COL4A5	Male	52.1	**30.2**
	Female	60.9	**N/A**
Biallelic *COL4A3/4*	Male	24.3	**20.1**
	Female	23.4	**28.1**

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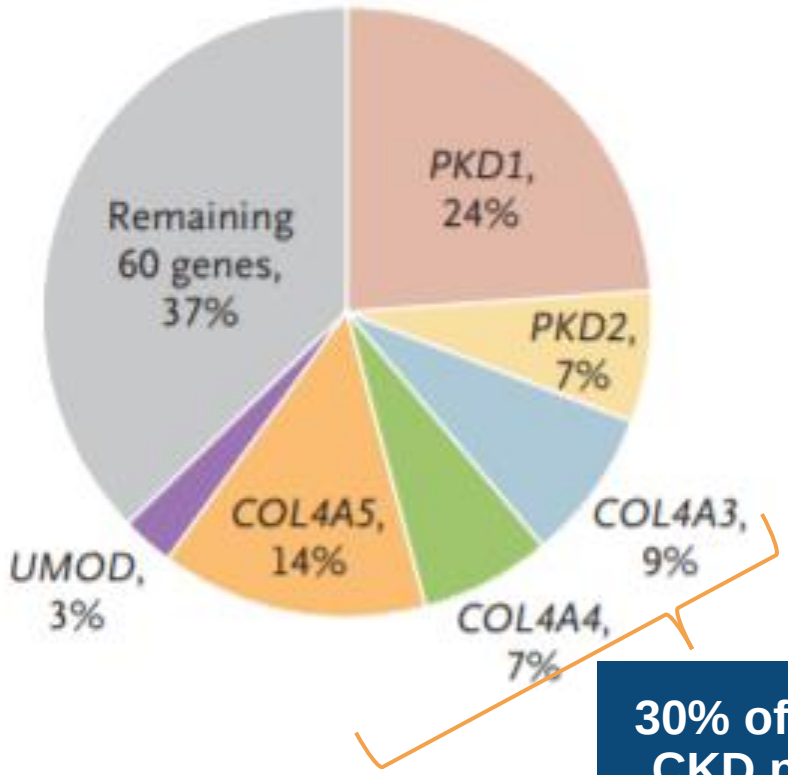
Alport variants are frequent but remain underdiagnosed

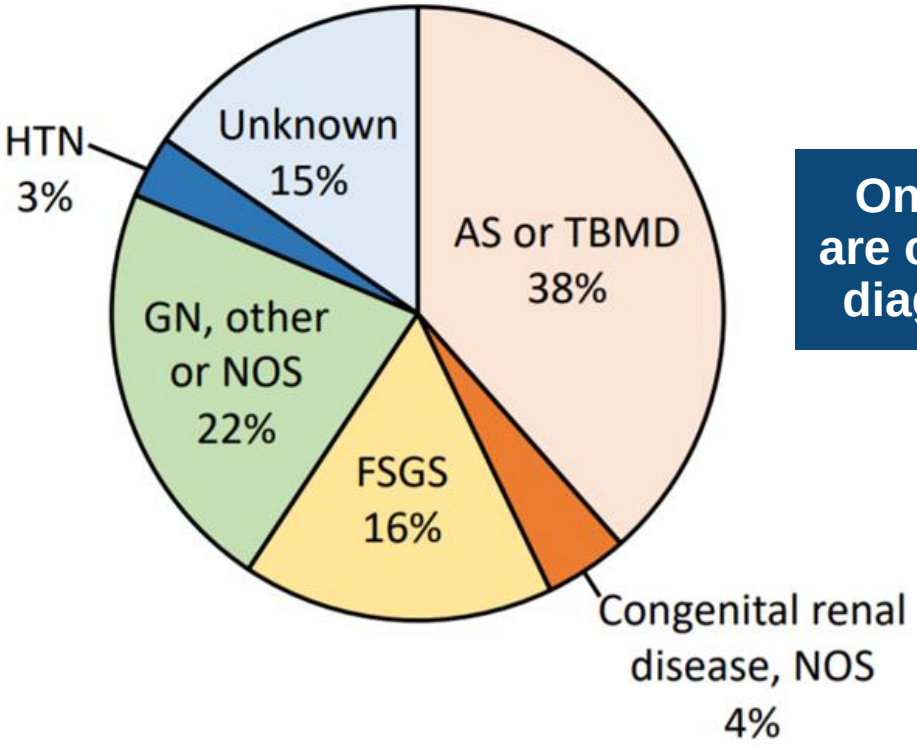
Diagnostic mutation testing in all patients with chronic kidney disease (CKD)*

9.3% of CKD patients have mutations



30% of genetic CKD patients have Alport

Clinical (mis)diagnosis in Alport patients



Only 38% are correctly diagnosed

*N Engl J Med 2019; 380:142-151

Perspectives on Clinical Development in Alport – Prof. Rachel Lennon

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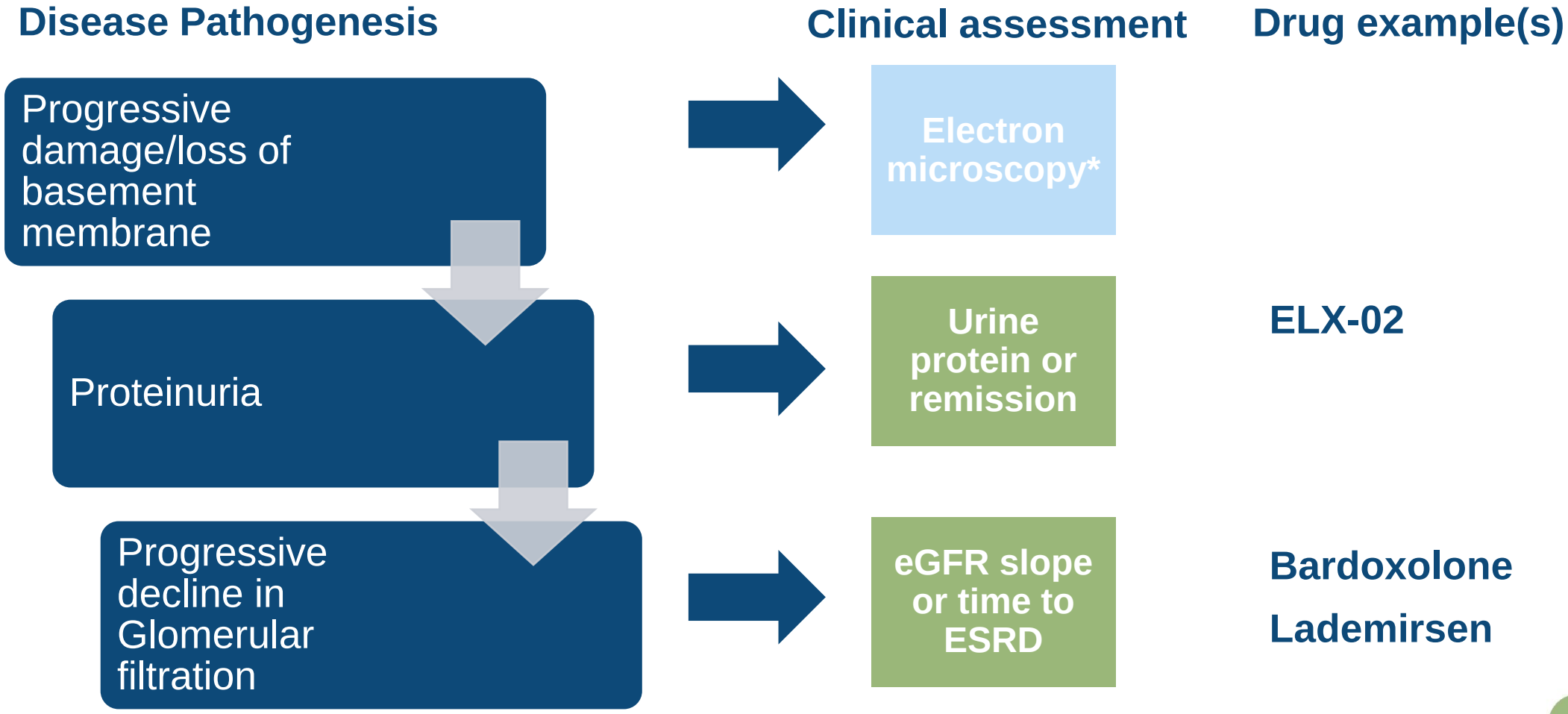
No approved therapy for Alport syndrome and current standard of care is supportive therapy

- Early initiation of RAAS blockade (ACE inhibitors/ARBs)
- Hearing aid for deafness
- Supportive therapy for kidney disease
  - Management of fluid and electrolyte issues related to chronic kidney disease
  - Management of anemia
- Despite early RAAS blockade patients need kidney replacement therapy
  - Dialysis
  - Kidney transplant

Effective therapies must measure impact on disease progression

Linkage of disease pathogenesis to assessments



*Has only been performed for research purposes

Past clinical program in Alport have not yielded viable therapies

Recent clinical programs

Drug	MOA	Disease impact	Gene therapy / Protein Restoration	Results
Bardoxolone	Nrf2 activator	Increase glomerular function	No	• Failed to gain regulatory approval • Increased proteinuria
Lademirsen	Anti-Mir21	Reduce fibrosis downstream of glomerular damage	No	• Failed on futility analysis

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Proteinuria remission reflects glomerular repair in Alport

Criteria for advancing programs for Alport clinical development

Parameter for confirming efficacy	Rationale
Remission rate: Number of patients in remission based on • >=50% UPCR decline, or • UPCR<=300mg/g	**Spontaneous remission not possible in this genetic disease** • Remission based on proteinuria is well accepted in renal glomeruli diseases

Proteinuria reduction has been shown to correlate with improvement in kidney function in glomerular diseases

[1]AJKD Vol75 Issue1 4-5 January 2020

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ELX-02 Alport Syndrome Phase 2 results: Prof. Bockenhauer

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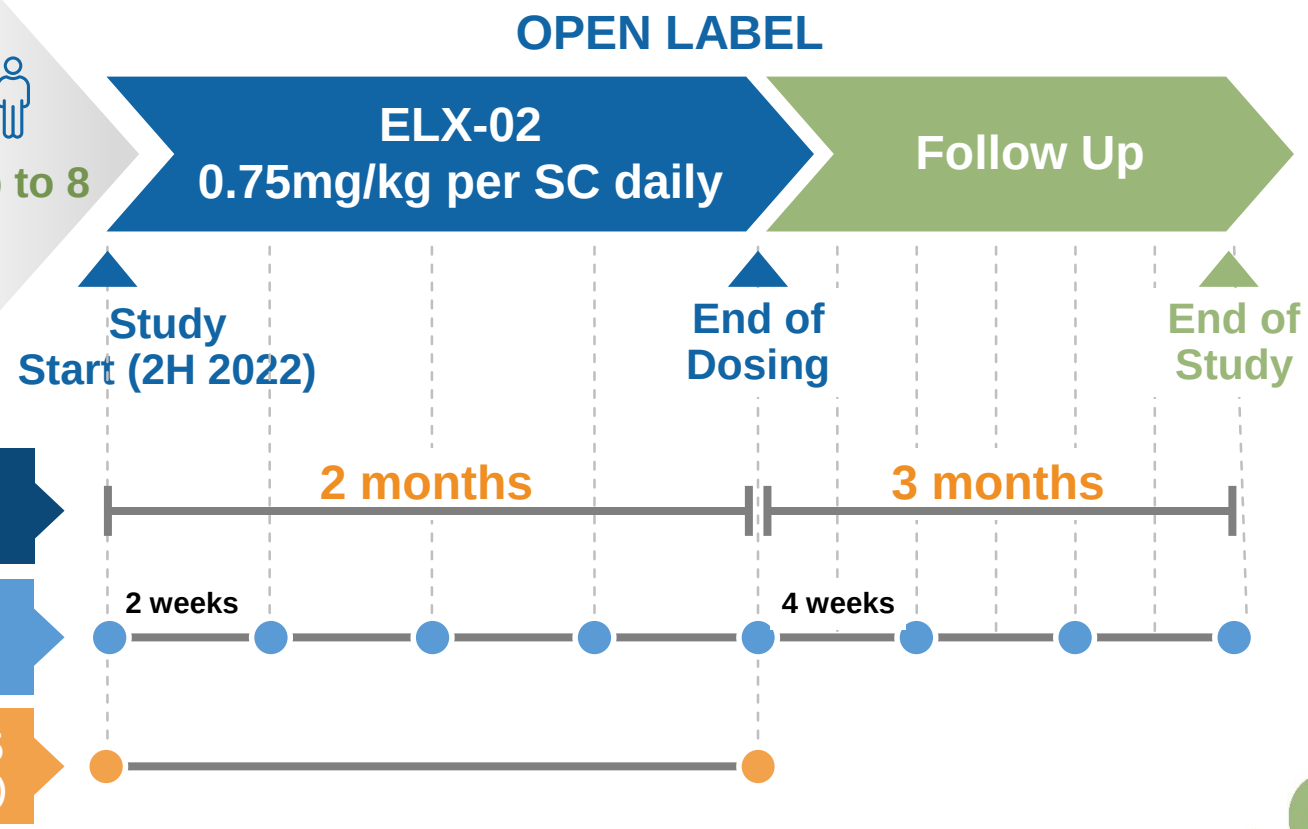
Alport Phase 2 trial design to assess safety and effect of ELX-02 on proteinuria

ELX-02 in Alport Syndrome Phase 2: Study Design

Inclusion Parameters	Criteria
Genotype	Any patient with nonsense mutations in the Col4 gene except UAA
Age	All patients >6 years
eGFR	>60ml/min/1.73m^2 BSA
Proteinuria	>500mg/g

n= up to 8



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Patients had autosomal recessive disease with differing levels of background RAAS blockade

Baseline characteristics of patients that have completed therapy

Patient	Age	Sex	COl4 Gene Affected	Nonsense Mutation	RAAS Block dose	Cr (mg/dL)	Proteinuria (mg/g)
4401-01	13	Male	*COL4A4*	**c.2906C>G*; p.Ser969X**	Enalapril 2.5 mg QD	0.7	1299
4401-02	13	Male	*COL4A4*	**c.2906C>G*; p.Ser969X**	Enalapril 32.5 mg QD	0.5	1646
4402-01	19	Female	*COL4A4*	**c.2906C>G*; p.Ser969X**	Enalapril 5 mg QD	1.31	1645

*Most common mutation in the UK

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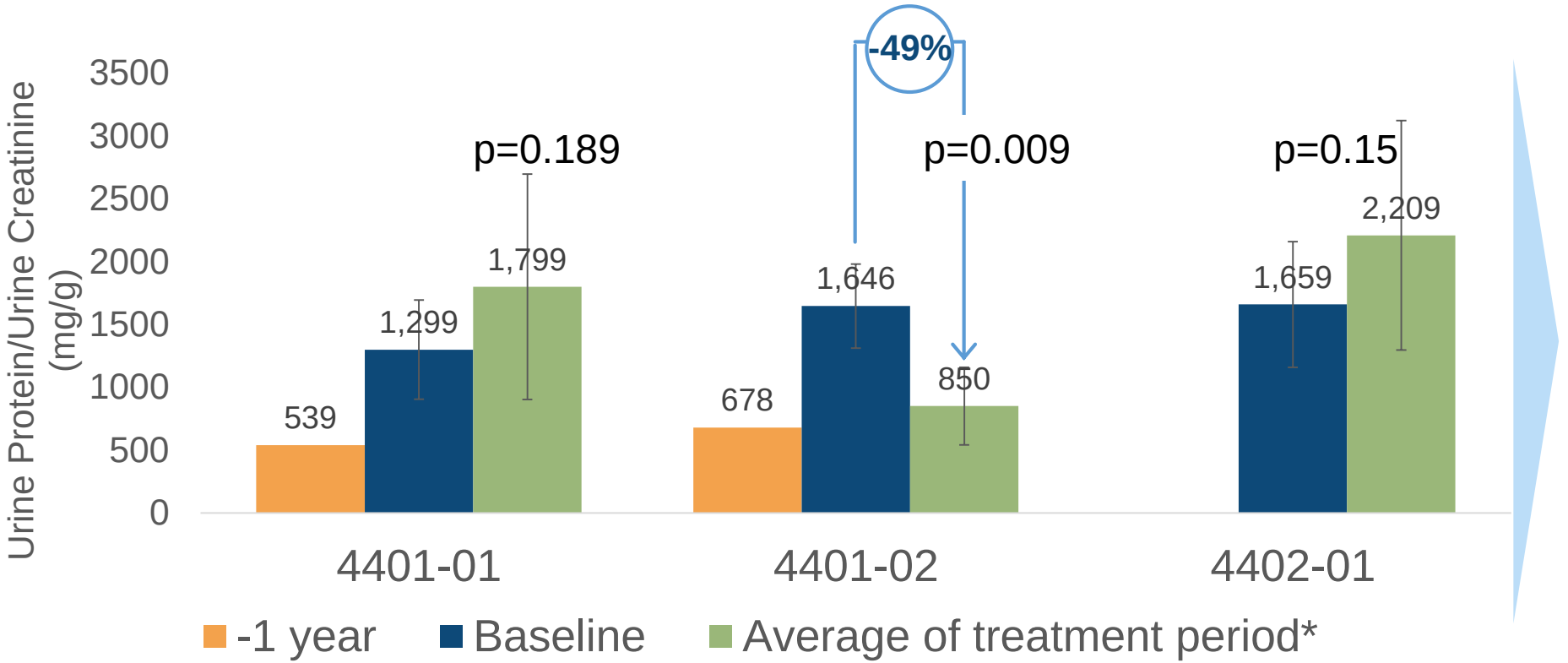
Remission in one Alport patient with an approx. 50% reduction from baseline

Phase 2 Alport patient results to date



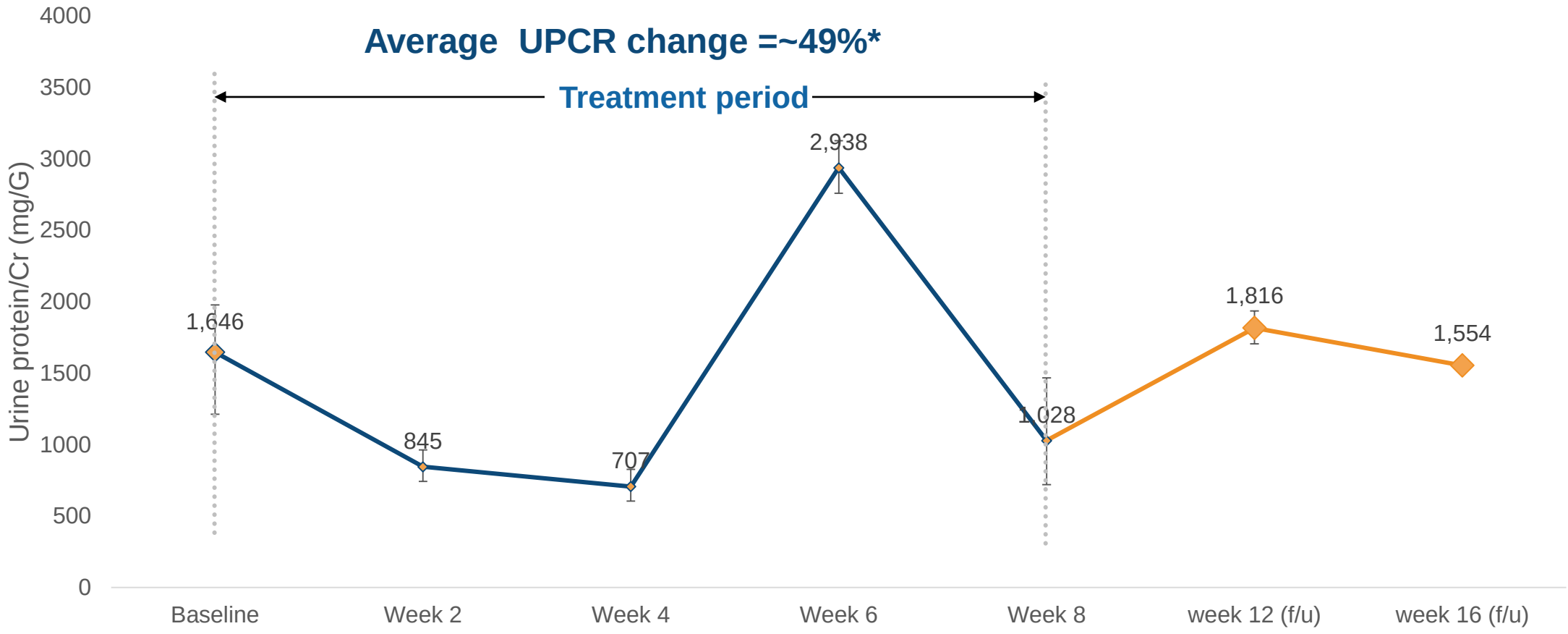
Patient 4401-02 achieved partial remission after completing 8 weeks of treatment

- Average reduction of baseline ~50%
- 5 out of 8 UPCR readings were on average 53% below baseline

* UPCR averaged over 6 values collected in 8 weeks for 4401-01 and 4401-02. UPCR values collected for 4401-01 and 4401-02 at week 6 were excluded as they were deemed to be unreliable due to inconsistent processing during Easter holidays and inconsistency with the clinical presentation. All 8 UPCR values included for 4401-02

Rapid remission in Patient 4401-02 with rebound 1 month after withdrawing treatment very encouraging

Proteinuria (UPCR) change in patient 4401-02



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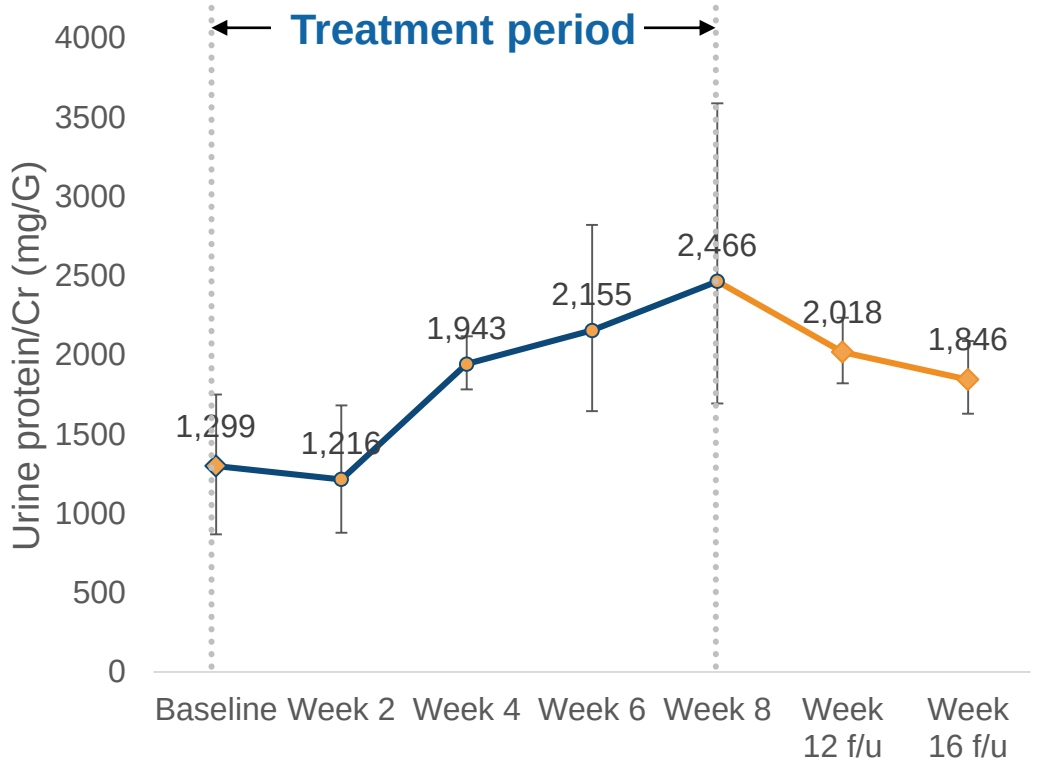
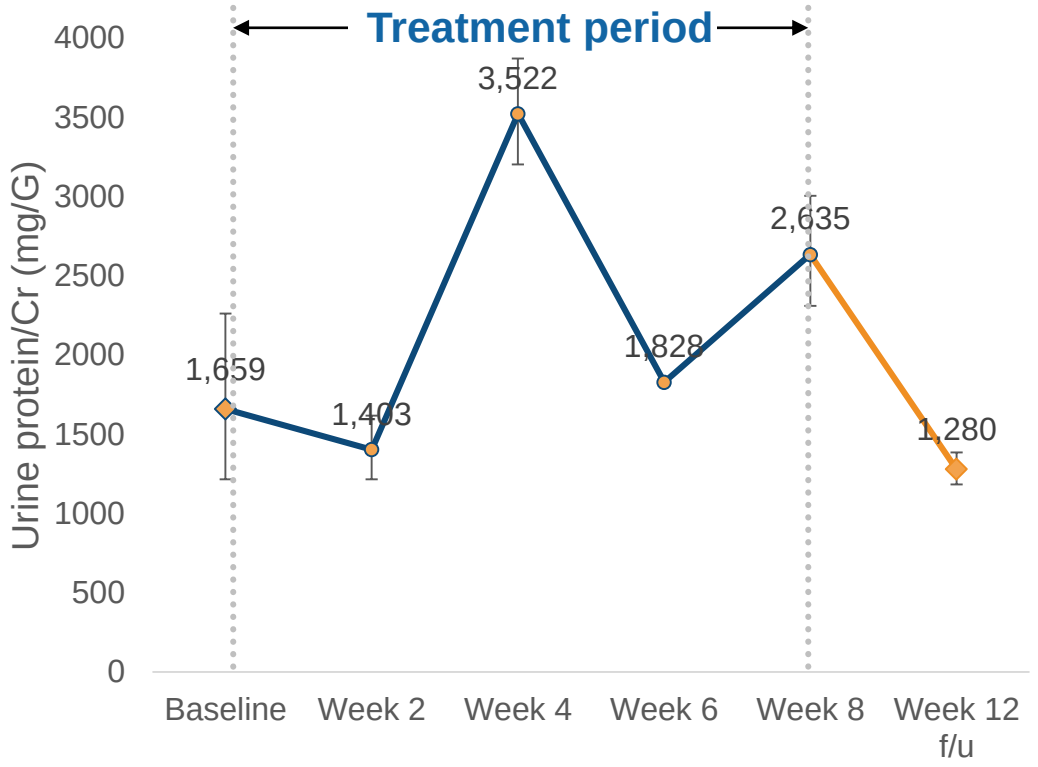
No change in other 2 patients after ELX-02 treatment

Proteinuria change in patient 4401-01 and 4402-01

Patient 4401-01 UPCR change over treatment



Patient 4402-01 UPCR change over treatment



Quantitative assay needed to assess degree of Collagen IV expression

Qualitative assessment of COL4A5 in immunofluorescence assay of kidney

Patient	COL4 Mutation	Glomerulus COL IV A5 at Baseline vs. Post treatment	Glomerulus COL IV A5 post treatment	Glomerulus COL IV A4 at Baseline vs. post treatment	Conclusion
4401-01	COL4A4/ S969XHet	Yes	Yes	Not measured	COLIVA5 in GBM <20%
4401-02	COL4A4/ S969XHet	Yes	Yes	Not measured	COLIVA5 in GBM <20%

- No safety issues identified
- Results suggests that there is a <20% increase in protein expression levels
- Low levels of protein restoration resulting in efficacy is consistent with preclinical expectations

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ELX-02 for Alport Syndrome: Dr. Hariri

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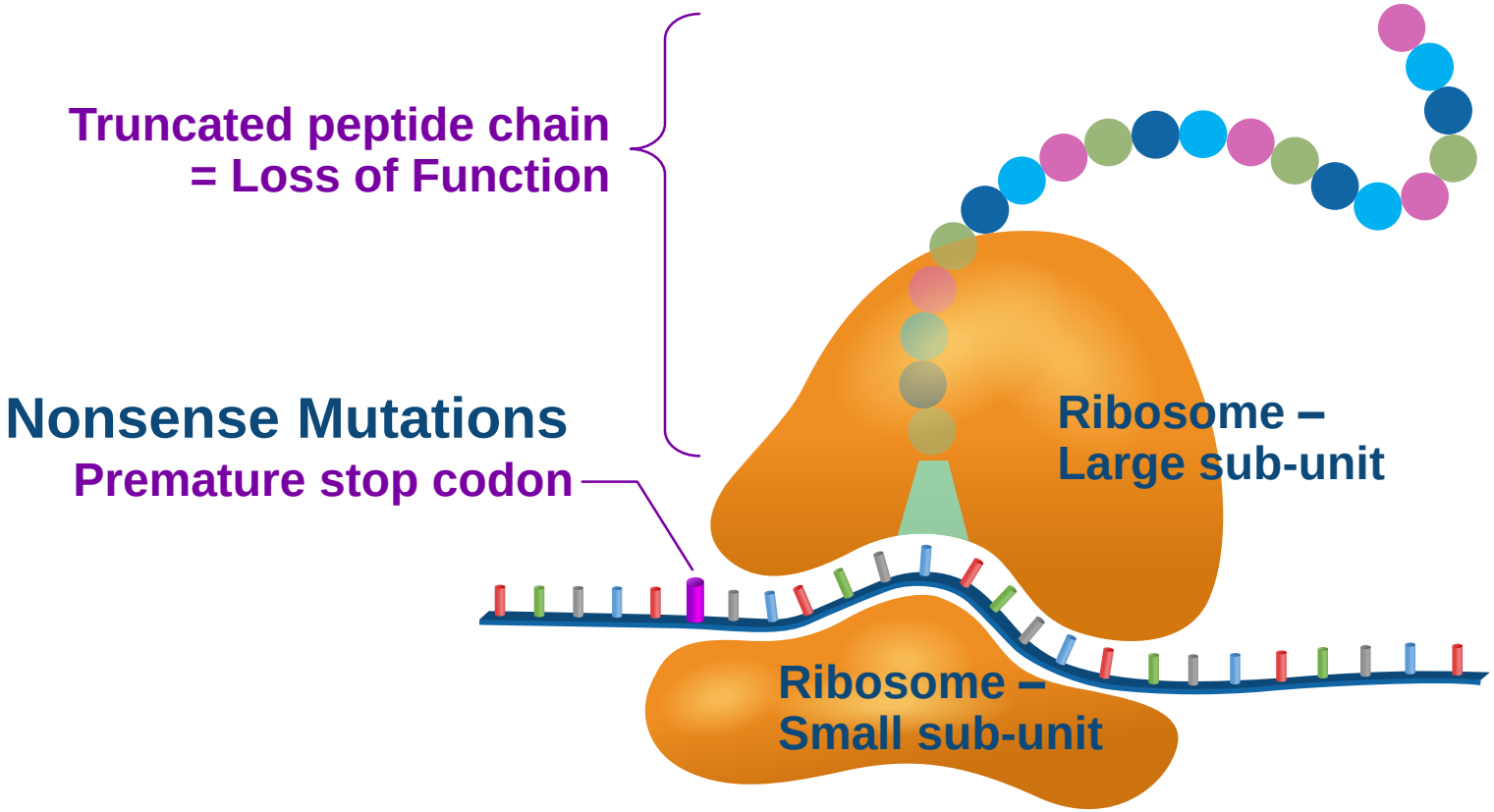
ELX-02 has potential to treat inherited diseases caused by nonsense (premature stop) mutations

Impact of nonsense mutations causing premature stop



- ELX-02 interacts with helix 44 in the human ribosomal18S rRNA
- Stabilizes cognate tRNA binding at Site A to facilitate formation of full-length protein

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ELX-02 has a proven mechanism of action

Indication (Gene)	Protein expression	Protein function	NMD rescue	*in vivo* function	Clinical
CF (CFTR)		✓	✓	✓	✓
RDEB (COL7)	✓	✓			
Alport (COL4A5)	✓				✓
ADPKD (PKD1/2)	✓	✓			
Cystinosis (CSTN)		✓	✓	✓	
JEB (LAMB3)	✓	✓			
Neurofibromatosis (NF1)				✓	
MPS I (IDUA)		✓		✓	
Rett (MCEP2)	✓	✓		✓	

Data generated in independent laboratories – with or without Eloxx funding

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ELX-02 well-tolerated at doses up to 3 mg/kg daily based on clinical studies

Summary of safety of ELX-02 across clinical studies

- A total of 148 human subjects (NHV and patients) have been exposed to ELX-02 over phase 1 and phase 2 clinical trials
  - 0.1 mg/kg to 5 mg/kg in healthy volunteers in Phase MAD study
  - 0.3 mg/kg to up to 3 mg/kg daily in CF patients
- No dose limiting toxicities in SAD, MAD and CF patients
  - Generally well tolerated at all dose and schedules
  - No drug-related nephrotoxicity (kidney) or vestibular (ear) toxicity
  - No drug related SAEs
  - No off target effects
  - Most common AEs were mild injection site reactions
- No new findings in Alport patients with CKD

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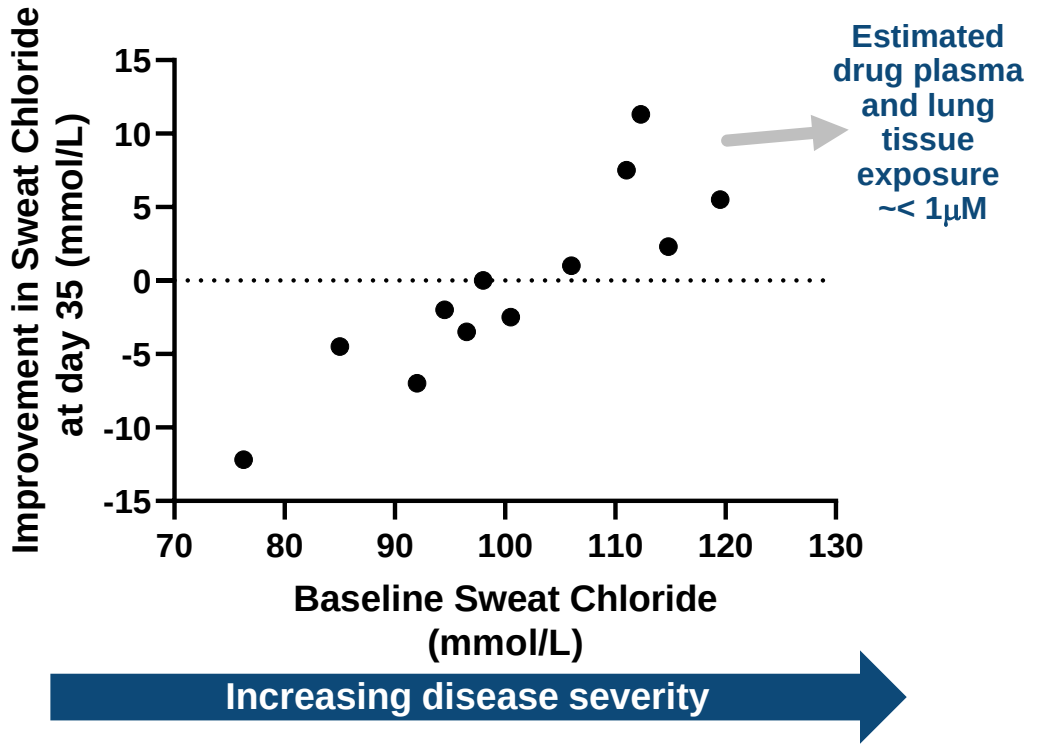
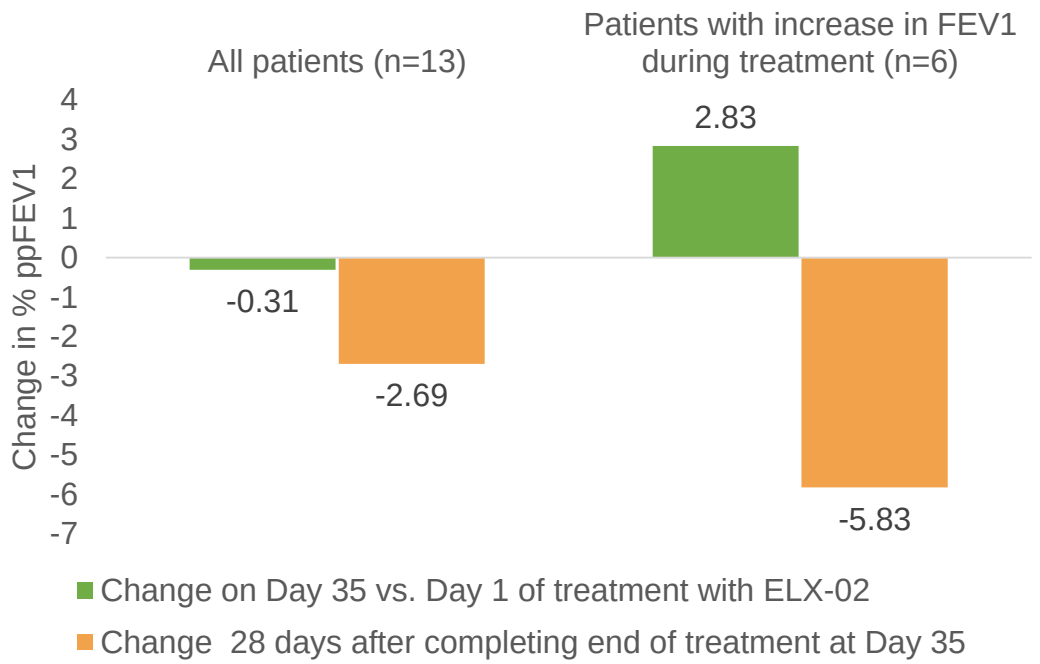
ELX-02 treatment in CF patients with nonsense mutations shows efficacy signal even at low drug levels

Results from Phase 2 trial in CF patients with ELX-02 1.5mg/kg daily and Ivacaftor

Biological activity: Change in sweat chloride vs. baseline sweat chloride

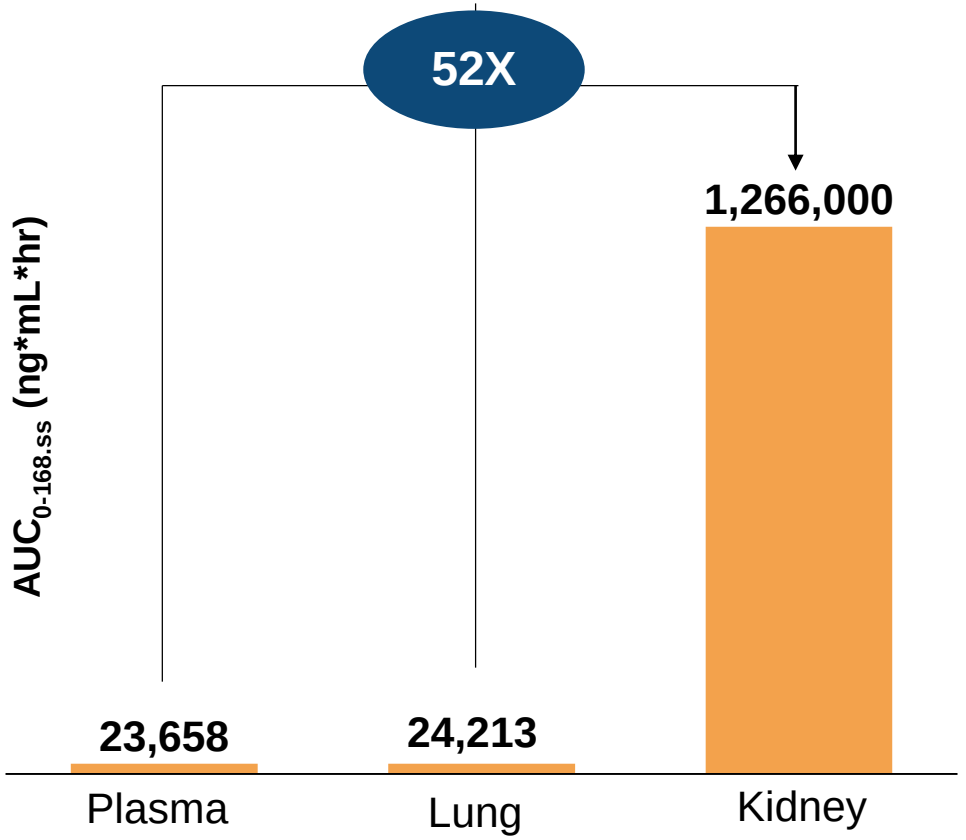


Clinical efficacy: Change in ppFEV1 (%) at end of treatment and safety follow up



ELX-02 well suited for treating rare genetic kidney diseases caused by nonsense mutations

Estimated human exposure in Plasma, Lung and Kidney at 1 mg/kg



Estimation based on allometric scaling of mouse, rat and dog plasma and kidney data PLUS plasma PK from SAD and MAD studies
Source: d1pbpk\pbpk\cognigen\2018-01-30-pbpk-elx02-refined-simulation\listing-ratio-auc168ss-human-bytissue.rtf.

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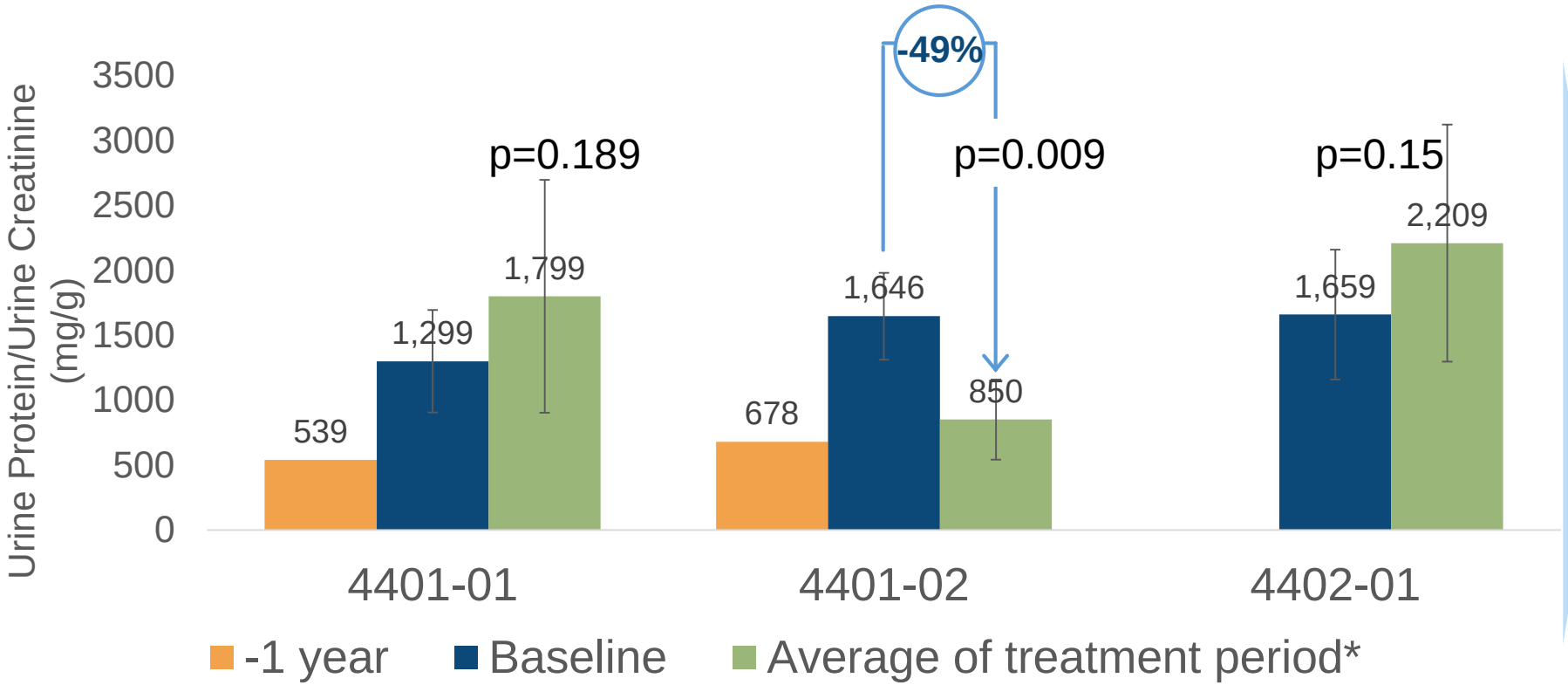
Remission in Alport patient meets criteria for advancing to pivotal study

Phase 2 Alport patient results to date



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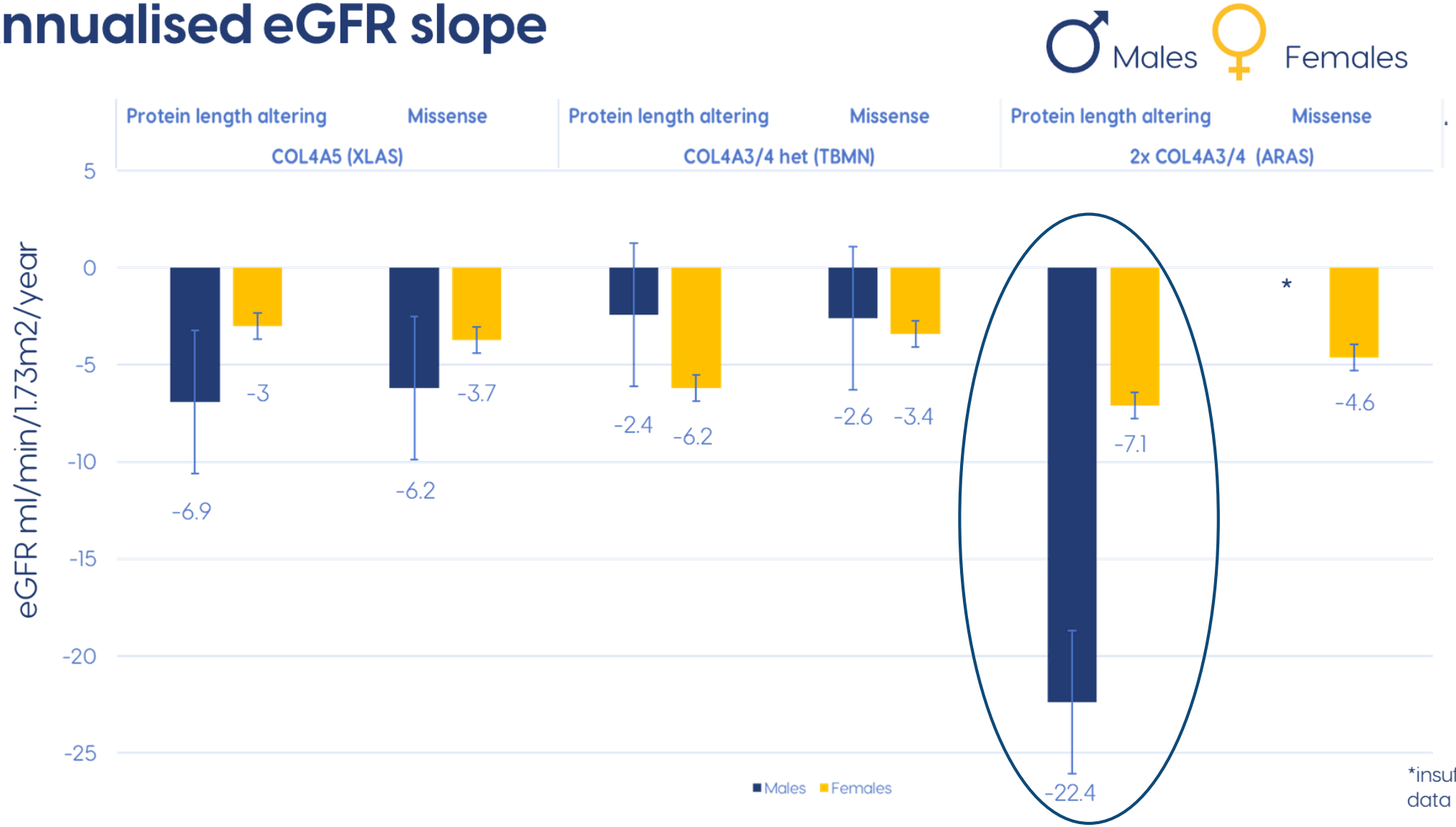
Alport patients with truncated proteins have poor renal outcomes and those with 2xCol4A3/4 having worst outcomes

Annualised eGFR slope

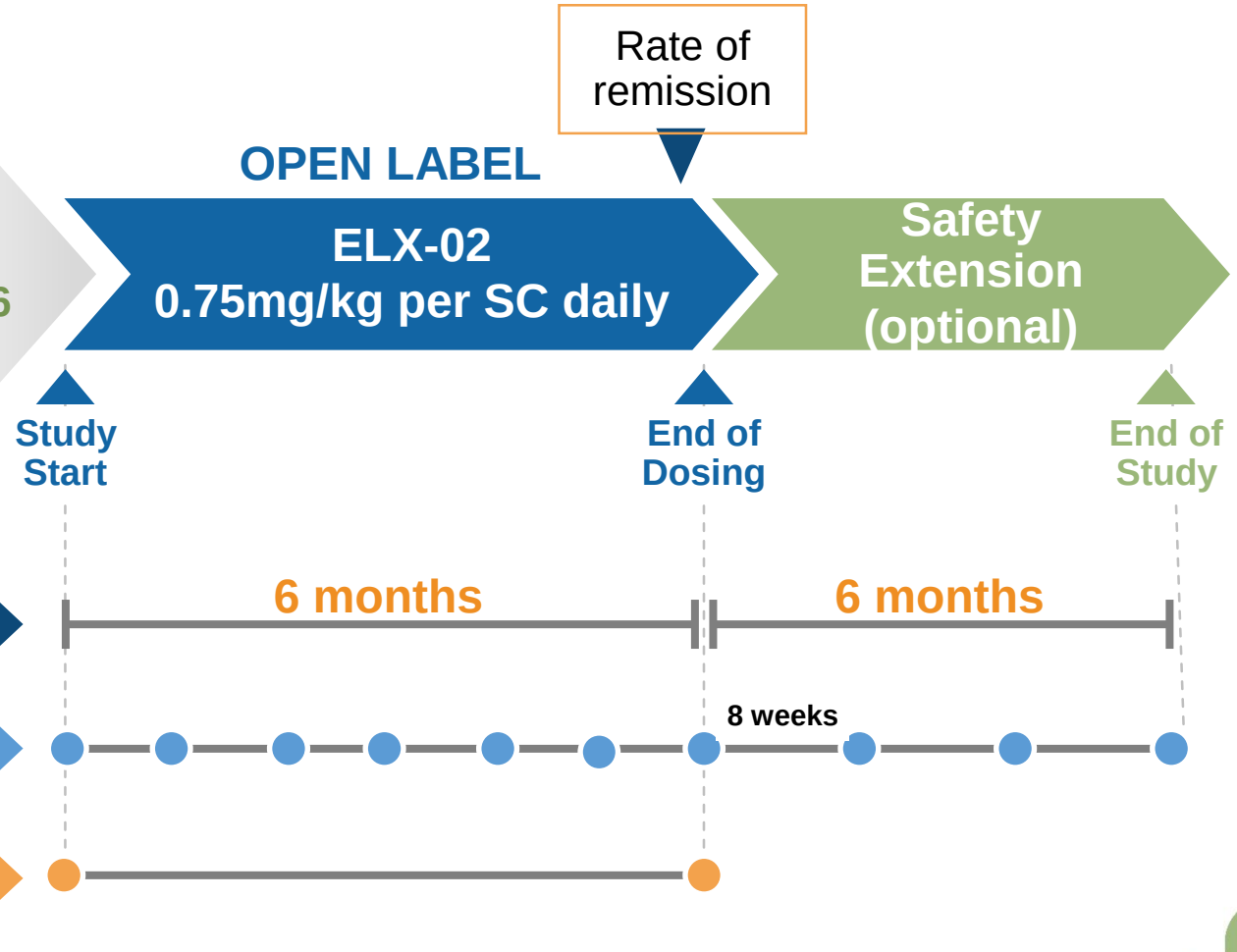


*insufficient data

Proposed Alport pivotal open label study based on ELX-02 disease remission rate of 30%

Inclusion Parameters	Criteria
Genotype	Any patient with nonsense mutations in the COL4 gene
Age	All patients >6 years
eGFR	>45ml/min/1.73m^2 BSA
Proteinuria	>300mg/g

N = 16



FDA accepts eGFR decline or proteinuria remission as approvable endpoints for kidney diseases

Excerpt of published viewpoint from the FDA*

Urine protein or remission

"FDA has indicated that it would accept a "complete remission" or near-"normalization" of proteinuria in patients with marked proteinuria at baseline as a surrogate end point and basis for full approval and some other "substantial" improvement in proteinuria in this population (short of a complete remission) as a "reasonably likely surrogate" and basis for accelerated approval"

eGFR slope or time to ESRD

"FDA has also accepted eGFR slope as an endpoint and basis for full approval of therapies for rare chronic kidney diseases"

*Am J Kidney Dis 2020 Jan;75(1):4-5

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Phase 2 data supports decision to advance to pivotal

Key questions for moving to pivotal study

- **Is one patient data sufficient to proceed to pivotal study?**
  - Spontaneous remission is unlikely in Alport
  - As low as a 1 in 10 patients showing remission would be potentially sufficient to seek regulatory approval as been demonstrated by approvals in lupus nephritis

- **Is an open label pivotal trial appropriate for seeking approval?**
  - Spontaneous remission not seen due to the genetic pathogenesis
  - The rapid progression Alport patients with nonsense mutation does not justify treating patients with placebo
  - Only 6% of Alport patients have nonsense mutations creating challenges with feasibility of a placebo controlled trial
  - An external control arm for this study can be used with data from UK patient registry (RaDaR)

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Summary and Q&A: Mr. Aggarwal

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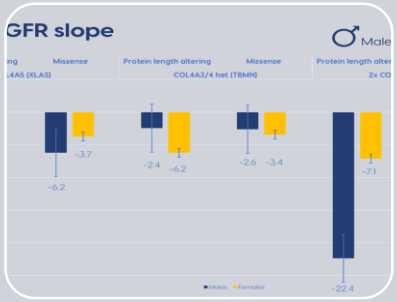
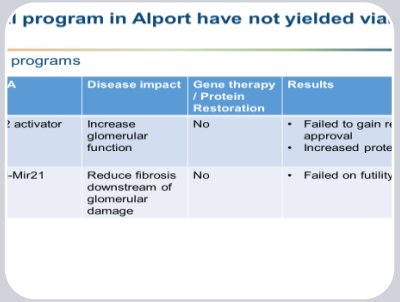
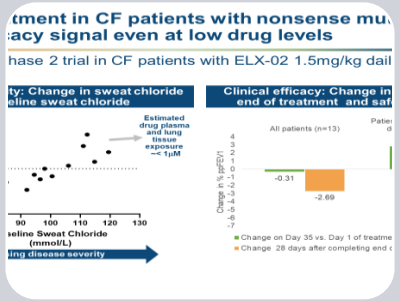
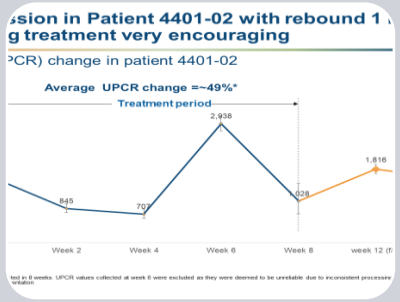
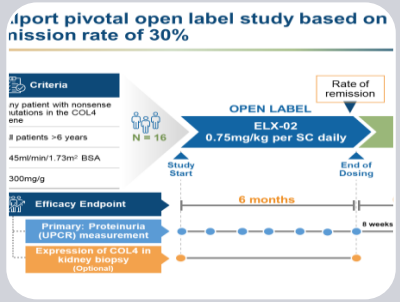
ELX-02 has potential as first gene therapy for Alport patients with nonsense mutations











High unmet need in Alport patients with nonsense mutations

Current treatments have **limited benefit**

ELX-02 proven to restore functional full length proteins

Robust treatment effect confirmed in Alport Phase 2 confirmed

Open Label pivotal trial planned with **Remission Rate** end point

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Thank you