RARE Thinking for RARE Solutions

Small Molecule Gene therapy Leader

Oppenheimer 33rd Annual Healthcare Conference
March 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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Clinical stage platform company developing potential treatments for rare genetic diseases with nonsense mutations

Novel small molecule genetic therapies that can **restore proteins**

Focused on high unmet need **nonsense mutation driven rare diseases**

Phase 2 Alport syndrome program with **data expected in 1H 2023**

Significant pipeline **expansion potential** in **rare diseases**

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Leadership team with track record of execution in 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

- Significant experience in rare disease and nephrology product development
- Expertise across a range of therapeutic areas

SANOFI GENZYME
IONIS
Takeda

Daniel Geffken
Interim Chief Financial Officer

- 30+ years building companies
- Closed $2B in equity and debt financings for public and private companies

Danforth Advisors
Knowledge. Discipline. Perspective.
Apellis
HOMOLOGY Medicines, Inc.
TKT

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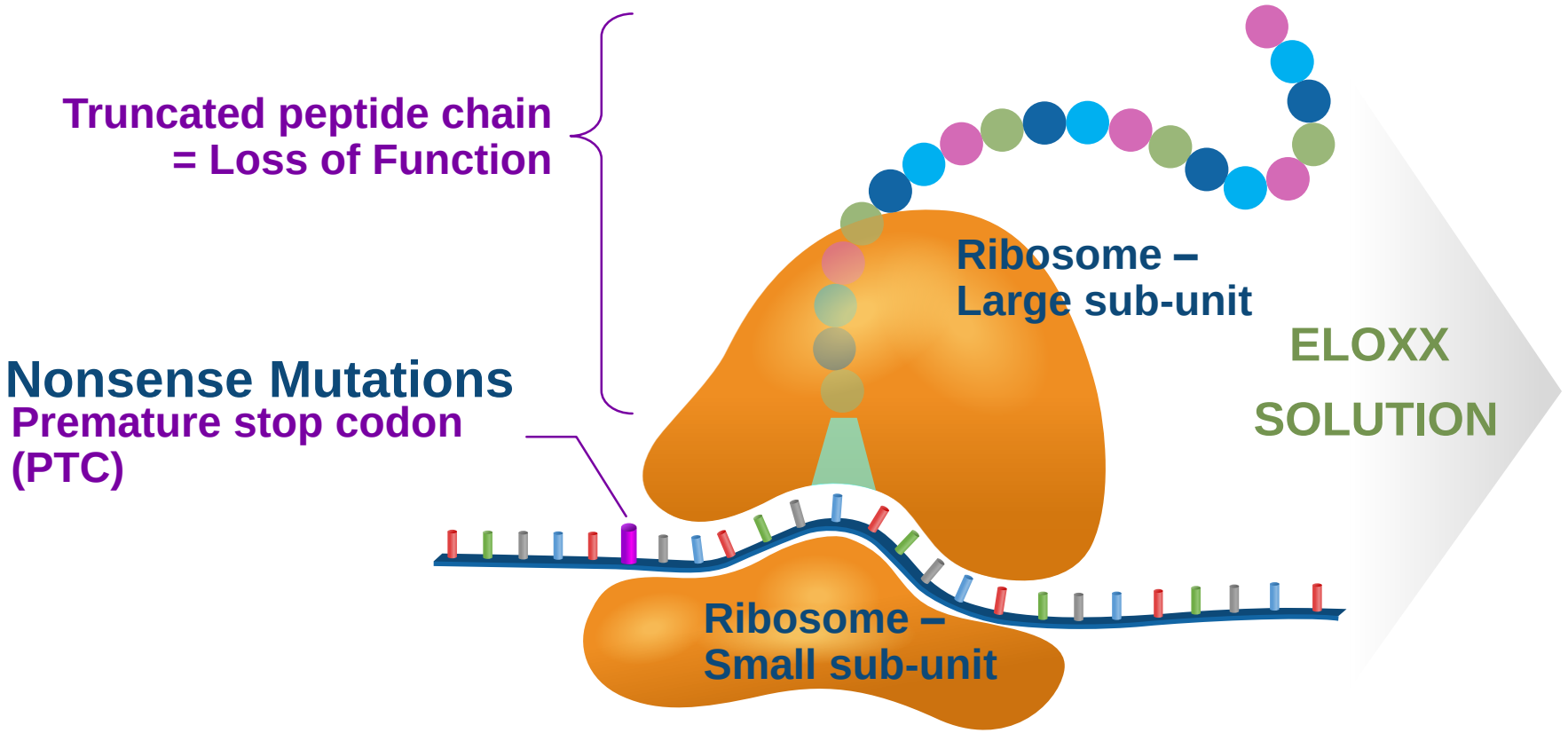
Developing genetic therapies to treat inherited diseases with nonsense mutations

Eloxx's small molecule gene therapy solution to restore truncated proteins



Novel, more potent versions of drugs with proven PTC readthrough

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Rare disease pipeline of potential first-in-class therapies

Indication	Protein restored	Discovery	Lead optimization	IND-enabling	Phase 1 – first-in-human	Phase 2	Key Milestones
Alport Syndrome (nonsense)	Collagen IV	ELX-02 (SC)					Top line results (1H 2023)
RDEB/JEB (nonsense)	Collagen VII/LAMB3	ZKN013 (oral)					IND submission (Q1 2023)
FAP (nonsense)	APC	ZKN013 (oral)					IND submission (Q2 2023)
Class 1 CF	CFTR	RMAs (oral)	CYSTIC FIBROSIS FOUNDATION				
Targeted oncology	Undisclosed	RMAs (oral)					
Class 1 CF (inhaled)	CFTR	ELX-02 (inhaled)					TBD

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

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ELX-02: Alport Syndrome with Nonsense Mutations

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ELX-02 has shown robust preclinical and clinical protein restoration across multiple indications

Summary of ELX-02 nonsense mutation readthrough activity

Disease	*In vitro*	*In vivo*	Organoids or Primary patient cells	Patients
Cystic fibrosis	✓	✓	✓	✓
Cystinosis	✓	✓	✓	✓
Alport syndrome	✓			
ADPKD	✓		✓	
RDEB	✓		✓	
JEB	✓		✓	
DMD	✓	✓		
MPS	✓	✓		
Rett syndrome	✓	✓		
Inherited retinal disorders	✓	✓		

Rare kidney diseases

ADPKD: Autosomal dominant polycystic kidney disease; **RDEB:** Recessive Dystrophic Epidermolysis Bullosa; **JEB:** Junctional Epidermolysis Bullosa; **DMD:** Duchenne muscular dystrophy; **MPS:** Mucopolysaccharidosis

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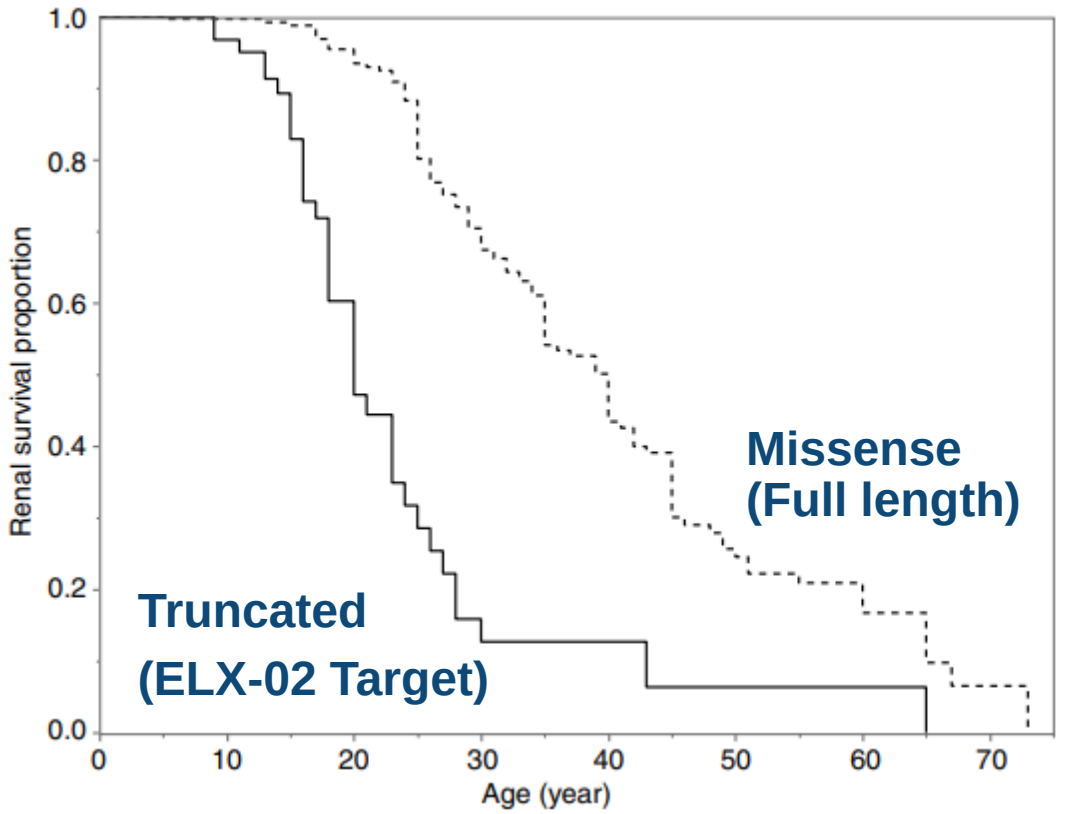
ELX-02 in Phase 2 for treatment of Alport syndrome with nonsense mutations in COL4 gene: Rare glomerular disease

Alport syndrome nonsense mutation disease overview

Alport disease overview[1,2]

- **Inherited glomerular kidney disease caused by defect in COL4 gene**
  - X-linked in 85% - COL4A5 gene
  - Recessive in ~15% - COL4A3 and COL4A4 genes
  - **Over 70 nonsense mutations** in Alport described
- **Fragile/no basement membrane** of the glomeruli
  - Nonsense mutations result in **truncated proteins**
  - **High proteinuria** and hematuria
  - Leads to kidney failure (CKD and ESRD)
- **Limited therapeutic options**
- **WW Addressable population of 9,000 to 12,500**

Kidney survival in Alport based on COL4 mutation[3]



[1]J Am Soc Nephrolv.28(6); 2017 JunPMC5461786
[2]J Clin Invest 1995 Sep;96(3):1404-13
[3]*Kidney International* (2020) 98, 1605–1614
CKD: Chronic kidney disease**; ESRD:** End-stage renal disease

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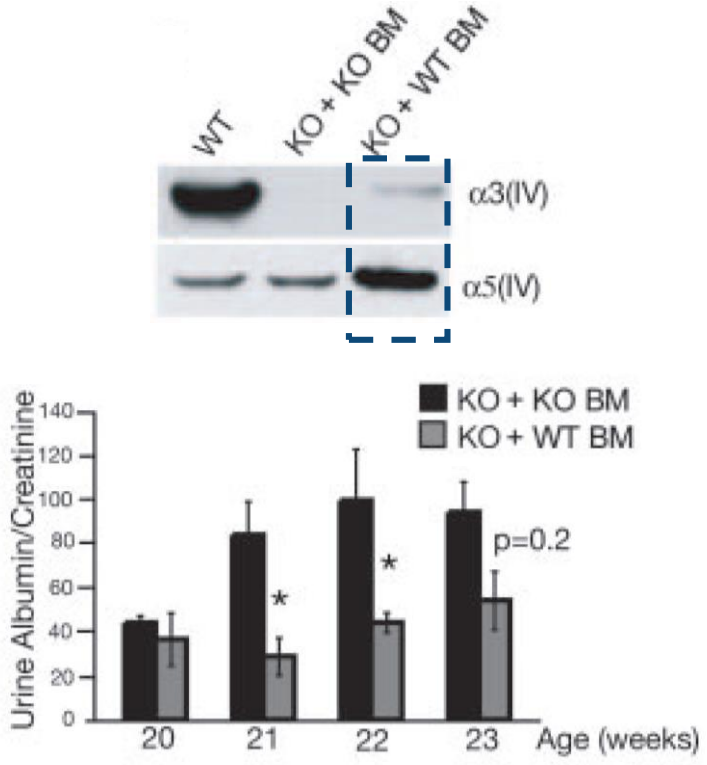
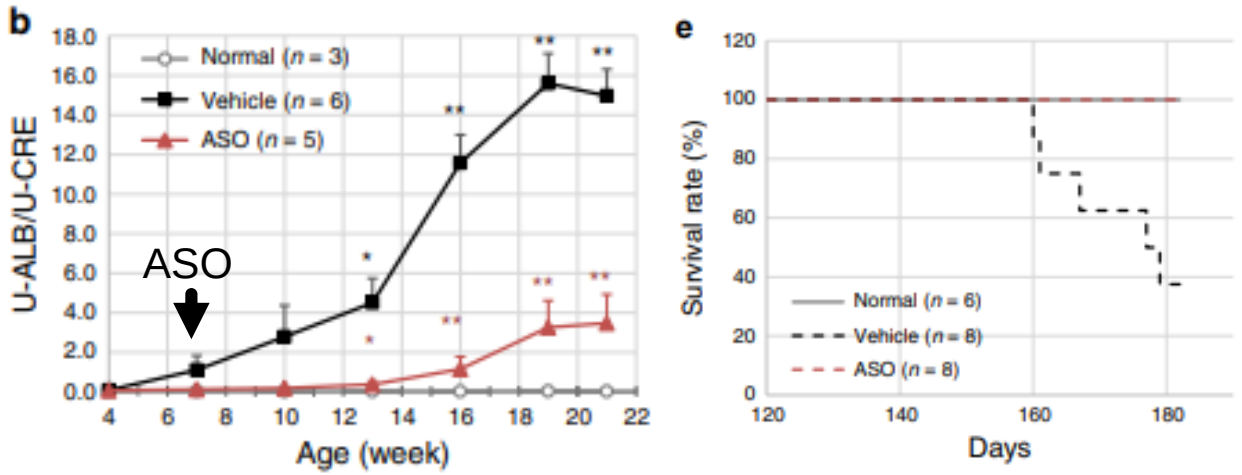
Minimal COL IV restoration sufficient for rapid and large proteinuria reduction in Alport mouse models

Treatment effect of COL IV protein restoration in Alport mouse studies

COL IV A3 bone marrow treatment of C57BL/6 Alport mice over 3 weeks[1]



Single dose exon skipping therapy in nonsense mutation Alport mouse[2]

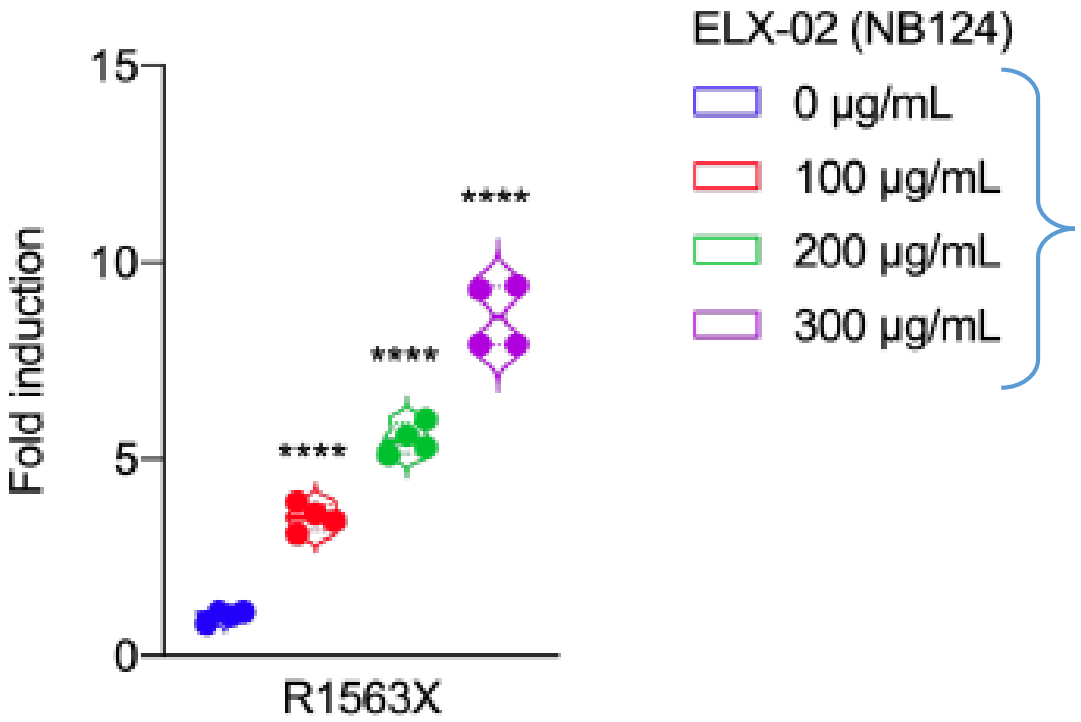


[1].JASN November 2009, 20 (11) 2359-2370. Wild type (WT) Bi-weekly COL4A3 +/- bone marrow (BM) treatment in C57BL/6 knockout mice aged 20 weeks over 3 weeks. treated mice: n=4; Knockout untreated mice: n=3 (*p<0.05)

[2] *Nat. Commun.* 11, 2777. Yamamura et. Al 2020https://doi.org/10.1038/s41467-020-16605-x. (* p<0.05; **p<0.01)

High levels COL IV protein restoration observed *in vitro* with ELX-02 after 24 hours

ELX-02 readthrough COL4A5 nonsense mutation in HEK293 cells at 24 hours[1]



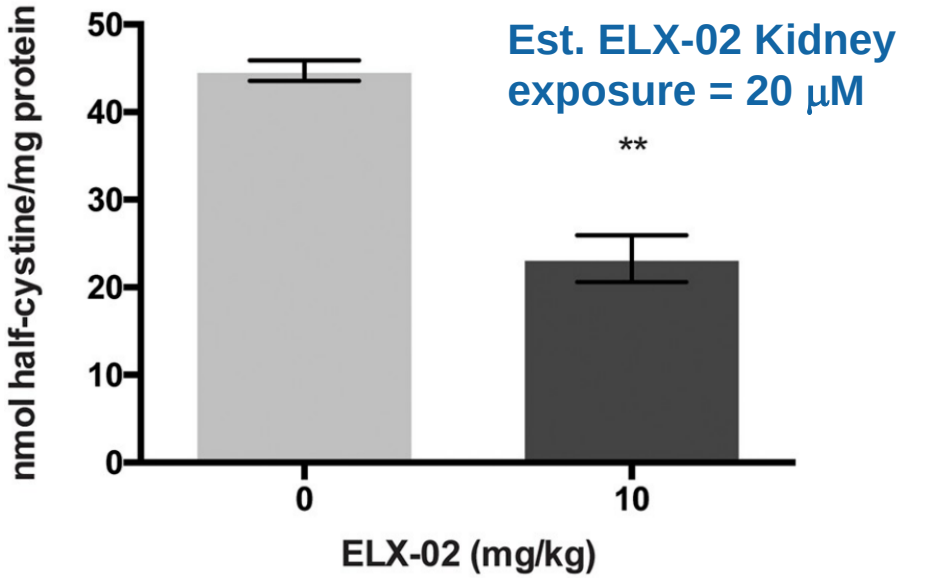
- **>3-fold readthrough in 31 of 32 of COL4A5** mutations tested with ELX-02 and derivatives[2]
- Equivalent to **6% to 15% full length** COL IV protein[1]
- **2- to 4-fold increase in expression** at 48- vs. 24-hr exposure

[1] doi: https://doi.org/10.1101/2021.06.11.448099: Experiment conducted at Washington University by Dr. Jeff Miner
[2] additional mutations tested in same system and lab at Washington university

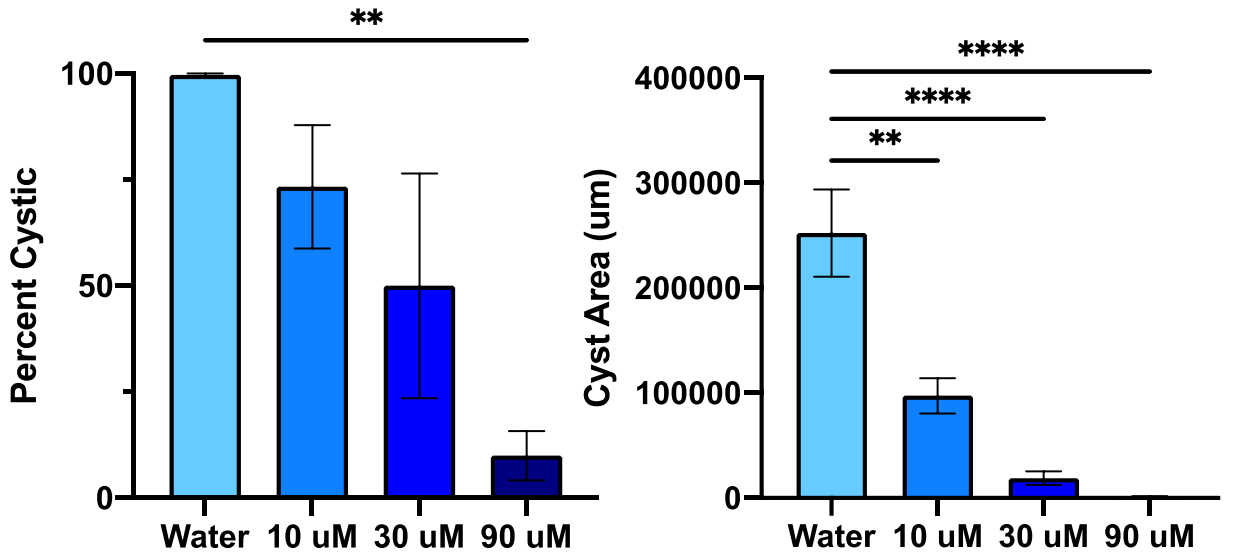
ELX-02 activity confirmed in two rare kidney diseases at low drug concentrations after 2 to 3 weeks of treatment

ELX-02 preclinical treatment effect in cystinosis and PKD models

Kidney cystine levels in CTNSY226X/Y226X mice after 3-week ELX-02 treatment[1]



Cyst burden in iPSC derived PKD2 organoids after 14-day ELX-02 treatment[2]



[1]PLoS One 2019 Dec 4;14(12); Bi-weekly treatment with ELX-02 of Cystinosis mouse with nonsense mutation

[2]Presented at ASN Kidney Week 2021. ABSTRACT: TH-OR39 November 04, 2021 | Location: Simulive, Virtual Only Abstract Time: 04:30 PM - 06:00 PM. Single organoids transferred to suspension culture 96-well plates. Treatment is initiated and cyst formation monitored over 14 days.

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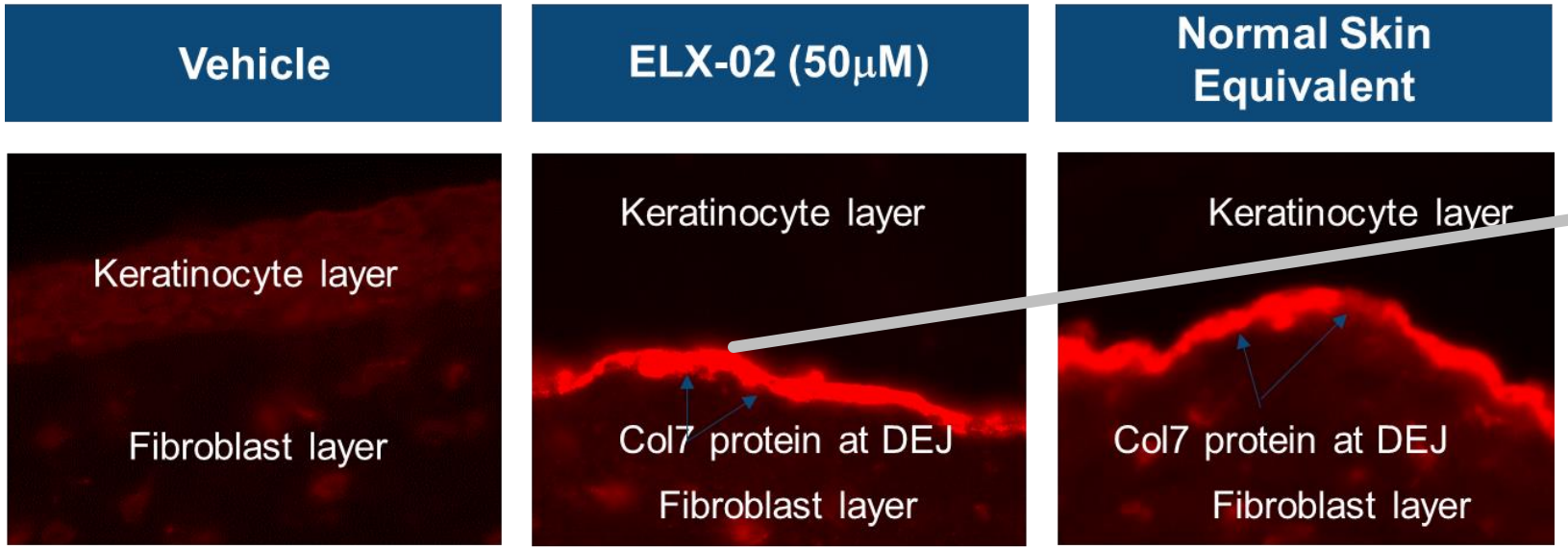
Long half-life of collagen proteins results in near normal functional protein restoration after longer treatment

6 to 8 day treatment effect of 50 μM ELX-02 in RDEB skin equivalent models with nonsense COL7 mutation*



Folding and trimerization of Collagen VII protein is required for secretion and deposition at the DEJ

Equivalent level calculations done by using Gent readthrough relative to NKC levels, from Cogan et al., 2014
RDEB: Recessive Dystrophic Epidermolysis Bullosa; **DEJ:** Dermal-epidermal junction

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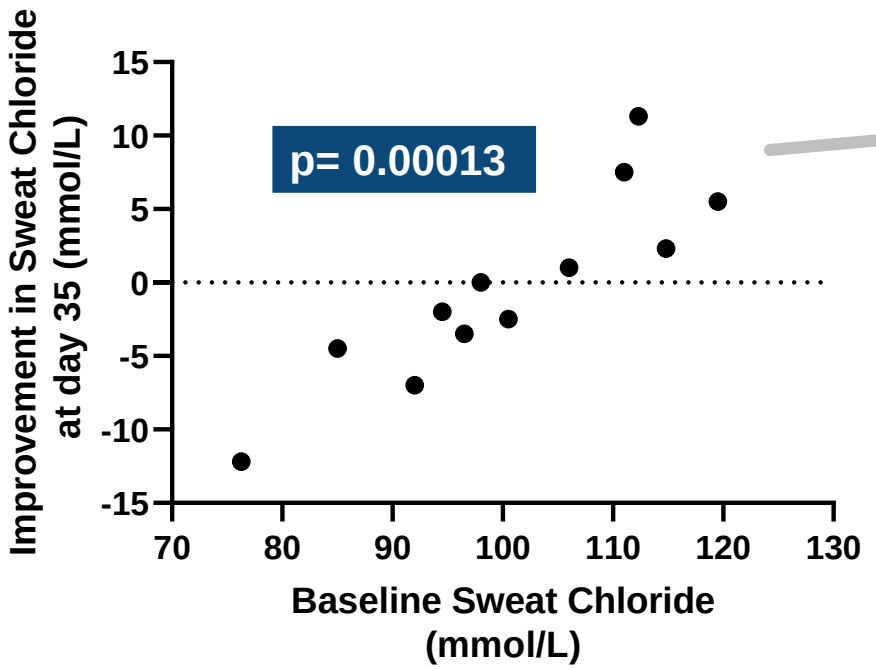
ELX-02 biologically active in Class 1 CF patients despite minimal drug exposure

ELX-02 functional protein restoration in CF patients with nonsense mutations

Results from Phase 2 study[1]



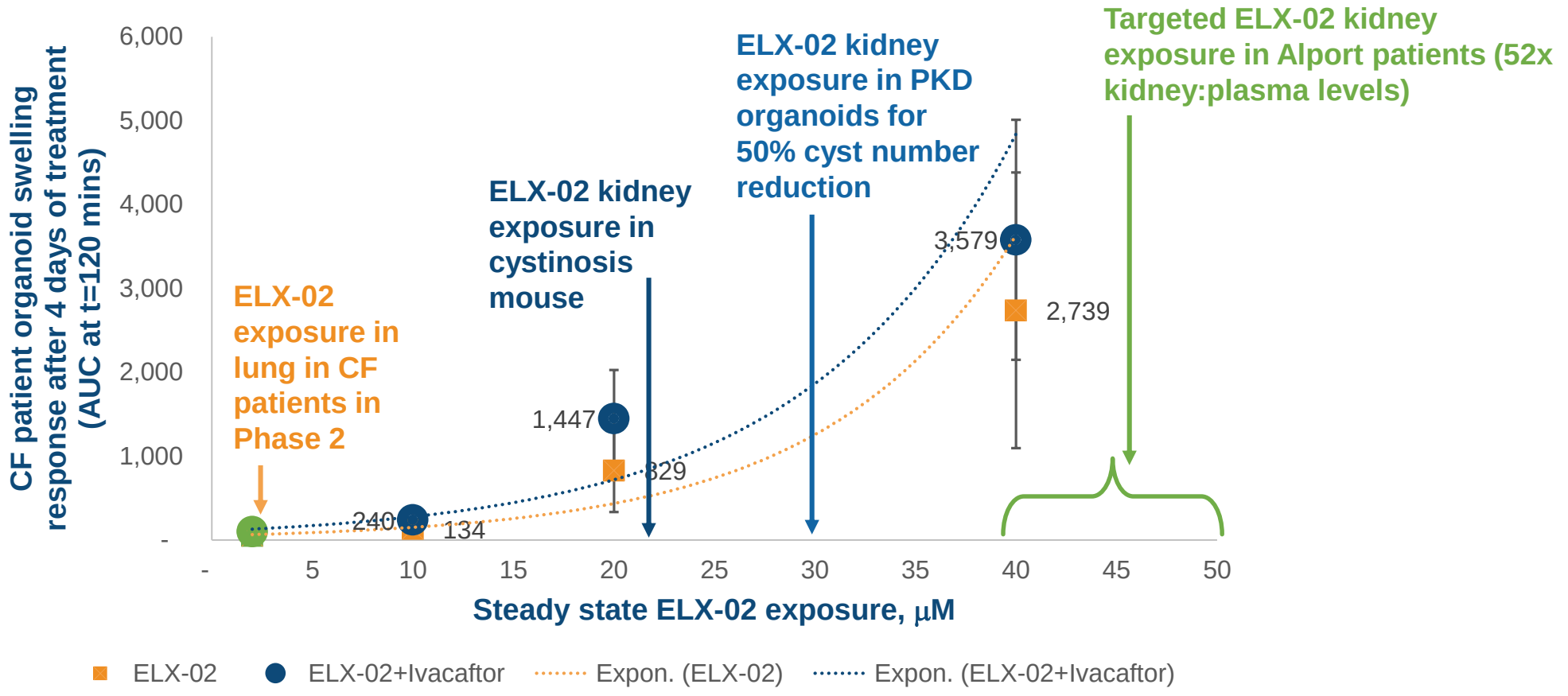
Estimated drug plasma and lung tissue expsore ~<1μM

Increasing disease severity

[1]Results from Phase 2 study in Class1 patients treated with ELX-02 at 1.5mg/kg and ivacaftor at Day 35

Targeting 2- to 3-fold higher ELX-02 kidney concentration than in cystinosis and PKD for maximal COL IV restoration

Exposure dependent activity in Class 1 CF patient organoids to ELX-02 treatment[1]



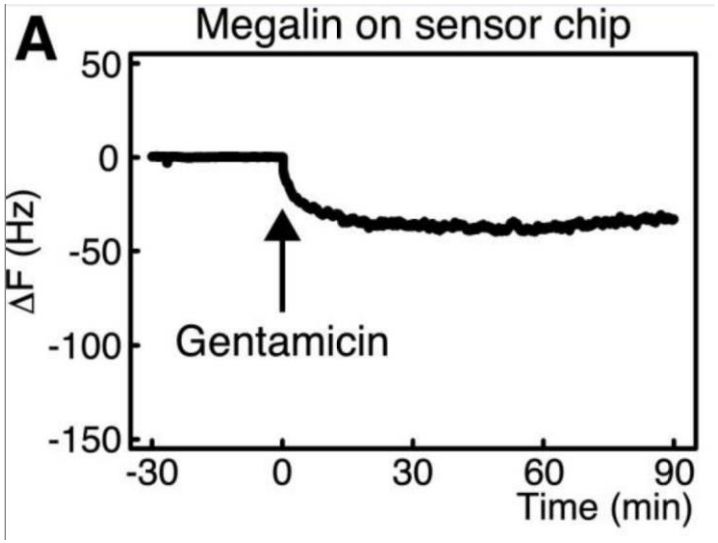
[1]Forskolin concentration: 0.8uM; Swelling adjusted for control. Data generated at HUB across multiple experiments. Values represent mean and standard deviation across multiple experiments

Target concentration expected to be achieved with dose of 0.75mg/kg/day based megalin binding in the glomeruli

Aminoglycoside binding affinity to megalin and expression in kidney cells

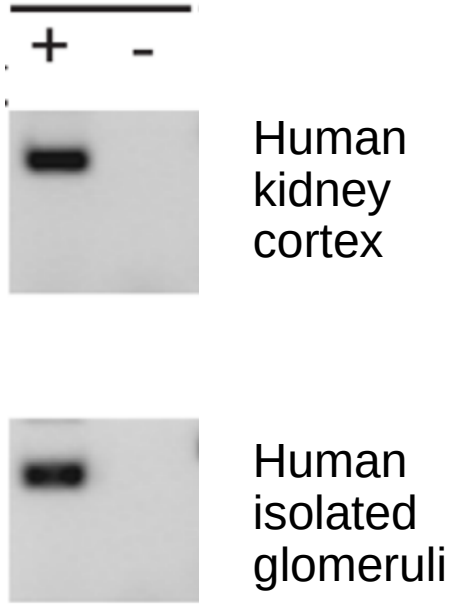
Megalin binding of aminoglycosides[1]

Quartz Crystal Microbalance experiment[1]

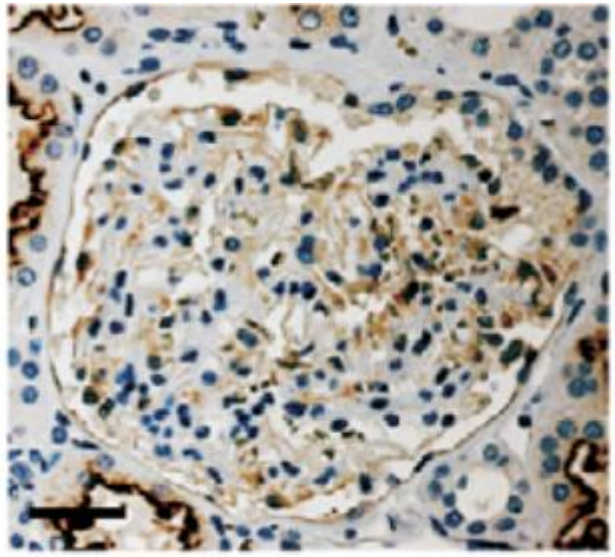


RNA levels for megalin in kidney (RT-PCR)[2]

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

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Sufficient safety margin expected at selected ELX-02 dose in Alport syndrome

Cumulative ELX-02 safety experience across all clinical studies

No ELX-02 related SAEs in Phase 1 and 2 studies at doses up to 7.5 mg/kg

ELX-02 was well tolerated at 1.5 mg/kg dose across Phase 2 patients (n=31)

- Combination therapy at 1.5 mg/kg showed drug related discontinuations
  - 2 patients discontinued due to injection site reactions (mild to moderate)
  - 1 patient withdrew from trial due to injection burden prior to dosing
  - 1 patient with tinnitus*

*Patient had an undisclosed history of tinnitus
SAE: Serious adverse events

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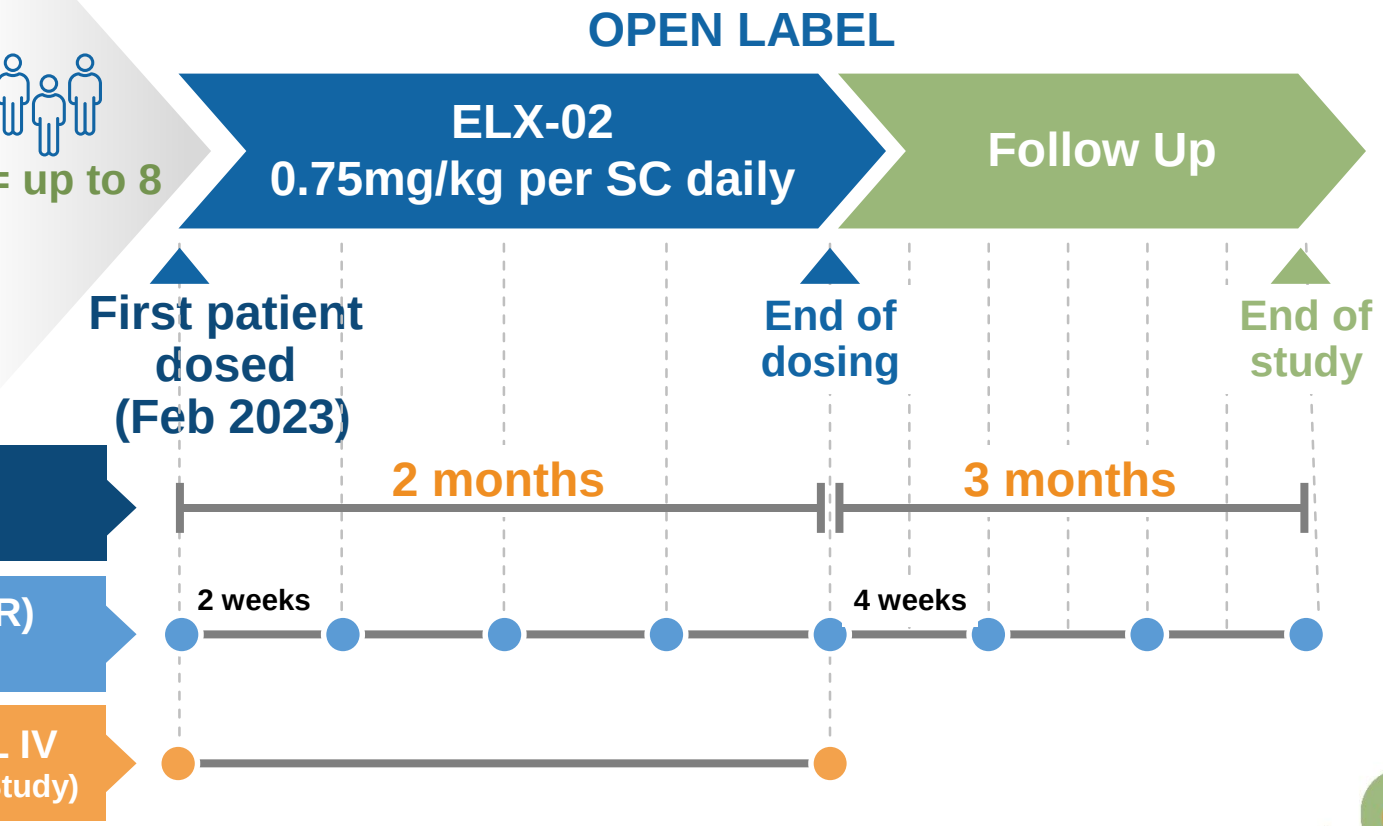
Assessing biweekly proteinuria reduction and COL IV expression after 2 months in Phase 2; data expected 1H 2023

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

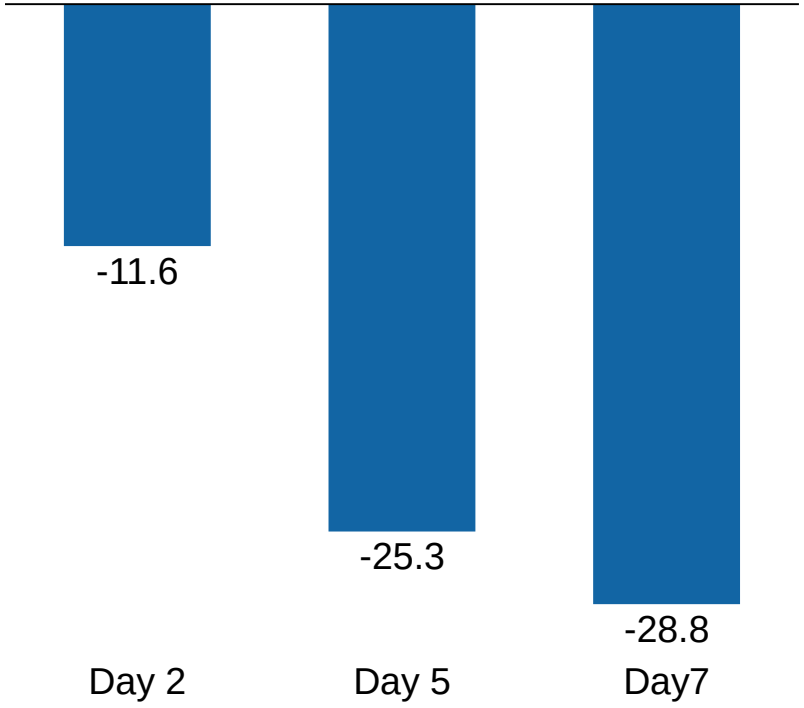
n= up to 8



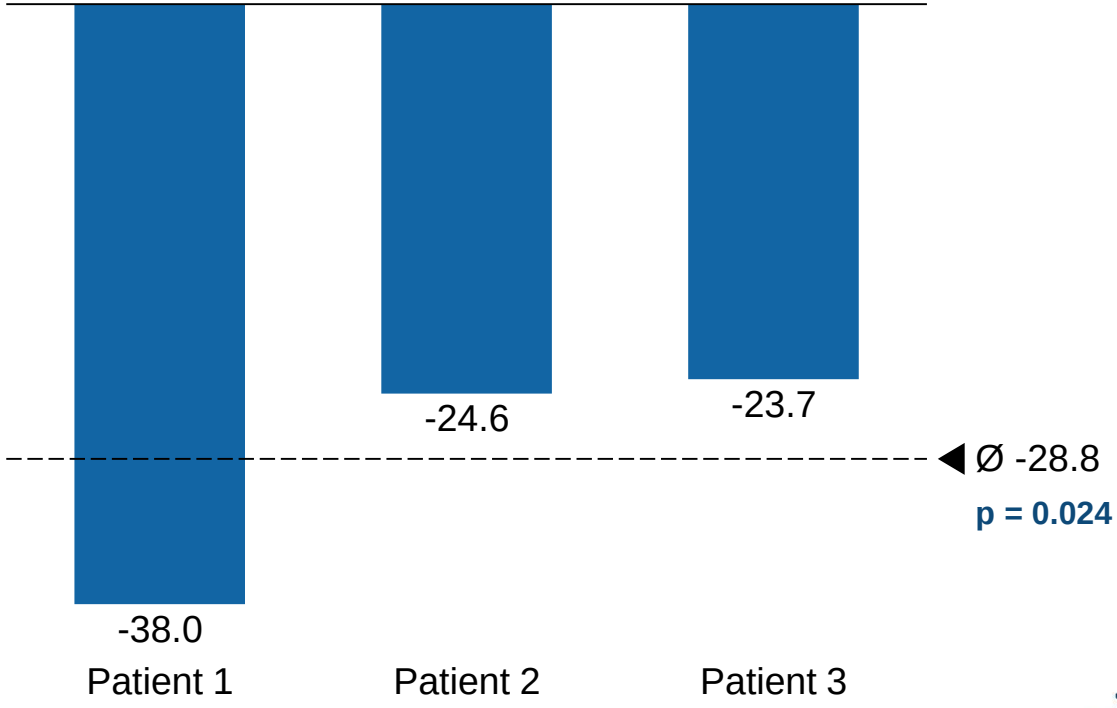
ELX-02 treatment showed a rapid and statistically significant treatment effect in cystinosis patients after only 1 week

Mean percentage change in white blood cystine levels in cystinosis patients with nonsense mutations treated with ELX-02 dosed 1mg/kg/day[1]

Change in WBC cystine levels over time (n=3)



Change in WBC cystine at Day 7



[1]ELX-02 Phase 2 study in Cystinosis patients with nonsense mutations

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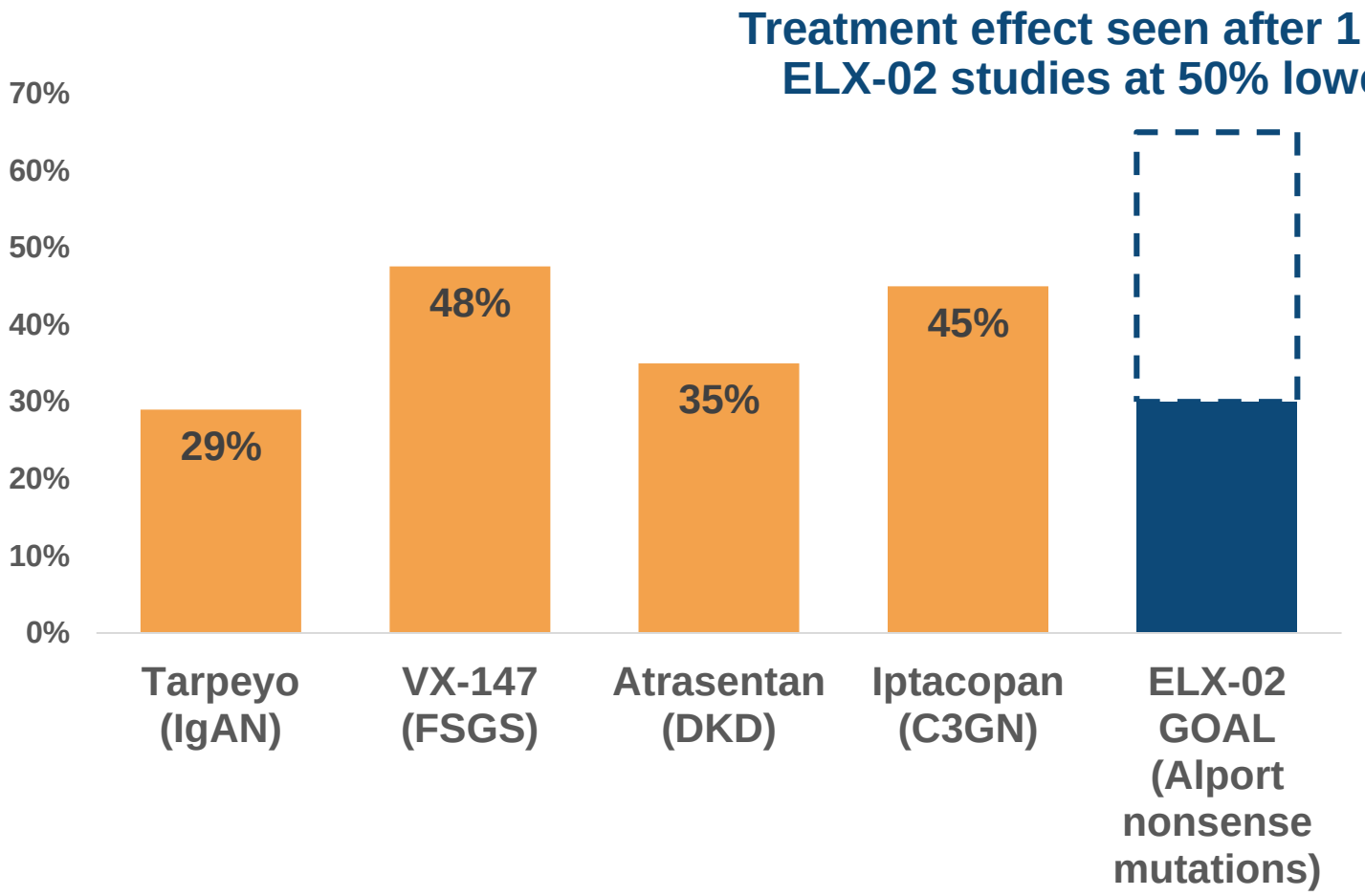
Our goal for advancing to Phase 3 in Alport is proteinuria reduction of at least 30% after 1 to 2 months

Proteinuria reduction in Phase 2 across primary glomerular diseases[1]



"FDA has already accepted [for a number of primary glomerular diseases] treatment effects on proteinuria as an end point and basis for accelerated and/or traditional approval" – *FDA Staff*[2]

[1]Proteinuria reduction in Phase 2 studies across range of drugs that advanced to Phase 3 for treating various primary glomerular diseases. Tarpeyo data is for Phase 3
[2]AJKD Vol75 Issue1 4-5 January 2020

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ZKN-013: RDEB and FAP

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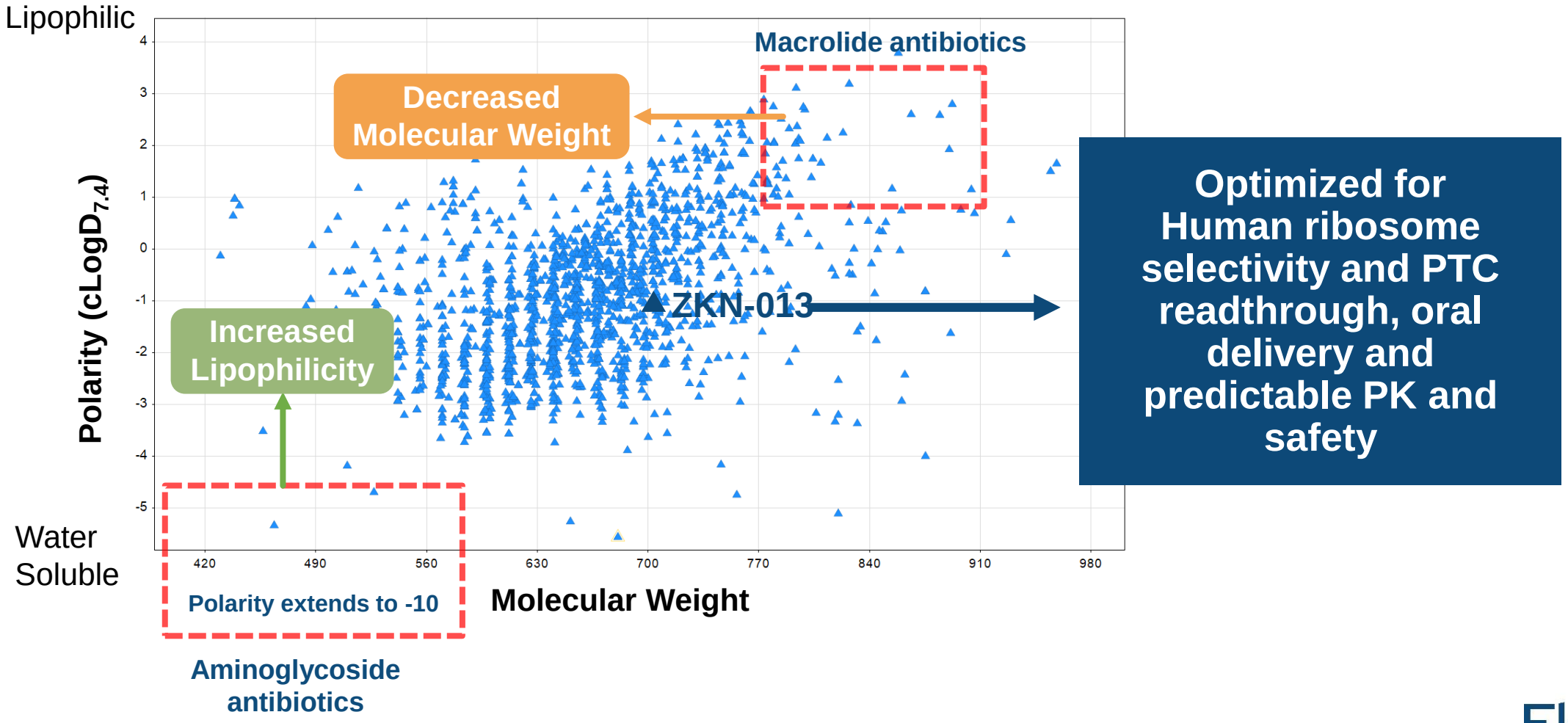
ZKN-013 selected from library of oral RMAs with favorable drug-like properties

Zikani Ribosome Modulating Agent Library of novel mcarolides (2000+)



RDEB/JEB are rare skin diseases frequently caused by nonsense mutations in the COL7A1 and LAMB3 genes

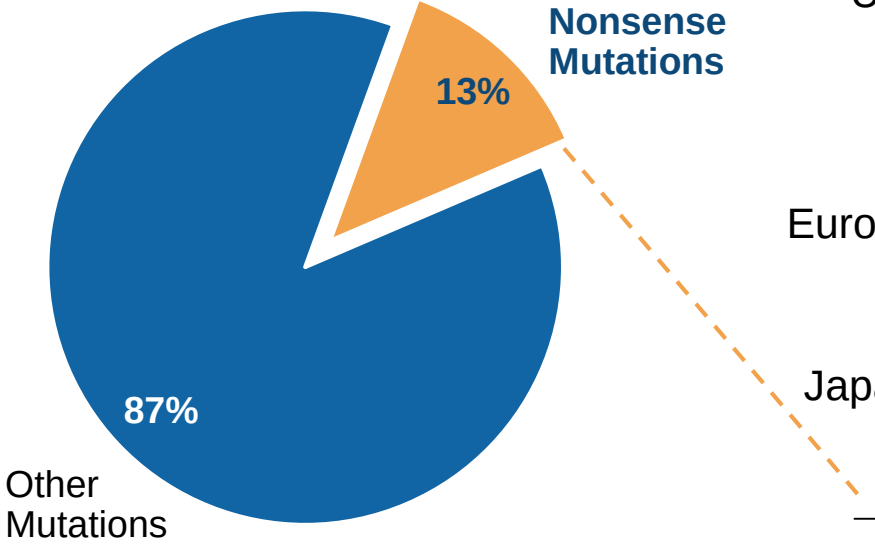
RDEB and JEB: recessive dystrophic and junctional epidermolysis bullosa

Disease overview

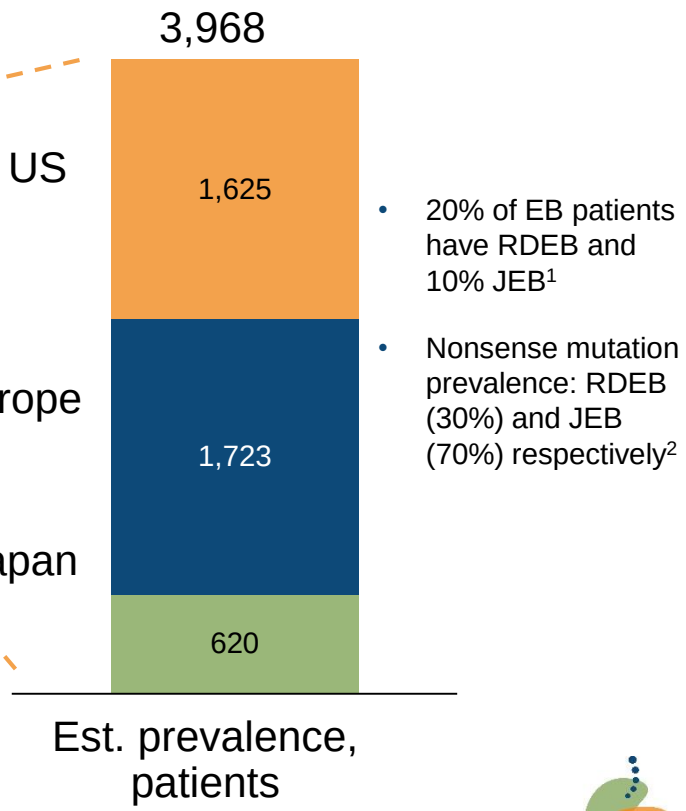
- Mutations in **COL7A1 gene** (RDEB) and **LAMB3** (JEB)
- **Skin tearing/blistering**
- **Impacts other organs including the GI tract (causes malnourishment) and heart**
- Skin cancer in RDEB by age 35
- JEB average mortality at 18 months

Disease prevalence

~30,000 total US/EU/Japan RDEB and JEB patients



Geographic breakdown of nonsense mutation patients



- 20% of EB patients have RDEB and 10% JEB[1]
- Nonsense mutation prevalence: RDEB (30%) and JEB (70%) respectively[2]

[1] International database of DEB patients with COL7A1 mutations: https://deb-central.org/
[2] Varik.et.al. 2006. *J. Med. Genet* 43: 641

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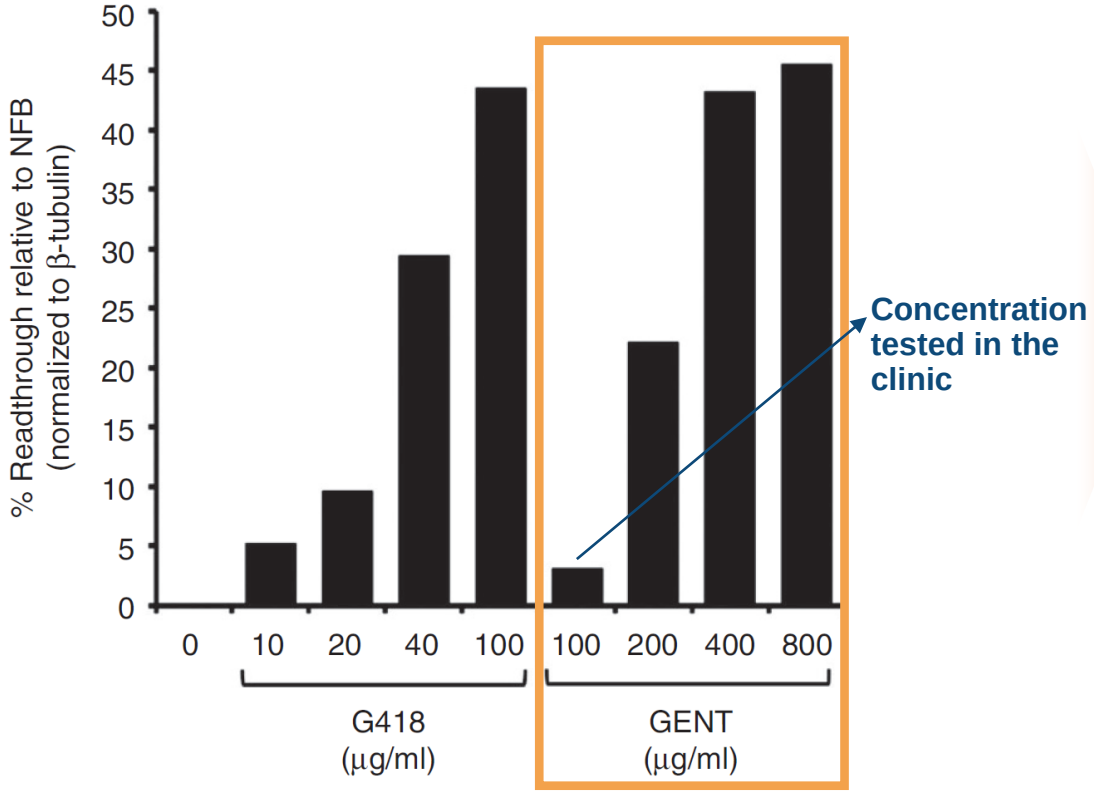
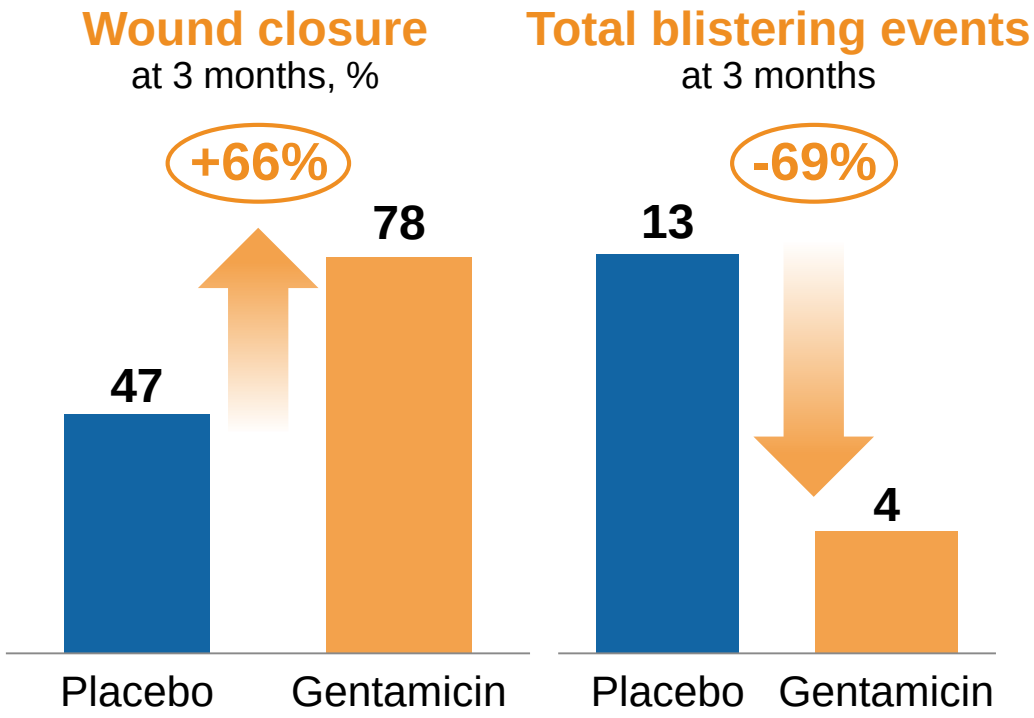
Gentamicin restored COL VII in RDEB patient cells and showed clinical benefit

COL VII protein restoration with gentamicin

COL VII protein expression in RDEB patient fibroblasts[1]



Gentamicin treatment of RDEB patients; n=5; treatment duration: 2 weeks



COL VII expression was 20-165% of normal skin

[1] Cogan et al., *Molecular Therapy* (2014)
[2] Woodley, DT. *J Clin Investig* 2017, 127, 3028-3038; 2 Hammersen, Johanna et al. *Dermatology* May 2019
RDEB: Recessive Dystrophic Epidermolysis Bullosa

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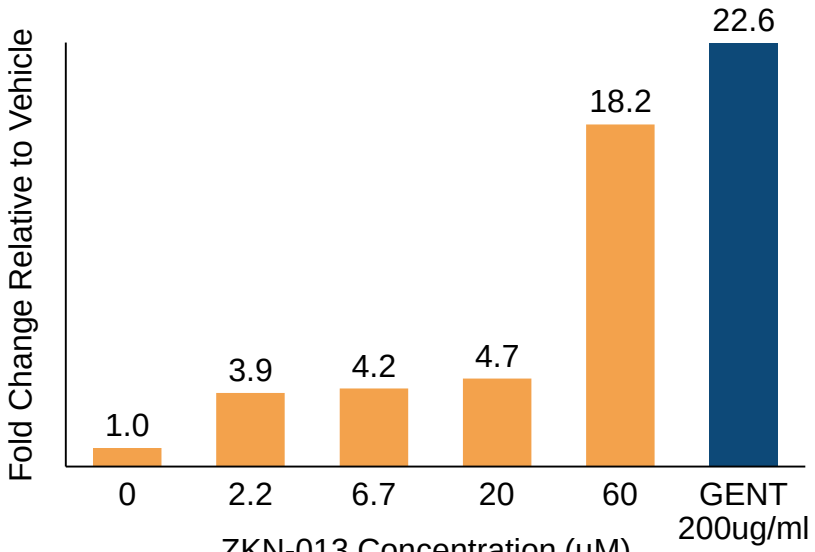
ZKN-013 showed a dose-dependent functional COL VII protein restoration in RDEB patient fibroblasts

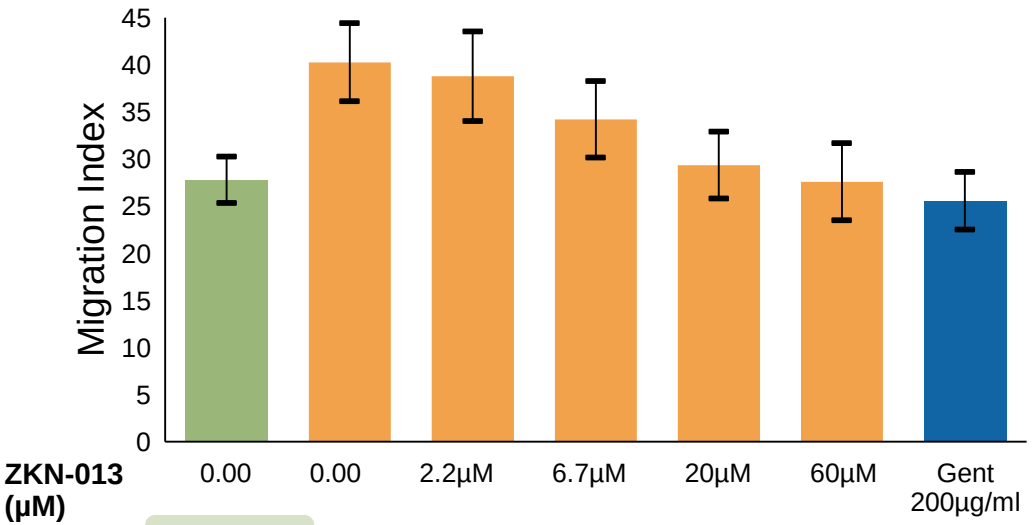
ZKN-013 treatment of primary patient fibroblasts[1]

COL VII protein expression in R578X/R578X RDEB fibroblasts with ZKN-013[2]



2x clinical conc.[2]

R578X/R578X patient fibroblast motility after ZKN-013 treatment[3]



2x clinical conc.[2]

[1]Fibroblasts derived from patients in Woodley et al. J Clin Invest. 2017.
[2]48 hours treatment with media and compounds replaced and refreshed at 24 hours
[3]Fibroblasts cultures suspended and allowed to migrate for 16-20h. Migration index=% of each non overlapping field consumed by cell migration tracks. Data generated in collaboration with Chen lab at USC.
RDEB: Recessive Dystrophic Epidermolysis Bullosa

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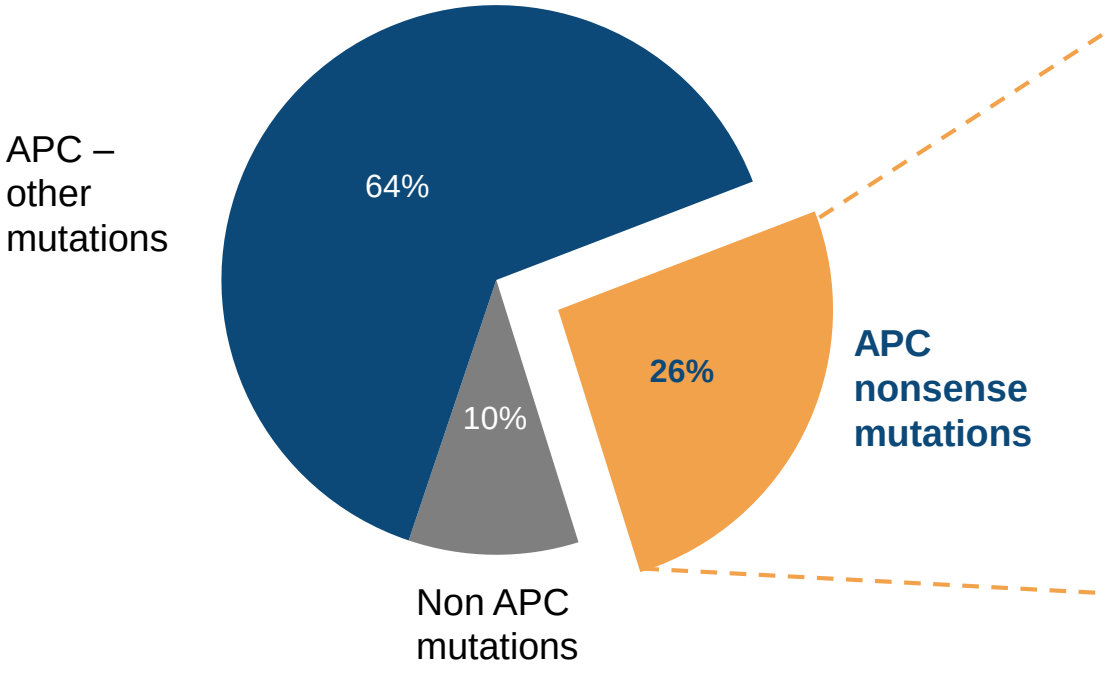
FAP is a rare GI disease with patients progressing to colon cancer caused by mutations in the APC gene

FAP nonsense mutation market opportunity

FAP patients in the US and Europe by mutation type[1,2]

62,000 – 75,000 Total Patients



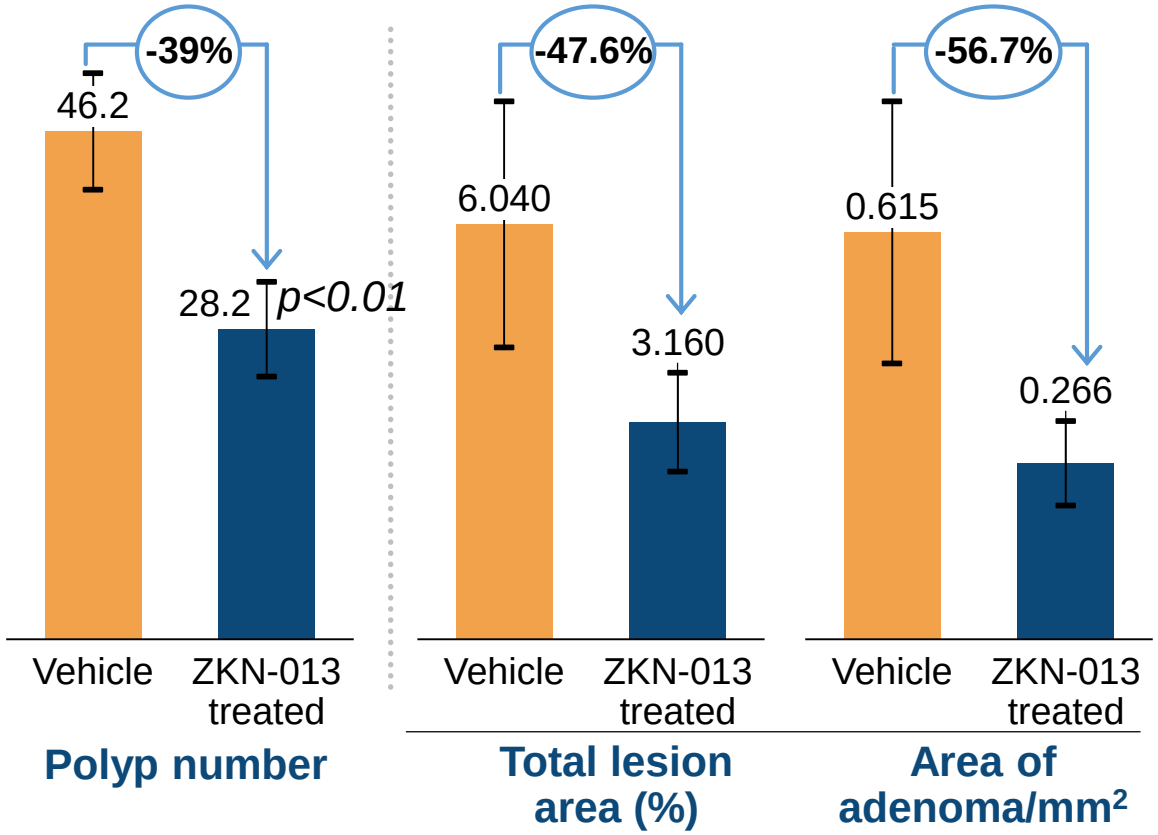
- **No functional APC** (most common mutation is R1450x)
- **Characterized by multiple colon polyps (frequently >1000)**
- Prophylactic colectomy is main treatment
- **Median age of colon cancer** ~40 years, if untreated; secondary GI cancers common

[1] Orphanet Journal of Rare Diseases 2009, 4:22 doi:10.1186/1750-1172-4-22
[2] https://doi.org/10.1016/j.critrevonc.2006.07.004
FAP: Familial adenomatous polyposis; **APC:** Adenomatous polyposis coli

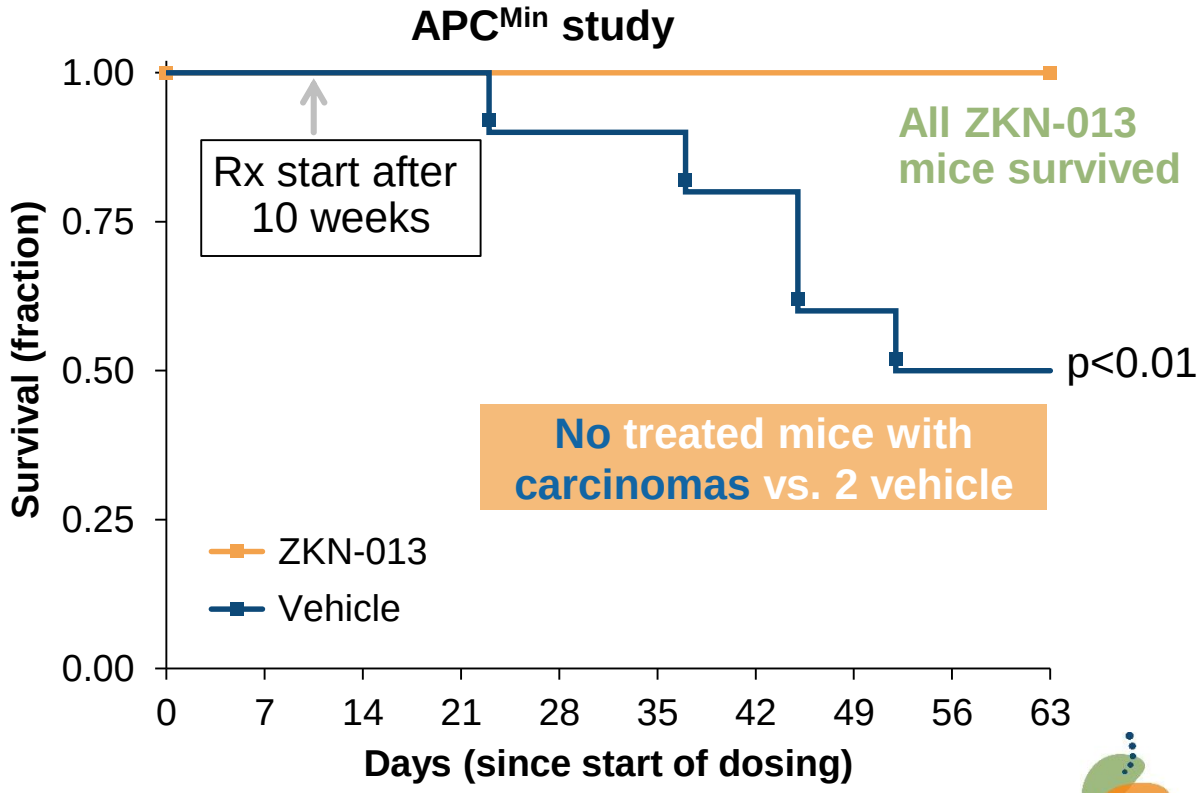
Polyp reduction and survival benefit in ZKN-013 treated APC^{Min} mice suggests robust response in FAP patients

Results for 8 weeks of treatment of APC^{min} mice (FAP model) with ZKN013*

Intestinal polyp number and polyp burden post treatment (n=10)[1]



Change in survival post treatment (n=10)[1]



[1]Study conducted at CRO

FAP: Familial adenomatous polyposis; **APC:** Adenomatous polyposis coli

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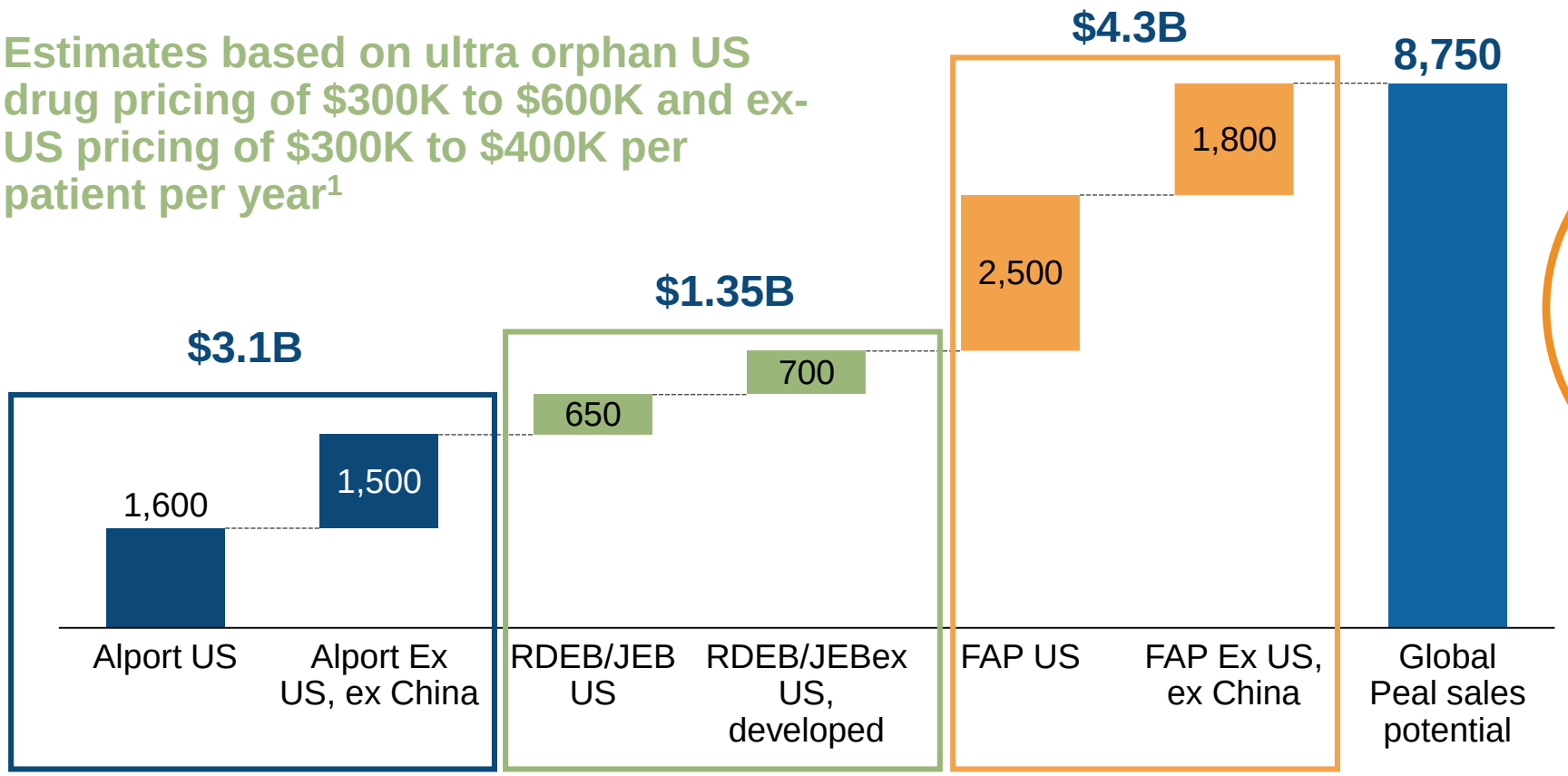
Substantial potential of three clinical stage programs leading with Alport syndrome

Estimated peak sales potential of current rare disease clinical programs, $M

Estimates based on ultra orphan US drug pricing of $300K to $600K and ex-US pricing of $300K to $400K per patient per year[1]



Total US : $4.75B

Alport US: $1.6B

[1]Recent orphan US drug pricing range from $300K to $570K for orphan drugs and >$800K for gene therapy drugs

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Alport syndrome clinical data expected in 1H 2023

	1H 2023	2H 2023
Alport Syndrome (SC ELX-02)	✓Enrollment start • Interim and full results of change in proteinuria	• End of Phase 2 meeting with FDA • Seek Breakthrough designation
RDEB/JEB (ZKN-013)	• IND submission	• Phase 1 start
FAP (ZKN-013)	• IND submission	

Cash expected to be sufficient to fund operations into 4Q23

RDEB/JEB: Recessive Dystrophic/Junctional Epidermolysis Bullosa; **FAP**: Familial adenomatous polyposis

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Clinical stage platform company developing potential treatments for rare genetic diseases with nonsense mutations

Novel small molecule genetic therapies that can **restore proteins**

Focused on high unmet need **nonsense mutation driven rare diseases**

Phase 2 Alport syndrome program with data **expected in 1H 2023**

Significant pipeline **expansion potential** in **rare diseases**

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