RARE Thinking for RARE Solutions

Leader in Ribosome Targeted Genetic Therapies

October 2022

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.

Eloxx PHARMACEUTICALS

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**

Clinical stage pipeline of three rare diseases with >$5B peak sales potential

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

Eloxx PHARMACEUTICALS

Eloxx leadership team with track record of execution

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 rare disease program at Sanofi

MERCK
NOVARTIS
SANOFI GENZYME

Dr. Ali Hariri
SVP & Chief Medical Officer

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

SANOFI GENZYME
IONIS
Takeda

Daniel Geffken
Interim Chief Financial Officer

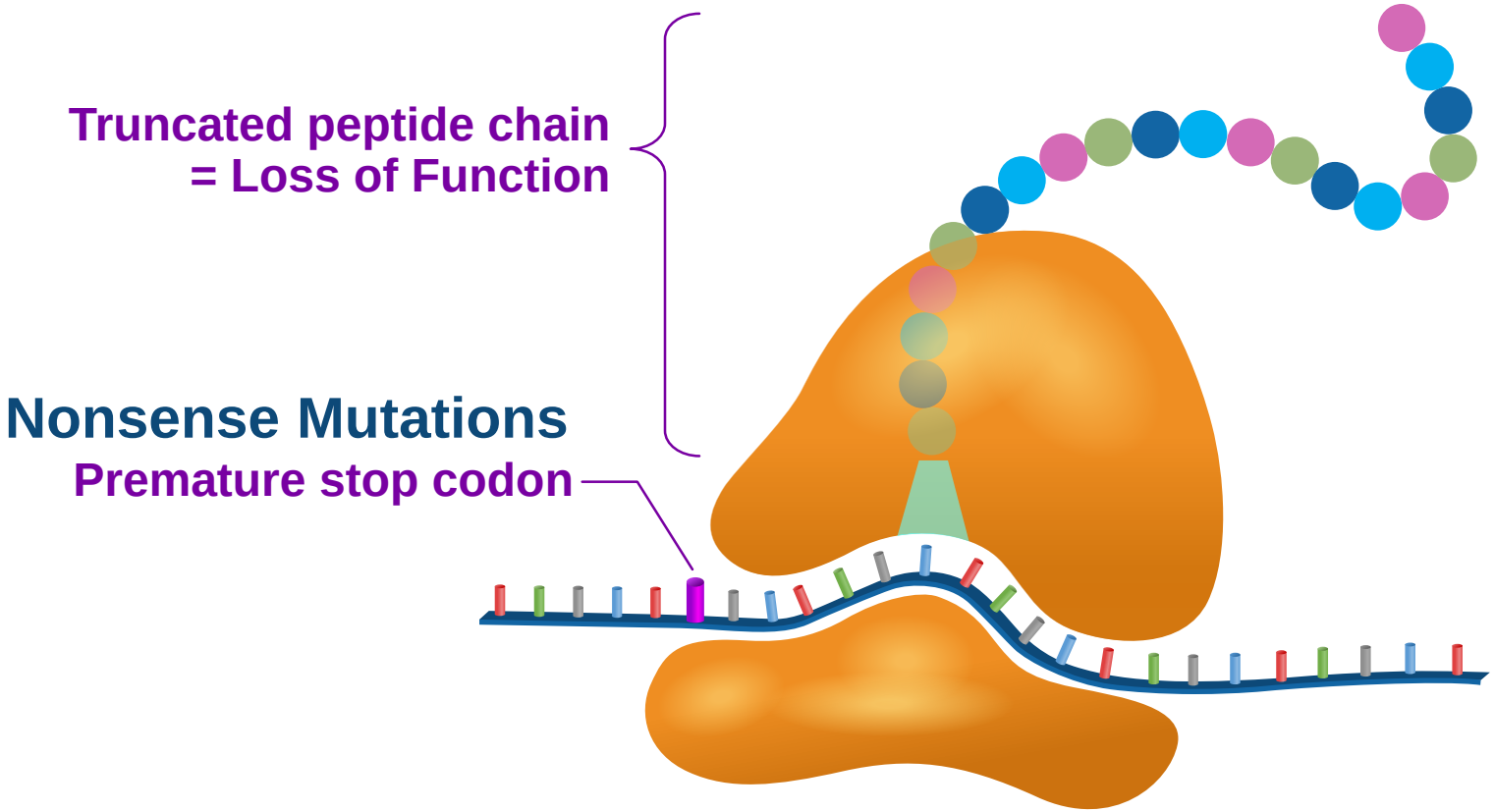
- 30+ years building companies
- Closed $2B in equity and debt financings for public and private companies

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

Eloxx PHARMACEUTICALS

Focused on restoring full-length proteins to treat rare diseases caused by nonsense mutations in mRNA

Ribosome = “protein factory”: mRNA nonsense mutations



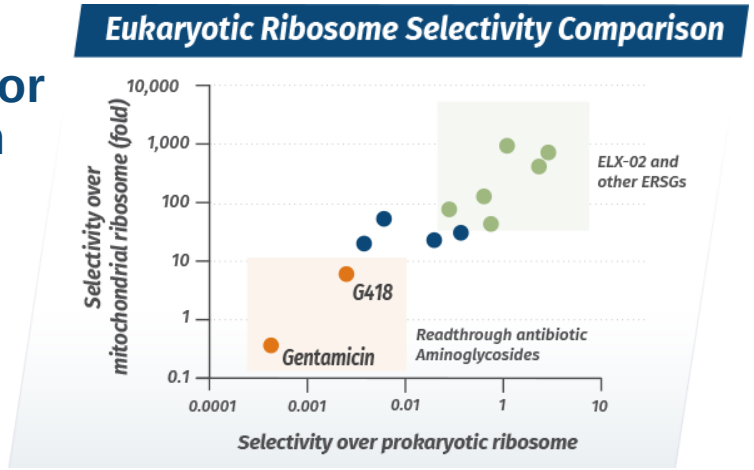
Antibiotics like Gentamicin and Erythromycin have shown to restore proteins in patients

Eloxx PHARMACEUTICALS

Our Solution: Build designer versions of validated drug classes with greater human ribosome affinity

1 Designer aminoglycosides: Eukaryotic ribosome selective glycosides (ERSGs)

ERSGs (including ELX-02) designed for nonsense mutation readthrough[1]

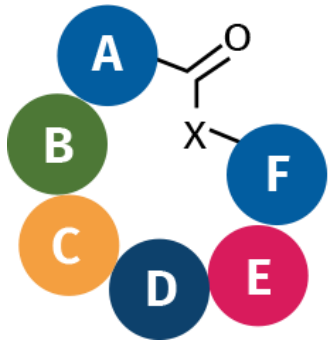


- Up to **1,000-fold more selective** than Gentamicin
- Minimal to **no antibiotic** activity
- Suitable chronic delivery

2 Designer Macrolides: Ribosome modulating agents (RMAs)

TURBO-ZM

TURBO-ZM™ (TUning the RiBOsome with Zikani Molecules



A Modulate
- Phamacokinetics
- Safety: cardiac, liver
- Oral bioavailability

B Optimize for
- Readthrough
- Protein translation inhibition

D Essential for ribosomal binding

E Modulate cytoplasm and mitochondrial ribosome-binding activity

- Library of **>2,000 RMAs** including **ZKN-013**
- Stronger human ribosome binding affinity; **minimal antibiotic** activity
- **Oral**, well-tolerated and **smaller** than macrolide antibiotics

[1]Data adapted from: *J Med Chem*. 2012 Dec 13;55(23):10630-43.1;

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Rare disease pipeline of synergistic 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)					PoC trial start (2H22)
RDEB/JEB (nonsense)	Collagen VII/LAMB3	ZKN013 (oral)					IND submission (2H22)
FAP (nonsense)	APC	ZKN013 (oral)					IND preparation
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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Advancing ELX-02 for treatment of Alport syndrome with nonsense mutations: Rare glomerular kidney disease

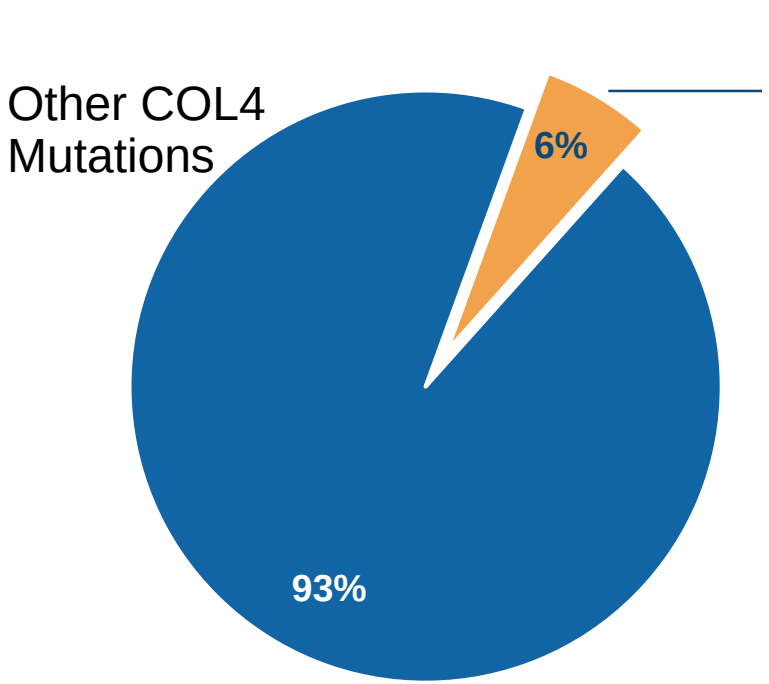
Alport syndrome nonsense mutation disease overview

Alport disease overview

- **Inherited glomerular kidney disease caused by defect in COL4 gene/protein**
  - 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
  - **High proteinuria** and hematuria
  - Leads to kidney failure (CKD and ESRD)
- **Limited therapeutic options**: ACE inhibitors/ARB, Dialysis, Kidney transplant, hearing aids
- Median age of **ESRD ~18- 22**

Global Alport prevalence

~155k to 215k Alport patients worldwide



China:
- **>3k patients**
- **On the Rare disease list in China**

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

Full length COL4 protein in Alport syndrome patients associated with better outcomes

Alport syndrom progression and patient prognosis based on mutation type[1]

Alport syndrome progression

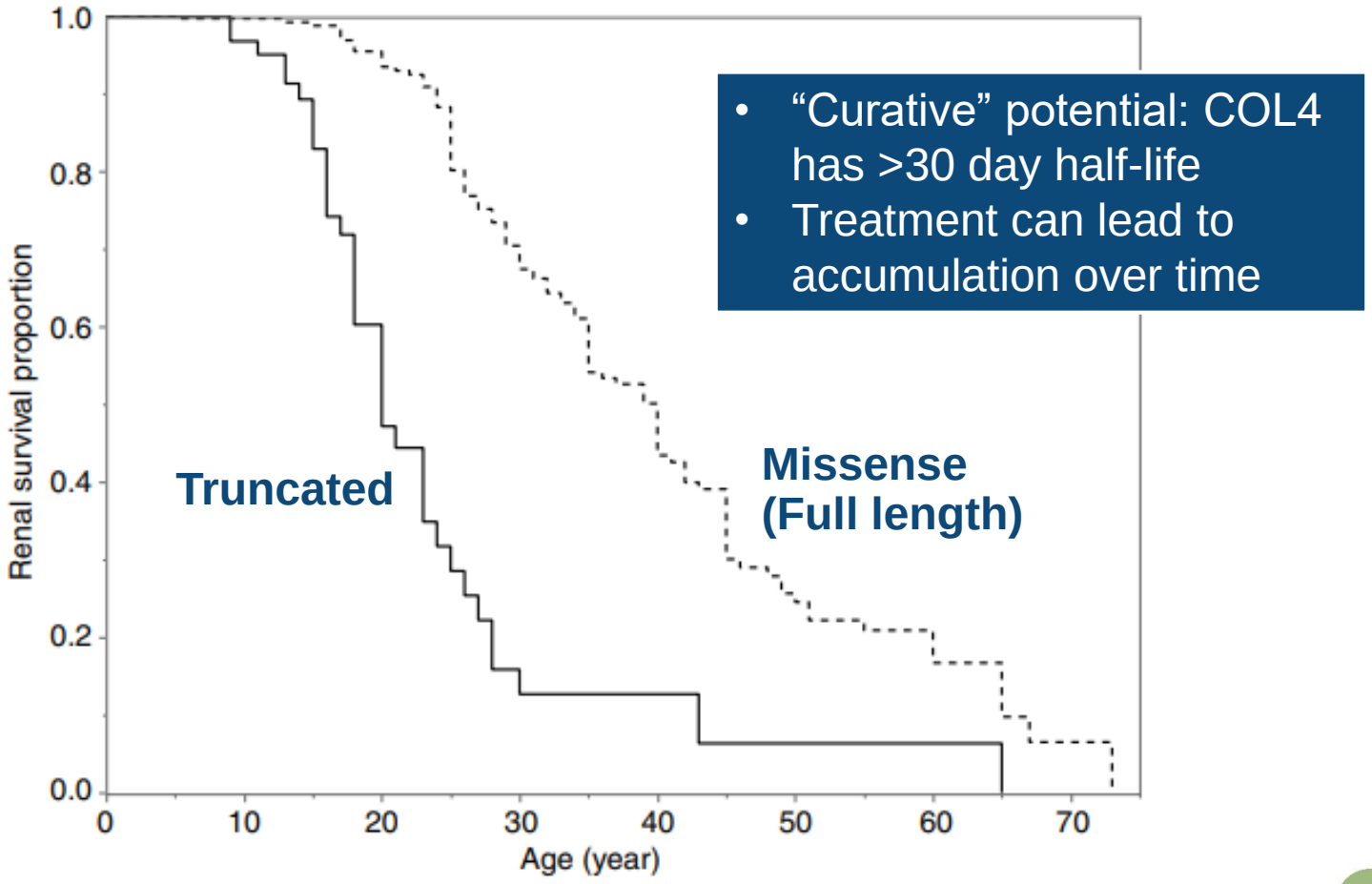
COL 4 mutations (truncated /missense)

↓

Glomerular damage = high proteinuria

↓

eGFR loss = Kidney failure



- "Curative" potential: COL4 has >30 day half-life
- Treatment can lead to accumulation over time

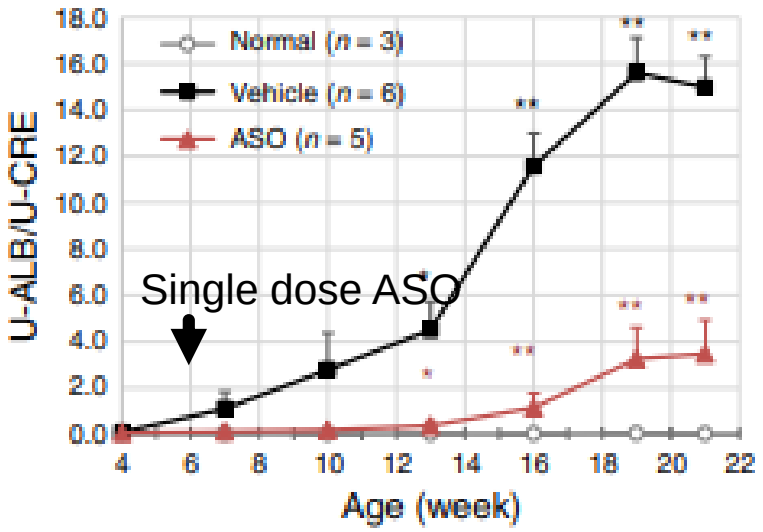
[1] *Kidney International* (2020) 98, 1605–1614

* 85% from COL45 which is x-linked

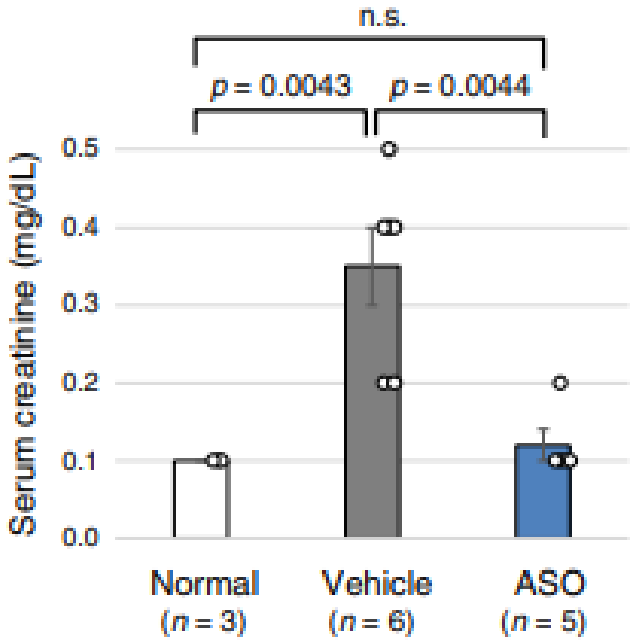
Partial protein restoration in Alport mice led to kidney preservation

Treatment of COL4A5 mutant mouse with exon 21 nonsense mutation

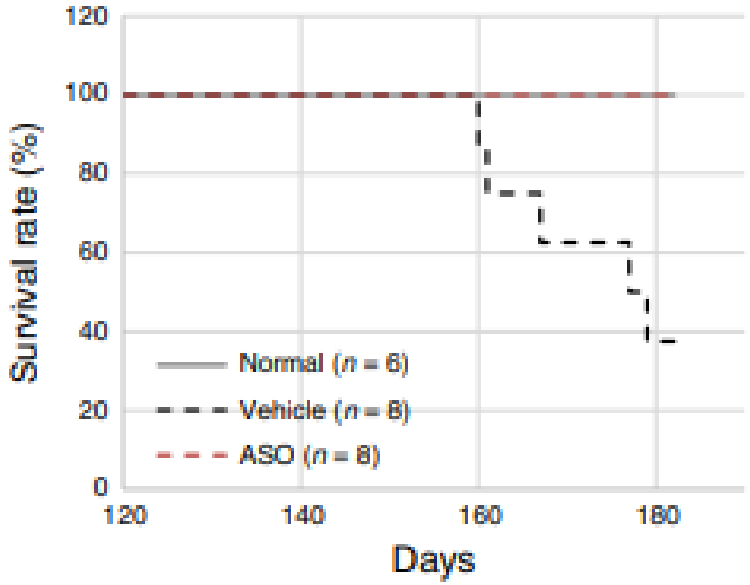
Albumin/creatinine ratio



Serum creatinine at end of 21 weeks



Survival rate



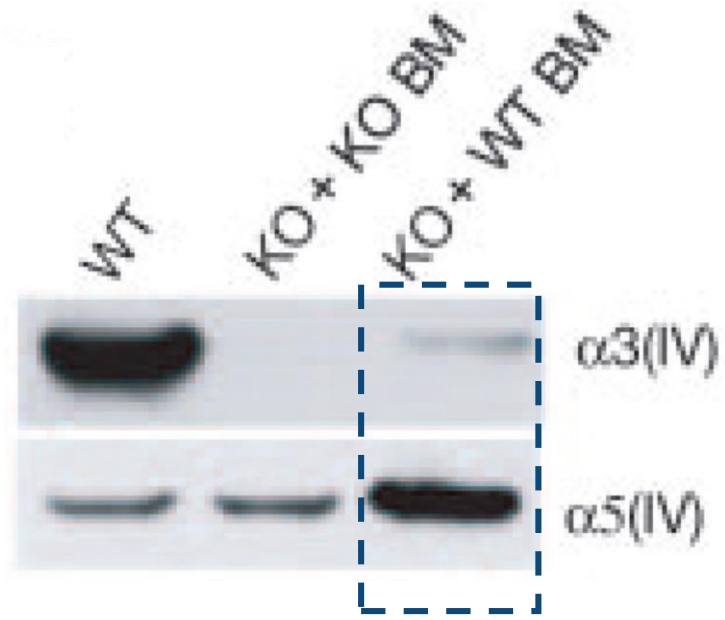
* p<0.05; **p<0.01

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

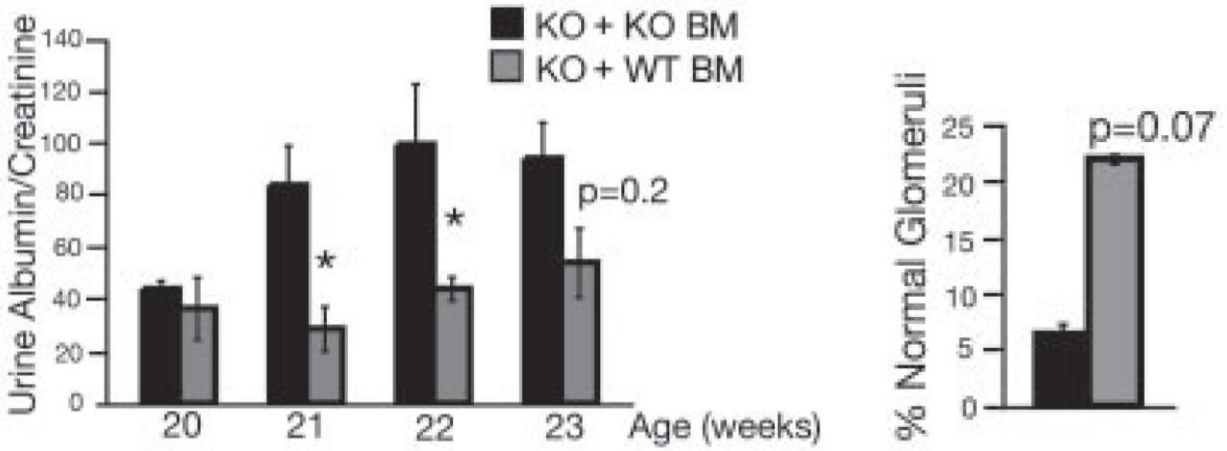
Minimal COL4 restoration resulted in rapid and large proteinuria reduction in knockout Alport mice

Bi-weekly COL4A3 +/- bone marrow (BM) treatment in C57BL/6 knockout mice aged 20 weeks over 3 weeks[1]

Western blot of COL4A3 in treated vs. untreated mice[2]



Treatment effect on albuminuria and glomeruli[2]



[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

Eloxx PHARMACEUTICALS

ELX-02 has potent protein restoration and favorable *in vitro* safety

Comparison of ELX-02 antibiotic activity, safety and readthrough

Protein restoration effect of aminoglycoside		
Indication (Mutation)	**Gentamicin**	**ELX-02**
Usher syndrome (R3X)	0.1	22
Usher syndrome (R245X)	0.3	2.1
Hurler syndrome (Q70X)	0.2	4.5
Cystic fibrosis (G542X)	0.5	6

Toxic ribosomal effects of aminoglycoside		
	Gentamicin	**ELX-02**
Antibacterial activity MIC (mM)	6	680
Mitochondria ICsom. (mM)	26 ± 2	965 ± 155
Cell toxicity LC50 (mM)	2.5 ± 0.3	22.2 ± 1.1

https://doi.org/10.1371/journal.pone.0223954.t001

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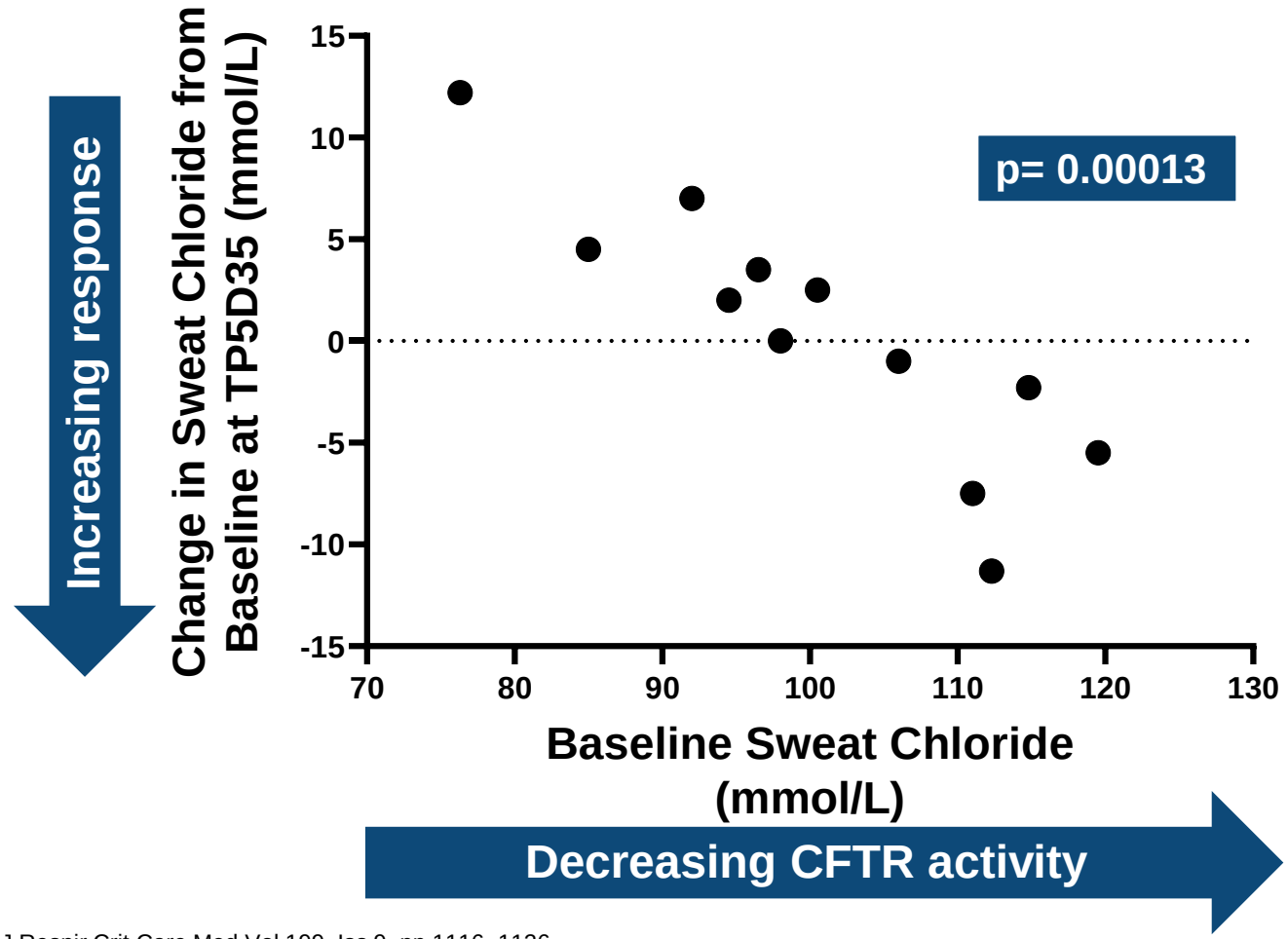
ELX-02 has consistently shown biological activity in Phase 2 trials in Class 1 Cystic Fibrosis (CF) patients

Baseline sweat chloride vs. sweat chloride change (SCC) at Day 35 in Phase 2 trial in Class 1 CF patients treated with ELX-02 (1.5mg/kg/day) + ivacaftor



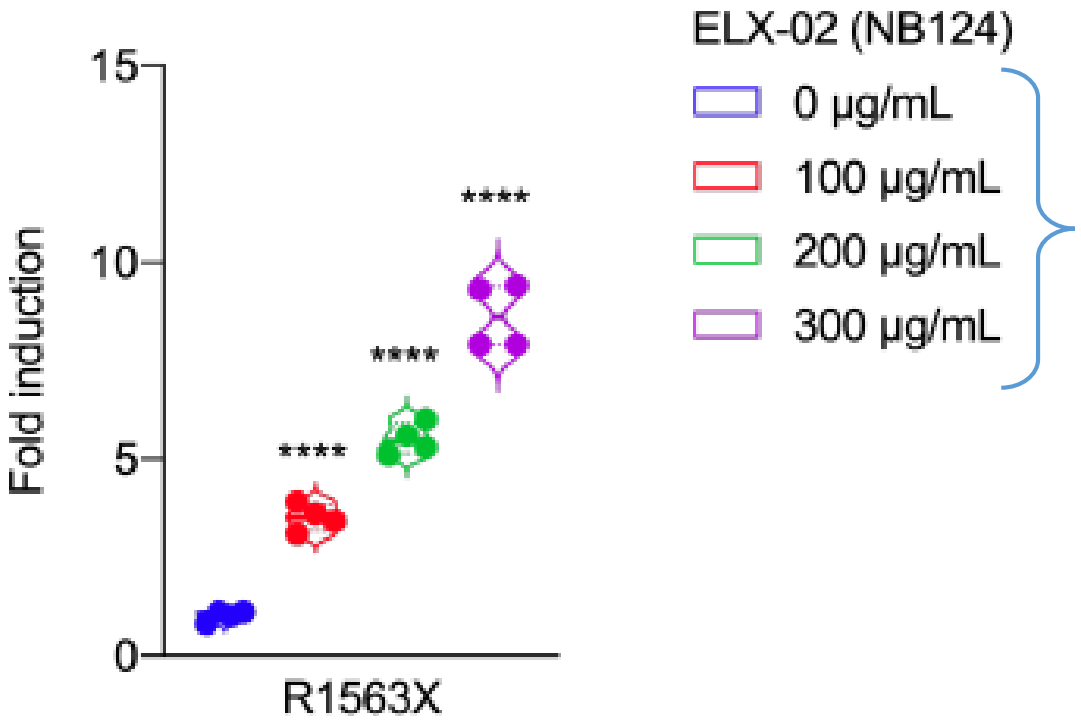
- **Phase 2 monotherapy showed a similar relationship with treatment response**
- **Patients with lowest baseline sweat chloride known to be highest responders to therapy***

*Am J Respir Crit Care Med Vol 199, Iss 9, pp 1116–1126

Eloxx PHARMACEUTICALS

High levels COL4A5 protein restoration observed *in vitro* with ELX-02

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



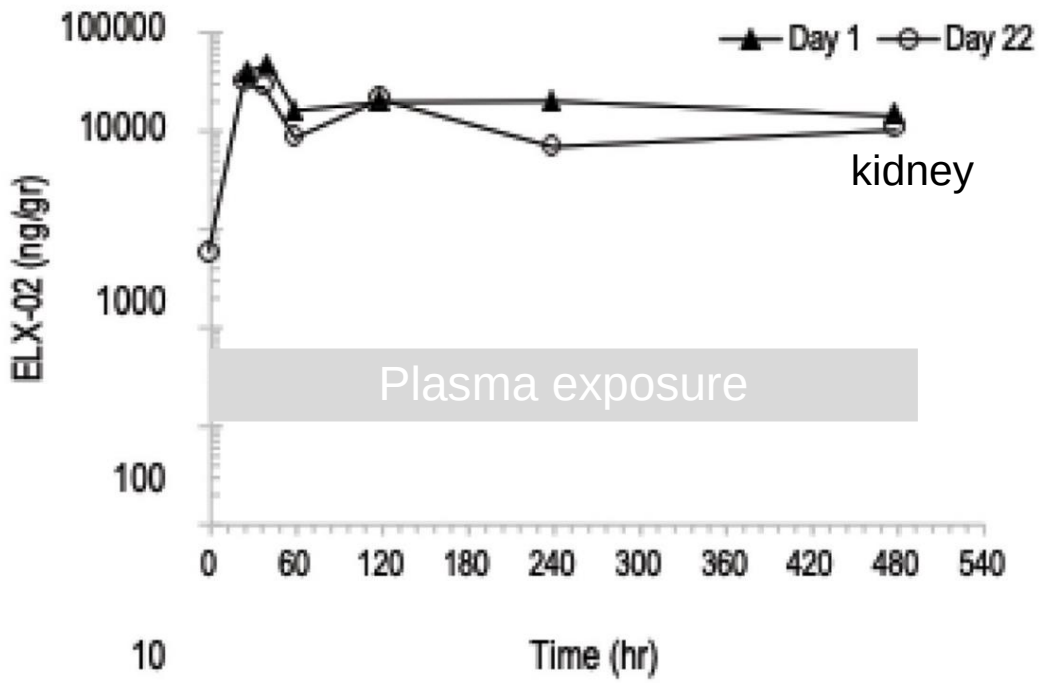
- **>3-fold readthrough in 31 of 32 of COL4A5 mutations tested with ELX-02 and derivatives[2]**
- **Equivalent to 6% to 15% full length COL4A5 protein[1]**
- **2- to 4-fold increase in expression at 48- vs. 24-hr exposure**

[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

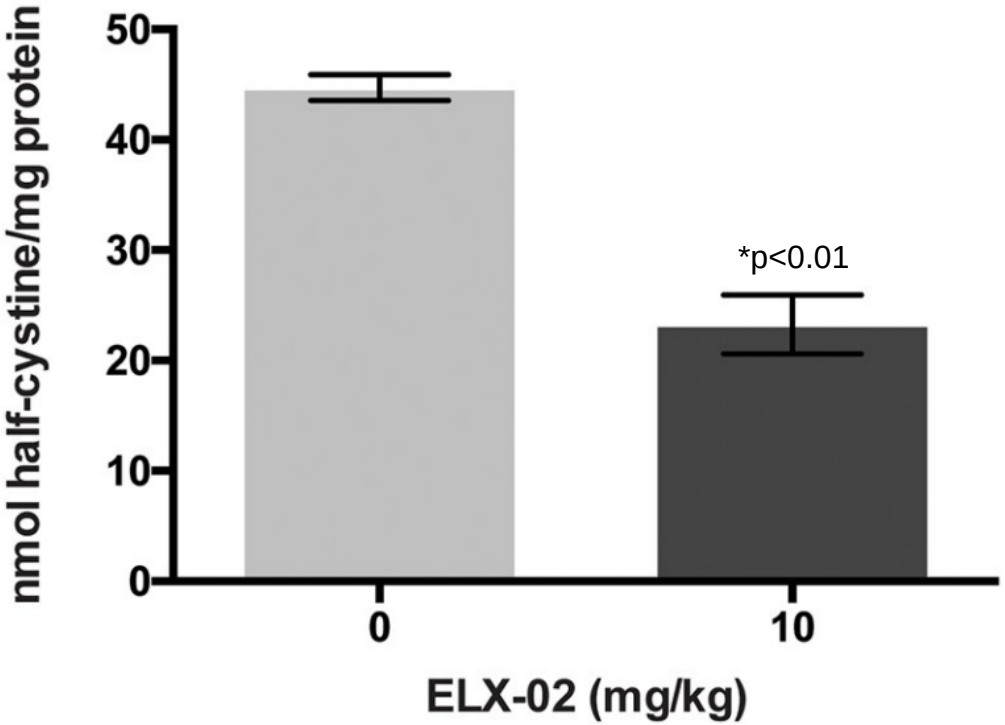
ELX-02 reduced kidney cysteine by >30% in cystinosis mice*

10 mg/kg bi-weekly in CTNSY226X/Y226X knock-in mice = 0.25mg/kg/day human equivalent dose

Exposure in mice 10 mg/kg bi-weekly



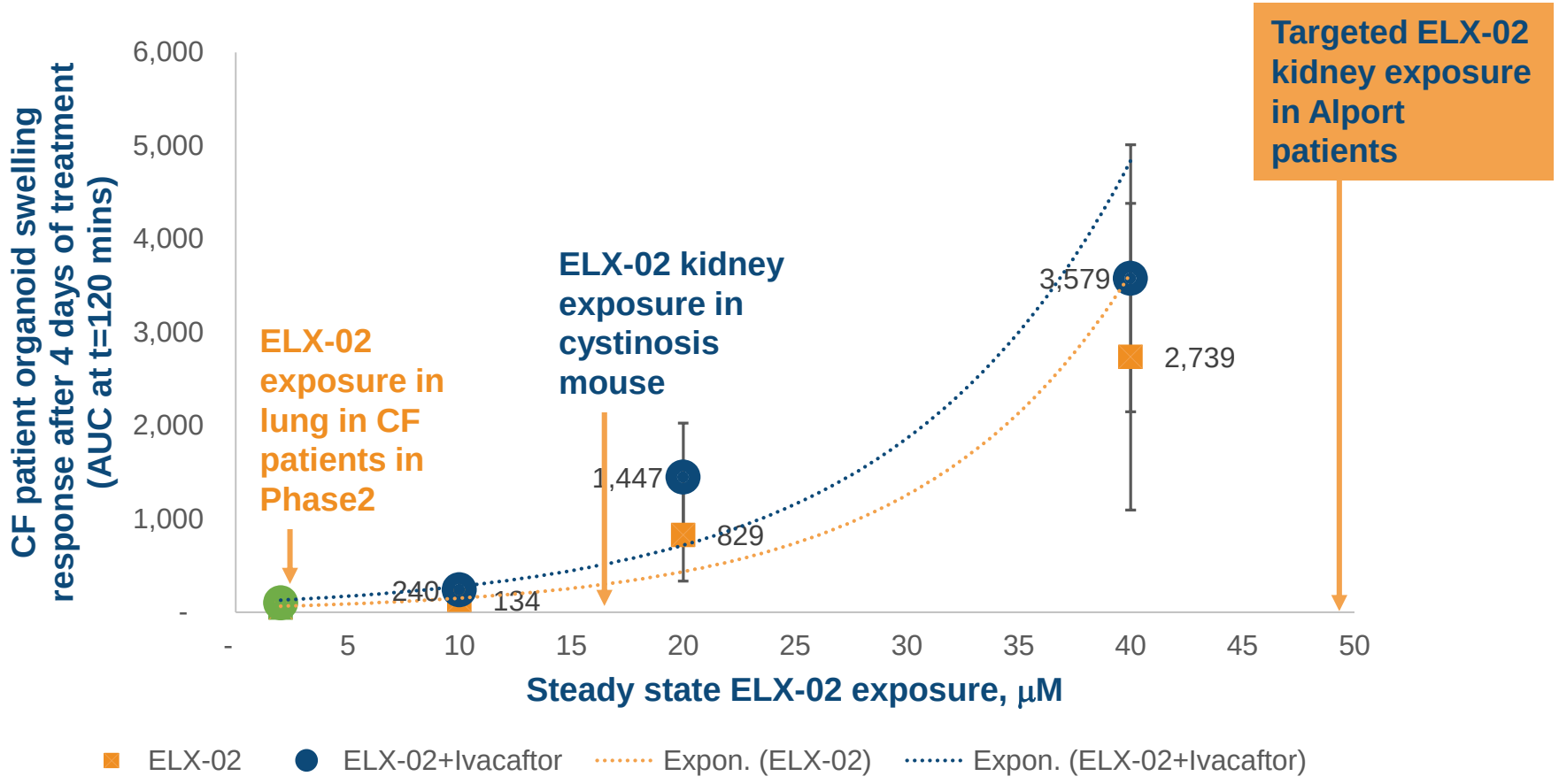
Effect in kidney cysteine after 3 weeks



*PLoS One 2019 Dec 4;14(12)

Targeting ELX-02 kidney exposures associated with high activity levels

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



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

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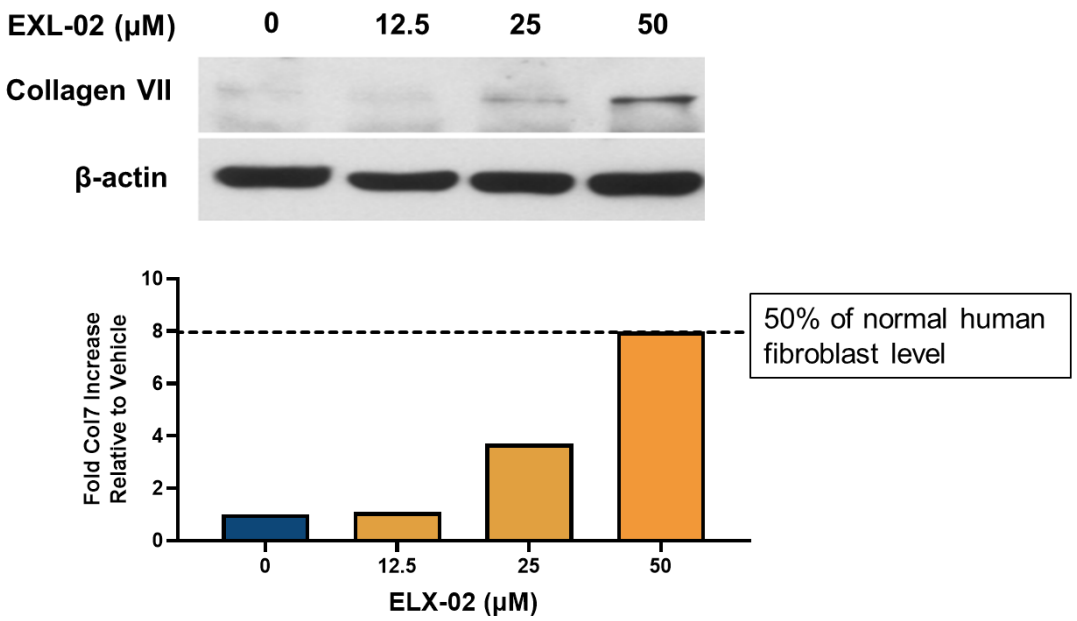
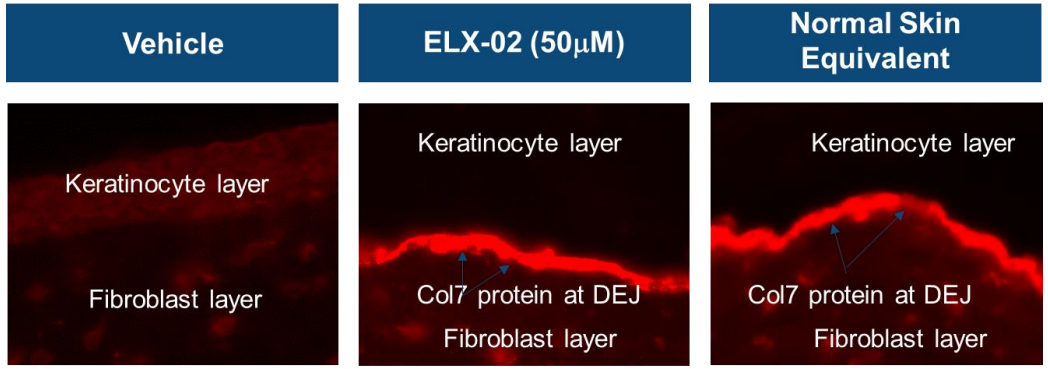
ELX-02 restored high levels of functional COL7 protein in RDEB models at target exposure levels for Alport

48 hr treatment effect of ELX-02 in RDEB fibroblasts and skin equivalent models*

ELX-02 mediated COL7 expression in RDEB patient fibroblasts**



ELX-02 mediated COL7 restoration in RDEB skin equivalent models



ELX-02 restored expression of COL7 protein to 86% of normal levels at dermal- epidermal junction

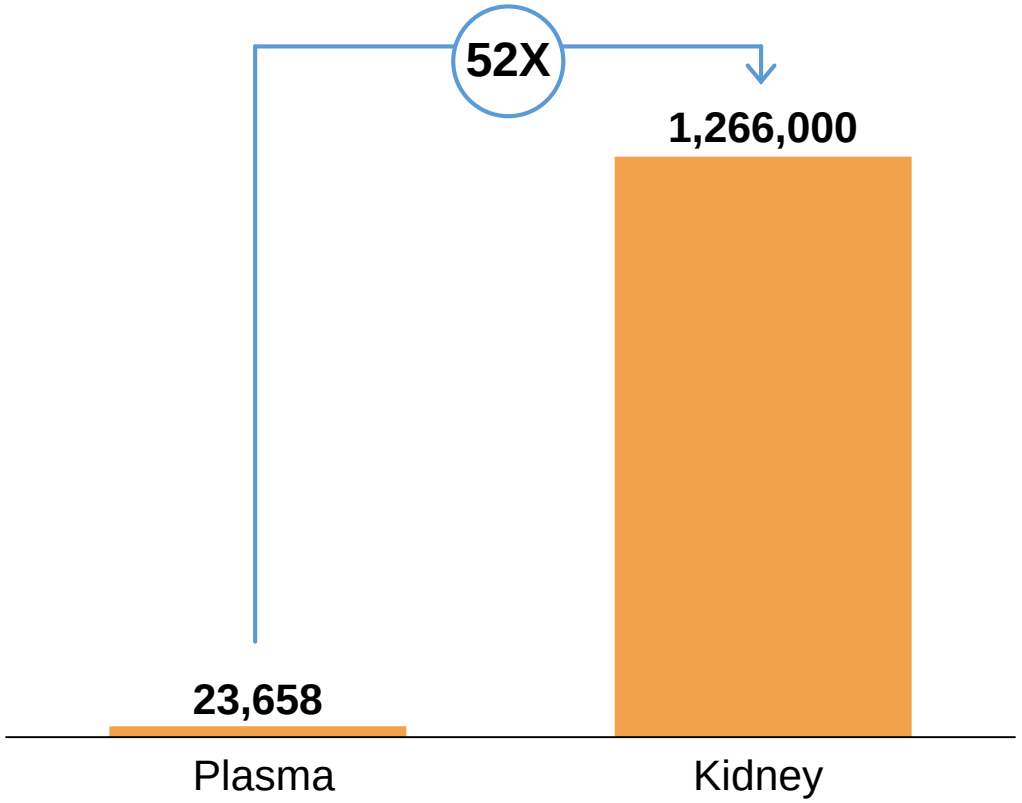
* Data from Chen lab using R578X/R578X fibroblasts

** Equivalent level calculations done by using Gent readthrough relative to NKC levels, from Cogan et al., 2014

Eloxx PHARMACEUTICALS

Target ELX-02 levels can be easily achieved in kidney

Estimated ELX-02 dose to exposure relationship in kidney at 1mg/kg, ng*hour/ml



- **Strong uptake in kidney due to Megalin binding similar to Gentamicin[1]**
- **Estimated kidney exposure of 50-100μM at 0.75 mg/kg**

1. J Am Soc Nephrolv.28(6); 2017 JunPMC5461786

Eloxx PHARMACEUTICALS

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

Summary of safety of ELX-02 across clinical studies

- Subcutaneous ELX-02 has been tested up to 5mg/kg in Phase 1 and Phase 2 trials
  - 0.1 mg/kg to 5 mg/kg twice weekly for two weeks in healthy volunteers in Phase MAD study
  - 0.3 mg/kg to up to 3 mg/kg daily in CF patients up to 5 weeks
- No dose limiting toxicities in SAD, MAD and CF patients
  - Generally well tolerated at all dose and schedules
  - No nephrotoxicity (kidney) or vestibular (ear) toxicity
  - No drug related SAEs
  - No off target effects
- Highly predictable drug exposures

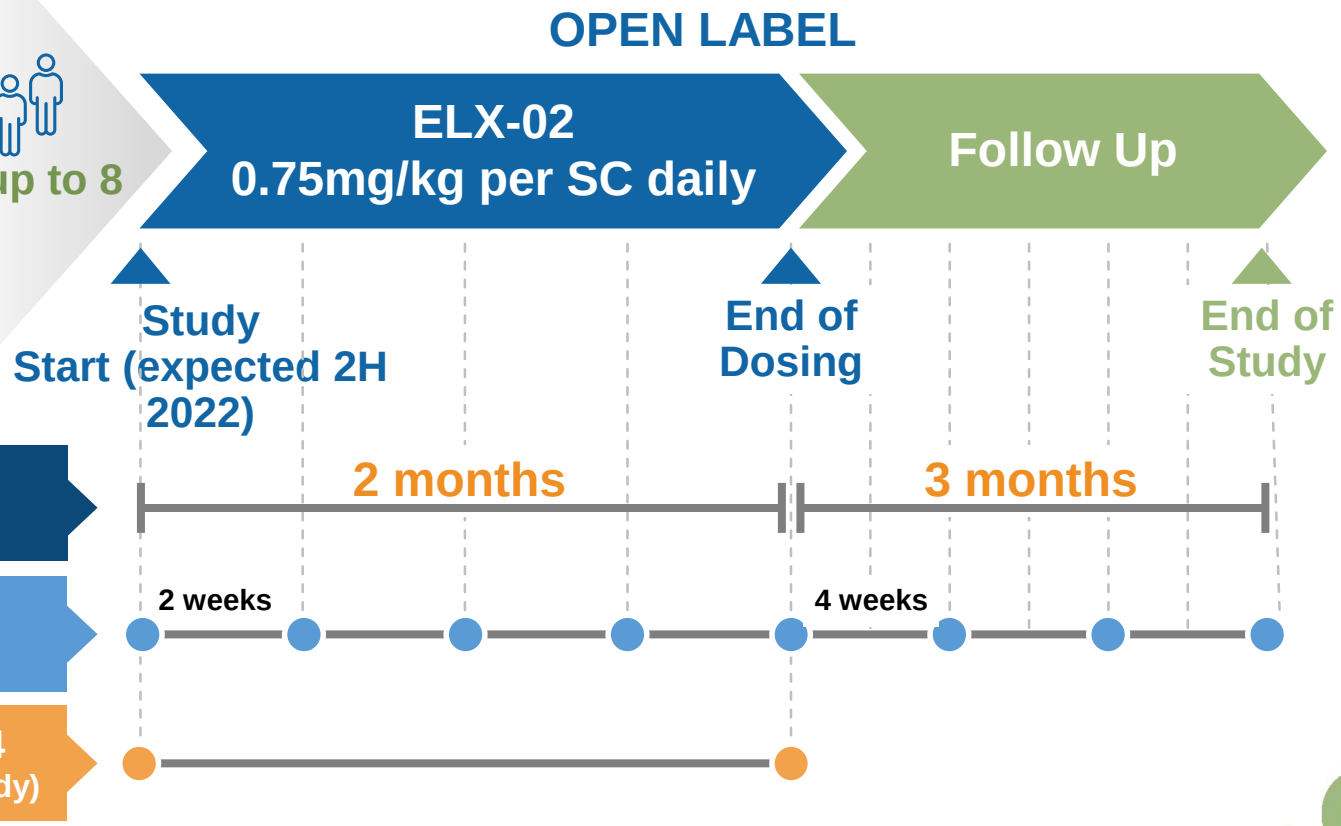
Eloxx PHARMACEUTICALS

Alport Phase 2 clinical proof of concept trial expected to readout in 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



Proteinuria reduction has been consistently used as POC clinical endpoint

"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**

Proteinuria reduction in Phase 2 across primary glomerular diseases

Drug (Company)	Indication	Duration	% Proteinuria reduction	Decision
Atrasentan (AbbVie)	DKD	12 weeks	35-38% (UACR)	Advanced to Phase 3
Finerenone (Bayer)	DKD	90 days	62-76% (UACR)	Advanced to Phase 3
Oms721 (Omeros)	IgAN	12 weeks	77%	Advanced to Phase 3
Iptacopan (Novartis)	IgAN	90 day	23%	Advanced to Phase 3
BION1301 (Chinook)	IgAN	6 months	50% (no control)	Advanced to Phase 3
Tarpeyo (Calliditas)	**IgAN**	**9 months**	**29% (Phase 3)**	**Accelerated Approval**
Sparsentan (Travere)	FSGS	8 weeks	44.8-18.5%	Advanced to Phase 3
Vx-147 (Vertex)	FSGS	13 week	47.6% (no control)	Advanced to Phase 3
APL2 (Apellis)	C3GN	12 weeks	50%	Advanced to Phase 3
Iptacopan (Novartis)	C3GN	12 weeks	45%	Advanced to Phase 3

*AJKD Vol75 Issue1 4-5 January 2020

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ZKN-013: RDEB and FAP

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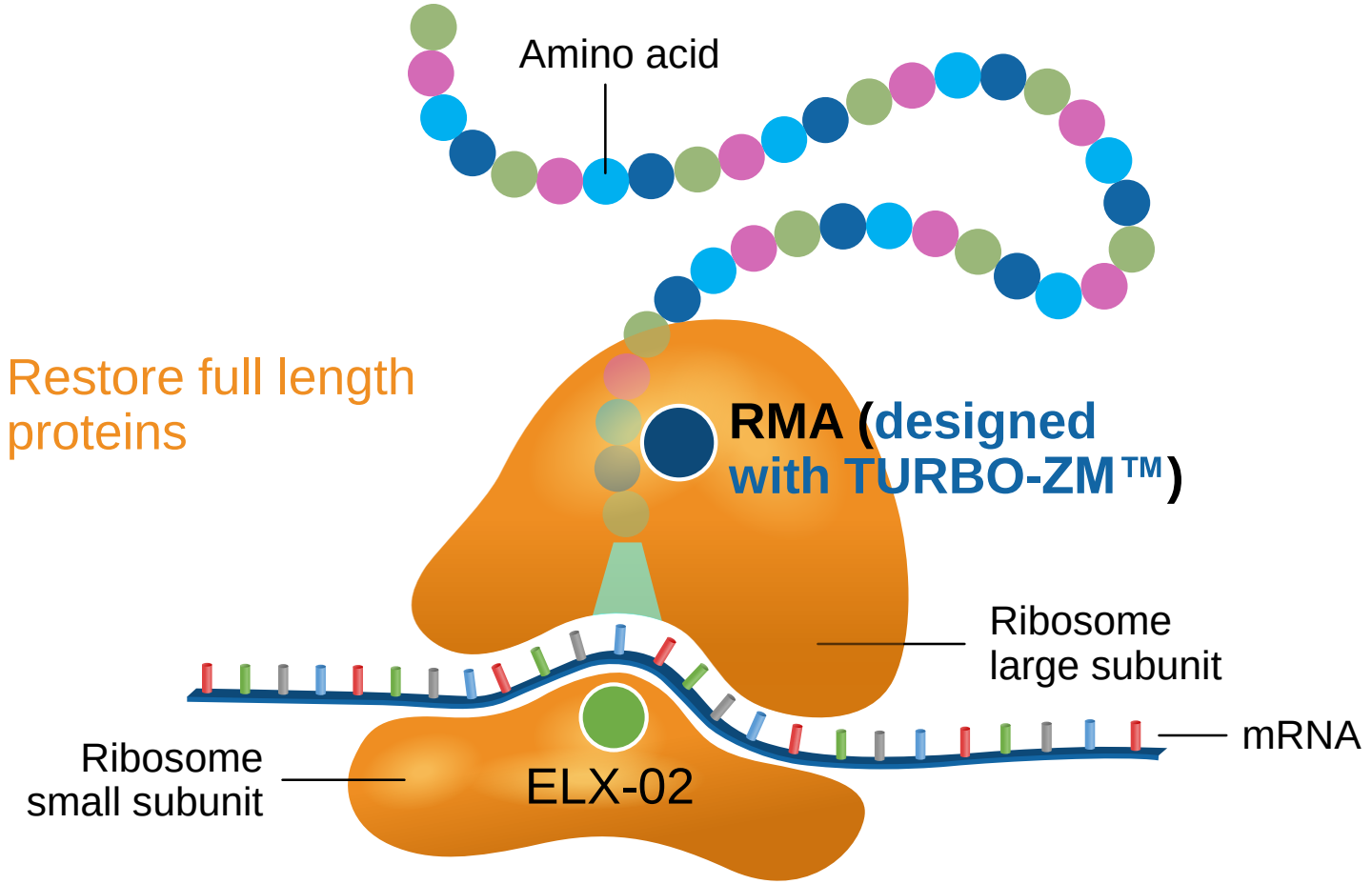
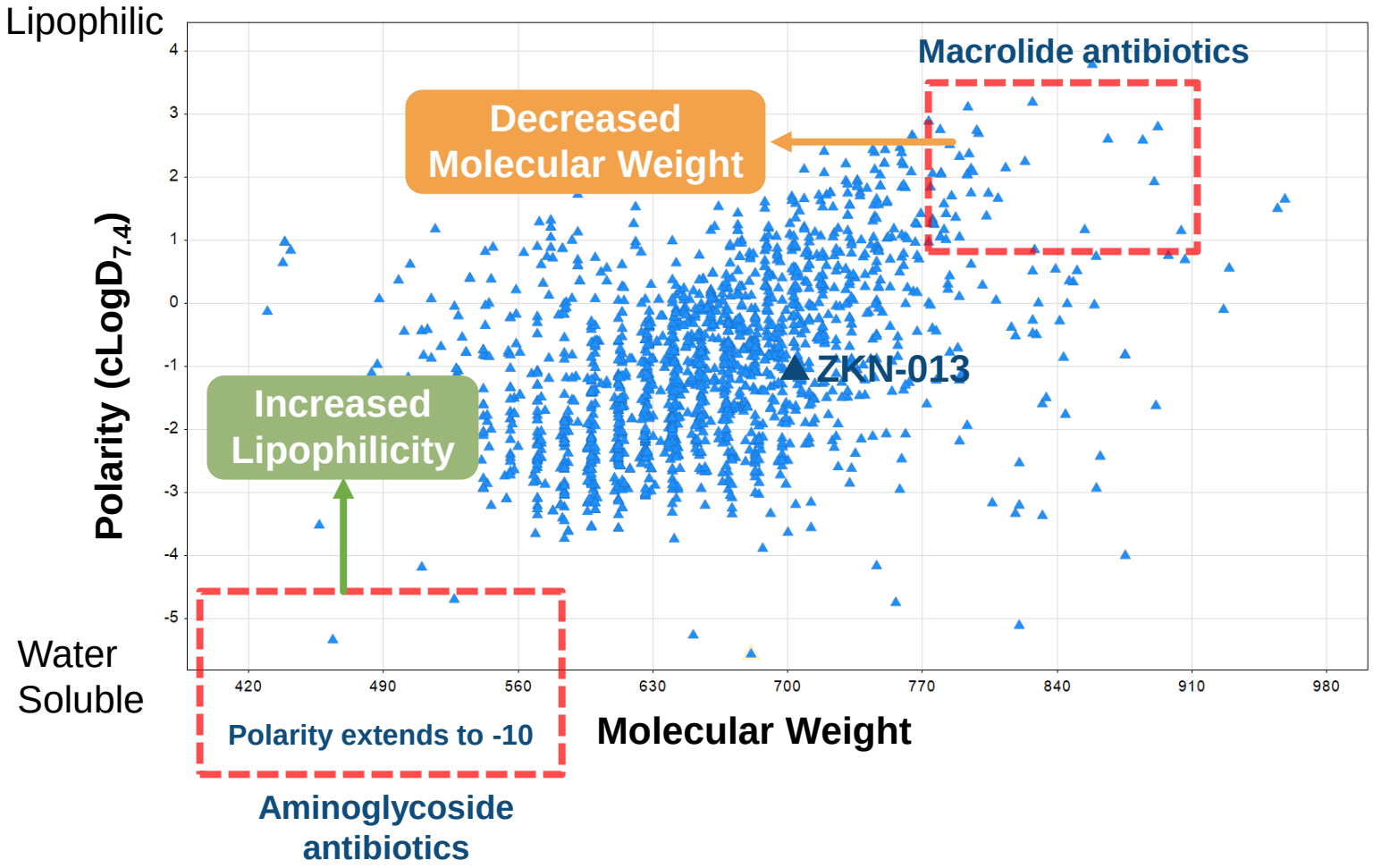
Oral RMAs modulate protein translation by interacting with the ribosome large subunit

Oral RMAs correct mRNA and ribosomal mutations



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

Zikani RMA Library (2000+)

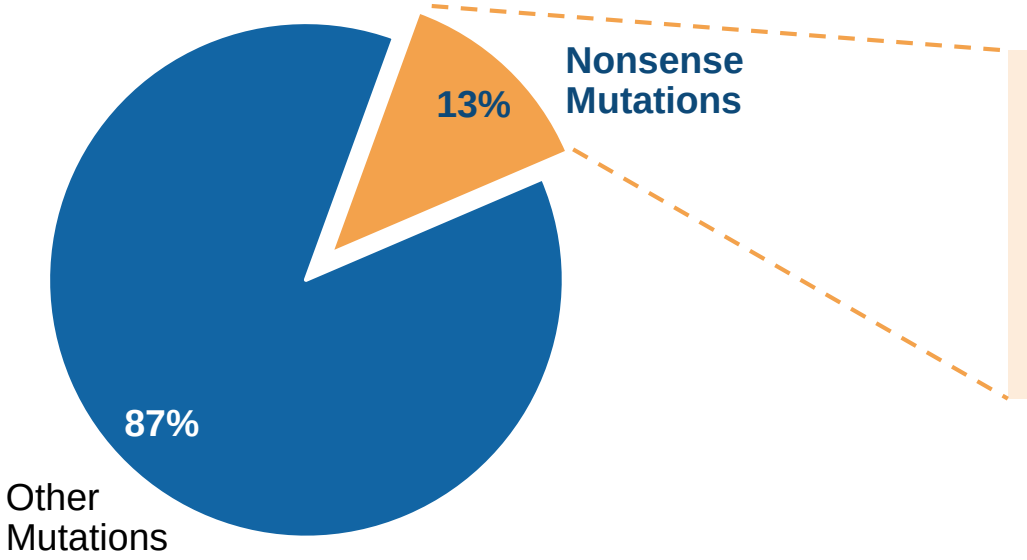


RDEB/JEB: ZKN-013 program in rare and severe skin diseases frequently caused by nonsense mutations

RDEB and JEB: Recessive Dystrophic and Junctional Epidermolysis Bullosa

Prevalence of RDEB/JEB in US, Europe and Japan by mutation subtype[1,2]

~30,000 Total US/EU/Japan RDEB and JEB Patients



- Mutations in **COL7A1 gene** (RDEB) and **LAMB3** (JEB)
- Skin tearing/blistering, malnourishment
- **Skin cancer** in RDEB by age 35
- JEB average **mortality at 18 months**

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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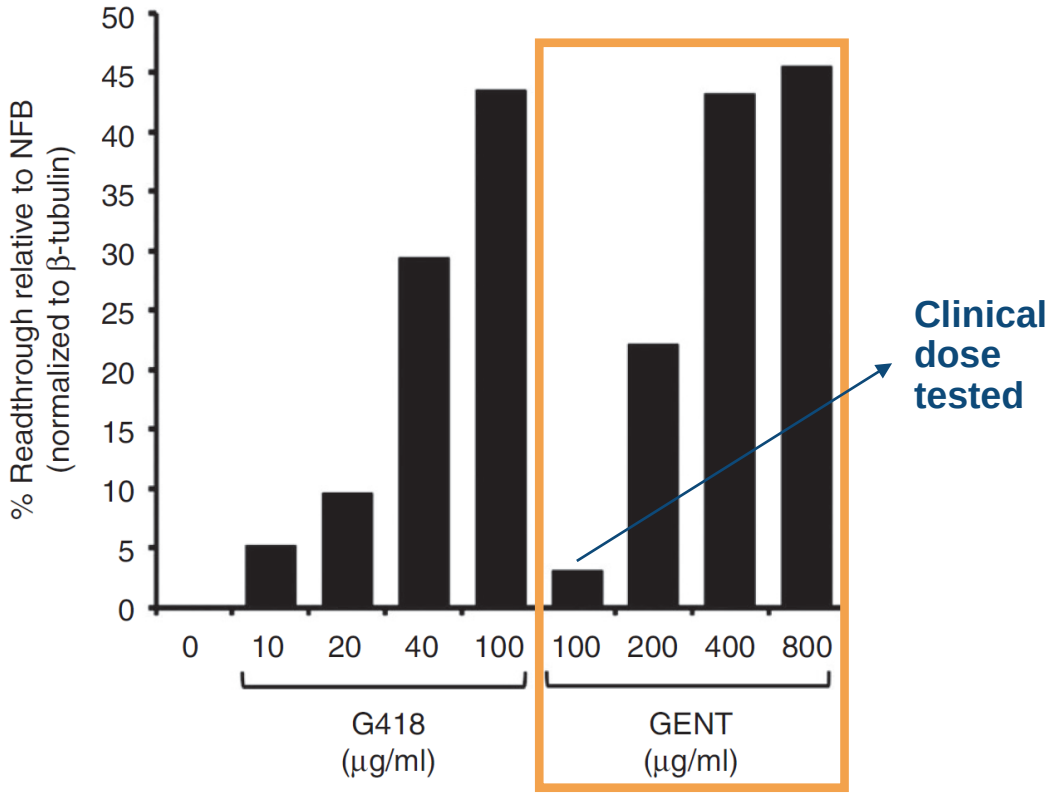
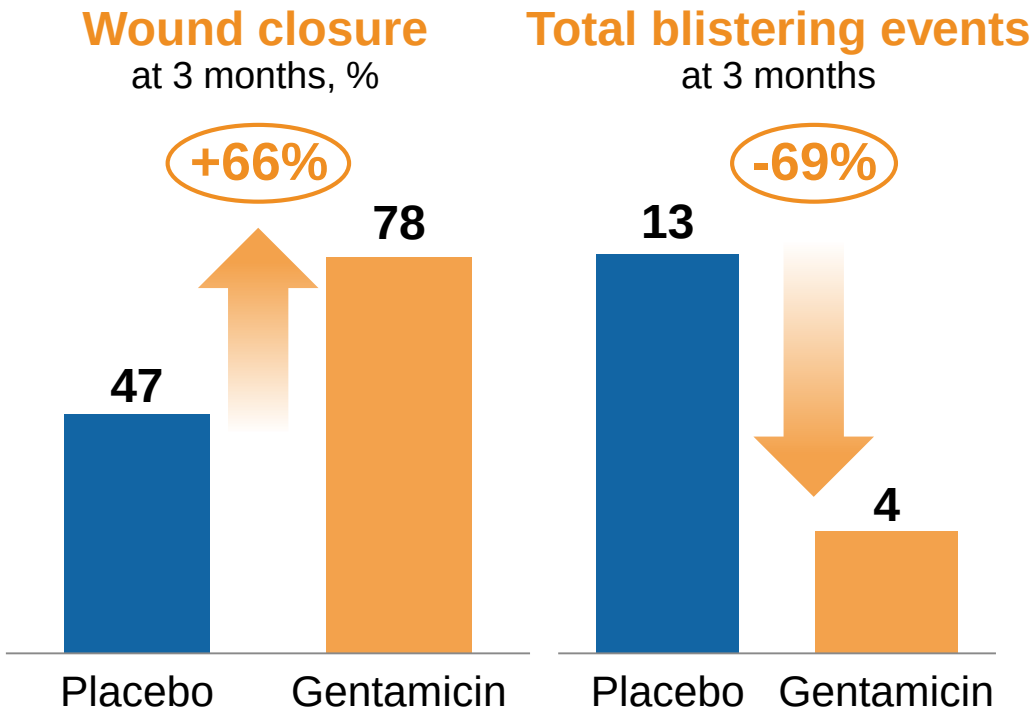
Gentamicin restores COL7 in patient cells and reduces disease burden in RDEB patients

Col7 protein expression in patient cells[1]



Gentamicin treatment of RDEB patients

(0.1% gentamicin (100ug/ml) ointment tid for 2 weeks; n=5)[1]



1Cogan et al., Molecular Therapy (2014)
2Woodley, DT. J Clin Investig 2017, 127, 3028-3038; 2 Hammersen, Johanna et al. Dermatology May 2019

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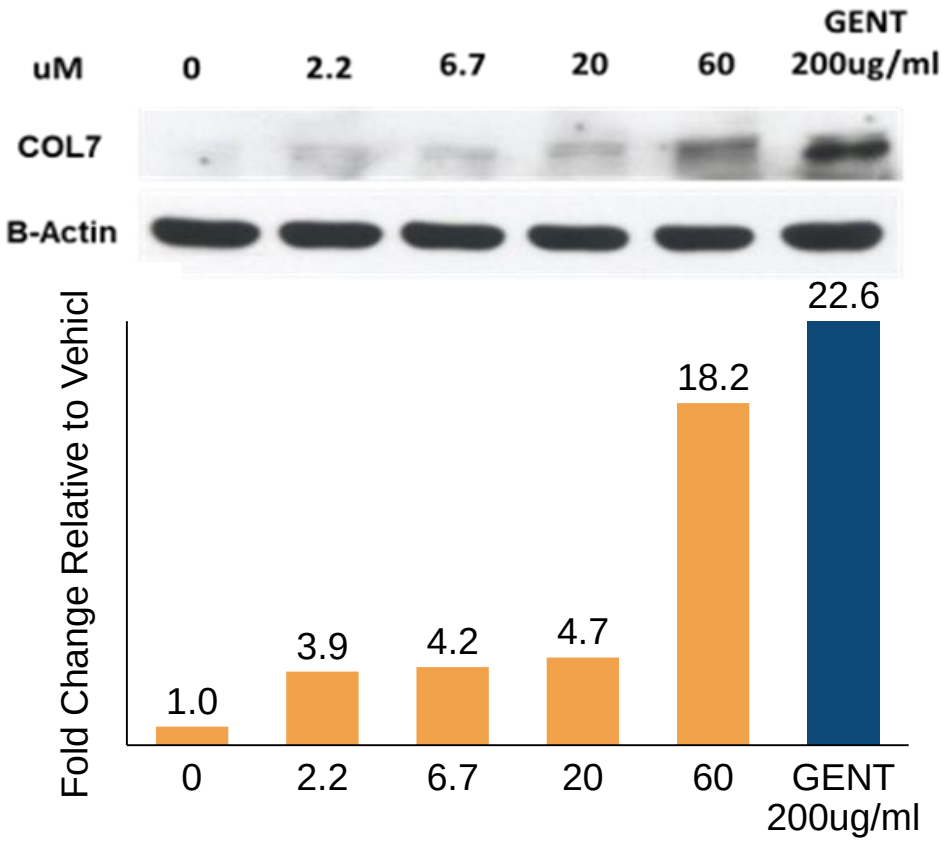
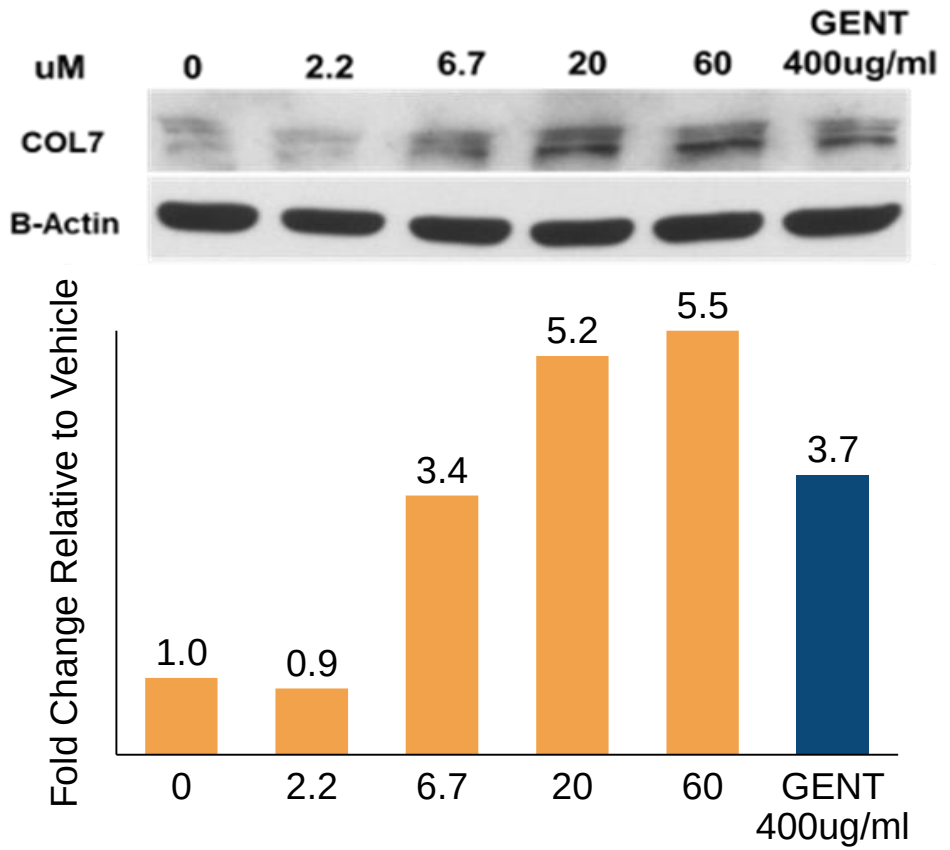
ZKN-013 induces dose dependent expression of full-length C7 Protein in RDEB patient fibroblasts

Dose response of patient fibroblasts treated for 24 hours in culture

RDEB patient#1 (COL7A1 R578X/R578X)



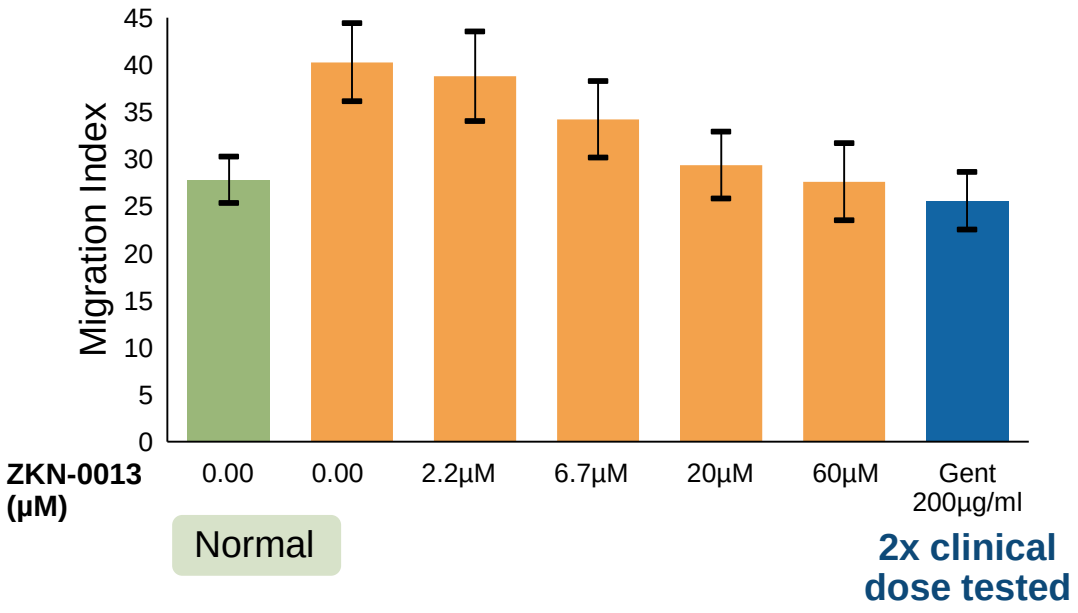
RDEB patient#2 (COL7A1 R163X/R1683X)



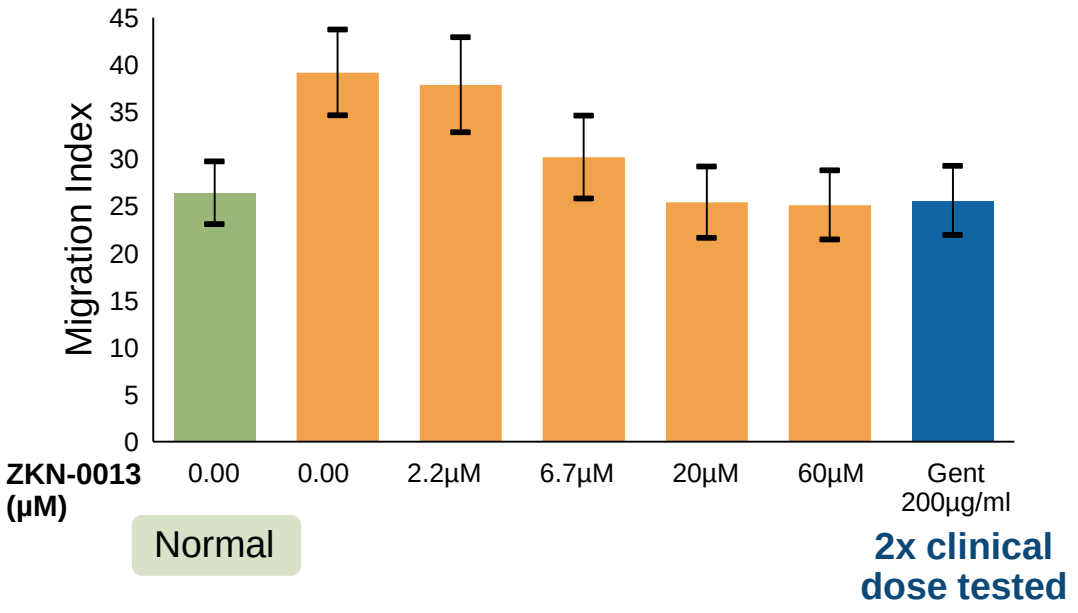
ZKN-013 normalizes function in primary RDEB patient fibroblast cells comparable to high dose gentamicin

ZKN-013 48-hour dose response of patient fibroblast motility treated in culture

RDEB patient fibroblast (COL7A1 R578X/R578X)*



RDEB patient fibroblast (COL7A1 R163X/R1683X)*



* Fibroblasts derived from patients in clinical trial. 48 hours treatment with media and compounds replaced and refreshed at 24 hours. Fibroblast 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 USC

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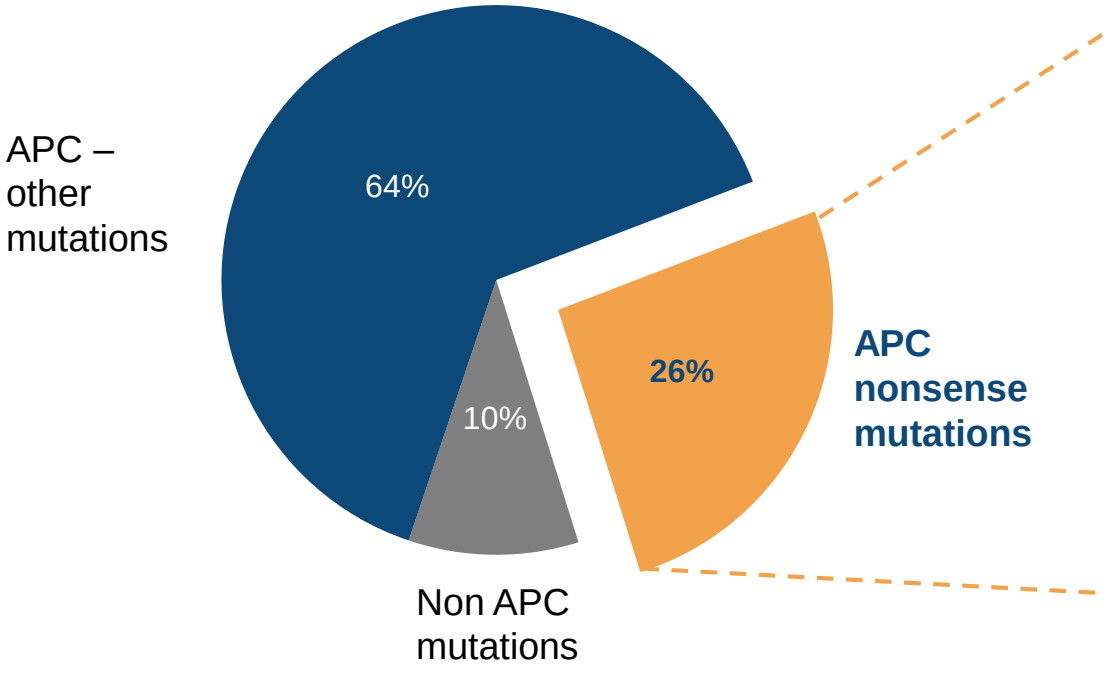
Developing ZKN-013 for treatment of FAP patients with nonsense mutations in APC gene

Familial Adenomatous Polyposis (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** (commonest mutations 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

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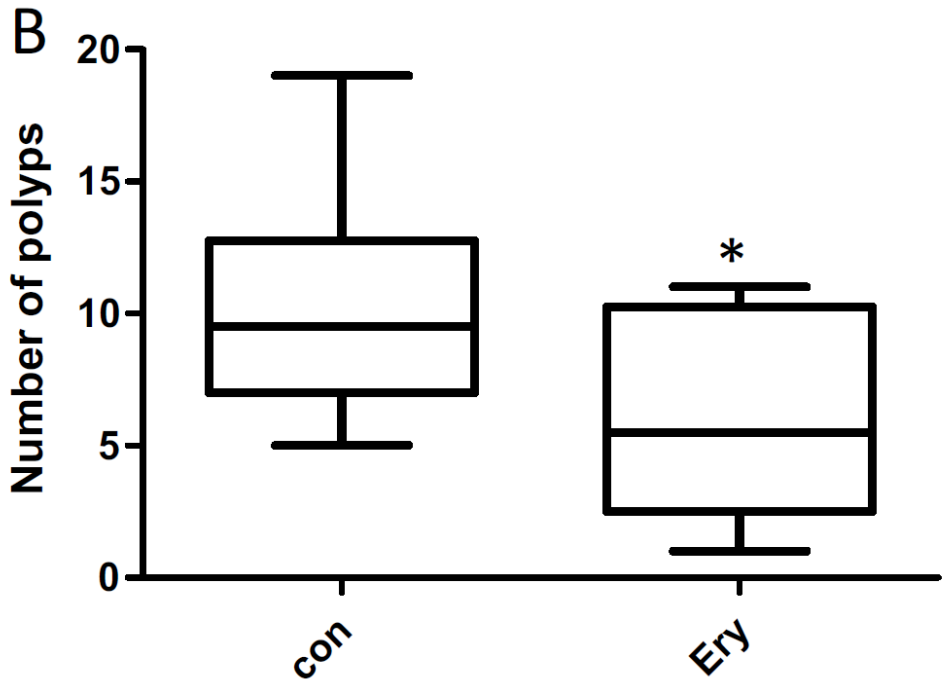
Erythromycin demonstrated positive in vivo and clinical activity in nonsense mutation FAP disease

Erythromycin in vivo and clinical results in FAP with nonsense mutations

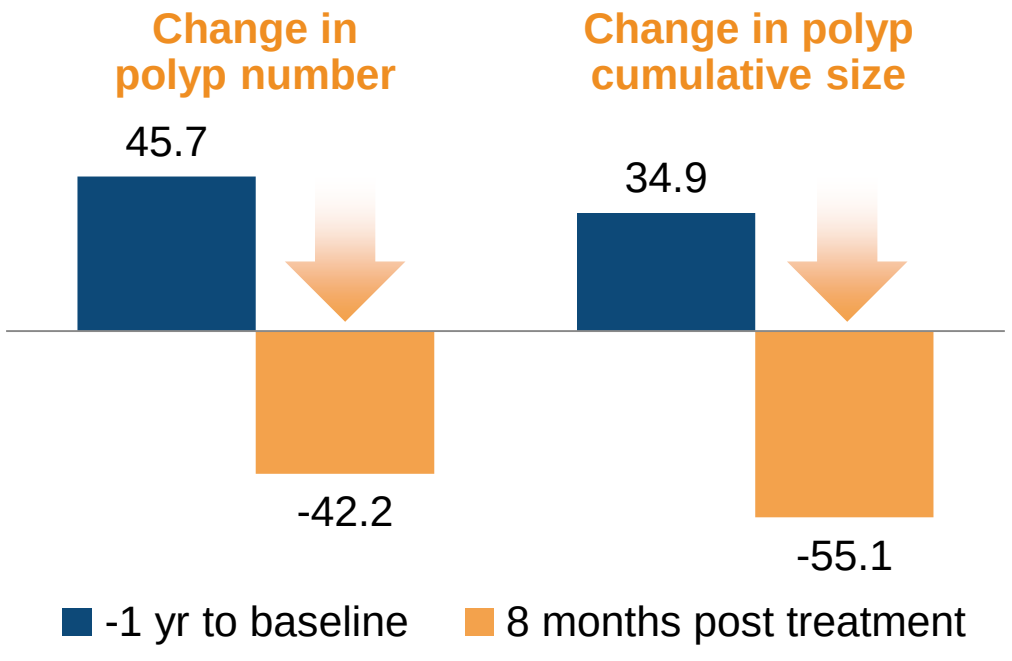
Polyp count change in APC^{Min} mice from Erythromycin treatment over 16 weeks[1]



Erythromycin FAP clinical results

Erythromycin treatment
(250 mg/day po for 4 months)

Change in polyp burden at 12 months[1]



[1]. Ref: Caspi. J Mol Med (Berl). 2016 94:469-82. Erythromycin 600 µg/day (~24mg/kg) treatment over 16 weeks (n=10)

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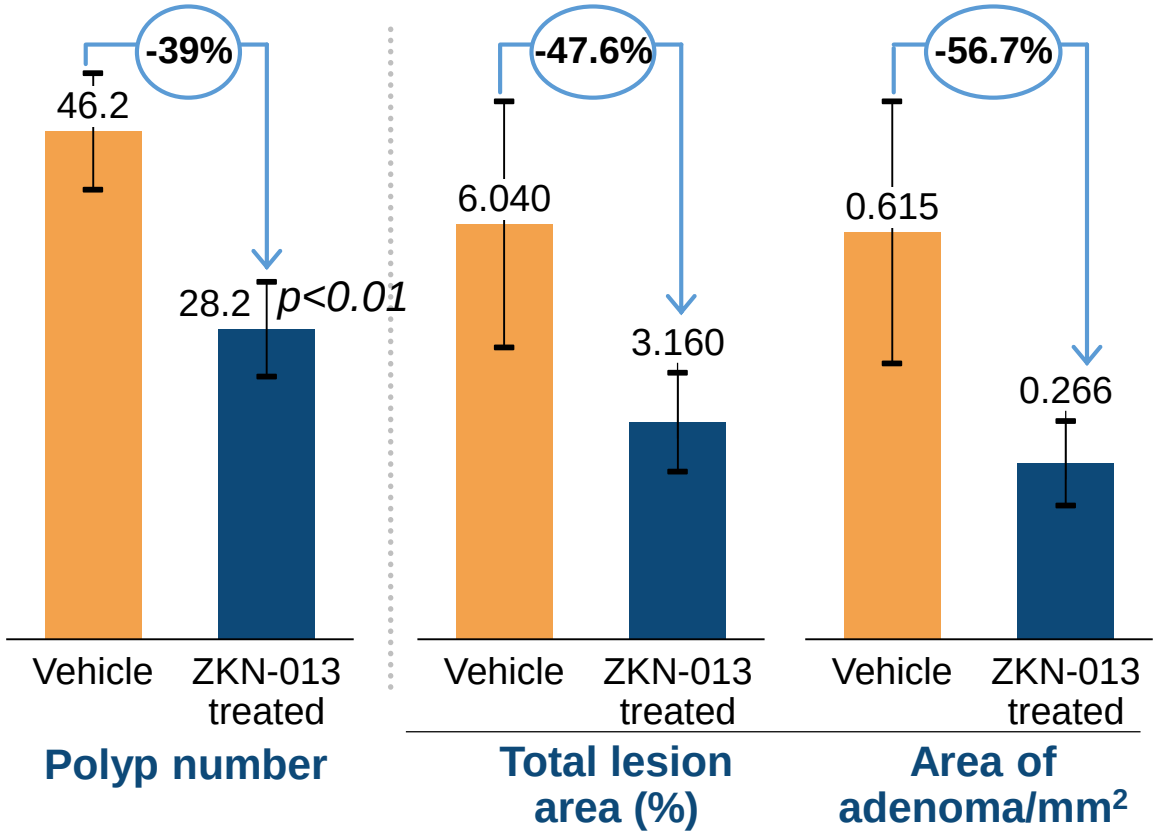
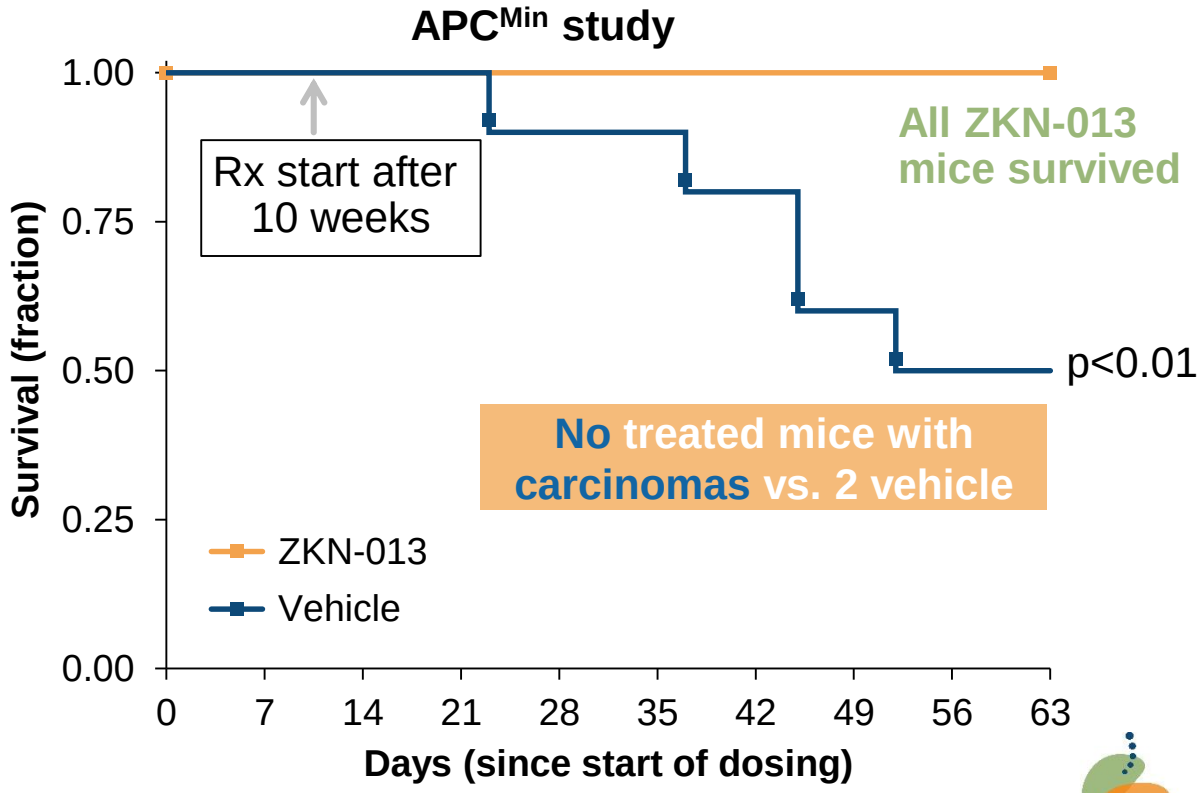
Promising results in APC^{Min} mice treated with ZKN-013 support likely patient benefit

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

Intestinal Polyp number and polyp burden post treatment (n=10)*



Change in survival post treatment (n=10)*

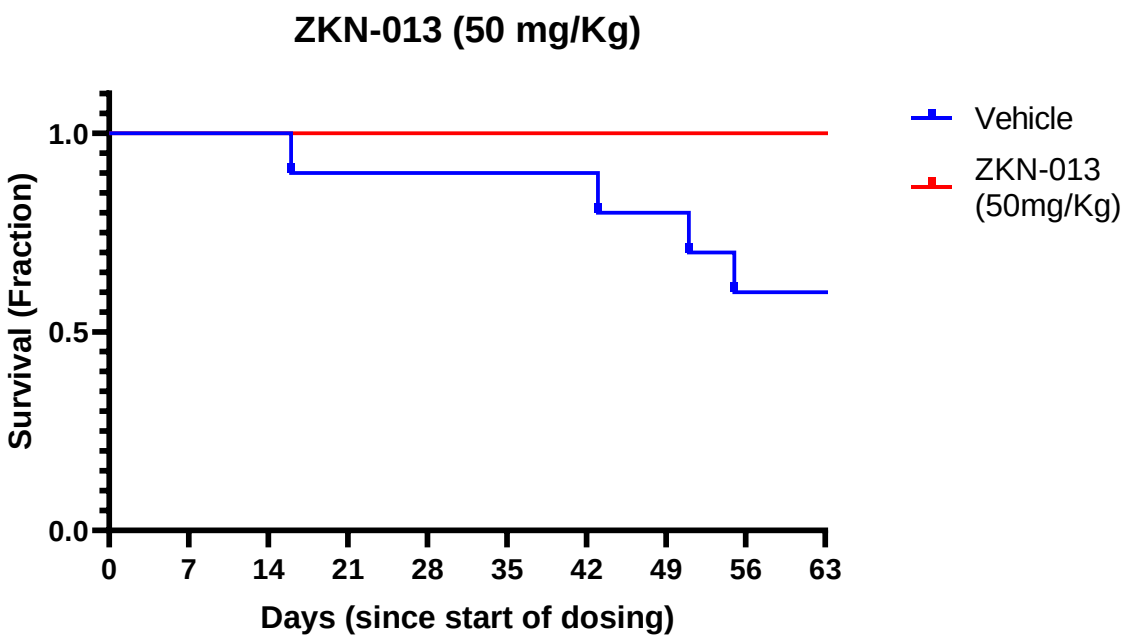


* Study conducted at CRO

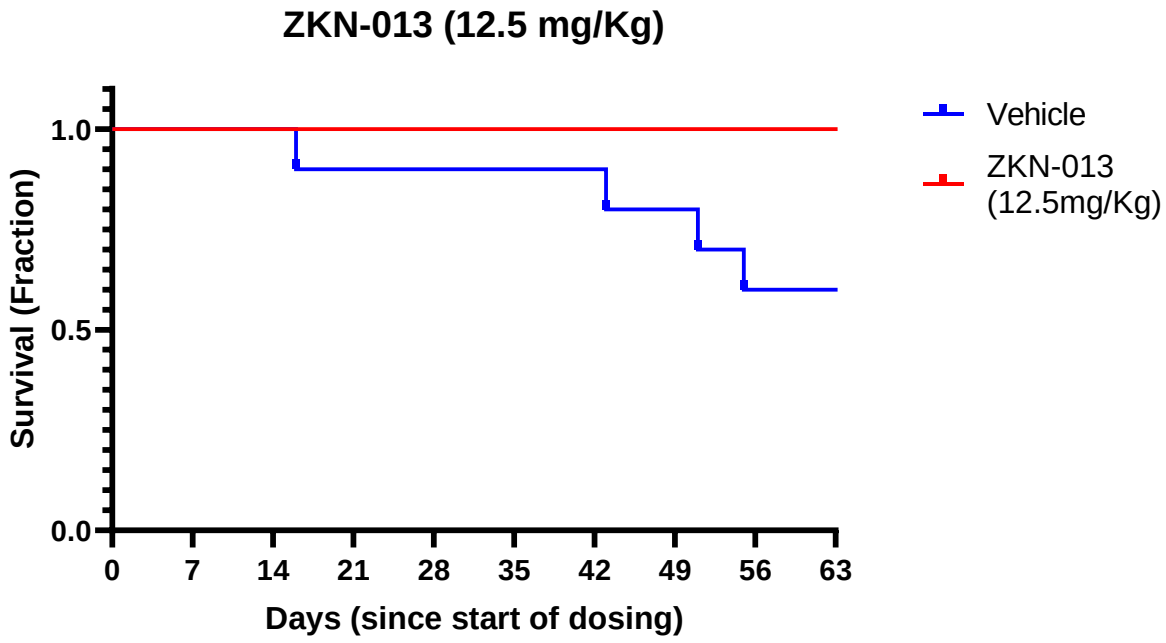
ZKN-013 FAP results confirmed in repeat APC^{Min} mice study

Survival rates in repeat dose response APC^{Min} study

ZKN-013 (50 mg/Kg)



ZKN-013 (12.5 mg/Kg)



ZKN-013 may be safely dosed to restore normal COL7 and APC function

No Effect Level Assessment (NOAEL) of ZKN-013

14-day non GLP rat oral safety study

	30 mg/kg	100 mg/kg	300 mg/kg
14-day Average skin Exposure (µM)	24.12	92.38	222.5
	NOAEL		

No Adverse Effect Level

Summary of *in vivo* safety studies to date

- **ZKN-013 exposure exceeds 20µM** shown to restore function at NOAEL dose
- 28-day GLP toxicity in-life studies completed
- On track for IND filing

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Rare disease pipeline of synergistic potential first-in-class therapies

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

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Significant pipeline milestones expected over next 12 months

	2H 2022	1H 2023
Alport Syndrome (SC ELX-02)	• Proof-of-concept trial start	• Top line results
RDEB/JEB (ZKN-013)	• IND submission	• Phase 1 start
FAP (ZKN-013)		• IND submission preparation
Class 1 Cystic Fibrosis (Inhaled ELX-02)	• Inhaled ELX-02 IND submission • Inhaled vs. SC *in vivo* efficacy readout	• TBD (in conjunction with CF Foundation)

Cash, including CFF award, 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 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**

De-risked **clinical stage pipeline of three rare diseases with >$5B** peak sales potential

Significant pipeline **expansion potential** in **rare diseases and targeted oncology**

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