Eloxx Pharmaceuticals

Unlocking protein production with **translational read-through** for **rare genetic** diseases

November 2020

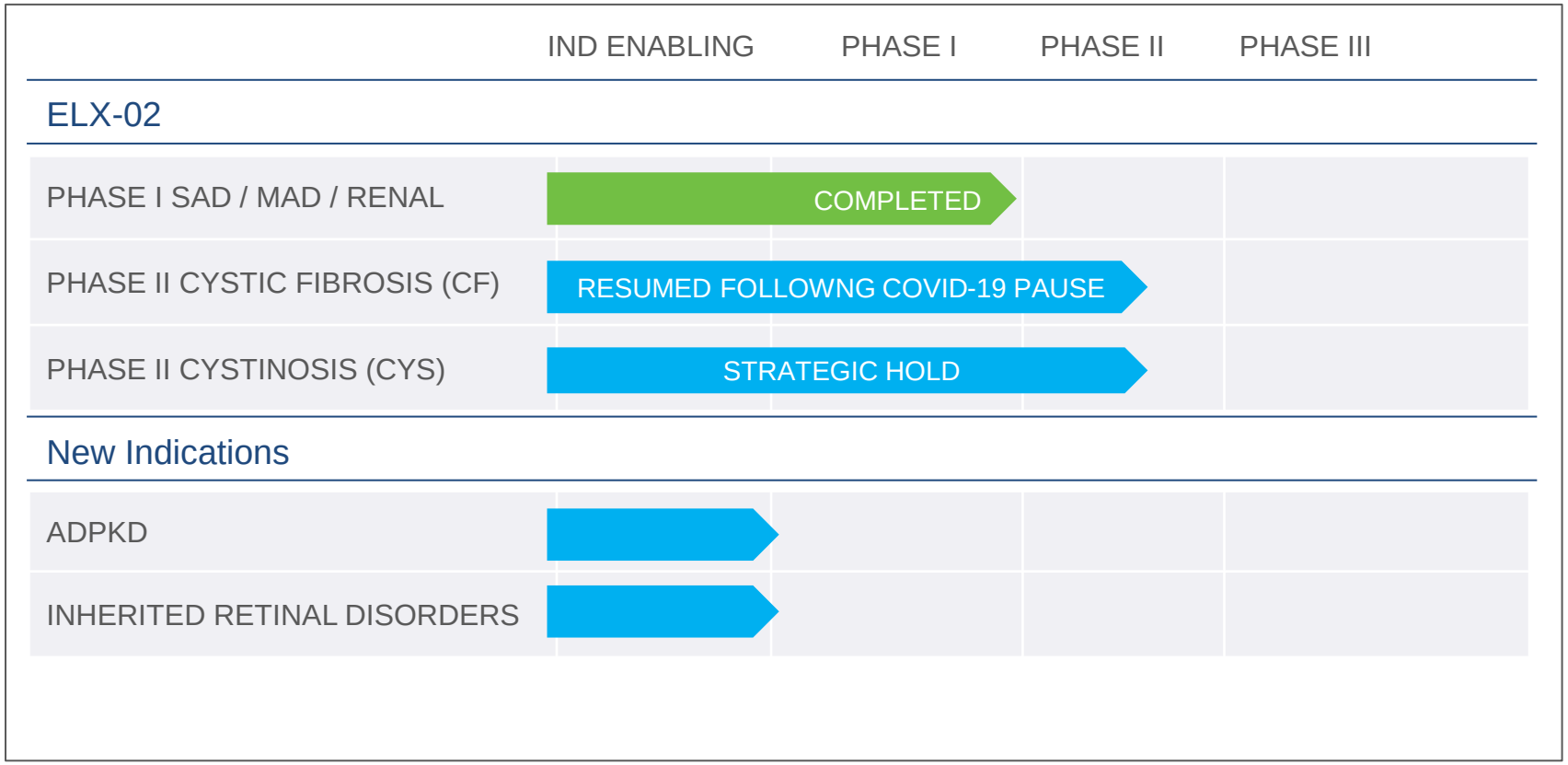
Forward-Looking Statements

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 read-through 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; 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 Pharmaceutical Highlights

- **Experienced Leadership Team**
- **Cash runway extends through the end of 2021**
- **Phase 2 ELX-02 Cystic Fibrosis Program**
  - **Expect to report top line data in the first half of 2021, barring any COVID disruptions**
  - **Independent Safety Review Committees have allowed dose escalation to the top dose**
  - **Evaluating safety, tolerability, PK and PD in cystic fibrosis patients with *G542X* Allele**
  - **ELX-02 received U.S. Orphan Drug Designation from FDA and EMA for cystic fibrosis**
  - **Cystic Fibrosis Medical Advisory Board of leading clinical CF investigators and experts**
- **ERSG Pipeline Development**
  - **Kidney; Autosomal Dominant Polycystic Kidney Disease**
    - **Preclinical studies demonstrate dose-dependent read-through across most prevalent *PKD1 and PKD2* alleles**
    - **Encouraging results of reduced cystogenesis and cyst size**
  - **Ocular; Inherited Retinal Disorders such as Usher**
    - **Ocular *Oca2* animal model shows POC for intravitreal tolerability and restored protein production**
    - ***In vitro* sustained release rates consistent with the target range of one to three months**

Eloxx Pipeline Overview



Our Orphan Drug Programs Have Strong Advocacy Support

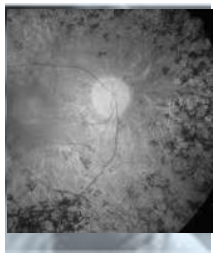
The Nonsense Mutation Problem

>1,800

Genetic diseases involve nonsense mutations

Cystic Fibrosis

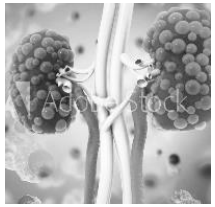
Cystinosis



Retinitis Pigmentosa

Usher Syndrome

Primary Ciliary Dyskinesia



Polycystic Kidney Disease

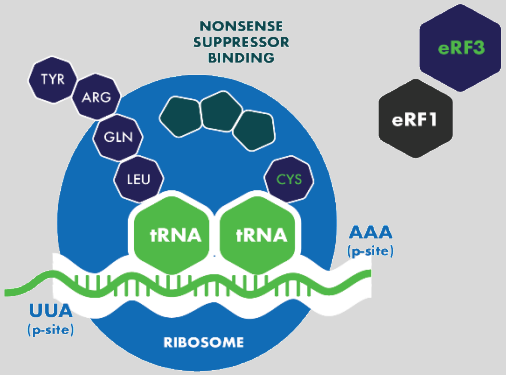
- In every genetic disease a subset of patients have nonsense mutations that impair the production of essential proteins
- Translational read-through is directed at restoring the production of full-length proteins by overcoming the premature stop codon and nonsense mediated decay

Unmet need for patients with nonsense mediated disease across multiple indications

Source: Pelz, Annu. Rev. Med. 2013. 64:407–25

Eloxx Small Molecule ERSG Solutions

Normal

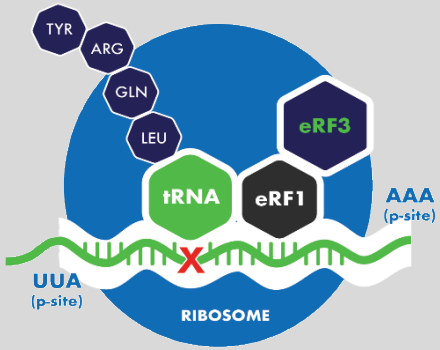


NORMAL TRANSLATION

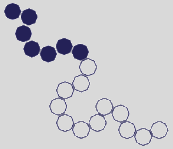
FULL LENGTH PROTEIN

mRNA TRANSCRIPT AVAILABLE FOR MORE TRANSLATION

Nonsense



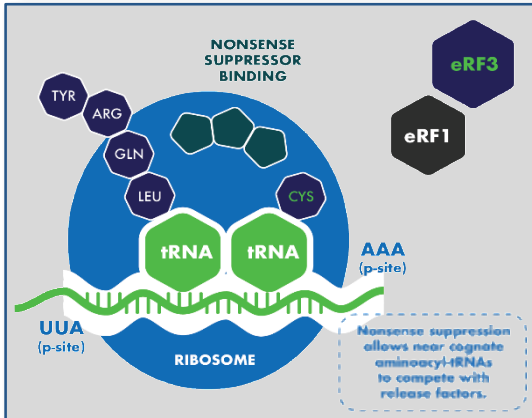
NONSENSE MUTATION



TRUNCATED PROTEIN

mRNA DEGRADATION

Read-through



NONSENSE MUTATION READTHROUGH

RESCUED FULL LENGTH PROTEIN

mRNA TRANSCRIPT STABILIZED

ELX-02: Phase 1 Program Completed

SAD (single ascending dose)

- ✓ Submission of CSR to regulators
- ✓ Published in *Clin. Pharm. Drug Dev*. 2019 Jan 16.
- ✓ PK presented at ECFS 2019
- ✓ **Full data presented at NACFC Oct. 31- Nov. 2, 2019**

MAD (multiple ascending dose)

- ✓ **Full data presented at NACFC Oct/Nov 2019**
- • **CSR and manuscript to follow**

Renal Impairment

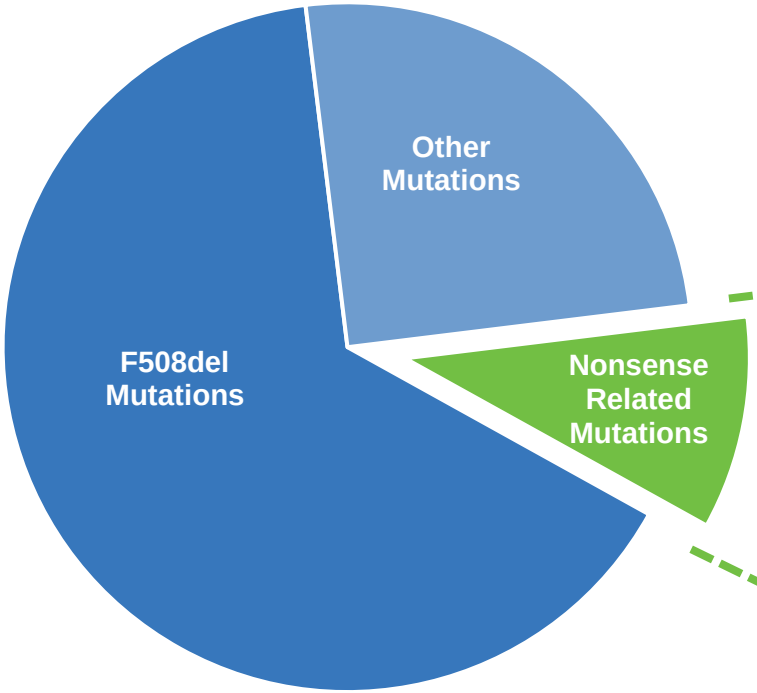
- ✓ **Full data presented at ASN Kidney Week Nov. 5-10, 2019**
- • **CSR and manuscript to follow**

Phase 1 Program Conclusions

- Generally well tolerated in clinical studies to date supporting evaluation in Phase 2
- Consistent PK results across single and multiple dose studies, with no accumulation
- High bioavailability (98%) upon SC administration with highly reproducible PK over the dosage range studied (0.3-7.5 mg/kg)

Cystic Fibrosis Nonsense Mutation Patients Represent a Key Unmet Need Population

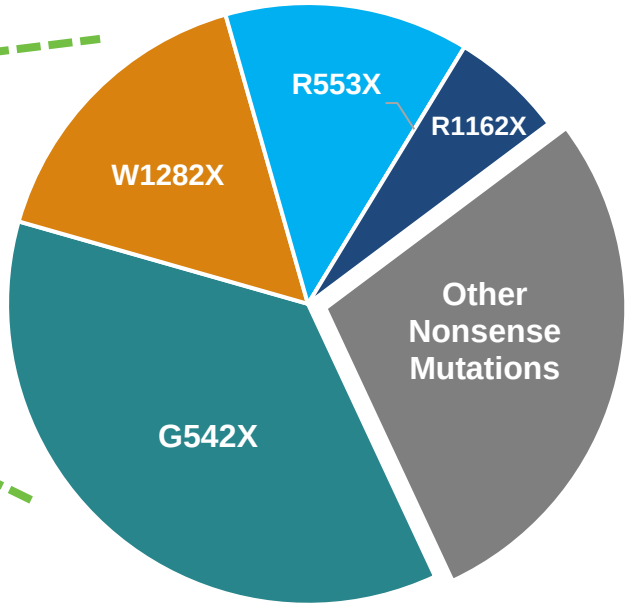
GLOBAL CYSTIC FIBROSIS PATIENTS BY MUTATION/GENOTYPE



10 -13%

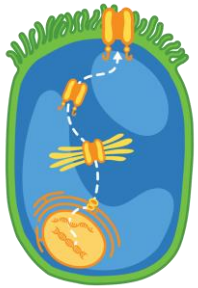
No Currently Approved Drugs To Treat CFTR Nonsense Mutations

CFTR NONSENSE MUTATION SUBTYPES



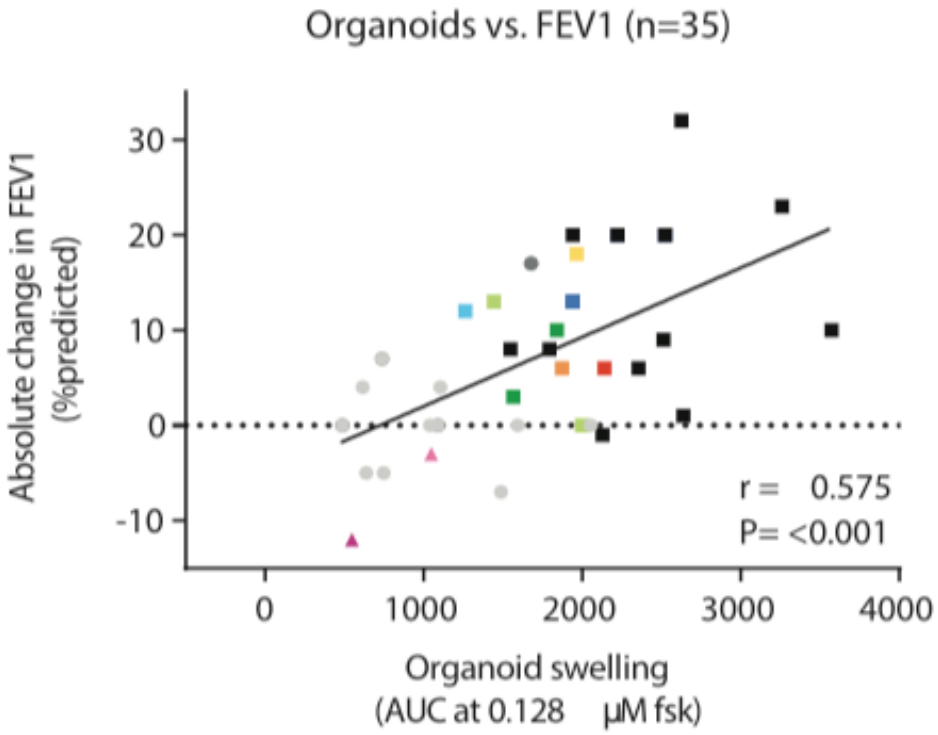
Source: Eloxx Internal Research/CFTR2 database

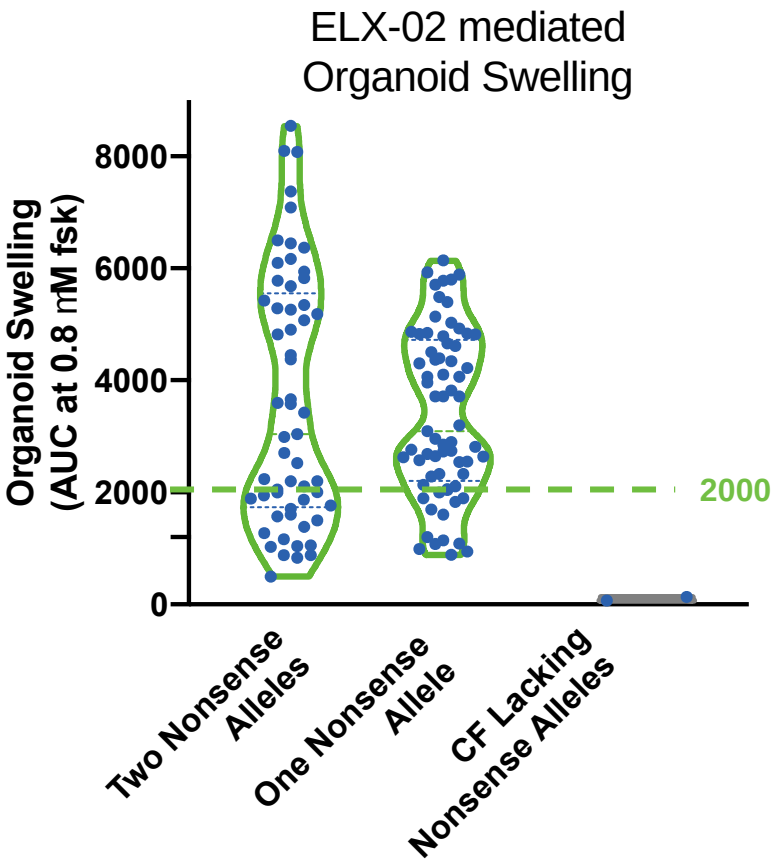
ELX-02: Preclinical Data De-Risks CF Phase 2



- **ELX-02 is a small molecule that permits read-through of nonsense mutations**
  - ✔ High selectivity for the eukaryotic cytoplasmic ribosome relative to mitochondrial ribosome
  - ✔ Defined MOA: Demonstrated significant increases in *Cystinosin* & *CFTR* *mRNA*, protein and function
  - ✔ Demonstrated read-through in assays focusing on high prevalence Cystic Fibrosis & Cystinosis nonsense mutations
- **ELX-02 high activity in multiple cellular and animal models**
  - ✔ Pronounced *CFTR* read-through demonstrated in plasmid, HBE, FRT, transgenic mice and patient-derived organoids
  - ✔ Pronounced Cystinosin read-though demonstrated in plasmid, patient derived fibroblasts and transgenic mice
- **Phase 2 Studies enroll patients with defined genotypes**
  - Cystic Fibrosis trial focuses on *G542X* on one or both alleles

ELX-02 Response in Organoids Compares Favorably to Published Results



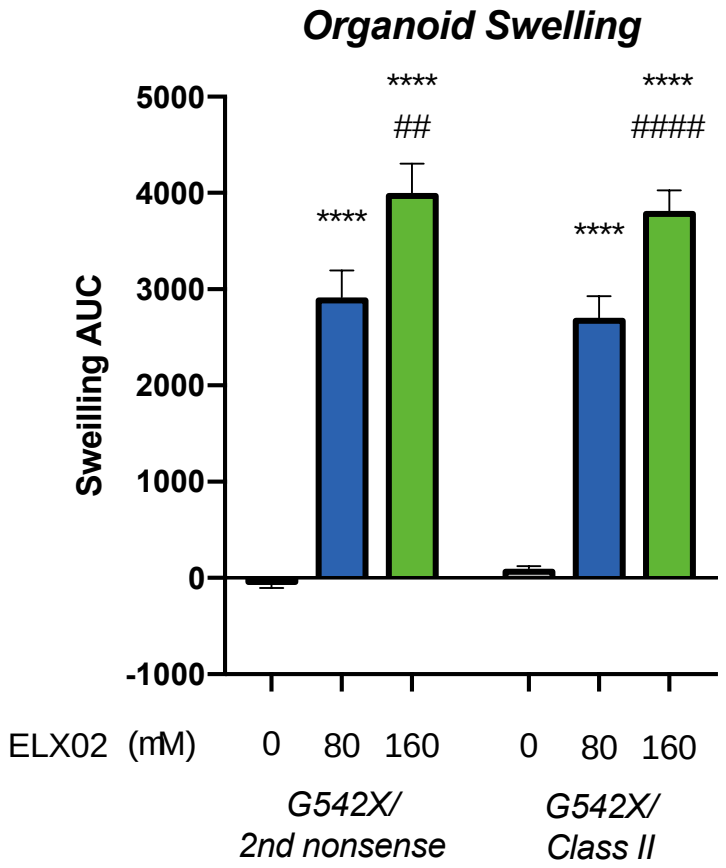


Berkers et al. Cell Reports (2019) Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis.

Eloxx data on file.

ELX-02 Mediated Organoid Swelling Is Equivalent in Organoids With One or Two Nonsense Mutations

- Significant increase in organoid swelling is observed in both *G542X* organoids with a second nonsense mutation and heterozygous organoids
- Experiments used 0.8 µM Forskolin



ordinary one-way ANOVA with Tukey's multiple comparison testing was used,, **** p<0.0001 versus vehicle control, ## p<0.01 versus next lower concentration, , #### p<0.0001 versus next lower concentration. Data represent >40 biological replicates per group from 2 or 4 independent patient organoids, respectively.

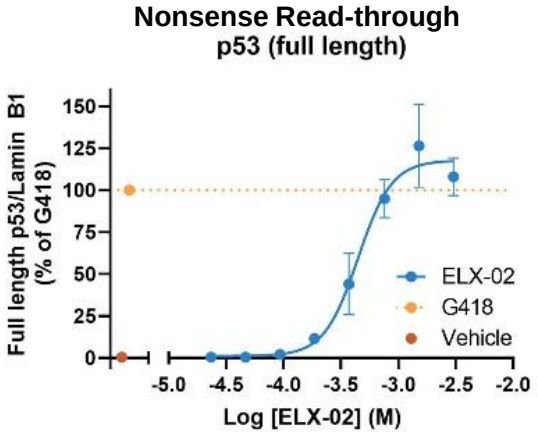
Eloxx data on file.

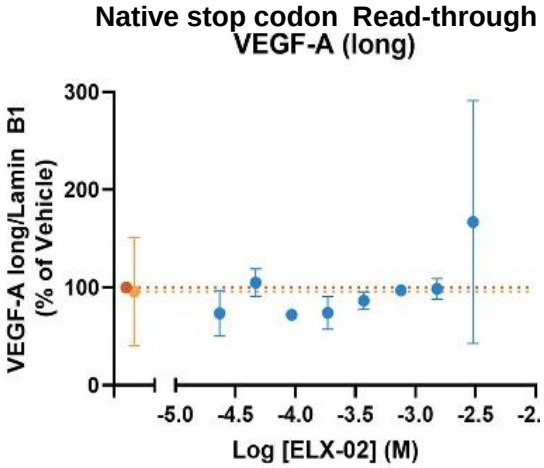
ELX-02 Mediates Read-through of Premature Stop Codons Without Read-through of Normal Stop Codons

- Recently published in JPET: “ELX-02 generates protein via premature stop codon read-through without inducing native stop codon read-through protein”

THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

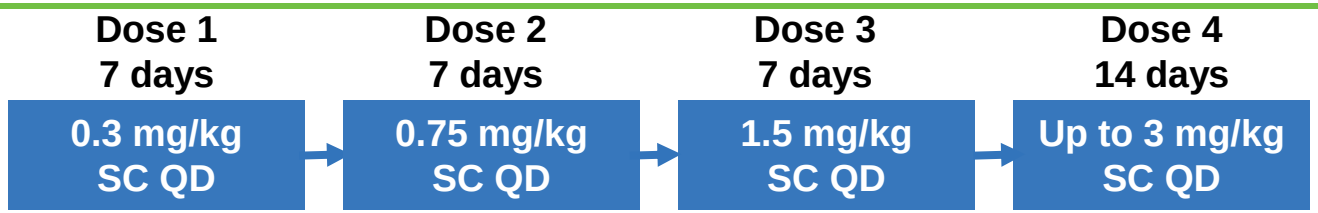
- Manuscript addresses a common question: “*If ELX-02 promotes read-through of premature stop codons, what about the normal stop codons?*”
- Manuscript demonstrates:
  - premature stop codon read-through at protein level with ELX-02
  - three-complimentary techniques demonstrating ELX-02 does not promote read-through of normal stop codons at relevant concentrations tested





Eloxx data on file.

ELX-02 Phase 2 Cystic Fibrosis – Trial Design



ClinicalTrials.gov Identifier: **US Trial** NCT04135495 **EU/IL Trial** NCT04126473

Population

- Targeting up to 16 CF patients with a *G542X* mutation on one or both alleles
- Intra-patient dose escalation
- 4 increasing doses of ELX-02 ranging from 0.3 up to 3.0 mg/kg/day

Primary Outcome Measures

- Safety, tolerability, and pharmacokinetics

Secondary Outcome Measures

- PD changes from baseline in sweat chloride levels and FEV1
- Consistent with other Phase 2 trials for approved drugs

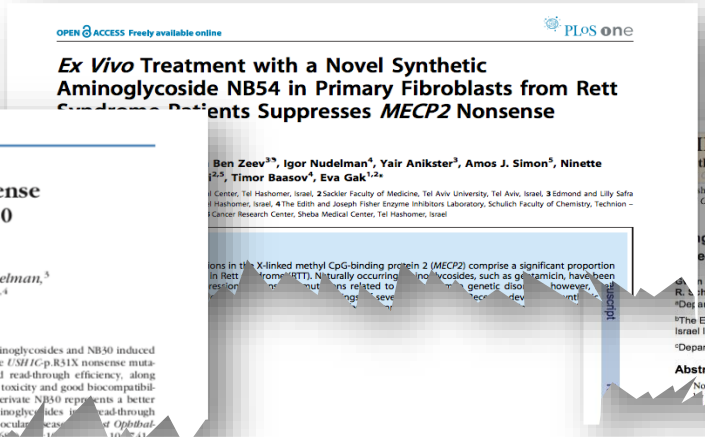
Locations

- Enrollment resumed in Europe, Israel & USA

Additionally

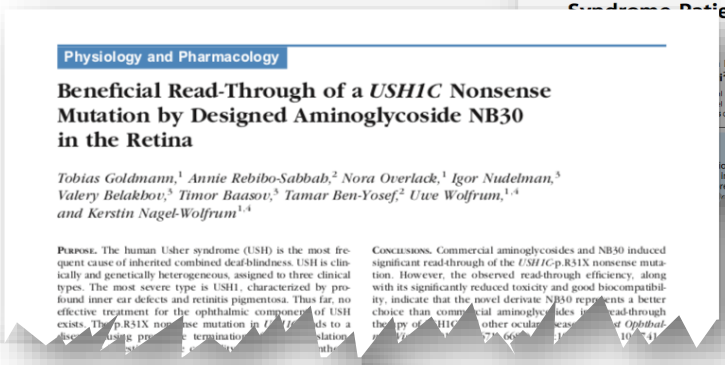
- Orphan drug designation granted in US and Europe
- Funding provided by CFF, sanctioned by CFF-TDN & ECFS-CTN (high priority ranking)

Eloxx is Developing New Indications for its ERSG Library to Expand the Portfolio

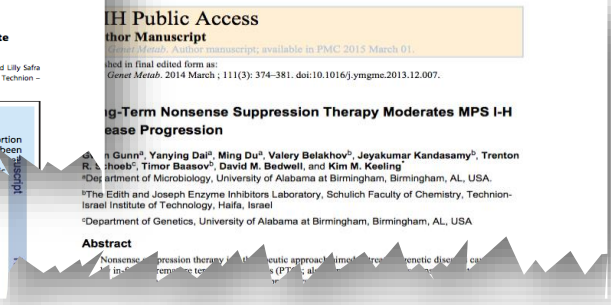

OPEN ACCESS Freely available online

PLoS one

Ex Vivo Treatment with a Novel Synthetic Aminoglycoside NB54 in Primary Fibroblasts from Rett Syndrome Patients Suppresses *MECP2* Nonsense


Physiology and Pharmacology

Beneficial Read-Through of a *USH1C* Nonsense Mutation by Designed Aminoglycoside NB30 in the Retina


NIH Public Access

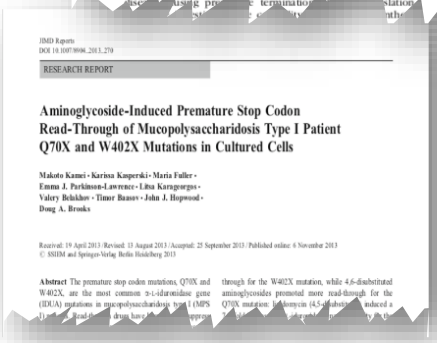
Author Manuscript

Genet Metab. Author manuscript; available in PMC 2015 March 01.

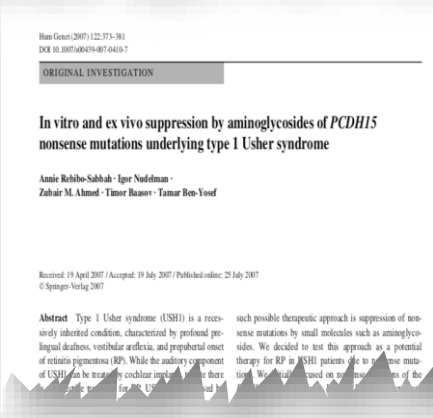
Published in final edited form as:

Genet Metab. 2014 March ; 111(3): 374–381. doi:10.1016/j.ymgme.2013.12.007.

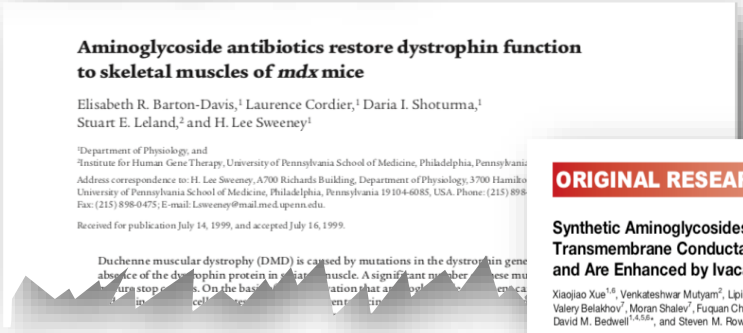
Long-Term Nonsense Suppression Therapy Moderates MPS I-H Disease Progression

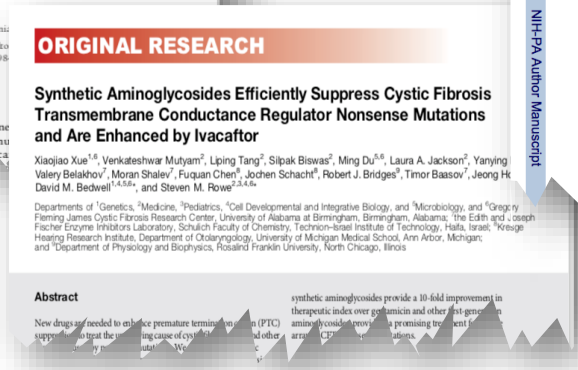

RESEARCH REPORT

Aminoglycoside-Induced Premature Stop Codon Read-Through of Mucopolysaccharidosis Type I Patient Q70X and W402X Mutations in Cultured Cells

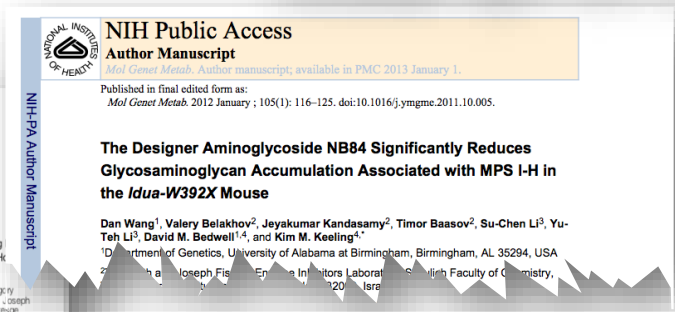

ORIGINAL INVESTIGATION

In vitro and ex vivo suppression by aminoglycosides of *PCDH15* nonsense mutations underlying type 1 Usher syndrome


Aminoglycoside antibiotics restore dystrophin function to skeletal muscles of *mdx* mice


ORIGINAL RESEARCH

Synthetic Aminoglycosides Efficiently Suppress Cystic Fibrosis Transmembrane Conductance Regulator Nonsense Mutations and Are Enhanced by Ivacaftor


NIH Public Access

Author Manuscript

Mol Genet Metab. Author manuscript; available in PMC 2013 January 1.

Published in final edited form as:

Mol Genet Metab. 2012 January ; 105(1): 116–125. doi:10.1016/j.ymgme.2011.10.005.

The Designer Aminoglycoside NB84 Significantly Reduces Glycosaminoglycan Accumulation Associated with MPS I-H in the *Idua-W392X* Mouse

ADPKD (*Autosomal Dominant Polycystic Kidney Disease)*

- 200,000-600,000 people with ADPKD in the US
  - 12 million people worldwide
- ~141,000 diagnosed cases of ADPKD in the US (2 main genes are *PKD1* and *2*)

***PKD1* Mutation**	***PKD2* Mutation**
• 85% of all ADPKD cases • Cysts may appear when patients are young adults • Disease can progress rapidly • Median age of ESRD onset is 54 yrs. • Gene location: short arm on chromosome 16 (16p13.3)	• 15% of all ADPKD cases • Disease progresses more slowly vs. PKD1 • Median age of ESRD onset is 74 years • Gene location: long arm on chromosome 4 (4q21)

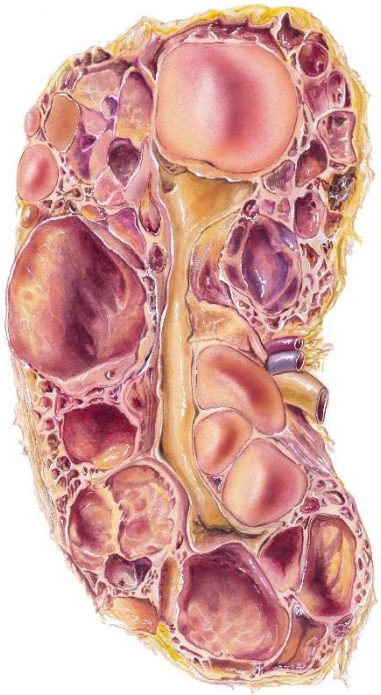
- ~6,000 new cases diagnosed each year in the US
- ***~6-10% of individuals receiving dialysis and renal transplant treatment in the US have ADPKD***

Blanchette, C. et al; Burden of Autosomal Dominant Polycystic Kidney Disease: Systematic Literature Review, Am J Pharm Benefits, 2015; 7(2): e27-e36
Uncoverpkd.com (Otsuka HCP site)
NORD, https://rarediseases.org/rare-diseases/autosomal-dominant-polycystic-kidney-disease/
PKD International, https://pkdinternational.org/what-is-pkd/adpkd

ADPKD Nonsense Mutation Prevalence

- Genetic disorder characterized by cysts localized within the kidney. Majority of patients progress to ESRD.
- Mutations in *PKD1* or *PKD2* cause a disruption in the production of functional polycystin, which through signaling process leads to excess vasopressin, leading to cyst growth.

ADPKD: Cyst formation



ADPKD US:
140k diagnosed pts.

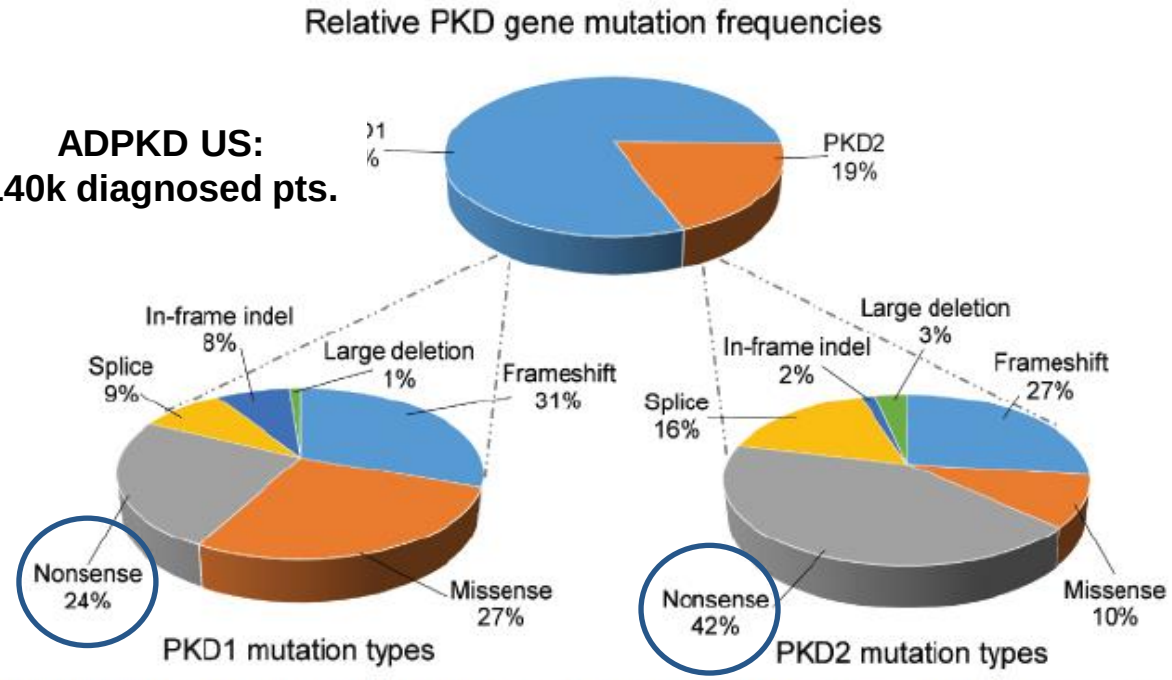
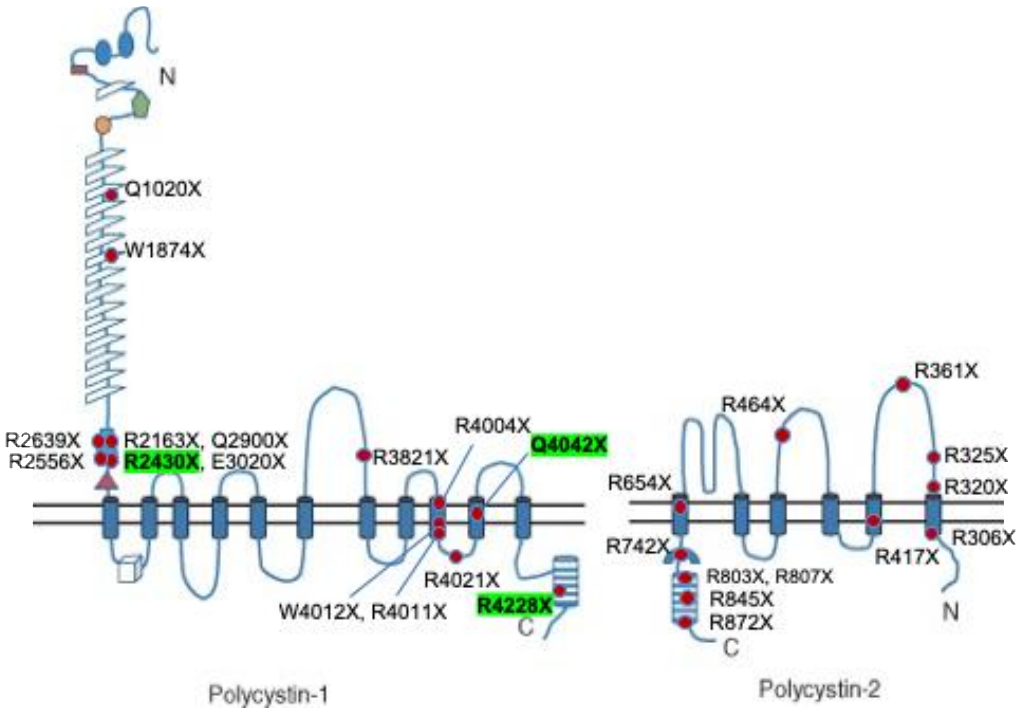
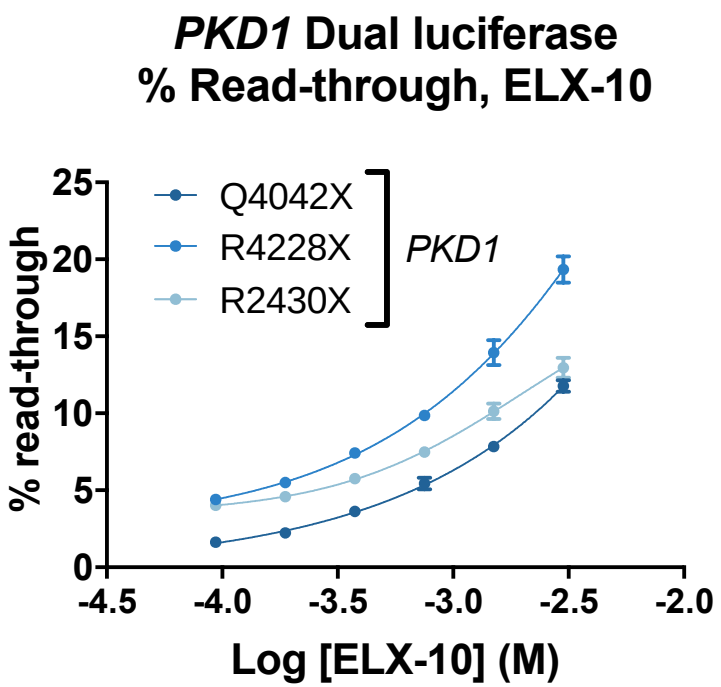


Figure 2. Frequency and type of *PKD1* and *PKD2* mutations from the PKD mutation database. All mutation types have been reported for both genes. The relative infrequency of missense mutations and in-frame insertions or deletions for *PKD2* could reflect the under-diagnosis of these patients present in the general population. The PKD mutation database is available at http://pkdb.mayo.edu/index.html (accessed 22 April 2016).

Mao et al., F1000 Research 2016

ERSGs Promote Read-through of Most Common *PKD1* and *PKD2* Nonsense Mutations



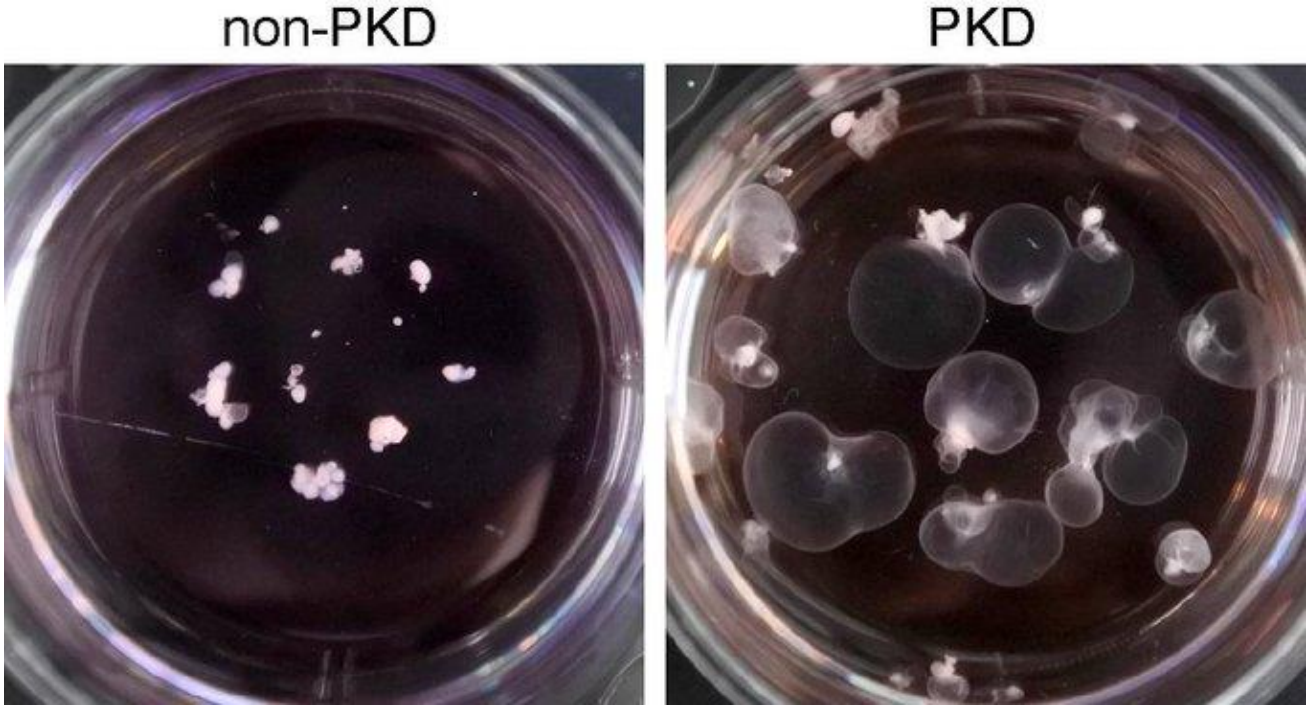


- Nonsense (X) mutations can be found across both *PKD1* (PC1) and *PKD2* (PC2) genes
- Read-through of most common nonsense alleles shown in dual luciferase assay
- Dose-dependent read-through of the top three *PKD1* nonsense alleles (according to the Mayo ADPKD database) is observed with multiple ERSGs

Eloxx data on file.

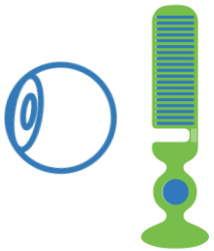
Encouraging ERSG Results in ADPKD Organoids

- Nonsense mutation kidney organoids model ADPKD cyst formation
  - Model system flexible enough to evaluate genetically heterogenous ADPKD population
  - Ongoing collaboration with Benjamin Freedman, University of Washington
- ERSG compounds are under evaluation in iPSC-derived (induced pluripotent stem cell-derived) and primary organoids for impact on cyst formation and reduction
  - Encouraging preliminary results show reduced cystogenesis and cyst size with ERSG treatment



Courtesy of Freedman lab

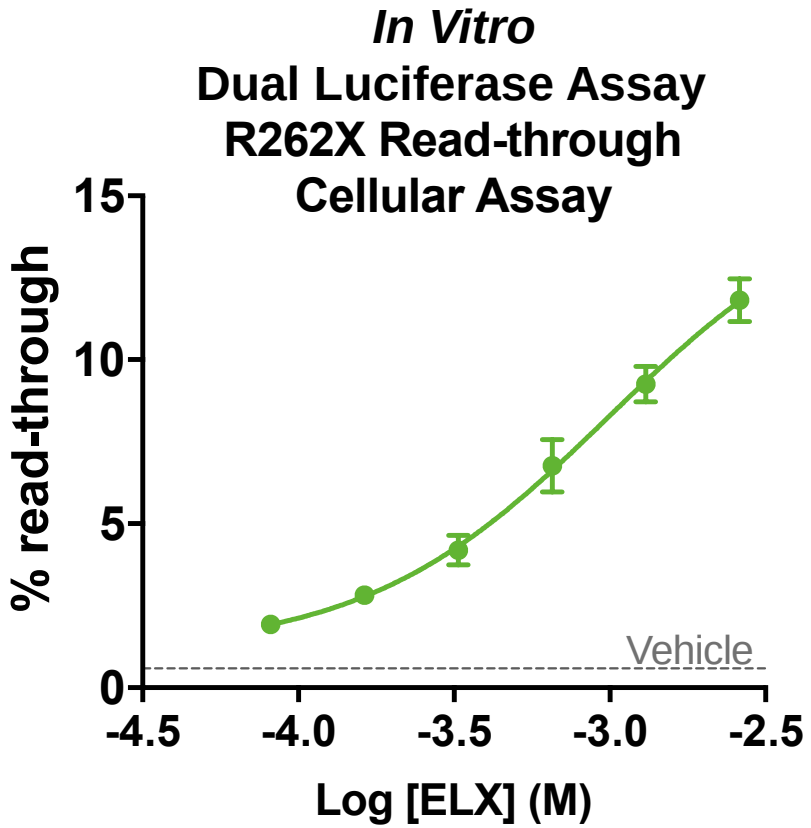
Ocular Program Development



- High unmet medical need and prevalence of nonsense mutations across inherited retinal diseases (IRDs)
- Screened multiple compounds from ERSG library for read-through and tolerability
- IND-enabling studies are progressing
- Emerging Profile Across Models
  - Compounds are appropriate for intravitreal administration
  - Compounds show retinal tolerability at doses 10-fold greater than anticipated efficacy range in sensitive species
    - No adverse ELX compound-related retinal anatomic or functional changes observed to date by histopathology and ERG
  - Dose-dependent read-through of Usher mutations greater than gentamicin reference
  - Encouraging PK demonstrating retina exposure
- In vitro sustained release rates are consistent with the target range of one to three months

Intravitreal Administration Modeling

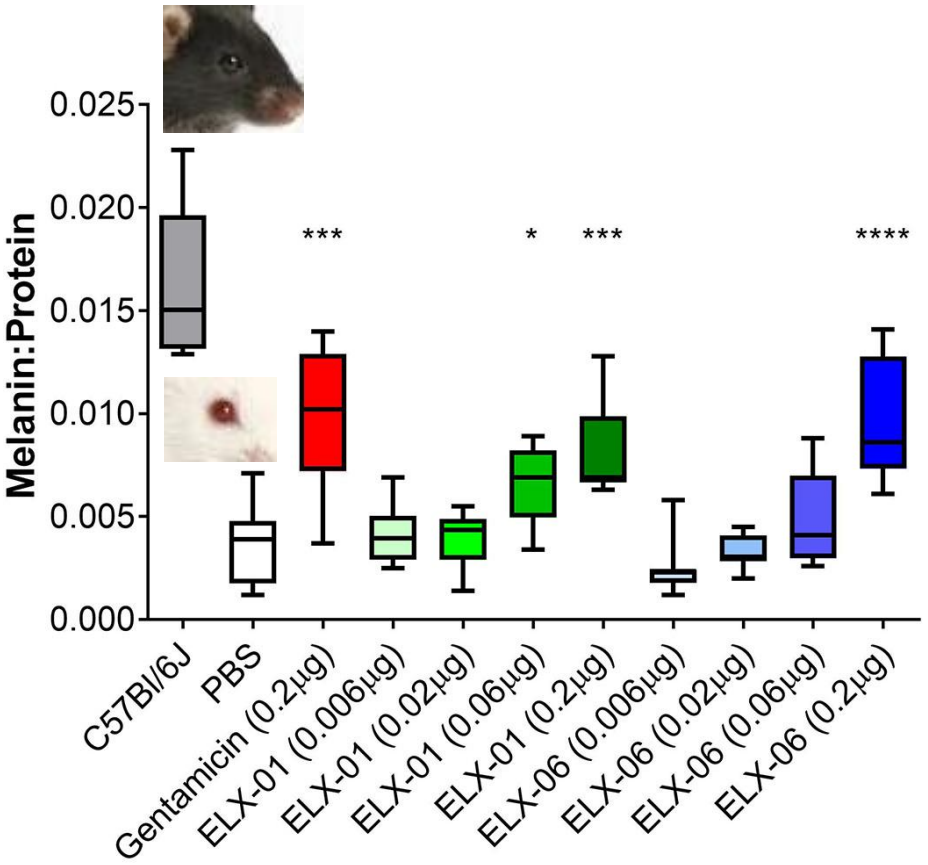
- SJL/J mice have a *R262X* mutation (UGA) in the *OCA2* gene1
- OCA2 is a channel involved in establishing organelle (melanocyte) pH in the RPE (retinal pigment epithelium)
- Cellular read-through testing demonstrates significant read-through potential across ELX compounds
- Model is being used to screen Eloxx compounds for *in vivo* read-through activity at the back of the eye



1. Shoji et al, Exp. Anim 2015; 64(2)
2. Bellono et al., eLife 2014
3. Eloxx data on file.

ERSGs Promote Functional Read-through in the Eye by Intravitreal Administration (*In Vivo*)

- Intravitreal dosing of ELX compounds demonstrate a dose-dependent increase in melanin production in the eye
  - Single dose on Study Day 1
  - Melanin measured on Study Day 3
- Multiple ERSG compounds demonstrate increased OCA2 function after single intravitreal injection
- Data support that ERSG compounds can reach cells deep in the neurosensory retina, including the retinal pigment epithelium and choroid
- New data presented at the **Association for Research in Vision and Ophthalmology (ARVO) Virtual Annual Meeting** May 6, 2020



Eloxx data on file.

Eloxx Pharmaceutical Highlights

- **Experienced Leadership Team**
- **Cash runway extends through the end of 2021**
- **Phase 2 ELX-02 Cystic Fibrosis Program**
  - **Expect to report top line data in the first half of 2021, barring any COVID disruptions**
  - **Independent Safety Review Committees have allowed dose escalation to the top dose**
  - **Evaluating safety, tolerability, PK and PD in cystic fibrosis patients with *G542X* Allele**
  - **ELX-02 received U.S. Orphan Drug Designation from FDA and EMA for cystic fibrosis**
  - **Cystic Fibrosis Medical Advisory Board of leading clinical CF investigators and experts**
- **ERSG Pipeline Development**
  - **Kidney; Autosomal Dominant Polycystic Kidney Disease**
    - **Preclinical studies demonstrate dose-dependent read-through across most prevalent *PKD1 and PKD2* alleles**
    - **Encouraging results of reduced cystogenesis and cyst size**
  - **Ocular; Inherited Retinal Disorders such as Usher**
    - **Ocular *Oca2* animal model shows POC for intravitreal tolerability and restored protein production**
    - ***In vitro* sustained release rates consistent with the target range of one to three months**

Eloxx Pharmaceuticals

Thank you

November 2020