Eloxx Pharmaceuticals

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

**Eloxx Investor Presentation**

**March 2019**

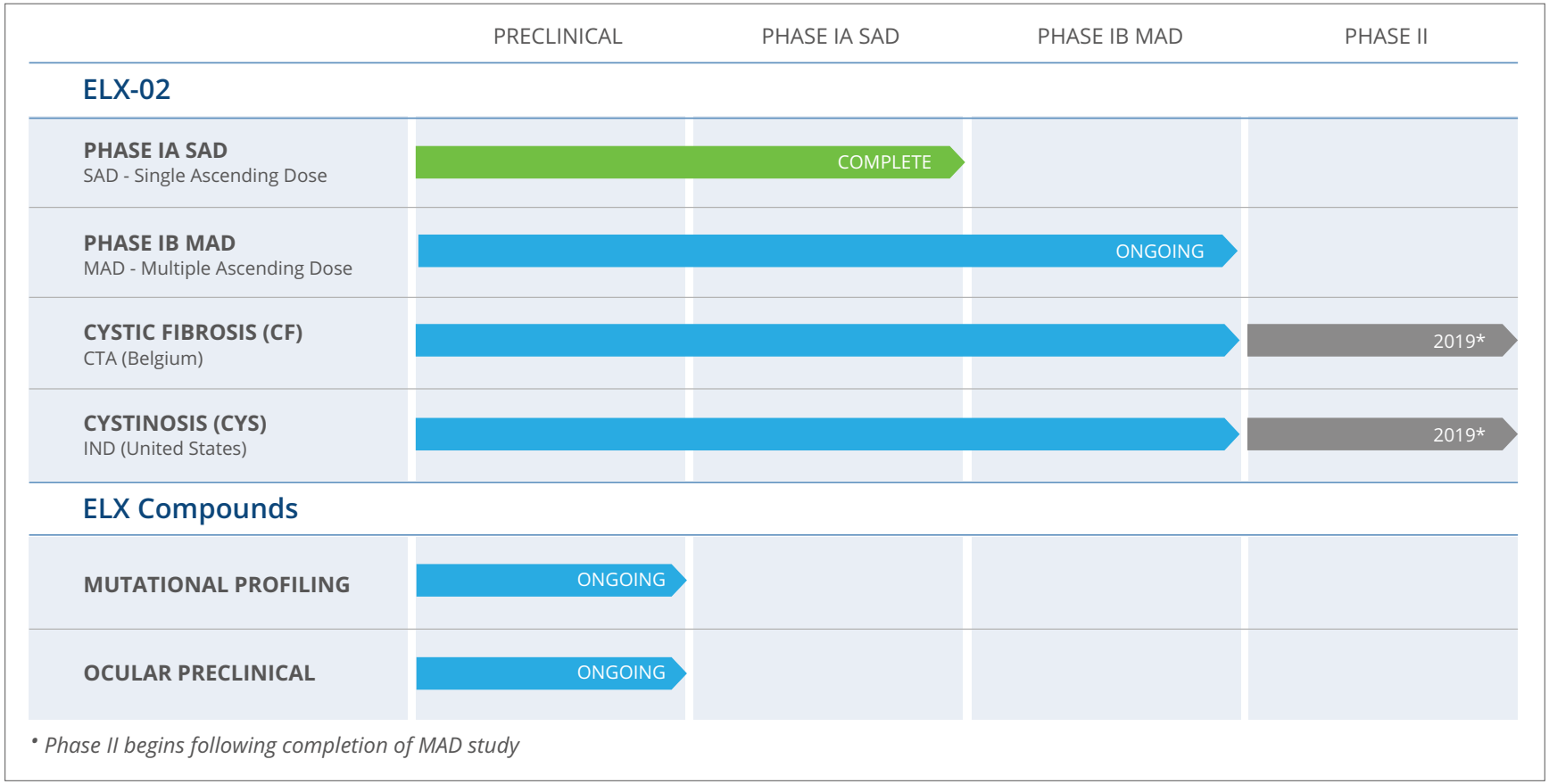
# Forward-Looking Statements

*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; 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**
  - Appointment of Dr. Susan Schneider SVP Ophthalmology
- **ELX-02 Clinical Progress**
  - EU Cystic Fibrosis Basic Science Meeting March 27th New Data
  - On Track for Completion of Phase 1b MAD 1H2019
  - Expect Topline Cystic Fibrosis Phase 2 in 2019
- **Building Ophthalmology Inherited Retinal Disorder Program**
  - Association for Research in Vision & Ophthalmology Meeting May New Data
  - IND Enabling Studies Focusing on Usher's Syndrome
  - Announced Partnership with Foundation Fighting Blindness
- **Actively Developing Opportunities for Collaboration to Advance Full Pipeline and Expand Therapeutic Programs**

# Eloxx Pipeline

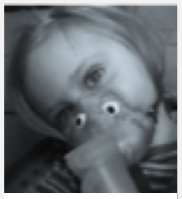



• *Phase II begins following completion of MAD study*

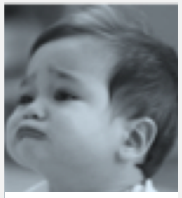
# The Potential for Read-Through of Rare Genetic Diseases

**>1,800**

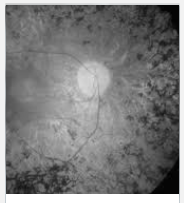
**Genetic diseases involve nonsense mutations**



**Cystic Fibrosis**



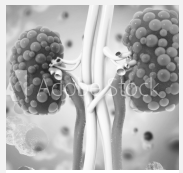
**Cystinosis**



**Retinitis Pigmentosa**

**Usher's Syndrome**

**Primary Ciliary Dyskinesia**



**Polycystic Kidney Disease**

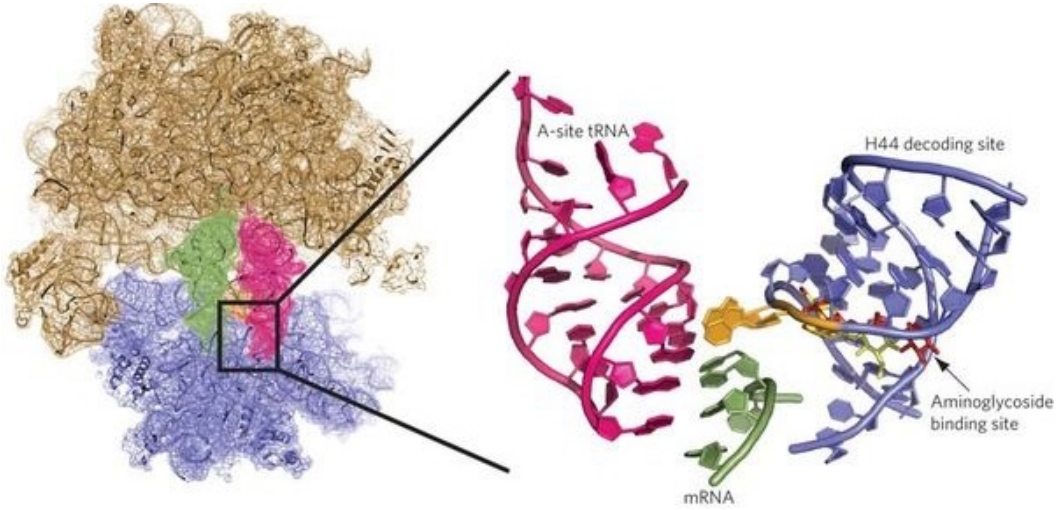
- In every genetic disease a subset of patients have nonsense mutations that impair the production of essential proteins
- Translational read through is directed at restoring the production of full length proteins by overcoming the premature stop codon and nonsense mediated decay

Aminoglycosides' tolerability profile historically limited suitability for read-through treatment of serious genetic diseases

Aminoglycosides first showed read-through activity in nonsense mediated diseases

**Advances in our understanding of translational read-through enables design of novel small molecules**

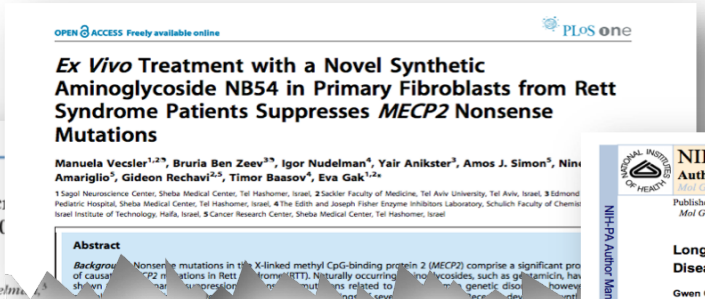
# Defined Ribosomal Binding Site




- Well defined molecular interaction with helix 44
- Role in stabilization of tRNA binding at Site A
- Optimizing scaffold by altering interaction with prokaryotic and mitochondrial ribosomes
- Defined tissue penetration and tolerability profile for read-through applications

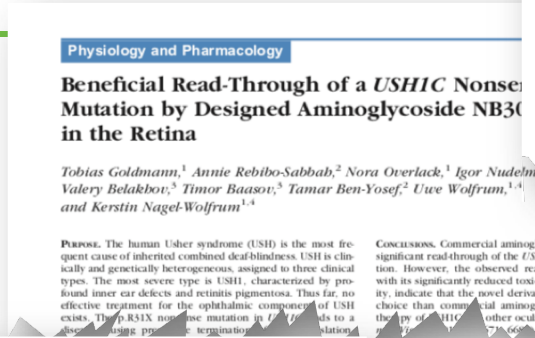
Aminoglycoside activity observed on single pre-translocation ribosome complexes. Feldman, MB; Terry DS; Altman RB; Blanchard SC. Nature Chemical Biology volume6, pages54–62 (2010)

# Novel Compound Library has Demonstrated Activity across Multiple Orphan Diseases


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 Mutations**


Physiology and Pharmacology

**Beneficial Read-Through of a *USH1C* Nonse Mutation by Designed Aminoglycoside NB3( in the Retina**


NIH Public Access

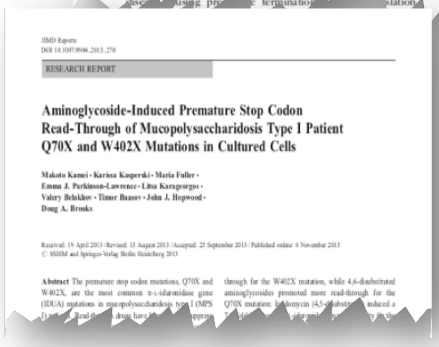
Author Manuscript

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

Published in final edited form as:

*Mol 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**

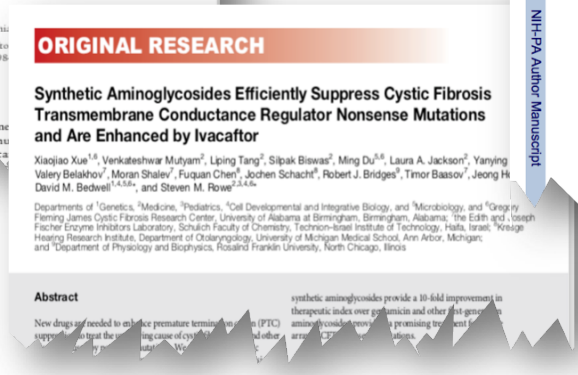

RESEARCH REPORT

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

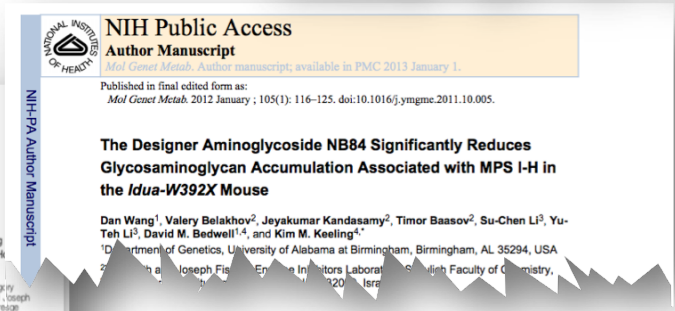

ORIGINAL INVESTIGATION

**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**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*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**

# Substantial Advantages for Orphan Drug Development

- **ELOXX Focus on High Unmet Medical Need**
  - Nonsense mutations represent important patient segments in over 1,800 diseases
  - Many of these diseases have no approved therapeutics
  - In some diseases the nonsense patient population is appropriate size for traditional clinical development
- **Developing Novel Therapeutics through Established Pathways**
  - Many orphan diseases have existing preclinical assays or animal models with correlations to clinical endpoints
  - Validated Phase 2 endpoints can guide phase transition and design of pivotal trials
- **Orphan Designation Confers Important Regulatory Considerations**
  - Potential for closer collaboration, accelerated development
  - Several economic or exclusivity incentives
  - In the US, Rare Pediatric Disease Priority Review Voucher Program
- **Ongoing Global Regulatory Interest in Accelerating Development for High Unmet Medical Need**

# ELX-02 Clinical Development – Phase 1 Studies

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology

January 16, 2019

Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of ELX 02, a Potential Treatment for Genetic Disorders Caused by Nonsense Mutations, in Healthy Volunteers

CLINICALTRIALS.GOV
**Identifier: NCT03292302**

**COMPLETED**

**TO DATE:**
- No SAE Observed
- No renal or otoacoustic SAE
- Generally well tolerated

CLINICALTRIALS.GOV
**Identifier: NCT03309605**

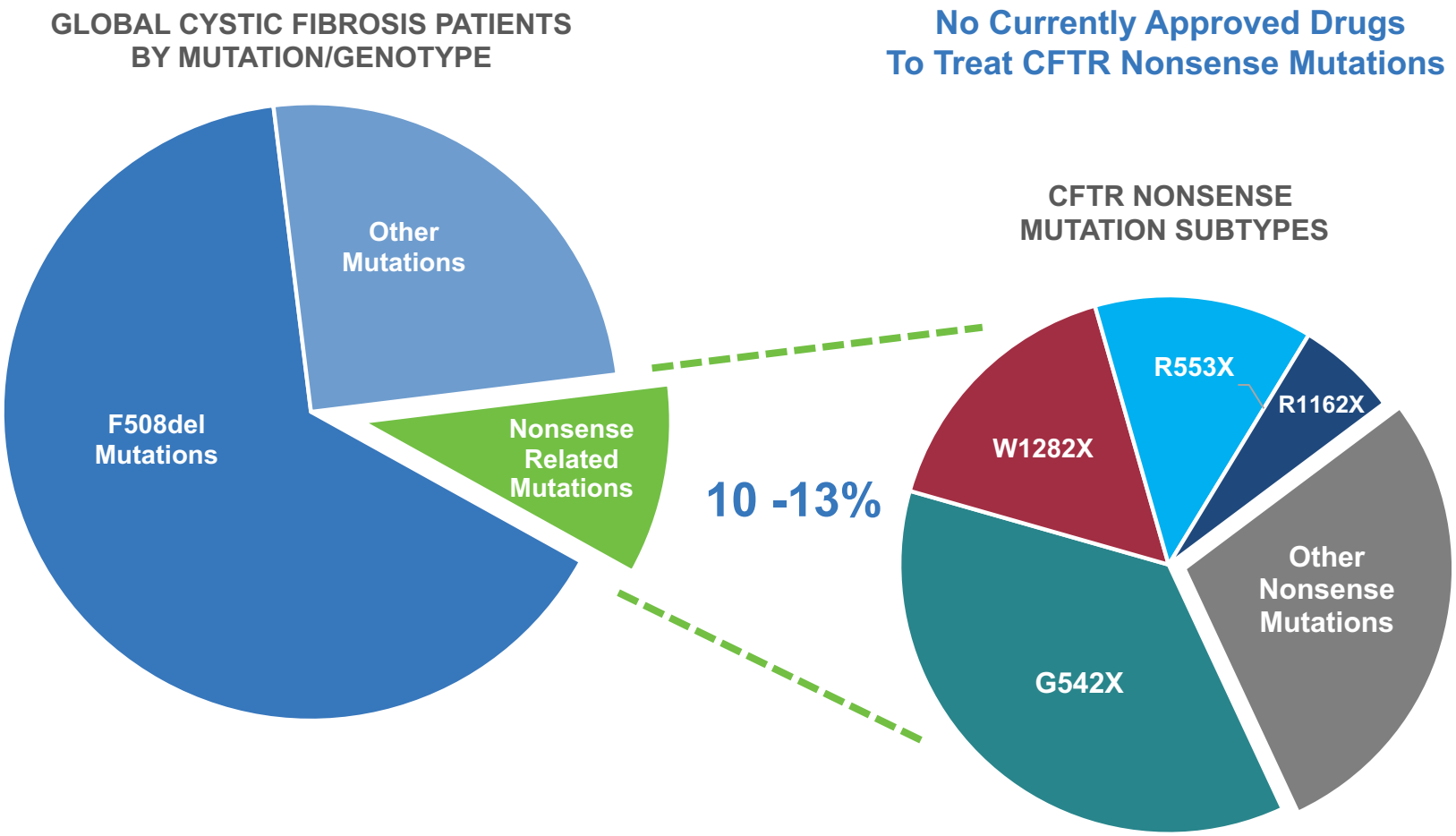
A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, Third Party Open, Multiple Dose Escalation, Single Center Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Subcutaneously Administered ELX-02 in Independent Consecutive Cohorts of Healthy Subjects

**ONGOING**

**INITIATED 6TH COHORT in Belgium**
**On track for final Cohort in US**

ELO

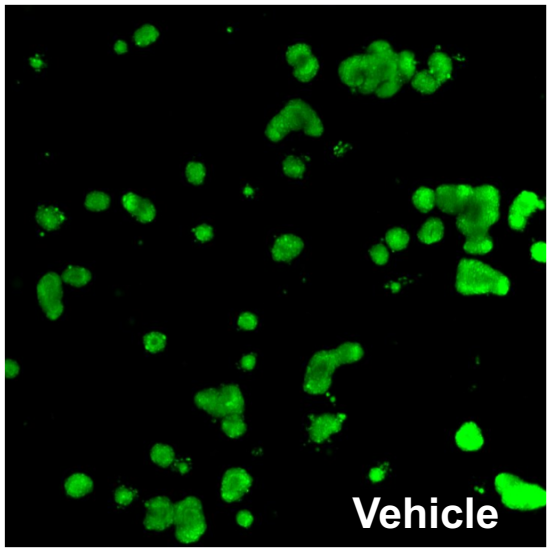
# Cystic Fibrosis Nonsense Mutation Patients Represent a Key Unmet Need Population



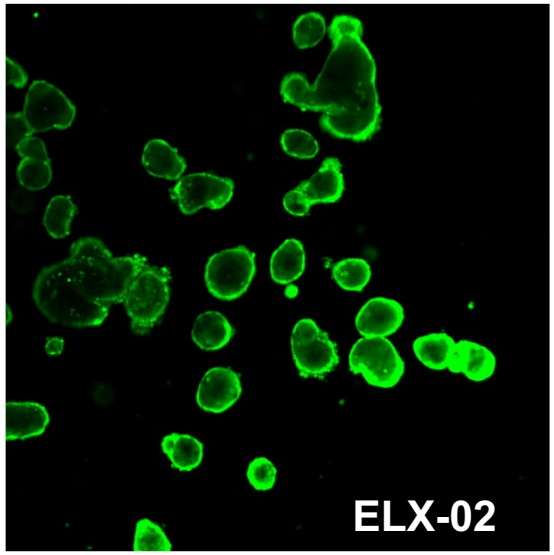

*Source: Eloxx Internal Research/CFTR2 database*

# Organoid Swelling Assay Demonstrates CFTR Function

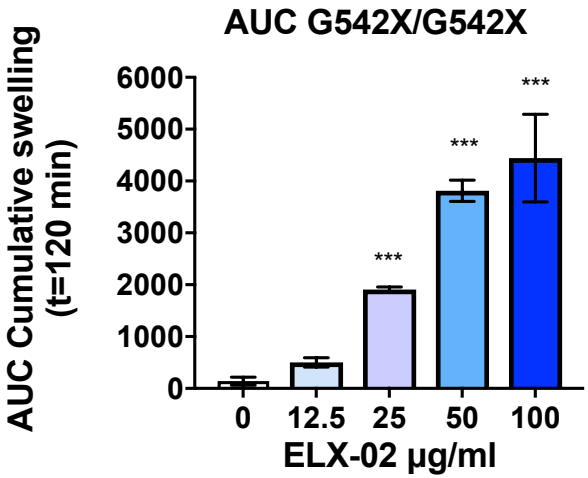
## Cystic Fibrosis Organoid dose-responsive swelling assay response




Patient Organoid without drug treatment: No Swelling of Organoids

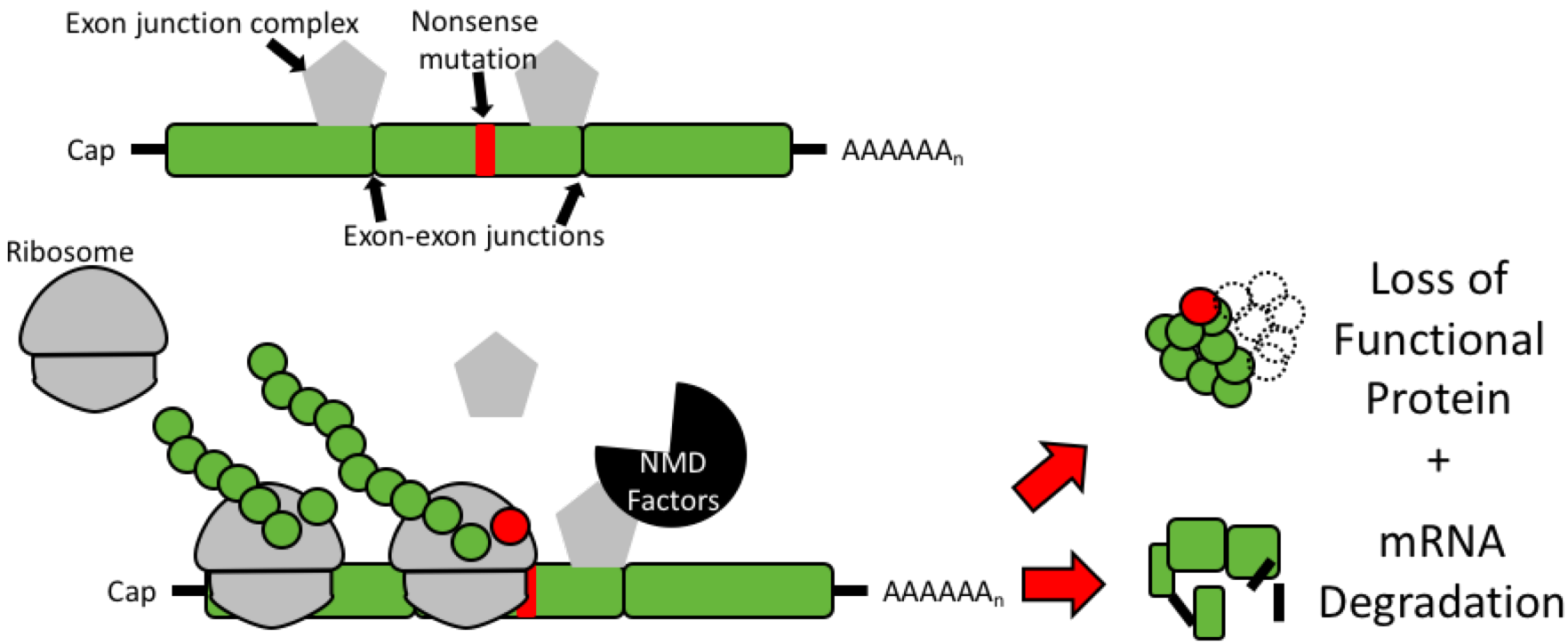



Patient Organoid with ELX-02 treatment: Swelling of Organoids




Swelling quantification of patient organoid with ELX-02 treatment.

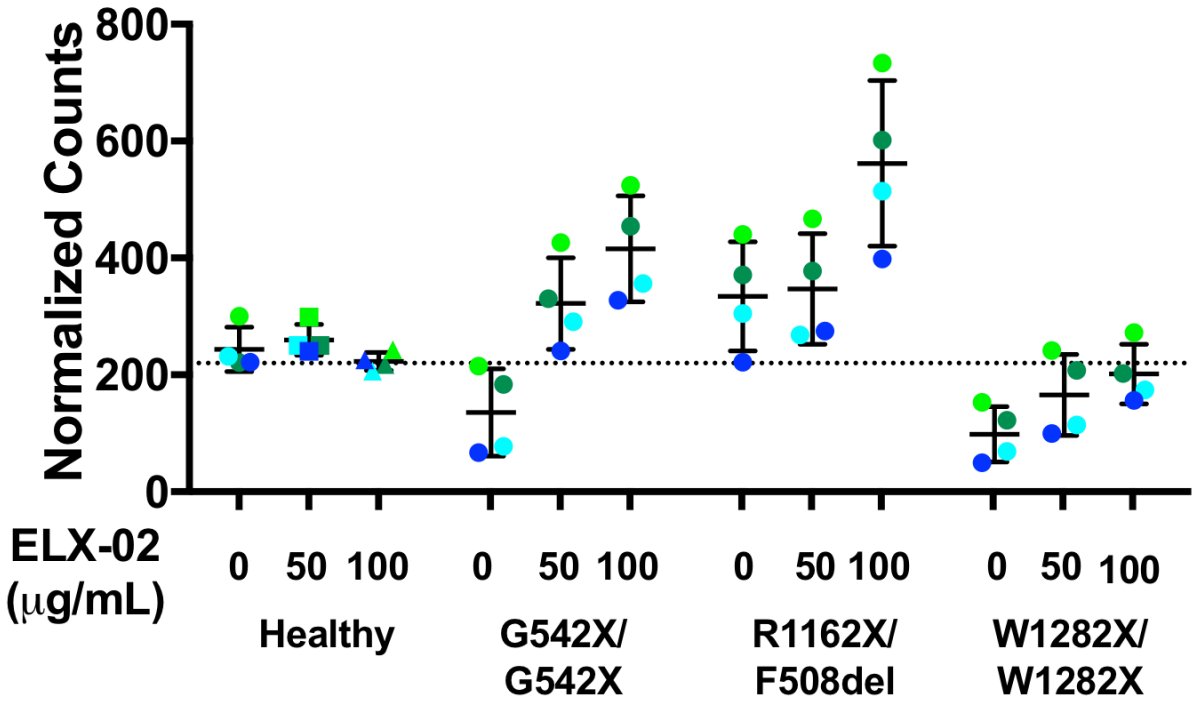
# Nonsense Mutations Can Cause a “Double-Hit”, Loss of mRNA and Functional Protein




For more information: Kurosaki & L.E. Maquat. Nonsense-mediated mRNA decay in humans at a glance. J. Cell Sci. 1;129(3):461-7 (2016).

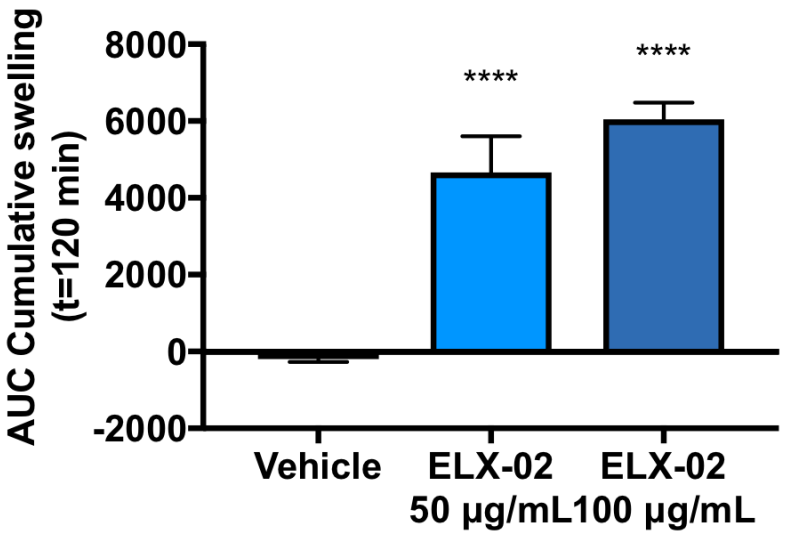
# *CFTR* mRNA Comparisons to Healthy, Wild-type Control

## Cystic Fibrosis Organoid Responsive to ELX-02 demonstrates elevations above wild-type

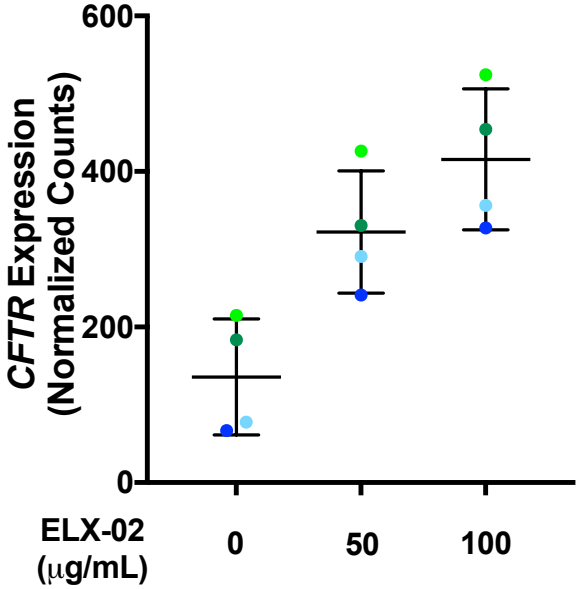


# Homozygous Nonsense Mutation (G542X)

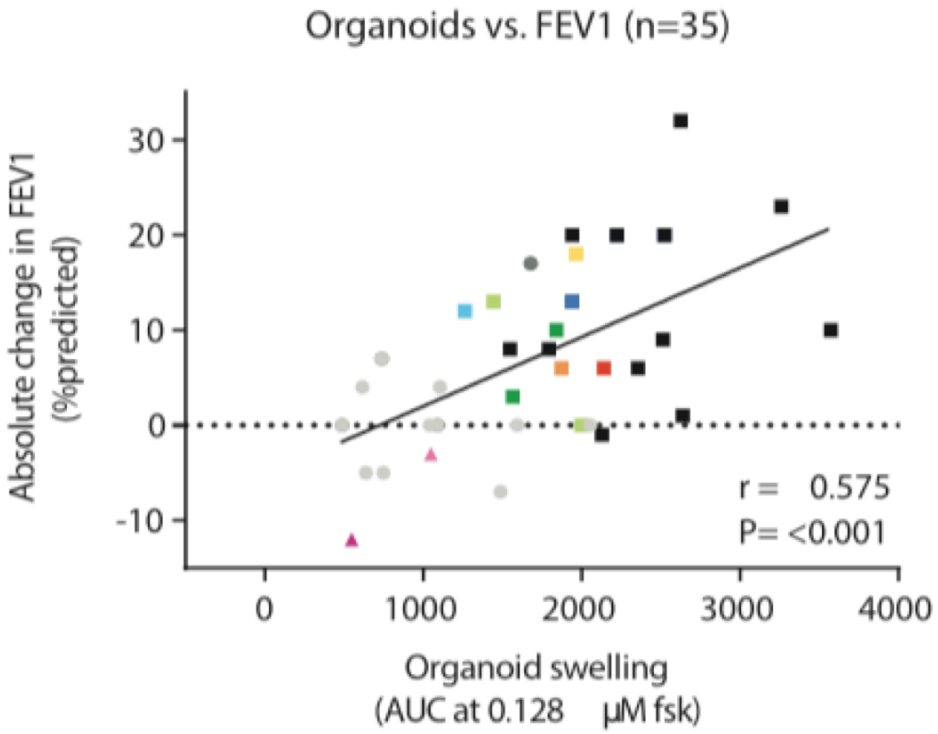
SWELLING (FUNCTION) ASSAY




NANOSTRING (MRNA) ASSAY



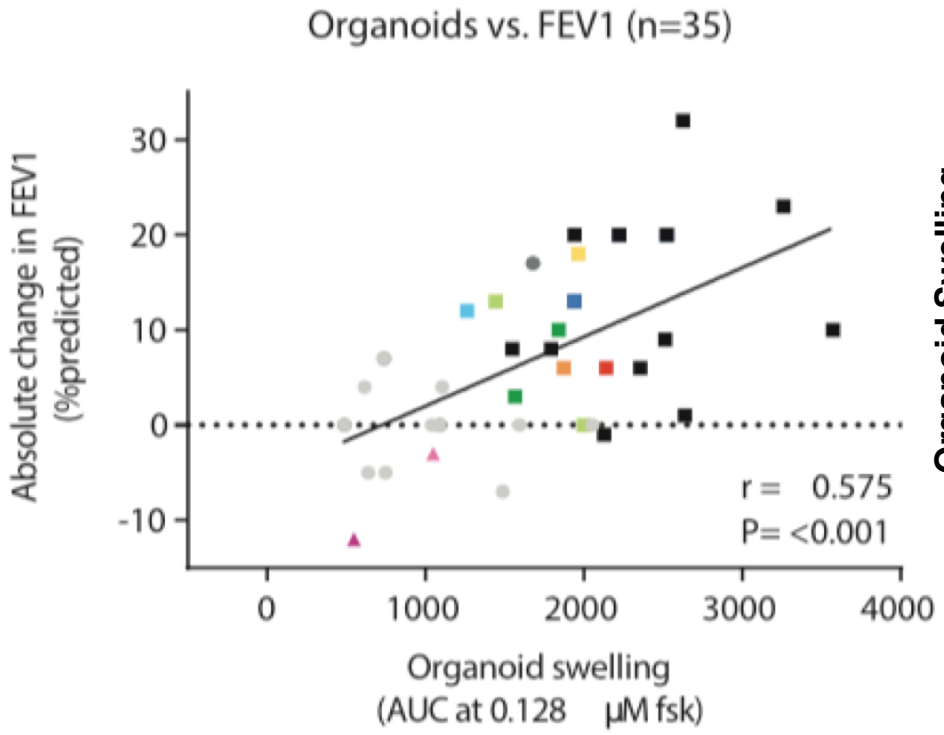
# New HUB Organoid Data Correlates with Clinical Response

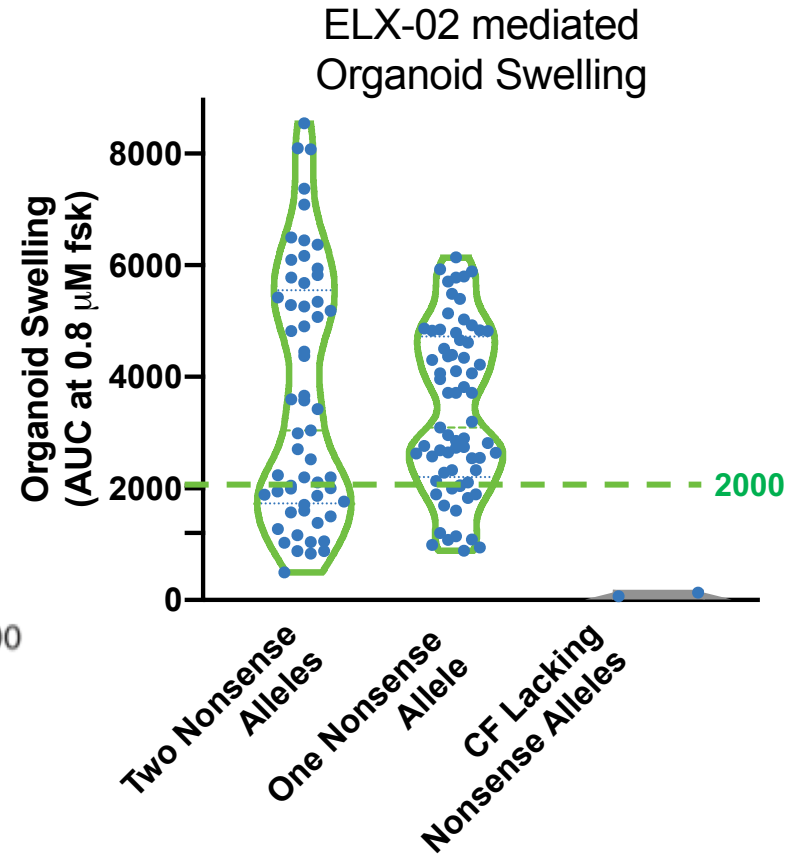



- FEV1 response correlates with organoid swelling in samples collected across multiple clinical trials.
  - Genistein & Curcumin (circles)
  - Ivacaftor (squares)
  - Lumacaftor & Ivacaftor (triangles)
- Organoid results correlate with sweat chloride change
  - (r = -0.708, p<0.001)

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

# ELX-02 Response in Organoids Compares Favorably to Published Results



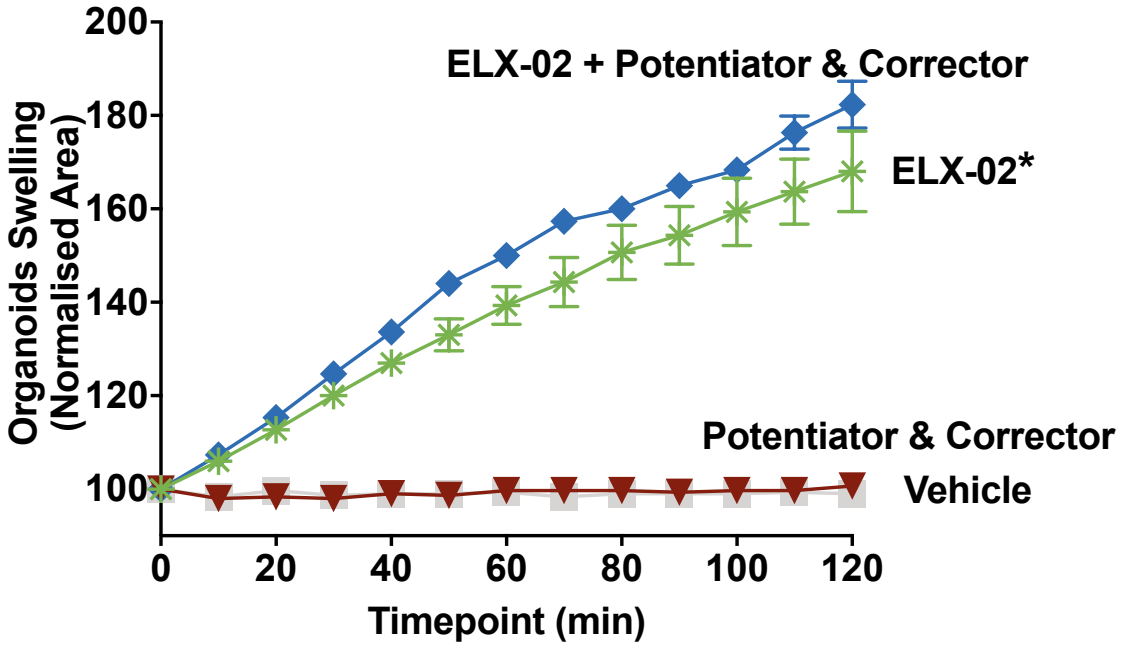




Berkers et al. Cell Reports (2019) Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis.

Eloxx data on file.

# Homozygous Nonsense Mutation (G542X)

## Cystic Fibrosis Organoid Responsive to ELX-02, Enhanced by Combination

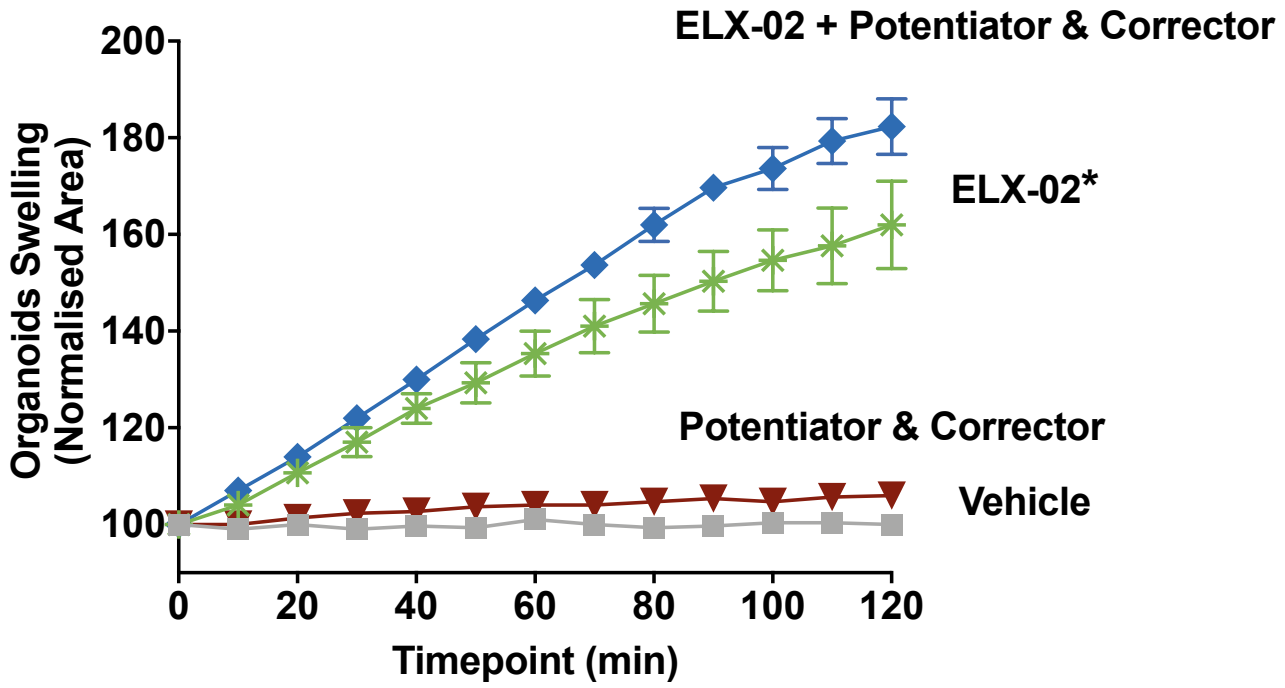



* Source: European Cystic Fibrosis Society 41st Conference, Belgrade, Serbia, June 2018

- 100 µg/mL ELX-02
- Error Bars represent SEM
- $p < 0.0001$ vs Vehicle, Potentiator & Corrector. N.S. vs. ELX-02 + Potentiator & Corrector by Ordinary One Way ANOVA With Sidak's Multiple Comparison Testing on AUC transformations

# Complex Heterozygous Nonsense Mutation (G542X:R1066C missense)

## Cystic Fibrosis Organoid Responsive to ELX-02, Enhanced by Combination

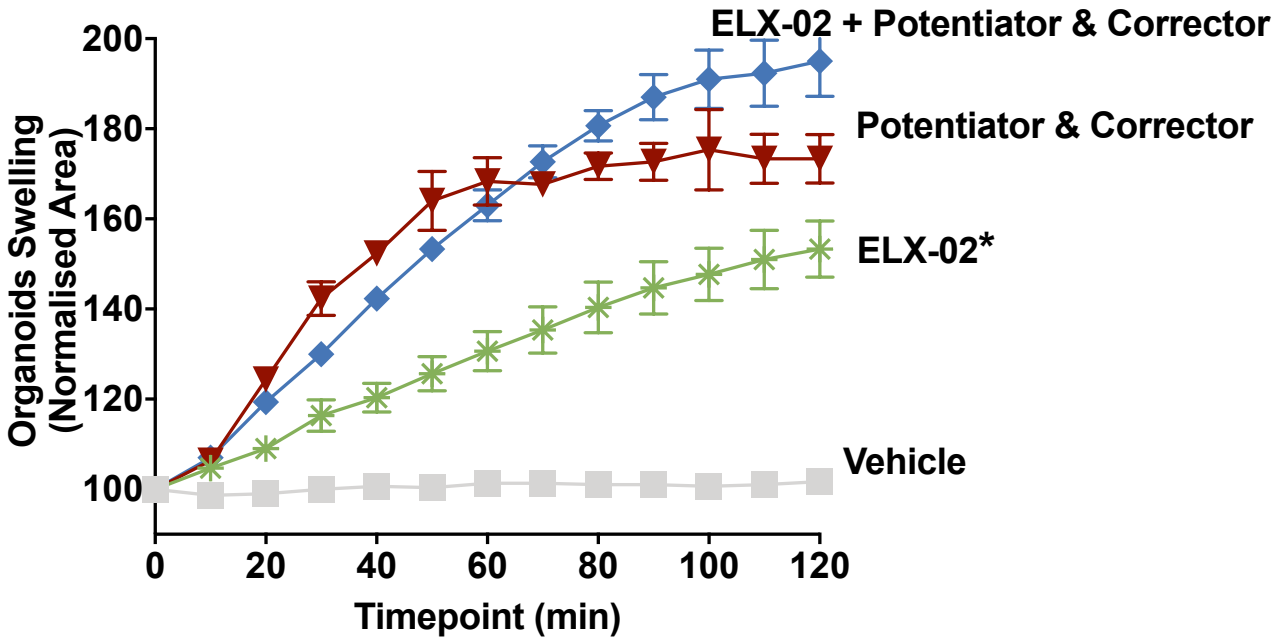



*Source: European Cystic Fibrosis Society 41st Conference, Belgrade, Serbia, June 2018

- 100 µg/mL ELX-02
- Error bars represent SEM
- p<0.0001 ELX-02 vs Potentiator & Corrector, Vehicle, p<0.05 ELX-02 vs Triple treatment by One Way Anova with Sidak's Multiple Comparison Testing on AUC transformations.

# Complex Heterozygous Nonsense Mutation (G542X:F508del)

## Cystic Fibrosis Organoid Responsive to ELX-02, Enhanced by Combination



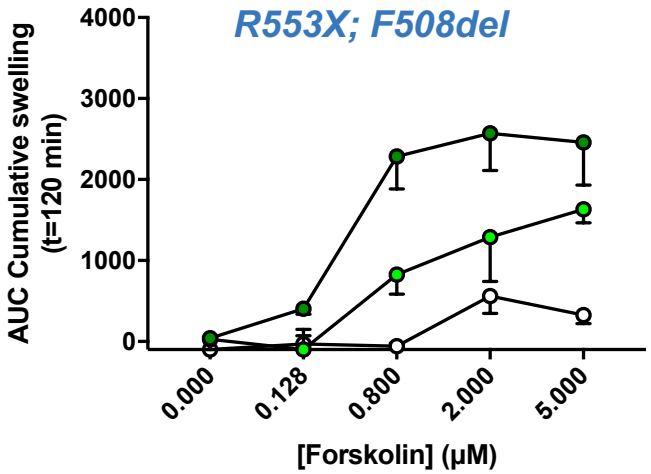

*Source: European Cystic Fibrosis Society 41st Conference, Belgrade, Serbia, June 2018

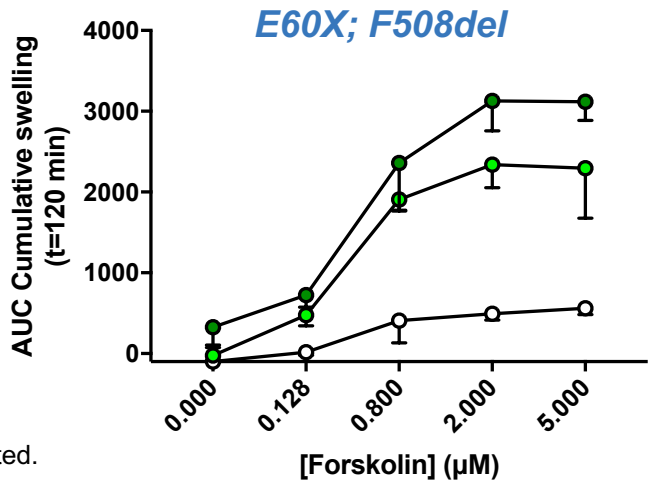
- 100 µg/mL ELX-02
- Error bars represent SEM
- p=0.00012 ELX-02 vs Potentiator & Corrector, p=0.0006 ELX-02 vs Vehicle, ELX-02 vs ELX-02+ Potentiator & Corrector by One Way Anova with Sidak's Multiple Comparison Testing on AUC transformations.

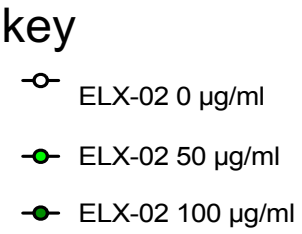
# ELX-02 Organoid Response is Observed Across a Range of CF Genotypes

- *G542X; G542X*
- *G542X; F508del*
- *G542X; R1066C*
- *R1162X; F508del*
- *G542X; W1282X*
- *W1282X; W1282X*
- ***R553X; F508del***
- ***E60X; F508del***

## New Genotypes



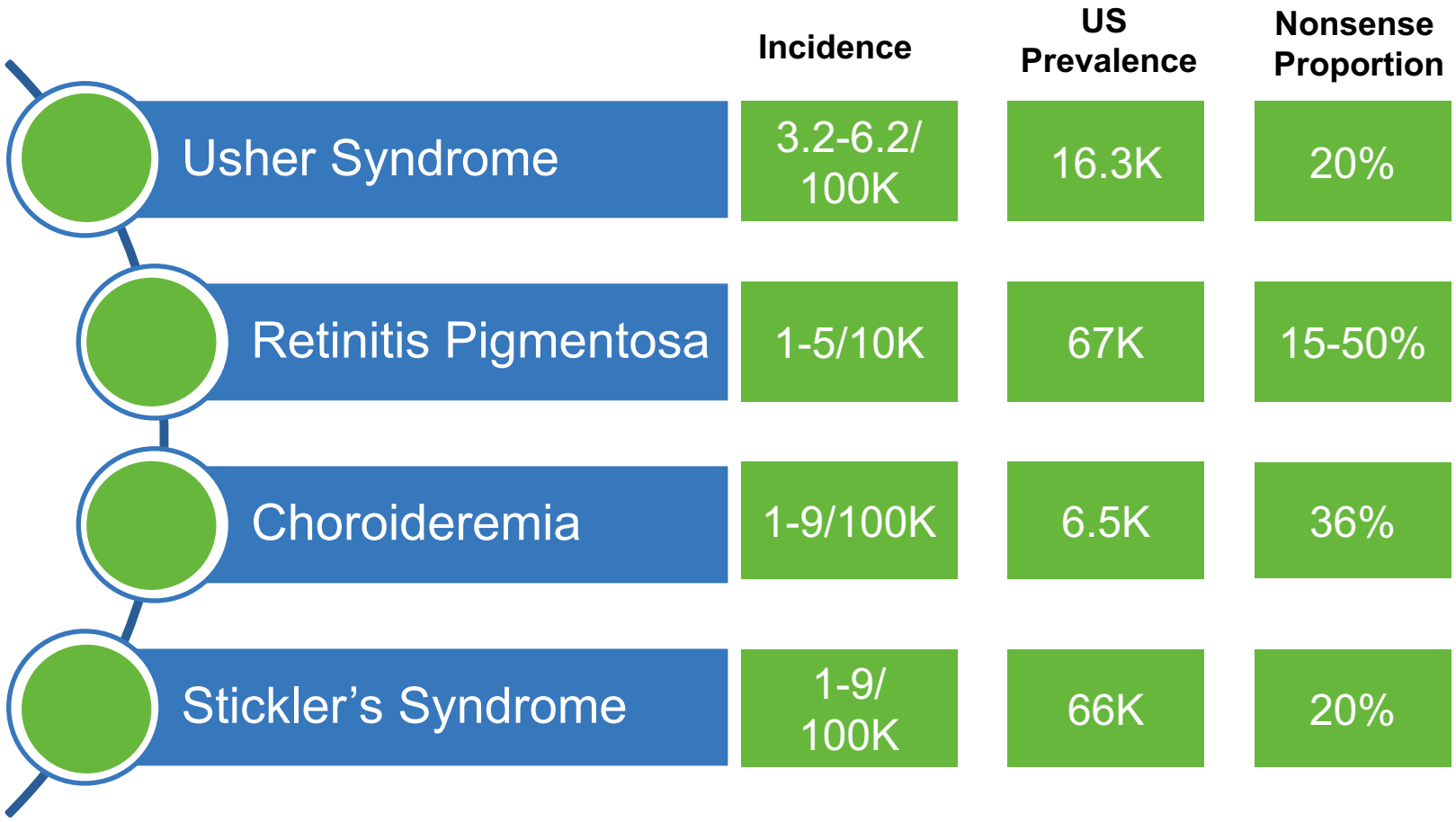




Eloxx data on file
Data from multiple individuals with the same genotypes also collected.

# Clinical Update for ELX-02 Phase 2 in Cystic Fibrosis

- ✓ **Orphan Drug Designation granted by EMA**
- ✓ **Clinical Trial Application (CTA) for Phase 2 Study received final approved by the FAMHP in Belgium**
- **Expanding MAD Study**
  - ✓ **6th cohort initiated in Belgium**
  - **Completion in 1H2019 with final cohort in US**
- **Engaging with investigators on a protocol for Phase 2 to insure rapid execution**
  - **No more than 24 patients**
  - **Will evaluate changes in sweat chloride at ascending doses**
  - **Planned enrollment will focus on patients with G542X nonsense mutation on one (complex heterozygote) or both alleles (homozygote)**
- **Expect Topline Cystic Fibrosis Phase 2 data in 2019**
- **EU Basic Science Meeting March 27th New Data**

# Substantial Opportunities in Inherited Retinal Diseases




Population values from National Organization for Rare Disorders (NORD) and Orphanet
Han et al, Korean J Pediatr 2016.; Wilkin et al, Am J Med Genet 2000; Freund et al, Mol Genet Genomic Med 2016; Aparisi et al, Orphan J Rare Dis 2014

# Inherited Retinal Disease Program Initiated

- **Advancing Several Compounds from our Library**
- **Currently in IND-Enabling Studies**
  - **Demonstrated positive activity on nonsense mutations across a variety of inherited retinal disorders**
  - **Favorable tolerability profile**
  - **Support the use for intravitreal injection**
- **Development Focus on Ushers Syndrome, Leber's Congenital Amaurosis, or Other Forms of Retinitis Pigmentosa Caused by Nonsense Mutations**
- **Wide Ranging Partnership with the Foundation Fighting Blindness**
  - **Partnership includes broad scientific engagement to support Eloxx's ocular portfolio development**
- **ARVO Meeting May 2, 2019 New Data**

# Usher Syndrome

- **No drugs approved or in late-stage development for nonsense variants**
- **Significant unmet medical need for nonsense forms**
  - **Over 4,000 patients in North America alone**
- **Academic collaborations have demonstrated activity with Eloxx Novel Library Compounds**
  - **Read through protein expression In vitro retinal compatibility**
- **Encouraging IND enabling studies supporting preservation of electroretinogram (ERG) and retinal histology**

# Eloxx Pharmaceutical Highlights

- **Experienced Leadership Team**
  - Appointment of Dr. Susan Schneider SVP Ophthalmology
- **ELX-02 Clinical Progress**
  - EU Cystic Fibrosis Basic Science Meeting March 27th New Data
  - On Track for Completion of Phase 1b MAD 1H2019
  - Expect Topline Cystic Fibrosis Phase 2 in 2019
- **Building Ophthalmology Inherited Retinal Disorder Program**
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  - IND Enabling Studies Focusing on Usher's Syndrome
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- **Actively Developing Opportunities for Collaboration to Advance Full Pipeline and Expand Therapeutic Programs**

Eloxx Pharmaceuticals

Thank you.

**Eloxx Investor Presentation**

**March 2019**