



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

2019 Cantor Global Healthcare Conference
October 3, 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**
- **Top Line ELX-02 Phase 2 Data in Cystic Fibrosis and Cystinosis in 2019**
 - **Phase 2 ELX-02 Clinical Trial in Cystic Fibrosis**
 - **Cystic Fibrosis Foundation Provided Funding & Additional Support, Protocol Sanctioned by the Cystic Fibrosis Therapeutics Development Network**
 - **Dr. Ahmet Uluer, Director of Adult Cystic Fibrosis Program, Boston Children's Hospital, U.S. Lead Investigator**
 - **Dr. Eitan Kerem, Head of Division of Pediatrics, Children's Hospital, Hadassah Medical Center, Global Lead Investigator**
 - **Phase 2 ELX-02 Clinical Trial in Cystinosis**
 - **Non-dilutive funding from Genome Quebec and Genome Canada**
 - **Dr. Paul Goodyer, Professor of Pediatrics, McGill University, Principal Investigator**
- **New Indication Screening Ongoing (Eye, Kidney, Lung)**
- **Actively Developing Business Development Opportunities to Advance Full Pipeline and Expand Therapeutic Programs**

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

Ben Zeev^{1,2}, Igor Nudelmann¹, Yair Anikster¹, Amos J. Simon³, Ninette Ziv^{1,2,3}, Timor Baasov¹, Eva Gak^{1,2,4}

¹ Center, Tel Hashomer, Israel, ² Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, ³ Edmond and Lily Safra Center, Tel Hashomer, Israel, ⁴ The Edith and Joseph Fisher Enzyme Inhibitors Laboratory, Schulich Faculty of Chemistry, Technion – Israel Institute of Technology, Haifa, Israel

Genetic mutations in the X-linked methyl CpG-binding protein 2 (*MECP2*) comprise a significant proportion of Rett syndrome (RTT). Naturally occurring aminoglycosides, such as gentamicin, have been shown to suppress premature termination codons (PTCs) in various genetic disorders, however, their use in RTT is limited due to their toxicity. We have developed a novel synthetic aminoglycoside, NB54, which is highly effective in suppressing PTCs in fibroblasts from RTT patients.

Public Access

Author Manuscript

Mol 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.gymg.2013.12.007.

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

Ami Gunn¹, Yanying Dai¹, Ming Du¹, Valery Belakhov², Jayakumar Kandasamy², Trenton R. Schoeb², Timor Baasov³, David M. Bedwell¹, and Kim M. Keeling¹

¹Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL, USA.

²The Edith and Joseph Enzyme Inhibitors Laboratory, Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel

³Department of Genetics, University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

Nonsense suppression therapy is a therapeutic approach to ameliorate genetic diseases caused by premature termination codons (PTCs). We have previously shown that long-term treatment with the synthetic aminoglycoside NB54 significantly reduces the levels of PTC-containing transcripts in fibroblasts from patients with MPS I-H.

Hum Genet (2007) 122:373–381
DOI 10.1007/s00439-007-0403-7

ORIGINAL INVESTIGATION

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

Annie Rebibo-Sabbah · Igor Nudelmann · Zahar M. Ahmed · Timor Baasov · Tamar Ben-Yosef

Received: 19 April 2007 / Accepted: 19 July 2007 / Published online: 25 July 2007
© Springer-Verlag 2007

Abstract Type I Usher syndrome (USH1) is a recessively inherited condition, characterized by profound prelingual deafness, vestibular ataxia, and progressive onset of retinitis pigmentosa (RP). While the auditory component of USH1 can be treated by cochlear implants, the vision component is not. We have previously shown that the synthetic aminoglycoside NB54 significantly reduces the levels of PTC-containing transcripts in fibroblasts from patients with USH1.

such possible therapeutic approach is suppression of nonsense mutations by small molecules such as aminoglycosides. We decided to test this approach as a potential therapy for RP in USH1 patients due to the same mutations. We treated fibroblasts from patients with USH1 with NB54 and found that it significantly reduced the levels of PTC-containing transcripts in fibroblasts from patients with USH1.

Hum Genet (2007) 122:373–381
DOI 10.1007/s00439-007-0403-7

RESEARCH REPORT

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

Maloto Kamei · Karina Kasperki · Maria Faller · Emílio J. Perleiros-Lawrence · Lívia Karsenguer · Valery Belakhov · Timor Baasov · John J. Hopwood · Doug A. Bruck

Received: 19 April 2003 / Revised: 11 August 2003 / Accepted: 25 September 2003 / Published online: 6 November 2003
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Abstract The premature stop codon mutations, Q70X and W402X, are the most common *α*-iduridase gene mutations in mucopolysaccharidosis type I (MPS I). We have previously shown that the synthetic aminoglycoside NB54 significantly reduces the levels of PTC-containing transcripts in fibroblasts from patients with MPS I.

through for the W402X mutation, while 4.6-fold increased read-through for the Q70X mutation. In addition, NB54 induced a 10-fold increase in the levels of PTC-containing transcripts in fibroblasts from patients with MPS I.

Novel ESRG Library has Demonstrated Activity across Multiple Orphan Diseases

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

Elisabeth R. Barton-Davis¹, Laurence Cordier¹, Daria I. Shoturma¹, Stuart E. Leland², and H. Lee Sweeney¹

¹Department of Physiology, and ²Institute for Human Gene Therapy, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
Address correspondence to: H. Lee Sweeney, A700 Richards Building, Department of Physiology, 3700 Hamlo University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-6085, USA. Phone: (215) 898-1100; Fax: (215) 898-0475; E-mail: lsweeney@mail.med.upenn.edu.

Received for publication July 14, 1999, and accepted July 16, 1999.

Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene that result in the absence of the dystrophin protein in skeletal muscle. A significant number of these mutations are premature stop codons. On the basis of the observation that aminoglycoside antibiotics induce read-through of premature stop codons in cultured cells, we tested the effect of these antibiotics on dystrophin function in *mdx* mice.

ORIGINAL RESEARCH

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

Xiaojiao Xue^{1,2}, Venkateshwar Mutyam³, Liping Tang³, Silpak Biewas³, Ming Du^{1,4}, Laura A. Jackson², Yanying Dai¹, Valery Belakhov², Moran Shalev³, Fuqian Chen³, Jochen Schacht³, Robert J. Bridges³, Timor Baasov¹, Jeong H. David M. Bedwell^{1,4,5,6,*}, and Steven M. Rowe^{1,4,6,*}

Departments of ¹Genetics, ²Medicine, ³Pediatrics, ⁴Cell Developmental and Integrative Biology, and ⁵Microbiology, and ⁶Gregory Fleming James Cystic Fibrosis Research Center, University of Alabama at Birmingham, Birmingham, Alabama; ⁷The Edith and Joseph Fisher Enzyme Inhibitors Laboratory, Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel; ⁸Kresge Hearing Research Institute, Department of Otolaryngology, University of Michigan Medical School, Ann Arbor, Michigan; and ⁹Department of Physiology and Biophysics, Rosalind Franklin University, North Chicago, Illinois

Abstract

New drugs are needed to enhance premature termination codon (PTC) suppression in the setting of cystic fibrosis (CF). We have previously shown that the synthetic aminoglycoside NB54 significantly reduces the levels of PTC-containing transcripts in fibroblasts from patients with CF.

synthetic aminoglycosides provide a 10-fold improvement in therapeutic index over gentamicin and other first-generation aminoglycosides. NB54 is a promising agent for the treatment of CF.

NIH-PA Author Manuscript

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.gymg.2011.10.005.

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

Dan Wang¹, Valery Belakhov², Jayakumar Kandasamy², Timor Baasov², Su-Chen Li³, Yu-Teh Li³, David M. Bedwell^{1,4}, and Kim M. Keeling¹

¹Department of Genetics, University of Alabama at Birmingham, Birmingham, AL 35294, USA

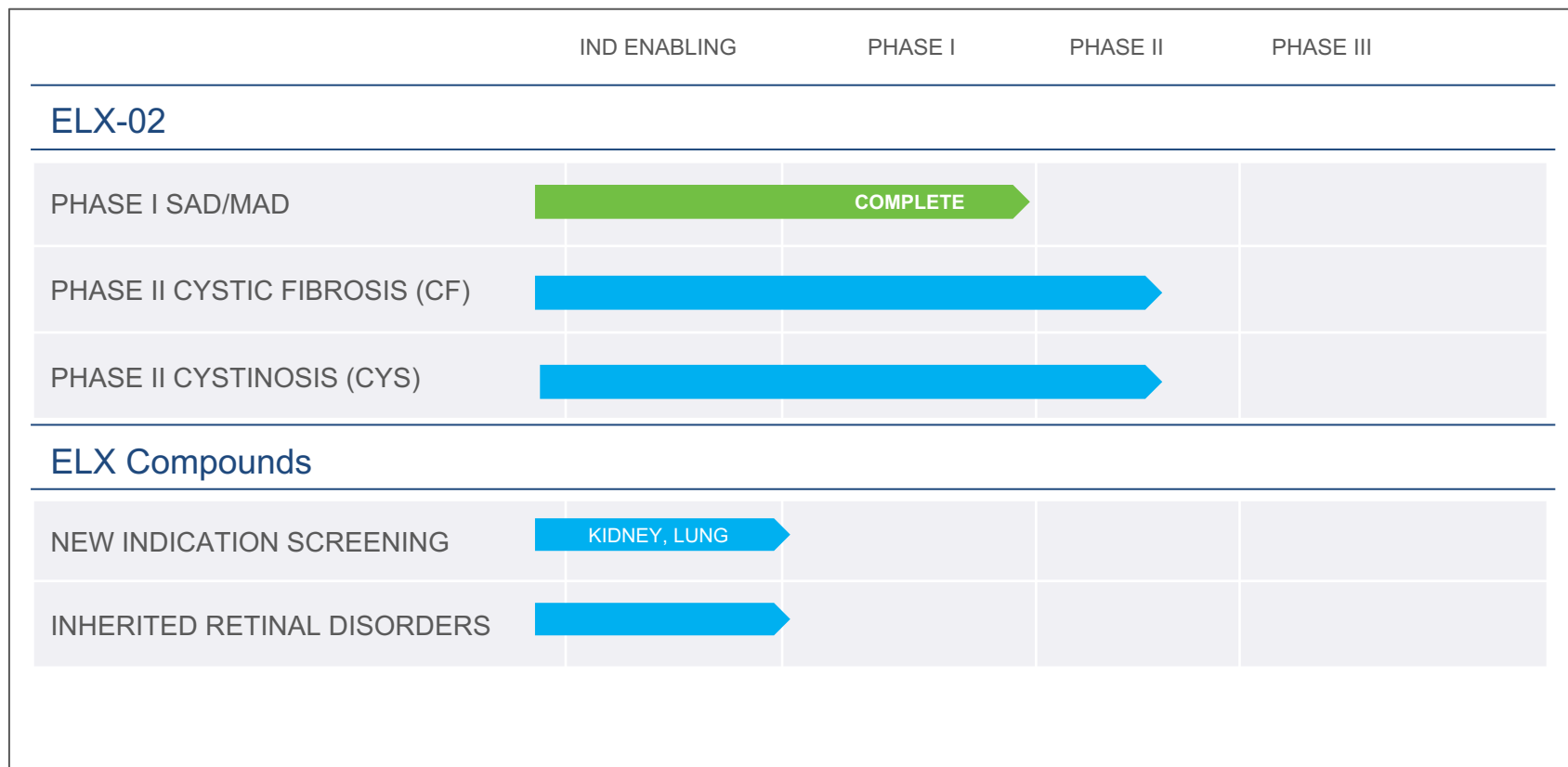
²The Edith and Joseph Enzyme Inhibitors Laboratory, Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel

³Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA

⁴Department of Physiology and Biophysics, Rosalind Franklin University, North Chicago, Illinois

Eloxx Pipeline

Phase 2 Top Line Data This Year in CF and Cystinosis



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 ECSF 2019
- Full data presentations at NACFC Oct. 31- Nov. 2, 2019

MAD

(multiple ascending dose)

- Full data presentations at NACFC Oct/Nov 2019
- CSR and manuscript to follow

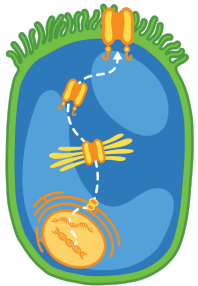
Renal Impairment

- Full data presentations at 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)

ELX-02: Preclinical Data De-Risks 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-through 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
 - Cystinosis trial focuses on nonsense mutations, like W138X

Our Orphan Drug Programs Have Strong Advocacy Support



GenomeQuébec



**CYSTIC FIBROSIS
FOUNDATION**

ADDING TOMORROWS



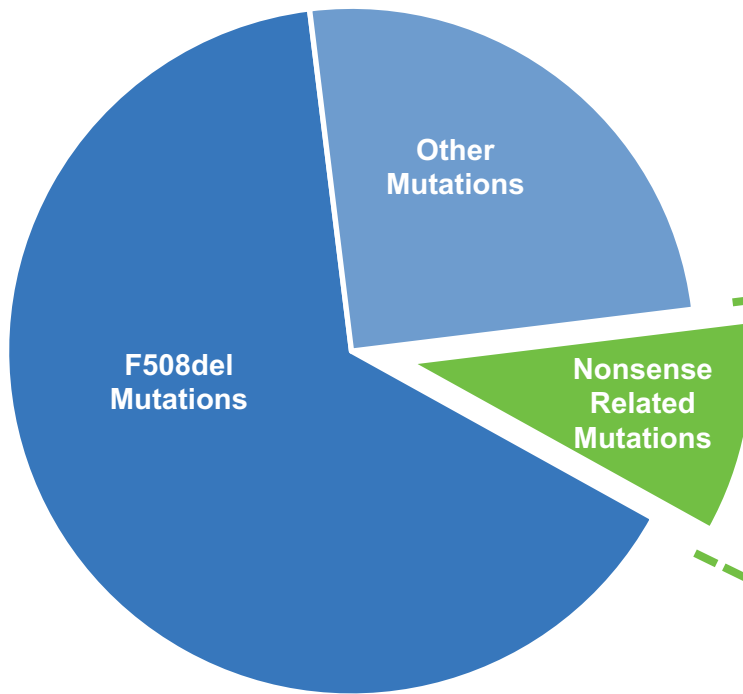
GenomeCanada



cystinosis
RESEARCH FOUNDATION
RESEARCH • HOPE • CURE

Cystic Fibrosis Nonsense Mutation Patients Represent a Key Unmet Need Population

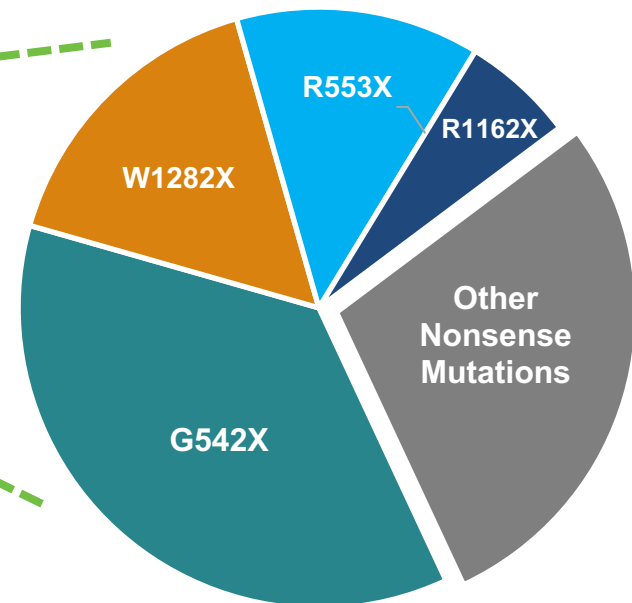
GLOBAL CYSTIC FIBROSIS PATIENTS
BY MUTATION/GENOTYPE



10 -13%

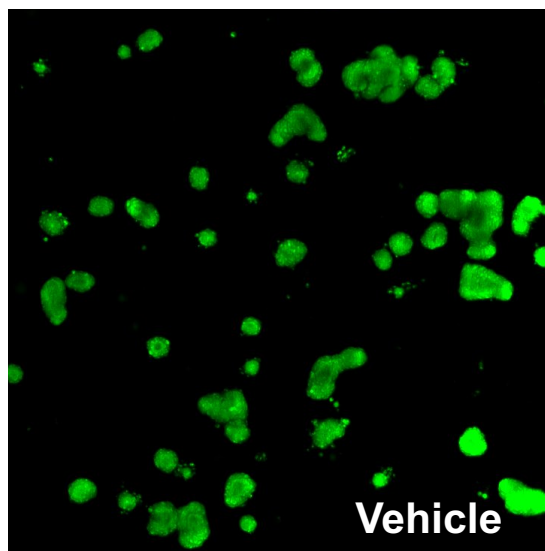
No Currently Approved Drugs
To Treat CFTR Nonsense Mutations

CFTR NONSENSE
MUTATION SUBTYPES

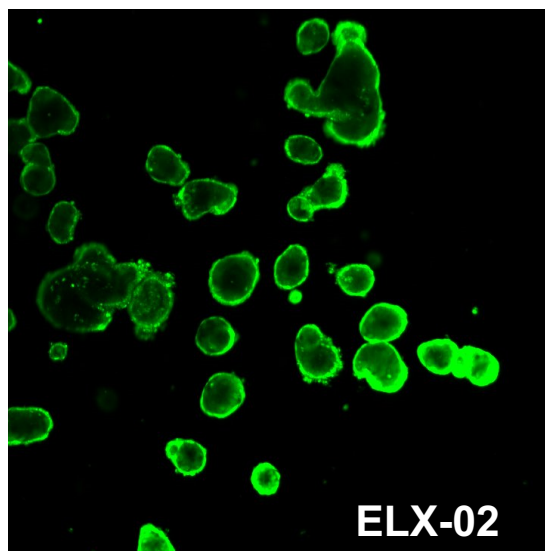


Organoid Swelling Assay Demonstrates CFTR Function

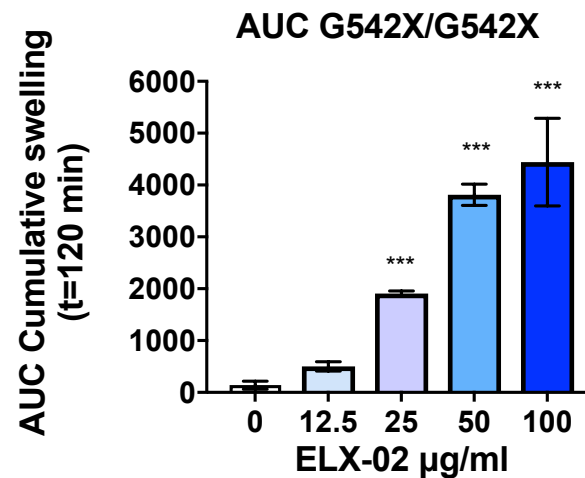
Cystic Fibrosis Organoid dose-responsive swelling assay response



Patient Organoid without drug treatment:
No Swelling of Organoids

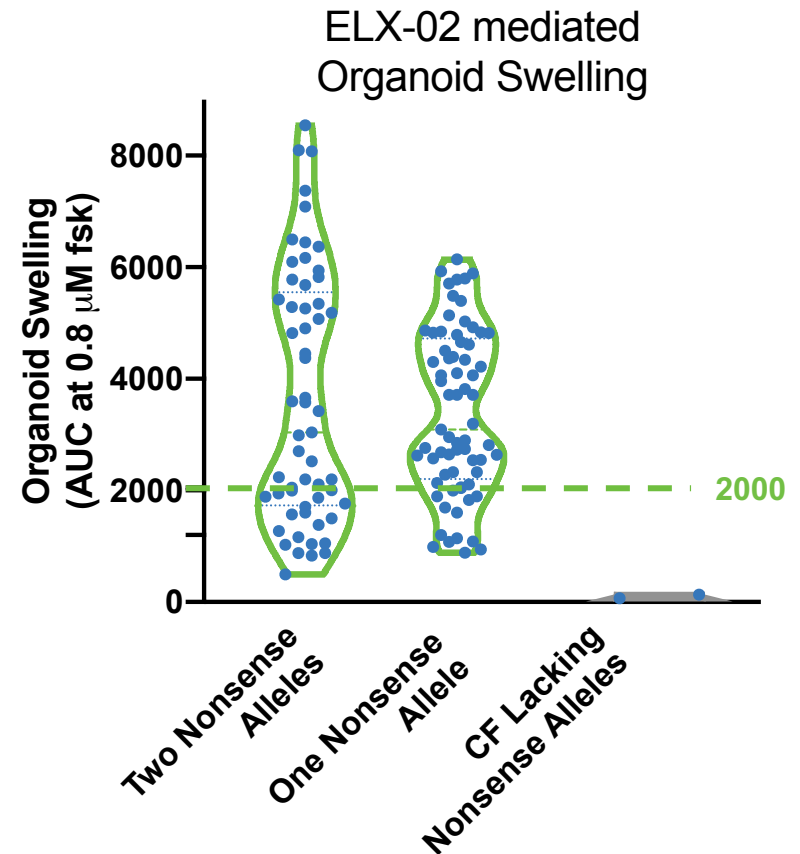
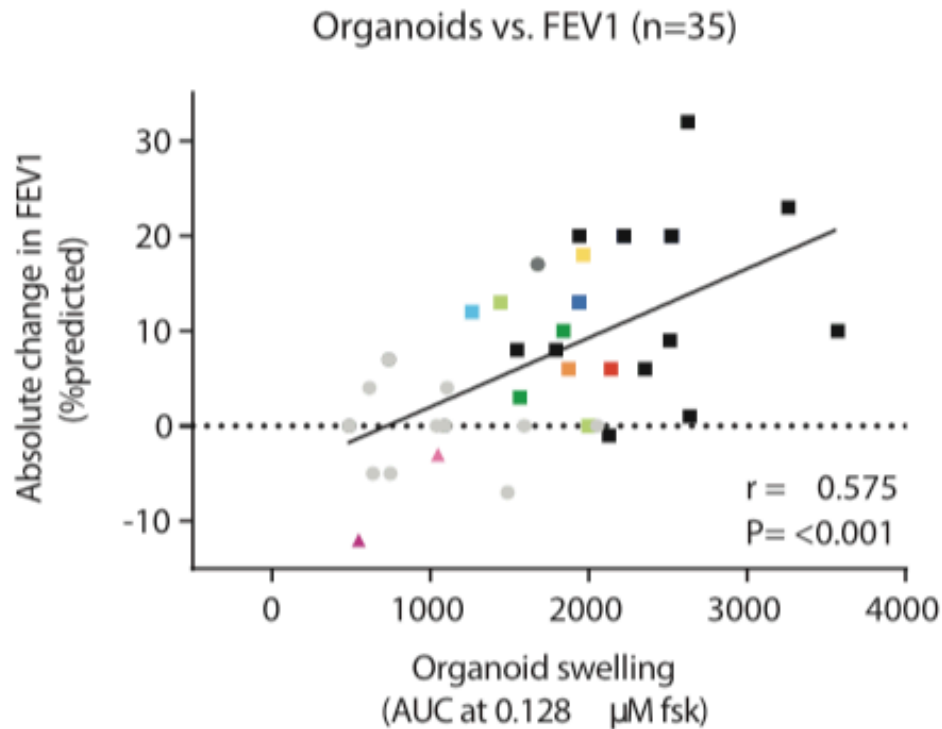


Patient Organoid with ELX-02 treatment:
Swelling of Organoids



Swelling quantification of patient organoid
with ELX-02 treatment.

ELX-02 Response in Organoids Compares Favorably to Published Results

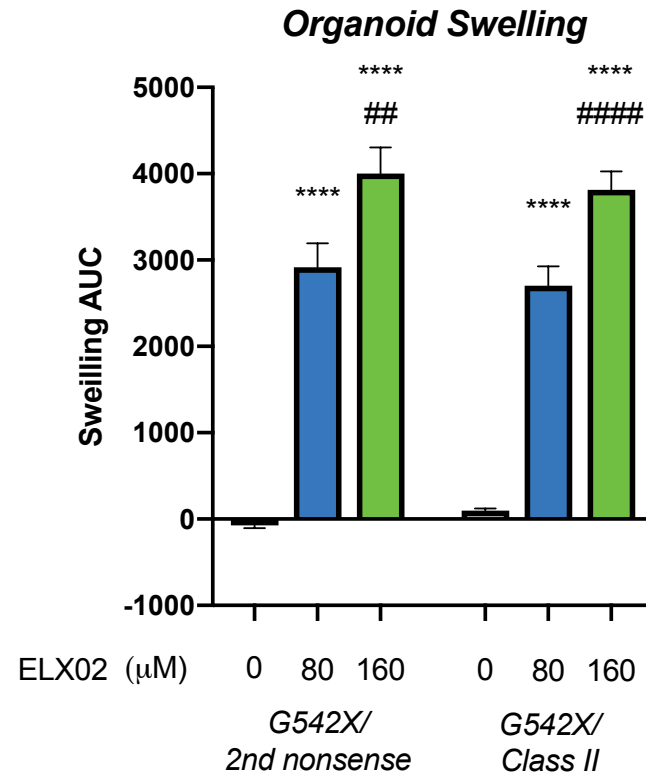


Berkers et al. Cell Reports (2019) Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis.

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 μ M 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.

ELX-02: Phase 2 CF Top Line in 2019

- **Phase 2 Clinical Trial Program**

- ✓ Cystic Fibrosis Foundation Provided Funding, Protocol Sanctioned by the Cystic Fibrosis Therapeutics Development Network
- ✓ Clinical Trial Application (CTA) approved, EU CFS “high priority” for Phase 2 Protocol
- ✓ Dr. Ahmet Uluer, Director, Adult Cystic Fibrosis Program at Boston Children’s Hospital, US Lead Investigator
- ✓ Dr. Eitan Kerem, Head of Division of Pediatrics, Children’s Hospital, Hadassah Medical Center, Global Lead Investigator

- **Phase 2 Protocol**

- Enrolling up to 24 patients with the G542X nonsense mutation on one or both alleles in the U.S., Europe and Israel
- 4 increasing doses of ELX-02 ranging from 0.3 up to 3.0 mg/kg/day
- Measuring changes in sweat chloride consistent with other Phase 2 trials for approved drugs

Phase 2 Cystic Fibrosis – Trial Design



Population

- Up to 24 CF patients with a G542X mutation on one or both alleles (includes up to 8 in US)

Primary Outcome Measures

- Safety, tolerability, PK and pharmacodynamics of multiple doses of ELX-02

Secondary Outcome Measures

- Changes from baseline in sweat chloride levels and FEV1 following ELX-02

Locations

- USA, Israel, Germany, Belgium

North American Cystic Fibrosis Conference (NACFC)

October 31 - November 2, 2019



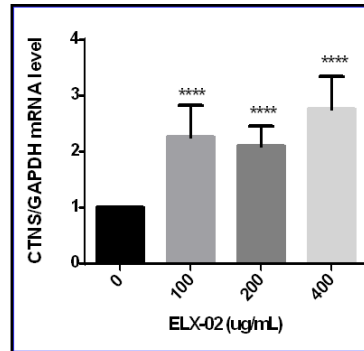
“Investigational Drug ELX-02 Mediates CFTR Nonsense Mutation Read-through To Increase *CFTR* mRNA CFTR Protein Translation and CFTR Function”
November 1, 2019 2:15 p.m. -3:50 p.m. CDT ORAL Workshop: New & Emerging Therapies to Correct the Basic Defect”

“Pharmacokinetics, Safety, and Tolerability of Multiple Ascending Doses of ELX-02 in Healthy Volunteers, a Potential Treatment for Cystic Fibrosis Caused by Nonsense Mutations” **October 31, 2019 11:15 a.m. – 1:45 p.m. CDT**
POSTER Session 1

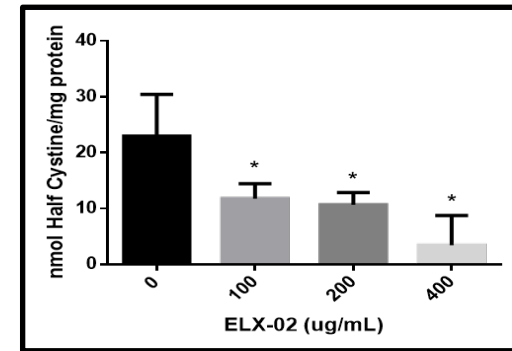
“Pharmacokinetics, Safety, and Tolerability of Single Ascending Doses of ELX-02 in Healthy Volunteers, a Potential Treatment for Cystic Fibrosis Caused by Nonsense Mutations” **October 31, 2019 11:15 a.m. – 1:45 p.m. CDT**
POSTER Session 1

ELX-02: Supportive Preclinical Nephropathic Cystinosis Data

in vitro model
CTNS^{W138X/W138X}
fibroblasts



Nonsense-mediated mRNA decay

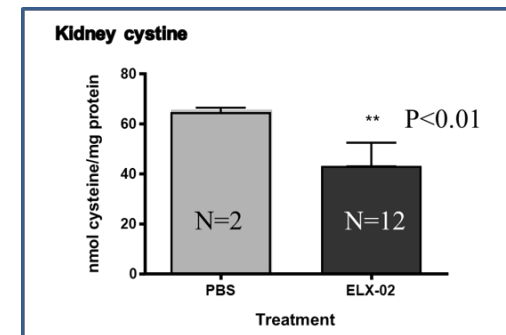


Cystine Accumulation



CTNS^{Y226X/Y226X} knock-in

14TH ANNUAL
WORLDsymposium™
February 5-9, 2018
We're Organizing Research on Lysosomal Diseases



Cystine Accumulation

ELX-02: Phase 2 Cystinosis Top Line in 2019

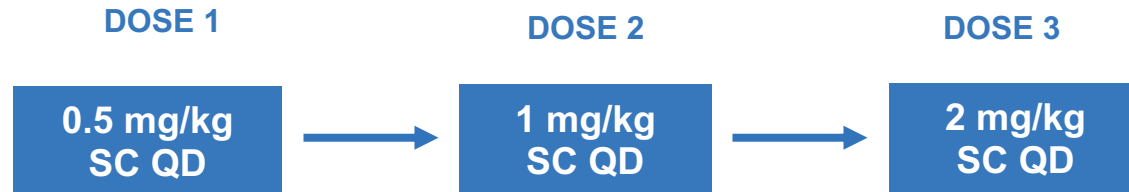
- **Phase 2 Clinical Trial Program**

- ✓ Enrolling in Canada
- ✓ Non-dilutive funding from Genome Quebec and Genome Canada
- ✓ Cystinosis Research Foundation provided funding for preclinical phase
- ✓ Dr. Paul Goodyer, Professor of Pediatrics at McGill University is the Principal Investigator

- **Phase 2 Protocol**

- Enrolling up to 6 patients with nephropathic cystinosis with at least 1 nonsense mutation in the cystinosis gene
- Three increasing doses of ELX-02 ranging from 0.3 up to 2.0 mg/kg/day
- Measuring the dose-dependent effect of ELX-02 on cysteine levels in white blood cells

Nephropathic Cystinosis Study Design (EL-003)



ClinicalTrials.gov Identifier: NCT04069260

Population

- Nephropathic cystinosis participants with biallelic CTNS mutations, including at least one nonsense mutation

Primary outcome measures

- Safety, tolerability, PK and pharmacodynamics of multiple doses of ELX-02

Secondary outcome measures

- Changes from baseline in white blood cell cystine levels following ELX-02

American Society of Nephrology (ASN) Kidney Week Conference Abstracts November 5-10, 2019

KIDNEYWEEK²⁰¹⁹

Washington, DC • Nov. 5 – 10

“An open label-single dose, parallel-group study to evaluate the effects of renal impairment on the pharmacokinetics of ELX-02: Results from subjects with mild and moderate renal impairment” - November 7, 2019
10:00 a.m. – 12:00 pm

“Cystinosis nonsense mutation read-through mediated by ELX-02 restores protein function using in vitro and in vivo models” - November 7, 2019
10:00 a.m. – 12:00 pm

Rare Kidney Diseases



- **> 150 identified Rare Kidney Diseases**
- **Overall Prevalence: 60-80 cases per 100,000**
- **Fifth most common cause of ESRD**

Patients with inherited kidney disorders rarely die
(many progress to renal transplantation)

Results in poor health, low quality of life, multisystemic complications.

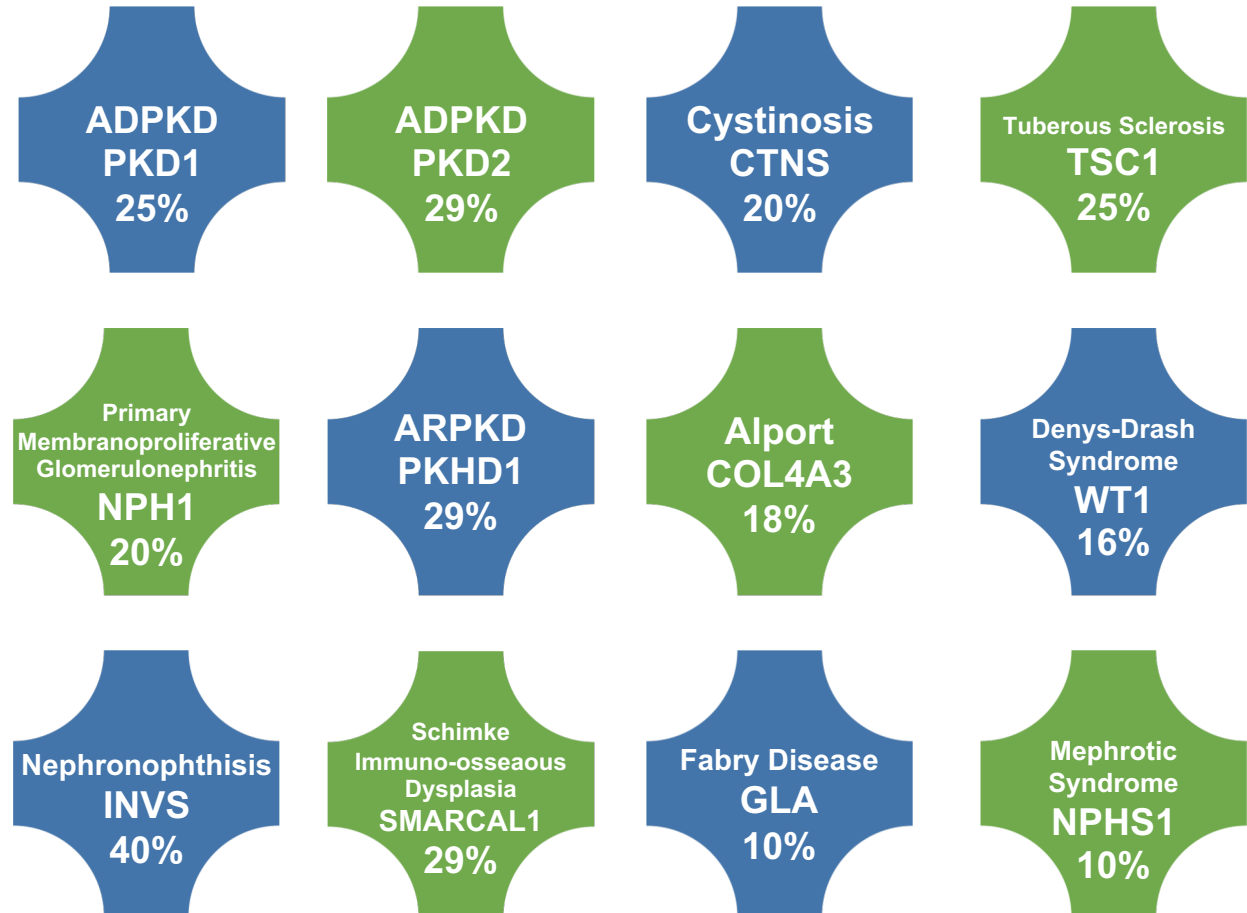
Devuyst & Gauy-Woodford - KDIGO Conference (2016)

Nephropathic cystinosis is an autosomal recessive storage disease caused by defective transport of cystine out of lysosomes. The renal tubular damage of cystinosis, begins at 6 to 12 months of age, glomerular damage generally becomes apparent by 2 to 5 years of age and results in end-stage renal disease by 9 to 10 years of age unless cystine-depleting therapy is initiated early in life. Renal transplantation, often by age of 20, has transformed cystinosis from an exclusively pediatric disease to one that affects individuals up to (and potentially beyond) 50 years of age.

Nonsense mutations are an important genetic variation in a wide range of rare kidney disorders including: Nephropathic Cystinosis, Autosomal Dominant Polycystic Kidney Disease, Cystinuria, and others

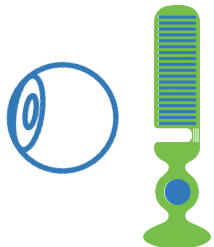
Nephrology NSM mediated disease opportunities

Inherited Disease
Target Gene
NSM %



Source: Torra et al, UGA hopping: a sport for nephrologists too? Nephrol Dial Transplant (2010) 25: 2391–2395

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



- Growing team of ophthalmic expertise
- Support from the FFB and Research Community

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- **Top Line ELX-02 Phase 2 Data in Cystic Fibrosis and Cystinosis in 2019**
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 - **Dr. Eitan Kerem, Head of Division of Pediatrics, Children's Hospital, Hadassah Medical Center, Global Lead Investigator**
 - **Phase 2 ELX-02 Clinical Trial in Cystinosis**
 - **Dr. Paul Goodyer, Professor of Pediatrics, McGill University, Principal Investigator**
 - **Non-dilutive funding from Genome Quebec and Genome Canada**
- **Reported Cash & Cash Equivalents at June 30, 2019 of \$76.3M Funded through Top Line Data and into 2021**



Thank you.

2019 Cantor Global Healthcare Conference
October 3, 2019