# Larimar Therapeutics

## Corporate Presentation

July 2021

# Forward Looking Statements

This presentation contains forward-looking statements that are based on the beliefs and assumptions of Larimar Therapeutics, Inc. (the "Company") and on information currently available to management. All statements contained in this presentation other than statements of historical fact are forward-looking statements, including but not limited to statements regarding the expectations and assumptions regarding the future of the Company's business, including its ability to resolve the clinical hold by the FDA related to CTI-1601, the Company's ability to develop and commercialize CTI-1601 and other planned product candidates, the Company's planned research and development efforts, and other matters regarding the Company's business strategies, use of capital, results of operations and financial position, and plans and objectives for future operations.

In some cases, you can identify forward-looking statements by the words "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue," "ongoing" or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. These statements involve risks, uncertainties and other factors that may cause actual results, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. These risks, uncertainties and other factors include, among others, the Company's ability to successfully engage with the FDA and satisfactorily respond to requests from the FDA for further information and data regarding CTI-1601, the timing and outcome of Larimar's planned interactions with the FDA, including the clinical hold on CTI-1601, the success, cost and timing of the Company's product development activities, non-clinical studies and clinical trials, including CTI-1601 clinical milestones; that clinical trial results may differ from final clinical trial results, that earlier non-clinical and clinical data and testing of CTI-1601 may not be predictive of the results or success of clinical trials, and that clinical trial data are subject to differing interpretations and assessments; the ongoing impact of the COVID-19 pandemic on the Company's clinical trials, manufacturing, regulatory and nonclinical study timelines, ability to raise additional capital and general economic conditions; the Company's ability to optimize and scale CTI-1601's manufacturing process; the Company's ability to obtain regulatory approval for CTI-1601 and future product candidates; the Company's ability to develop sales and marketing capabilities, whether alone or with potential future collaborators, and to successfully commercialize any approved product candidates; the Company's ability to raise the necessary capital to conduct its product development activities; and other risks described in the filings made by the Company with the Securities and Exchange Commission (SEC), including but not limited to the Company's periodic reports, including the annual report on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K, filed with or furnished to the SEC and available at www.sec.gov. These forward-looking statements are based on a combination of facts and factors currently known by the Company and its projections of the future, about which it cannot be certain. As a result, the forward-looking statements may not prove to be accurate. These forward-looking statements are based on information currently available to us, and we assume no obligation to update any forward-looking statements, except as required by law.

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# Investment Highlights

**Clinical-stage biotechnology company with a novel protein replacement therapy platform**
Focused on addressing unmet needs in Friedreich's ataxia (FA) and other complex rare diseases based on a platform technology backed by a strong intellectual property portfolio

**Lead candidate: CTI-1601, a recombinant fusion protein designed to deliver frataxin to mitochondria**
Has Orphan Drug (US & EU), Rare Pediatric Disease (US), Fast Track (US) and PRIME (EU) designations for FA

**Double-blind, placebo-controlled Phase 1 proof-of-concept trials in FA patients complete**
Data show dose dependent increases in FXN levels from baseline compared to placebo in all evaluated tissues with daily dosing and that CTI-1601 was generally well tolerated when dosed for up to 13 days
-Clinical hold pending data from an ongoing 180-day NHP study as it relates to initiating additional clinical studies with CTI-1601

**Series A investment by Deerfield in Nov. 2016; went public through a reverse merger/PIPE in May 2020**
Shareholder base includes high-quality institutional investors

**Strong balance sheet**
~$81.4 million in cash as of March 31, 2021, with projected runway through the end of 2022
-Raised ~$20 million in gross proceeds in a June ATM transaction of ~ 2.3 million shares

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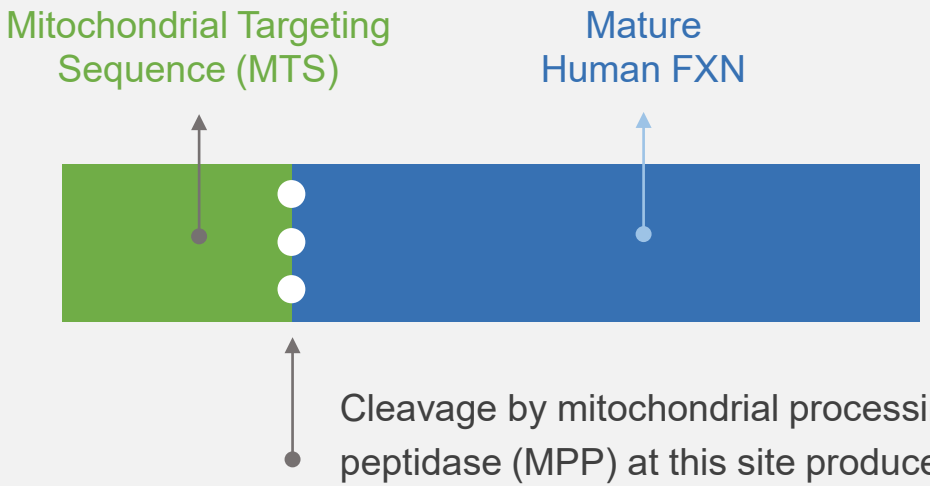
FXN: Frataxin

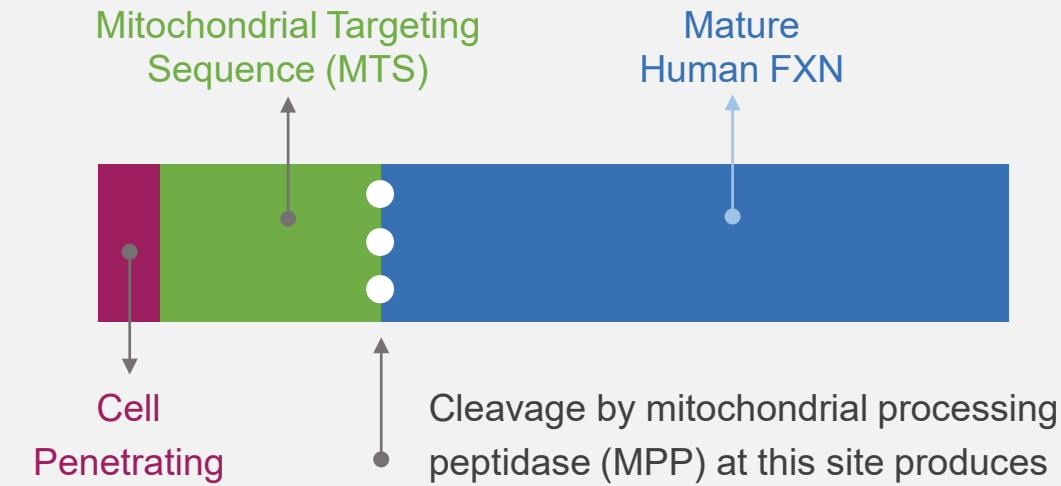
# CTI-1601 is Designed to Deliver Additional Frataxin (FXN)

## CTI-1601 Maintains the Cleavage Site Between the MTS and Mature Human FXN

### STRUCTURE OF ENDOGENOUS FXN




### STRUCTURE OF CTI-1601




**The maintenance of the cleavage site allows the CPP and MTS to be removed by mitochondrial processing peptidase to produce mature human FXN in the mitochondria**

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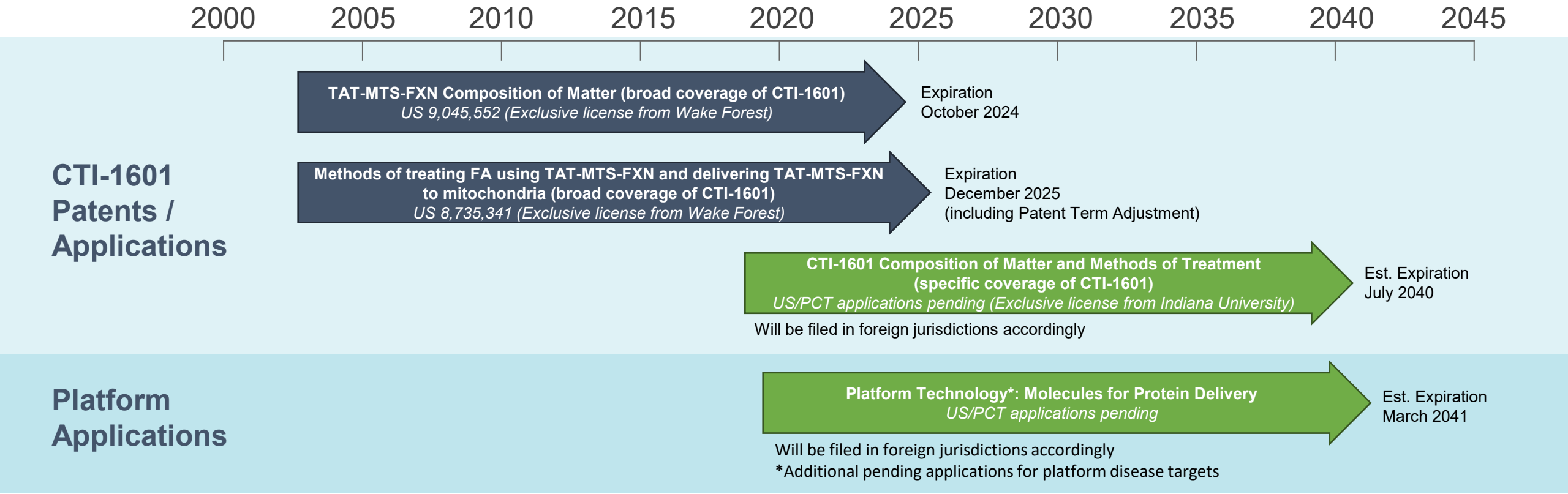
# Platform Technology is Supported by a Strong IP Portfolio

**Pending CTI-1601 patent application, if issued, extends IP into 2040**




## Additional CTI-1601 IP protection

- CTI-1601 pending applications cover key biomarkers, analytical tools and quantification methods
- CTI-1601 is eligible for **12 years of market exclusivity** upon approval in the US (independent of patents) and at least **10 years of market exclusivity** upon approval in Europe (independent of patents)

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Granted Pending

# Friedreich's Ataxia (FA)

## Rare and Progressive Disease

### Caused by genetic defect resulting in low levels of frataxin

- Patients with FA only produce ~20-40% of normal frataxin levels depending on the tissue, sampling technique, and assay considered[1]
- Affects ~5,000 patients in the U.S. & ~20,000 patients in the EU

### >70% of patients present before age 14

- Initial symptoms may include unsteady posture, frequent falling and progressive difficulty in walking
- By the time symptoms occur, heart damage may have already occurred
- Progressive disease: Symptoms worsen and patients are eventually confined to a wheelchair with speech becoming hesitant and jerky (often referred to as "scanning of speech")

### Life expectancy of 30-50 years

- Early death usually caused by heart disease

### No approved therapies available

- Current treatment options are limited to symptom management

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1. E.C. Deutsch et al. Molecular Genetics and Metabolism 101 (2010) 238–245

# Strong Relationship with FARA

**Company has strong relationship with Friedreich's Ataxia Research Alliance (FARA)**

- National, non-profit organization dedicated to the pursuit of scientific research leading to treatments and a cure for FA

**FARA provides industry with several key items**

- Assistance with patient recruitment and education
- Access to Global Patient Registry with demographic and clinical information on more than 1,000 FA patients
- Sponsored a Patient-Focused Drug Development Meeting in 2017 resulting in a publication titled "The Voice of the Patient"

FARA Friedreich's Ataxia Research Alliance

# Executive Summary of Phase 1 POC Data

| | |
|---|---|
| **Safety** | CTI-1601 appears to be generally well tolerated at doses up to 100 mg administered daily for 13 days |
| **Pharmacodynamics** | Daily dosing of CTI-1601 resulted in dose-dependent increases in FXN levels from baseline compared to placebo controls in all evaluated tissues |
| **Pharmacokinetics** | Pharmacokinetic analyses support evaluating a once-daily dosing regimen for CTI-1601 |
| **Conclusion** | Daily subcutaneous (SC) administration of 50mg and 100mg doses of CTI-1601 resulted in FXN levels in buccal cells that are at, or in excess of, those we would expect to see in phenotypically normal heterozygous carriers (who have FXN levels of ~50% of unaffected persons) |

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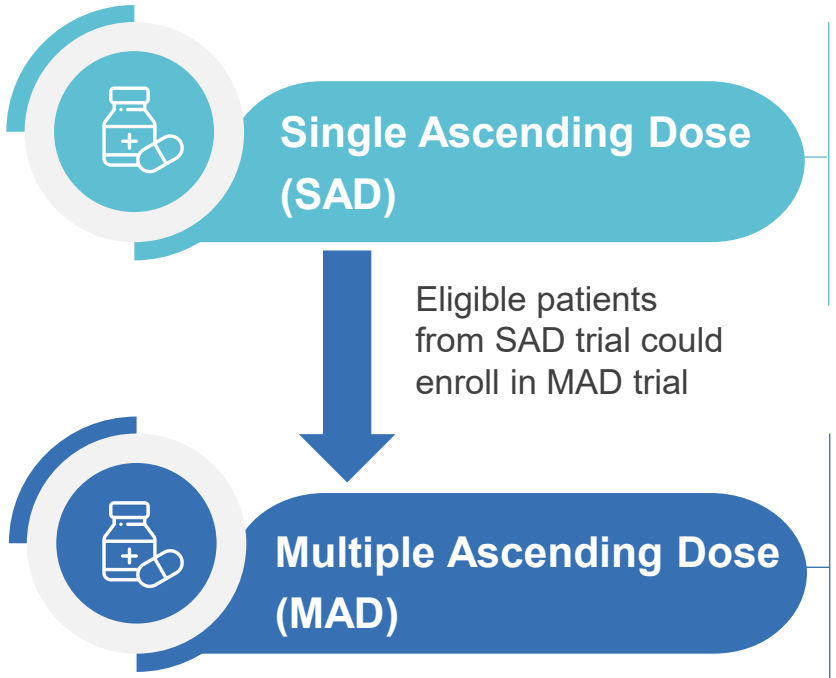
POC: Proof-of-concept

# CTI-1601: Phase 1 Clinical Program in Patients with FA

## Program consisted of double-blind, placebo controlled single- and multiple-ascending dose trials

**Phase 1 Development Plan**

- Two double-blind, placebo-controlled dosing trials in patients with FA
- Patient dosing began December 2019
- Safety Review Committee assessed all blinded data between each cohort to ensure patient safety




**Number of subjects:** 28

**Dose levels:** 25 mg, 50 mg, 75 mg and 100 mg (subcutaneous administration)

**Treatment Duration:** 1 day

**1º Endpoint:** Safety and tolerability

**2º Endpoints:** PK; PD; FXN levels; multiple exploratory

**Status:** Complete with analysis ongoing

**Number of Subjects:** 27

**Dose Range:** 25 mg, 50 mg, 100 mg (subcutaneous administration)

**Treatment Regimen:** Multiple increasing doses administered subcutaneously over 13 days

**1º Endpoint:** Safety and tolerability

**2º Endpoints:** PK; PD; FXN levels (buccal cells, platelets, optional skin biopsies); multiple exploratory

**Status:** Complete with analysis ongoing

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# MAD Trial Patient Enrollment

**16 out of 28 patients who participated in the SAD trial enrolled in the MAD trial**

| MAD Trial Patient Enrollment (n=27) | | |
|---|---|---|
| **Parameter** | **Statistic** | **Overall** |
| **Participated in SAD trial?** | | |
| Yes | n (%) | 16 (59%) |
| No | n (%) | 11 (41%) |
| **Cohort 1 (25 mg) Active vs. Placebo** | | |
| Active | n (%) | 6 (75%) |
| Placebo | n (%) | 2 (25%) |
| **Cohort 2 (50 mg) Active vs. Placebo** | | |
| Active | n (%) | 7 (78%) |
| Placebo | n (%) | 2 (22%) |
| **Cohort 3 (100 mg) Active vs. Placebo** | | |
| Active | n (%) | 7 (70%) |
| Placebo | n (%) | 3 (30%) |

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# Multiple Ascending Dose Study Design

## Treatment Schedules for Each Cohort

**Cohort 1 (25 mg; n = 8)**

**13-day Treatment Period**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

= Administration of CTI-1601 or placebo

= No Administration

**Cohort 2 (50 mg; n = 9)**

**13-day Treatment Period**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

= Administration of CTI-1601 or placebo

= No Administration

**Cohort 3 (100 mg n = 10)**

**13-day Treatment Period**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

= Administration of CTI-1601 or placebo

= No Administration

## FXN Level Sampling Days Presented for Each Cohort

| Cohort 1 Sampling Days | |
|---|---|
| **Buccal Cells** | Baseline, Day 4, Day 13 |
| **Skin** | Baseline, Day 13 |
| **Platelets** | Baseline, Day 4, Day 13 |

| Cohort 2 Sampling Days | |
|---|---|
| **Buccal Cells** | Baseline, Day 7, Day 13 |
| **Skin** | Baseline, Day 13 |
| **Platelets** | Baseline, Day 7, Day 13 |

| Cohort 3 Sampling Days | |
|---|---|
| **Buccal Cells** | Baseline, Day 7, Day 13 |
| **Skin** | Baseline, Day 13 |
| **Platelets** | Baseline, Day 7, Day 13 |

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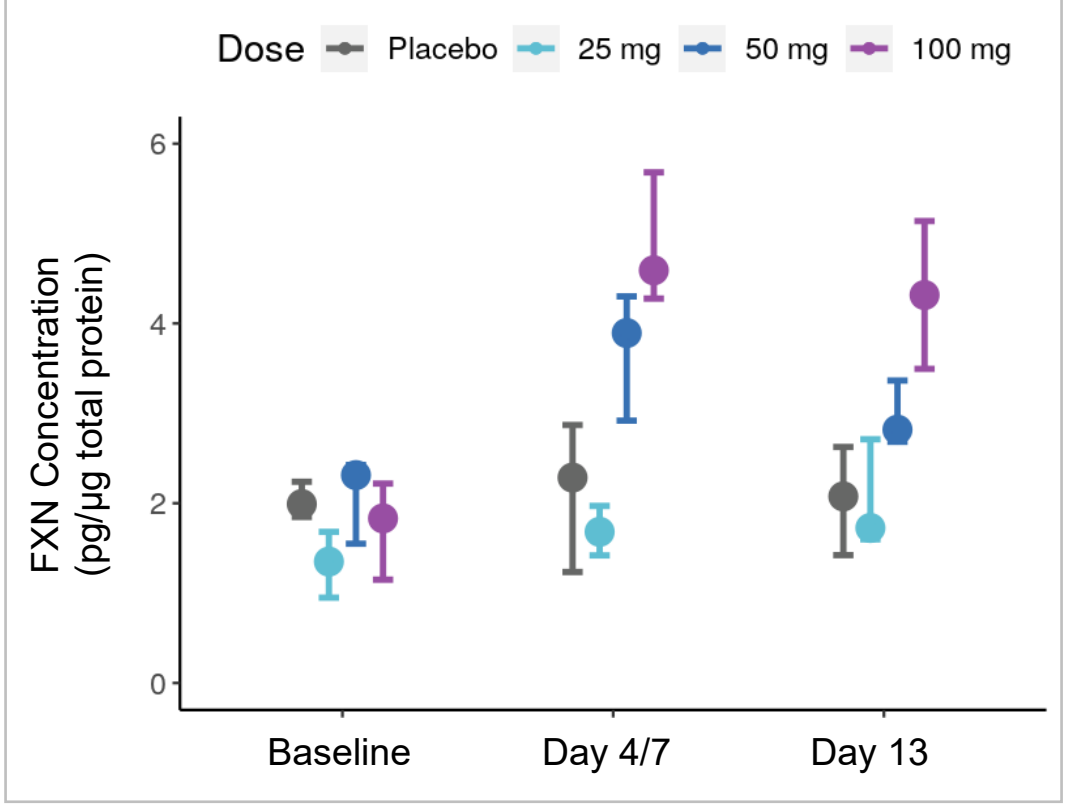
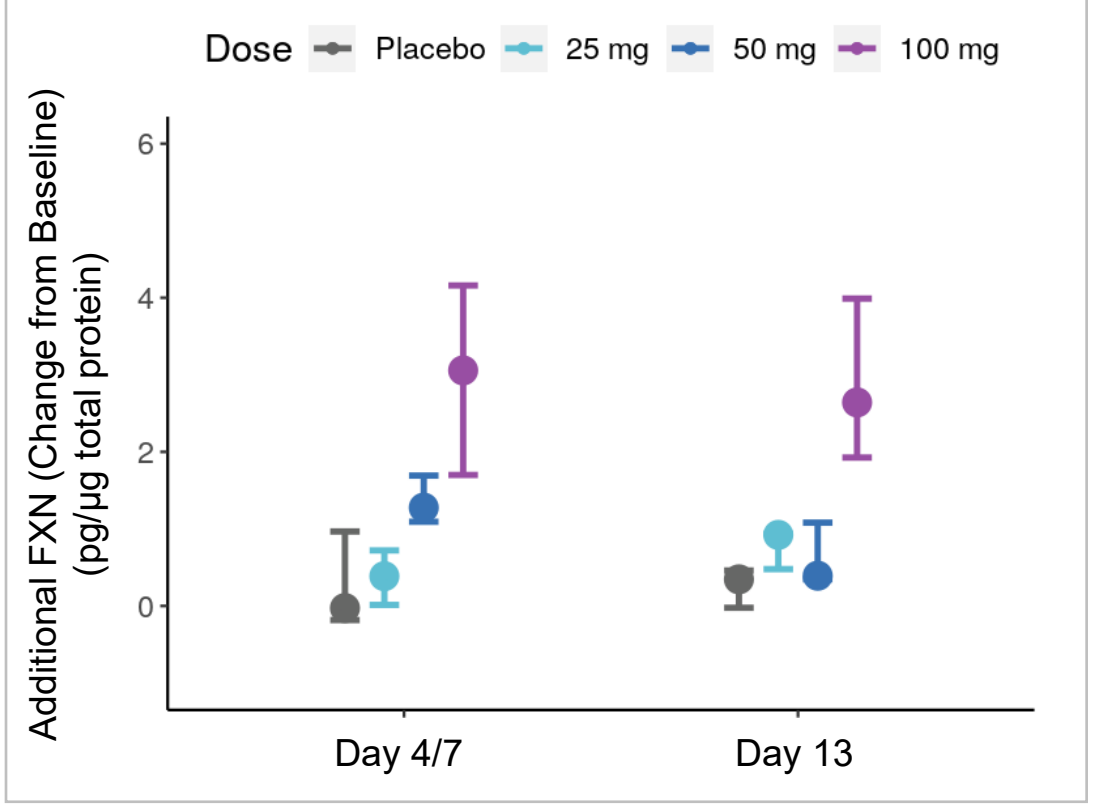
# Dose Dependent Increases in FXN Levels Observed in Buccal Cells

**Daily SC injections of 100 mg CTI-1601 resulted in an ~2.5 fold increase in FXN levels from baseline**

## FXN* Levels By Dose Group (Buccal Cells)




## FXN* Change from Baseline By Dose Group (Buccal Cells)

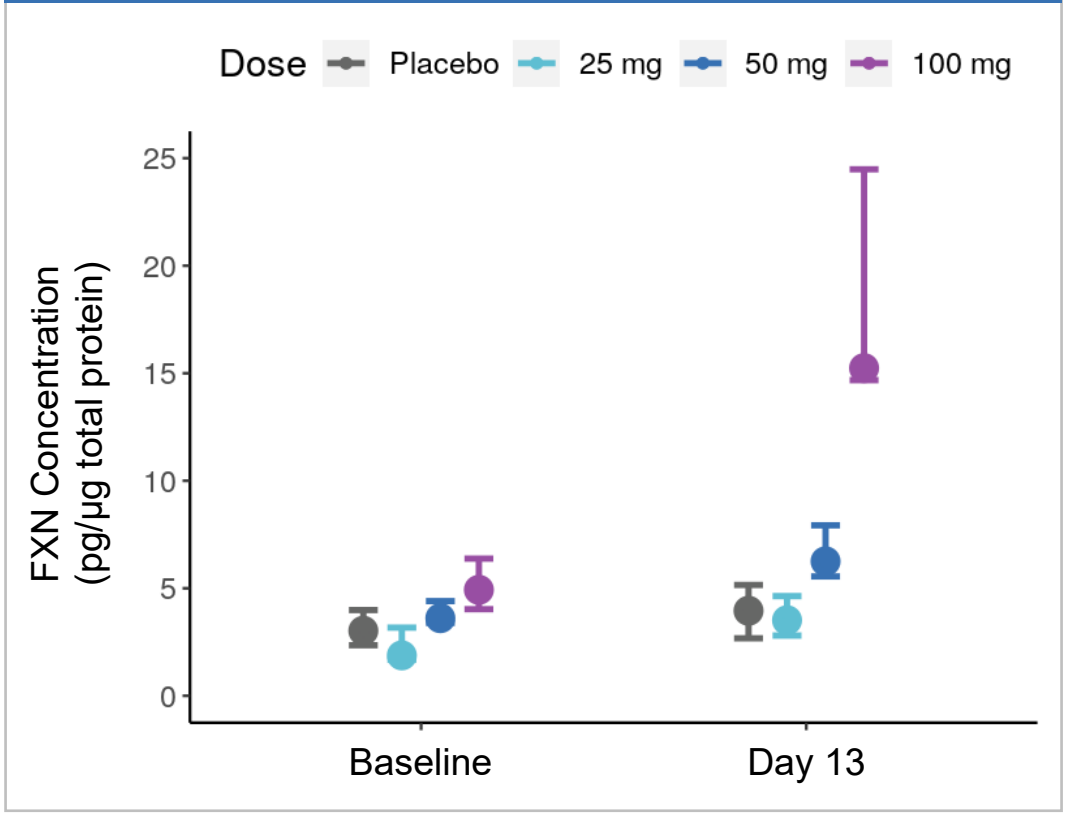



*FXN levels measured via detection of peptide derived from mature FXN; Data represent median and 25th and 75th percentiles; FXN levels from baseline, Day 4, & Day 13 measurements are shown for data derived from the 25 mg cohort; FXN levels from baseline, Day 7 & Day 13 measurements are shown for data derived from the 50 & 100 mg cohorts; Sample collection days varied in each cohort per the trial protocol

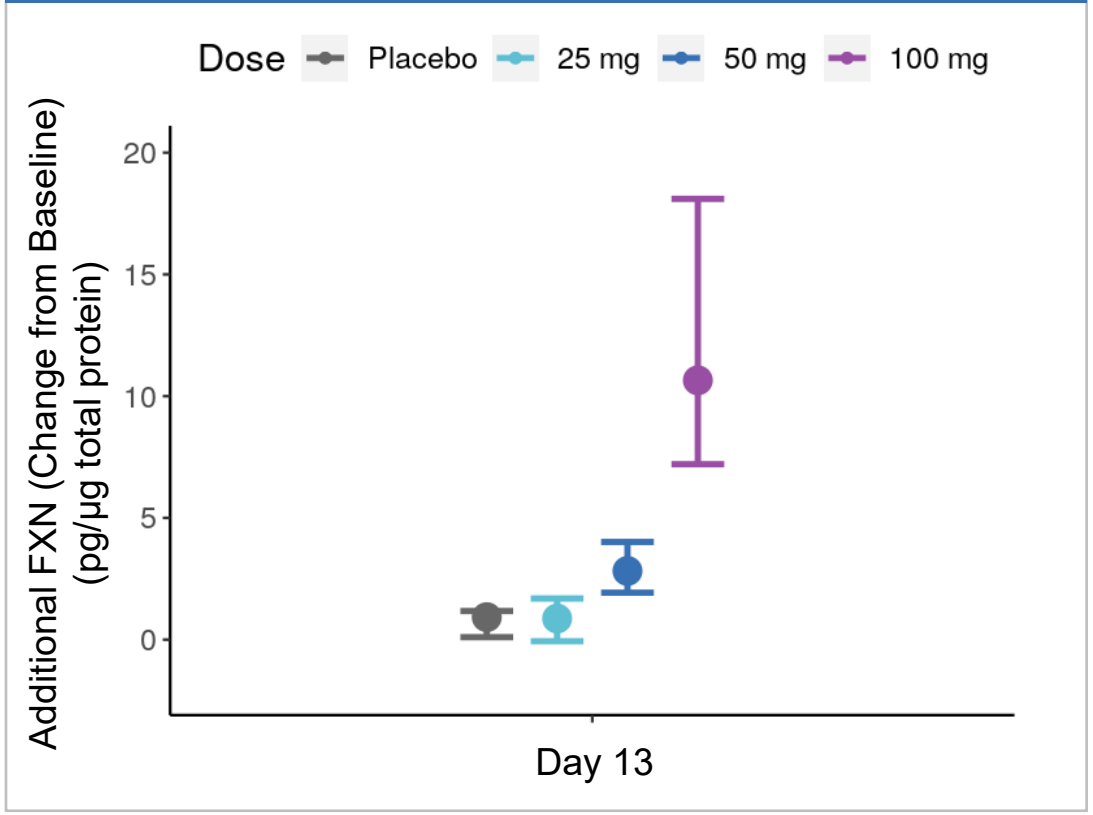
# Dose Dependent Increases in FXN Levels Observed in Skin

**Daily SC injections of 100 mg CTI-1601 resulted in an ~3 fold increase in FXN levels from baseline**

## FXN* Levels By Dose Group (Skin Biopsies)




## FXN* Change from Baseline By Dose Group (Skin Biopsies)

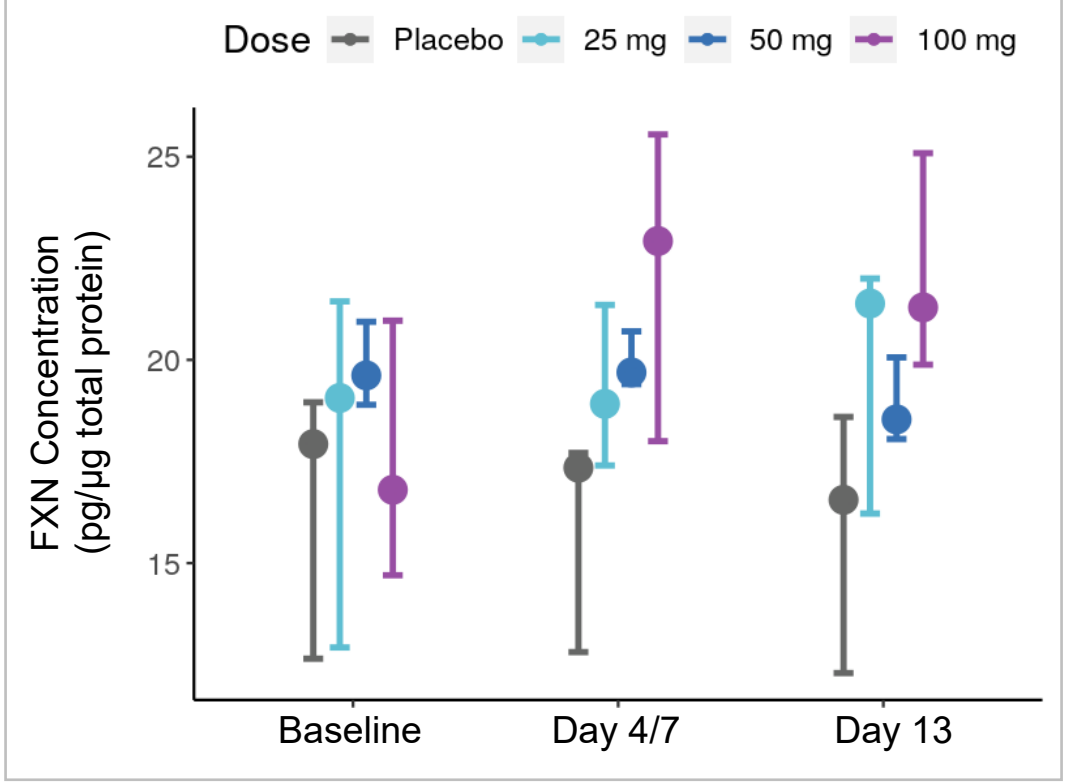



*FXN levels measured via detection of peptide derived from mature FXN; Data represent median and 25th and 75th percentiles

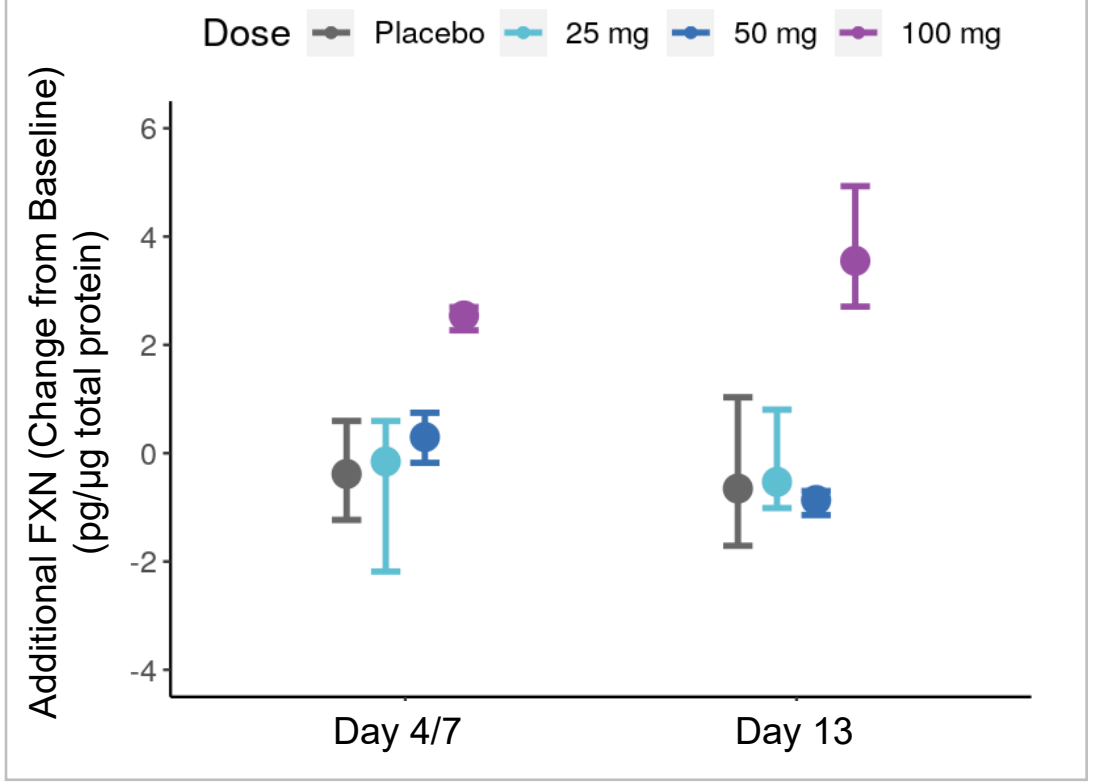
# Dose Dependent Increases in FXN Levels Observed in Platelets with Daily Dosing

**Daily SC injections of CTI-1601 resulted in increases in FXN levels from baseline compared to placebo**

## FXN* Levels By Dose Group (Platelets)




## FXN* Change from Baseline By Dose Group (Platelets)

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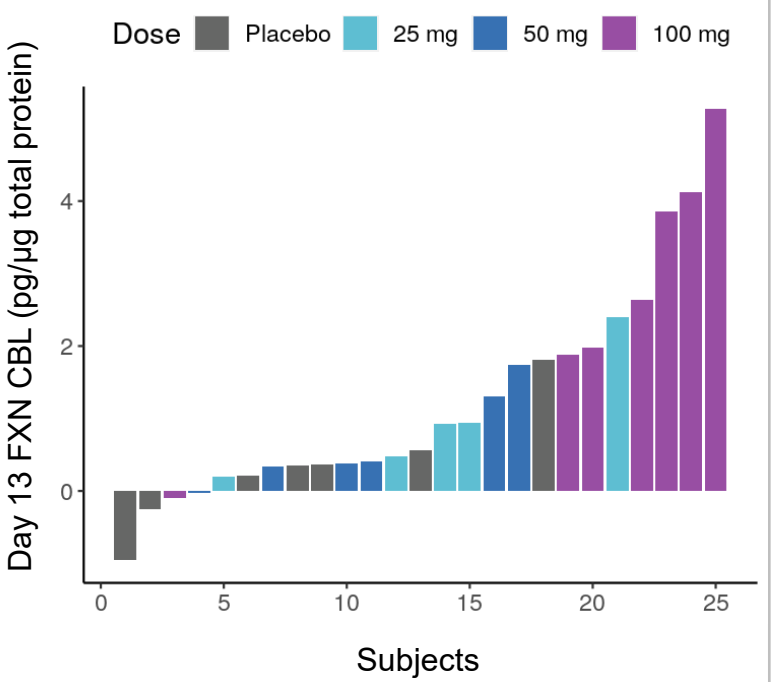
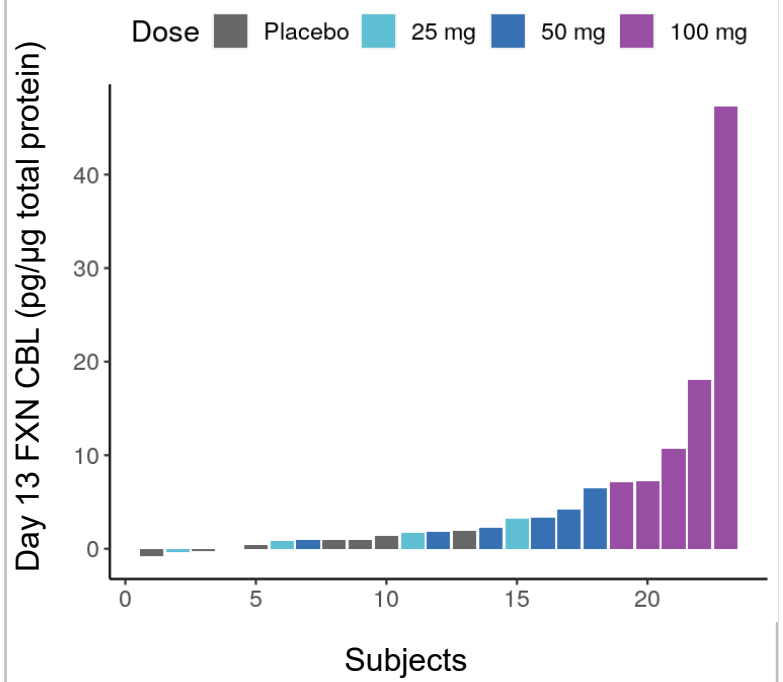
# Increases in FXN Correlated with Increasing CTI-1601 Dose

## Individual patient data further supports the dose-dependent effects of CTI-1601 in all tissues studied

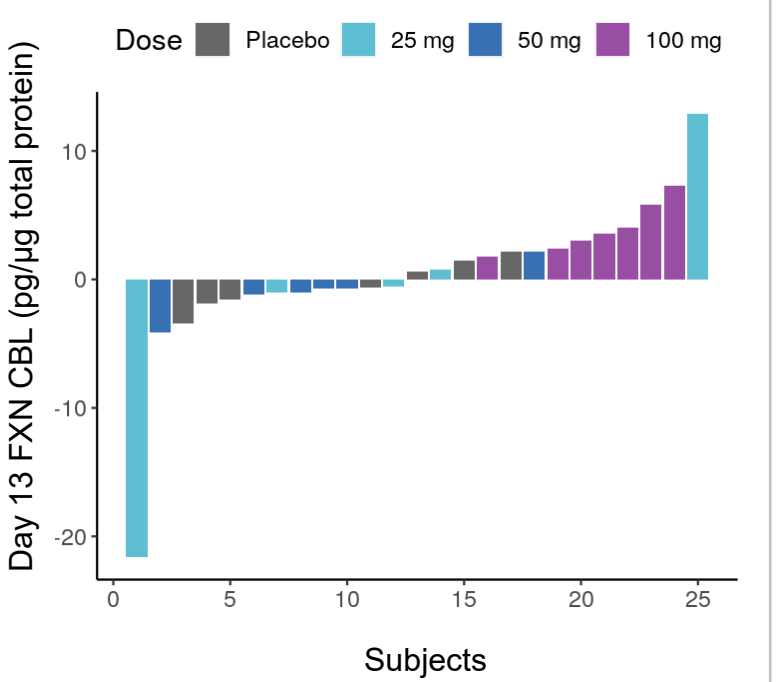
### Buccal Cells Day 13 FXN* Change from Baseline




### Skin Biopsies# Day 13 FXN* Change from Baseline




### Platelets Day 13 FXN* Change from Baseline




*FXN levels measured via detection of peptide derived from mature FXN; #Two patients in the 100 mg cohort declined skin biopsies
Day 13 observation excluded from one subject in 25 mg group that did not get a Day 13 dose.

# Data Compare Favorably to FXN Levels Expected in Heterozygous Carriers

**Achieved median FXN levels that were >60% of the median FXN levels observed in healthy controls**

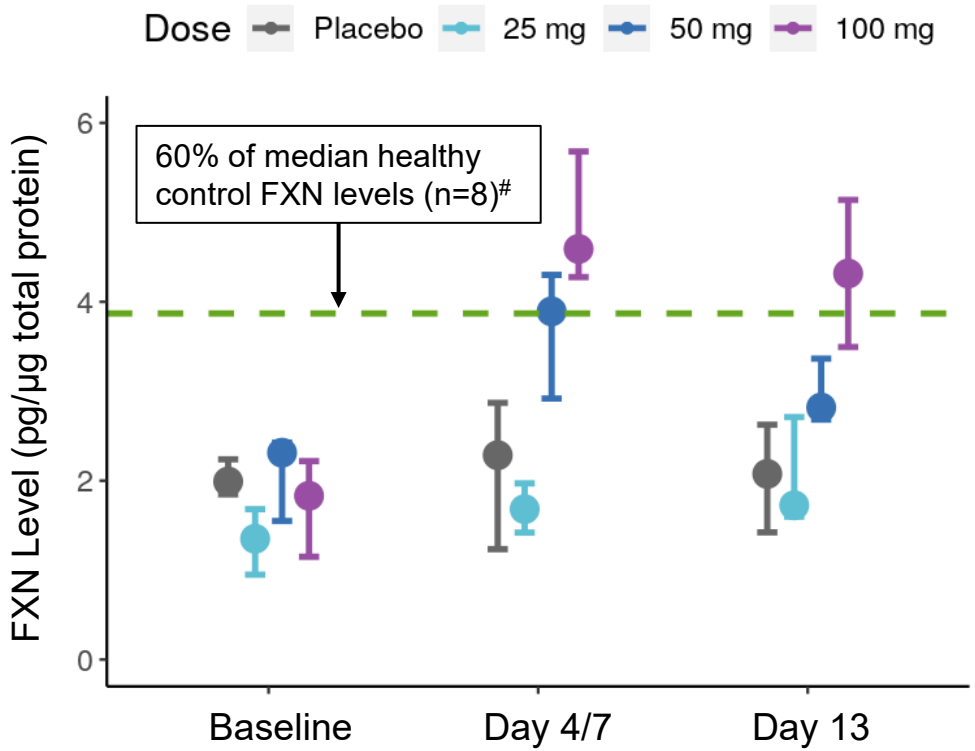
## Benchmarking Clinical Relevance

- FXN levels in buccal cells and blood have been shown to correlate with neurological function in FA patients[1]
- Patients with FA only produce ~20-40% of normal frataxin levels depending on the tissue considered[2]
- Heterozygous carriers who show no signs of disease have FXN levels of ~50% of unaffected healthy persons[2]

## Comparison to Healthy Controls

- FXN levels were measured in buccal cells from 8 healthy controls using the same assay and sampling technique employed in the Phase 1 MAD trial
- With daily administration, patients in Cohorts 2 & 3 of the Phase 1 MAD trial achieved median buccal cell FXN levels that were >60% of the median FXN levels observed in healthy controls
- Data from additional healthy control buccal cells, skin, and platelets will be collected in a separate non-interventional study

**FXN* Levels By Dose Group (Buccal Cells)**

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**Repeated SC injections of CTI-1601 appear to be generally well tolerated at doses up to 100 mg administered daily for 13 days**

## Summary of MAD trial safety data:

Repeated doses (25 mg, 50 mg, and 100 mg) of CTI-1601 or placebo were administered subcutaneously. 27 patients were dosed in the trial. 26 patients completed the trial. 1 patient receiving CTI-1601 in Cohort 2 (50 mg) withdrew after experiencing mild/moderate symptoms (nausea and vomiting).

- No serious adverse events (SAEs), important medical events, or treatment-related severe adverse events
- The most common adverse events were mild and moderate injection site reactions (at least one injection site reaction was seen in 43% of placebo patients and in 100% of CTI-1601 patients)
- The number and severity of adverse events did not increase with increasing exposure to CTI-1601

# PK analyses support evaluating a once-daily dosing regimen for CTI-1601

## Summary of PK Analyses

- CTI-1601 was quickly absorbed after subcutaneous administration
- Dose-proportional increases in exposure observed with increasing doses of CTI-1601
- Mean half life of CTI-1601 in plasma was approximately 11 hours
- CTI-1601 appears to be at or close to steady state exposure after 13 days of dosing 100 mg once daily

# Phase 1 Topline Data Demonstrated POC for CTI-1601 in FA

## FXN levels in buccal cells & blood have been shown to correlate with disease severity in FA patients[1]

### Safety Data

Repeated SC injections of CTI-1601 appear to be generally well tolerated at doses up to 100 mg administered daily for 13 days

The most common AEs were mild and moderate injection site reactions

No SAEs have been reported

### Frataxin Measurements

Daily SC injections of CTI-1601 resulted in dose-dependent increases in FXN levels from baseline compared to placebo controls in all evaluated tissues

With daily dosing (50mg and 100mg), achieved median FXN levels that were >60% of the median FXN levels observed in healthy controls

### Pharmacokinetic Data

CTI-1601 was quickly absorbed after subcutaneous administration

Dose-proportional increases in exposure observed with increasing doses of CTI-1601

Data support evaluating a once-daily dosing regimen for CTI-1601

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1. Lazaropoulos et al. Ann Clin Transl Neurol. 2015 Aug; 2(8): 831–842; POC: Proof-of-concept; OLE: Open label extension; AE: Adverse events

# CTI-1601 has a Significant Estimated Safety Margin Based on the 90-day Cynomolgus Monkey Study

## Sprague Dawley Rat (28-day and 90-day studies)

**Injection Site Observations**

- Some injection sites showed edema and erythema; associated histologic changes were localized to the injection site

**Systemic Toxicity Analysis**

- No significant clinical observations or clinical pathology results
- No significant systemic histopathological findings

## Cynomolgus Monkey (28-day and 90-day studies)

**Injection Site Observations**

- Some injection sites raised and firm; dose dependent histologic changes around the injection sites

**Systemic Toxicity Analysis**

- No system toxicity observed in 28-day study
- Minimal to mild histopathological findings in some animals at the highest dose level in the 90-day study
- Based on $C_{max}$ and AUC from the 90-day study, Cohort 3 (100 mg) from the MAD trial has safety margins of 15.4 and 13.9, respectively*.

**A 180-day cynomolgus monkey study is ongoing to support extended dosing of patients (exposure data pending). FDA to review data from the completed study in association with the CTI-1601 clinical program and clinical hold.**

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*Safety margins are the ratio of no-observed-adverse-effect exposure levels and the geometric mean values from Day 13, Cohort 3 (100 mg) data in MAD trial

# Upcoming Trials and Regulatory Interactions

**Additional analyses from the Phase 1 program planned for presentation at a scientific meeting**

## Future Planned Trials and Regulatory Interactions Include:

Continued interactions with FDA regarding clinical trials and non-clinical studies, including discussions of resolution of clinical hold


Jive open label extension (OLE) trial for eligible patients who participated in SAD or MAD trials (expected initiation 2H 2021/1H 2022)

MAD trial in patients under 18 years of age (expected initiation 2H 2021 /1H 2022). Participants eligible to screen for Jive OLE trial

Global double-blind placebo-controlled pivotal trial (expected initiation as early as 2H 2022)

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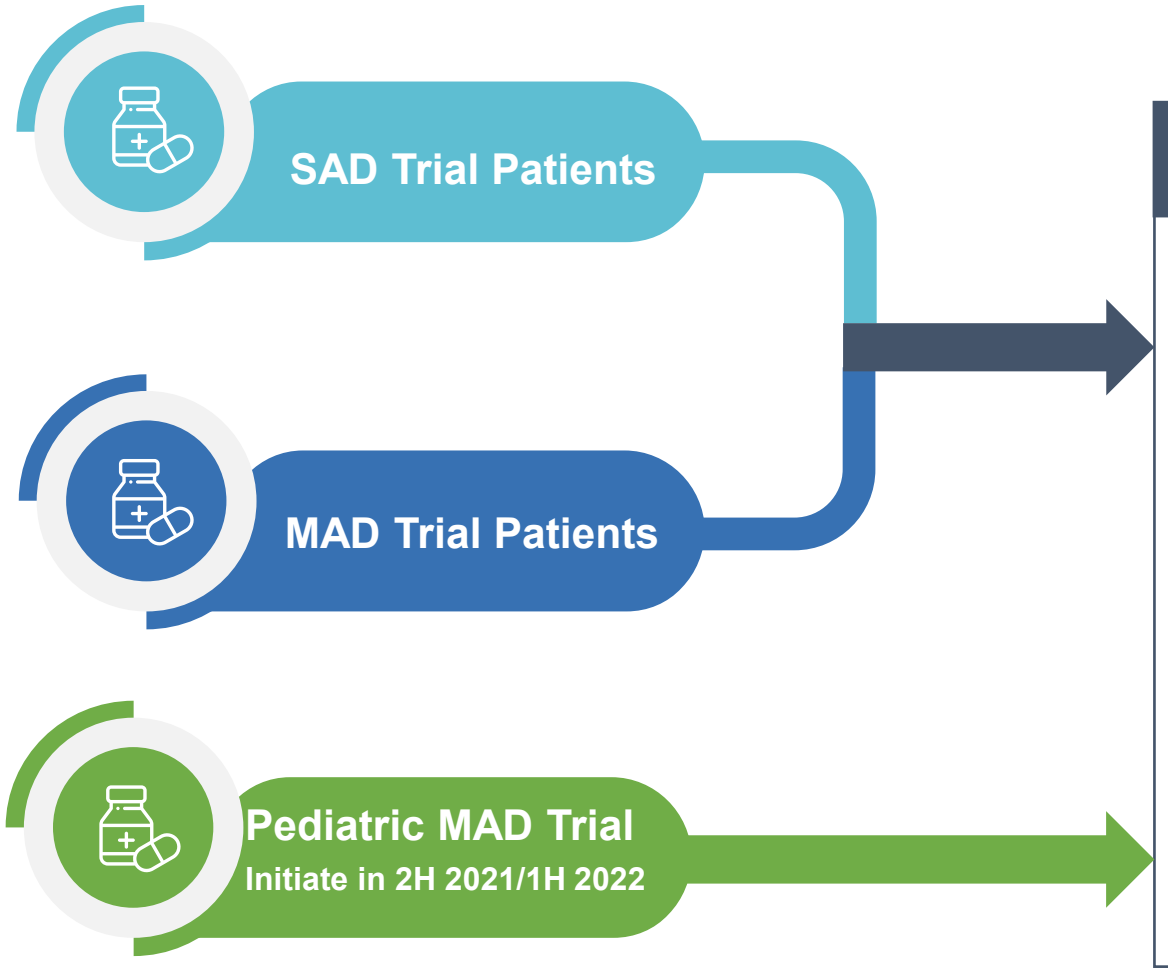
# Expect to Initiate Two Additional Trials in 2H 2021/1H 2022

**Patients from SAD, MAD, and pediatric trials are eligible to screen for the Jive open label extension trial**




## Jive OLE Trial

**Dose Level:** To be determined based on additional analysis of data from SAD and MAD trials

**Treatment Duration:** Planned for 24 months with any necessary extensions

**Number of Subjects:** Up to 50

**Dose Regimen:** Once-daily doses administered subcutaneously

**External Control Arm:** Derived from Critical Path Institute Data

**1º Endpoint:** Safety and tolerability

**Key 2º Endpoints:** Long-term PD; efficacy assessments

**Expected Initiation:** 2H 2021/1H 2022

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# Investment Highlights

**Clinical-stage biotechnology company with a novel protein replacement therapy platform**
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- Raised ~$20 million in gross proceeds in a June ATM transaction of ~ 2.3 million shares

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FXN: Frataxin

# Larimar Therapeutics

## Corporate Presentation

THANK YOU

# Leadership Team

**Carole Ben-Maimon, MD**
Chief Executive Officer

Impax teva

**Michael Celano**
Chief Financial Officer

OraSure Technologies Kensey Nash Regenerating Medicine

**Nancy Ruiz, MD, FACP, FIDSA**
Chief Medical Officer

Schering-Plough MERCK

**Jennifer Johansson, JD**
VP, Regulatory Affairs & Counsel

Andrx PHARMACEUTICALS, INC. SQUIRE PATTON BOGGS

**Mohamed Hamdani**
VP, Biostatistics & Data Management

Apellis Shire

**David Bettoun, PhD**
VP, Discovery & Non-clinical R&D

gsk MERCK

**Keith E. Lynch, Jr.**
VP, Manufacturing and Supply Chain

MERCK Oncobiologics

**John Berman, CPA**
VP, Finance & Operations

teva Cell Pathways, Inc.

**Noreen Scherer**
VP, Clinical Operations

Shire Wyeth Pharmaceuticals

**Francis Michael Conway**
Vice President Controller

TELA BIO stryker

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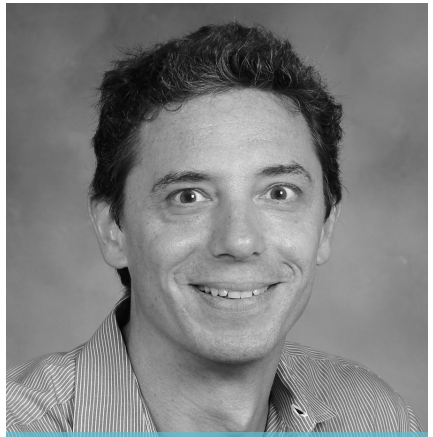
# Scientific Advisory Board

**Russell Clayton, DO (Chairman)**

Former Chief Medical Officer at Alcresta Therapeutics, a medical device company

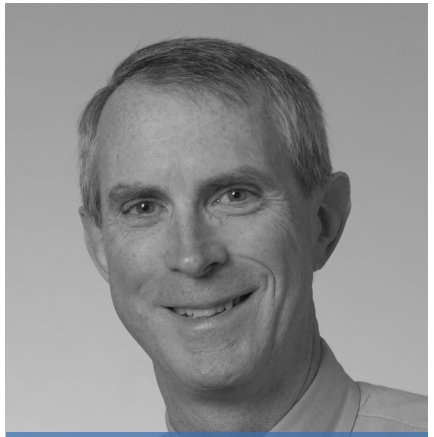
Former Senior Vice President of Research and Development at Discovery Labs, a pharmaceutical and medical device company



**Giovanni Manfredi, MD, PhD**

Finbar and Marianne Kenny Professor in Clinical and Research Neurology at Weill Cornell Medicine.

Professor of Neuroscience at Weill Cornell Medicine.



**Mark Payne, MD**

Co-founder of Chondrial Therapeutics, which became Larimar Therapeutics, Inc.

Professor of Pediatrics at Indiana University School of Medicine

**Marshall Summar, MD**

Chief of the Division of Genetics and Metabolism, Director of the Rare Disease Institute, and Margaret O'Malley Chair of Genetic Medicine at Children's National Hospital

**Marni J. Falk, MD**

Executive Director of the Mitochondrial Medicine Frontier Program at The Children's Hospital of Philadelphia (CHOP)

Professor in the Division of Human Genetics, Department of Pediatrics at University of Pennsylvania Perelman School of Medicine

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# MAD Trial Patient Demographics

| Parameter | Statistic | All placebo (n=7) | 25 mg CTI-1601 (n=6) | 50 mg CTI-1601 (n=7) | 100 mg CTI-1601 (n=7) | All CTI-1601 (n=20) | Overall (n=27) |
|---|---|---|---|---|---|---|---|
| **Sex** | | | | | | | |
| Male | n (%) | 5 (71.4) | 3 ( 50.0) | 4 ( 57.1) | 3 ( 42.9) | 10 ( 50.0) | 15 (55.6) |
| Female | n (%) | 2 (28.6) | 3 ( 50.0) | 3 ( 42.9) | 4 ( 57.1) | 10 ( 50.0) | 12 (44.4) |
| **Age (years)** | | | | | | | |
| | Mean | 25.7 | 39.7 | 34.7 | 28.0 | 33.9 | 31.7 |
| | SD | 6.37 | 16.59 | 9.03 | 8.96 | 12.13 | 11.40 |
| | Median | 23 | 37 | 36 | 24 | 34 | 28 |
| | Min, Max | 20,36 | 21,65 | 19,47 | 20,44 | 19,65 | 19,65 |
| **Race** | | | | | | | |
| White | n (%) | 6 ( 85.7) | 6 (100.0) | 6 ( 85.7) | 6 ( 85.7) | 18 ( 90.0) | 24 (88.9) |
| Asian | n (%) | 0 | 0 | 1 ( 14.3) | 1 ( 14.3) | 2 ( 10.0) | 2 ( 7.4) |
| American Indian | n (%) | 1 ( 14.3) | 0 | 0 | 0 | 0 | 1 (3.7) |
| **Ethnicity** | | | | | | | |
| Hispanic/Latino | n (%) | 2 (28.6) | 0 | 0 | 0 | 0 | 2 (7.4) |
| Not Hispanic/Latino | n (%) | 5 (71.4) | 6 (100.0) | 7 (100.0) | 7 (100.0) | 20 (100.0) | 25 (92.6) |

SD: Standard deviation

# MAD Trial Patient Disease Characteristics

| Parameter | Statistic | All placebo (n=7) | 25 mg CTI-1601 (n=6) | 50 mg CTI-1601 (n=7) | 100 mg CTI-1601 (n=7) | All CTI-1601 (n=20) | Overall (n=27) |
|---|---|---|---|---|---|---|---|
| **Age at Symptom Onset** | | | | | | | |
| | Mean | 14.1 | 24.0 | 19.3 | 11.9 | 18.1 | 17.1 |
| | SD | 5.34 | 14.48 | 6.21 | 6.72 | 10.37 | 9.39 |
| | Median | 15.0 | 18.0 | 19.0 | 10.0 | 18.0 | 16.0 |
| | Min, Max | 8,23 | 12,44 | 8,28 | 5,22 | 5,44 | 5,44 |
| **Age at Diagnosis** | | | | | | | |
| | Mean | 18.3 | 31.5 | 26.4 | 15.9 | 24.3 | 22.7 |
| | SD | 7.87 | 19.88 | 4.28 | 8.21 | 13.24 | 12.23 |
| | Median | 20.0 | 25.5 | 28.0 | 13.0 | 27.0 | 21.0 |
| | Min, Max | 9,32 | 14,64 | 17,30 | 5,27 | 5,64 | 5,64 |
| **Assistive Device** | | | | | | | |
| Walker | n (%) | 0 | 2 (33.3) | 3 (42.9) | 0 | 5 (25.0) | 5 (18.5) |
| Wheelchair | n (%) | 4 (57.1) | 3 (50.0) | 1 (14.3) | 6 (85.7) | 10 (50.0) | 14 (51.9) |
| Other | n (%) | 1 (14.3) | 0 | 1(14.3) | 0 | 1 (5.0) | 2 (7.4) |
| None | n (%) | 2 (28.6) | 1 (16.7) | 2 (28.6) | 1 (14.3) | 4 (20.0) | 6 (22.2) |

SD: Standard deviation

# CTI-1601: Positive Mouse Model Data Support Development

## Proof-of-Concept Demonstrated In Mouse Models of FA

### Cardiac Knock Out Mouse Model Studies
(MCK-Cre FXN KO Mouse)

- Extended survival
- Demonstrated ability to deliver hFXN to mitochondria
- Increased in a dose dependent manner, succinate dehydrogenase (SDH) activity. SDH is an FXN dependent enzyme, whose activity is indicative of mitochondrial function.
- Prevented left ventricle dilation and maintained function

### Neurologic Knock Out Mouse Model Study
(Pvalb-CRE FXN KO Mouse)

- Prevented development of ataxic gait
- Showed that treated mice survive longer than untreated mice
- Demonstrated CNS penetration, as hFXN was present in brain, dorsal root ganglia & spinal cord

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# CTI-1601 Extends Survival in FXN-deficient KO Mice

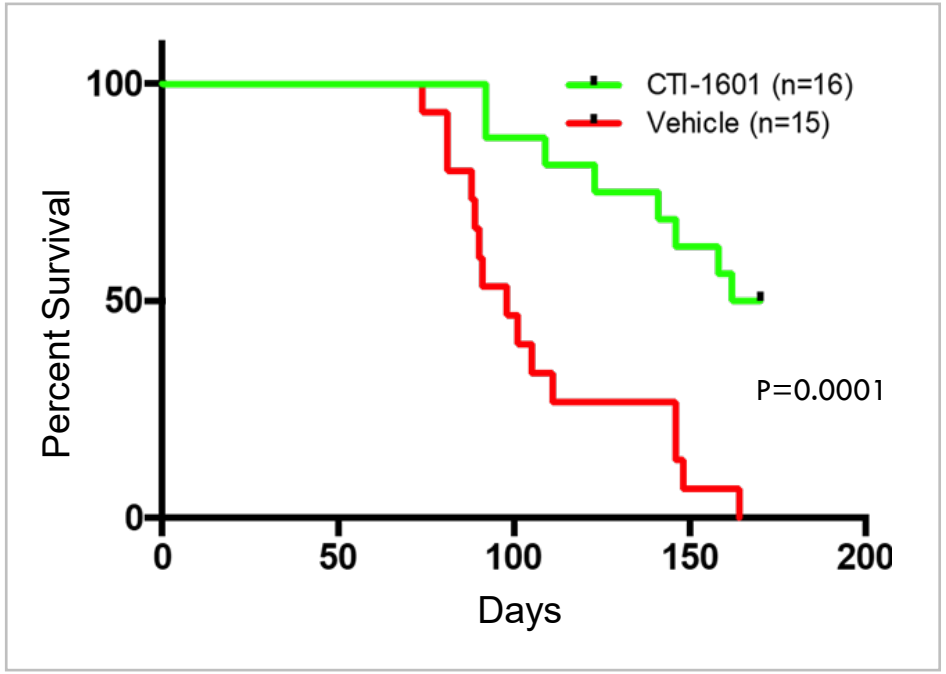
## Initial Proof of Concept for FXN Replacement Therapy in Cardiac Mouse Model of FA

### Median Survival of MCK-Cre FXN-KO Mice

- 166 days (CTI-1601) vs. 98 days (Vehicle)
- CTI-1601 was administered 10 mg/kg SC every other day

### Survival beyond vehicle mean (107.5 days)

- 87.5% (CTI-1601) vs. 33% (Vehicle)
- Demonstrates that CTI-1601 is capable of delivering sufficient amounts of FXN to mitochondria




**CTI-1601 rescues a severe disease phenotype in a well-characterized cardiac mouse model of FA**

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# CTI-1601 Prevents The Development of Ataxic Gait in KO mice

## In-Vivo Efficacy Data in Neurologic KO Mouse Model

### Pvalb-Cre FXN-KO mouse

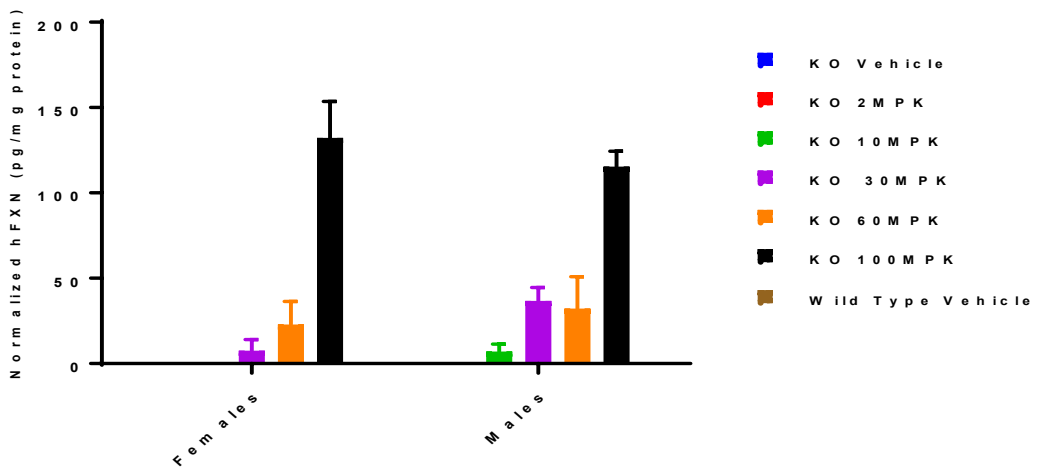
Single dose level: 10 mg/kg CTI-1601 or vehicle given intraperitoneally three times per week

- hFXN replacement with CTI-1601 **prevents the development of ataxic gait**
- CTI-1601-treated mice **survive longer** than untreated mice
- Human frataxin **present in brain, dorsal root ganglia and spinal cord** demonstrating central nervous system penetration

# CTI-1601 Delivers hFXN to Mitochondria in KO Mice

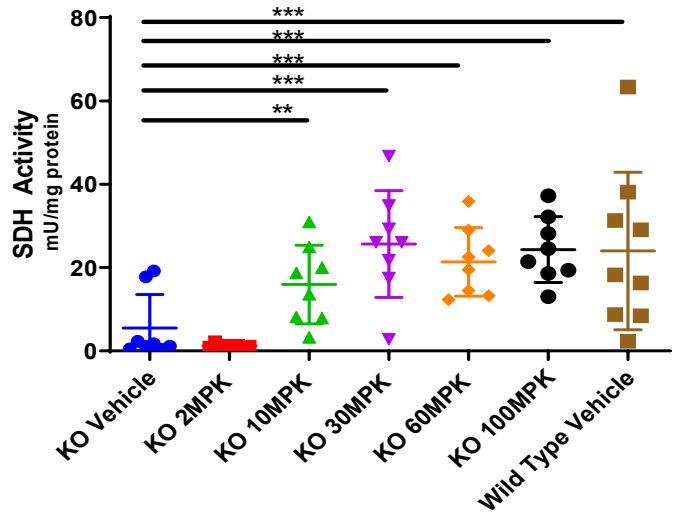
- hFXN concentration within mitochondria increases in a dose-dependent manner
- Given subcutaneously, CTI-1601 functionally replaces hFXN in mitochondria of KO mice
- Succinate dehydrogenase (SDH) activity, which is indicative of mitochondrial function, increases in a dose-dependent manner after administration of CTI-1601; activity plateaus at 30 mg/kg and is equivalent to activity in wild type animals
- Demonstrated normalization of gene expression in cardiac tissue

## Normalized Mitochondrial FXN (Heart)




MPK = mg/kg

## Normalized SDH Activity (Muscle)




MPK = mg/kg

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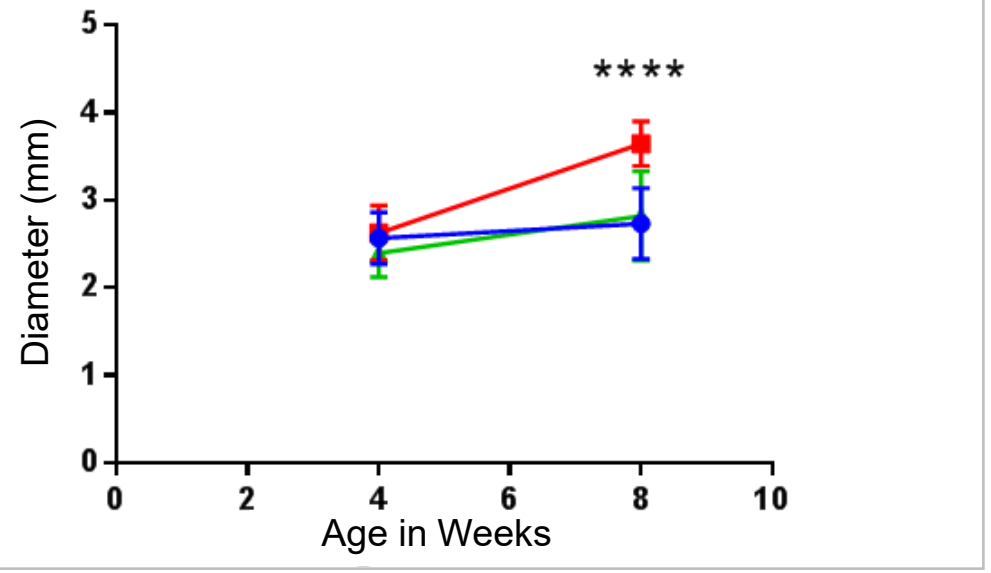
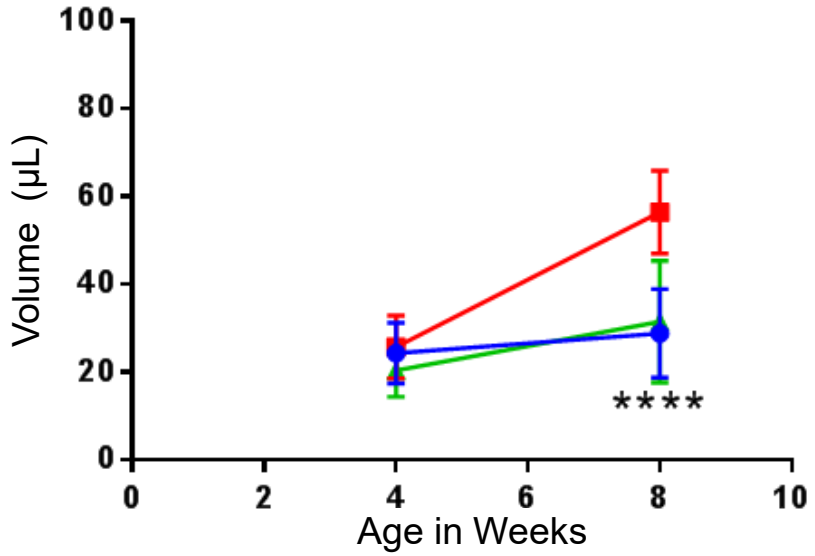
# CTI-1601 Prevents Left Ventricle Dilation in KO Mice

- Left ventricular (LV) volume increases in systole in untreated mice by 8 weeks (after 4 weeks of dosing with vehicle), but remains similar to wildtype when treated with CTI-1601 (10 mg/kg every other day)
- CTI-1601-treated mice have similar LV volume as healthy controls; echocardiogram shows significant differences between vehicle and CTI-1601 treated (10 mg/kg every other day) KO mice

## Left Ventricle Internal Diameter (Systole)




## Left Ventricle Volume (Systole)




KO: CTI-1601 KO: Vehicle Wild-type: Vehicle

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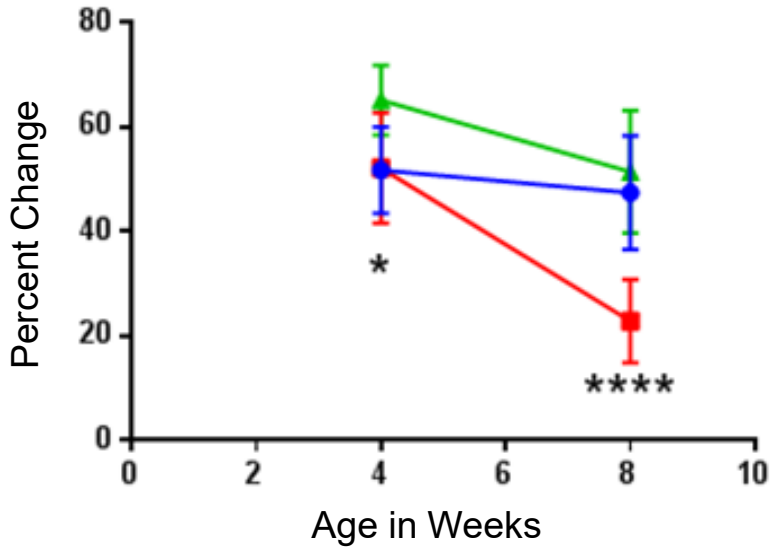
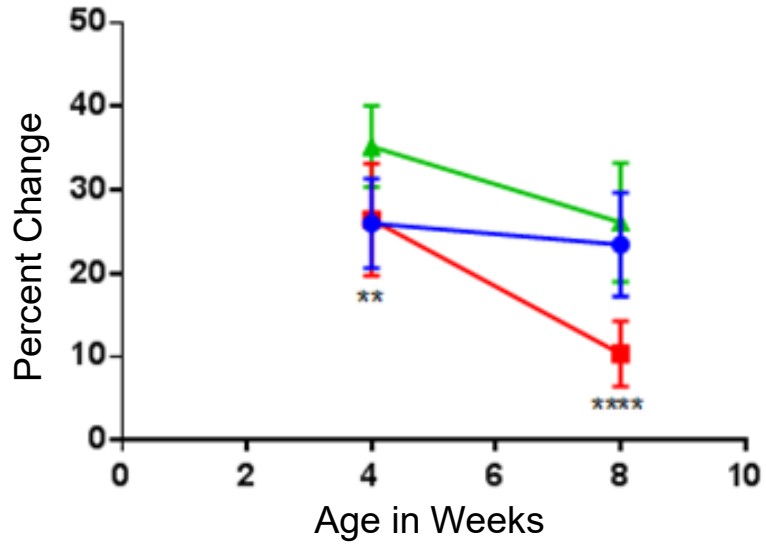
# CTI-1601 Preserves Left Ventricle Function in KO Mice

- Left ventricular (LV) function drops significantly in vehicle treated mice by week 8
- CTI-1601-treated (10 mg/kg every other day) mice have similar LV as healthy controls; echocardiogram shows significant differences between vehicle and CTI-1601 treated KO mice

## Left Ventricle Ejection Function




## Left Ventricle Fractional Shortening




KO: CTI-1601 KO: Vehicle Wild-type: Vehicle

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# Favorable PK/PD Profile in Healthy Cynomolgus Monkeys

**Study Design (14-Days of CTI-1601 dosing)**

6 healthy cynomolgus monkeys (3M / 3F)

**Pre-dosed for 2 days with Vehicle**

Pre-dose collection of platelets, cerebrospinal fluid, buccal swab, skin punch
Dosing starts 15 mg/kg SC BID

**Day 10 (7 days dosing)**

Collection of platelets, buccal swab, skin punch

**Day 16 (following 14th day of dosing)**

Collection of cerebrospinal fluid, platelets, buccal swab, skin punch

- CTI-1601 is bioavailable when given subcutaneously
- Sustained levels of hFXN are found in blood cells (platelets) and peripheral tissues (buccal cells, skin) as early as the 7th day and still present after 14 days
- Sustained levels of hFXN are found after 14 days in the cerebrospinal fluid of monkeys, suggesting CNS penetration

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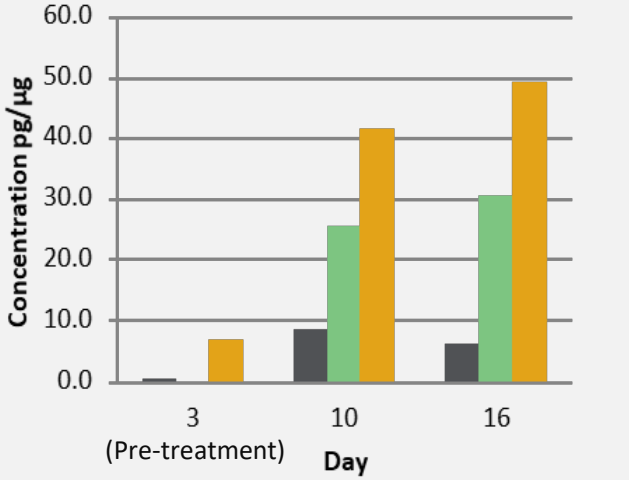
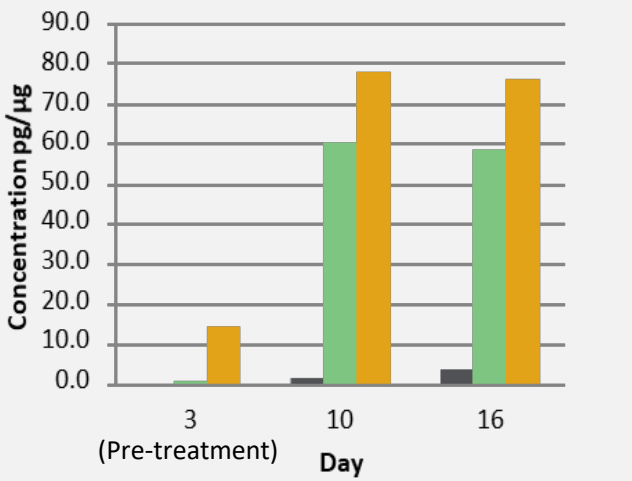
# Biodistribution in Healthy Cynomolgus Monkeys

## Sustained levels of human FXN (hFXN) in peripheral tissues after 14 days of CTI-1601 dosing

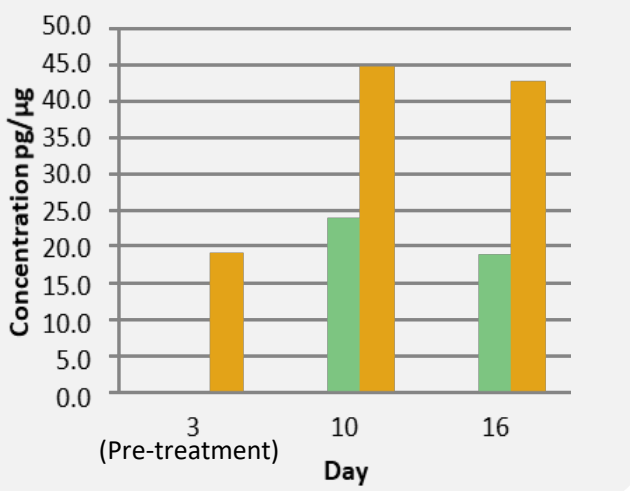
### Buccal Swabs




### Skin Biopsies




### Platelets




CTI-1601 | Human FXN | Human + Monkey FXN

- Treatment of monkeys with CTI-1601 results in sustained levels of hFXN in peripheral tissues that are accessible in the clinic
- FXN levels increase ~4X or more following CTI-1601 administration
  - For comparison, FA patients show FXN levels that range from ~20-40% of normal FXN levels depending on the tissue considered[1]
    - Heterozygous carriers show no phenotype and display levels of FXN representing ~2-3X higher than most FA patients[1]

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1. E.C. Deutsch et al. Molecular Genetics and Metabolism 101 (2010) 238–245