



2024 International Congress for
Ataxia Research (ICAR)

Poster Presentations

Disease characteristics and tissue frataxin concentrations in adults with Friedreich’s ataxia participating in nomlabofusp interventional studies



Mohamed Hamdani¹, Noreen Scherer¹, Magdi Shenouda², and Russell Clayton¹

¹Larimar Therapeutics, Bala Cynwyd, PA, USA; ²Clinilabs, Inc, Eatontown, NJ, USA



ABSTRACT

Methods: Disease characteristics (eg, age at onset, guanine adenine adenine [GAA] repeat length) of adults with Friedreich’s ataxia (FRDA) participating in Phase 1 and 2 nomlabofusp interventional studies were summarized and evaluated relative to baseline buccal and skin cell frataxin concentrations.

Results: Sixty-one subjects participated in at least one study; 18 participated in more than one study. Mean age was 31.9 years (range 19-69). Mean age of onset was 15.9 years (range 5-60). Mean (range) shorter and longer GAA repeat lengths were 555.8 (99-1000) and 890.2 (265-1300). Mean baseline modified Friedreich’s ataxia rating scale neurologic score was 49.5 (13.2-74.5). Mean (range) baseline buccal and skin cell frataxin concentrations were 1.90 (0.70-4.95) and 3.25 (1.40-8.10) pcg/mcg, respectively. There is a relationship between frataxin concentrations and age of onset and GAA repeat length. There is also a relationship between skin and buccal cell frataxin concentrations.

Discussion: Early age of onset is associated with more rapid disease progression. Data from the nomlabofusp interventional studies are consistent with previously published data that suggest that lower tissue frataxin concentrations are associated with more rapid disease progression. Increasing frataxin concentrations in patients with FRDA may decrease the rate of disease progression.

Conclusion: The study population in the nomlabofusp interventional studies is representative of the FRDA population, and tissue frataxin concentration data from these studies are consistent with prior studies demonstrating that lower frataxin concentrations are associated with earlier onset of disease. Buccal and skin cell frataxin levels correlate with each other.

INTRODUCTION

- Friedreich’s ataxia (FRDA) is an autosomal recessive neurodegenerative disorder caused by a guanine adenine adenine (GAA) repeat expansion in the FXN gene that results in frataxin (FXN) deficiency.
- Affected individuals develop a progressive ataxia that leads to a loss of ambulation.
- Tissue FXN concentrations are correlated with age of disease onset and inversely correlated with the number of GAA repeats and rate of disease progression. (Deutsch, et al.)
- The range of the number of GAA repeats observed in the population of patients with FRDA results in a diverse spectrum of disease characteristics.
- The goal of this study was to describe the characteristics, including tissue FXN concentrations, in adults with FRDA who participated in Phase 1 and Phase 2 clinical studies evaluating nomlabofusp as a potential treatment for patients with FRDA.

METHODS

Clinical Studies

- Demographic and disease characteristics, as well as skin FXN concentration data, were collected from 3 completed clinical studies in adults with FRDA
 - Single ascending dose (CLIN-1601-101) study evaluating 25 mg 50 mg, 75 mg, and 100 mg nomlabofusp (nomlabofusp concentrations only)
 - Multiple ascending dose (CLIN-1601-102) study evaluating 25 mg, 50 mg, and 100 mg nomlabofusp
 - Dose exploration study (CLIN-1601-200) evaluating 25 mg and 50 mg nomlabofusp

- Baseline buccal and skin cell samples for FXN obtained prior to Day 1

Statistical Analysis

- Linear regression model was used to investigate:
 - The relation of FXN levels in buccal cells to disease severity and progression
 - The relation of age of onset of disease manifestations to GAA repeat length on the shorter allele
 - The relation of frataxin levels in buccal cells to frataxin levels in skin cells

RESULTS

Summary of Demographics and Baseline Disease Characteristics from Adults with FRDA Participating in Phase 1 and 2 Nomlabofusp Interventional Studies

	N*	Median	Mean	Min	Max
Age	61	28.0	31.9	19	69
Age of Onset	61	15.0	15.9	5	60
Age of Diagnosis	61	19.0	21.0	5	64
Shorter GAA (GAA ₁)	60	550.0	555.8	99	1000
Longer GAA (GAA ₂)	60	900.0	890.2	265	1300
Frataxin, % of Control**	57	24.4	23.9	8.7	61.9
mFARS Score	61	52.0	49.5	13.2	74.5
Upright Stability Score	61	32.0	26.9	7.0	35.0
Dominant Hand 9-hole Peg Test	61	71.0	84.8	26.0	229.2
T25-FW Test Score	51	9.9	13.4	4.3	48.5
Left Ventricular Mass (g)	61	163.4	168.0	73.7	398.8
LVEF %	61	63.0	63.5	52	76
Ambulatory Status***					
No	36				
Yes	25				

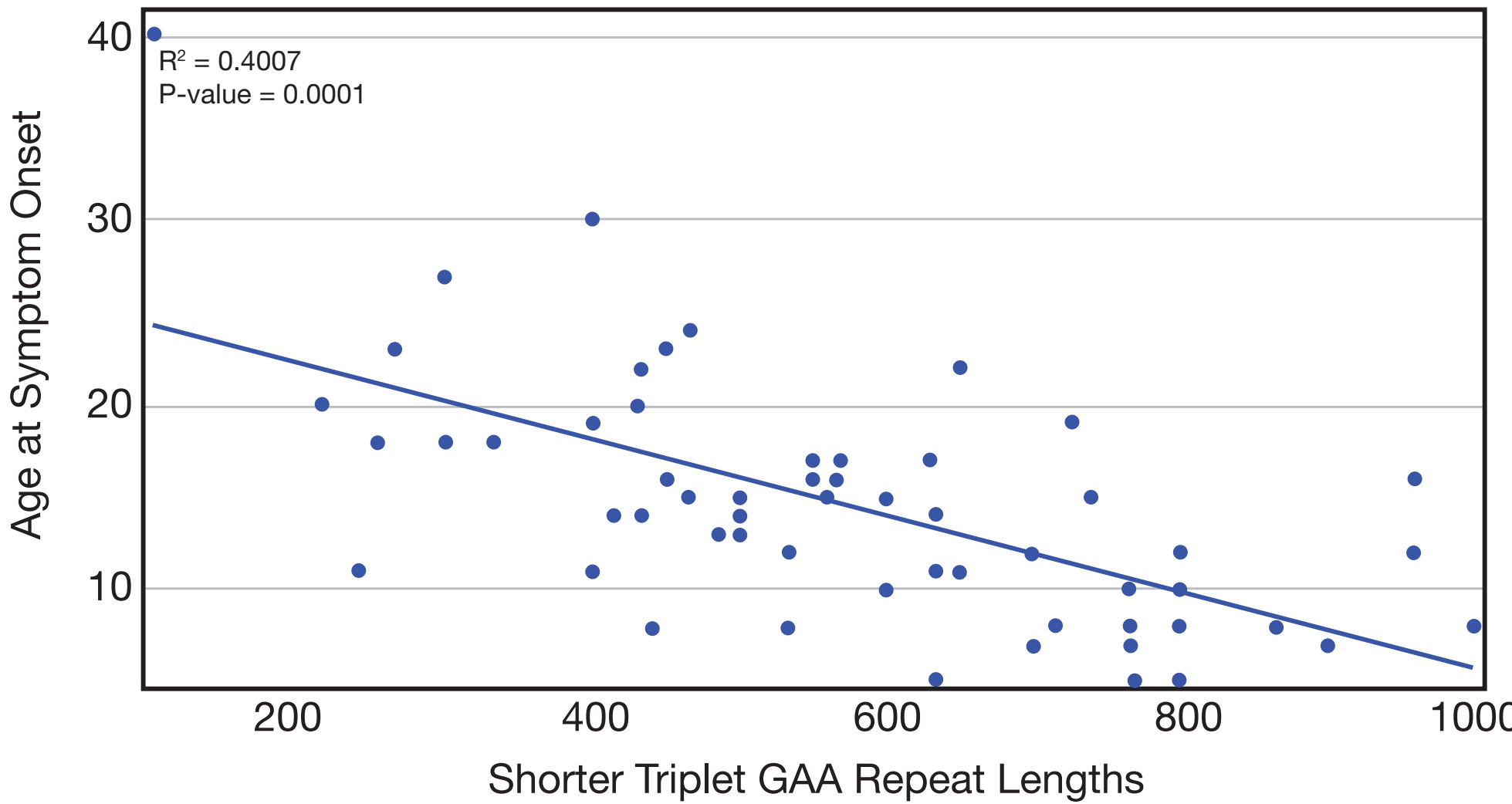
*18 subjects participated in more than 1 study
**Quantifiable buccal cells FXN levels relative to the median of healthy controls
***Ambulatory status is based on the gait score (E7=5 vs <5) of the upright stability subscore of the mFARS

Disease Characteristics of Adults with FRDA Participating in Nomlabofusp Interventional Studies Organized by Quartiles Based on Quantifiable Buccal Cell FXN Concentrations

Quartile	FXN Concentration* (pg/mcg)	Age at Symptom Onset**	Age at Diagnosis**	GAA ₁ **	GAA ₂ **	Baseline mFARS**
Q1 (N=14)	<1.31	10.5	14.5	616.5	899.5	66.3
Q2 (N=14)	1.31 - <1.95	13.5	23.0	486.0	866.0	46.8
Q3 (N=14)	1.95 - <2.30	16.0	19.0	555.0	871.5	50.8
Q4 (N=15)	≥2.30	19.0	27.0	400.0	933.0	34.5

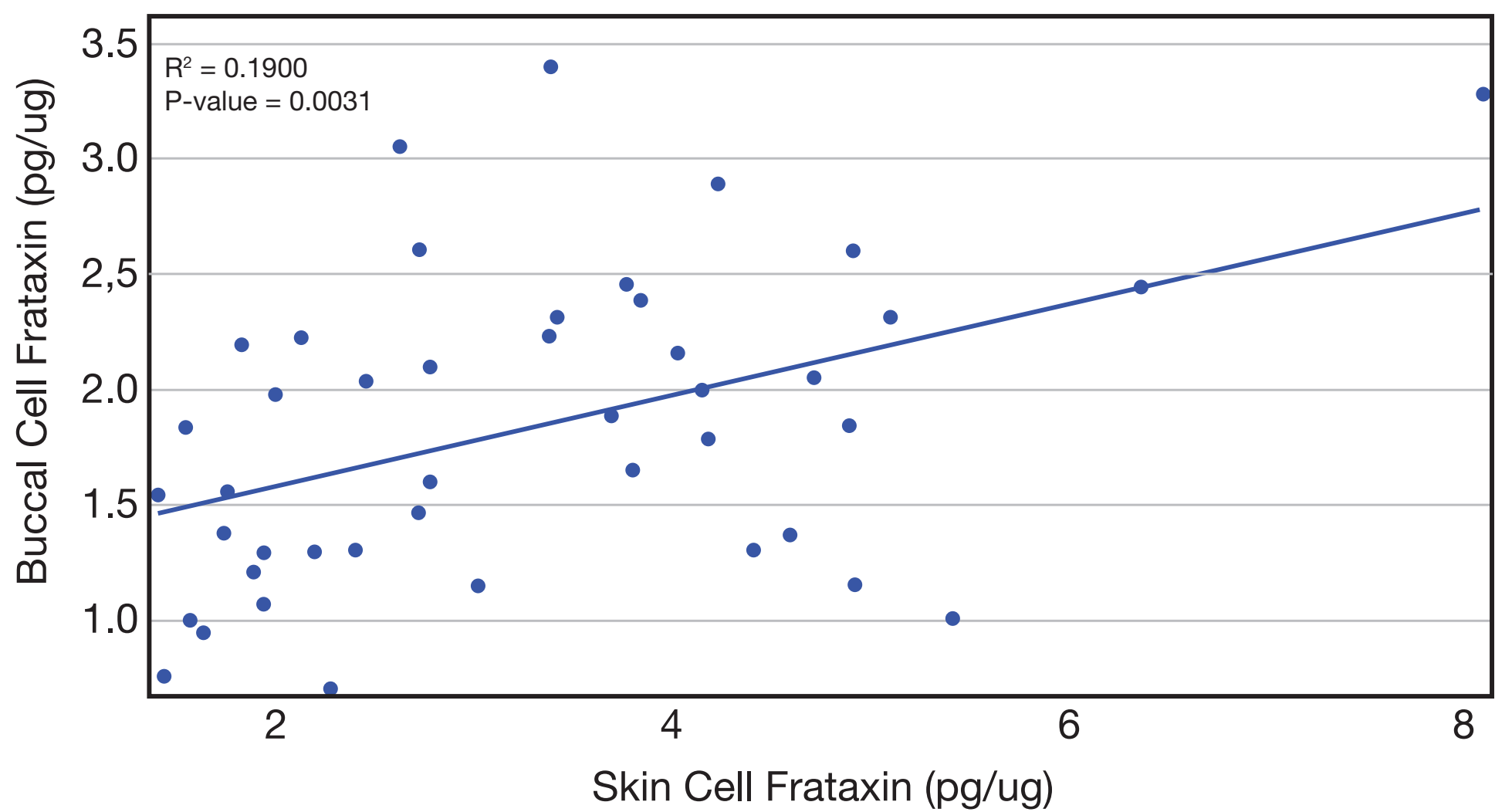
*Quantifiable buccal cells frataxin levels
**Median values
Median buccal cell FXN concentration in healthy controls = 8.1 pg/mcg

Relationship Between Age at Onset and GAA₁ Repeat Length



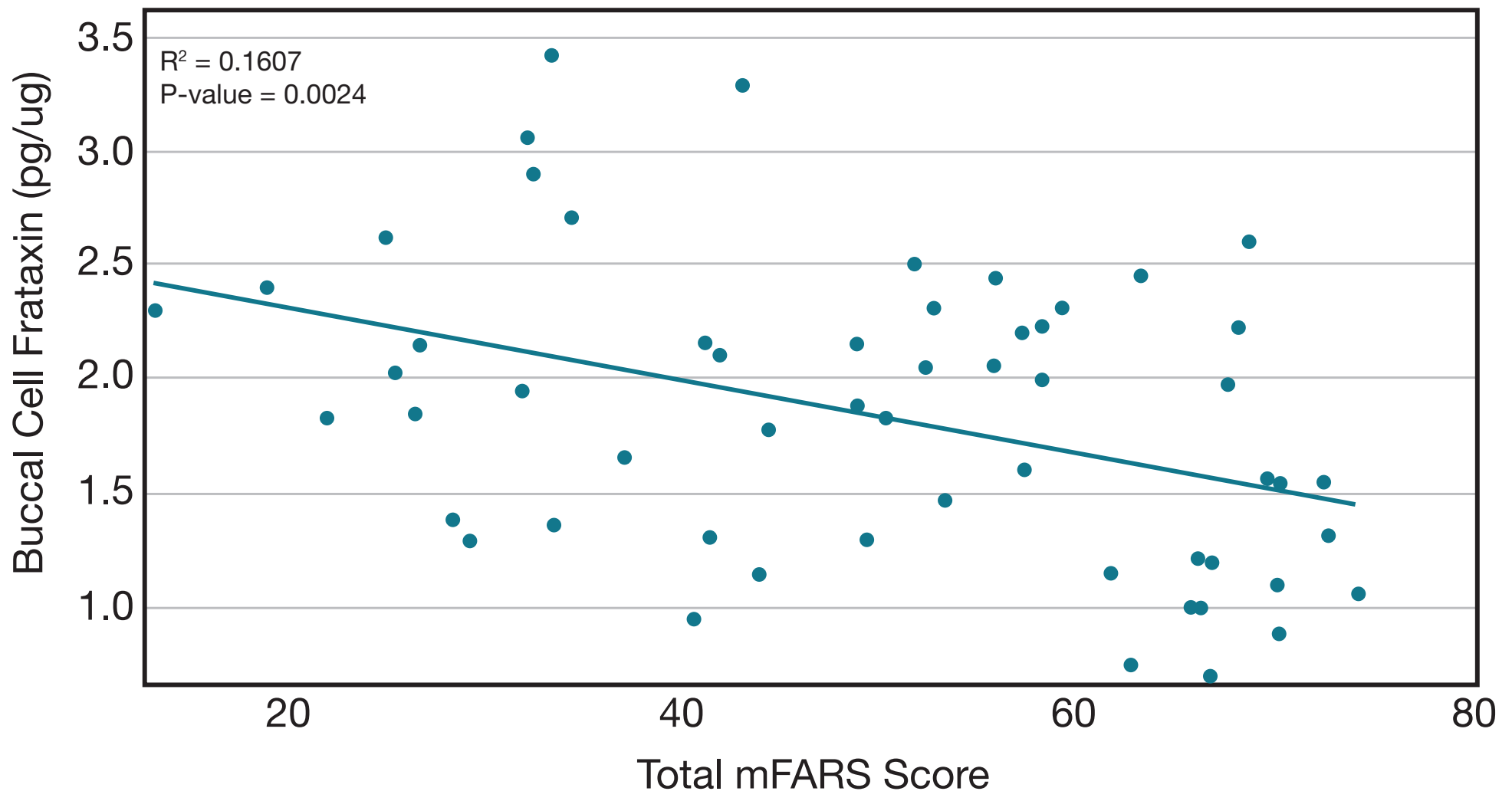
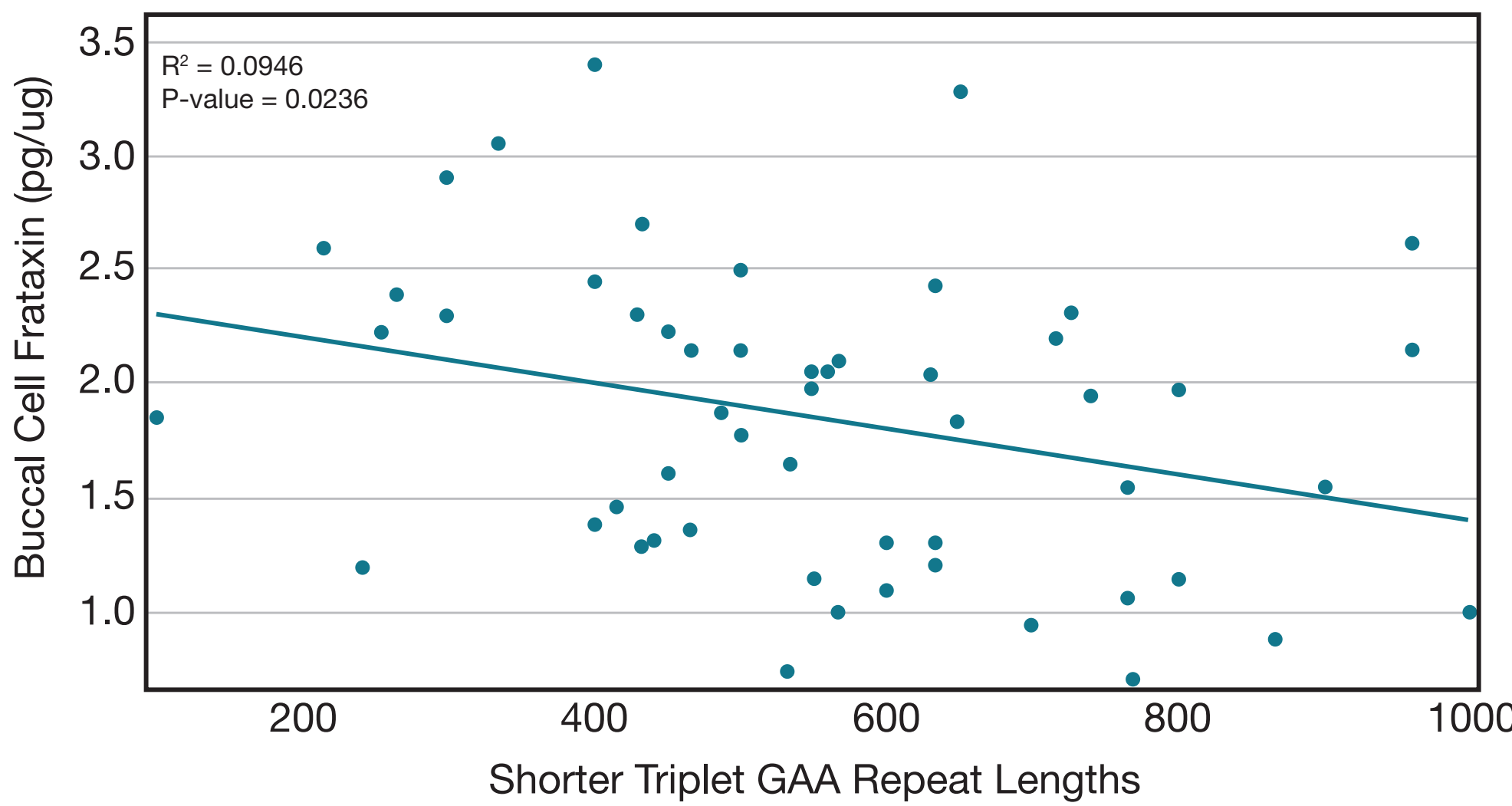
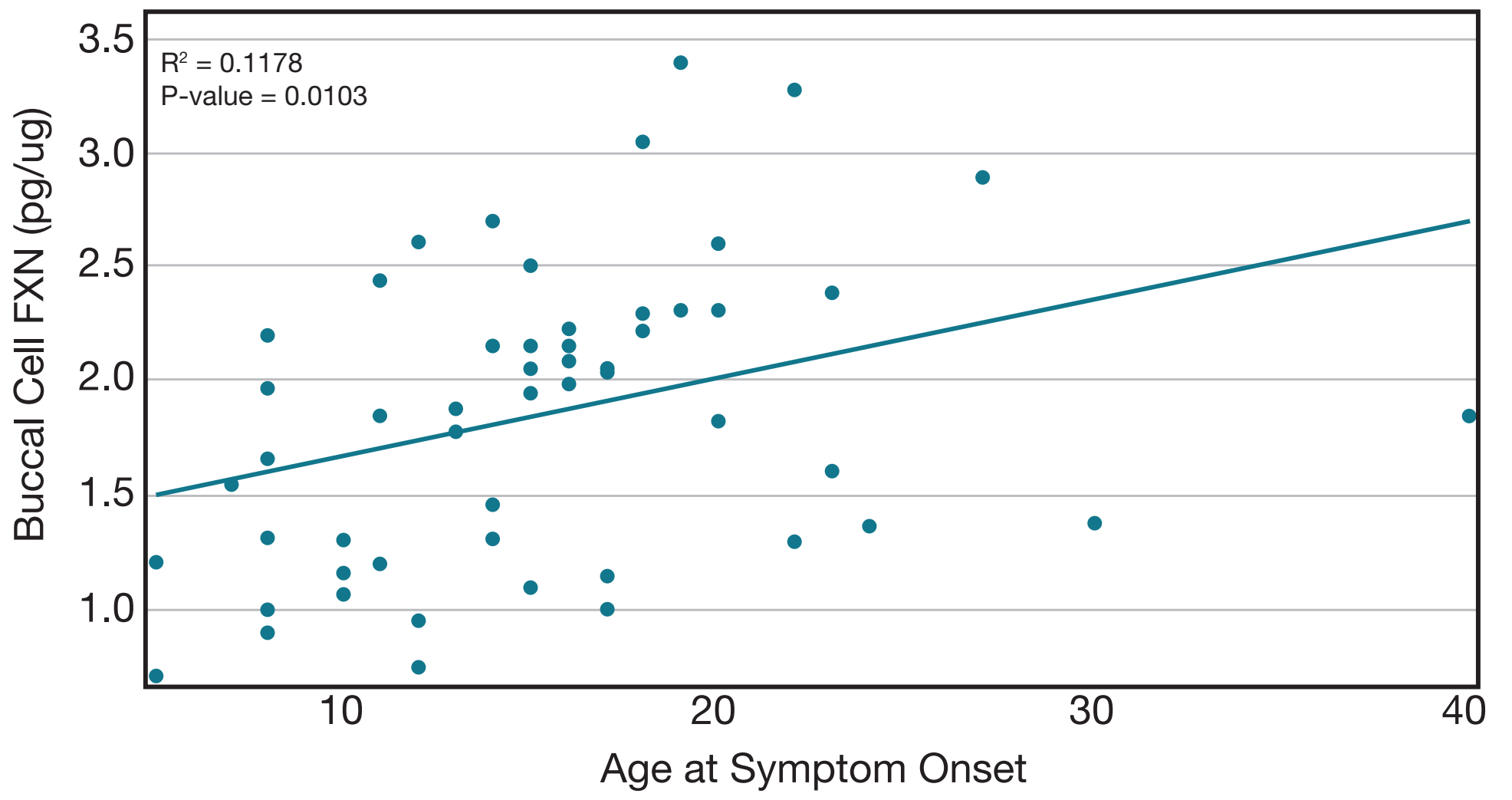
Age at onset inversely correlated with GAA₁ repeat length in adults with FRDA participating in nomlabofusp interventional clinical studies

Relationship Between Baseline Buccal Cell and Skin Cell Frataxin Concentrations



Baseline buccal cell FXN concentrations correlate with skin cell FXN concentrations in adults with FRDA participating in nomlabofusp interventional clinical studies

Relationship Between Baseline Buccal Cell Frataxin Concentrations and Disease Characteristics



Baseline buccal cell FXN concentrations correlate with age at onset and inversely correlate with GAA₁ repeat length and mFARS score in adults with FRDA participating in nomlabofusp interventional clinical studies

Reference to go here if needed

GAA, guanine adenine adenine; LVEF, left ventricular ejection fraction; mFARS, modified Freidreich’s ataxia rating scale; T25FW, timed 25-foot walk

CONCLUSIONS

- Population of 61 participants in nomlabofusp interventional studies represent a wide range of adults with FRDA.
- Relationships observed between disease characteristics and baseline buccal cell FXN concentrations in population of participants in nomlabofusp interventional studies are consistent with reports from previous studies.
- As reported in previously published studies, lower tissue FXN concentrations are associated with more severe disease.
- Baseline buccal cell FXN concentrations are correlated with skin cell FXN concentrations.

Larimar
Therapeutics



ABSTRACT

INTRODUCTION

- ## METHODS

RESULTS

CONCLUSIONS

- Nomlabofusp is an investigational product and is not approved for use.

Prediction of tissue frataxin levels with long-term administration of nomlabofusp in adults with Friedreich’s ataxia using modeling and simulations

Flavia De Toni¹, Noreen Scherer¹, Emily Schapiro², Magdy Shenouda³, Mohamed Hamdani¹, Gopi Shankar¹, and Russell Clayton¹

¹Larimar Therapeutics, Bala Cynwyd, PA; ²A2-Ai, Ann Arbor, MI; ³Clinilabs, Eatontown, NJ



ABSTRACT

Methods: Plasma nomlabofusp concentrations and skin frataxin (FXN) concentrations from adults with Friedreich’s ataxia (FRDA) before and after short term (<30 days) subcutaneous administration of 25, 50, 75, and 100 mg nomlabofusp in Phase 1 and 2 clinical studies were used to construct an exposure-response model. Simulations of a population of virtual FRDA patients receiving daily doses of 25, 50, 75, or 100 mg of nomlabofusp were performed (n=100, 100 trials) and skin FXN profiles over time at each dose were predicted.

Results: The simulations predicted that skin FXN concentrations should reach steady state at approximately 28 days after daily administrations across all doses. Daily administration of 25, 50, 75, and 100 mg nomlabofusp was predicted to attain a median maximum skin FXN concentration of 6.22, 9.06, 11.9, and 14.7 pcg/mcg, respectively.

Discussion: In a separate study, the mean skin FXN concentration in healthy controls with 2 normal FXN alleles was 16.35 pcg/mcg. Prior published studies indicate that the mean FXN concentration in asymptomatic heterozygous carriers is 50% of healthy controls. In relation to these findings, 59% of patients with FRDA receiving daily 50 mg nomlabofusp are predicted to achieve skin FXN concentrations that are equal or above approximately 50% of the concentrations found in healthy controls.

Conclusion: Modeling and simulation using data from short-term studies of nomlabofusp administration can be used to predict a potential long-term therapeutic dose. Daily administration of 50 mg nomlabofusp is predicted to result in skin FXN concentrations that are ≥ 50% of concentrations found in healthy controls.

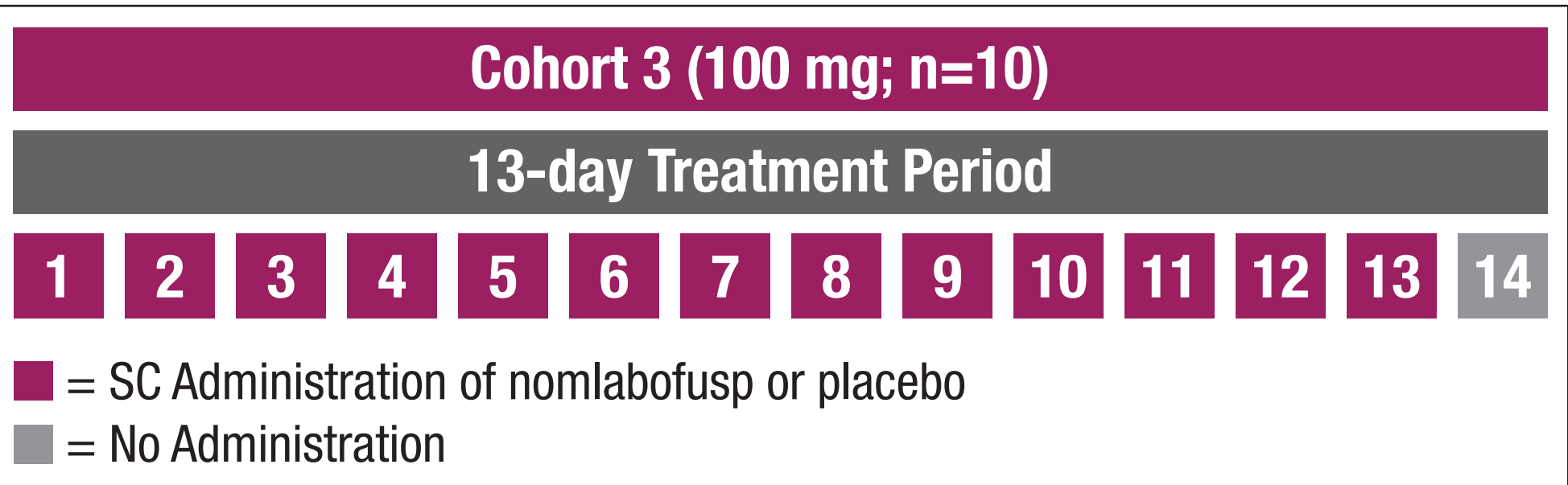
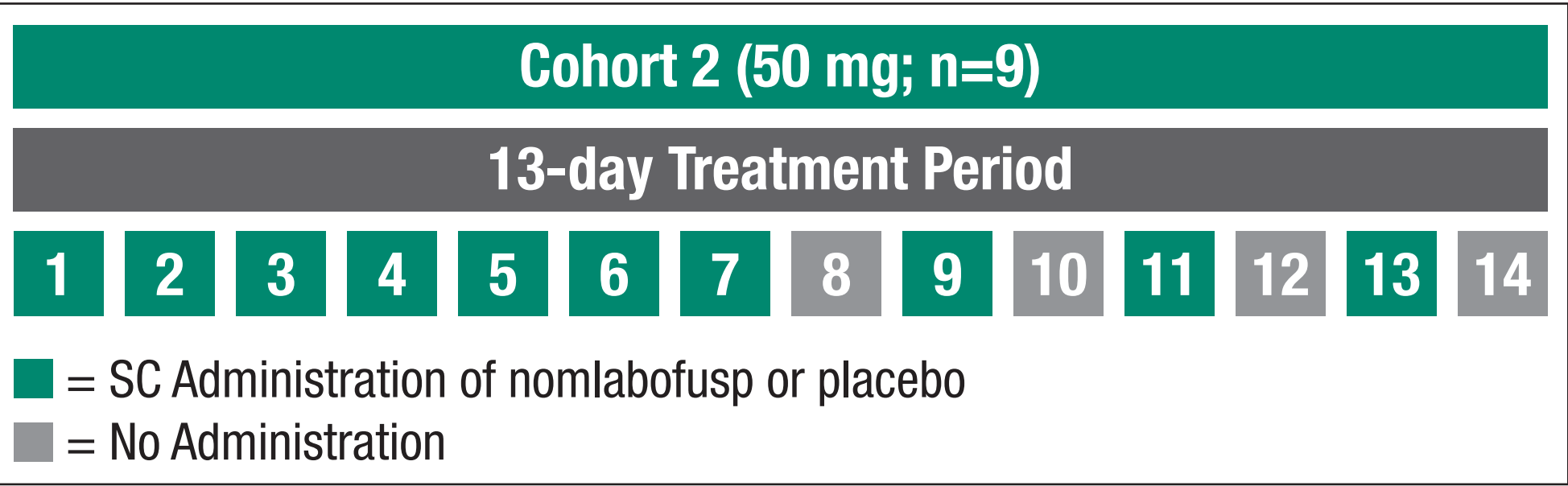
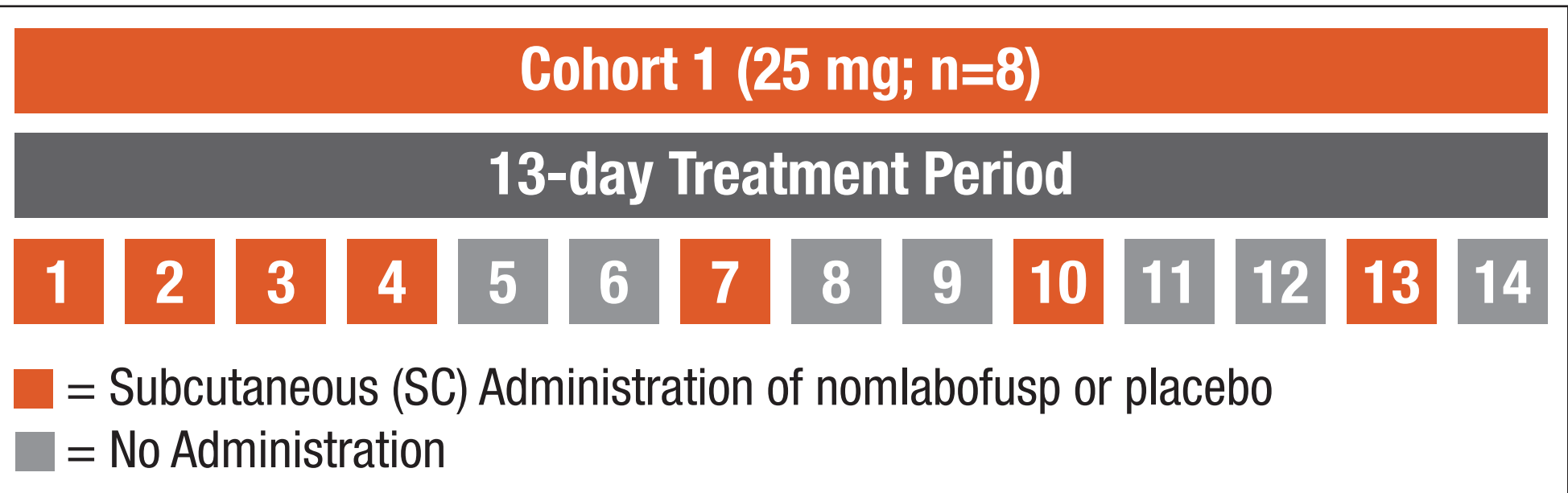
INTRODUCTION

- Frataxin (FXN) deficiency is the root cause of Friedreich’s ataxia (FRDA)
 - Mean tissue FXN concentrations in patients with FRDA range from 21% to 35% relative to healthy controls with 2 normal FXN gene alleles (Deutsch, et al. 2010)
 - In asymptomatic heterozygous carriers, mean tissue FXN concentrations are approximately 50% of controls (Deutsch, et al. 2010)
- Increases in tissue FXN concentrations were observed in adults with FRDA who received nomlabofusp in short-term Phase 1 and Phase 2 studies
 - Over a dose range from 25 mg to 100 mg nomlabofusp, observed increases in tissue FXN concentration appeared to be proportional to both dose and plasma nomlabofusp concentrations
- The objective of this study was to predict the potential increase in tissue FXN concentrations after long-term administration of 25 mg to 100 mg nomlabofusp

METHODS

Clinical Studies

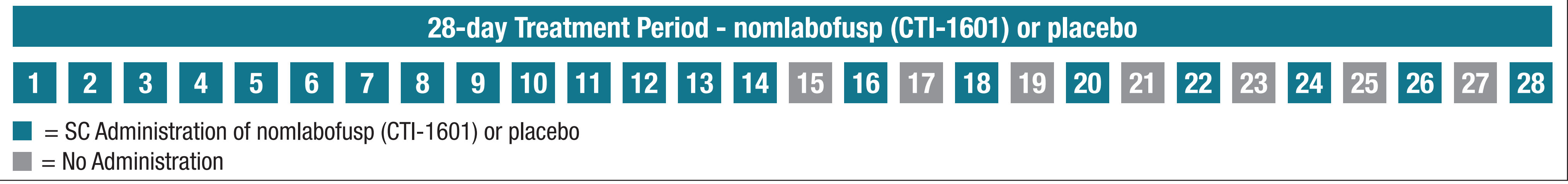
- Plasma nomlabofusp pharmacokinetic (PK) and skin FXN concentration (pharmacodynamic [PD]) data were collected from 3 completed clinical studies in adults with FRDA
 - Single ascending dose (CLIN-1601-101) study evaluating 25 mg, 50 mg, 75 mg, and 100 mg nomlabofusp (nomlabofusp concentrations only)
 - Multiple ascending dose (CLIN-1601-102) study evaluating 25 mg, 50 mg, and 100 mg nomlabofusp



Plasma nomlabofusp concentration samples obtained Days 1, 4/7, 13; Skin FXN concentration samples obtained at baseline and Day 13

METHODS (continued)

- Dose exploration study (CLIN-1601-200) evaluating 25 mg and 50 mg nomlabofusp

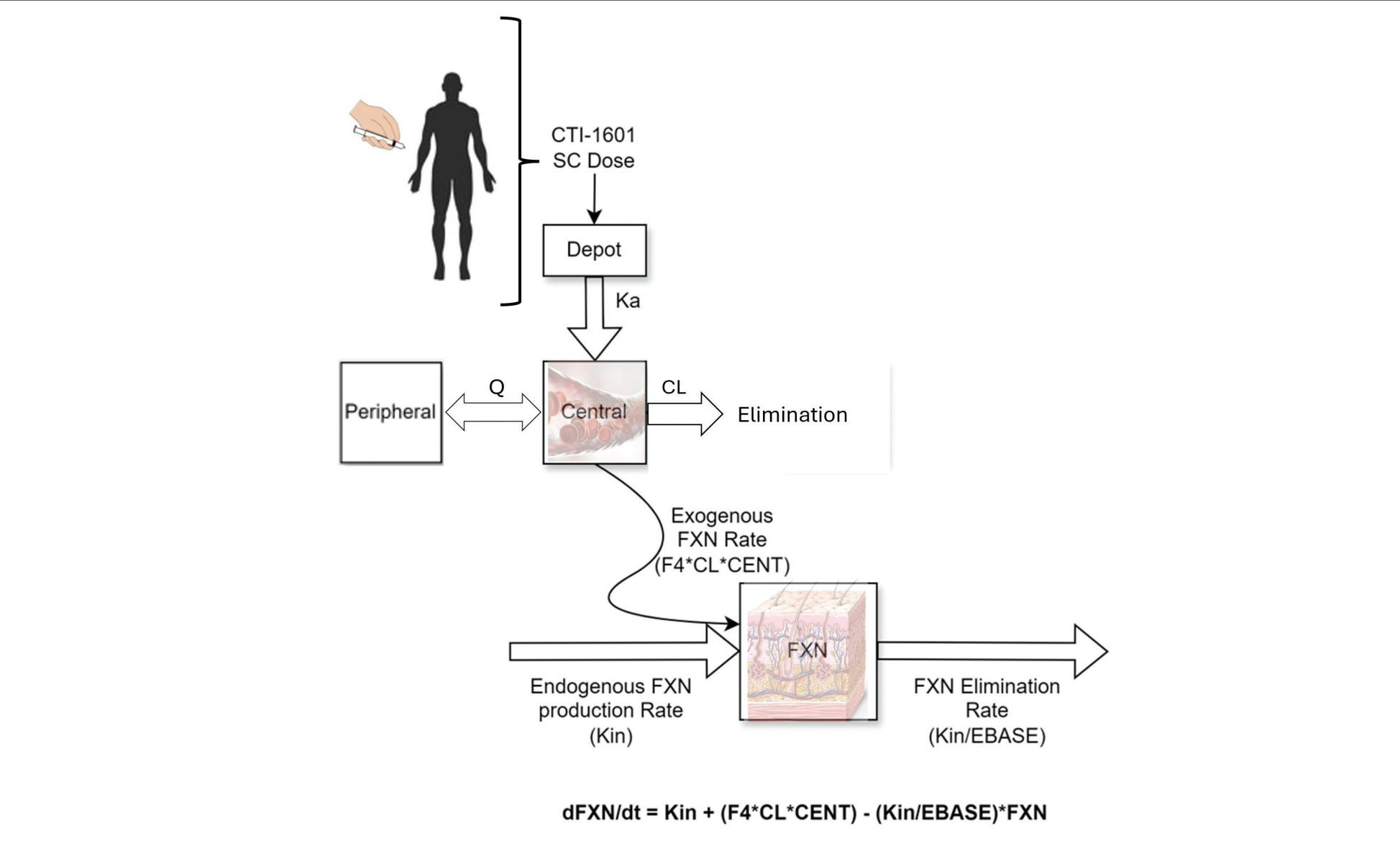


Full plasma nomlabofusp PK profiles obtained Days 1, 7, 14, and 28; Skin FXN concentration samples obtained at baseline, Day 14 and 28

PK/PD

- A Populational PK model (popPK) was developed from 1502 PK samples using NONMEM[®]. Beal’s M3 method was applied to allow inclusion of BLQ data. A two-compartment model with first order absorption and linear elimination was used.
- A PK/PD model (Figure 1) was developed using 95 non-BLQ post-dose observations collected from 61 unique subjects with FRDA.
- Model verification was conducted by visual predictive checks (VPCs).
- A population of virtual FRDA patients receiving subcutaneous daily doses of 25, 50, 75, or 100 mg nomlabofusp for 40 days was simulated (n=100, 100 trials). Body weight and age of diagnosis were simulated based on the observed covariate distributions.
- Distribution of increases in FXN concentration from 50 sets of 2500 virtual FRDA patients was stratified by baseline FXN concentrations and the age of onset.

Figure 1: PK/PD Model Diagram

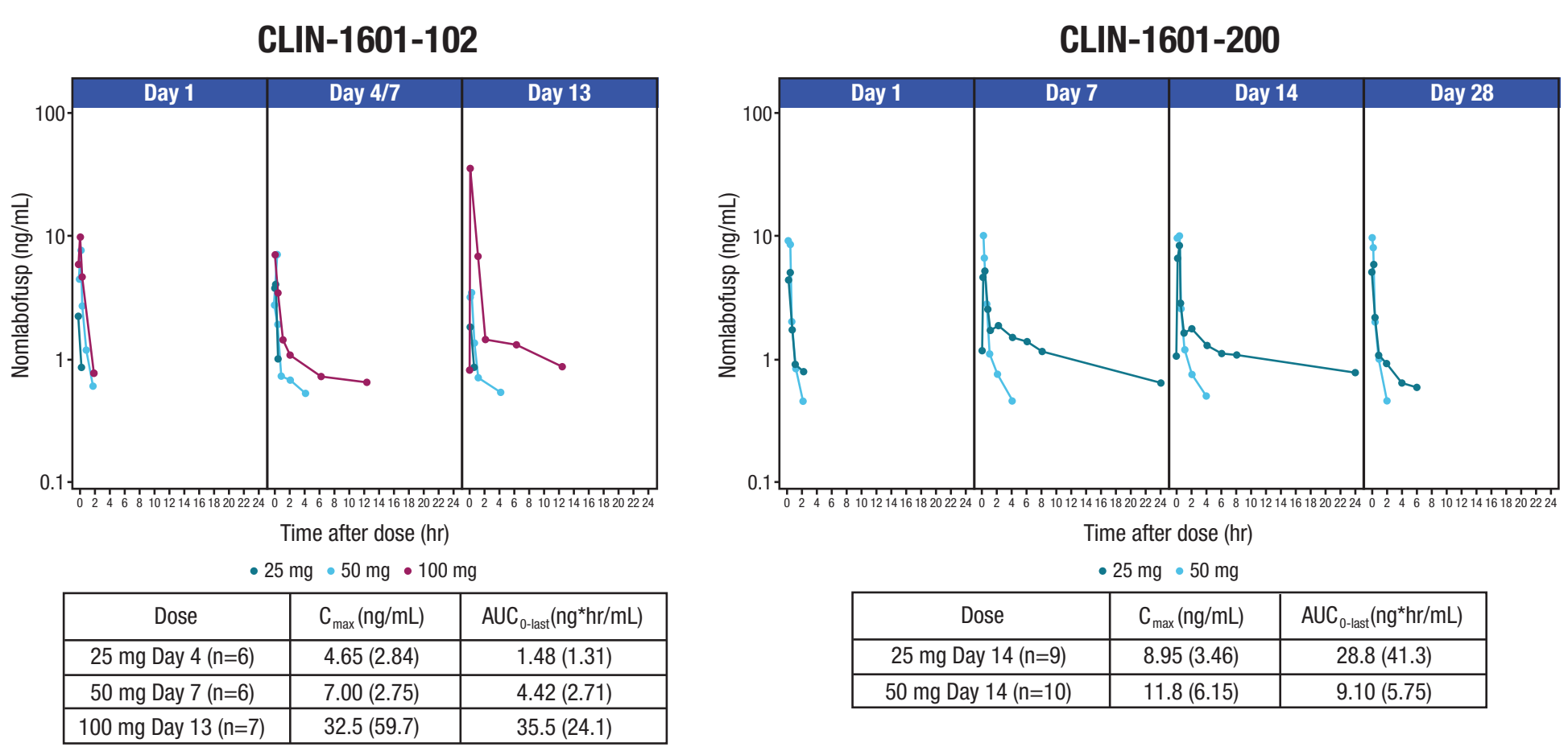


Model Parameters: Kin (zero order rate constant for FXN) 0.0241 1/h; EBASE (estimated baseline) 3.28 pg/μg_{prot}; F4 (proportionality constant for FXN input from central compartment) 0.0194 10³ pg/μg/μg_{prot}

Results

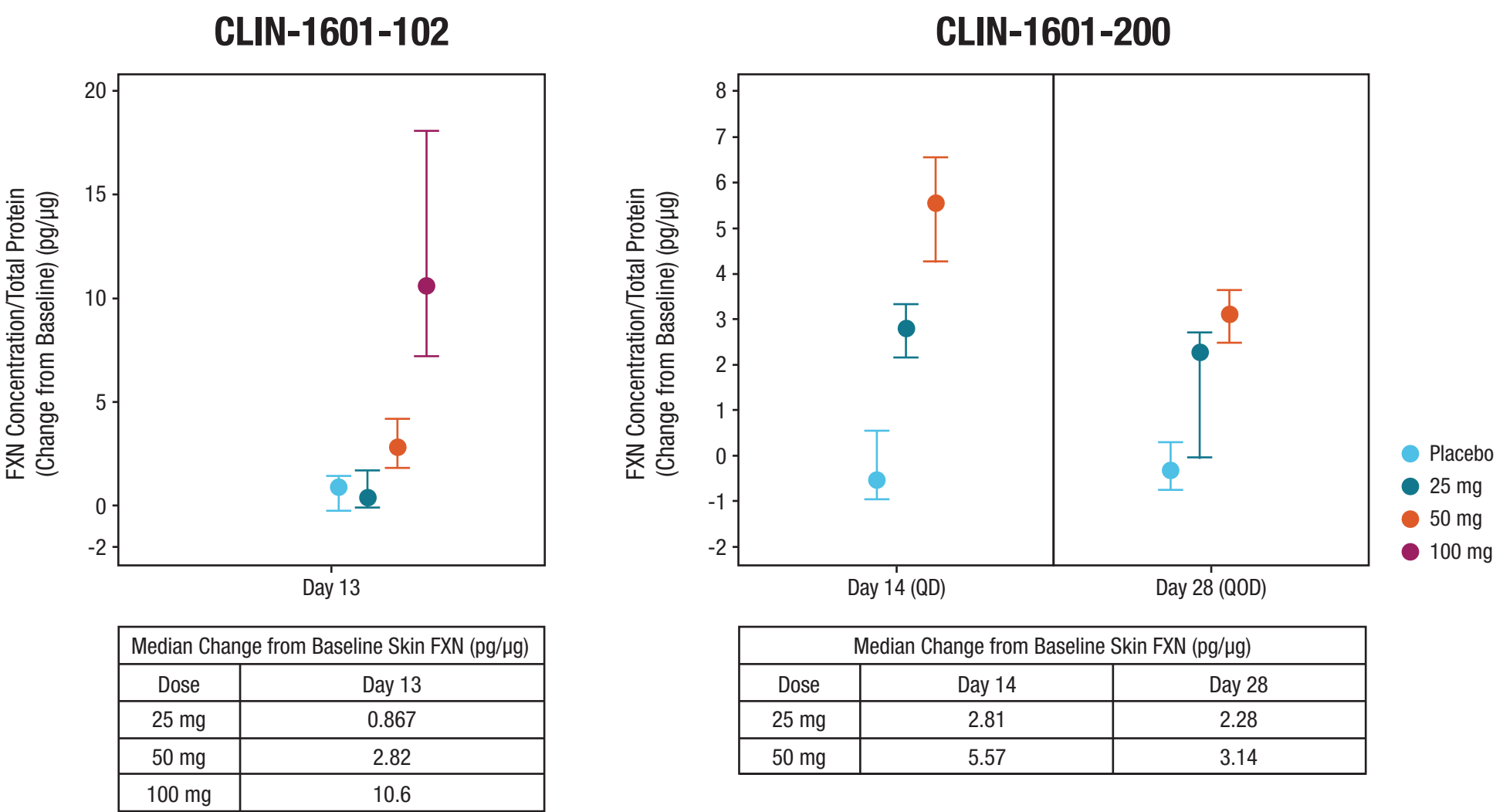
Nomlabofusp PK

- After SC nomlabofusp administration rapid absorption with a multi-exponential decline in concentrations was observed with dose-proportional increases in exposure.



Nomlabofusp PD

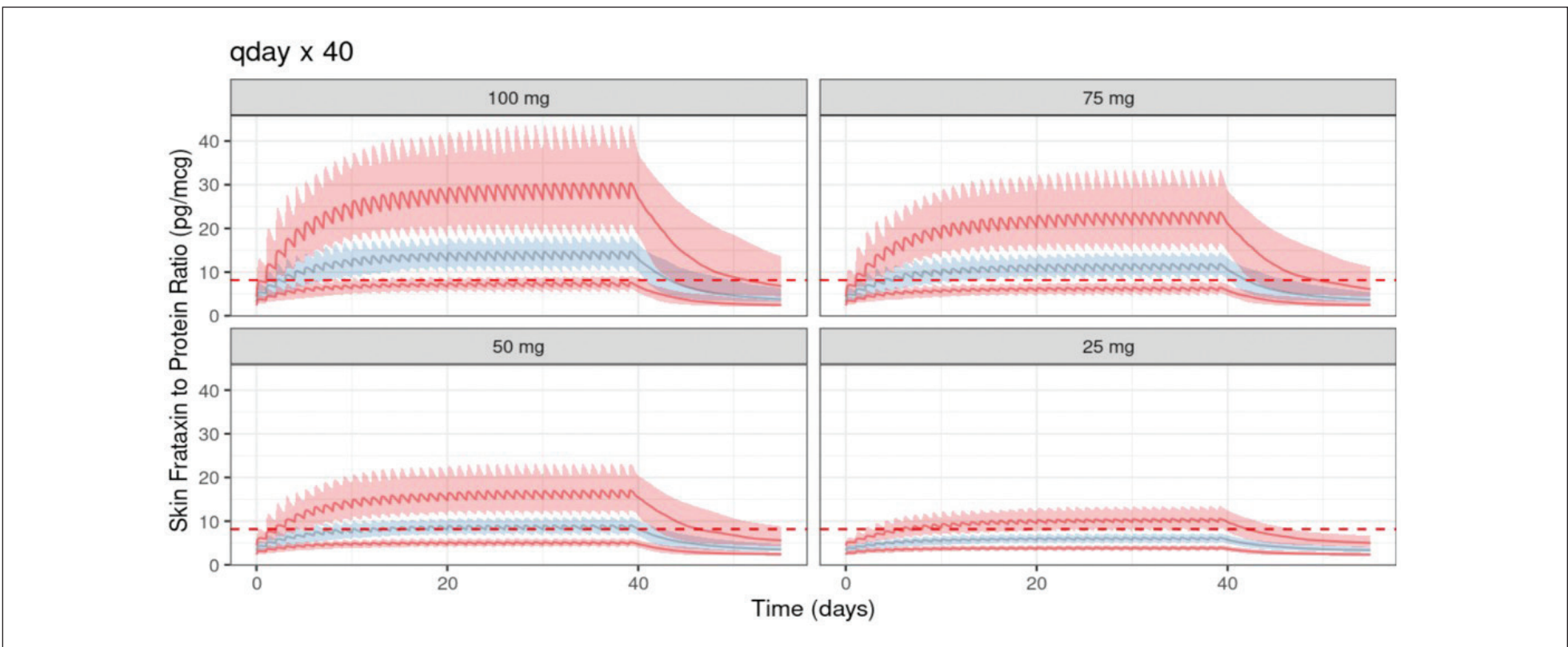
- Dose-dependent increases in skin FXN concentrations were observed in multiple-dose studies:



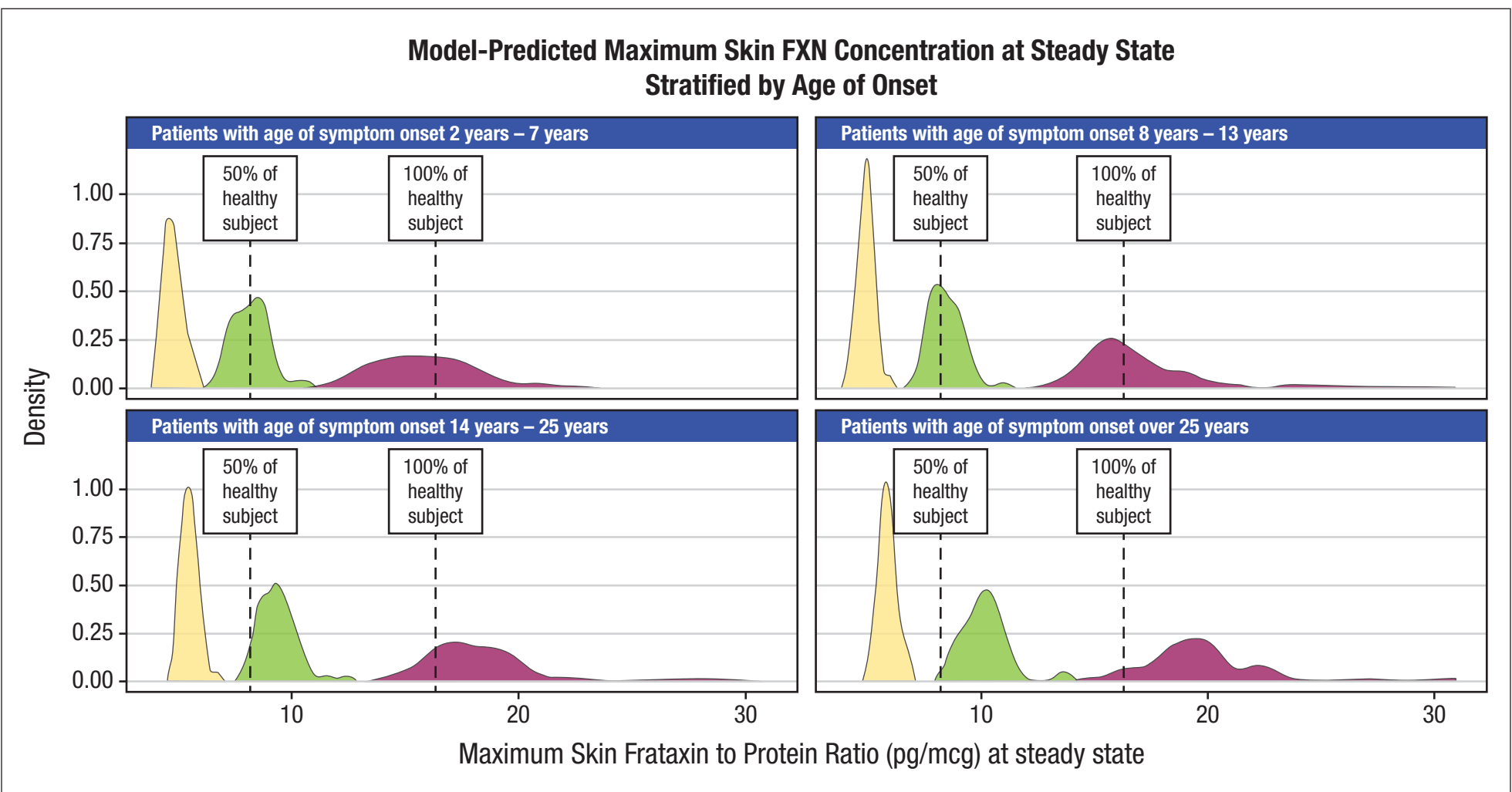
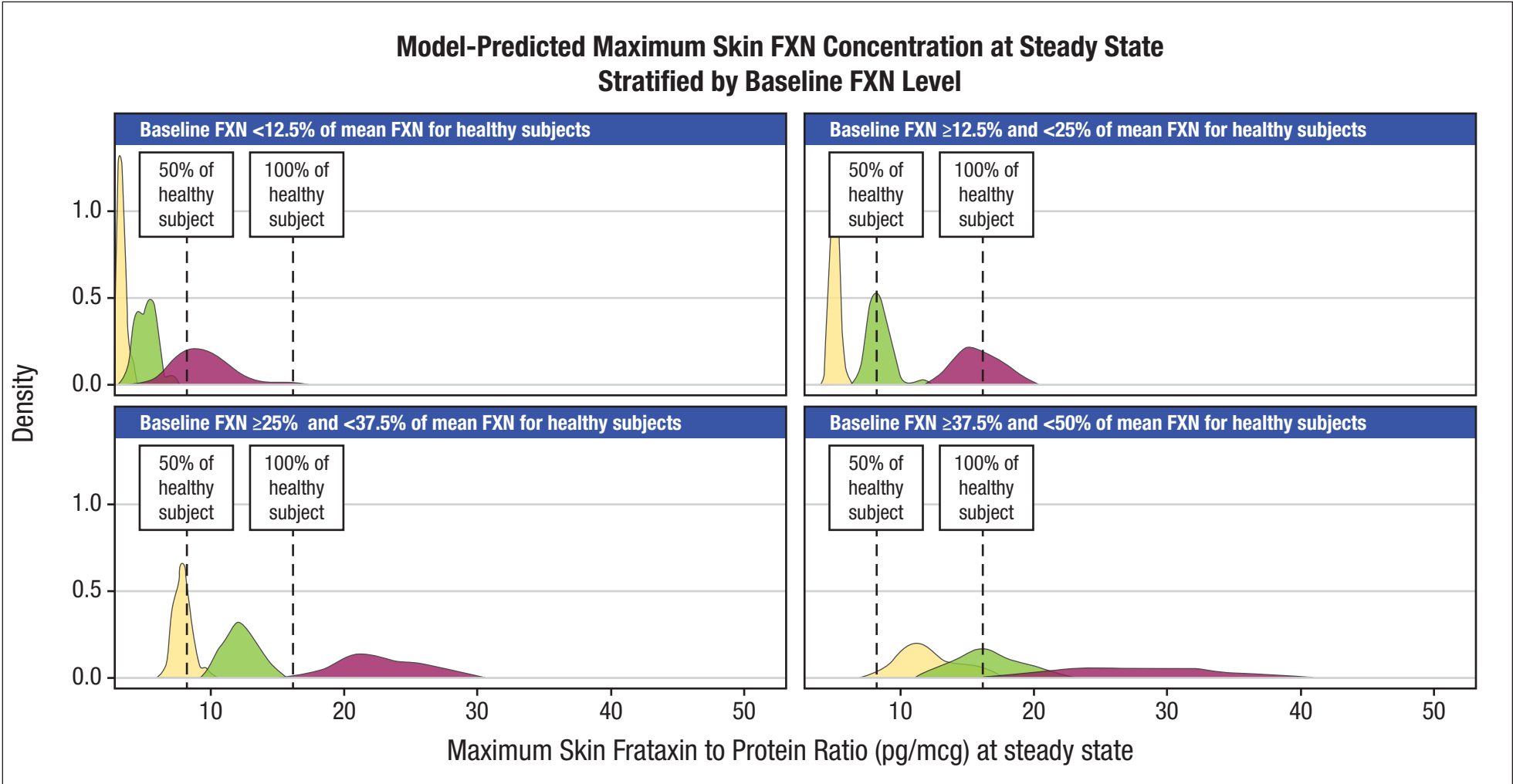
Results (continued)

PK/PD simulations - Dose

- Daily administration of 50 mg nomlabofusp is predicted to result in skin FXN concentrations that are ≥50% of concentrations found in healthy controls.



PK/PD Simulations - Distribution of FXN



The black dashed lines represent 50% (8.17 pg/mcg) and 100% (16.35 pg/mcg) of the mean skin FXN concentrations in healthy controls. The densities correspond to the 10th percentile (yellow), medians (green), and 90th percentile (red) of the simulated maximum skin FXN to protein ratio at steady state.

- Median simulated values indicate that 50 mg nomlabofusp daily is predicted to increase tissue FXN concentrations to a range that approaches or surpasses the 50% level relative to the mean healthy control FXN concentrations in patients with FRDA over a range of different baseline FXN concentrations and ages of onset.

CONCLUSIONS

- Dose-dependent increases in nomlabofusp exposure and skin FXN concentrations were observed in adults with FRDA after short-term administration of 25 mg-100 mg nomlabofusp.
- Modeling and simulation indicate that daily administration of 50 mg nomlabofusp is predicted to result in skin FXN concentrations that are ≥50% of concentrations found in healthy controls.
- Further extension of the model applications to the pediatric population is planned to predict the impact of nomlabofusp administration on FXN concentrations across different age groups.
- Data from an ongoing open-label extension study will be used to confirm nomlabofusp exposure and changes in tissue FXN concentrations after long-term administration of nomlabofusp to patients with FRDA.