Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Study to Evaluate Efficacy, Tolerability, and Pharmacokinetics of Multiple Doses of Oral TAK-831 in Adult Subjects With Friedreich Ataxia

NCT Number: NCT03214588

Protocol Approve Date: 06 October 2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Study to Evaluate Efficacy, Tolerability, and Pharmacokinetics of Multiple Doses of Oral TAK-831 in Adult Subjects With Friedreich Ataxia

Short Title: TAK-831 in Friedreich Ataxia

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015		
Study Number:	TAK-831-1501		
IND Number:	132,633	**EudraCT Number:**	Not Applicable
Compound:	TAK-831		
Date:	06 October 2017	**Version Number:**	Amendment No. 01

Amendment History:

Date	Amendment Number	Amendment Type	Region
12 April 2017	Initial Protocol	Not applicable	Global
06 October 2017	Amendment 01	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center Americas, Inc. (TDC Americas) sponsored investigators per United States (US) requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol and study drug) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The electronic signatures of the responsible Takeda medical officer (and other signatories, as listed below) are provided on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** TAK-831	
Title of Protocol: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Study to Evaluate Efficacy, Tolerability, and Pharmacokinetics of Multiple Doses of Oral TAK-831 in Adult Subjects with Friedreich Ataxia	**IND No.:** 132,633	**EudraCT No.:** Not Applicable
Study Number: TAK-831-1501	**Phase: 2**	

Study Design:

TAK-831-1501 is a phase 2, randomized, double-blind, placebo-controlled, parallel-arm study designed to evaluate the efficacy, safety, pharmacodynamic (PD) effects, and pharmacokinetics (PK) of 2 dose levels of oral TAK-831 in adult subjects with Friedreich ataxia (FRDA).

The study will include a Screening Period (Days -28 to -2), a Training Period (Day -1), Treatment (Days 1 to 84), a Phone Exit Interview (within 7 days from the last dose of study medication of the Double-Blind Treatment Period or within 7 days of notification of termination for the Early Termination Visit), and a Safety Follow-up Phone Call (7 to 17 days after last dose of study drug).

Approximately 65 subjects that meet the study entry criteria during Screening will be invited on Day -1 to attend training to minimize practice effect on efficacy assessment. On Day 1, subjects who continue to meet inclusion and none of the exclusion criteria will be randomized in a 2:1:2 ratio to TAK-831 high dose, TAK-831 low dose, or placebo, respectively. Randomization will be stratified by ambulation status (ambulatory vs nonambulatory).

Subjects will receive study drug or placebo dosing twice daily (BID) from Day 1 through Day 84. Clinic visits include Day 1 and end of Weeks 2, 7, and 12. Clinical assessments, blood collections, and laboratory tests will be conducted at specific time points per the schedule of study procedures. A semistructured Exit Interview will be conducted by phone to provide an in-depth, qualitative evaluation of the subject experience and subject-perceived change due to treatment, and a Safety Follow-up Phone Call will be conducted.

Table 1. Schematic of Study Design

		Treatment (TAK-831 high dose, TAK-831 low dose, or placebo)			
Screening	**Efficacy Assessment Training**	**Randomization, Baseline, and Dosing**	**Efficacy, PK, PD, and Safety Assessments**	**Phone Exit Interview**	**Safety Follow-up Phone Call (a)**
Days -28 to -2	Day -1	Day 1	Day 14 (±3 days), Day 49 (±3 days), Day 84 (±2 days)	≤7 days after Final Visit or termination	7 to 17 days after last dose

(a) The Follow-up phone call will occur 7 to 17 days after the last dose of study drug by telephone unless subject report concerning AEs. In these cases, subjects will be brought back into the clinic for re-evaluation at the investigator's discretion.

Primary Objective:

- To evaluate the efficacy of TAK-831 versus placebo on upper extremity (arm and hands) motor function and manual dexterity, as measured by the 9-hole peg test (9-HPT).

Secondary Objectives:

- To evaluate the efficacy of TAK-831 versus placebo on Activities of Daily Living (ADL), as measured by the ADL component of the Friedreich Ataxia Rating Scale (FARS), and those items that are related to upper limb function.
- To evaluate the efficacy of TAK-831 versus placebo on neurological function, as measured by the modified Friedreich Ataxia Rating Scale neurological examination (mFARS-neuro) Total Score.
- To evaluate the efficacy of TAK-831 versus placebo on lower extremity motor function, as measured by the Timed 25-Foot Walk (T25FW).
- To evaluate the efficacy of TAK-831 versus placebo on limb ataxia, as measured by the composite of the T25FW and 9-HPT.
- To evaluate the efficacy of TAK-831 versus placebo on visual acuity, as measured by the low-contrast letter acuity (LCLA) testing with Sloan charts.
- To evaluate the efficacy of TAK-831 versus placebo on global improvement, as measured by the Clinical Global Impression-Improvement (CGI-I).
- To evaluate the efficacy of TAK-831 versus placebo on global improvement, as measured by the Patient Global Impression-Improvement (PGI-I).
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional improvement, as measured by the CGI-I.
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional improvement, as measured by the PGI-I.
- To evaluate the efficacy of TAK-831 versus placebo on global severity, as measured by the Clinical Global Impression-Severity (CGI-S).
- To evaluate the efficacy of TAK-831 versus placebo on global severity, as measured by the Patient Global Impression-Severity (PGI-S).
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional severity, as measured by the CGI-S.
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional severity, as measured by the PGI-S.
- To evaluate the safety and tolerability of TAK-831.

Exploratory Objectives:

- To evaluate the efficacy of TAK-831 versus placebo on speech, as measured by digital assessments.
- To evaluate the efficacy of TAK-831 versus placebo on motor function such as gait, balance, and upper limb coordination, as measured by digital sensors.
- To evaluate the PK and PD (plasma D-serine and L-serine levels and D-serine:Total serine ratios), and explore the relationships between TAK-831 exposures and D- and L-serine levels or selected measures of efficacy.
- To correlate plasma D-serine and L-serine levels, and D-serine:Total serine ratios with clinical parameters of disease status.
- To quantify subject-perceived meaningful change in upper limb motor function, as evaluated by the Exit Interview.

CCI

CCI [redacted]

Subject Population: Male and female subjects aged 18 to 55 years, inclusive, with genetically-confirmed FRDA disease of stages 2 to 5, as determined by the Functional Staging for Ataxia, and able to complete the 9-HPT in ≤150 seconds.

Number of Subjects:	**Number of Sites:**
2:1:2 ratio for placebo, low, and high dose, respectively Estimated total: 65 subjects randomized	Approximately 6 or more specialized academic neurological clinical centers in the United States
Dose Levels: Placebo BID TAK-831 75 mg BID TAK-831 300 mg BID	**Route of Administration:** Oral
Duration of Treatment: 12 weeks	**Period of Evaluation:** 12 weeks of treatment + 7 to 17 days after the last administration of study drug

Main Criteria for Inclusion:

- The subject is an adult male or female aged 18 to 55 years, inclusive, with genetically-confirmed diagnosis (homozygous for guanine-adenine-adenine repeat expansions in the frataxin (FXN) gene in the affected range of FRDA or a compound heterozygous expansion with a point mutation or deletion), with an established disease stage of 2 to 5, inclusive, as determined by the Functional Staging for Ataxia, at Screening.
- The subject is able to complete the 9-HPT test in ≤150 seconds at Screening.
- Male subjects who are nonsterilized and sexually active with a female partner of childbearing potential must agree to use adequate contraception from signing of informed consent throughout the duration of the study and for 95 days after last dose.
- Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and must agree to use adequate contraception from signing of informed consent throughout the duration of the study and for 35 days after last dose.
- The subject is able to swallow study drug in tablet form.
- If a subject requires a caregiver to accompany him/her during the study for clinic visits, a caregiver and backup caregivers should be available.

Main Criteria for Exclusion:

- The subject has a diagnosis of ataxic syndromes other than FRDA.
- The subject has, based on medical history and investigator clinical judgment, uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, endocrine disease (including uncontrolled diabetes), or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the efficacy and safety evaluation. The subject has medical history or conditions that, in the opinion of the investigator, may interfere with study conduct or clinical assessments.
- The subject has received treatment with other experimental therapies within the last 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug.

- The subject has a known hypersensitivity to any component of the formulation of TAK-831.
- The subject has taken any excluded medication, or has had insufficient washout of medications as listed in the Excluded/Allowed Medications, Procedures, and Treatments table listed in Section 7.3 or is unable or unwilling to discontinue medications as required by the protocol.
- The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property or subjects who within the past year prior to Screening have attempted suicide or have positive answers on item 4 or 5 on the Columbia Suicide Severity Rating Scale ([C-SSRS], life-time version) at Screening or Day 1.
- The subject has clinically significant cardiac abnormalities at Screening that, in the opinion of the investigator, would make the subject unsuitable for enrollment, including but not limited to heart failure meeting criteria for class IV insufficiency by the New York Heart Association or documented ejection fraction <40%.
- The subject has a QT interval with Fridericia correction method (QTcF) >450 ms (males) or>470 ms (females), confirmed with 1 repeat testing, at Screening or Day 1.
- If female, the subject is of childbearing potential and lactating, pregnant (positive prerandomization serum pregnancy test), or plans to become pregnant before participating in the study, during the study, or within 35 days after last dose of the study drug.

Main Criteria for Evaluation and Analyses:

Primary Endpoint

The primary endpoint for this study is the change from Baseline to Week 12 in the inverse of the time to complete the 9-HPT (9-HPT^{-1}) after treatment with TAK-831, compared with placebo.

Secondary endpoints

- The change from Baseline to Weeks 2, 7, and 12 on the ADL component of the FARS, after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the ADL component upper limb function items (ADL items 3-5) of the FARS, after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2 and 7 on the 9-HPT after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2 and 7 on the ADL individual items after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the mFARs-neuro total score after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the mFARS-neuro subscales and individual items after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the T25FW after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the 9-HPT and T25FW composite score after treatment with TAK-831, compared with placebo.
- Percentage of subjects whose 9-HPT completion time is reduced by at least 15% and at least 20% from Baseline.
- The change from Baseline to Weeks 2, 7, and 12 on LCLA test score after treatment, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on CGI-I (global change) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI-I (global change) after treatment with TAK-831, compared with placebo.

- The change from Baseline to Weeks 2, 7, and 12 on CGI-I (upper extremity functional change) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI- I (upper extremity functional change) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on CGI-S (global severity) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI-S (global severity) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on CGI-S (upper extremity functional severity) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI-S (upper extremity functional severity) after treatment with TAK-831, compared with placebo.

Safety endpoints

- Adverse events and clinical laboratory and electrocardiogram measures after treatment with TAK-831, compared with placebo.
- Assessment of suicidal ideation and behavior as measured by the C-SSRS at Screening, Baseline, and all other timepoints.

Exploratory endpoints

- The change from Baseline to Weeks 2, 7 and 12 on the digital speech assessment after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the digital motor sensors measurements such as gait, stability and upper limb coordination after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on TAK-831 plasma D-serine and L-serine levels and D-serine:Total serine ratios after treatment with TAK-831, compared with placebo.
- Percent of subjects reporting a meaningful change in upper limb function from Baseline to Week 12 after treatment with TAK-831, compared with placebo, as evaluated by the Exit Interview.
- Correlation of change in 9-HPT with that of patient reported improvement of change in upper limb function, such as ADL items 3 to 5 and PGI.
- TAK-831 plasma concentration.

Statistical Considerations:

The primary endpoint for this study is the change from Baseline to Week 12 in the inverse of the time to complete the 9-HPT (9-HPT^{-1}) after treatment with TAK-831, compared with placebo. The 2 TAK-831 doses will be compared with placebo, controlling multiplicity using Holm's method. The dose with the smaller p-value will be tested at the 1-sided 0.05 level, then the dose with the larger p-value will be tested at the 1-sided 0.10 level only if the smaller p-value is significant. This procedure will control the overall type I error rate at the 1-sided 0.10 level.

Sample Size Justification:

Approximately 65 subjects will be randomized in a 2:1:2 ratio to the high dose, low dose, or placebo, respectively. It is assumed that approximately 60 subjects (92%) will complete 12 weeks and be evaluable on the primary endpoint. If the rate of early withdrawal is substantially greater than predicted, then an increase to the number of randomized subjects may be considered. Assuming an effect size of 0.6 for each dose, this approach gives 77% power for at least 1 dose to be deemed superior to placebo and 54% power for both doses. The effect size was chosen based on expert advice that a treatment effect equivalent to preventing or reversing 2 years of decline due to Friedreich ataxia (FDRA) would be clinically meaningful. The target effect size should be approximately 0.6 for each endpoint.

2.1 Protocol Amendment No. 01 Summary of Changes

Rationale for Amendment No. 01

This document describes the changes in reference to the protocol incorporating Amendment No. 01. The primary reasons for this amendment are to amend the dose, clarify/recategorize study objectives and endpoints, modify study procedures to reduce the number of visits and blood draws and update randomization scheme, clarify study entrance criteria and excluded medications, update the clinical data summary, and add an internal Data Monitoring Committee (DMC). Personnel changes, inconsistencies, and minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific description of text changes and where the changes are located, see Appendix E.

Changes in Amendment No. 01

1. Revision of study procedures (reduce the number of visits and blood draws, and update the randomization scheme).
2. Revision of TAK-831 dose.
3. Recatagorizing of objectives and endpoints related to Activities of Daily Living.
4. Clarification of endpoints related to the 9-hole peg test.
5. Revision and clarification of study entry criteria.
6. Clarification of excluded medications and products.
7. Revision of statistical analysis.
8. Inclusion of the summary of clinical data from Studies TAK-831-1004 and TAK-831-1005.
9. Engagement of an internal DMC to review unblinded safety data.
10. Personnel change

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

Term	Definition
9-HPT	9-hole peg test
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CGI	Clinical Global Impression Scale
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C_{max}	maximum observed concentration
CNS	central nervous system
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DAO	D-amino acid oxidase
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EIIBs	eosinophilic intranuclear inclusion bodies
FACOMS	Friedreich Ataxia Clinical Outcome Measures Study
FARS	Friedreich Ataxia Rating Scale
FAS	full analysis set
FDA	Food and Drug Administration
FRDA	Friedreich ataxia
FSH	follicle-stimulating hormone
FXN	frataxin gene
GAA	guanine-adenine-adenine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HPLC	high-performance liquid chromatography
HRQoL	health-related quality of life
ICH	The International Council for Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio

Term	Definition
IRB	institutional review board
IRT	interactive response technology
LCLA	low-contrast letter acuity
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mFARS	modified Friedreich Ataxia Rating Scale
mFARS-neuro	modified Friedreich Ataxia Rating Scale neurological examination
MMRM	mixed model for repeated measures
MRD	multiple-rising dose
NMDA	*N*-methyl-D-aspartate
PD	pharmacodynamic(s)
PET	positron emission tomography
PGI-I	Patient Global Impression-Improvement
PGI-S	Patient Global Impression-Severity
PGx	pharmacogenomics
C CI	[redacted]
PTE	pretreatment event
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAP	statistical analysis plan
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
T25FW	Timed 25-Foot Walk
UGT	uridine 5'-diphosphate glucuronosyltransferase
ULN	upper limit of normal

3.4 Corporate Identification

TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Study Drug

TAK-831 is a highly selective and potent small molecule inhibitor of D-amino acid oxidase (DAO) being developed by Takeda. DAO is the major enzyme responsible for the catabolism/degradation of small neutral amino acids like D-serine and is highly expressed in the cerebellum [1]. Inhibiting DAO leads to a measurable increase in D-serine levels in plasma, cerebrospinal fluid (CSF), and cerebellum in rodents (Study TAK-831-10031). D-serine is a potent *N*-methyl-D-aspartate (NMDA)-type glutamate receptor coagonist and an agonist for the δ2 glutamate receptor, which has been implicated in synaptic plasticity and long-term depression [2,3]. As a DAO inhibitor that increases D-serine in the cerebellum, TAK-831 has the potential to increase NMDA-dependent glutamatergic signaling. The literature suggests that D-serine is a critical mediator of glutamate receptor–dependent functions of the cerebellum, which coordinates muscular activity [2,3]. Therefore, inhibition of DAO and a subsequent increase in D-serine in the cerebellum may lead to an improvement in cerebellar output.

4.1.2 Friedreich Ataxia

Ataxia manifests as impaired coordination of muscle movements. It is a nonspecific clinical manifestation indicative of dysfunction in the parts of the central nervous system (CNS) that coordinate movement. Patients with ataxia have trouble regulating the force, range, direction, velocity, and rhythm of muscle contractions, resulting in a characteristic type of irregular, uncoordinated movement that can manifest itself in many possible ways, such as asthenia, asynergy, delayed reaction time, and dyschronometria [4]. Patients also display instability of gait, difficulty with eye movements, dysarthria, dysphagia, hypotonia, dysmetria, and dysdiadochokinesia (impaired ability to perform rapid, alternating movements). These difficulties can affect employability, lead to disability, increase caregiver burden, and significantly reduce a person's health-related quality of life (HRQoL) [5].

There are numerous types of ataxias, many genetically mediated and others idiopathic. Friedreich ataxia (FRDA) is the most common of the hereditary ataxias and occurs in approximately 50% of overall cases of hereditary ataxia in Europe and North America (prevalence of 1:50,000 Caucasians) [6,7]. The number of individuals affected with FRDA at any given time in the United States is approximately 5,000 [8]. In people with FRDA, a guanine-adenine-adenine (GAA) trinucleotide repeat expansion mutation in intron 1 of the frataxin gene (FXN) results in drastically reduced levels of the frataxin protein [9,10], which in turn leads to mitochondrial dysfunction, neurodegeneration, cardiomyopathy, diabetes mellitus, and skeletal deformities [7,11,12]. A small number of cases are caused by a compound heterozygous expansion with a point mutation or deletion [12]. This disorder has a sensory ataxia component secondary to involvement of the dorsal root ganglia and spinocerebellar tracts, with loss of proprioceptive function and sensory neuropathy, as well as gradual decreases in sensory function that lead to visual and hearing impairments [13]. There is also progressive destruction of the cerebellar dentate nucleus and the

corticospinal tract [13]. FRDA is a debilitating, life-shortening, and degenerative multiple system disorder. Onset of symptoms can vary from 5 years old to adulthood, with the childhood onset tending to be associated with a more rapid progression. A progressive loss of coordination and muscle strength leads to motor incapacitation and often the full-time use of a wheelchair. Most young people diagnosed with FRDA require mobility aids such as a cane, walker, or wheelchair by their teens or early twenties. As a rare disease with no currently approved treatments, FRDA represents an area of significant unmet medical need.

Various compounds are under investigation [14]. However, there is currently no cure or approved effective treatment for FRDA [15]. Thus, there is a great need to identify and develop effective therapies for FRDA.

4.1.3 Nonclinical Background

In nonclinical studies, TAK-831 increased D-serine levels in rat cerebellum and plasma. In the YG8sR transgenic mouse model, a model relevant for FRDA, TAK-831 at an oral daily dose of 3 mg/kg significantly improved motor coordination deficits of the mutant mice in the beam-walk test. Five hours after administration of the first dose, TAK-831–treated mutant mice crossed the beam approximately 30% faster than vehicle-treated animals, and TAK-831 treatment completely reversed the motor coordination deficit in these mice back to Baseline observed in healthy mice on Day 15. Therefore, TAK-831 holds the potential to treat patients with FRDA.

In vivo enzyme occupancy studies with a tracer molecule in mice demonstrated that TAK-831 binds to DAO in the kidney, cerebellum, and brain stem in a dose-dependent manner. Increasing enzyme occupancy by TAK-831 in the cerebellum correlated with plasma concentrations of drug, with maximal enzyme occupancy achieved at a dose of 10 mg/kg in mice.

Cerebellar enzyme activity was examined ex vivo. TAK-831 potently inhibited DAO activity in mouse cerebellum in a dose-dependent manner with a 50% inhibitory dose for DAO activity at 10 mg/kg. Similarly, TAK-831 increased rat cerebellar D-serine levels in a dose- and time-dependent manner with a maximal effect observed at an oral dose of 10 mg/kg at 10 hours postdose. These findings indicate that TAK-831 can increase D-serine levels via inhibition of DAO in vivo.

The development of TAK-831 included an extensive nonclinical safety pharmacology program that contributed to its overall safety assessment. Summaries of these studies and results can be found in the Investigator's Brochure.

4.1.4 Clinical Background

Five phase 1 clinical studies have been conducted in healthy subjects: a first-in-human study to determine the pharmacokinetic (PK) profiles of TAK-831 oral suspension after single-rising dose (SRD) and multiple-rising dose (MRD) administration, as well as the relative bioavailability and effect of food on the PK of the T1 tablet formulation of TAK-831 (TAK-831-1001); and a study to demonstrate DAO target engagement in the brain as measured by positron emission tomography (PET) (TAK-831-1003). Plasma D-serine levels, TAK-831 plasma concentrations and safety were also evaluated. Since these studies were conducted, a single dose PK and food-effect,

bioavailability study with the T2 tablet formulation (TAK-831-1004) has completed active dosing, and a study examining additional escalating multiple doses of TAK-831 higher than those achieved in the TAK-831-1001 study was initiated and is ongoing (TAK-831-1005).

After both single and multiple dosing with TAK-831 (Study TAK-831-1001), increases in the area under the effect curve from time 0 to 24 hours of D-serine were dose-dependent; changes in D-serine were noticeably higher after multiple daily doses of TAK-831 400 mg than after multiple daily doses of TAK-831 30, 100, and 200 mg. Single oral doses of TAK-831 temporally increased plasma concentrations of D-serine in the PET study (TAK-831-1003); the results are similar to those obtained from Study TAK-831-1001.

TAK-831 was safe and well tolerated in doses studied in the 103 healthy subjects dosed with active drug in studies TAK-831-1001 and TAK-831-1003. Headache was the most common treatment-emergent adverse event (TEAE) potentially related to treatment. Headaches were mild to moderate in intensity and generally self-limiting. The rate of postural dizziness in TAK-831-treated subjects did not markedly differ from the rate observed in placebo-treated subjects. There were no concerning trends in laboratory, electrocardiogram (ECG), or vital sign data.

TAK-831-1004 was a phase 1, randomized, open-label, single-dose, 2-period crossover study designed to characterize the pharmacokinetics (PK) of a single dose of 400 mg of TAK-831 and assess the effect of food on the bioavailability of TAK-831 400 mg when administered as 4 100 mg oral tablets of the T2 formulation in 15 healthy adult subjects. In the TAK-831-1004 study, there was only a single adverse event (AE) of mild upper respiratory tract infection, judged to be unrelated to study treatment. One subject met criteria for orthostatic hypotension at a single time point without an accompanying report of a dizziness AE. There were no concerning trends in laboratory, ECG, or vital sign data. TAK-831 given as T2 tablet coadministered with the nutritional drink (Ensure Plus) increased mean C_{max} and AUC_{∞} values by 35% and 21%, respectively. Treatment with a single oral dose of 400mg TAK-831 T2 formulation temporally increased plasma concentration of D-serine, similar to the results obtained in the Study TAK-831-1001. The magnitude and kinetics of the change in plasma D-serine was similar when the drug was administered in either water or Ensure.

TAK-831-1005 is an ongoing investigator and subject blinded, sponsor unblinded, placebo-controlled clinical study progressively assessing independent cohorts of healthy subjects to continue evaluation of the safety, tolerability, PK, and pharmacodynamics (PD) of escalating multiple doses of TAK-831 at doses higher than those achieved in the TAK-831-1001 study. The following study information is preliminary and is based on blinded AE data reported by the investigator and blinded safety endpoint data in study TAK-831-1005. Although not expected, these data are subject to change upon finalization following study monitoring, source data verification, and discrepancy query management prior to database lock. At this time, 2 cohorts with 8 subjects each (6 TAK-831 and 2 placebo) have completed treatment at dose levels of 600 mg QD (T2 tablet formulation) or 800 mg QD (oral suspension) administered first as a single dose, and then administered for up to 14 days of multiple dosing. In addition to standard safety assessments, subjects in these cohorts underwent catheterized CSF collection for a 24 hour period

starting prior to dosing on Day 1 single dose treatment and on Day 14 of multiple dose treatment. Nausea and post-lumbar puncture syndrome were the most common treatment-emergent AEs; nausea in the absence of post-lumbar puncture syndrome was reported by one subject in each cohort. All episodes of nausea were mild in intensity and self-limiting. Two subjects in each cohort met categorical criteria for orthostatic hypotension on at least one assessment; none of these findings were associated with an AE of dizziness. There were no concerning trends in laboratory, ECG, or vital sign data collected in these cohorts.

Following once-daily dosing, mean plasma exposures of TAK-831 were higher (C_{max}: 1.3-fold and AUC: 1.8-fold) when dosed as an oral suspension than as T2 tablets. Geometric mean C_{max} values were 1466 and 1976 ng/mL with 600 mg QD (T2 tablet formulation) and 800 mg QD (oral suspension), respectively. Mean steady-state exposures (AUC_t) over the 24-hour dosing interval were on average 4993 and 8853 ng.hr/mL for the respective 600 mg and 800 mg QD dosing cohorts. The mean 24-hour TAK-831 PK profile in CSF was parallel to that of plasma and observed TAK-831 CSF concentrations were well in agreement with the TAK-831 unbound fraction in plasma. After both single and multiple dosing with TAK-831, there was a notable increase in the area under the effect curve from time 0 to 24 hours of CSF D-serine for both the 600 mg T2 and 800 mg oral suspension treatment groups when compared to placebo; changes in CSF D-serine were noticeably higher after multiple doses of TAK-831 than after administration of a single dose of TAK-831. The magnitude of the increase in the area under the effect curve for CSF D-serine was similar for both the 600 mg T2 and 800 mg oral suspension, suggesting that the maximal PD effect in the CSF was achieved at drug exposures attained with the 600 mg T2 dose and 800 mg suspension.

Overall, the emerging safety data from the TAK-831-1004 and TAK-831-1005 studies are consistent with the data collected in prior clinical studies and do not alter the risk profile of the compound.

The safety data from healthy subjects cannot be directly generalized for patients with FRDA. However, no safety signal has manifested that would prevent additional studies in healthy subjects or in subjects with FRDA.

The clinical efficacy of TAK-831 has not been studied.

4.2 Rationale for the Proposed Study

Phase 1 studies have demonstrated acceptable PK characteristics and no safety issues to date. This study will be the first phase 2 study to test the efficacy and safety of TAK-831 in subjects with FRDA. The literature suggests that D-serine is a critical mediator of glutamate receptor–dependent functions of the cerebellum and was shown to reduce ataxia in animal model of spinocerebellar ataxia [3]. As a DAO inhibitor that increases D-serine in the cerebellum, TAK-831 has the potential to increase NMDA-dependent glutamatergic signaling. One disease state that could be treated through this mechanism is FRDA. TAK-831 showed efficacy in a mouse model of FRDA with single doses and dosed daily for 15 days at 3 mg/kg.

There is currently no cure or approved effective treatment for FRDA [14]. Thus, there is a great need to identify and develop effective therapies for patient populations with ataxia. The current

phase 2 study in subjects with FRDA will be the first to explore the potential benefits of TAK-831 in this population.

4.3 Benefit/Risk Profile

The proposed phase 2 study is being conducted to evaluate the efficacy, safety, PD effects, and PK of 2 dose levels of oral TAK-831 in adult subjects with FRDA for up to 84 days. The proposed doses of TAK-831 have been selected based on PK data from the SRD/MRD studies (TAK-831-1001 and TAK-831-1005), brain target occupancy data from the PET study (TAK-831-1003), CSF D-serine data from the TAK-831-1005 study, and safety data from all clinical studies after oral administration of TAK-831 in healthy subjects described above. The dose and study duration of TAK-831 used in prior studies have not resulted in a safety signal that would prevent additional studies in subjects with FRDA.

Potential risks, and risk mitigation measures to be implemented in studies with TAK-831, are described below. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, the phase 1 studies conducted to date, and general considerations in the development of new chemical entities. These procedures may be modified during the study if necessary based on evaluation of any additional clinical or nonclinical safety data.

- Acute hypersensitivity/anaphylactic reactions to new chemical entities are always a possible risk in any clinical study. Appropriate procedures should be used to manage such possible risks.
- Subjects with a risk of suicide according to the investigator's clinical judgment (eg, per the Columbia-Suicide Severity Rating Scale [C-SSRS]) [16,17] or who have made a suicide attempt in the previous 6 months, will be excluded from studies with TAK-831. Subjects should be monitored for any signs of suicidal ideation or behaviors, and appropriate psychiatric interventions or other precautions should be instituted, if warranted.
- Emesis and diarrhea were reported in laboratory animals exposed to TAK-831. If a subject develops emesis or diarrhea, the investigator should assess the clinical status. For mild emesis or diarrhea that is self-limited, the subject should be encouraged to increase fluid intake. Hydration status should be assessed with physical examination and vital signs, including orthostatic pulse and blood pressure measurements. For more severe emesis or diarrhea, where the subject has had more than 3 episodes and signs and symptoms of dehydration are present (ie, lightheadedness, vertigo, syncope, and/or orthostatic changes in blood pressure or pulse are present), measurement of serum electrolytes, blood urea nitrogen, and creatinine, as well as the consideration of more aggressive hydration, including the administration of an appropriate parenteral solution, should be undertaken.
- Eosinophilic intranuclear inclusion bodies (EIIBs) were observed in the proximal tubule epithelium of the kidneys at doses of ≥10 mg/kg/day in rats. The EIIBs were not accompanied by apparent necrosis, inflammation, or impaired renal function and were not considered adverse. Similar findings have been reported in the literature and are considered to be species-specific to the rat [18]. Creatinine will be measured in the clinical studies.

- Postural hypotension and dizziness were observed in prior studies in healthy subjects. However, the incidence of dizziness in subjects treated with TAK-831 and placebo was similar. In addition, 2 subjects who received 250 mg TAK-831 showed blood pressure variations consistent with orthostatic hypotension without clinical symptoms. These measurements were taken at the Study Exit Visit and were considered not-related to TAK-831. As FRDA patients experience gait disturbance, motor dysfunction, and thus are susceptible to fall, subjects should be instructed to take appropriate precautionary measures to prevent falling while under treatment with TAK-831. Additionally, subjects with current history of symptomatic orthostatic hypotension will be excluded from the study.
- Study procedure–specific risks include issues relating to the requirement for fasting (which may lead to AEs of lightheadedness or stomach cramps) as well as blood collection for safety assessment/PK monitoring (venipuncture may cause bruising), and the placement.

The investigator has discretion to use his/her clinical judgment as to whether to allow a subject to proceed in the study or whether to unblind the subject in order to determine his/her treatment allocation. These cases would normally be discussed with the sponsor beforehand, but that is not an absolute requirement in case of medical emergency, and the clinical needs of the individual subject will always take precedence.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of TAK-831 versus placebo on upper extremity (arms and hands) motor function and manual dexterity, as measured by the 9-hole peg test (9-HPT).

5.1.2 Secondary Objectives

- To evaluate the efficacy of TAK-831 versus placebo on Activities of Daily Living (ADL), as measured by the ADL component of the Friedreich Ataxia Rating Scale (FARS), and those items that are related to upper limb function.
- To evaluate the efficacy of TAK-831 versus placebo on neurological function, as measured by the modified FARS neurological examination (mFARS-neuro) total score.
- To evaluate the efficacy of TAK-831 versus placebo on lower extremity motor function, as measured by the Timed 25-Foot Walk (T25FW).
- To evaluate the efficacy of TAK-831 versus placebo on limb ataxia, as measured by the composite of the T25FW and 9-HPT.
- To evaluate the efficacy of TAK-831 versus placebo on visual acuity, as measured by the low-contrast letter acuity (LCLA) testing with Sloan charts.
- To evaluate the efficacy of TAK-831 versus placebo on global improvement, as measured by the Clinical Global Impression-Improvement (CGI-I).
- To evaluate the efficacy of TAK-831 versus placebo on global improvement, as measured by the Patient Global Impression-Improvement (PGI-I).
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional improvement, as measured by the CGI-I.
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional improvement, as measured by the PGI-I.
- To evaluate the efficacy of TAK-831 versus placebo on global severity, as measured by the Clinical Global Impression-Severity (CGI-S).
- To evaluate the efficacy of TAK-831 versus placebo on global severity, as measured by the Patient Global Impression-Severity (PGI-S).
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional severity, as measured by the CGI-S.
- To evaluate the efficacy of TAK-831 versus placebo on upper extremity functional severity, as measured by the PGI-S.

- To evaluate the safety and tolerability of TAK-831.

5.1.3 Exploratory Objectives

- To evaluate the efficacy of TAK-831 versus placebo on speech, as measured by digital assessments.
- To evaluate the efficacy of TAK-831 versus placebo on motor function such as gait, balance, and upper limb coordination, as measured by digital sensors.
- To evaluate the PK and PD (plasma D-serine and L-serine levels and D-serine:Total serine ratios), and explore the relationships between TAK-831 exposures and D- and L-serine levels or selected measures of efficacy.
- To correlate plasma D-serine and L-serine levels, and D-serine:Total serine ratios with clinical parameters of disease status.
- To quantify subject-perceived meaningful change in upper limb function, as evaluated by the Exit Interview.

CCI [redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint for this study is the change from Baseline to Week 12 in the inverse of the time to complete the 9-HPT (9-HPT^{-1}) after treatment with TAK-831, compared with placebo.

5.2.2 Secondary Endpoints

- The change from Baseline to Weeks 2, 7, and 12 on the ADL component of the FARS, after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the ADL component upper limb function items (ADL items 3 to 5) of the FARS, after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2 and 7 on the 9-HPT^{-1} after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the ADL individual items after treatment with TAK-831, compared with placebo.

- The change from Baseline to Weeks 2, 7, and 12 on the mFARs-neuro total score after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the mFARS-neuro subscales and individual items after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the T25FW after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the 9-HPT and T25FW composite score after treatment with TAK-831, compared with placebo.
- Percentage of subjects whose 9-HPT completion time is reduced by at least 15% and at least 20% from Baseline.
- The change from Baseline to Weeks 2, 7, and 12 on LCLA test score after treatment, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on CGI-I (global change) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI-I (global change) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on CGI-I (upper extremity functional change) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI- I (upper extremity functional change) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on CGI-S (global severity) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI-S (global severity) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on CGI-S (upper extremity functional severity) after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on PGI-S (upper extremity functional severity) after treatment with TAK-831, compared with placebo.

5.2.3 Safety Endpoints

- AEs, clinical laboratory assessments, ECG measures, changes in physical examinations and vital signs after treatment with TAK-831, compared with placebo.
- Assessment of suicidal ideation and behavior as measured by the C-SSRS at Screening, Baseline, and all other timepoints after treatment with TAK-831, compared with placebo.

5.2.4 Exploratory Endpoints

- The change from Baseline to Weeks 2, 7, and 12 on the digital speech assessment after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on the digital motor sensors measurements such as gait, stability and upper limb coordination after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2, 7, and 12 on TAK-831 plasma D-serine and L-serine levels and D-serine:Total serine ratios after treatment with TAK-831, compared with placebo.
- Percent of subjects reporting a meaningful change in upper limb function from Baseline to Week 12 after treatment with TAK-831, compared with placebo, as evaluated by the Exit Interview.
- Correlation of change in 9-HPT with that of patient reported improvement of change in upper limb function, such as ADL items 3 to 5 and PGI.
- TAK-831 plasma concentration.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

TAK-831-1501 is a phase 2, randomized, double-blind, placebo-controlled, parallel-arm study designed to evaluate the efficacy, safety, PD effects, and PK of 2 dose levels of oral TAK-831 in adult subjects with FRDA.

The study will include a Screening Period (Days -28 to -2), a Training Period (Day -1), Treatment (Days 1 to 84), a Phone Exit Interview (within 7 days from the last dose of study medication of the Double-Blind Treatment Period or within 7 days of notification of termination for the Early Termination Visit), and a Safety Follow-up Phone Call (7 to 17 days after last dose of study drug).

Approximately 65 subjects who meet the study criteria during Screening will be invited to attend training to minimize practice effects on performance-based efficacy assessments on Day -1. On Day 1, subjects who continue to meet inclusion and none of the exclusion criteria will be randomized in a 2:1:2 ratio to TAK-831 high dose, TAK-831 low dose, or placebo, respectively. (If the rate of early withdrawal is substantially greater than predicted, then an increase to the number of randomized subjects may be considered.) Randomization will be stratified by ambulation status (ambulatory vs. nonambulatory).

The study will be conducted in approximately 6 or more specialized academic neurological clinical centers in the United States with expertise in, and access to, patients with FRDA.

Subjects will receive twice daily (BID) study drug dosing or placebo from Day 1 through Day 84. Clinic visits during the treatment period include Day 1, end of Weeks 2, 7, and 12. Clinical assessments, blood collections, and laboratory tests will be conducted at specific time points per the schedule of study procedures (Appendix A). A semistructured Exit Interview will be conducted by phone to provide an in-depth, qualitative evaluation of the subject experience and subject-perceived change due to treatment, and a Safety Follow-up Phone Call will be conducted (Table 6.a).

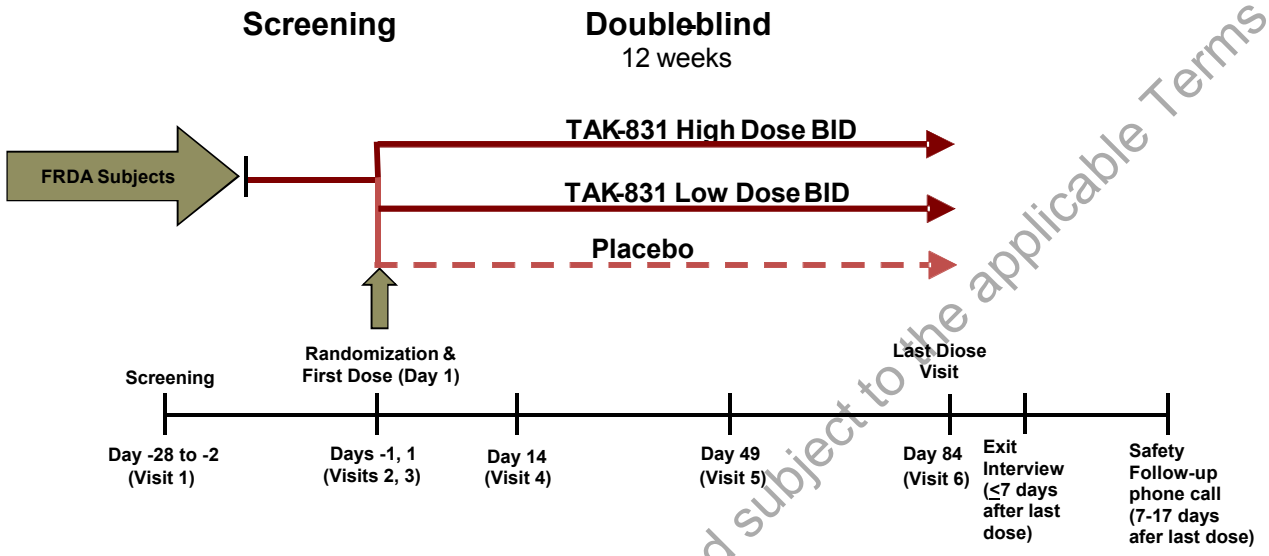
Table 6.a Schematic of Study Design

Screening	Efficacy Assessment Training	Treatment (TAK-831 high dose, TAK-831 low dose, or placebo)		Phone Exit Interview	Safety Follow-up Phone Call (a)
		Randomization, Baseline, and Dosing	Efficacy, PK, PD, and Safety Assessments		
Days -28 to -2	Day -1	Day 1	Day 14 (±3 days), Day 49 (±3 days), Day 84 (±2 days)	≤7 days after Final Visit or termination	7 to 17 days after last dose

(a) The Follow-up Phone Call will occur 7 to 17 days after the last dose of study drug by telephone unless subject report concerning AEs. In these cases, subjects will be brought back into the clinic for re-evaluation at the investigator's discretion.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

TAK-831 is a selective inhibitor of DAO. Inhibition of DAO leads to higher D-serine levels in the plasma, CSF, and cerebellum of animal models. D-serine enhances glutamate receptor–mediated mechanisms that may be impaired or contribute to cerebellar dysfunction symptoms, such as ataxia. Increasing D-serine levels by way of inhibition of its catabolizing enzyme DAO may improve motor symptoms and HRQoL of patients with cerebellar dysfunction. Accordingly, the focus of this study is to target and mitigate symptoms of cerebellar dysfunction in subjects with FRDA.

6.2.1 Justification of Study Design and Subject Population

The double-blind, placebo-controlled study design is appropriate to assess the objectives of this study. Clinical outcome assessment measures including performance-based, clinician-reported, and patient-reported outcome measures will be evaluated. The inclusion of a placebo group allows for the evaluation of efficacy and safety objectives related to TAK-831. Placebo tablets will match the TAK-831 tablets for blinding purposes.

Nonclinical studies in mice models of FRDA suggest potential efficacy of TAK-831 in improving motor coordination or function symptomatically. TAK-831 is hypothesized to treat ataxia symptomatically in a broad range of FRDA patients at various stages of disease progression, including patients who are ambulatory and nonambulatory.

In this initial efficacy study in the FRDA population, including a broad population (rather than limiting the population to ambulatory or nonambulatory, for example) will help identify subgroups

that may benefit better from the treatment, and therefore inform future studies. Overall mobility can be scored by using the Functional Ataxia Staging (total score range from 0 to 6). Stage 1 patients show minimal signs detected by the physician during Screening, patients can run or jump without loss of balance, and there is no disability. Sensory ataxia is more prominent than limb ataxia in this stage, likely due to a developmental pathology in combination with the progressive pathology of dorsal root ganglia and dorsal columns. It is unlikely that TAK-831 will dramatically improve sensory ataxia symptoms of FRDA in stage 1, based on the hypothesized mechanism of action. Stage 6 patients are confined to a wheelchair or bed and have total dependency for all ADLs. These patients might be too severe to respond with meaningful improvement to symptomatic drug treatment. It is likely that the disease severity in stages 2 to 5 is severe enough to result in a measurable improvement in function.

The duration of treatment for this study is 12 weeks. Although TAK-831 is anticipated to act symptomatically with a relatively rapid onset of action (based on its mechanism of action and the nonclinical data), a duration of 12 weeks was chosen for Study TAK-831-1501 to better characterize the onset of action as well as the maintenance of effect of the drug. Twelve weeks is the maximum treatment duration supported by currently available TAK-831 nonclinical toxicology data.

The sample size of 65 subjects being randomized in a 2:1:2 ratio to TAK-831 high dose, TAK-831 low dose, or placebo, respectively, was based on the following assumptions. It was assumed that approximately 60 subjects (93%) will complete 12 weeks and be evaluable on the primary endpoint. Assuming an effect size of 0.6 for each dose, this approach gives 77% power for at least 1 dose to be deemed superior to placebo and 54% power for both doses. The effect size was chosen based on expert advice that a treatment effect equivalent to preventing or reversing 2 years of decline due to FRDA would be clinically meaningful. Using published data [19], the target effect size should be approximately 0.6 for each endpoint.

6.2.2 Justification of Dose

The doses of TAK-831 (300 mg and 75 mg BID) selected for the current study are based on PK data from the SRD/MRD study (TAK-831-1001) and brain target occupancy data from the PET study (TAK-831-1003), PK and food effect study (TAK-831-1004), CSF D-serine study (TAK-831-1005), and safety data from all clinical studies after oral administration of TAK-831 in healthy subjects. Preliminary PK/PD modeling analyses showed that the high dose regimen resulted in steady-state exposures associated with peak target occupancy of >90%. The lower dose is to provide at least 3-fold exposure difference from the high dose to understand the relationship between TAK-831 and response relationship. In addition, CSF D-serine levels at 600 mg QD using T2 tablet and 800 mg suspension produced similar level of CSF D-serine, suggesting that 600 mg QD produced levels of D-serine approaching maximal DAO inhibition in the brain. These 2 doses (300 and 75 mg BID) may allow characterization of an exposure-response relationship with PD or efficacy measures in adult subjects with FRDA. Subjects will be instructed to take 3 tablets by mouth 2 times a day in the fasted condition (at least 1 hour before or after a meal) or with a light meal (less than 600 calories total with <30% from fat). This will keep the TAK-831 exposure at levels that have been shown to be well tolerated in healthy subjects.

6.2.3 Justification of Measurements

6.2.3.1 Primary Outcome Measure: 9-HPT

The 9-HPT is a quantitative performance-based measure of timed upper extremity (arm and hand) function and manual dexterity. The 9-HPT was developed in the 1970s as a performance-based measure of upper limb dexterity [20]. This measure has been used extensively in stroke and Parkinson's disease patients and is the gold standard test recommended by the MS Outcome Assessments Consortium for measuring manual dexterity in multiple sclerosis [21]. The 9-HPT has been used more recently in FRDA[19,22] and is recommended as the best performance-based measure of upper limb function for inclusion in clinical studies of FRDA [23].

Participants pick up pegs 1 at a time (9 in total), using 1 hand only, and place them into holes on the board as quickly as possible, in any order until all holes are filled. Then, without pausing, participants remove the pegs 1 at a time and return them as quickly as possible. Each participant performs this task twice with each hand separately. Results on both tests are then averaged for an overall task completion time. The 9-HPT quantifies the speed at which participants put all of the pegs in and take them out again.

The 9-HPT is a useful measure of upper limb function in FRDA and has established reliability in FRDA as well as normative reference values to assist with score interpretation [24-26]. This measure correlates with neurological disability and disease duration as well as other performance-based measures in FRDA [27]. Additional analysis of natural history data based on the Friedreich Ataxia Clinical Outcome Measures Study (FACOMS) show a correlation of 9-HPT with ADL total scores and subscores that reflect functions such as cutting food and handling utensils, dressing, and hygiene (personal communications with Jennifer Farmer from Friedreich Ataxia Research Alliance and Dr. David Lynch).

The 9-HPT is the optimal choice for the primary endpoint in this study as determined by the relevance of impairment in upper limb function to FRDA patients, likely impact of TAK-831, the broad study population, and greater precision and accuracy in outcome measurement over other measures including the T25FW, visual acuity tests, mFARS, and ADL as indicated by FACOMS data [19], and from author personal communication. Anchor- and distribution-based methods in accordance with Food and Drug Administration (FDA) guidance [28] will be used to derive a responder definition for the 9-HPT in the study population (see Section 13.1.3.1).

6.2.3.2 Secondary Outcome Measure:

ADL

FARS ADL scale has a total score range of 0 to 36 (higher scores represent greater severity/dependency). Each ADL subscale is scored from 0 (normal) to 4 (severe disability/inability to carry out activity independently). The 9 ADL subscales include speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, and bladder function. Note items 3 to 5 are directly related to upper limb function [29,30].

mFARS-neuro

The FARS neurological examination is based on neural substrates affected in FRDA including bulbar, upper limb, lower limb, peripheral nerve, and upright stability/gait functions (maximum scores of 11, 36, 16, 26, and 36, respectively; maximum deficit=125) [29,31]. A functional staging was incorporated with a total score ranging from 0 to 6 (higher scores represent greater disability). The mFARS-neuro is the modified version of the FARS neurological examination that excludes the peripheral nerve component and bulbar assessment item 1-2. The mFARS-neuro has demonstrated clinical utility in FRDA and is considered a better functional assessment than the FARS as it separates out the functional assessment from assessment of neurological signs. It is a clinician-rated measure. In this study, the entire FARS neurological examination will be performed and the mFARS-neuro will be extracted after data entry.

T25FW

The T25FW is a quantitative performance-based measure of mobility and leg function used in ambulatory FRDA patients. This measure exhibited the highest correlation with accelerometer measures and is considered the most accurate measure of ambulation in FRDA [27,32]. The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the subject has reached the 25-foot mark. The task is immediately administered again by having the subject walk back the same distance. Subjects may use assistive devices when doing this task.

The T25FW is a useful measure of lower limb function in ambulatory FRDA patients and correlates with disease status and duration as well as other performance-based measures in FRDA (including the 9-HPT) [27].

T25FW and 9-HPT Composite Measure

The T25FW and 9-HPT will be evaluated together as a performance-based composite measure of limb ataxia which has been shown to be a reliable assessment of function in FRDA [30]. The composite measure is created using the basic methods used in the MSFC [33]. In brief, raw scores from each test are tabulated and converted to test-specific Z scores by subtracting the cohort mean from the raw score, and then dividing by the cohort SD to create a Z score for the test. The inverse is taken for the 9-HPT (9-HPT^{-1}). The composite Z scores will be created by subtracting Z-score for T25FW from the Z-score for 9-HPT^{-1}.

LCLA

The LCLA test provides a simple and reliable clinical outcome assessment measure for evaluating visual dysfunction, a highly prevalent manifestation, in FRDA [34]. Testing will be performed binocularly using Low-Contrast Sloan Letter Charts at different contrast levels.

Clinical Global Impression (CGI-I, CGI-S)

The Clinical Global Impression Scale (CGI) provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the subject's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the subject's ability to function.

The CGI comprises 2 companion 1-item measures evaluating the following: (a) CGI-S, severity of psychopathology from 1 to 7 and (b) CGI-I, improvement from the initiation of treatment on a similar 7-point scale.

The CGI-S will be administered at baseline and at various time points to assess overall severity and severity of upper extremity function.

Patient Global Impression (PGI-I, PGI-S)

The PGI rating scales capture global efficacy as perceived by the subject and provide "anchors" to determine clinically-relevant effects.

The PGI-S requires the subject to rate his/her disease severity at the time of assessment on a 5-point scale ranging from normal to extremely severe.

The PGI-I measures improvement due to treatment relative to Baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

The PGI-S and the PGI-I will be administered similarly to the CGI-S and CGI-I.

6.2.3.3 Exploratory Outcome Measures

Digital Quantification of Gait (for Ambulatory Patients Only), Upper Body Stability, and Upper Limb Movement

The use of digital devices, such as the Lab Mobility Test, provides means of objective measures of subject's gait and stability to explore the effect of TAK-831 treatment. This work will be of an exploratory nature to assess utility of digital measurements of disease activity in ataxia. Data from this exploratory measurement will not be included in the clinical database.

Digital Assessments of Speech

Each subject will be asked to complete a speech battery suitable for measuring components of speech and voice resulting from ataxia. Speech data will be analyzed objectively using acoustic analysis software. This assessment is of an exploratory nature and will be used to evaluate the

effect of TAK-831 on voice characteristics in ataxia [35]. Please refer to the Redenlab study manual for additional details.

Subject Exit Interview

A semistructured, qualitative subject Exit Interview is planned. The key objectives of the Exit Interview are as follows:

- To understand the subject experience with FRDA (including symptoms and day-to-day impacts), previous management of symptoms, and treatment expectations.
- To understand the most relevant and important outcomes that subjects desire so that meaningful treatment from the subject perspective can be better understood.
- To evaluate the subject-perceived meaningfulness of change in upper limb function due to TAK-831 (given the planned primary endpoint).
- To determine the overall perception of treatment with TAK-831.

The interviews will be conducted over the phone within 7 days from the last dose of study medication of the double-blind Treatment Period or within 7 days of notification of termination for the Early Termination Visit. Experienced interviewers from a third-party research organization will conduct the interviews. All interviewers will be blinded to treatment assignment and interviews will be audio-recorded pending subject consent.

D-Serine Levels

Plasma D-serine levels could be used as a biomarker for peripheral inhibition of DAO enzyme. PD parameters will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-831, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Subjects experience any of the Takeda Medically Significant List events.

- Abnormal liver function:
  - Two or more subjects experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5× the upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.*
  - One or more subjects experience ALT and/or AST elevations >3×ULN in the presence of a total bilirubin increase >2×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (ie, "Hy's Law cases").
  - Two or more subjects experience ALT and/or AST elevations >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

*Note that the study may be terminated early prior to full attainment of these criteria (eg, if just 1 subject experiences 1 of these events) if warranted by safety data from the other subjects dosed in the study to date.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding the informed consent, and capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent.
3. The subject is an adult male or female aged 18 to 55 years, inclusive, at the time of informed consent.
4. The subject has a genetically-confirmed diagnosis (homozygous for GAA repeat expansions in the FXN in the affected range of FRDA or a compound heterozygous expansion with a point mutation or deletion), with an established disease stage of 2 to 5, inclusive, as determined by the Functional Staging for Ataxia, at Screening.
5. The subject is able to complete the 9-HPT test in ≤150 seconds at Screening.
6. The subject weighs ≥43 kg and has a body mass index (BMI) between 16.0 and 40.0 kg/m^2, inclusive at Screening.
7. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agrees to use barrier method of contraception (eg, condom with spermicide cream or jelly)* from signing of informed consent throughout the duration of the study and for 95 days after last dose. The male subject agrees to advise the female partner to use a highly effective/effective method of contraception.*
8. A female subject is of nonchildbearing potential or, a female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use 2 highly effective/effective methods of contraception* from signing of informed consent throughout the duration of the study and for 35 days after the last dose.

   *Definitions and highly effective methods of contraception are defined in Section 9.1.11 and reporting responsibilities are defined in Section 9.1.12.

9. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening.
10. The subject is able to swallow study drug in tablet form.
11. If a subject requires a caregiver to accompany him/her during the study for clinic visits, a caregiver and backup caregivers should be available.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received a diagnosis of ataxic syndromes other than FRDA.
2. The subject has, based on medical history and judgment of the investigator, uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease (including uncontrolled diabetes) or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the efficacy and safety evaluation. The subject has medical history or conditions that, in the opinion of the investigator, may interfere with study conduct or clinical assessments.
3. The subject has received treatment with other experimental therapies within the last 30 days or 5x half-lives, whichever is longer, prior to the first dose of study drug.
4. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
5. The subject has a history of cancer, except squamous cell carcinoma or basal cell carcinoma that have been treated or excised, or in situ cervical cancer that has been in remission for ≥5 years prior to first dose of study drug.
6. The subject is known to have a history of having been infected with human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus.
7. Urine drug screen positive for drugs of abuse at Screening or, except for a prescribed drug allowed by the protocol at Screening. Cannabinoid use is not permitted either recreationally or medically.
8. The subject has a known hypersensitivity to any component of the formulation of TAK-831.
9. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening.
10. The subject has taken any excluded medication, or has had insufficient washout of medications as listed in the Excluded/Allowed Medications, Procedures, and Treatments table listed in Section 7.3 or is unable or unwilling to discontinue medications as required by the protocol.
11. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property or subjects who within the past year prior to Screening have attempted suicide or have positive answers on item 4 or 5 on the C-SSRS, life-time version, at Screening or Day 1.
12. The subject has clinically significant cardiac abnormalities at Screening that, in the opinion of the investigator, makes the subject unsuitable for enrollment, including but not limited to heart failure meeting criteria for class IV insufficiency by the New York Heart Association or documented ejection fraction <40%.

13. The subject has a QT interval with Fridericia correction method (QTcF) >450 msec (males) or >470 msec (females), confirmed with 1 repeat testing, at Screening or Day -1.
14. If male, the subject intends to donate sperm during the course of this study or for 95 days after the last dose of study drug.
15. If female, the subject is of childbearing potential and lactating, pregnant (positive prerandomization serum pregnancy test), or plans to become pregnant before participating in the study, during the study, or within 35 days after last dose of the study drug, or intending to donate ova during such time period.
16. The subject has a history of neuroleptic malignant syndrome, water intoxication, or paralytic ileus or other conditions that may interfere with absorption of study medication.
17. The subject has 1 or more laboratory values outside the normal range that are considered by the investigator to be clinically significant at the Screening Visit; or the subject has any of the following at the Screening Visit: a serum creatinine value >1.5 times the ULN, a total serum total bilirubin value >1.5×ULN, or a serum ALT or AST value >2×ULN.
18. The subject has current history of symptomatic orthostatic hypotension.

7.3 Excluded Medications, Supplements, and Dietary Products

The following are excluded:

- Inhibitors for uridine 5'-diphosphate-glucuronosyltransferase (UGT) enzymes (Probenecid and valproic acid) should be excluded for 14 days prior to dosing.
- Subjects must be instructed not to start any medications during the study, including over-the-counter products, without first consulting with the investigator. Occasional use of acetaminophen and aspirin are allowed.
- Disallowed agents with CNS effects including but not limited to stimulants, lithium, or monoamine-oxidase inhibitor antidepressant agents, dextromethorphan, memantine, amantadine, antipsychotics medications. See Table 7.a for details.
- Sedative or hypnotic medication at equivalent doses greater than lorazepam 2 mg should not be used within 24 hours of the conduct of any clinical assessments.
- Other agents with CNS effects may be allowed after consultation with the study sponsor or sponsor's designee.

Table 7.a provides a list of excluded and allowed medications. This table however is not a comprehensive list and consultation with sponsor/representative might be warranted.

Table 7.a Excluded/Allowed Medications and Treatments

Drug Class	Disallowed (X) During the Study (sections without X indicate no restriction)		
	Chronic Use	**Episodic Use**	**Comments or Exceptions**
Inhibitors for UGT enzymes (Probenecid and valproic acid)	X	X	Wash-out for at least 14 days prior to randomization
Any investigational drug	X	X	Must have completed clinical trial and stopped investigational drug 30 days before Screening or 5 half-lives, whichever is longer
Dextromethorphan, memantine, amantadine, or other glutamatergic drugs	X	X	Wash-out of at least 3 weeks prior to randomization and approval for patient inclusion by sponsor/representative
Psychotropic agents not otherwise specified (including but not limited to stimulants, tryptophan, melatonin)	X	X	Wash-out of at least 3 weeks prior to randomization and approval for patient inclusion by sponsor/representative
Antipsychotics	X	X	Excluded
Narcotic analgesics	X	X	Except chronic use on stable dose for at least 30 days prior to randomization
Anticonvulsants (gabapentin, pregabalin or related drugs)	X	X	Except chronic use on stable dose for at least 30 days prior to randomization for the management of pain. Phenytoin is excluded. All other anticonvulsants need approval for inclusion by sponsor.
Antidepressant SSRIs, SNRIs		X	Except chronic use on stable dose for at least 8 weeks prior to randomization and consultation with sponsor/representative
Herbal remedies, which are psychoactive (eg, St. Johns Wort, kava kava, valerian, ginkgo biloba, melatonin), OTC (e.g., caugh syrup)	X	X	All OTC excluded. Patients should be instructed to consult with PI regarding prior to starting any medications
Sedatives/hypnotics	X	X	Except as described in Section 7.3
Muscle relaxants including but not limited to baclofen, tizanidine, 4 aminopyridine	X	X	Except chronic use on stable dose for at least 14 days prior to randomization
Antiparkinsonian drugs including dopamine agonists	X	X	Except chronic use on stable dose for at least 14 days prior to randomization
Benzodiazepines	X	X	Except chronic use on stable dose for at least 14 days prior to randomization

MAOI=monoamine oxidase inhibitor, NSAIDs=nonsteroidal anti-inflammatory drugs, OTC=over-the-counter, RIMA=reversible inhibitor of monoamine oxidase type A, SNRI=serotonin–norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor.

7.4 Diet, Fluid, Activity Control

Subjects will maintain their regular routine of exercise and physical therapy or speech therapy.

Alcohol intake will be restricted to no more than 1 unit in 1 occasion and less than 3 units per week. One unit is equivalent to a half-pint of beer or 1 single measure of spirits or 1 small glass of wine. Subject will not drink alcohol with 24 hours of the conduct of any clinical assessments.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.18.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

   - Liver function test (LFT) abnormalities:

     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.10), if the following circumstances occur at any time during study drug treatment:

     – ALT or AST >8×ULN, or

     – ALT or AST >5×ULN and persists for ≥2 weeks, or

     – ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or INR >1.5, or

     – ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

   - ECG abnormalities

     – QTcF > 500 ms

2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal because of an AE should not be recorded in the "voluntary withdrawal" category; similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.

6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.12.

7. Severe gastrointestinal intolerance. The subject develops severe gastrointestinal intolerance that cannot be ameliorated by supportive treatment.

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

TAK-831 100 mg, 25 mg, and matching placebo tablets will be provided as unmarked, round, yellow-red, film-coated tablets for oral administration. TAK-831 is manufactured by Takeda Pharmaceuticals, Osaka, Japan.

The TAK-831 100 mg, 25 mg, and matching placebo tablets will be supplied in round, high-density polyethylene, 150 cc, round white bottles with child resistant caps. Each bottle will contain 180 tablets and will be labeled with a single-panel, double-blind label. The label will include pertinent study information and appropriate country-specific regulatory caution statements.

8.1.1.2 Sponsor-supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following: TAK-831 100 mg, 25 mg, and matching placebo tablets.

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Treatment doses and regimens for the study are provided in Table 8.a.

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	
		Active	**Placebo**
Placebo	Placebo BID	Zero active tablets	3 TAK-831 placebo tablets
Low dose	TAK-831 75 mg BID	3 TAK-831 25 mg tablets	Zero TAK-831 placebo tablets
High dose	TAK-831 300 mg BID	3 TAK-831 100 mg tablets	Zero TAK-831 placebo tablets

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

If sponsor-supplied drug TAK-831 100 mg, 25 mg, or placebo tablets are lost or damaged, the site can request a replacement from interactive response technology (IRT).

At the first and subsequent drug-dispensing visits, the investigator or designee will access the IRT to request study drug for a subject. The medication identification (ID) number of the study drug to be dispensed will be provided by the IRT.

8.3 Randomization Code Creation and Storage

The designee of the sponsor will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The study drug blind will be maintained using the IRT.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be obtained by the investigator, by accessing the IRT.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being destroyed or returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug TAK-831 100 mg, 25 mg, and matching placebo tablets, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and by recording in IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot/medication ID/job number used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs, TAK-831 100 mg, 25 mg, and matching placebo tablets on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, date and amount dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature

of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are destroyed or returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures to be performed and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

A unique subject identification number (site number plus subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

CCI

[redacted]

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, alcohol use, reproductive status, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to FRDA (including age at disease onset) that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.9).

Medication history information to be obtained includes any medication relevant to eligibility criteria.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to the first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. All clinically significant findings/changes will be recorded as a pretreatment event (PTE) or concurrent medical condition in the source document and in the eCRF described in Section 10.0.

On subsequent examinations, any abnormal change from the baseline physical examination must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. Any clinically significant change or new diagnosis as a result of a clinically significant change, as determined by the investigator, will be recorded as an AE in the source document and on the PTE/AE page of the eCRF.

Neurological exams: FARS neurological exam will substitute for the standard neurological exams. FARS includes neurological signs that specifically reflect neural substrates affected in FRDA. Based on a neurological examination, bulbar, upper limb, lower limb, peripheral nerve, and upright stability/gait functions are assessed. See Section 9.1.7.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off (not applicable for subjects who are in wheelchairs and their weight can be obtained by alternative methods or based on medical history). The BMI is calculated at Screening using metric units with the formula below. Height is recorded in centimeters without decimal places, and weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as follows:

Metric $\quad \text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then BMI=$79.2/1.76^2$=25.56818 kg/m^2.

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs will include oral body temperature, respiratory rate, sitting blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (beats per minute).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

If vital signs are abnormal, a repeat measurement may be performed and recorded approximately 15 minutes after the first measurement.

9.1.6 Other Safety Measurements

The C-SSRS will be administered at all timepoints including Screening and Baseline. The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical trial of centrally acting drugs.

The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject (by a trained operator/interviewer). If possible, the same interviewer should be used throughout the study for the same subject. All events such as suicidal ideations or behaviors should be reported as AEs [36].

9.1.7 Primary and Secondary Efficacy Measurements

The sequence of efficacy assessment should take into consideration of subject fatigue and morning dosing time of study drug. In particular, the 9-HPT and digital speech recording should be done first among the assessments and procedures, and around or between 2-4 hours after the morning dose of the study drug unless stated otherwise in the Schedule of Study Procedures For example, on Day 1 assessments will all be conducted before dosing the subjects.

The following assessments will be administered by a neurologist who has experience with the FARS. Each site will also have a trained neurologist to serve as back-up to the primary neurologist. However, it is strongly recommended that the same neurologist assess the same subjects at each visit throughout the study, as much as possible. The time of the day for the assessment should be consistent throughout the study as much as possible (eg, all mornings or a rough window of time).

- FARS neurological exam.
- CGI-S (global severity).
- CGI-I (global improvement).
- CGI-S (upper extremity functional severity).
- CGI-I (upper extremity functional improvement).

The following assessments will be administer by qualified study personnel (nurse, study coordinator) appointed by the principal investigator. Each should have a record of successful completion of the required training, and have experience in FRDA or ataxia clinical trials. Each site should also have a back-up administrator meeting the same requirements. However, it is strongly recommended that the same administrator assess the same subjects at the various visits throughout the study, as much as possible. The time of the day for the assessment should be consistent throughout the study as much as possible (eg, all mornings or a rough window of time).

- 9-HPT.
- T25FW (for ambulatory subjects only. This will be done with the digital sensors for gait assessment).

- LCLA test.
- Digital speech assessment.
- Digital balance and upper limb assessment.
- C-SSRS.

The following assessments are patient-reported outcome measures:

- FARS ADL.
- PGI-S (global severity).
- PGI-I (global improvement).
- PGI-S (upper extremity functional severity).
- PGI-I (upper extremity functional improvement).

9.1.8 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.9 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening examination. The condition (ie, diagnosis) should be described.

9.1.10 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual. Section 9.4 describes procedures for specimen handling.

The tests that will be performed for each clinical laboratory specimen are listed in Table 9.a.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBCs WBCs with differential (% and absolute) Hemoglobin Hematocrit Platelets	ALT Albumin Alkaline phosphatase AST Total bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase γ-Glutamyl transferase Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Ketones Bilirubin Urobilinogen Leukocyte esterase Microscopic Analysis: (a) Erythrocytes/RBCs/high power field Leukocytes/WBCs/high power field Epithelial cells, casts, etc

Serum	Urine
	Urine drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methamphetamine, opiates.
Female subjects of childbearing potential only: hCG (for pregnancy) at Screening and ET visit. FSH	*Female subjects of childbearing potential only:* hCG (for pregnancy) at Visits 2, 4, 5, and 6.

ET=early termination, FSH=follicle-stimulating hormone, GGT=γ-glutamyl transferase, hCG=human chorionic gonadotropin, RBC=red blood cell, WBC=white blood cell.
(a) Microscopic examination of sediment to be performed only if the dipstick results are positive.

The central laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed preferably within 48 to 72 hours and no later than 7 days after the abnormality was noted (please refer to Section 10.2.3 for reporting requirements related to abnormal LFT results).

If ALT or AST remains elevated >3×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details, and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 for reporting requirements related to abnormal LFT results).

The investigator or designee is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose of study drug will require clear and complete documentation in the source documents as to the investigator's assessment of not clinically significant before proceeding with enrollment or randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.11 Contraception and Pregnancy Avoidance Procedure

9.1.11.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 95 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. The male subject must agree to advise the female partner to use additional contraception as shown in the list containing highly effective/effective contraception in Section 9.1.11.3.

9.1.11.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 35 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use 2 highly effective/effective methods of contraception (from the list in Section 9.1.11.3).

In addition they must be advised not to donate ova during this period.

9.1.11.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post–bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where devices containing hormones are excluded, the only acceptable methods of contraception are:
    - Nonhormonal methods:
        - Intrauterine device.
        - Bilateral tubal occlusion.
        - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success.
        - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 35 days after last dose.
        - Cervical cap with spermicide and male condom.
        - Diaphragm with spermicide and male condom.
        - Sponge with spermicide and male condom.
2. Double-barrier methods are acceptable for this study if used each time the subject has intercourse.

    Acceptable double-barrier methods (each time the subject has intercourse):
    - Cap (plus spermicidal cream or jelly) *PLUS* male condom and spermicide.
    - Diaphragm (plus spermicidal cream or jelly) *PLUS* male condom and spermicide.
3. Unacceptable methods of contraception are:
    - Hormonal methods.
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
    - Spermicides only.
    - Withdrawal.
    - No method at all.
    - Use of female and male condoms together.
    - Cap/diaphragm/sponge without spermicide and without condom.
4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a

consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

5. During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c) Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
6. In addition to a negative serum or urine hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), and a negative urine hCG pregnancy test on Day -1. Additional pregnancy testing will also be conducted during the study.

9.1.12 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (TAK-831) should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or within 95 days after the last dose, should also be recorded following authorization from the subject's partner.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.13 ECG Procedure

Standard 12-lead ECGs will be recorded. When an ECG is scheduled at the same time as the blood draws or vital signs, then the blood draws and vital signs will take priority and the ECG will be obtained within 0.5 hours before or after the scheduled blood draw or vital sign assignment. If an ECG coincides with a meal, the ECG will take precedence followed by the meal.

All 12-lead ECG machines will be supplied by the study site. Subjects should be in a supine position following an approximate 5-minute rest period for ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

The investigator (or a qualified observer at the study site who should have access to a cardiology consult) will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded. The following parameters will be calculated automatically by the ECG machine and recorded on the eCRF: heart rate, RR interval, PR interval, QT interval, QRS interval, QT interval with Bazett correction method, and QTcF interval. QTcF interval may be calculated manually by the study site. The QTcF interval is calculated as shown below:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source. The study site uses a fully validated ECG system. The investigator assessment is recorded electronically within this system.

All ECGs will be recorded at the time points detailed in the Schedule of Study Procedures (Appendix A).

9.1.14 PGx Sample Collection

CCI

[redacted]

CCI

9.1.15 PK Sample Collection and Analysis

Serial blood samples (one 4-mL sample per scheduled time) for PK analysis of TAK-831 plasma concentrations will be collected into chilled Vacutainers containing the anticoagulant K_2EDTA, according to the schedule shown in Appendix A.

The actual date and time of each PK sample collection as well as the date and time of study drug dosing for the most recent dose will be recorded accurately in the eCRF.

Instructions for sample collection, processing and shipment are provided in the laboratory manual.

9.1.15.1 Bioanalytical Methods

Plasma concentrations of TAK-831 will be measured by a validated high-performance liquid chromatography (HPLC) with tandem mass spectrometry method.

9.1.16 PD Sample Collection and Analysis

Serial blood samples (one 6-mL sample per scheduled time) for PD (D- and L-serine) analysis of TAK-831 will be collected into chilled Vacutainers containing the anticoagulant K_2EDTA, according to the schedule shown in in Appendix A.

The actual date and time of sample collection, time since last dose was administered, and time since last meal will be recorded on the source document and eCRF.

Instructions for sample collection, processing and shipment are provided in the laboratory manual.

9.1.16.1 Bioanalytical Methods

Plasma concentrations of D- and L-serine will be measured by a validated HPLC with tandem mass spectrometry assay method.

9.1.17 PD Parameters of D- and L-Serine

PD parameters will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

9.1.18 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the Screening Visit, the investigator should complete the eCRF. The IRT should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject identification numbers assigned to subjects who fail screening should not be used again. Subjects can only be rescreened after approval by the sponsor.

9.1.19 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

All measurements will be recorded on the source documents and in the eCRF.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study drug containers/unused study drugs to each dispensing site visit.

If a subject is persistently noncompliant with the study drug (80% of the allocated study drug for the period since the last visit), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visits.

9.3.1 Screening

Subjects will be screened as specified in Appendix A. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.18 for procedures for documenting screen failures.

9.3.2 Study Entrance/Randomization

Randomization will take place as described in Appendix A.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IRT, as described in Section 8.2. Subjects will be instructed on when to take the first dose of study drug as described in Section 6.1. The procedure for documenting screen failures is provided in Section 9.1.18.

9.3.3 Treatment Phase

Study-related procedures will be conducted according to the Schedule of Study Procedures in Appendix A.

9.3.4 Interim Phone Calls

Interim phone calls will be performed at the time specified in Appendix A.

9.3.5 Safety Follow-up Phone Call or Early Termination

The final safety phone call will be performed at the time specified in Appendix A or at the Early Termination Visit.

For all subjects receiving study drug, the investigator must complete the End of Study eCRF page.

9.3.6 Exit Interview Phone Call

A semistructured Exit Interview will be conducted by phone as specified in Appendix A.

9.3.7 Post Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

9.4 CCI

CCI [redacted]

CCI

[redacted]

9.5 Blood Volume

Approximate blood volumes to be collected for each subject are shown in Table 9.b.

Table 9.b Approximate Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples (a)		Total Volume (mL)
		Screening and Day -1	Treatment Period	
Clinical laboratory (hematology and serum chemistry)	21	1	2	63
CCI	[redacted]			
PK	4	1	5	24
PD (D- and L-serine)	6	1	3	24
Total approximate blood sampling volume (mL)				117

(a) Does not include blood draws at any unscheduled visits.

For each subject, the maximum volume of blood collected at any single visit is approximately 37 mL, and the approximate total volume of blood for the study is 117 mL.

Direct venipuncture is recommended for all blood collections: if a catheter is used, then use the saline lock (catheter) for the blood draws without the extra tubing (eg, BD Insyte Autoguard

#381434 [needle] and ICU Medical, Inc Clave Connector #PM30-2381 or similar). Any other method will need to be approved by the sponsor.

10.0 PRETREATMENT EVENTS AND AES

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding is not

considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs /Serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Acute liver failure
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Convulsive seizure	Pulmonary fibrosis
Hepatic necrosis	Spontaneous abortion / stillbirth and fetal death
Malignant hypertension	Pulmonary hypertension
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.9 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

10.1.10 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved—there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.

- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Visit 3) or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug (Visit 3). Routine collection of AEs will continue until the follow-up phone call.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date. The timing of the AE in relation to first dose of study drug (predose or postdose) will be indicated if the AE occurs on the first day of dosing.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).

8. Outcome of event.
9. Seriousness.

The Exit Interview and the ADL component of FARS will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.10 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form (or provide other written documentation) and fax it within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the FDA, European Medicines Agency, investigators, and IRBs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

This study does not include endpoints related to assessing mortality or major adverse health outcomes, and the study population is not at risk of serious safety events given the clinical characteristics of the disorder and known trajectory of disease progression. In addition, as summarized in Section 4.1.4, TAK-831 has been well tolerated and safe across the full range of doses examined in clinical studies, and there have not been any safety findings that indicate the need for an independent Data Monitoring Committee (DMC).

However, in addition to the ongoing review of blinded safety data by the sponsor and designee during the conduct of this study, the sponsor will establish an internal DMC independent of the study and project team to periodically review unblinded safety data during conduct of this study to complement the routine safety monitoring approach for compounds at this stage of development. The functions and procedures of the committee will be outlined in a DMC Charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

After lock of the clinical study database or submission of the eCRFs to the sponsor, any change of, modification of, or addition to the data on eCRFs should be made by the investigator with use of change and modification records of eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the Data Clarification Form for completeness and accuracy, and must sign and date the form.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, The

International Council for Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of treatment assignments. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of treatment assignments. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

Multiplicity across doses will be controlled for the primary endpoint as described in Section 13.1.3.1. Multiplicity will not be controlled for the secondary endpoints.

13.1.1 Analysis Sets

13.1.1.1 Full Analysis Set

The full analysis set (FAS) will include all subjects who were randomized and received at least 1 dose of the study drug for the treatment period. In FAS efficacy summaries, subjects will be analyzed by the treatment to which they were randomized.

13.1.1.2 Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who receive at least 1 dose of double-blind study medication. In safety summaries, subjects will be analyzed according to the treatment they received.

13.1.1.3 PD Analysis Set

The PD analysis set will consist of subjects who receive at least 1 dose of double-blind study medication and who have a Baseline D-serine and L-serine plasma concentration measurement and at least corresponding 1 postdose plasma concentration measurement.

13.1.1.4 Per-Protocol Set

The per-protocol set will include all FAS subjects who had no major protocol violations.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and baseline characteristics including age, gender, race, BMI, and medical history will be listed and summarized by each treatment group and overall based on the FAS.

Baseline values for efficacy assessments will also be summarized by each treatment group and overall based on the FAS.

For continuous variables, comparability of treatment groups will be assessed using an analysis of variance with treatment and pooled site as factors. For discrete variables, comparability will be assessed using the Cochran-Mantel-Haenszel general association test, stratified by pooled site.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy Analysis

The primary endpoint for this study is the change from Baseline to Week 12 in the inverse of the time to complete the 9-HPT (9-HPT^{-1}) after treatment with TAK-831, compared with placebo.

The primary analysis of change from Baseline in 9-HPT^{-1} will be based on the FAS. Comparisons between TAK-831 and placebo will be made over all assessed time points using estimates from a mixed model for repeated measures (MMRM) with Baseline 9-HPT^{-1} as a covariate; pooled site, visit, treatment, and ambulation status (randomization factor) as fixed factors; and treatment-by-visit and 9-HPT^{-1} by-visit interactions. Based on a Missing at Random Assumption, this analysis will be performed using observed case data only. The effect at each time point for each treatment is allowed to vary freely and an unstructured covariance matrix is assumed. If the model does not converge, other covariance structures (unstructured, compound symmetry, 2-Toeplitz, etc) will be considered. A suite of appropriate sensitivity analyses will be specified in the SAP.

Since 2 doses of TAK-831 are compared to placebo, multiplicity will be controlled at the Holm's method. The dose with the smaller p-value will be tested at the one-sided 0.05 level, then dose with the larger p-value will be tested at the one-sided 0.10 level only if the smaller p-value is significant. This procedure will control the overall type I error rate at the one-sided 0.10 level. The one-sided alternative hypothesis is that the mean time to complete the 9-HPT is shorter on the TAK-831 arm compared to placebo.

Subgroup analyses will be conducted according to ambulation status and Baseline D-serine concentration.

13.1.3.2 Secondary Efficacy Analysis

Analysis of secondary efficacy endpoints will be based on the FAS. For these endpoints, which are continuous change from Baseline endpoints, comparisons between TAK-831 and placebo will be based on similar methodology to that described for the primary efficacy analysis. For binary or ordinal endpoints, Cochran-Mantel-Haenszel tests will be used with ambulation status at randomization as a stratification factor. For binary or ordinal endpoints, missing data will be imputed as no change from Baseline. For each secondary endpoint, the 1-sided alternative hypothesis is that TAK-831 is superior to placebo in the clinically favorable direction, for example, a lower mean score on the FARS ADL scale.

Analysis of exploratory efficacy endpoints will be described in the SAP.

13.1.4 PK and PD Modeling Analysis

Plasma concentrations of TAK-831 will be listed for each subject and summarized by each time point for each dose of the study.

Individual concentration-time data will be pooled to describe the population PK of TAK-831. As data permit, a nonlinear mixed effects modeling approach (NONMEM software) will be used to

assess TAK-831 exposure. PK information generated in this study will be further utilized in subsequent population PK-PD analyses. The relationships between TAK-831 plasma concentrations and drug response (D- or L-serine plasma levels and/or selected measures of efficacy) will be explored. As appropriate, historical data may be used in this analysis to increase the robustness of the model and precision of estimated parameters. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses may be reported separately.

13.1.5 PD Analysis

For each regimen, the concentrations of D-serine, L-serine, and the ratio of D-serine to total serine with change and percent change from Baseline will be summarized at each time point of each dose level using descriptive statistics. In addition, mixed effects regression models will be fitted to the change from Baseline in these concentrations. Pairwise comparisons between the test regimens (high dose, low dose and placebo) will be made and the CIs for the difference in the LS means will be constructed for selected time points. Additional details and further analyses will be specified in the SAP. (See also Section 13.1.4.)

13.1.6 Safety Analysis

Analysis of safety variables will be based on the safety analysis set.

13.1.6.1 Analysis of AEs

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. AEs that are reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

13.1.6.2 Analysis of Other Safety Assessments

Other safety endpoints include:

- Laboratory values.
- Vital signs.
- Weight.
- ECGs.
- Physical examination findings.

Absolute values and changes from Screening/Baseline in clinical laboratory tests, vital signs, weight and ECG parameters will be summarized for each treatment group at all visits assessed using descriptive techniques. Physical examination findings will also be summarized for each treatment group. Values outside the reference ranges and markedly abnormal laboratory values will be flagged and tabulated.

13.1.7 Responder Analysis

A responder analysis to estimate the responder definition/threshold for the 9-HPT will be conducted. The methods used will be based on recommended methods presented in the FDA PRO guidance [28].

The main responder analysis will use patient global ratings, as measured by the PGI-I, on the change in upper limb function as the anchor. Other patient and clinician global ratings for upper limb function (PGI-S, CGI-S, CGI-I) will be candidate measures as supportive anchors. All anchors will be reviewed for appropriateness. FARS ADL items 3 to 5 will also be considered.

The basis of the threshold for meaningful change in the main responder analysis will correspond to the mean (or median) change score on the 9-HPT from Baseline to Week 12 corresponding to Improvement on the PGI-I for upper limb function. Supportive responder thresholds will be estimated similarly using the CGI-I for upper limb function and also estimated based on a one-category improvement on the PGI-S and CGI-S.

A distribution-based method based on one-half SD at Baseline, which corresponds to a moderate effect size, will also be estimated to provide a supportive responder threshold estimate [37-39].

Additional analyses will explore if a patient-reported improvement in upper limb function is meaningful from the patient perspective, as captured by the Exit Interview.

Application of the main and supportive responder definitions will be done by comparing the percentage of responders on the 9-HPT between TAK-831and placebo groups at Week 12.

Responder analyses will be replicated for each time point assessed (eg, Weeks 2 and 7).

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Approximately 65 subjects will be randomized in a 2:1:2 ratio for the placebo, low, and high dose respectively. It is assumed that approximately 60 subjects (92%) will complete 12 weeks and be evaluable on the primary endpoint. If the rate of early withdrawal is substantially greater than predicted, then an increase to the number of randomized subjects may be considered.

Assuming an effect size of 0.6 for each dose, there will be 77% power for at least 1 dose to be deemed superior to placebo and 54% power for both doses (overall alpha=0.10, 1-sided). Validated software (EAST 6.3, Cytel Inc.) was used to determine the power. The effect size was chosen based on the premise that a treatment effect equivalent to preventing or reversing 2 years of decline due to FDRA would be clinically meaningful. Using published data [19], the target effect size is approximately 0.6 for the 9-HPT.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator guarantees access to source documents by the sponsor or its designee contract research organization and by the IRB or independent ethics committee (IEC).

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations noted in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or ethics committee, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The investigator should document all protocol deviations via the eCRF.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB

IRBs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, a copy of the Exit Interview protocol, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

CCI

[redacted]

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda

contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

1. Sacchi S. D-Serine metabolism: new insights into the modulation of D-amino acid oxidase activity. Biochem Soc Trans 2013;41(6):1551-6.
2. Kakegawa W, Miyoshi Y, Hamase K, Matsuda S, Matsuda K, Kohda K, et al. D-serine regulates cerebellar LTD and motor coordination through the delta2 glutamate receptor. Nat Neurosci 2011;14(5):603-11.
3. Saigoh K, Matsui K, Takahashi K, Nishikawa T, Wada K. The stereo-specific effect of D-serine ethylester and the D-cycloserine in ataxic mutant mice. Brain Res 1998;808(1):42-7.
4. Fredericks CM. Disorders of the cerebellum and its connections. In: Fredericks C, Saladin LK, editors. Pathophysiology of the Motor Systems: Principles and Clinical Presentations. Philadelphia, PA: F. A. Davis; 1996.
5. Wilson CL, Fahey MC, Corben LA, Collins VR, Churchyard AJ, Lamont PJ, et al. Quality of life in Friedreich ataxia: what clinical, social and demographic factors are important? Eur J Neurol 2007;14(9):1040-7.
6. Pandolfo M. Friedreich's ataxia. In: Wells RD, Ashizawa T, editors. Genetic Instabilities & Neurological Diseases. Burlington, Massachusetts: Academic Press; 2006; Chapter 17, p. 277-96.
7. Pandolfo M. Friedreich ataxia: the clinical picture. J Neurol 2009;256 Suppl 1:3-8.
8. Labuda M, Labuda D, Miranda C, Poirier J, Soong BW, Barucha NE, et al. Unique origin and specific ethnic distribution of the Friedreich ataxia GAA expansion. Neurology 2000;54(12):2322-4.
9. Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271(5254):1423-7.
10. Campuzano V, Montermini L, Lutz Y, Cova L, Hindelang C, Jiralerspong S, et al. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. Hum Mol Genet 1997;6(11):1771-80.
11. Durr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med 1996;335(16):1169-75.
12. Parkinson MH, Boesch S, Nachbauer W, Mariotti C, Giunti P. Clinical features of Friedreich's ataxia: classical and atypical phenotypes. J Neurochem 2013;126 Suppl 1:103-17.
13. Koeppen AH, Mazurkiewicz JE. Friedreich ataxia: neuropathology revised. J Neuropathol Exp Neurol 2013;72(2):78-90.
14. Aranca TV, Jones TM, Shaw JD, Staffetti JS, Ashizawa T, Kuo SH, et al. Emerging therapies in Friedreich's ataxia. Neurodegener Dis Manag 2016;6(1):49-65.
15. Akbar U, Ashizawa T. Ataxia. Neurol Clin 2015;33(1):225-48.

16. Sham PC, Gottesman, II, MacLean CJ, Kendler KS. Schizophrenia: sex and familial morbidity. Psychiatry Res 1994;52(2):125-34.
17. Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo UH, Bassett AS, Cornblatt BA, Kestenbaum CJ, et al. The New York High-Risk Project. Psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch Gen Psychiatry 1995;52(10):857-65.
18. Radi ZA, Stewart ZS, Grzemski FA, Bobrowski WF. Renal pathophysiologic role of cortical tubular inclusion bodies. Toxicol Pathol 2013;41(1):32-7.
19. Patel M, Isaacs CJ, Seyer L, Brigatti K, Gelbard S, Strawser C, et al. Progression of Friedreich ataxia: quantitative characterization over 5 years. Ann Clin Transl Neurol 2016;3(9):684-94.
20. Kellor M, Frost J, Silberberg N, Iversen I, Cummings R. Hand strength and dexterity. Am J Occup Ther 1971;25(2):77-83.
21. Rehabilitation Measures Database. Rehab measures: nine-hole peg test. Published 30 October 2010. Updated 24 May 2016. Accessed 12 March 2017. Available at: http://www.rehabmeasures.org/Lists/RehabMeasures/DispForm.aspx?ID=925.
22. Feys P, Lamers I, Francis G, Benedict R, Phillips G, LaRocca N, et al. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler 2017:1352458517690824.
23. Corben LA, Tai G, Wilson C, Collins V, Churchyard AJ, Delatycki MB. A comparison of three measures of upper limb function in Friedreich ataxia. J Neurol 2010;257(4):518-23.
24. Mathiowetz V, Weber K, Kashman N, Volland G. Adult norms for the nine hole peg test of finger dexterity. Occup Ther J Res 1985;5(1):24-38.
25. Oxford Grice K, Vogel KA, Le V, Mitchell A, Muniz S, Vollmer MA. Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. Am J Occup Ther 2003;57(5):570-3.
26. Wang YC, Bohannon RW, Kapellusch J, Garg A, Gershon RC. Dexterity as measured with the 9-Hole Peg Test (9-HPT) across the age span. J Hand Ther 2015;28(1):53-9; quiz 60.
27. Lynch DR, Farmer JM, Wilson RL, Balcer LJ. Performance measures in Friedreich ataxia: potential utility as clinical outcome tools. Mov Disord 2005;20(7):777-82.
28. Psychopharmacolgic Drugs Advisory Committee (PDAC) meeting of the June 9-10, 2009. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research. 08 May 2009.
29. Subramony SH, May W, Lynch D, Gomez C, Fischbeck K, Hallett M, et al. Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale. Neurology 2005;64(7):1261-2.

30. Lynch DR, Farmer JM, Tsou AY, Perlman S, Subramony SH, Gomez CM, et al. Measuring Friedreich ataxia: complementary features of examination and performance measures. Neurology 2006;66(11):1711-6.

31. Friedman LS, Farmer JM, Perlman S, Wilmot G, Gomez CM, Bushara KO, et al. Measuring the rate of progression in Friedreich ataxia: implications for clinical trial design. Mov Disord 2010;25(4):426-32.

32. Fahey MC, Corben L, Collins V, Churchyard AJ, Delatycki MB. How is disease progress in Friedreich's ataxia best measured? A study of four rating scales. J Neurol Neurosurg Psychiatry 2007;78(4):411-3.

33. Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999;122 (Pt 5):871-82.

34. Lynch DR, Farmer JM, Rochestie D, Balcer LJ. Contrast letter acuity as a measure of visual dysfunction in patients with Friedreich ataxia. J Neuroophthalmol 2002;22(4):270-4.

35. Vogel AP, Wardrop MI, Folker JE, Synofzik M, Corben LA, Delatycki MB, et al. Voice in Friedreich Ataxia. J Voice 2017;31(2):243 e9- e19.

36. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266-77.

37. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41(5):582-92.

38. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Rev Pharmacoecon Outcomes Res 2011;11(2):163-9.

39. Wyrwich KW, Krishnan S, Poon JL, Auguste P, von Maltzahn R, Yu R, et al. Interpreting important health-related quality of life change using the Haem-A-QoL. Haemophilia 2015;21(5):578-84.

Appendix A Schedule of Study Procedures

	Screening	Baseline and Treatment Period								Phone Exit Interview	Safety Phone Follow-up	Early Termination Visit
Clinic Visit	**Visit 1**	**Visit 2**	**Visit 3**		**Visit 4**		**Visit 5**		**Visit 6**			
Study Day	**Within 28 days**	**-1**	**1 (a)**	**2-13 (home)**	**14 (±3) days**	**15-48 (home)**	**49 (±3) days**	**50- 83 (home)**	**84 (±2) days**	**≤7 days after Visit 6 or termination**	**7-17 days after last dose**	
Informed consent	X											
Randomization			X									
Inclusion/exclusion criteria	X	X	X									
Demographics and medical history	X											
Medication history	X											
Concurrent medical conditions	X											
Physical examination	X								X			X
Height and BMI (Screening only), weight	X								X			X
Clinical laboratory tests (b)	X				X				X			X
Urine drug screen	X											
FSH	X											
Urinalysis	X				X				X			X
Pregnancy test (hCG) (c)	X	X			X		X		X			X

Footnotes are on last table page.

	Screening	Baseline and Treatment Period								Phone Exit Interview	Safety Phone Follow-up	Early Termination Visit
Clinic Visit	**Visit 1**	**Visit 2**	**Visit 3**		**Visit 4**		**Visit 5**		**Visit 6**			
Study Day	**Within 28 days**	**-1**	**1 (a)**	**2-13 (home)**	**14 (±3) days**	**15-48 (home)**	**49 (±3) days**	**50- 83 (home)**	**84 (±2) days**	**≤7 days after Visit 6 or termination**	**7-17 days after last dose**	
ECG	X								X			X
FARS Functional Staging for Ataxia	X											
Vital signs (a)	X	X	X		X		X		X			X
C-SSRS	X	X			X		X		X			X
Concomitant medications	X	X	X		X		X		X			X
Dispense study medication (d)			X		X		X					
Study drug dosing (d)			X	X	X	X	X	X	X (e)			
PTE/AE assessment (a)		X	X	X	X	X	X	X	X	X	X	X
Interim phone calls (f)				X		X		X				
CCI												
PK blood collection (h)		X	X		X		X		X			X
PD blood collection (D- and L-serine) (i)		X			X		X		X			X
9-HPT (j) (k) (l)	X	X	X		X		X		X			X
FARS ADL (j)	X		X		X		X		X			X
FARS-neuro (j) (l)	X	X	X		X		X		X			X
T25FW and digital gait with sensors (j) (l)	X	X	X		X		X		X			X

Footnotes are on last table page.

	Screening	Baseline and Treatment Period								Phone Exit Interview	Safety Phone Follow-up	Early Termination Visit
Clinic Visit	**Visit 1**	**Visit 2**	**Visit 3**		**Visit 4**		**Visit 5**		**Visit 6**			
Study Day	**Within 28 days**	**-1**	**1 (a)**	**2-13 (home)**	**14 (±3) days**	**15-48 (home)**	**49 (±3) days**	**50- 83 (home)**	**84 (±2) days**	**≤7 days after Visit 6 or termination**	**7-17 days after last dose**	
Digital speech assessment (j) (l)	X	X	X		X		X		X			X
Digital balance and upper limb assessment (j) (l)	X	X	X		X		X		X			X
Low contrast letter acuity (j) (l)		X	X		X		X		X			X
CGI-S (overall severity) (j) (l)			X		X		X		X			X
CGI-I (overall improvement) (j) (l)					X		X		X			X
CGI-S (upper extremity functional severity) (j) (l)			X		X		X		X			X
CGI-I (upper extremity functional improvement) (j) (l)					X		X		X			X
PGI-S (overall severity)			X		X		X		X			X
PGI-I (overall improvement) (l)					X		X		X			X
PGI-S (upper extremity functional severity)			X		X		X		X			X
PGI-I (upper extremity functional improvement) (l)					X		X		X			X
Exit Interview (m)										X		X

Footnotes are on last table page.

Note: The Follow-up phone call will occur 7 to 17 days after the last dose of study drug by telephone unless subject report concerning AEs. In these cases, subjects will be brought back into the clinic for re-evaluation at the investigator's discretion.
(a) On Day 1 (Visit 3), subjects will complete all efficacy and safety baseline assessment before dosing. After all baseline assessment and procedures, subjects will be dosed in the clinic and will remain in the clinic for approximately 3 to 4 hours after dosing. During this time, subjects will be observed or monitored by clinic staff for any unexpected serious or severe AEs. Vital signs/AEs should be taken twice during this time, one around 1 to 2 hours postdose and one before patients are discharged. As noted in Section 1.1, all subjects will be provided with emergency medical contact information cards. They will be allowed to take a break for lunch in the vicinity of the clinic, if necessary. Prior to going to the hotel, vital signs will be recorded and all AEs recorded. A responsible clinician will review AEs and vital signs before sending the patients to hotels/homes.
(b) Clinical laboratory samples will be collected under nonfasting conditions.
(c) Urine test only except at Screening and Safety Follow-up/ET visit.
(d) Specific instructions: Subjects will be instructed to take 3 tablets by mouth two times a day in the fasted condition (at least 1 h before or after a meal) or with a light meal (less than 600 calories total with <30% from fat).
(e) On Day 84, subjects will only get the morning dose as their last dose.
(f) Interim phone calls will be conducted on Day 2, approximately at end of Week 1 and at the midpoints between Visits 4 and 5 and Visits 5 and 6. Subjects will be asked how they are doing and whether they are taking the drugs BID as directed. Reported AEs and concomitant medications will be captured in the source documents and eCRF. All questions will be addressed.
(g) CCI [redacted]
(h) Blood samples for the determination of concentrations of TAK-831 will be collected as shown below in the Schedule of Samples. One blood sample will be collected for subjects at the early termination visit. The sampling schedule may change based on emerging data but will not exceed the number of planned samples (N=10).
(i) Blood samples for PD will be collected immediately following the first PK sample collection for each visit a PD sample is to be collected per the Schedule of Samples.
(j) The efficacy assessments should be conducted by the same administrator throughout the entire study for a particular subject, as much as possible.
(k) The 9-HPT assessment consists of 2 trials of dominant hand, followed by 2 trials of nondominant hand. The 9-HPT assessment will be repeated twice with at least 1 hour in between the 2 sets of 9-HPT assessments.
(l) Sequence and timing of assessments will consider patient fatigue. The first set of 9-HPT and digital speech should be conducted first. In addition, during treatment period, subjects will be taking the drugs at home/hotel. This will be followed by other assessment/procedures. Timing of efficacy assessments should also be taken into consideration. During the treatment period (Visits 4-7), 9-HPT and digital speech should be assessed approximately 2-4 hours after the morning dose. All assessments should be approximately 2 to 6 hours post morning dose. Note for Visit 5, blood samples for PK and PD will be collected 1 to 2 hours post morning dose which the subjects takes at home/hotel and the collection of blood sample can be the first procedure on that day.
(m) A semistructured subject Exit Interview will be conducted by phone within 7 days from the last dose of study medication of the Double-Blind Treatment Period or within 7 days of notification of termination for the Early Termination Visit.

Schedule of Samples

Visit	Visit 1 (Screening)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Early Termination Visit
Day(s)	**-28 to -2**	**-1**	**1**	14 (±3)	49 (±3)	84 (±2)	
Clinical laboratory samples	X			X		X	X
CCI							
PK blood collection		Predose	0.25 and 2 hours postdose	1-2 hours post morning dose	At the end of the visit >4 hours after morning dose	At the end of the visit >4 hours after morning dose	X
PD blood collection (D- and L-serine)		Predose		1-2 hours post morning dose	At the end of the visit >4 hours after morning dose	At the end of the visit >4 hours after morning dose	X

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization Section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. CCI [redacted]
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 35 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 95 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Revision of study procedures (reduce the number of visits and blood draws, and update the randomization scheme).

The primary changes occur in Section 6.1 Study Design.

Initial wording:

...

The study will include a Screening Period (Days -28 to -2), a Training Period to minimize practice effect on efficacy assessment (Day -1), treatment (Days 1 to 84), a follow-up clinic visit (~1-2 weeks after last administration of study drug), and a subject Exit Interview (conducted over the phone within 7 days from the last dose of study medication of the Double-Blind Treatment Period or within 7 days of notification of termination for the Early Termination Visit) will be based on the last visit of the last subject. In addition, several interim phone calls will also be conducted.

Approximately 65 subjects who meet the study criteria during Screening will be invited to attend training to minimize practice effects on performance-based efficacy assessments on Day -1. On Day 1, subjects who continue to meet inclusion and none of the exclusion criteria will be randomized in a 2:1:2 ratio to TAK-831 high dose, TAK-831 low dose, or placebo, respectively. (If the rate of early withdrawal is substantially greater than predicted, then an increase to the number of randomized subjects may be considered.) Randomization will be stratified by ambulation status (ambulatory vs. nonambulatory). The first 5 subjects will be randomized to either placebo or TAK-831 low dose in a 2:3 ratio; the randomization ratio for the remaining 60 subjects will be adjusted to approximate a 2:1:2 ratio overall.

The study will be conducted in approximately 4 or more specialized academic neurological clinical centers in the United States with expertise in, and access to, patients with FRDA.

Subjects will receive twice daily (BID) study drug dosing or placebo from Day 1 through Day 84. Clinic visits during the treatment period include Day 1, Day 2, end of Week 2, end of Week 7, and end of Week 12. Clinical assessments, blood collections, and laboratory tests will be conducted at specific time points per the schedule of study procedures (Appendix A). A follow-up safety assessment visit will be conducted and a separate semistructured subject Exit Interview will be conducted by phone to provide an in-depth, qualitative evaluation of the subject experience and subject-perceived change due to treatment (Table 6.a).

Amended or new wording: ...

The study will include a Screening Period (Days -28 to -2), a Training Period ~~to minimize practice effect on efficacy assessment~~ (Day -1), treatment (Days 1 to 84), a ~~follow-up clinic visit (~1-2 weeks after last administration of study drug), and a subject~~ **phone** Exit Interview (~~conducted over the phone~~ within 7 days from the last dose of study medication of the Double-Blind Treatment Period or within 7 days of notification of termination for the Early Termination Visit~~) will be based on the last visit of the last subject. In addition, several interim phone calls will also be conducted.~~ **and a Safety Follow-up Phone Call (7 to 17 days after last dose of study drug).**

Approximately 65 subjects who meet the study criteria during Screening will be invited to attend training to minimize practice effects on performance-based efficacy assessments on Day -1. On Day 1, subjects who continue to meet inclusion and none of the exclusion criteria will be randomized in a 2:1:2 ratio to TAK-831 high dose, TAK-831 low dose, or placebo, respectively. (If the rate of early withdrawal is substantially greater than predicted, then an increase to the number of randomized subjects may be considered.) Randomization will be stratified by ambulation status (ambulatory vs. nonambulatory). ~~The first 5 subjects will be randomized to either placebo or TAK-831 low dose in a 2:3 ratio; the randomization ratio for the remaining 60 subjects will be adjusted to approximate a 2:1:2 ratio overall.~~

The study will be conducted in approximately 4**6** or more specialized academic neurological clinical centers in the United States with expertise in, and access to, patients with FRDA.

Subjects will receive twice daily (BID) study drug dosing or placebo from Day 1 through Day 84. Clinic visits during the treatment period include Day 1, ~~Day 2,~~ end of Week 2, end of Week 7, and end of Week 12. Clinical assessments, blood collections, and laboratory tests will be conducted at specific time points per the schedule of study procedures (Appendix A). A ~~follow-up safety assessment visit will be conducted and a separate~~ semistructured ~~subject~~ Exit Interview will be conducted by phone to provide an in-depth, qualitative evaluation of the subject experience and subject-perceived change due to treatment**, and a Safety Follow-up Phone Call will be conducted** (Table 6.a).

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Table 6.a Schematic of Study Design.
- Figure 6.a Schematic of Study Design.

- 5.2.2 Secondary Endpoints
- 5.2.4 Exploratory Endpoints
- Appendix A Schedule of Study Procedures.

Rationale for change: To reduce patient burden by making the original Day 2 in clinic visit and follow up visit to be conducted by phone. By following up with the subjects by phone, the investigators still have the liberty to invite the subjects for an in person clinical visit if concerning AE is reported, thus better balance the patient burden and evaluation of tolerability and safety. Additional safety and tolerability study data support the testing of the compound in the FRDA population and randomization across the high dose and low dose groups.

Change 2 Revision of TAK-831 dose.

The primary changes occur in Section 6.2.2 Justification of Dose:

Initial wording:

6.2.2 Justification of Dose

The doses of TAK-831 (200 mg BID and 20 mg BID) selected for the current study are based on PK data from the SRD/MRD study (TAK-831-1001) and brain target occupancy data from the PET study (TAK-831-1003), and safety data from both clinical studies after oral administration of TAK-831 (suspension) in healthy subjects. Preliminary PK/PD modeling analyses showed that the high dose regimen resulted in steady-state exposures associated with peak target occupancy of >90%, while the low dose regimen produced daily exposures associated with peak target occupancy of >50%. These 2 doses may allow characterization of an exposure-response relationship with PD or efficacy measures in adult subjects with FRDA. Of note, the study drug will be administered as a tablet, which exhibits lower oral bioavailability and higher variability relative to the oral suspension. Nutritional drinks (Ensure Plus) are proposed to be used in this rare disease population which may have difficulty with swallowing. It is anticipated that TAK-831 exposure may increase with food when TAK-831 T2 tablets are administered. Nutritional drinks can be easily standardized and can potentially increase drug exposure without requiring subjects to have repeated high fat diet over a long duration, which may not be well tolerated for some subjects. Therefore, a phase 1 study to evaluate the effect of food (a nutritional drink) on the PK of a T2 tablet formulation of TAK-831 in healthy subjects (TAK-831-1004) is currently planned to ensure the projected TAK-831 steady-state exposures can be achieved for optimal target occupancy, while remaining within the range of those observed at doses up to 400 mg daily dose, which were found to be safe.

Amended or new wording:

6.2.2 Justification of Dose

The doses of TAK-831 (~~200 mg BID~~**300 and** ~~20~~**75 mg BID**) selected for the current study are based on PK data from the SRD/MRD study (TAK-831-1001) and brain

target occupancy data from the PET study (TAK-831-1003), **PK and food effect study (TAK-831-1004), CSF D-serine study (TAK-831-1005),** and safety data from ~~both~~all clinical studies after oral administration of TAK-831 (suspension) in healthy subjects. Preliminary PK/PD modeling analyses showed that the high dose regimen resulted in steady-state exposures associated with peak target occupancy of >90%, ~~while the low dose regimen produced daily exposures associated with peak target occupancy of >50%~~. ~~These 2 doses~~ **The lower dose is to provide at least 3-fold exposure difference from the high dose to understand the relationship between TAK-831 and response relationship. In addition, CSF D-serine levels at 600 mg QD using T2 tablet and 800 mg suspension produced similar level of CSF D-serine, suggesting that 600 mg QD produced levels of D-serine approaching maximal DAO inhibition in the brain. These 2 doses (300 mg BID and 75 mg BID)** may allow characterization of an exposure-response relationship with PD or efficacy measures in adult subjects with FRDA. ~~Of note, the study drug will be administered as a tablet, which exhibits lower oral bioavailability and higher variability relative to the oral suspension. Nutritional drinks (Ensure Plus) are proposed to be used in this rare disease population which may have difficulty with swallowing. It is anticipated that TAK-831 exposure may increase with food when TAK-831 T2 tablets are administered. Nutritional drinks can be easily standardized and can potentially increase drug exposure without requiring subjects to have repeated high fat diet over a long duration, which may not be well tolerated for some subjects. Therefore, a phase I study to evaluate the effect of food (a nutritional drink) on the PK of a T2 tablet formulation of TAK-831 in healthy subjects (TAK-831-1004) is currently planned to ensure the projected TAK-831 steady-state exposures can be achieved for optimal target occupancy, while remaining within the range of those observed at doses up to 400 mg daily dose, which were found to be safe.~~ **Subjects will be instructed to take 3 tablets by mouth two times a day in the fasted condition (at least 1 h before or after a meal) or with a light meal (less than 600 calories total with <30% from fat). This will keep the TAK-831 exposure at levels that have been shown to be well tolerated in healthy subjects.**

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 8.1.1.1 Study Drug.
- Section 8.1.1.2 Sponsor-supplied Drug.
- Table 8.a Dose and Regimen.
- Section 8.2 Study Drug Assignment and Dispensing Procedures.
- Section 8.6 Accountability and Destruction of Sponsor-Supplied Drugs.

Rationale for change: Additional clinical studies in healthy volunteers and understanding CSF D-serine levels in relationship withTAK-831 dose indicate that a 600 mg daily dose produced nearly maximal pharmacological effect. This provided better precision in recommending the high dose. The lower dose is adjusted to provide at least 3-fold exposure difference from the high dose to understand the relationship between TAK-831 PK and response.

Change 3: Recatagorizing of objectives and endpoints related to Activities of Daily Living.

The primary changes occur in Section 5.1 Objectives and Section 5.2 Endpoints:

Initial wording:

5.1.2 Key Secondary Objective

The key secondary objective of the study is to evaluate the efficacy of TAK-831 versus placebo on Activities of Daily Living (ADL), as measured by the ADL component of the Friedreich Ataxia Rating Scale (FARS).

5.1.3 Other Secondary Objectives

The secondary objectives of the study are:

...

5.2.2. Key Secondary Endpoint

The key secondary endpoint for this study is the change from Baseline to Week 12 on the ADL component of the FARS after treatment with TAK-831, compared with placebo.

5.2.3 Other Secondary Endpoints

....

- The change from Baseline to Day 2, Weeks 2 and 7 on the 9-HPT after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2 and 7 on the ADL individual items after treatment with TAK-831, compared with placebo.

...

5.2.4 Exploratory Endpoints

....

Amended or new wording:

5.1.2 ~~Key~~ Secondary ~~Objective~~Objectives

- ~~The key secondary objective of the study is to~~**To** evaluate the efficacy of TAK-831 versus placebo on Activities of Daily Living (ADL), as measured by the ADL component of the Friedreich Ataxia Rating Scale (FARS), **and those items that related to upper limb function.**

~~**5.1.3 Other Secondary Objectives**~~

~~The secondary objectives of the study are~~.

...

5.2.2. ~~Key~~ Secondary ~~Endpoint~~Endpoints

- The ~~key secondary endpoint for this study is the~~ change from Baseline to Week 12 on the ADL component of the FARS after treatment with TAK-831, compared with placebo.

~~**5.2.3 Other Secondary Endpoints**~~

~~Other secondary endpoints for this study as follows:~~

- The change from Baseline to ~~Day 2, Weeks 2 and 7 on the 9-HPT~~**Weeks 2, 7, and 12 on the ADL component upper limb function items (ADL items 3 to 5) of the FARS**, after treatment with TAK-831, compared with placebo.
- The change from Baseline to Weeks 2 and 7 **on the 9-HPT^{-1} after treatment with TAK-831, compared with placebo.**
- **The change from Baseline to Weeks 2, 7, and 12** on the ADL individual items after treatment with TAK-831, compared with placebo.

....

- **Percentage of subjects whose 9-HPT completion time is reduced by at least 15% and at least 20% from Baseline.**

....

5.2.4 Exploratory Endpoints

....

CCI [redacted]

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 13.1 Statistical and Analytical Plans.

Rationale for change: While the ADL is important, the probability of detecting significant change in this study of short duration is low and therefore it is recategorized as one of the secondary endpoints.

Change 4: Clarification of endpoints related to the 9-hole peg test.

The primary changes occur in Section 5.2 Endpoints:

Initial wording:

5.2.1 Primary Endpoint

The primary endpoint for this study is the change from Baseline to Week 12 in the time (in seconds) to complete the 9-HPT after treatment with TAK-831, compared with placebo.

...

5.2.3 Other Secondary Endpoints

Other secondary endpoints for this study as follows:

- The change from Baseline to Day 2, Weeks 2 and 7 on the 9-HPT after treatment with TAK-831, compared with placebo.

...

5.2.5 Exploratory Endpoints

Exploratory endpoints for this study as follows:

...

Amended or new wording:

5.2.1 Primary Endpoint

The primary endpoint for this study is the change from Baseline to Week 12 in the **inverse of the** time ~~(in seconds)~~ to complete the 9-HPT **(9-HPT^{-1})** after treatment with TAK-831, compared with placebo.

...

5.2.3~~3~~2 ~~Other~~ Secondary Endpoints

~~Other secondary endpoints for this study as follows:~~

- The change from Baseline to ~~Day 2,~~ Weeks 2 and 7 on the 9-HPT^{-1} after treatment with TAK-831, compared with placebo.

...

- **Percentage of subjects whose 9-HPT completion time is reduced by at least 15% and at least 20% from Baseline.**

...

5.2.5~~4~~ Exploratory Endpoints

~~Exploratory endpoints for this study as follows:~~

...

CCI [redacted]

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Rationale for change: To clarify details on endpoints.

Change 5: Revision and clarification of study entry criteria.

The primary changes occur in Section 7.1 Inclusion Criteria and Section 7.2 Exclusion Criteria:

Initial wording:

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent. If written consent is not possible due to physical incapacity, written consent on behalf of the participant will be sought from the participant's relatives or caregivers (or from a legally acceptable representative).

...

7.2 Exclusion Criteria

...

2. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease (including uncontrolled diabetes) or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the efficacy and safety evaluation. The subject has medical history or conditions that, in the opinion of the investigator, may interfere with study conduct or clinical assessments.

...

5. The subject has a history of cancer, except basal cell carcinoma or in situ cervical cancer that has been in remission for ≥5 years prior to first dose of study drug.
6. The subject is known to be currently infected or have been infected with human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus.

7. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use without a valid prescription or medical need) at Screening.

...

9. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 3 or more units per day on 1 occasion per week or 7 or more units in any given week) within 1 year prior to Screening. One unit is equivalent to a half-pint of beer or 1 single measure of spirits or 1 small glass of wine.

...

11. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property or subjects who within the past year prior to Screening have attempted suicide or have positive answers on item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS, life-time version) at Screening or Day 1.

...

17. The subject has 1 or more laboratory values outside the normal range that are considered by the investigator to be clinically significant at the Screening Visit; or the subject has any of the following at the Screening Visit: a serum creatinine value >1.5 times the ULN. A total serum total bilirubin value >1.5×ULN. A serum ALT or AST value >2×ULN, or prolactin ≥100 ng/mL.

Amended or new wording:

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is **capable of understanding the informed consent, and** capable of understanding and complying with protocol requirements.

2. The subject signs and dates a written, informed consent. ~~If written consent is not possible due to physical incapacity, written consent on behalf of the participant will be sought from the participant's relatives or caregivers (or from a legally acceptable representative).~~

...

7.2 Exclusion Criteria

...

2. The subject has**, based on medical history and judgment of the investigator,** uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease (including

uncontrolled diabetes) or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the efficacy and safety evaluation. The subject has medical history or conditions that, in the opinion of the investigator, may interfere with study conduct or clinical assessments.

...

5. The subject has a history of cancer, except **squamous cell carcinoma or** basal cell carcinoma **that have been treated or excised,** or in situ cervical cancer that has been in remission for ≥5 years prior to first dose of study drug.
6. The subject is known to ~~be currently infected or~~ have **a history of having** been infected with human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus.
7. ~~The subject has a~~ **Urine drug screen** positive ~~urine drug result~~ for drugs of abuse ~~(defined as any illicit~~**at screening or, except for a prescribed** drug ~~use without a valid prescription or medical need)~~**allowed by the protocol** at Screening. **Cannabinoid use is not permitted either recreationally or medically.**

...

9. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse ~~(defined as regular consumption of 3 or more units per day on 1 occasion per week or 7 or more units in any given week) within 1 year prior to Screening. One unit is equivalent to a half pint of beer or 1 single measure of spirits or 1 small glass of wine~~**within 1 year prior to Screening.**

...

11. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property or subjects who within the past year prior to Screening have attempted suicide or have positive answers on item 4 or 5 on the ~~Columbia Suicide Severity Rating Scale (~~C-SSRS, life-time version~~)~~ at Screening or Day 1.

...

17. The subject has 1 or more laboratory values outside the normal range that are considered by the investigator to be clinically significant at the Screening Visit; or the subject has any of the following at the Screening Visit: a serum creatinine value >1.5 times the ULN~~. A~~**, a** total serum total bilirubin value >1.5×ULN~~. A~~**or a** serum ALT or AST value >2×ULN~~, or prolactin ≥100 ng/mL~~.

18. The subject has current history of symptomatic orthostatic hypotension.

The following sections also contain this change:
Section 2.0 STUDY SUMMARY.

Rationale for change: To clarify study entrance criteria. In addition, squamous cell carcinomas with excision that have been treated or excised are added to the exceptions of exclusion. To reduced patient risk of falling, subjects with current history of symptomatic orthostatic hypotension are excluded.

Change 6: Clarification of excluded medications and products.

The primary changes occur in Section 7.3 Excluded Medications, Supplements, and Dietary Products and Section 7.4 Diet, Fluid, Activity Control:

Initial wording:

Section 7.3 Excluded Medications, Supplements, and Dietary Products

...

Table 7.a Excluded/Allowed Medications and Treatments.

- Psychotropic agents not otherwise specified (including stimulants, tryptophan, melatonin and dopamine agonists)
- Herbal remedies, which are psychoactive (eg, St. John's Wort, kava kava, valerian, ginkgo biloba, melatonin)
- Muscle relaxants
- Antiparkinson drugs

Section 7.4 Diet, Fluid, Activity Control

Subjects will maintain their regular routine of exercise and physical therapy or speech therapy.

Alcohol intake will be restricted to no more than 1 unit in 1 occasion and less than 3 units per week. One unit is equivalent to a half-pint of beer or 1 single measure of spirits or 1 small glass of wine.

Amended or new wording:

Section 7.3 Excluded Medications, Supplements, and Dietary Products

...

Table 7.a Excluded/Allowed Medications and Treatments.

- Psychotropic agents not otherwise specified (including **but not limited to** stimulants, tryptophan, melatonin~~and dopamine agonists~~)
- Herbal remedies, which are psychoactive (eg, St. John's Wort, kava kava, valerian, ginkgo biloba, melatonin)**, OTC (e.g., cough syrup)**
- Muscle relaxants **including but not limited to baclofen, tizanidine, 4 aminopyridine**

- ~~Antiparkinson drugs~~**Antiparkinsonian drugs including dopamine agonists**

Section 7.4 Diet, Fluid, Activity Control

Subjects will maintain their regular routine of exercise and physical therapy or speech therapy.

Alcohol intake will be restricted to no more than 1 unit in 1 occasion and less than 3 units per week. One unit is equivalent to a half-pint of beer or 1 single measure of spirits or 1 small glass of wine. **Subject will not drink alcohol with 24 hours of the conduct of any clinical assessments.**

Rationale for change: To clarify excluded medications and products.

Change 7: Revision of statistical analysis.

The primary changes occur in Section 13.1.2 Analysis of demographics and other baseline characteristics and Section 13.1.3.1 Primary Efficacy Analysis

Initial wording:

13.1.2 Analysis of demographics and other baseline characteristics

Demographics and baseline characteristics including age, gender, race, BMI, and medical history will be listed and summarized by each treatment group and overall based on all randomized subjects.

Baseline values for efficacy assessments will also be summarized by each treatment group and overall based on all randomized subjects.

....

13.1.3.1 Primary Efficacy Analysis

The primary endpoint to be measured is the change from Baseline in the time (in seconds) to complete the 9-HPT at 12 weeks. An inverse transform will be used to reduce skewness. The primary efficacy comparison will be the comparison between TAK-831 and placebo in change from Baseline in the time to complete the 9-HPT at 12 weeks.

...

13.1.3.2 Secondary Efficacy Analysis

Analysis of secondary efficacy endpoints will be based on the FAS. For these endpoints, which are continuous change from Baseline endpoints, comparisons between TAK-831 and placebo will be based on similar methodology to that described for the primary efficacy analysis. However, for the CGI-I and PGI-I endpoints the corresponding Baseline severity scores (CGI-S or PGI-S, respectively) will be used as the Baseline covariate in the MMRM and analysis of covariance models. For each secondary endpoint, the 1-sided alternative hypothesis is that TAK-831 is superior to placebo in the clinically favorable direction, for

example, a lower mean score on the FARS ADL scale.

Amended or new wording:

13.1.2 Analysis of demographics and other baseline characteristics

Demographics and baseline characteristics including age, gender, race, BMI, and medical history will be listed and summarized by each treatment group and overall based on ~~all randomized subjects.~~**the FAS**.

Baseline values for efficacy assessments will also be summarized by each treatment group and overall based ~~on all randomized subjects~~**the FAS**.

....

13.1.3.1 Primary Efficacy Analysis

The primary endpoint ~~to be measured~~**for this study** is the change from Baseline **to Week 12** in the **inverse of the** time ~~(in seconds)~~ to complete the 9-HPT ~~at 12 weeks. An inverse transform will be used to reduce skewness. The primary efficacy comparison will be the comparison between~~**(9-HPT^{-1}) after treatment with** TAK-831 ~~and~~**, compared with** placebo ~~in change from Baseline in the time to complete the 9-HPT at 12 weeks.~~

....

13.1.3.2 Secondary Efficacy Analysis

Analysis of secondary efficacy endpoints will be based on the FAS. For these endpoints which are continuous change from Baseline endpoints, comparisons between TAK-831 and placebo will be based on similar methodology to that described for the primary efficacy analysis. ~~However, for the CGI-I and PGI-I endpoints the corresponding Baseline severity scores (CGI-S or PGI-S, respectively) will be used as the Baseline covariate in the MMRM and analysis of covariance models.~~**For binary or ordinal endpoints, Cochran-Mantel-Haenszel tests will be used with ambulation status at randomization as a stratification factor. For binary or ordinal endpoints, missing data will be imputed as no change from Baseline.** For each secondary endpoint, the 1-sided alternative hypothesis is that TAK-831 is superior to placebo in the clinically favorable direction, for example, a lower mean score on the FARS ADL scale.

Rationale for change: To update statistical analysis.

Change 8: Inclusion of the summary of clinical data from Studies TAK-831-1004 and TAK-831-1005.

The primary changes occur in Section 4.1.4 Clinical Background.

Initial wording:

4.1.4 Clinical Background

Two phase 1 clinical studies have been conducted in healthy subjects: a first-in-human study to determine the pharmacokinetic (PK) profiles of TAK-831 oral suspension after single-rising dose (SRD) and multiple-rising dose (MRD) administration, as well as the relative bioavailability and effect of food on the PK of the T1 tablet formulation of TAK-831 (TAK-831-1001); and a study to demonstrate DAO target engagement in the brain as measured by positron emission tomography (PET) (TAK-831-1003). Plasma D-serine levels, TAK-831 plasma concentrations and safety were also evaluated. There is an ongoing clinical study, TAK-831-1004, to study the food (nutritional drink) effect of T2 tablet formulation.

...

4.3 Benefit/Risk Profile

The literature suggests that D-serine is a critical mediator of glutamate receptor–dependent functions of the cerebellum [2]. As a DAO inhibitor that increases D-serine in the cerebellum, TAK-831 has the potential to increase NMDA-dependent glutamatergic signaling. One disease state that could be treated through this mechanism is FRDA. TAK-831 showed efficacy in a mouse model of FRDA with single doses and dosed daily for 15 days at 3 mg/kg.

...

The proposed phase 2 study is being conducted to evaluate the efficacy, safety, PD effects, and PK of 2 dose levels of oral TAK-831 in adult subjects with FRDA for up to 84 days. The proposed doses of TAK-831 have been selected based on PK data from the SRD/MRD study (TAK-831-1001), brain target occupancy data from the PET study (TAK-831-1003), and safety data from both clinical studies after oral administration of TAK-831 (suspension) in healthy subjects as a single dose up to 750 mg (TAK-831-1001 and TAK-831-1003) or for 13 days as a multiple dose up to 400 mg/day (TAK-831-1001). The dose and study duration of TAK-831 used in prior studies have not resulted in a safety signal that would prevent additional studies.

Potential risks, and risk mitigation measures to be implemented in studies with TAK-831, are described below. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, and the 2 phase 1 studies conducted to date. These procedures may be modified during the study if necessary based on evaluation of any additional clinical or nonclinical safety data.

...

- Postural hypotension and dizziness were observed in prior studies in healthy subjects, although the incidence for subjects treated with TAK-831 and placebo was similar. As FRDA patients experience gait disturbance, motor dysfunction, and thus are susceptible to fall, subjects should be carefully monitored for possible orthostatic hypotensive effects of TAK-831 administration. Additionally, subjects should be instructed to take appropriate precautionary measures to prevent falling while under treatment with TAK-831.

...

Amended or new wording:

4.1.4 Clinical Background

~~Two~~ **Five** phase 1 clinical studies have been conducted in healthy subjects: a first-in-human study to determine the pharmacokinetic (PK) profiles of TAK-831 oral suspension after single-rising dose (SRD) and multiple-rising dose (MRD) administration, as well as the relative bioavailability and effect of food on the PK of the T1 tablet formulation of TAK-831 (TAK-831-1001); and a study to demonstrate DAO target engagement in the brain as measured by positron emission tomography (PET) (TAK-831-1003). Plasma D-serine levels, TAK-831 plasma concentrations and safety were also evaluated. ~~There is an ongoing clinical study, TAK-831-1004, to study the food (nutritional drink) effect of T2 tablet formulation.~~**Since these studies were conducted, a single dose PK and food-effect, bioavailability study with the T2 tablet formulation (TAK-831-1004) has completed active dosing, and a study examining additional escalating multiple doses of TAK-831 higher than those achieved in the TAK-831-1001 study was initiated and is ongoing (TAK-831-1005).**

...

TAK-831-1004 was a phase 1, randomized, open-label, single-dose, 2-period crossover study designed to characterize the PK of a single dose of 400 mg of TAK-831 and assess the effect of food on the bioavailability of TAK-831 400 mg when administered as four 100 mg oral tablets of the T2 formulation in 15 healthy adult subjects. In the TAK-831-1004 study, there was only a single AE of mild upper respiratory tract infection, judged to be unrelated to study treatment. One subject met criteria for orthostatic hypotension at a single time point without an accompanying report of a dizziness AE. There were no concerning trends in laboratory, ECG, or vital sign data. TAK-831 given as T2 tablet coadministered with the nutritional drink (Ensure Plus) increased mean C_{max} and AUC_{∞} values by 35% and 21%, respectively. Treatment with a single oral dose of 400mg TAK-831 T2 formulation temporally increased plasma concentration of D-serine, similar to the results obtained in the Study TAK-831-1001. The magnitude and kinetics of the change in plasma D-serine

was similar when the drug was administered in either water or Ensure.

TAK-831-1005 is an ongoing investigator and subject blinded, sponsor unblinded, placebo-controlled clinical study progressively assessing independent cohorts of healthy subjects to continue evaluation of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of escalating multiple doses of TAK-831 at doses higher than those achieved in the TAK-831-1001 study. The following study information is preliminary and is based on blinded adverse event data reported by the investigator and blinded safety endpoint data in study TAK-831-1005. Although not expected, these data are subject to change upon finalization following study monitoring, source data verification, and discrepancy query management prior to database lock. At this time, two cohorts with 8 subjects each (6 TAK-831 and 2 placebo) have completed treatment at dose levels of 600 mg QD (T2 tablet formulation) or 800 mg QD (oral suspension) administered first as a single dose, and then administered for up to 14 days of multiple dosing. In addition to standard safety assessments, subjects in these cohorts underwent catheterized CSF collection for a 24 hour period starting prior to dosing on Day 1 single dose treatment and on Day 14 of multiple dose treatment. Nausea and post-lumbar puncture syndrome were the most common treatment-emergent AEs; nausea in the absence of post-lumbar puncture syndrome was reported by one subject in each cohort. All episodes of nausea were mild in intensity and self-limiting. Two subjects in each cohort met categorical criteria for orthostatic hypotension on at least one assessment; none of these findings were associated with an AE of dizziness. There were no concerning trends in laboratory, ECG, or vital sign data collected in these cohorts.

Following once-daily dosing, mean plasma exposures of TAK-831 were higher (C_{max}: 1.3-fold and AUC: 1.8-fold) when dosed as an oral suspension than as T2 tablets. Geometric mean Cmax values were 1466 and 1976 ng/mL with 600 mg QD (T2 tablet formulation) and 800 mg QD (oral suspension), respectively. Mean steady-state exposures (AUC_t) over the 24-hour dosing interval were on average 4993 and 8853 ng.hr/mL for the respective 600 mg and 800 mg QD dosing cohorts. The mean 24-hour TAK-831 PK profile in CSF was parallel to that of plasma and observed TAK-831 CSF concentrations were well in agreement with the TAK-831 unbound fraction in plasma. After both single and multiple dosing with TAK-831, there was a notable increase in the area under the effect curve from time 0 to 24 hours of CSF D-serine for both the 600 mg T2 and 800 mg oral suspension treatment groups when compared to placebo; changes in CSF D-serine were noticeably higher after multiple doses of TAK-831 than after administration of a single dose of TAK-831. The magnitude of the increase in the area under the effect curve for CSF D-serine was similar for both the 600 mg T2 and 800 mg oral suspension, suggesting

that the maximal PD effect in the CSF was achieved at drug exposures attained with the 600mg T2 dose and 800 mg suspension

Overall, the emerging safety data from the TAK-831-1004 and TAK-831-1005 studies are consistent with the data collected in prior clinical studies and do not alter the risk profile of the compound.

...

The literature suggests that D-serine is a critical mediator of glutamate receptor–dependent functions of the cerebellum **and was shown to reduce ataxia in animal model of spinocerebellar ataxia** [2]. As a DAO inhibitor that increases D-serine in the cerebellum, TAK-831 has the potential to increase NMDA-dependent glutamatergic signaling. One disease state that could be treated through this mechanism is FRDA. TAK-831 showed efficacy in a mouse model of FRDA with single doses and dosed daily for 15 days at 3 mg/kg.

4.3 Benefit/Risk Profile

The proposed phase 2 study is being conducted to evaluate the efficacy, safety, PD effects, and PK of 2 dose levels of oral TAK-831 in adult subjects with FRDA for up to 84 days. The proposed doses of TAK-831 have been selected based on PK data from the SRD/MRD ~~study~~**studies** (TAK-831-1001 **and TAK-831-1005**), brain target occupancy data from the PET study (TAK-831-1003), **CSF D-serine data from the TAK-831-1005 study,** and safety data from ~~both~~**all** clinical studies after oral administration of TAK-831 ~~(suspension)~~ in healthy subjects ~~as a single dose up to 750 mg (TAK-831-1001 and TAK-831-1003) or for 13 days as a multiple dose up to 400 mg/day (TAK-831-1001).~~**described above.** The dose and study duration of TAK-831 used in prior studies have not resulted in a safety signal that would prevent additional studies~~.~~ **in subjects with FRDA.**

Potential risks, and risk mitigation measures to be implemented in studies with TAK-831, are described below. These measures are based on what is known about the mechanism of action of TAK-831, nonclinical data, ~~and~~ the ~~2~~ phase 1 studies conducted to date**, and general considerations in the development of new chemical entities.** These procedures may be modified during the study if necessary based on evaluation of any additional clinical or nonclinical safety data.

...

- Postural hypotension and dizziness were observed in prior studies in healthy subjects~~, although~~**. However,** the incidence ~~for~~**of dizziness in** subjects treated with TAK-831 and placebo was similar. **In addition, 2 subjects who received 250 mg TAK-831 showed blood pressure variations consistent with orthostatic hypotension without clinical symptoms. These measurements were taken at the Study exit visit and were considered not-related to**

TAK-831. As FRDA patients experience gait disturbance, motor dysfunction, and thus are susceptible to fall, subjects should be ~~carefully monitored for possible orthostatic hypotensive effects of TAK-831 administration. Additionally, subjects should be~~ instructed to take appropriate precautionary measures to prevent falling while under treatment with TAK-831. **Additionally, subjects with current history of postural hypotension will be excluded from the study.**

Rationale for change: To provide the most current clinical data available for TAK-831.

Change 9: Engagement of an internal DMC to review unblinded safety data.

The primary changes occur in Section 11.0 STUDY-SPECIFIC COMMITTEES.

Initial wording:

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, clinical endpoint committee, or adjudication committee will be used in this study.

Amended or new wording:

11.0 STUDY-SPECIFIC COMMITTEES

~~No steering committee, data safety monitoring committee, clinical endpoint committee, or adjudication committee will be used in this study.~~

This study does not include endpoints related to assessing mortality or major adverse health outcomes, and the study population is not at risk of serious safety events given the clinical characteristics of the disorder and known trajectory of disease progression. In addition, as summarized in Section 4.1.4, TAK-831 has been well tolerated and safe across the full range of doses examined in clinical studies, and there have not been any safety findings that indicate the need for an independent Data Monitoring Committee (DMC).

However, in addition to the ongoing review of blinded safety data by the sponsor and designee during the conduct of this study, the sponsor will establish an internal DMC independent of the study and project team to periodically review unblinded safety data during conduct of this study to complement the routine safety monitoring approach for compounds at this stage of development. The functions and procedures of the committee will be outlined in a DMC Charter.

Rationale for change: To coordinate the monitoring of safety and tolerability data for the TAK-831 compound, together with other upcoming clinical trials in the schizophrenia population.

Change 10: Personnel change

The primary changes occur in Section 1.1 and Section 1.2

Initial wording:

Section 1.1

PPD

Section 1.2

PPD

Amended or new wording:

Section 1.1

PPD

Section 1.2

PPD

Rationale for change: To update personnel responsibilities.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	09-Oct-2017 12:09 UTC
	Clinical VP Approval	09-Oct-2017 12:12 UTC
	Biostatistics Approval	09-Oct-2017 21:19 UTC