CLINICAL PROTOCOL

The AUDYT trial: An open-label Study to Define the Safety, Tolerability and Clinical Activity of deutetrabenazine (AUstedo) in Adult Study subjects with DysTonia (NCT04173260)

Compound name:	Deutetrabenazine (AUSTEDO™) Auspex Pharmaceuticals Inc. AUS-001 U.S. Patent No: 8,524,733
Sponsor:	Teva Pharmaceuticals USA, Inc. North Wales, PA 19454 United States
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Version:	1
Principal Investigator:	Andres Deik, MD, MSEd University of Pennsylvania Parkinson's Disease and Movement Disorders Center Philadelphia, Pennsylvania, United States

Table 1
ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AUC	Area under the plasma concentration-time curve
BP	Blood pressure
CGI-I	Clinical Global Impression of Improvement Scale
Cmax	Peak plasma concentration of a drug
CS	Clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
CYP2D6	Cytochrome P450 family 2 subfamily D member 6
DA	Dopamine
DD	Day (numeric)
DYT	Dystonia
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GDS	Global Dystonia Rating Scale
HD	Huntington's Disease
HR	Heart rate
HTBZ	Active deuterated dihydro metabolites
ICF	Informed consent form
ICH	International Committee on Harmonization
Maintenance period	Six-week study period during which study subjects are expected to remain on AUSTEDO 48 mg/day (36 mg/day in study subjects receiving a strong CYP2D6 inhibitor), or the highest well-tolerated dose.
MDS	Movement Disorders Society
mg	Milligrams
mL	Milliliters
msec	Milliseconds
MMSE	Mini Mental State Examination
MMM	Month (first three letters)
Ng	Nanograms
NCS	Non clinically significant
PD	Parkinson's Disease
PGI-I	Patient Global Impression of Improvement
pKa	Logarithmic constant of the quantitative measure of the strength of an acid in solution

QT interval	The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.
QTc interval	Heart rate-corrected QT interval
Ramp-up period	Titration period during which study subjects are expected to increase AUSTEDO from 12 mg/day to up to 48 mg/day.
RR	Respiratory rate
SAE	Serious adverse event
Sec	Second
Significant QT prolongation	QTc interval of 450 (458) milliseconds in men or 460 (472) milliseconds in women.
SSS	Stanford Sleepiness Scale
TBZ	Tetrabenazine
TD	Tardive Dyskinesias
UPDRS	Unified Parkinson’s Disease Rating Scale
VMAT2	Vesicular monoamine transporter 2
WT	Weight (in pounds)
YYYY	Year (numeric)

SYNOPSIS

Title: The AUDYT trial: An open-label Study to Define the Safety, Tolerability and Clinical Activity of deutetrabenazine (AUstedo) in Adult Study subjects with DYsTonia
Investigator: Deik, Andres F
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Background / Rationale
A number of studies have demonstrated Tetrabenazine (TBZ) is effective in the symptomatic treatment of dystonia. Tetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor that modulates synaptic dopamine. Unfortunately, the use of TBZ is often limited by its side effect profile, which includes, but is not limited to, depression (including suicidal depression), sedation and parkinsonism. Deutetrabenazine (AUSTEDO™) is a novel, highly selective VMAT2 inhibitor that contains deuterium, a stable isotope of hydrogen. Deuterium attenuates the metabolism of AUSTEDO, leading to reduced fluctuations in plasmatic levels as compared to TBZ. This, is turn, reduces adverse events associated to peak drug concentrations. AUSTEDO is approved by the Food and Drug Administration (FDA) for the treatment of chorea associated with Huntington's disease (HD) and Tardive Dyskinesias in adults, but not for the treatment of dystonia. Given its shared mechanism of action with TBZ, an opportunity exists to establish the safety, tolerability and clinical activity of AUSTEDO in subjects with dystonia.

Primary Study Objective
To explore the safety and tolerability of the daily oral administration of AUSTEDO in adult study subjects with dystonia.

Secondary Study Objectives
1. To establish the degree of symptomatic effect of AUSTEDO as measured by the Clinical Global Impression of Improvement Scale (CGI-I) after 6 weeks of AUSTEDO 48 mg daily, or at the highest tolerated dose.
2. To establish the degree of symptomatic effect of AUSTEDO as measured by the Patient Global Impression of Improvement Scale (PGI-I) after 6 weeks of AUSTEDO 48 mg daily, or at the highest tolerated dose.
3. To establish the degree of symptomatic effect of AUSTEDO as measured by the change in the Global Dystonia Rating Scale between baseline and after 6 weeks of AUSTEDO 48 mg daily, or at the highest tolerated dose.

Design
This is a single-center, open-label study of AUSTEDO in study subjects with dystonia. The study will provide preliminary experience of the safety, tolerability, and clinical activity of AUSTEDO in study subjects with dystonia. Study duration will be up to 13 weeks from screening (Visit 1) to the post treatment evaluation (Visit 5). Treatment period from drug initiation to final on-treatment Visit will be 12 weeks, or less, as follows: during the ramp-up period, study drug will start at 12 mg/day (6 mg twice daily) and will be titrated weekly by 6 mg/day increments until either 1) the maximal allowable dose (48 mg/day) is reached, or 2) dose-limiting side-effects occur. In study subjects receiving a strong CYP2D6 inhibitor, the maximum allowed dose of AUSTEDO will be 36 mg/day, reducing study duration (due to a reduction in the ramp-up period) to 11 weeks. Study subjects who experience dose-limiting side effects will be maintained on their maximum tolerated dose. Once the maximal dose is established for each participant, they will complete 6 continuous weeks on this dose (maintenance period), followed by a 1-week washout. For study subjects unable to titrate up to 48 mg/day due to side effects, the 6 weeks of maintenance will start once they reduce the study drug back to the maximum well-tolerated dose. Adverse events will be monitored throughout the

study and will be reported after drug initiation. Dose reductions, suspensions, and withdrawals due to adverse events will be recorded. ECG readings will be measured at screening, during week 2, during the first week of the maintenance period (whenever this is established to be, typically week 7 for subjects able to titrate up to 48 mg/day), immediately before washout (week 12 for those study subjects who are able to titrate up to 48 mg/day) and during week 13. Assessment of Columbia Suicide Severity Rating Scale and Stanford Sleepiness Scale scores will occur at screening and all clinic Visits. The Mini Mental (MMSE) Scale will be performed at screening and at the final on-treatment Visit (week 12). A video examination of the study subjects will be made at screening (right before initiation of the study drug), and after 6 weeks on AUSTEDO at a steady dose (right before drug cessation). Part III of the MDS-UPDRS will be performed at both of these Visits as well to screen for the appearance of drug-induced parkinsonism. Videos will be sent to raters blinded to treatment, Visit number and recording date.

Inclusion Criteria

1. Study subjects with definite dystonia (e.g. focal, segmental, multifocal and generalized), as established by a movement disorder specialist.
2. Study subjects of any race and either gender, age 18 or more on the date the informed consent form (ICF) is signed and with the capacity to provide voluntary informed consent.
3. Study subjects able to read and understand English and the ICF and are willing to comply with all study procedures, treatment and follow-up.
4. Study subjects who are taking any central nervous system acting medications (e.g., benzodiazepines, antidepressants, hypnotics), including medications for the treatment of dystonia, will be on a stable regimen for at least 30 days prior to the screening Visit, and will willing to remain on the same dose for the duration of the study.
5. Female of child-bearing potential will not be pregnant and will be using an acceptable method of contraception.
6. Study subjects with an MMSE >24.

Exclusion Criteria

1. Exposure to dopamine blockers prior to the onset of dystonia that could, in the investigator's opinion, have caused dystonia.
2. Study subjects with genetically-confirmed dopa-responsive dystonia.
3. Study subjects with a diagnosis of Parkinson's or an atypical parkinsonian syndrome.
4. Study subjects with a history of bipolar disorder or major depression, or the presence of active depression.
5. Study subjects with a history of a suicide attempt or suicidal ideations, as well as the presence of active suicidal ideation as detailed on the C-SSRS administered during Visit 1.
6. Study subjects with a history of schizophrenia or schizophrenia spectrum disorders.
7. Treatment with tetrabenazine, reserpine, valbenazine, a monoamino oxidase inhibitor, a-methyl-p-tyrosine, strong anticholinergic medications, metoclopramide, antipsychotics, dopamine agonists, levodopa, and/or stimulants within 30 days of screening.
8. Treatment with botulinum toxin less than 11 weeks prior to screening (Visit 1); subjects receiving injections sooner than every 12 weeks will be excluded if their next injection is scheduled farther than 6 days from screening.
9. Presence of a neurologic condition that could confound dystonia assessments.
10. Study subjects with a history of clinically relevant hepatic disease.
11. Study subjects with a history of renal insufficiency.
12. Any unstable medical illness.

13. A corrected QT (Bazett) interval of 450 (458) milliseconds in men or 460 (472) milliseconds in women on 12-lead ECG at screening, or a history of cardiac arrhythmias.
14. Study subjects participating in any drug or device clinical investigation concurrently or within 30 days prior to screening for this study.
15. Study subjects with a known hypersensitivity or contraindication to the study drug or its components.

Population
Subjects with dystonia being managed at the University of Pennsylvania, or referred to this center for the purpose of participation in the trial.

Primary Efficacy Variables
Tolerability will be assessed based on the proportion of study subjects able to titrate up to 48 mg/d (or up to 36 mg/d if receiving a strong CYP2D6 inhibitor) and able to complete the study at this dosage.

Secondary Efficacy Variables
The following Scales will be assessed:
1. Patient Global Impression of Improvement Scale (PGI-I).
2. Clinical Global Impression of Improvement Scale (CGI-I).
3. Global Dystonia Rating Scale.

Safety Variables
Safety will be assessed by the documentation of all adverse events. In addition, the following Scales will be assessed:
1. Columbia Suicide Severity Rating Scale.
2. Stanford Sleepiness Scale.
3. Mini Mental Scale.
4. MDS-Unified Parkinson's Disease Rating Scale.

Statistical Methods
Within subjects paired t-tests will be used to assess significance of change in the different Scales used.

Sample Size Calculation
A number of 15 study subjects was selected to guarantee recruitment. This is a pilot feasibility study to evaluate for common side effects. The study will support the development of future larger clinical trials. The study design is not powered to detect significant effects, but rather to determine feasibility of administering Austedo for 6 weeks in this population.

Planned Number of Sites: One (1). Parkinson's Disease and Movement Disorders Center at the University of Pennsylvania. Philadelphia, PA.
Number of Subjects: 15
Study Duration per Subject/Visit Schedule: Thirteen (13) weeks, or less, if unable to titrate up to 48 mg/day of AUSTEDO.
Expected rate of enrollment (subjects/month): Two (2).

Study Start/FPFV: 02/01/2018; Study End/LPLV: 12/31/2018; Final Report: 05/31/2019

Publication Plan:

Once the data is analyzed, manuscript submission is planned in a scientific journal relevant to the field of movement disorders. The following is a list of journals in descending order of preference:
1. Movement Disorders (Wiley).
2. Parkinsonism & related disorders (Elsevier).
3. Tremor and other hyperkinetic movements (Columbia University Libraries).

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1. INTRODUCTION

1.1 Overview of dystonia and its treatments

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. Dystonia is classified along two axes: clinical characteristics, including age at onset, body distribution, temporal pattern and associated features (additional movement disorders or neurological features); and etiology, which includes nervous system pathology and inheritance. The clinical characteristics fall into several specific dystonia syndromes that help to guide diagnosis and treatment.[1]

Whenever a cause for the dystonia is identified, it opens the door to specific, etiology-based treatments. However, in the majority of cases, a cause cannot be recognized, and treatments are based on symptoms. Treatment options include counseling and education, oral medications, botulinum toxin injections, and several surgical procedures.[2] Of note, none of the oral medications commonly used to treat dystonia has been subject to large-Scale, double-blinded, placebo-controlled trials, and there is no FDA-approved oral medication for treatment of dystonia. Much of the evidence supporting their use comes from small controlled trials, non-blinded trials, retrospective reviews, and anecdotal experience.[2]

Different classes of medications are often used to treat dystonia.[2] These include:

- Anticholinergics: These drugs are thought to work by blocking muscarinic acetylcholine receptors in the basal ganglia. Examples include trihexyphenidyl, benztropine, biperidin, ethopropazine, orphenadrine and procyclidine.
- Benzodiazepines: Benzodiazepines amplify transmission through GABA receptors. Commonly used benzodiazepines include alprazolam, chlordiazepoxide, clonazepam, and diazepam.
- Dopaminergics: Augmenting dopamine transmission with levodopa is dramatically effective in dopa-responsive dystonia, which is most often caused by mutations in the *GCH1* gene encoding the enzyme GTP-cyclohydrolase.
- Dopamine depleters: Tetrabenazine, a reversible vesicular monoamine transporter 2 (VMAT2) inhibitor for oral administration, may be useful for some subjects with dystonia, particularly those with tardive dystonia.

1.2 Background

1.2.1 Overview on AUSTEDO

As described in the drug's package insert,[3] deutetrabenazine (which will be referred to by its trade name "AUSTEDO" in this protocol) is a novel VMAT2 inhibitor for oral administration. It is believed to deplete monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. It is closely related to Tetrabenazine (TBZ), which has been approved for the treatment of Huntington's disease chorea. However, its high affinity for VMAT2 makes AUSTEDO better tolerated than TBZ. AUSTEDO has been FDA approved for the treatment of Huntington's disease chorea and, more recently,

for the treatment of Tardive Dyskinesias (TD). AUSTEDO has not been studied yet for the treatment of dystonia.

1.2.2 Clinical studies with AUSTEDO

Double-Blind, Placebo-Controlled Study – Chorea associated with HD

The efficacy of AUSTEDO as a treatment for chorea associated with Huntington's disease was established primarily in Study 1, a randomized, double-blind, placebo-controlled, multi-center trial conducted in 90 ambulatory subjects with manifest chorea associated with Huntington's disease. The diagnosis of Huntington's disease was based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks, including an 8-week dose titration period and a 4-week maintenance period, followed by a 1-week washout. Subjects were not blinded to discontinuation. AUSTEDO was started at 6 mg per day and titrated upward, at weekly intervals, in 6 mg increments until satisfactory treatment of chorea was achieved, intolerable side effects occurred, or until a maximal dose of 48 mg per day was reached. The primary efficacy endpoint was the Total Maximal Chorea Score, an item of the Unified Huntington's Disease Rating Scale (UHDRS). On this Scale, chorea is rated from 0 to 4 (with 0 representing no chorea) for 7 different parts of the body. The total score ranges from 0 to 28. Of the 90 subjects enrolled, 87 subjects completed the study. The mean age was 54 (range 23 to 74). Subjects were 56% male and 92% Caucasian. The mean dose after titration was 40 mg per day. Total Maximal Chorea Scores for subjects receiving AUSTEDO improved by approximately 4.4 units from baseline to the maintenance period (average of Week 9 and Week 12), compared to approximately 1.9 units in the placebo group. The treatment effect of -2.5 units was statistically significant ($p<0.0001$). The Maintenance Endpoint is the mean of the Total Maximal Chorea Scores for the Week 9 and Week 12 Visits. At the Week 13 follow-up Visit (1 week after discontinuation of the study medication), the Total Maximal Chorea Scores of subjects who had received AUSTEDO returned to baseline. A patient-rated global impression of change assessed how subjects rated their overall Huntington's disease symptoms. Fifty-one percent of subjects treated with AUSTEDO rated their symptoms as "Much Improved" or "Very Much Improved" at the end of treatment, compared to 20% of placebo-treated subjects. In a physician-rated clinical global impression of change, 42% percent of subjects treated with AUSTEDO rated their symptoms as "Much Improved" or "Very Much Improved" at the end of treatment compared to 13% of placebo-treated subjects.[3]

Double-Blind, Placebo-Controlled Study – Tardive dyskinesia

Double-blind, randomized, placebo-controlled, phase 3 trial at 75 centers in the USA and Europe. Subjects aged 18-80 years with tardive dyskinesia (≥3 months before screening) were randomly assigned centrally (1:1:1:1), via interactive response technology, to receive one of three fixed doses of AUSTEDO (12 mg/day, 24 mg/day, or 36 mg/day) or matching placebo. Randomization was stratified by baseline use of dopamine receptor antagonists. Subjects were started on oral AUSTEDO 12 mg/day, and this dose was increased through week 4 until the randomized dose was achieved, then maintained over 8 weeks. During the treatment period, subjects, investigators, their site personnel, and sponsor were masked to group assignment. The primary efficacy endpoint was change in Abnormal Involuntary Movement Scale (AIMS) score from baseline to week 12 in subjects with at least one post-baseline rating. The primary efficacy analysis was done in the modified intention-to-treat population (baseline AIMS score ≥6 and at least one post-baseline rating). The safety analysis was done in subjects who received any study drug. AUSTEDO 24 mg/day and 36 mg/day provided a significant reduction in tardive dyskinesia, with favorable safety and tolerability. These findings suggest that dosing regimens could be individualized and tailored for subjects on the basis of dyskinesia control and tolerability.[4]

Double-Blind Study – Tardive dyskinesia

One hundred seventeen subjects with moderate to severe TD received AUSTEDO or placebo in this randomized, double-blind, multicenter trial. Eligibility criteria included an Abnormal Involuntary Movement Scale (AIMS) score of ≥6 assessed by blinded central video rating, stable psychiatric illness, and stable psychoactive medication treatment. Primary endpoint was the change in AIMS score from baseline to week 12. Secondary endpoints included treatment success at week 12 on the Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change. For the primary endpoint, AUSTEDO significantly reduced AIMS scores from baseline to week 12 vs. placebo (least-squares mean [standard error] -3.0 [0.45] vs. -1.6 [0.46], p = 0.019). Treatment success on CGIC (48.2% vs. 40.4%) favored AUSTEDO but was not significant. AUSTEDO and placebo groups showed low rates of psychiatric adverse events: anxiety (3.4% vs. 6.8%), depressed mood/depression (1.7% vs. 1.7%), and suicidal ideation (0% vs. 1.7%, respectively). In addition, no worsening in parkinsonism, as measured by the Unified Parkinson's Disease Rating Scale motor subscale, was noted from baseline to week 12 in either group.[5]

Open label Study – Tardive dyskinesia

In this open-label study of 12-18-year-old subjects with TS-related tics, AUSTEDO was titrated up to 36 mg/day over 6 weeks to adequately suppress tics without bothersome adverse effects (AEs), followed by maintenance at optimal dose for 2 weeks. An independent blinded rater assessed tic severity using the Yale Global Tic Severity Scale (YGTSS), which was the primary outcome measure. Secondary outcome measures included the TS Clinical Global Impression (TS-CGI) and TS Patient Global Impression of Change (TS-PGIC). Twenty-three enrolled subjects received AUSTEDO and had at least 1 post-baseline YGTSS assessment. The mean (SD [standard deviation]) baseline YGTSS Total Tic Severity Score (TTS) was 31.6 (7.9) and had decreased by 11.6 (8.2) points at week 8, a 37.6% reduction in tic severity ($p<0.0001$). The TS-CGI score improved by 1.2 (0.81) points ($p<0.0001$) and the TS-PGIC results at week 8 indicated that 76% of subjects were much improved or very much improved compared with baseline. The mean (SD) daily AUSTEDO dose at week 8 was 32.1 (6.6) mg (range 18-36 mg). One week after withdrawal of AUSTEDO, the TTS scores increased by 5.6 (8.4) points, providing confirmation of the drug effect. No serious or severe adverse events were reported.[6]

1.3 Study Rationale

Clinicians have a limited armamentarium in terms of oral medications that are effective in the treatment of dystonia. None of these are FDA-approved for this indication, and their efficacy is limited by their side effect profile and dystonia severity. A number of studies have demonstrated Tetrabenazine (TBZ) is effective in the symptomatic treatment of dystonia.[7-14] Tetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor that modulates synaptic dopamine.[15] As with other medications used for the treatment of dystonia, the use of TBZ is often limited by its side effect profile, which includes, but is not limited to, depression (including suicidal depression), sedation and parkinsonism. AUSTEDO is a novel, highly selective VMAT2 inhibitor that contains deuterium, a stable isotope of hydrogen. Deuterium attenuates the metabolism of AUSTEDO, leading to reduced fluctuations in plasmatic levels as compared to TBZ. This, in turn, reduces adverse events associated to peak drug concentrations.[16] AUSTEDO is approved by the Food and Drug Administration (FDA) for the treatment of chorea associated with Huntington's disease (HD) and Tardive Dyskinesias in adults, but not for the treatment of dystonia. Given its shared mechanism of action with TBZ, and its more favorable safety profile, an opportunity exists to establish the safety, tolerability and clinical activity of AUSTEDO in subjects with dystonia.

1.3.1 Selection of AUSTEDO Dose and Schedule of Administration

AUSTEDO is available in 6, 9 and 12 mg tablets. To allow a precise dose titration among study subjects, only 6 mg tablets will be used in the AUDYT trial. As this is an open label trial, all subjects will receive the study drug; there is no placebo arm. All subjects will be instructed to take AUSTEDO with food, and not to chew, crush or break the tablets. The trial will consist of 3 periods:

1. Ramp-up period: During this titration period, AUSTEDO will be started at 12 mg/day and increased up to 48 mg/day for most study subjects, up to 36 mg/day for study subjects receiving a strong CYP2D6 inhibitor, or up to the maximum, well-tolerated dose for those subjects unable to tolerate the maximum recommended dose of AUSTEDO. Dose-limiting toxicity will be defined in this protocol as the development of any of the following during the titration period: a) new or worsening depression, b) worsening of dystonic symptoms, c) QTc increase of >39 but <60 milliseconds from baseline, or d) any other sign or symptom that, at the PI's discretion, would preclude further safe titration of the study drug. AUSTEDO will be increased by 6 mg/week as recommended in the package insert,[3] as shown in Table 2 below:

Table 2
Recommended AUSTEDO
titration

	Total daily dose (mg)
Week 1	12
Week 2	18
Week 3	24
Week 4	30
Week 5	36
Week 6	42
Week 7	48

2. Maintenance period: Once on the maximum dose, subjects will complete 6 weeks of treatment on that dose, unless a side effects ensues. If so, it will remain at the investigator's discretion whether to discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose, on which the study subject will complete 6 weeks of treatment. Details on dose reduction will be discussed further elsewhere in this protocol.
3. Post treatment period: Following 6 weeks of treatment with AUSTEDO, the medication will be discontinued and a final safety evaluation will be performed once the subject has been 1 week off study drug.

2. TRIAL OBJECTIVES

2.1 Primary Objective

To explore the safety and tolerability of the daily oral administration of AUSTEDO in adult study subjects with dystonia.

2.2 Secondary Objectives

1. To establish the degree of symptomatic effect of AUSTEDO as measured by the Clinical Global Impression of Improvement Scale (CGI-I) after 6 weeks of AUSTEDO 48 mg daily, or at the highest tolerated dose.

2. To establish the degree of symptomatic effect of AUSTEDO as measured by the Patient Global Impression of Improvement Scale (PGI-I) after 6 weeks of AUSTEDO 48 mg daily, or at the highest tolerated dose.
3. To establish the degree of symptomatic effect of AUSTEDO as measured by the change in the Global Dystonia Rating Scale between baseline and after 6 weeks of AUSTEDO 48 mg daily, or at the highest tolerated dose.

2.3 Safety Outcome Assessments

The following assessments will establish the safety and tolerability of AUSTEDO during the AUDYT trial:

- Tolerability will be established by the proportion of study subjects able to titrate up to 48 mg/d (or up to 36 mg/d if receiving a strong CYP2D6 inhibitor) and able to complete the study at this dosage.
- Adverse events will be surveyed during all study Visits and during weekly telephone communications with the study subjects that will happen during the ramp-up period.
- AUSTEDO may prolong the QT interval. QT interval prolongation is associated with the development of tachyarrhythmias and Torsades de Pointes. To screen for the development of significant QT prolongation (defined as a corrected QT –Bazett– interval of 450 (458) milliseconds –or higher– in men or 460 (472) milliseconds –or higher– in women), a 12-lead electrocardiogram (ECG) will be performed during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Should there be evidence of QT prolongation, it will remain at the investigator's discretion whether to discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose. A follow up ECG will be performed 1 week after the dose reduction (during an unscheduled Visit) to ensure the QTc is no longer significantly prolonged.
- A complete physical examination will be performed at the time of the initial and final study Visit, as well as during the early termination Visit, if applicable. Any and all changes in the examination happening during the trial will be recorded, and reported when appropriate.
- Vital Signs (including weight) will be measured and recorded during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Any and all gross abnormalities or significant changes will be reported.
- Suicidal thoughts or actions are a possible side effect of AUSTEDO use. The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Development of suicidality as determined by this instrument at any point during the trial will warrant the immediate discontinuation of the study drug, as well as psychiatric care as determined necessary by the investigator. Subjects with any signs or suicidality during Visit 1 as detected by the scale will be immediately excluded from participating in the trial.
- Somnolence is a possible side effect of AUSTEDO use. The Stanford Sleepiness Scale (SSS) will be administered during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Should this side effect develop, the investigator will decided whether to continue AUSTEDO at the current dose, to discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose.
- To assess the impact AUSTEDO may have on cognitive function, if any, the Mini Mental State Examination (MMSE) will be administered during Visits 1, 4 and during the early termination Visit, if such a Visit happens. It will remain at the investigator's discretion to either discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose if clinically-

significant, new-onset cognitive impairment is identified at any point during the course of the trial, even if detected during Visits during which the MMSE is not administered.

- To screen for the development of drug-induced parkinsonism, a possible side effect of AUSTEDO use, the MDS-UPDRS (Part III) will be administered during Visits 1, 4 and during the early termination Visit, if such a Visit happens. It will remain at the investigator's discretion to either discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose if clinically-significant, new-onset drug-induced parkinsonism is identified at any point during the course of the trial, even if detected during Visits during which the MDS-UPDRS (Part III) is not administered.

2.4 Efficacy Outcome Assessments

Although the AUDYT trial is not powered to accurately establish efficacy of AUSTEDO, the following assessments will be performed:

- Patient Global Impression of Improvement: During Visit 4, subjects will be asked to rate the change in their dystonic symptoms using this Scale.
- Clinical Global Impression of Improvement Scale: A video will be made of each subject's movement disorder examination during Visits 1 and 4. Videos will be sent to raters blinded to Visit number and recording date. Raters will be asked to compare the videos looking for any change in the subjects' dystonic symptoms. Their impressions will be recorded using this Scale.
- Global Dystonia Rating Scale: Blinded video raters will also be asked to rate the severity of the subjects' dystonia in all videos using this Scale.

3. STUDY METHODS

3.1 Study Design

This is a single-center, open-label study of AUSTEDO in study subjects with dystonia. The study will provide preliminary experience of the safety, tolerability, and clinical activity of AUSTEDO in study subjects with dystonia. Study duration will be up to 13 weeks from screening (Visit 1) to the post treatment evaluation (Visit 5) for study subjects able to titrate up to 48 mg/day. Treatment period from drug initiation to final on-treatment Visit will be 12 weeks, or less, as follows: during the ramp-up period, study drug will start at 12 mg/day (6 mg twice daily) and will be titrated weekly by 6 mg/day increments until either 1) the maximal allowable dose (48 mg/day) is reached, or 2) dose-limiting side-effects occur. Dose-limiting toxicity will be defined in this protocol as the development of any of the following during the titration period: a) new or worsening depression, b) worsening of dystonic symptoms, c) QTc increase of >39 but <60 milliseconds from baseline, or d) any other sign or symptom that, at the PI's discretion, would preclude further safe titration of the study drug. In study subjects receiving a strong CYP2D6 inhibitor, the maximum allowed dose of AUSTEDO will be 36 mg/day, reducing study duration to 11 weeks (given a shortening in the ramp-up period). Study subjects who experience dose-limiting side effects will be maintained on their maximum tolerated dose. Once the maximal dose is established for each participant, they will complete 6 continuous weeks on this dose (maintenance period), followed by a 1-week washout. For study subjects unable to titrate up to 48 mg/day due to side effects, the 6 weeks of maintenance will start once they reduce the study drug to the maximum dose they can tolerate well.

Adverse events will be monitored throughout the study and will be reported after drug initiation. Dose reductions, suspensions, and withdrawals due to adverse events will be recorded. ECG readings, the Columbia Suicide Severity Rating Scale and the Stanford Sleepiness Scale will be assessed at all scheduled study Visits. The Mini Mental (MMSE) Scale will be performed at screening and at the final on-treatment Visit (Visit 4, usually during week 12). A video examination of the study subjects will be made at screening (right before initiation of the study drug), and after 6 weeks on AUSTEDO at a steady dose (right before drug cessation). Part III of the MDS-UPDRS will be performed at both of these Visits as well to screen for the appearance of drug-induced parkinsonism. Videos will be sent to raters blinded to Visit number and recording date, who will assess changes in the subjects' dystonic symptoms. Patients will be contacted on a weekly basis via telephone during the ramp-up.

3.2 Site

The AUDYT trial will be a single-center trial to be conducted at the University of Pennsylvania's Parkinson's Disease and Movement Disorders Center. This Center has ample experience in conducting clinical trials, and has the necessary infrastructure and qualified research staff to do so.

3.3 Number of Subjects

Given this is a pilot, single-center, open-label trial, a number of 15 study subjects was selected to guarantee recruitment (it is expected that 2 subjects will be recruited/month).

3.4 Study Population

Study subjects for the AUDYT trial will be subjects with dystonia being managed at the University of Pennsylvania, or referred to this center for the purpose of participation in the trial.

Subjects undergoing botulinum toxin injections for the treatment of dystonia will be eligible to participate in the study as long as they are willing to keep their upcoming injection paradigm identical to their latest injections, and as long as they are having suboptimal dystonia control with their current injection paradigm, as verified by their treating movement disorders specialist. Subjects receiving botulinum toxin injections will only be eligible to enroll in the AUDYT trial if their last injections were at least 11 weeks prior to screening (Visit 1). Subjects receiving injections sooner than every 12 weeks will be eligible to participate in the study as long as their upcoming injections are scheduled 6 days, or less, from the time of screening. It will be allowed for study subjects to undergo Visit 1 on the same day as their regularly-scheduled botulinum toxin injections, as long as Visit 1 (in its entirety) happens BEFORE the injections.

Subjects who have undergone Deep Brain Stimulation surgery for the treatment of dystonia will be eligible to participate in the study if their stimulation settings have remained unchanged for at least 3 months prior to study enrollment, and as long as they continue to have suboptimal dystonia control despite neurostimulation, as verified by their treating movement disorders specialist.

3.4.1 Inclusion Criteria

1. Study subjects with definite dystonia (e.g. focal, segmental, multifocal and generalized), as established by a movement disorder specialist.
2. Study subjects of any race and either gender, age 18 or more on the date the informed consent form (ICF) is signed and with the capacity to provide voluntary informed consent.
3. Study subjects able to read and understand English and the ICF and are willing to comply with all study procedures, treatment and follow-up.

4. Study subjects who are taking any central nervous system acting medications (e.g., benzodiazepines, antidepressants, hypnotics), including medications for the treatment of dystonia, will be on a stable regimen for at least 30 days prior to the screening Visit, and will willing to remain on the same dose for the duration of the study.
5. Female of child-bearing potential will not be pregnant and will be using an acceptable method of contraception.
6. Study subjects with an MMSE >24.

3.4.2 Exclusion Criteria

1. Exposure to dopamine blockers prior to the onset of dystonia that could, in the investigator's opinion, have caused dystonia.
2. Study subjects with genetically-confirmed dopa-responsive dystonia.
3. Study subjects with a diagnosis of Parkinson's or an atypical parkinsonian syndrome.
4. Study subjects with a history of bipolar disorder or major depression, or the presence of active depression.
5. Study subjects with a history of a suicide attempt or suicidal ideations, as well as the presence of active suicidal ideation as detailed on the C-SSRS administered during Visit 1.
6. Study subjects with a history of schizophrenia or schizophrenia spectrum disorders.
7. Treatment with tetrabenazine, reserpine, valbenazine, a monoamino oxidase inhibitor, a-methyl-p-tyrosine, strong anticholinergic medications, metoclopramide, antipsychotics, dopamine agonists, levodopa, and/or stimulants within 30 days of screening.
8. Treatment with botulinum toxin less than 11 weeks prior to screening (Visit 1); subjects receiving injections sooner than every 12 weeks will be excluded if their next injection is scheduled farther than 6 days from screening.
9. Presence of a neurologic condition that could confound dystonia assessments.
10. Study subjects with a history of clinically relevant hepatic disease.
11. Study subjects with a history of renal insufficiency.
12. Any unstable medical illness.
13. A corrected QT (Bazett) interval of 450 (458) milliseconds in men or 460 (472) milliseconds in women on 12-lead ECG at screening, or a history of cardiac arrhythmias.
14. Study subjects participating in any drug or device clinical investigation concurrently or within 30 days prior to screening for this study.
15. Study subjects with a known hypersensitivity or contraindication to the study drug or its components.

3.4.3 Duration of Subject Participation

The duration of study participation will be 13 weeks from screening (Week 1) to the post treatment evaluation (Week 13). Treatment period from drug initiation to final on-treatment Visit will be 12 weeks, or less, as follows:

- Study subjects able to titrate up to 48 mg/day will have 6 weeks of ramp-up and 6 weeks of maintenance.
- Study subjects receiving a strong CYP2D6 inhibitor will only be allowed to titrate AUSTEDO up to a dose of 36 mg/day. They will have will have 4 weeks of ramp-up and 6 weeks of maintenance, for a total of 10 weeks on treatment. The total study duration for these subjects will be 11 weeks, when the final post treatment evaluation is included.
- Study subjects who experience dose-limiting side effects will be maintained on their maximum tolerated dose. Once the maximal dose is established for a study subject, they will complete 6

continuous weeks on this dose (maintenance period), followed by a 1-week washout. For these study subjects, the 6 weeks of maintenance will start once they reduce the study drug to the maximum well-tolerated dose, independent of the duration of the ramp-up period.

- The duration of the trial for study subjects who experience dose-limiting side effects that arise during the ramp-up period will depend on the dose at which the side effects appear. For these subjects, maintenance will continue to last 6 weeks, and they will also have a 1 week washout.
- Premature, unexpected withdrawal from the trial will shorten study duration for that subject in unpredictable ways; subjects will be asked to undergo an early termination safety Visit, whenever possible.

3.4.4 Estimated Study Duration

As mentioned in the previous section, the AUDYT trial will have a maximal duration of 13 weeks/subject, which includes a 6-week ramp-up period, a 6-week maintenance period, and a 1 week washout. It is expected that 2 subjects will be recruited per month, on average. Thus, recruitment of all study subjects should take 8 months. If the last study subject (recruited during month 8) participates in the study for 13 weeks (the longest possible study duration per subject), this would bring complete study duration from the time of recruitment of the first study subject (Visit 1) to Visit 5 of the last study subject to about 11 months.

3.5 Study Visit and Assessment Schedule

3.5.1 Schedule for subjects able to increase to and maintain maximum AUSTEDO dose

A diagram summarizing all study visits can be found in the Appendix section (Appendix 1). Details on each of the individual study visits are depicted below.

3.5.1.1 Visit 1: Screening (Week 1)

This will be the first study Visit. During this Visit, subjects will sign the informed consent form, their eligibility for study participation will be confirmed, and study drug will be dispensed. Demographic and baseline characteristics (age at screening, gender, weight, height, BMI, race, ethnicity, medical history, physical examination) will be listed for individual subjects. The activities to be performed during Visit 1 include:

- Informed consent
- Medical history will be obtained
- Medication history will be obtained. All prior medications will be assigned a generic name based on the World Health Organization (WHO) Dictionary.
- Concomitant medications will be reviewed (subjects receiving a strong CYP2D6 inhibitor will be instructed to titrate up to 36 mg during the ramp-up period, not to 48 mg, once study drug is dispensed). All concomitant medications will be assigned a generic name based on the World Health Organization (WHO) Dictionary. When applicable, date of last and next botulinum toxin injections will be recorded, as well as the date of the last DBS setting changes.
- Complete physical exam
- Vital signs
- 12-lead ECG
- C-SSRS
- SSS
- MMSE
- First video of the movement disorder examination

- MDS-UPDRS Part III
- Revision of eligibility criteria (inclusion/exclusion criteria will be reviewed)
- Dispense study drug (if eligible for participation)

3.5.1.2 Visit 2: Ramp-up period (Week 2 +/- 2 Days)

Visit 2 will be the first one on study drug. This is a safety Visit, which will happen 5-9 days after study drug initiation. The activities to be performed during Visit 2 include:

- Adverse events will be assessed
- Vital signs
- 12-lead ECG
- C-SSRS
- SSS

Patients will be contacted on a weekly basis via telephone during the ramp-up period to assess study drug tolerability. Dose reductions will be allowed in this period at the discretion of the investigator, but also during the maintenance period. A dose reduction during the ramp-up period will determine the start of the maintenance period, as it will be assumed that the new, lower AUSTEDO dose is the maximum well-tolerated dose of AUSTEDO for that study subject. Similarly, subjects will remain on the new, maximum well-tolerated dose of AUSTEDO for the remainder of the trial once a dose reduction is done during the maintenance period.

3.5.1.3 Visit 3: Maintenance dose starts

This is a safety Visit. The time during which this Visit will happen may vary depending on the duration of the ramp-up period, as follows:

- For subjects able to titrate up to 48 mg/day, Visit 3 will be scheduled during week 7.
- For subjects receiving a strong CYP2D6 inhibitor and, hence, able to titrate only up to 36 mg/day, Visit 3 will happen during week 5.
- For subjects with dose-limiting side effects during the ramp-up period, Visit 3 will be scheduled up to 3 days after the maximal, well-tolerated dose is established (this landmark will determine when the maintenance period has started).

The activities to be performed during Visit 3 include:

- Adverse events will be assessed
- Vital signs
- 12-lead ECG
- C-SSRS
- SSS

3.5.1.4 Visit 4: Maintenance dose ends

Visit 4 will happen during the last week of the maintenance period: during week 12 for subjects on 48 mg/day of AUSTEDO, during week 10 for those subjects receiving a strong CYP2D6 inhibitor, and 6 weeks after the initiation of the maintenance period for subjects who experienced dose-limiting side effects during the ramp-up period. This will be the last visit while on study drug, and at this time

subjects will be instructed on when to stop AUSTEDO. According to the package insert,[3] treatment with AUSTEDO can be discontinued without tapering. The activities to be performed during Visit 4 include:

- Adverse events will be assessed
- Vital signs
- 12-lead ECG
- C-SSRS
- SSS
- MMSE
- Second video of the movement disorder examination
- MDS-UPDRS Part III
- Patient Global Impression of Improvement

3.5.1.5 Visit 5: Post treatment evaluation

Visit 5 will be scheduled 1 week (or up to 9 days, if necessary) after study drug cessation. This is a safety Visit. The activities to be performed during Visit 5 include:

- Adverse events will be assessed
- Complete physical exam
- Vital signs
- 12-lead ECG
- C-SSRS
- SSS
- Returned bottles will be collected and compliance will be assessed

3.5.2 Special situations that could cause changes in Study Visit Schedule

3.5.2.1 Shortened Ramp-up Period

There are three scenarios that could shorten the duration of the ramp-up period:

1. Study subjects taking a strong CYP2D6 inhibitor: The maximum dose of AUSTEDO allowed for subjects taking a strong CYP2D6 inhibitor will be 36 mg/day. These study subjects will start AUSTEDO at 12 mg/day and increase at weekly intervals in increments of 6 mg per day up to 36 mg/day, if tolerated, as instructed in the package insert.[3] For these subjects, the maximum length of the ramp-up period will be 4 weeks.
2. Subjects unable to titrate up to the maximum recommended dose: Whether it is 48 mg/day or 36 mg/day, study subjects may experience dose-limiting side effects that do not allow them to titrate up to their individual, maximal recommended dose. Any side effects encountered during the ramp-up period will be recorded and reported as appropriate. Study subjects who encounter these side effects will be instructed to reduce the total daily AUSTEDO dose by 6 mg (1 tablet) every day until a new, maximum well-tolerated dose of AUSTEDO is established. A faster dose reduction will be allowed if deemed necessary by the investigator. Once this new dose is determined, the maintenance period will be considered initiated and subjects will be asked to complete Visit 3 at the study site within 3 days.
3. Subjects unable to tolerate 12 mg/day of AUSTEDO: Subjects who are unable to tolerate the starting dose of the study drug will be withdrawn from the trial. Side effects encountered will be recorded and reported as appropriate.

3.5.2.2 Early Termination

If at any time during the study a patient requests to withdraw from treatment, or if a decision is made to withdraw the patient from the study, the patient will be requested to return for an Early Termination Visit.

3.5.2.3 Unscheduled Visit

A patient may return for an unscheduled Visit at any time at the Investigator's discretion (for example, when a one week post dose-reduction ECG is required). The procedures conducted at the unscheduled Visit may be limited, depending on the reason for the Visit (for example, for dispensing of new study drug to replace a lost bottle of study drug would only require those specific procedures relevant to the reason for the unscheduled Visit to be done).

3.5.2.4 Dose Adjustment

Adjustments in the dose of AUSTEDO will be allowed throughout the study. If a reduction in the dose of AUSTEDO is required during the ramp-up period due to dose-limiting side effects, study subjects will be instructed to reduce the total daily AUSTEDO dose by 6 mg (1 tablet) every day until a new, maximum well-tolerated dose of AUSTEDO is established. A faster dose reduction will be allowed if deemed necessary by the investigator. Once this new dose is determined, the maintenance period will be considered initiated, and subjects will be instructed to complete Visit 3 and to remain on this dose for 6 weeks. Any side effects encountered will be recorded and reported as appropriate.

Dose-limiting toxicity will be defined in this protocol as the development of any of the following during the titration period: a) new or worsening depression, b) worsening of dystonic symptoms, c) QTc increase of >39 but <60 milliseconds from baseline, or d) any other sign or symptom that, at the PI's discretion, would preclude further safe titration of the study drug.

If a reduction in the dose of AUSTEDO is required during the maintenance period due to dose-limiting side effects, study subjects will be instructed to reduce the total daily AUSTEDO dose by 6 mg (1 tablet) every day until a new, maximum well-tolerated dose of AUSTEDO is established. A faster dose reduction will be allowed if deemed necessary by the investigator. Once this new dose is determined, subjects will be instructed to remain on this dose until the 6 weeks of the maintenance period are completed. A new maintenance period will NOT start every time a dose reduction is performed. Any side effects encountered will be recorded and reported as appropriate.

Increments in the total daily dose of AUSTEDO will not exceed 6 mg/week, as recommended by the package insert.[3] Treatment interruptions will be discouraged unless necessary. In these cases, resuming AUSTEDO at the previous maintenance dose without titration will be allowed as long as the subject has been off study drug for 6 days or less. Subjects who require drug cessation for a week or more will be consider withdrawn from the trial, and will be asked to complete an early termination Visit.

3.5.2.5 Subject Withdrawal

Subjects will be advised that they are free to withdraw from the study at any time. Reasons that subjects may be withdrawn from the study include the following:

- Subject discontinued study medication: according to the package insert,[3] following treatment interruption of greater than one week, AUSTEDO therapy would need to be re-titrated when resumed, and, thus, subjects who require drug cessation for a week or more will be considered

withdrawn from the trial. For treatment interruption of less than one week, treatment can be resumed at the previous maintenance dose without titration, as per the package insert.[3]

- Subject consent is withdrawn
- QTc changes: A study subject will be asked to discontinue study drug if at any point during the trial he or she is found on ECG to have developed a QTc> 500 milliseconds or a QTc increase of >60 milliseconds from baseline.
- Sponsor decision, after discussion with the Investigator

If a subject is withdrawn from the study, all efforts will be made to complete the early termination Visit that includes efficacy assessments and safety follow-up. In addition, women of childbearing potential will have a pregnancy test performed at the early termination Visit. All information, including the reason for withdrawal, will be reported. For subjects who are lost to follow-up, three recorded attempts will be made to contact the subject for follow-up information, including reason for discontinuation and follow-up of AEs. Subjects who withdraw from the study will not be replaced.

3.6 Study Procedures and Assessments

3.6.1 Safety assessments

3.6.1.1 Adverse Events

During the study, the Investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs). In this study AEs and SAEs will be reported from the time of study drug administration until Visit 5 or death, whichever occurs first.

An adverse event (AE) is any untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to the medicinal product. According to the package insert,[3] adverse reactions experienced by at least 4% of subjects on AUSTEDO and with a greater incidence than on placebo include somnolence, diarrhea, dry mouth, fatigue, urinary tract infection, insomnia, anxiety, constipation and contusion.

All AEs will be recorded regardless of the severity or relationship to study medication. All AEs that result in permanent discontinuation of the study drug being studied, whether serious or nonserious, will be reported. Figure 1 below shows the form that will capture this data.

Figure 1

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 1 2 3 4 5 Early termination Visit Other _____

The AUDYT Trial
Adverse Event Documentation Form

Description of the AE: _____

Diagnosis (if known): _____

If AE is an overdose: Medication error _____ Accidental overdose _____

Intentional overdose _____ N/A _____

Serious adverse event: Yes _____ No _____

Date/Time of Onset: _____

Date/Time of Resolution: _____

Relationship to drug: Probable _____ Possible _____ Not related _____

Severity: Mild _____ Moderate _____ Severe _____

Outcome: Recovered _____ Recovering _____

Recovered with sequelae ____ Not recovered _____

Death ____

Action taken: No action taken _____ Study drug stopped _____

Study drug discontinued _____ Other _____

3.6.1.2 ECG

AUSTEDO may prolong the QT interval. QT interval prolongation is associated with the development of tachyarrhythmias and Torsades de Pointes. To screen for the development of significant QT

prolongation (defined as a corrected QT –Bazett– interval of 450 (458) milliseconds in men or 460 (472) milliseconds in women), a 12-lead electrocardiogram (ECG) will be performed during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Should there be evidence of QT prolongation, it will remain at the investigator's discretion to either discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose. A follow up ECG will be performed 1 week after the dose reduction (during an unscheduled Visit) to ensure the QT prolongation is no longer significant.

However, a study subject will be asked to discontinue study drug if at any point during the trial he or she is found on ECG to have developed a QTc> 500 milliseconds or a QTc increase of >60 milliseconds from baseline. Study subjects will be asked to come in for an Early Termination Visit within 3 business days of study drug discontinuation.

3.6.1.3 Physical Examination

A complete physical and neurologic examination will be performed at the time of the initial and final study Visit, as well as during the early termination Visit, if applicable. Abnormalities in the examination appreciated during Visit 1 and reflective of the subject's known dystonia will be recorded and labeled as non-clinically significant. Any and all changes in the examination happening during the course of the trial will be recorded and reported, when appropriate. Figure 2 below shows the form that will capture this data.

Figure 2

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 1 5 Early termination Visit

The AUDYT Trial
Physical Exam Form

Vital signs: BP:____/____HR:____ RR:____ WT:____lbs

General examination

Skin:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Cardiovascular:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Respiratory:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Abdomen:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Extremities:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:

Neurologic examination

Mental Status:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Cranial Nerves:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Motor:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Cerebellar:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:
Reflexes:	Normal _____ Abnormal – CS _____ Abnormal – NCS _____	If abnormal, describe:

Gait: Normal _____ If abnormal, describe:
Abnormal – CS _____
Abnormal – NCS _____

3.6.1.4 Vital Signs and Weight

Vital Signs (including weight) will be measured and recorded during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Any and all gross abnormalities or significant changes will be reported. Figure 3 shown below shows the form that will capture this data.

Figure 3

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 2 3 4

The AUDYT Trial
Vital signs Form

Vital signs: BP:____/____HR:____ RR:____ WT:____lbs

3.6.1.5 Columbia Suicide Severity Rating Scale

Suicidal thoughts or actions are a possible side effect of AUSTEDO use. The rater/clinician-administered versions of the Columbia-Suicide Severity Rating Scale (C-SSRS)[17] for research (http://cssrs.columbia.edu/the-columbia-Scale-c-ssrs/cssrs-for-research/) assess severity and intensity of suicidal ideation, types of suicidal behaviors, and lethality of suicide attempts at time points and over time periods that are typical for randomized control trials. The Columbia Suicide Severity Rating Scale

will be administered during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Development of suicidality as determined by this instrument at any point during the trial will warrant the immediate discontinuation of the study drug, as well as psychiatric care as determined necessary by the investigator. Subjects with any signs of suicidality during Visit 1 as detected by the scale will be immediately excluded from participating in the trial. Figure 4 shown below shows this Scale embedded in a data capture form:

Figure 4

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 1 2 3 4 5 Early termination Visit

The AUDYT Trial

Columbia Suicide Severity Rating Scale

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

3.6.1.6 Stanford Sleepiness Scale

Somnolence is a possible side effect of AUSTEDO use. The Stanford Sleepiness Scale will be administered during all scheduled study Visits, including the early termination Visit, if such a Visit happens. Should this side effect develop, it will be at the discretion of the investigator whether to continue AUSTEDO at the current dose, discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose. Figure 5 shown below shows this Scale embedded in a data capture form:

Figure 5

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 1 2 3 4 5 Early termination Visit

The AUDYT Trial
Stanford Sleepiness Scale

Stanford Sleepiness Scale

Using the 7-point scale below pick what best represents how you are feeling and note the corresponding number on the chart below.

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not fully alert	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

3.6.1.7 Mini Mental State Examination

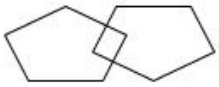
To assess the impact AUSTEDO may have on cognitive function, if any, the Mini Mental State Examination (MMSE)[19] will be administered during Visits 1, 4 and during the early termination Visit, if such a Visit happens. It will remain at the investigator's discretion to either discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose if clinically-significant, new-onset cognitive impairment is identified at any point during the course of the trial, even if detected during Visits during which the MMSE is not administered. Figure 6 shown below shows this Scale embedded in a data capture form:

Figure 6

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 1 4 Early termination Visit

The AUDYT Trial
Mini Mental Status Examination

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

3.6.1.8 MDS-UPDRS (Part III)

To screen for the development of drug-induced parkinsonism, a possible side effect of AUSTEDO use, the MDS-UPDRS (Part III)[20] will be administered during Visits 1, 4 and during the early termination Visit, if such a Visit happens. It will remain at the investigator's discretion to either discontinue the study drug, or to reduce the dose to a new, maximum, well-tolerated dose if clinically-significant, new-onset drug-induced parkinsonism is identified at any point during the course of the trial, even if detected during Visits during which the MDS-UPDRS (Part III) is not administered. Figure 7 shown below shows this Scale embedded in a data capture form:

Figure 7

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 1 4 Early termination Visit

The AUDYT Trial
MDS-UPDRS (Part III)

3.1	Speech	
3.2	Facial expression	
3.3a	Rigidity– Neck	
3.3b	Rigidity– RUE	
3.3c	Rigidity– LUE	
3.3d	Rigidity– RLE	
3.3e	Rigidity– LLE	
3.4a	Finger tapping– Right hand	
3.4b	Finger tapping– Left hand	
3.5a	Hand movements– Right hand	
3.5b	Hand movements– Left hand	
3.6a	Pronation- supination movements– Right hand	
3.6b	Pronation- supination movements– Left hand	
3.7a	Toe tapping–Right foot	
3.7b	Toe tapping– Left foot	
3.8a	Leg agility– Right leg	
3.8b	Leg agility– Left leg	

3.9	Arising from chair	
3.10	Gait	
3.11	Freezing of gait	
3.12	Postural stability	
3.13	Posture	
3.14	Global spontaneity of movement	
3.15a	Postural tremor– Right hand	
3.15b	Postural tremor– Left hand	
3.16a	Kinetic tremor– Right hand	
3.16b	Kinetic tremor– Left hand	
3.17a	Rest tremor amplitude– RUE	
3.17b	Rest tremor amplitude– LUE	
3.17c	Rest tremor amplitude– RLE	
3.17d	Rest tremor amplitude– LLE	
3.17e	Rest tremor amplitude– Lip/jaw	
3.18	Constancy of rest	
	Were dyskinesias presen	☐ No ☐ Yes
	Did these movements interfere with ratings?	☐ No ☐ Yes

3.6.2 Efficacy assessments

3.6.2.1 Video of dystonia examination

As part of the informed consent, all subjects will agree to have their movement disorders examination videotaped. The video recordings, which include sound, will show a subject's entire body and face, in order to view their overall movement. The videos will be de-identified as much as possible and stored in a HIPAA-compliant drive. Staff will do their best to avoid saying subject's name. Only study staff will have access to the videos. The video data will be kept for a minimum of 3 years prior to destruction. The video names will be formatted in a way that the blinded staff remain blinded. The video will not be used

for any commercial, advertising, or promotional purposes. The following protocol will be followed when videotaping:

General instructions

- Remove shoes and socks, roll long pants up to see feet. Remove glasses, if applicable. Remove food or chewing gum from mouth. Pull long hair away from neck in a clip or rubber band.
- Use a tripod. To prevent shadows, avoid strong overhead or back lighting on the subject, more light on face than behind. Video should be taken from straight in front of the participant, except where stated otherwise.
- Avoid recording the participant's name, date of birth, other identifiers, and people other than the subject or staff. Subjects will be identified by the number assigned to them during study enrollment.

Part I: Participant is seated in a chair without head support. Feet are resting flat on floor and hands are resting flat in lap. Zoom camera in to capture head and shoulders only. Be sure to capture full face.

1. At rest, eyes open for 10 seconds
2. At rest, eyes closed gently for 10 seconds
3. At rest, after opening eyes, for another 10 seconds
4. Squeeze eyes closed, 5 times, for 1 second each, then open eyes and observe for 10 seconds
5. Ask participant to repeat each sentence or sound below, one at a time:
    a. "We mow our lawn all year"
    b. "We eat eggs every day"
    c. "He had half a head of hair"
    d. "The puppy bit the tape"
    e. "TaTaTa"
    f. "GaGaGa"
    g. "PaPaPa"
6. Ask the participant to hold long vowel sounds: a. "AHHHHHH" (5 seconds); b. "EEEEEEE" (5 seconds)
7. Stick tongue out as far as possible and hold for 5 seconds
8. Open and close mouth as wide as possible 2 times
9. Ask: "do you have trouble swallowing?" If yes, ask: "occasional or frequent?"
10. Ask: "do you choke?" If yes, ask: "occasional or frequent?"

Part II: Participant is seated in a chair without head support. Feet are resting flat on floor and hands are resting flat in lap. Zoom camera out to capture upper body, including head and both upper limbs.

11. Front view, at rest, eyes closed: instruct participant to let head drift to its most comfortable (dystonic) position, 10 secs
12. Front view, at rest, eyes open: instruct participant to keep head straight at midline for 1 minute. Assist verbally if necessary for initial placement. Do not ask participant to reposition if the head drifts.
13. Front view, with maximum range of motion, instruct participant to:
    a. Turn head to right, then left, both as far as possible, hold each position for 5 secs
    b. Tilt ear to right shoulder, then left shoulder, both as far as possible, hold each position for 5 secs
    c. Look up and extend neck, then look down and flex neck, both as much as possible, hold each position 5 secs

14. Roll sleeves up for both arms, use a stable writing table, do not allow any tricks or compensations, non-active hand should rest on table without holding paper, viewing video from the front of the participant (participant may put glasses on at this point):
    a. Write “TODAY IS A NICE DAY” 3 times with dominant hand on associated recording form
    b. Write “TODAY IS A NICE DAY” 3 times with non-dominant hand on associated recording form
    c. Draw spiral with right hand, then with left hand, on recording form (active hand should not rest on table)
    d. Hold tip of pen over dot with right hand for 10 secs, as close as possible. Do not let pen or hand touch surface
    e. Hold tip of pen over dot with left hand for 10 secs, as close as possible. Do not let pen or hand touch surface
    f. Hold up written page for video
15. Extend arms/hands supinated towards camera for 5 secs
16. Extend arms/hands pronated towards camera for 5 secs
17. Flex elbows and hold hands/arms steady without touching in front of chest, 5 secs eyes open
18. Finger-to-nose test, slow enough to capture accuracy, 5 trials for each hand

<u>Part III: Participant stays seated. Zoom camera out further to capture entire body, including head and all limbs</u>

19. Finger tapping (thumb and forefinger) 10 times for each hand, as big and fast as possible
20. Open and close both hands all the way, simultaneously and rapidly, 5 times
21. Tap heel on floor then toe on floor in rapid alternations, 5 repeated pairs each side

<u>Part IV: Participant stands. Zoom camera out further to capture entire body, including head and all limbs</u>

22. Standing frontal view (5 seconds)
23. Standing lateral (right) view (5 seconds)
24. Standing back view (5 seconds)
25. Walking at least 10 steps away from camera (posterior view) and at least 10 steps towards camera (front view)
26. Walking on toes at least 10 steps away from camera, and on heels at least 10 steps towards camera
27. Walking in toe-heel-tandem, at least 10 steps away from camera and at least 10 steps back towards camera

<u>Part V (perform these only if applicable):</u>

28. Ask if there is anything that can be done to reduce the severity of the dystonia (sensory trick), and demonstrate
29. If participant has a task specific dystonia not captured in protocol above, such as playing musical instrument or chewing, please video record the dystonic symptoms while participant performs such tasks.
30. If participant is in “Blepharospasm Tools” protocol, conduct this task: Participant seated. Zoom camera in to capture all of head and shoulders only: At rest, eyes open, for 2 minutes (blink as natural)

Figure 8

Date: DD – MMM – YYYY Study subject number: ____

Visit Number (circle one): 1 4 Early termination Visit

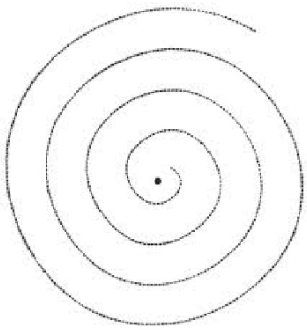
The AUDYT Trial
VIDEO PROTOCOL – WORKSHEET

1. Write the following sentence three times with your usual writing hand: Today is a nice day.

2. Write the following sentence three times with your other hand: Today is a nice day.

3. Copy the following spiral with each hand, starting near the dot for each hand and working out.

Left hand Right hand



4. ●

3.6.2.2 Patient Global Impression of Improvement Scale

During Visit 4, subjects will be asked to assess their dystonic symptoms using the Patient Global Impression of Improvement Scale (PGI-I). Figure 8 shown below shows this Scale embedded in a data capture form:

Figure 9

Date: DD – MMM – YYYY Study subject number: ____

Visit Number 4

The AUDYT Trial
Patient Global Impression of Improvement

Please check the one number that best describes how your dystonia is now compared to when you started your participation in the AUDYT trial:

1 Very much better
2 Much better
3 A little better
4 No change
5 A little worse
6 Much worse
7 Very much worse

3.6.2.3 Clinical Global Impression of Improvement Scale

Raters will be provided 2 videos for every study subject: one recorded during Visit 1, and another recorded during Visit 4. Videos will be randomly labeled as Video A and Video B for each subject, but the letter assigned will have no correlation with the order in which the videos were captured. The raters will be asked to make a global comparison of both videos, and to record their assessment using the form shown in Figure 9 below:

Figure 10

Date: DD – MMM – YYYY Study subject number: ____

To be filled out by blinded video rater

The AUDYT Trial
Clinical Global Impression of Improvement Scale

Please select the option that best describes the change in this subject's dystonia between videos A and B:

1 _____ This subject's dystonia is very much better in Video A compared to Video B
2 _____ This subject's dystonia is much better in Video A compared to Video B
3 _____ This subject's dystonia is a little better in Video A compared to Video B
4 _____ This subject's dystonia is unchanged between Videos A and B
5 _____ This subject's dystonia is a little better in Video B compared to Video A
6 _____ This subject's dystonia is much better in Video B compared to Video A
7 _____ This subject's dystonia is very much better in Video B compared to Video A

3.6.2.4 Global Dystonia Rating Scale

Besides performing CGI-I for the videos, raters will be ask to evaluate the severity of the dystonia in each video supplied. The Dystonia Study Group developed the Global Dystonia Rating Scale (GDS) to serve as an instrument to assess dystonia severity. Figure 10 shown below shows the Global Dystonia Rating Scale[21] embedded in a data capture form:

Figure 11

Date: DD – MMM – YYYY Study subject number: ____

To be filled out by blinded video rater

Please circle the video for which this form is used:
Video A Video B

The AUDYT Trial
Global Dystonia Rating Scale

BODY REGION SCORED	CLINICAL NOTES (Optional)	Score (0-10)	
EYES & UPPER FACE			
LOWER FACE (including platysma)			
JAW & TONGUE			
LARYNX (including pharynx)			
NECK			
SHOULDER & PROXIMAL ARM		R	L
ELBOW, DISTAL ARM, HAND		R	L
PELVIS & UPPER LEG		R	L
DISTAL LEG & FOOT		R	L
TRUNK			
TOTAL SCORE (Sum of all body parts)			

Rate the patient according to body part indicated from 1-10, in relationship to all patients. A score of 0 is no dystonia in that body area. A score of 5 is moderate dystonia. A score of 10 is the most severe dystonia encountered. If the dystonia changes during the examination, rate the maximal dystonia. For mixed motor syndromes, rate only dystonia and not the other components.

3.7 Study Endpoints

3.7.1 Safety Endpoints

3.7.1.1 Primary Safety Endpoint

The primary safety endpoint for the AUDYT trial will be the proportion of study subjects able to titrate up to 48 mg/d (or up to 36 mg/d if receiving a strong CYP2D6 inhibitor) and able to complete the study at this dosage. The reason(s) why subjects are unable to titrate or maintain the maximal recommended AUSTEDO dose will be recorded and reported, when appropriate.

3.7.1.2 Secondary Safety Endpoints

Safety will be assessed by the documentation of all adverse events throughout the study. Serious adverse events will be reported, as appropriate. Twelve lead ECG will be performed during all scheduled study Visits (including an early termination Visit, if one happens) to screen for prolongation of the QT interval. In addition, the following Scales will be assessed:

1. Columbia Suicide Severity Rating Scale.
2. Stanford Sleepiness Scale.
3. Mini Mental Scale.
4. MDS-Unified Parkinson's Disease Rating Scale.

3.7.2 Efficacy Endpoints

3.7.2.1 Primary Efficacy Endpoint

The AUDYT trial will be a patient-driven study. Accordingly, the primary efficacy endpoint will be patient-driven as well: during Visit 4, study subjects will be administered the Patient Global Impression of Improvement Scale (PGI-I), with which they will quantify the degree of change (if any) in their dystonic symptoms that is attributable to their participation in the trial. The median of all of these assessments will be considered the primary efficacy endpoint.

3.7.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be:

- the median of all CGI-I
- within subjects paired t-tests to assess significance of change in the GDS between Visits 1 and 4.

Both the CGI-I and GDS will be extracted by blinded raters who will evaluate video examinations of the study subjects following an established protocol, as mentioned elsewhere in this document.

3.8 Criteria for Study Termination

The Sponsor reserves the right to discontinue the trial at any time; reasons will be provided in the event of this happening. The Principal Investigator reserves the right to discontinue participation in the study for safety or other reasons at any time in collaboration with the Sponsor. The Investigator will notify the IRB/REC/IEC in writing of the trial’s completion or early termination and provide a copy of the notification to the Sponsor.

4. STUDY DRUG MATERIALS AND MANAGEMENT

4.1 Study Drug

4.1.1 Description

As described in the drug's package insert,[3] AUSTEDO (AUSTEDO) is a vesicular monoamine transporter 2 (VMAT2) inhibitor for oral administration. The molecular weight of AUSTEDO is 323.46; the pKa is 6.31. AUSTEDO is a hexahydro-dimethoxybenzoquinolizine derivative and has the following chemical name: (RR, SS)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10-di(methoxy-d3)-3-(2-methylpropyl)2H-benzo[a]quinolizin-2-one. The molecular formula for AUSTEDO is $C_{19}H_{21}D_6NO_3$. AUSTEDO is a white to slightly yellow crystalline powder that is sparingly soluble in water and soluble in ethanol.

AUSTEDO tablets contain 6 mg, 9 mg, or 12 mg AUSTEDO, and the following inactive ingredients: ammonium hydroxide, black iron oxide, n-butyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate 80, polyvinyl alcohol, povidone, propylene glycol, shellac, talc, titanium dioxide, and FD&C blue #2 lake. The 6 mg tablets also contain FD&C red #40 lake. The 12 mg tablets also contain FD&C yellow #6 lake. Only 6 mg AUSTEDO tablets will be used in the AUDYT trial.

4.1.2 Mechanism of action

According to the package insert,[3] the precise mechanism by which AUSTEDO (AUSTEDO) exerts anti-chorea effects is unknown but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. The major circulating metabolites (α-dihydrotetrabenazine [HTBZ] and β-HTBZ) of AUSTEDO, are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores.

4.1.3 Pharmacodynamics

The following considerations are mentioned in AUSTEDO's package insert:[3]

<u>Cardiac Electrophysiology</u>
The effect of a single 12-mg or 24-mg dose of AUSTEDO on the QT interval was studied in a randomized, double-blind, placebo-controlled crossover study in healthy male and female subjects with moxifloxacin as a positive control. At 24 mg, AUSTEDO caused an approximately 4.5 milliseconds mean increase in QTc (90% CI: 2.4, 6.5 msec). Effects at higher exposures to AUSTEDO or its metabolites have not been evaluated. The effect of a single 25-mg or 50-mg dose of tetrabenazine, a closely related VMAT2 inhibitor, on the QT interval was studied in a randomized, double-blind, placebo-controlled crossover study in healthy male and female subjects with moxifloxacin as a positive control. At 50 mg, tetrabenazine caused an approximately 8 milliseconds mean increase in QTc (90% CI: 5.0, 10.4 msec). Effects at higher exposures to either tetrabenazine or its metabolites have not been evaluated.

<u>Melanin Binding</u>
AUSTEDO or its metabolites bind to melanin-containing tissues (i.e., eye, skin, fur) in pigmented rats. After a single oral dose of radiolabeled AUSTEDO, radioactivity was still detected in eye and fur at 35 days following dosing.

4.1.4 Pharmacokinetics

As stated in the drug's package insert,[3] after oral dosing up to 25 mg, plasma concentrations of AUSTEDO are generally below the limit of detection because of the extensive hepatic metabolism of AUSTEDO to the active deuterated dihydro metabolites (HTBZ), α-HTBZ and β-HTBZ. Linear dose dependence of Cmax and AUC was observed for the active metabolites following single or multiple doses of AUSTEDO (6 mg to 24 mg and 7.5 mg twice daily to 22.5 mg twice daily).

<u>Absorption</u>
Following oral administration of AUSTEDO, the extent of absorption is at least 80%. Plasma concentrations of AUSTEDO are generally below the limit of detection after oral dosing. Peak plasma concentrations (Cmax) of deuterated α-HTBZ and β-HTBZ are reached within 3 to 4 hours after dosing.

Effect of Food

The effects of food on the bioavailability of AUSTEDO were studied in subjects administered a single dose with and without food. Food had no effect on the area under the plasma concentration-time curve (AUC) of α-HTBZ or β-HTBZ, although Cmax was increased by approximately 50% in the presence of food.

Distribution

The median volume of distribution (Vc/F) of the α-HTBZ, and the β-HTBZ metabolites of AUSTEDO are approximately 500 L and 730 L, respectively. Results of PET-scan studies in humans show that following intravenous injection of 11C-labeled tetrabenazine or α-HTBZ, radioactivity is rapidly distributed to the brain, with the highest binding in the striatum and lowest binding in the cortex. The in vitro protein binding of tetrabenazine, α-HTBZ, and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine binding ranged from 82% to 85%, α-HTBZ binding ranged from 60% to 68%, and β-HTBZ binding ranged from 59% to 63%.

Elimination

AUSTEDO is primarily renally eliminated in the form of metabolites. The half-life of total (α+β)-HTBZ from AUSTEDO is approximately 9 to 10 hours. The median clearance values (CL/F) of the α-HTBZ, and the β-HTBZ metabolites of AUSTEDO are approximately 47 L/hour and 70 L/hour, respectively, in the Huntington's disease patient population.

Metabolism

In vitro experiments in human liver microsomes demonstrate that AUSTEDO is extensively biotransformed, mainly by carbonyl reductase, to its major active metabolites, α-HTBZ and βHTBZ, which are subsequently metabolized primarily by CYP2D6, with minor contributions of CYP1A2 and CYP3A4/5, to form several minor metabolites.

Excretion

In a mass balance study in 6 healthy subjects, 75% to 86% of the AUSTEDO dose was excreted in the urine, and fecal recovery accounted for 8% to 11% of the dose. Urinary excretion of the α-HTBZ and β-HTBZ metabolites from AUSTEDO each accounted for less than 10% of the administered dose. Sulfate and glucuronide conjugates of the α-HTBZ and β-HTBZ metabolites of AUSTEDO, as well as products of oxidative metabolism, accounted for the majority of metabolites in the urine.

4.2 Study Drug Packaging and Labeling

As mentioned in the package insert,[3] AUSTEDO tablets are available in the following strengths and packages: 6 mg: round, purple-coated tablets, with "SD" over "6" printed in black ink on one side. Bottles of 60 tablets: NDC 68546-170-60. 9 mg: round, blue-coated tablets, with "SD" over "9" printed in black ink on one side. Bottles of 60 tablets: NDC 68546-171-60. 12 mg: round, beige-coated tablets, with "SD" over "12" printed in black ink on one side. Bottles of 60 tablets: NDC 68546-172-60. Only 6 mg AUSTEDO tablets will be used in the AUDYT trial.

4.3 Study Drug Storage

As per the package insert,[3] AUSTEDO will be stored at 25º C (77ºF); excursions permitted to 15°C to 30ºC (59°F to 86ºF). It will be protected from light and moisture.

4.4 Administration

4.4.1 Route of Administration and Dose Schedule

According to the package insert,[3] the dose of AUSTEDO is determined individually for each patient with Huntington's Disease based on reduction of chorea and tolerability. When first prescribed to subjects who are not being switched from tetrabenazine (a related VMAT2 inhibitor), the recommended starting dose of AUSTEDO is 6 mg administered orally once daily. The dose of AUSTEDO may be increased at weekly intervals in increments of 6 mg per day to a maximum recommended daily dosage of 48 mg. Total daily dosages of 12 mg or above will be administered in two divided doses. AUSTEDO will be administered with food. AUSTEDO will be swallowed whole. It will not be chewed, crushed or broken.

Based on these recommendations (and as shown in Table 3 below), for the purpose of the AUDYT trial, each study subject is expected to start, increase, maintain and then discontinue AUSTEDO 6 mg tablets as follows:

Table 3
Expected study drug titration for subjects able to increase AUSTEDO to 48 mg/day

	Number of morning tablets	Number of afternoon tablets	Total daily dose (mg)	Total number of tablets per day	Total number of tablets per week
Week 1	1	1	12	2	14
Week 2	1	2	18	3	21
Week 3	2	2	24	4	28
Week 4	2	3	30	5	35
Week 5	3	3	36	6	42
Week 6	3	4	42	7	49
Week 7	4	4	48	8	56
Week 8	4	4	48	8	56
Week 9	4	4	48	8	56
Week 10	4	4	48	8	56
Week 11	4	4	48	8	56
Week 12	4	4	48	8	56
Week 13	0	0	0	0	0

Table 4 below shows how subjects receiving a strong CYP2D6 inhibitor will start, increase, maintain and then discontinue AUSTEDO 6 mg tablets:

Table 4
Expected study drug titration for subjects able to increase AUSTEDO to 36 mg/day

	Number of morning tablets	Number of afternoon tablets	Total daily dose (mg)	Total number of tablets per day	Total number of tablets per week
Week 1	1	1	12	2	14
Week 2	1	2	18	3	21
Week 3	2	2	24	4	28
Week 4	2	3	30	5	35
Week 5	3	3	36	6	42
Week 6	3	3	36	6	42
Week 7	3	3	36	6	42
Week 8	3	3	36	6	42
Week 9	3	3	36	6	42
Week 10	3	3	36	6	42
Week 11	0	0	0	0	0

In subjects receiving a strong CYP2D6 inhibitor, the ramp-up period will be reduced to 4 weeks, reducing the duration of their participation in the study to 11 weeks.

4.4.2 Dose Increase / Dose Reduction

As per the package insert,[3] increments in AUSTEDO dosing will be done by 6 mg/week up to a maximum of 48 mg/day. Study subjects who are unable to tolerate this dose will be allowed to remain on the maximum well-tolerated dose of AUSTEDO. If this dose has not been previously established, they will be instructed to reduce the total daily AUSTEDO dose by 6 mg (1 tablet) every day until the maximum well-tolerated dose of AUSTEDO is established. A faster dose reduction will be allowed if deemed necessary by the investigator. In study subjects receiving a strong CYP2D6 inhibitor, the maximum allowed dose of AUSTEDO will be 36 mg/day.

Patients will be contacted on a weekly basis via telephone during the ramp-up period to assess study drug tolerability. Dose reductions will be allowed in this period at the discretion of the investigator, but also during the maintenance period. A dose reduction during the ramp-up period will determine the start of the maintenance period, as it will be assumed that the new, lower AUSTEDO dose is the maximum well-tolerated dose of AUSTEDO for that study subject. Similarly, subjects will remain on the new, maximum well-tolerated dose of AUSTEDO for the remainder of the trial once a dose reduction is done during the maintenance period.

4.5 Study Drug Accountability

All study drug supplied is for use only in this clinical study and will not be used for any other purpose. The Investigator is responsible for the study drug accountability, reconciliation and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff will maintain study drug accountability records throughout the course of the study.

This person will document the amount of study drug received and the amount supplied and/or administered to and returned by subjects, if applicable. Copies of all packing slips for the study drug shipments will be retained.

A Study Drug Accountability Record will be kept current and will contain at a minimum the following information:

- The identification of the subject to whom the drug was dispensed
- The date(s) and quantity of the drug dispensed to the subject
- Any product accidentally or deliberately destroyed
- Current quantity of total study drug supply

Subjects will be instructed to return all used and unused bottles (with unused capsules) of study drug for drug accountability purposes. All used and unused bottles (with unused capsules) will be saved for reconciliation by the Sponsor's study monitor or an assigned designee. During the study, the study drug and all shipment, accountability and dispensing records will be available for inspection by the study monitor. Drug supply reconciliation is required at the end of the study.

4.6 Study Drug Handling and Disposal

After reconciliation, unused or partially used study drug may be destroyed by the Investigator only after authorization from Teva, and according to instructions provided by Teva, provided such disposition does not expose humans to risk from the drug. The Investigator or their designee will maintain records of any such alternative disposition of the study drug. These records will show the identification and quantity of each unit that has been disposed, the method of destruction, and the person who disposed of the study drug. Alternatively, the Investigator may elect to return unused or partially used drug supplies to Teva, or the sponsor's designee, instead of destroying them on-site.

4.7 Prohibited Medications and Restrictions

<u>Reserpine</u>

Reserpine is an irreversible VMAT2 inhibitor, and, thus, will not be used concomitantly with AUSTEDO. In clinical practice, at least twenty (20) days must elapse after stopping reserpine before starting AUSTEDO.

<u>Monoamine Oxidase Inhibitors</u>

AUSTEDO is contraindicated in subjects taking MAOIs. In clinical practice, AUSTEDO will not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI.

<u>Tetrabenazine</u>

AUSTEDO is contraindicated in subjects currently taking tetrabenazine. In clinical practice, AUSTEDO may be initiated the day following discontinuation of Tetrabenazine.

AUSTEDO is also contraindicated in subjects:

- Who are suicidal, or in subjects with untreated or inadequately treated depression.
- With hepatic impairment.

4.8 Concomitant Medications

<u>Strong CYP2D6 inhibitors</u>

As per the package insert,[3] concomitant use of strong CYP2D6 inhibitors has been shown to increase the systemic exposure to the active dihydro-metabolites of AUSTEDO by approximately 3 fold. The daily dose of AUSTEDO will not exceed 36 mg per day, and the maximum single dose of AUSTEDO will not exceed 18 mg in subjects taking these inhibitors.

Table 5 below shows a list of strong CYP2D6 inhibitors:

Table 5 Strong CYP2D6 inhibitors
Bupropion Fluoxetine Paroxetine Quinidine Terbinafine

Neuroleptics

The risk for parkinsonism, NMS, and akathisia may be increased by concomitant use of AUSTEDO and dopamine antagonists or antipsychotics. As per the inclusion/exclusion criteria, subjects with a history of psychiatric disease or taking an antipsychotic (even if for a non-psychiatric reason) are not eligible for participation in the AUDYT trial.

Alcohol or other sedatives

Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence. As mentioned in the exclusion criteria, no change in the dose of psychoactive medications will be allowed for the duration of the trial, or at least 30 days prior to screening. Subjects will be encouraged to abstain from alcohol for the duration of the trial.

Drugs causing QTc prolongation

Table 6 below shows a list of medications that are known to prolong the QTc. Subjects taking these medication will be allowed to participate in the trial as long as their ECG during visit 1 (and while already on one or more of these drugs at steady state) shows no QTc prolongation. Any evidence of QTc prolongation during subsequent ECGs will require an adjustment in the AUSTEDO dose as detailed elsewhere. The introduction of these medications will not be allowed for the duration of the trial. If it is determined that a subject requires one of these medications during their participation in the trial, AUSTEDO will be stopped and the subject will be considered withdrawn from the trial.

Table 6 Drugs causing QTc prolongation
Moxifloxacin Quinidine Procainamide Amiodarone Sotalol

4.9 Overdose

According to the package insert,[3] overdoses ranging from 100 mg to 1 g have been reported in the literature with tetrabenazine, a closely related VMAT2 inhibitor. The following adverse reactions occurred with overdosing: acute dystonia, oculogyric crisis, nausea and vomiting, sweating, sedation, hypotension, confusion, diarrhea, hallucinations, rubor, and tremor.

All overdoses will be reported to the sponsor. Minor overdoses will be managed according to the sponsor's guidelines. However, suicide attempts, should they happen, will be managed in the same way as attempts by non-study subjects: 911 will be called to guarantee prompt access to the nearest medical facility. As with the management of overdosage with any central nervous system-active drug, general supportive and symptomatic measures will be recommended. Cardiac rhythm and vital signs should be monitored. In managing overdosage, the possibility of multiple drug involvement should be considered. The treating physician during hospitalization will consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed on the American Association of Poison Control Centers website www.aapcc.org.

4.10 Treatment Compliance

During Visit 1, the total number of tablets that each study subject will need for the duration of the trial will be dispensed. Compliance will be assessed during Visit 5, that is, during the 1-week post-treatment Visit. The number of returned tablets will be counted by the Investigator, or a designee, and recorded in the Drug Dispensing Log. At least 80% compliance will be defined as acceptable in this study. Compliance with study drug intake will be assessed verbally (subject's report, no tablet counting) and encouraged during all other study Visits.

5. ADVERSE EVENTS

5.1 Definitions

5.1.1 Adverse Event Definitions

During the study, the Investigator or study site personnel will be responsible for querying and recording adverse events (AEs) and serious adverse events (SAEs), as detailed in this section of the protocol. This includes the weekly communications with the study subjects via telephone during the ramp-up period. In this study AEs and SAEs will be reported from the time of study drug administration until the last study Visit or death, whichever occurs first.

An adverse event (AE) is any untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to the medicinal product. An AE can, therefore, be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is a direct consequence of study drug use.

Any medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration will be considered to be pre-existing, and will not be recorded as an AE. Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration up to and including the designated follow-up safety Visit will be recorded as an AE. All AEs will be recorded regardless of the severity or relationship to study medication. All AEs that result in permanent discontinuation of the study drug being studied, whether serious or nonserious, will be reported.

An AE does include:

- an exacerbation of a pre-existing illness
- an increase in frequency or intensity of a pre-existing episodic event or condition
- a condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study
- persistent disease or symptoms present at baseline which worsen following the start of the study

An AE does not include:

- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) Note: in this case, the condition that led to the procedure is an AE
- pre-existing diseases or conditions present or detected prior to start of study drug administration, which do not worsen
- the disease or disorder being studied or a sign or symptom associated with that disease (i.e., signs or symptoms associated with lack of efficacy will generally be considered to reflect underlying disease, rather than AEs)
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social, and/or convenience admissions)
- overdose of either study drug or concomitant medication without any signs or symptoms

All AEs will be fully and completely recorded. The following attributes will be assigned: description of AE, dates and times of onset and resolution (or whether ongoing), severity, causality to study drug, whether an SAE or not, and action taken (i.e., no action taken; study medication interrupted; study medication discontinued; other).

In the event that a subject is withdrawn from the study because of an AE, it will be recorded. The subject will be followed and treated by the investigator until the AE has resolved or a new chronic baseline has been established. The investigator will report all directly observed AEs and all spontaneously reported AEs. At each Visit the investigator will ask the subject a nonspecific question (e.g., “Have you noticed anything different since your last Visit?”) to assess whether any AEs have occurred since the last report or Visit. AEs will be identified and recorded in appropriate medical terminology.

5.1.1.1 Common Adverse Events

According to the package insert, [3] adverse reactions experienced by at least 4% of subjects on AUSTEDO and with a greater incidence than on placebo include somnolence, diarrhea, dry mouth, fatigue, urinary tract infection, insomnia, anxiety, constipation and contusion.

5.1.1.2 Serious Adverse Events

A serious adverse event (SAE) is any AE occurring at any dose that:

- results in death
- is life-threatening (subject is at immediate risk of death at the time of the event)
- requires inpatient hospitalization or results in prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect in the offspring of a subject who received study drug
- is a significant or important medical event, i.e., an event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the above mentioned criteria (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse).

When a causality assessment is provided for an SAE, a rationale for the assessment will be included, so that a better understanding of the reported event can be compiled. The rationale will be accompanied by all available supporting evidence, including relevant laboratory tests, histopathology evaluations, and

the results of other diagnostic procedures. The Investigator's rationale with supporting evidence is valuable when the Sponsor performs a cumulative analysis of similar events.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any serious adverse event that is considered related to the investigational product, and that is also unexpected. SUSARs qualify for expedited reporting to applicable Health Authorities and IRB/REB/IECs.

According to the package insert,[3] the following serious adverse reactions can happen with the use of AUSTEDO:

- Depression and suicidality: Subjects with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors (suicidality). AUSTEDO may increase the risk for suicidality in subjects with Huntington's disease. In a 12-week, double-blind, placebo-controlled trial, suicidal ideation was reported by 2% of subjects treated with AUSTEDO, compared to no subjects on placebo; no suicide attempts and no completed suicides were reported. Depression was reported by 4% of subjects treated with AUSTEDO.
- Neuroleptic malignant syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission. While NMS has not been observed in subjects receiving AUSTEDO, it has been observed in subjects receiving tetrabenazine (a closely related VMAT2 inhibitor). The management of NMS will include (1) immediate discontinuation of AUSTEDO; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. Recurrence of NMS has been reported with resumption of drug therapy, and, thus, any subject developing this will be immediately withdrawn from the trial.
- Akathisia, agitation and restlessness: AUSTEDO may increase the risk of akathisia, agitation, and restlessness in subjects with Huntington's disease. In a 12-week, double-blind, placebo-controlled trial, akathisia, agitation, or restlessness was reported by 4% of subjects treated with AUSTEDO, compared to 2% of subjects on placebo. If a patient develops akathisia during treatment with AUSTEDO, the AUSTEDO dose will be reduced; some subjects may require discontinuation of therapy and withdrawal from the trial.
- Parkinsonism: AUSTEDO may cause parkinsonism in subjects with Huntington's disease. Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some subjects with Huntington's disease. If a patient develops parkinsonism during treatment with AUSTEDO, the AUSTEDO dose will be reduced; some subjects may require discontinuation of therapy.
- Sedation and somnolence: Sedation is a common dose-limiting adverse reaction of AUSTEDO. In a 12-week, double-blind, placebo-controlled trial, 11% of AUSTEDO-treated subjects reported somnolence compared with 4% of subjects on placebo and 9% of AUSTEDO-treated subjects reported fatigue compared with 4% of placebo-treated subjects.
- QTc prolongation: Tetrabenazine increases the QTc by about 8 msec. A clinically relevant QT prolongation may occur in subjects treated with AUSTEDO who are co-administered a strong CYP2D6 inhibitor, which is why these subjects will not be allowed to titrate to more than 36 mg/day.
- Hyperprolactinemia: Tetrabenazine elevates serum prolactin concentrations, but it is unclear whether AUSTEDO has this effect. Caution is advised with the use of AUSTEDO in subjects with

known or suspected hyperprolactinemia, or in subjects with breast cancer with prolactin receptors.
- Binding to Melanin-Containing tissues: Possible accumulation of AUSTEDO in these tissues over time could cause long-term ophthalmologic effects.

5.1.2 Adverse Event Assessment Definitions

5.1.2.1 Assessment of Severity

The severity of each AE/SAE will be classified into one of three defined categories as follows:

- Mild: the AE is easily tolerated by the subject, causes minimal discomfort, and does not interfere in a significant manner with the subject's normal functioning level or activities
- Moderate: the AE is sufficiently uncomfortable to interfere with normal everyday activities, but is not hazardous to health
- Severe: the AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

These three categories are based on the investigator's clinical judgment, which in turn depends on consideration of various factors such as the subject's reports, the physician's observations, and the physician's prior experience.

5.1.2.2 Assessment of Causal Relationship

The Investigator will assess and record the causal relationship between the AE and the study drug using the following definitions:

- Probable: the AE has a strong temporal relationship to the study drug, and another etiology is unlikely or significantly less likely.
- Possible: the AE has a suggestive temporal relationship to the study drug, and an alternative etiology is equally or less likely.
- Not related: the AE has no temporal relationship to the study drug or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the study drug and the adverse event).

An AE will be considered causally related to the use of the study drug when the causality assessment is probable or possible.

5.1.2.3 Assessment of Outcome

The Investigator will assess and record the outcome of the AE using the following definitions:

- Recovered: the subject has recovered completely, and no symptoms remain.
- Recovering: the subject's condition is improving, but symptoms still remain.
- Recovered with sequelae: the subject has recovered, but some symptoms remain
- Not recovered: the subject's condition has not improved and the symptoms are unchanged
- Death

5.2 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of AUSTEDO in pregnant women. Administration of AUSTEDO to rats during organogenesis produced no clear adverse effect on embryofetal development. However, administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Oral administration of AUSTEDO (5, 10, or 30 mg/kg/day) or tetrabenazine (30 mg/kg/day) to pregnant rats during organogenesis had no clear effect on embryofetal development. The highest dose tested was 6 times the maximum recommended human dose of 48 mg/day, on a body surface area (mg/m2) basis. The effects of AUSTEDO when administered during organogenesis to rabbits or during pregnancy and lactation to rats have not been assessed. Tetrabenazine had no effects on embryofetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day. When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day, and delayed pup maturation was observed at all doses.

A pregnancy is not an AE. If a subject becomes pregnant while enrolled in the study following administration of study drug, the Sponsor or designee will be notified within 24 hours of the Investigator learning of the pregnancy. Administration of study drug will be discontinued immediately and the subject will be followed through the outcome of the pregnancy.

5.3 Recording Adverse Events

Adverse events will be recorded on an Adverse Event Documentation Form (see Figure 1). The investigator will provide information on the AE, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to study drug; action taken; and outcome. If the AE is an overdose, the nature of the overdose will be stated (medication error, accidental overdose, or intentional overdose). If the AE is serious, this will be indicated on the Adverse Event Form. Furthermore, the Investigator will report the SAE to Teva within 24 hours after becoming aware of it.

5.4 Reporting Serious Adverse Events

The Investigator will report SAEs to Teva immediately (within 24 hours) after becoming aware of them by completing a Serious Adverse Event Form. As much information as possible will be recorded. If more information about the patient's condition becomes available at a later date, the Serious Adverse Event Form will be updated with the additional information. Teva will assume responsibility for reporting SAEs to the authorities in accordance with U.S. regulations.

5.5 Treatment and Follow-Up of Adverse Events

Subjects with AEs will be treated in accordance with usual clinical practice at the discretion of the investigator. At the post treatment evaluation, information on new SAEs, if any, and stop dates for previously reported AEs will be recorded. It is the responsibility of the Investigator to follow up on SAEs

until the patient has recovered, stabilized, or recovered with sequelae. Relevant information includes discharge summaries, autopsy reports, and medical consultations.

5.6 Stopping Rule

A study subject will be asked to discontinue study drug if at any point during the trial he or she is found on ECG to have developed a QTc> 500 milliseconds or a QTc increase of >60 milliseconds from baseline. Study subjects will be asked to come in for an Early Termination Visit within 3 business days of study drug discontinuation.

6. DATA ANALYSIS / STATISTICAL METHODS

6.1 Data Summary

6.1.1 Summary of Safety Data

The safety analysis population will include all enrolled subjects who receive at least one dose of study drug. Demographic data and key baseline characteristics will be summarized for the Safety population. Safety data will be summarized from the time of first dose and include all available safety data.

6.1.2 Summary of Efficacy Data

The efficacy analysis population will include all enrolled subjects who receive at least one dose of study drug and who undergo both dystonia video examinations. Demographic data and key baseline characteristics will be summarized for the Efficacy population.

6.2 Protocol Deviations

Protocol deviations will be avoided whenever possible. If significant protocol deviations ensue, they will be listed and categorized (for example, deviations related to entry criteria, dosing, prohibited concomitant medications, other).

7. STUDY DOCUMENTATION AND RECORD KEEPING

7.1 Investigator's Files and Retention of Study Data

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully recorded and the study data to be subsequently verified. These documents will be separated into two categories: Investigator's study file and patient clinical source documents, as follows:

1. The Investigator's study file will contain the protocol and protocol amendments (if applicable), query forms, IRB and governmental regulatory approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents and correspondence.

2. Patient clinical source documents may include patient and/or hospital clinical records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant's letters, screening and enrollment log, etc.

The patient's involvement in the study will be clearly recorded in the study site's clinical records. Details will include the study protocol number, the patient's study number, the patient's consent to take part in the study (including the date of consent), the dates of all study Visits, details of any treatments withdrawn because of study participation, the dates of dispensing study drug, details of any AEs (including any SAEs), and changes in concomitant medications. The documents in these two categories will be kept on file by the Investigator for at least 15 years after completion or termination of the study. Study documents will not be destroyed without prior written agreement between Teva and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, Teva will be notified in advance. If the Investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements will be made between the Investigator and Teva to store these in a sealed container(s) outside the site. The sealed container(s) can therefore be returned to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies will be made for storing outside the site.

7.2 Background Data

The Investigator will supply Teva, on request, with any required background data from the study documentation or clinic records. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have direct access to the completed study records, provided that patient confidentiality is protected.

7.3 Monitoring, Verification of Data, Audit, and Inspection

The Teva monitor may periodically Visit the site to discuss the progress of the study and review source documents with the study personnel, for accuracy of data recording, study drug accountability, and correspondence. The Investigator will ensure that the study participants are aware of and consent that personal information may be reviewed during the data verification process as part of monitoring/auditing by properly authorized agents of Teva or subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent the applicable law permits and not publically available.

The Investigator will notify Teva of an announced inspection by a regulatory authority. During audits and inspections, the Investigator will allow access to all the source documents, including medical records and other documents pertinent to the study. During audits and inspections, the auditors and inspectors may copy relevant parts of medical records. No personal identification apart from the study number will appear on these copies. Patient data will not be disclosed to unauthorized third parties, and patient confidentiality will be maintained at all times.

8. ADMINISTRATIVE PROCEDURES

8.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with Institutional Review Board/Independent Ethics Committee (IRB) and International Committee on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the study participants. This study will be conducted in general according to the Declaration of Helsinki and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Before initiating a study, the Investigator/institution will have written and dated approval/favorable opinion from the IRB for the study protocol, written informed consent form, patient recruitment procedures (e.g., advertisements), and data collection instruments which will be completed by subjects. Protocol amendments, consent form updates, and any amendments to the documents described before will be approved by the IRB prior to implementation unless such changes are necessary to address immediate safety concerns.

8.2 Informed Consent

The ICF documents the study-specific information the Investigator provides to the subject and the subject's agreement to participate. Among other things, the Investigator or designee will fully explain in layman's terms the nature of the study, along with the objectives, methods, potential risks, and any discomfort that participation may entail. It will be explained that the study is for research purposes only and may not provide any therapeutic benefit to the individual. Each subject will acknowledge receipt of this information by giving written informed consent for participation in the study. No study-related procedures, including washout of any medications, will be performed prior to obtaining written informed consent.

The Investigator will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time and for any reason. Similarly, the Investigator or Teva is free to withdraw the patient from the study at any time for safety reasons. Any other requirements necessary for the protection of the human rights of the patient will also be explained, according to current ICH GCP Guidelines.

A sample copy of the patient information sheet and consent form will be provided by the sponsor. These documents may, however, be subject to country specific changes and the IRB may ask for them to be altered. In this case, any modifications are to be approved by Teva. A copy of the patient information sheet and consent form that is approved for this study by the IRB and Teva will be kept in the trial master file.

The Informed Consent will comply with all applicable US Code of Federal Regulations and ICH Good Clinical Practice guidelines. It will also include any additional information required by local laws relating to institutional review. A statement that subject medical records must be available for investigations into SAEs will be included in the ICF. It will also include any additional information required by local laws relating to institutional review.

8.3 Confidentiality of Patient Information

All subjects who provide written informed consent will be assigned a patient number. Any information published as a result of the study will be such that it will not permit identification of any patient. The information from this study will be available within Teva and may be shared with regulatory authorities. It may also be the subject of an audit by a regulatory agency, such as the Food and Drug Administration (FDA), within the local government. The patient's identity will remain protected except as required for legal or regulatory inquiries.

8.4 Conditions For Modification of the Protocol

Protocol modifications that could potentially adversely affect the safety of participating subjects, or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated or patient selection criteria may be made only after consultation with appropriate representatives of Teva and the Investigator. Any modifications to the protocol that are made after receipt of the IRB approval must be submitted by the Investigator to the IRB in accordance with local procedures and regulatory requirements, before the changes can be implemented. Modifications to the protocol that eliminate an apparent immediate hazard to subjects do not require pre-approval by the IRB.

8.5 Clinical Study Report and Publications

8.5.1 Data Ownership

The data collected in this study are the property of the Principal Investigator.

8.5.2 Publications

The results of this study will be submitted for publication. The primary publication based on this study must be published before any secondary publications are submitted for publication.

9. LIST OF TABLES

10. LIST OF FIGURES

11. APPENDICES

11.1 Appendix 1: Subject Visit schedule

	Screening	Dosing			Visit 5	Early termination Visit
Visit	Visit 1 Ramp-up starts	Visit 2	Visit 3 Maintanance starts	Visit 4 Maintanance ends	Post treatment	
Informed consent	X					
Eligibility Criteria	X					
Medical History	X					
Medication History	X					
Collect/review Adverse Events and Con Meds	X	X	X	X	X	X
Complete Physical Exam	X				X	X
Vital signs	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X
Epworth Sleepiness Scale	X	X	X	X	X	X
MMSE	X			X		X
Video	X			X		X
MDS-UPDRS Part III	X			X		X
Patient Global Impression of Improvement				X		X
Dispense Study Drug (bottles)	X					
Collect returned bottles & assess compliance					X	X

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