UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM

Protocol Title:	The AUDYT Trial: An Open-Label Study to Define the Safety, Tolerability, and Clinical Activity of Deutetrabenazine (**AU**stedo) in Adult Study subjects with **DY**s**T**onia
Principal Investigator:	Andres Deik, MD
Emergency Contact:	On-Call Neurologist (215) 829-3606
Sponsor	Teva Pharmaceuticals USA, Inc.

You are being invited to participate in a research study. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you make your decision, you will need to know what the study is about, the possible risks and benefits if being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study and they will give you this informed consent form (ICF) to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or research team about this form. Your doctor may be an investigator in this research study. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor. After reading this consent form, if you would like to participate, you will be asked to sign this form. You will be given a signed copy of your consent form to take home and keep for your records. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

RESEARCH STUDY SUMMARY

- **Purpose:** This research study is being conducted to explore the safety and tolerability of deutetrabenazine, a drug whose trade name is Austedo, for treatment of adults with dystonia.
- **Procedures & Activities:** If you agree to join the study, you will be asked to complete 5 research visits, physical exam, medical history, completion of questionnaires/assessments, video recording, and multiple electrocardiograms.
- **Duration:** Your participation will last for a maximum of 13 weeks.

- **Risks:** The most common risks of treatment with deutetrabenazine are sleepiness, diarrhea, dry mouth, fatigue, urinary tract infection, insomnia, anxiety, constipation, and bruising.
- **Benefits:** There is no guarantee that you will personally benefit from participation in this study. Information from this study may be used to help patients with dystonia in the future.
- **Alternatives:** As an alternative to participation, you would continue receiving standard of care treatment for dystonia. Your choice to not participate would have no impact on that care.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?
You are being invited to participate in this research study because you have been diagnosed with dystonia by a physician. Dystonia is defined as a movement disorder characterized by uncontrollable muscle spasms causing abnormal movements or postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Many different classes of medication are used to treat dystonia.

A number of studies have shown that tetrabenazine, a drug closely related to deutetrabenazine, is effective in the symptomatic treatment of dystonia. The safety profile of deutetrabenazine may be more favorable, and this study will evaluate its use in treatment of dystonia. Both drugs are approved by the U.S. Food and Drug Administration (FDA) for treatment of other movement disorders, but not for treatment of dystonia. For that reason, deutetrabenazine is considered an experimental drug in this study.

What is the purpose of this research study?
The purpose of this research study is to explore the safety and tolerability of the daily oral administration of deutetrabenazine, whose trade name is Austedo, in adults with dystonia.

How long will I be in the study? How many other people will be in the study?
The study is being conducted at the Parkinson's Disease and Movement Disorders Center of the University of Pennsylvania. Approximately 15 men and women over the age of 18 who have been diagnosed with dystonia will take part in this study. Participants will be patients whose dystonia is being managed at the University of Pennsylvania or are referred to this center for the purpose of participating in this trial.

Your participation in the study will last for up to 13 weeks, with the length of time depending on how long it takes to determine the appropriate dose of Austedo for you.

What am I being asked to do?
There will be a total of five office visits - a screening visit (Visit 1), a ramp-up period visit (Visit 2), maintenance visit (Visit 3), end of maintenance visit (Visit 4), and post-treatment evaluation visit (Visit 5).

During Visit 1, you will begin taking Austedo, 6 mg twice daily (12 mg a day). If the safety assessment in Visit 2 shows that you tolerated the 12-mg daily dose, your dosage will be increased, or ramped up, by 6 mg daily per week

based on assessments of effectiveness and tolerability made in weekly telephone calls. Visit 3, the maintenance visit, will be scheduled when you reach your maximum well-tolerated dosage level.

The maximum Austedo dose you may receive in this study is 48 mg daily – or 36 mg daily if you are receiving drugs known as strong CYOP2D6 inhibitors, such as fluoxetine (Prozac), bupropion (Wellbutrin), and quinidine. Dose reductions may be made during the ramp-up period if you experience side effects due to Austedo, and a well-tolerated lower dose will be considered your maximum dosage level as you enter the maintenance period.

Dose reductions also may be made during the maintenance period if you experience side effects. In this case, the time when you start a well-tolerated lower dose would mark the beginning of a restarted maintenance period. It is also possible that the study doctor may end your participation at any time because of side effects, if necessary to protect your health or safety or to meet research standards.

AUSTEDO will be used as an adjunctive medication. You will be able to continue to receive other medications for dystonia (including botox).

There are no placebo pills in this study. All subjects will be given Austedo.

STUDY PROCEDURES

You will be asked to complete a series of questionnaires at each office visit. These questionnaires will assess your quality of life and assess the overall severity of your dystonia. Additionally, some visits require a movement disorder evaluation that is video recorded, an electrocardiogram (ECG), and a complete physical exam.

Visit 1: Screening Visit (Week 1)

During this visit, once you understand the study procedures and decide to participate in the study, you will sign this consent form. Your eligibility for study participation will then be determined, and your demographic information will be recorded. Additional activities to be completed during Visit 1 include the following:

- Review and collection of medical history
- Review of medication history
- Review of current medications and dates of the last and upcoming botulinum toxin injection, and date of last change in setting for deep brain stimulation (DBS) (if applicable).
- Complete physical exam including recording of vital signs
- A 12-lead electrocardiogram (ECG)
- The Mini Mental Status Examination (MMSE)
- The Stanford Sleepiness Scale (SSS)
- The Columbia Suicide Severity Rating Scale (C-SSRS)
- Video recording of Movement Disorder Examination
- The MDS-UPDRS Part III, an assessment of body position, involuntary movements, muscle strength, and muscle tone
- Dispensing of Austedo

NOTE: This visit will take about 2 hours.

Visit 2: Ramp-up Period Starts (Week 2)

Visit 2 will be the first visit while you are taking Austedo. This is a safety visit, which will happen 5 to 9 days after you start taking the drug. You must bring your Austedo bottles to this visit. study drug initiation. The activities to be completed during Visit 2 include the following:

- Review of adverse events
- Collection of vital signs
- A 12-lead ECG
- The Stanford Sleepiness Scale (SSS)
- The Columbia Suicide Severity Rating Scale (C-SSRS)
- Assessment of Austedo dosage compliance

NOTE: This visit will take about 1 hour.

Visit 3: Maintenance Period Starts (timing of this visit varies)

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

- If you are able to tolerate up to 48mg of Austedo per day, Visit 3 will be scheduled during Week 7.
- If you are receiving a strong CYP2D6 inhibitor, and only permitted to receive up to 36 mg of Austedo per day, visit 3 will occur during Week 5.
- If you experience dose-limiting side effects during the ramp-up period, visit 3 will be scheduled up to 3 days after the maximum, well-tolerated dose is established.

You must bring your Austedo bottles to this visit. The activities to be completed during Visit 3 include the following:

- A review of adverse events
- Collection of vital signs
- A 12-lead ECG
- The Stanford Sleepiness Scale (SSS)
- The Columbia Suicide Severity Rating Scale (C-SSRS)
- Assessment of Austedo dosage compliance

NOTE: This visit will take about 1 hour.

Visit 4: Maintenance Period Ends (timing of this visit varies)

Visit 4 will take place during the last week of the maintenance period; however, the timing will vary as follows:

- If you are taking 48 mg/day of Austedo, then Visit 4 will be scheduled during Week 12.
- If you are taking 36 mg/day of Austedo because you are receiving a strong CYP2D6 inhibitor, then Visit 4 will be scheduled during Week 10.
- If you experienced dose-limiting side effects, then Visit 4 will be scheduled 6 weeks after your maintenance dose was initiated.

This will be the last visit while on study drug, and at this time, you will be instructed on when to stop taking AUSTEDO. You will not be required to taper off this medication. The activities completed during visit 4 include:

- A review of adverse events
- Collection of vital signs

- A 12-lead ECG
- The Stanford Sleepiness Scale (SSS)
- The Columbia Suicide Severity Rating Scale (C-SSRS)
- The Mini Mental Status Examination (MMSE)
- A video of Movement Disorder Examination
- The MDS-UPDRS Part III
- The Global Impression of Improvement
- Assessment of Austedo dosage compliance

NOTE: This visit will take about 2 hours.

Visit 5: Post Treatment Evaluation

Visit 5 is a safety visit that will take place up to 9 days after you stop taking Austedo. The following activities will be completed during visit 5:

- A review of adverse events
- A complete physical exam including recording of vital signs
- A 12-lead ECG
- The Columbia Suicide Severity Rating Scale (C-SSRS)
- The Stanford Sleepiness Scale (SSS)

NOTE: This visit will take about 2 hours

Unscheduled Visits

You may return for an unscheduled visit at any time at the study doctor's discretion. The procedures conducted at the unscheduled visit may be limited depending on the reason for the visit.

Early Termination Visits

If at any time during the study you ask to withdraw from treatment or if the study doctor decides to withdraw you from the study due to a need for intervention, you will be required to complete an early termination visit. The following activities will be completed during the early termination visit:

- Review of concomitant medications
- Review of adverse events
- A complete physical exam, including vital signs
- A 12-lead ECG
- The Columbia Suicide Severity Rating Scale (C-SSRS)
- The Stanford Sleepiness Scale (SSS)
- The Mini Mental Status Examination (MMSE)
- A video of Movement Disorder Examination
- The MDS-UPDRS Part III
- The Global Impression of Improvement
- Collection of returned Austedo bottles and assessment of dosages compliance

NOTE: This visit will last for about 2 hours.

VIDEO RECORDING

While participating in AuDYT, you will be video recorded during the research study visits while completing specific assessments. The video recordings, which include sound, will show your entire body and face, in order to view your overall movement. The videos will be saved in a secure HIPAA-compliant study-specific file at the University of Pennsylvania. The video data will be kept for a minimum of 3 years prior to destruction. The video will not be used for any commercial, advertising, or promotional purposes.

PARTICIPANT RESPONSIBILITIES

In order for this study to provide good information on dystonia, you will be expected to do the following:

- Fill out the questionnaires honestly.
- Tell the study staff about any health problems you are having even if you do not think they are important
- Notify the study staff if you wish to stop being in the study.

What are the possible benefits of the study?

There is no guarantee that you will personally benefit from participation in this study. Your dystonia may or may not improve, or it may get worse while you are in this study. Information from this study may be used to help patients with dystonia in the future.

What are the possible risks and discomforts?

There are risks, discomforts, and inconveniences associated with participation in any research study. For this study, they are described below. In addition, there may be risks that are not yet known.

Common but low risks and side effects related to taking Austedo include:

- ❖ sleepiness
- ❖ diarrhea
- ❖ dry mouth
- ❖ fatigue
- ❖ urinary tract infection
- ❖ insomnia
- ❖ anxiety
- ❖ constipation
- ❖ bruising

Possible adverse reactions that are more serious, but to occur infrequently, with the use of the AUSTEDO and in this study are:

- ❖ Depression and thoughts of suicide
- ❖ Neuroleptic malignant syndrome, a potentially life-threatening reaction including high fever, muscle stiffness, and altered mental status
- ❖ Akathisia (a need to be in constant motion), agitation, and restlessness
- ❖ Parkinsonism
- ❖ Sedation and sleepiness
- ❖ QTc Prolongation, a potentially life-threatening disturbance of heart rhythm
- ❖ Hyperprolactinemia
- ❖ Binding to melanin-containing tissue

Signs of hyperprolactinemia include, but not limited to, infertility, irregular periods, change in menstrual flow, pause in menstrual cycle, loss of libido, lactation (galactorrhea), pain in breasts, and vaginal dryness for women. For men, signs include, but not limited to, abnormal breast growth (gynecomastia), lactation, infertility, erectile dysfunction, loss of sexual desire, headaches, and vision change.

Clinical relevance of Austedo's binding to melanin-containing tissue is unknown. Austedo or its metabolites can bind to melanin-containing tissues, which can lead to an increase of these tissues over time. This raises the

possibility that Austedo may cause toxicity in these tissues after extended use. However, a previous study has not found such findings.

Additionally, you may be uncomfortable or experience stress while completing the questionnaires; however, you may skip any questions that you are uncomfortable with. There is also a potential loss of privacy for your medical information or personal identification. However, all possible precautions will be taken to ensure your privacy and the confidentiality of your information.

REPRODUCTIVE RISKS

Because of the effects of this drug, there could be serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. If you are currently pregnant, it is important that you inform the investigator because you will not be able to participate in the study. If you are able to become pregnant, you will be given a serum pregnancy test before entry into the study. You must also use a medically accepted method of birth control (e.g. IUD, hormonal oral contraceptive pill, tubal ligation) while you participate in the study. If you are a female of child-bearing age, you should not become pregnant while you are taking this drug. If you do become pregnant, you must tell the investigator and consult an obstetrician or maternal-fetal specialist. If you are a male who is fertile and have a partner of childbearing potential, you must agree to use reliable contraception (e.g. condoms, vasectomy) throughout the duration of the study.

OTHER RISKS

Your condition may not get better or may get worse during this study.

What other choices do I have if I do not participate in this study?

The alternative to participating in this research study is to not participate, with no effect on the quality of your existing medical care.

What if new information becomes available about the study?

During the course of the study, new information may be found that could be important to you. The study doctor and the team will relay any and all information to you as soon as it becomes available. This includes information that, once learned, may cause you to change your mind about participating in this study. You may contact the study doctor and team at any time after your participation ends to find out if any new information about this study has become available.

Will I receive results of research testing?

Most tests done in research studies are only for research and have no clear meaning for health care. Research results from this study will not be returned to you because they would not be relevant to your health care.

Will I have to pay for anything?

There is no cost to you for participating in this study. You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance. There will be no charge for Austedo and procedures that are done only for the study will not be billed to you or your insurance company.

Will I be paid for being in the study?

You will receive $50.00 for completing each office visit, totaling $250.00 for the entire study. You will be paid in the form of a Greenphire ClinCard, a reloadable prepaid card. This card will be loaded while you are in clinic for your visit and the funds will be available immediately.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600.00 in a calendar year.

What happens if I am injure from being in the study?

If you are injured or get sick as a result of being in this study, tell the study doctor immediately. We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. The Sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or Sponsor.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in the study. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed on the first page of this form.

When is the study over? Can I leave the study before it ends?

Your decision to participate is entirely voluntary. You may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which you are otherwise entitled. Your ongoing medical care will not be affected by your decision to be in this study or to withdraw from the study.

If you agree to participate in the study and later change your mind, call the study doctor at (215) 829-6500.

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the FDA without your consent because:

- The Principal Investigator (i.e. the study doctor) feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- You have withdrawn your consent.
- The Sponsor, the study Principal Investigator, or the FDA has decided to stop the study.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The IRB at the University of Pennsylvania will have access to your records. If this study is being overseen by the FDA, they may review your research records.

What information may be collected, used, or shared with others?

Your personal health information from your original medical records and all data resulting from your participation in this research will be collected during the course of this study. Your study doctor may ask you to sign a separate authorization to obtain some or all of your original medical records. Personal health information that will be collected includes:

- Your name, date of birth, address, and telephone number, email address
- Demographic information including race and gender
- Past and present medical records and research records
- Social security number
- Results from physical examinations, tests or procedures

Results of questions you are asked by the study doctor or by filling out questionnaires.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The Principal Investigator of the study and the study team
- Other authorized personnel at Penn, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of the school of medicine, might receive my information?

- Your health insurance company
- The study sponsor (Teva Pharmaceuticals USA, Inc.) or sponsor representatives such as monitors and/or auditors
- The U.S. Food and Drug Administration (FDA)
- The Department of Health and Human Services (DHHS)
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported

- ❖ Any laboratories and other individual organizations that analyze your health information in connection with this study in accordance with the study's protocol

Once your personal information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

What may happen to my information collected in this study?

Your information will be de-identified, meaning that all identifiers will be removed. The information could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you because we would provide any identifiable information about you to future researchers. This sharing of information can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- ❖ You have given written authorization
- ❖ The University of Pennsylvania's IRB grants permission
- ❖ As permitted by law

ELECTRONIC MEDICAL RECORDS AND RESEARCH RESULTS

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In

order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Can I change my mind about giving permission for use of my information?
You may withdraw or take away your permission to use and disclose your health information at any time. If you no longer want to share your protected health information, you may cancel your permission by writing to the study doctor at the address below:

Dr. Andres Deik, MD
Parkinson's Disease and Movement Disorders Center
330 S. 9th Street, 3rd Floor
Philadelphia, PA 19107

If you cancel your permission after you have started in the study, the study staff and the study doctor will stop providing questionnaires for you to complete and stop collecting your health information. Although they will stop collecting new information about you, they will need to use the information they have already collected to evaluate the study results. If you start the study and then cancel your permission, you will not be able to participate in the study at a later date.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

You will be given a copy of this Research Subject Informed Consent and HIPAA Authorization Form describing your confidentiality and privacy rights for this study. By signing this document, you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

RIGHTS TO YOUR DATA:
You may have the right to access, correct and make a copy of your medical records as allowed by applicable privacy laws. You may ask to see your records by requesting such records from your doctor. However, to ensure the valid results of the research, you agree that you may not be able to review or make a copy of some of your records related to the research until after the research has been completed.

Who can I call with questions, complaints, or concerns about my rights as a research subject?
If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one

IRB Approval From: 11/07/2023 To: 11/06/2024

of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the Office of Regulatory Affairs: (215) 829-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

_____
Printed Name of Person Conducting
Informed Consent Discussion

_____ _____
Signature of Person Conducting Date
Informed Consent Discussion

IRB Approval From: 11/07/2023 To: 11/06/2024