Prospective, Open-label Clinical Study of INGREZZA (valbenazine) for the treatment of Cervical Dystonia

Date: 11NOV2021

NCT: not yet assigned

Protocol and ICF attached

RESEARCH SUBJECT CONSENT FORM

Protocol Title: Prospective, Open-label Clinical Study of INGREZZA® (valbenazine) for the Treatment of Cervical Dystonia

Marketing Authorization Holder: Neurocrine Continental, Inc.
Protocol ID: 1002, v1

Principal Investigator: Martin Taylor, D.O., PhD
The Orthopedic Foundation

24-Hour Number: 614-890-6555

This Informed Consent Form has two parts:

- **Information Section (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Section

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

Introduction

Dr Martin Taylor (Principal Investigator) is conducting a research study to investigate the safety and efficacy of the medication INGREZZA® (valbenazine) in patients with a diagnosis of cervical dystonia. You will be presented with information regrading this study and you may decide to participate or not participate. You are encouraged to ask questions and request clarification from the study staff or the physician if there is anything that you do not understand. You are under no obligation and you may withdraw at any point during the study if you chose to participate.

Purpose of the research
Cervical dystonia is part of a category of conditions known as hyperkinetic movement disorders. These disorders are characterized by involuntary muscle movements, including spasms, tremors, and other types of involuntary movements. There is another condition called tardive dyskinesia (TD). TD is a side effect of long-term use of some antipsychotic medications that are used to treat certain mental health disorders. The use of these medications can cause repetitive, involuntary movements in the face and body. INGREZZA® (valbenazine) is a medication that patients with TD can be prescribed to help reduce involuntary, repetitive movements. There are similarities in the way that both cervical dystonia and TD affect certain parts of the brain to trigger involuntary movements. Cervical dystonia is commonly treated using botulinum toxin injections which have shown some success in reducing involuntary movement; but, these injections become less effective as they are eliminated from the body. In other words, botulin toxin is most effective at reducing involuntary movement shortly following the injection and are less effective several weeks after the injection. This research is attempting to find out if adding valbenazine as a treatment for a person with cervical dystonia can further lessen the amount of involuntary movement and/or pain as the effects of botulinum toxin wears off. The use of INGREZZA® (valbenazine) is not approved by the FDA for use in cervical dystonia and it's use in this study is investigational.

Type of Research Intervention
Participants in this study will be given valbenazine, which will be in the form of a pill that is to be taken by mouth daily. You will not be required to change or discontinue any of their current medications. You will be evaluated by the investigator in the clinic approximately every 4 weeks for 12 weeks.

Participant selection
You are being asked to participate because the Investigator has identified you as a patient diagnosed with moderate-to-severe cervical dystonia and are currently treating this condition with botulin toxin injections.

Voluntary Participation
Your participation in this research is entirely voluntary. If you chose not to participate in this research, you will continue to receive the same care that your physician routinely offers patients with your condition. If you choose to participate in this research, you are still free to change your mind and withdraw from the study at any time. If you decide to not participate, or decide to withdraw from the study, there will not be any penalty or loss of benefits to which you are otherwise entitled.

Information on the Trial Drug INGREZZA® (valbenazine)
The drug being tested is called INGREZZA® (valbenazine). It has been approved by the FDA for the treatment of tardive dyskinesia. It has not been approved for the treatment of cervical dystonia and its use in the study is investigational.

Potential Risks

There are possible side-effects that you may experience when taking valbenazine. The most common side effect of valbenazine is somnolence (sleepiness). Other side effects include dizziness, headache, feelings of restlessness, dry mouth, constipation and blurred vision. Parkinson-like symptoms, some of which were severe, have been reported in the postmarketing period. In some individuals, valbenazine may cause a heart condition known as QT prolongation. QT prolongation is a condition that causes the heart to take longer to "recharge" between beats. This can lead to irregular heartbeat, shortness of breath and dizziness. As a safety precaution, study staff will perform an electrocardiogram (ECG) prior to administering valbenazine. If the investigator determines that you are at an increased risk of developing QT prolongation, you may not be eligible to participate in the study. You will be closely monitored by the investigator and the study team for these as well as any other side-effects.

Table 1:

Adverse Reaction 1	**INGREZZA (n=262) (%)**
General Disorders	
Somnolence (somnolence, fatigue, sedation)	10.9%
Nervous System Disorders	
Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)	5.4%
Balance disorders/fall (fall, gait disturbances, dizziness, balance disorder)	4.1%
Headache	3.4%
Akathisia (akathisia, restlessness)	2.7%
Gastrointestinal Disorders	
Vomiting	2.6%
Nausea	2.3%
Musculoskeletal Disorders	
Arthralgia	2.3%

INGREZZA may cause foetal abnormalities and all precautions should be taken to avoid pregnancy and breast feeding. Please talk to the study doctor about acceptable methods of contraception.

In addition to these risks, taking part in this research may harm you in unknown ways.

As with any drug, an allergic reaction can occur. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing

Blood draw
The risks of having blood drawn include pain, bruising, and fainting.
ECG
You may have skin irritation from the contacts used.

Procedures and Protocol
If you participate in this study, the following procedures and assessments may be performed:

- A brief physical exam on the following body systems being described as normal or abnormal will be performed at the beginning and end of the study: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological.
- Vital signs will be collected at each visit; these may include height, weight, temperature, respiratory rate, heart rate and blood pressure.
- The Toronto Western Spasmodic Torticollis Rating Scale will be performed at several visits. This is a non-invasive assessment to determine the severity of symptoms associated with cervical dystonia and will be used to help identify improvements or worsening of the condition.
- The Twenty-four-hour pain/spasm/ tightness/range of motion VAS will be performed at several visits. This is a non-invasive assessment to determine the severity of symptoms associated with cervical dystonia and will be used to help identify improvements or worsening of the condition.
- Three (3) vials of blood will be drawn during your initial visit and tested to ensure it is safe for you to participate in the study.
- A 12-lead ECG will be performed during the initial visit to ensure that it is safe for you to participate in the study and to determine if any special measures should be taken with your study medication dosage.
- All females of child-baring potential will complete a urine pregnancy test during their initial visit.
- You will be given the option to wear a device during the period that you are awake each day. This device is about the size of an electronic key fob and is worn on the back of the head. This device records head movement and may be used to measure progress or worsening of your symptoms during the study
- You will be required to take 40mg of INGREZZA, daily for 4 weeks. If you tolerate this dosage, you will be required to increase the dosage to 80mg INGREZZA daily for an additional 3 weeks. If you do not tolerate 80mg, your dosage may be reduced back to 40mg at the Investigator's discretion for the remainder of the study.

Benefit
You may not receive any benefit from participation in this study; however if the INGREZZA is beneficial, your dystonia may improve.

Duration
The research takes place over a period of 16 weeks. You will be asked to come to the clinic for visits approximately every 4 weeks for a total of 5 visits. Clinic visits will take approximately one (1) hour.

Reimbursement
You may receive $75.00 per clinic visit to offset travel costs and lost wages due to study appointments.

Costs
There will be no cost to you for participating in this study. In some cases, insurance does not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

Confidentiality and Sharing of the Results
The information that we collect from this research study will be kept confidential. Information about you that will be collected during the research will only be accessible to the researchers. Any information that is published or made available will be anonymized so that no identifiable information is included.
Your private information and your medical record will be shared with individuals and organizations that conduct or watch over this research, including:

- The research sponsor
- People who work with the research sponsor
- Government agencies, such as the Food and Drug Administration
- WCG IRB, the Institutional Review Board (IRB) that reviewed this research

We may publish the results of this research. However, we will keep your name and other identifying information confidential.
We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

What happens to the information collected for this research?

Your private information and your medical record will be shared with individuals and organizations that conduct or watch over this research, including:

- The research sponsor
- People who work with the research sponsor
- Government agencies, such as the Food and Drug Administration
- WCG IRB, the Institutional Review Board (IRB) that reviewed this research

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

What if I am injured because of taking part in this research?

If you are injured or get sick because of being in this research, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance may be billed for this treatment. The study sponsor will pay any charges that are not covered by insurance policy or the government, provided the injury was not due to your underlying illness or condition and was not caused by you or some other third party. No other payment is routinely available from the study doctor or sponsor.

What other choices do I have besides taking part in this research?

You may choose to continue the standard, current treatment being offered to you by your physician. Your decision not to participate in this study will not affect your current medical care in any way.

Can I be removed from this research without my approval?

The person in charge of this research can remove you from this research without your approval. Possible reasons for removal may include, but are not limited to:

- You have a side effect that requires stopping the research
- You need a treatment not allowed in this research
- You become pregnant
- The research is canceled by the FDA or the sponsor
- You are unable to take the research medication
- You are not compliant with the study requirements (failure to take study medication, failure to wear sensor equipment, etc)
- You are unable to keep your scheduled appointments

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

Who can answer my questions about this research?

If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.
This research is being overseen by WCG IRB. An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289 or researchquestions@wcgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.

- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____
Day/month/year

Print Name of Person Taking the Consent_____

Signature of Person Taking the Consent_____

Date _____
Day/month/year

Protocol Title	**Prospective, Open-label Clinical Study of INGREZZA® (valbenazine) for the Treatment of Cervical Dystonia**
Protocol ID #	**1002**
Medicinal Product	**INGREZZA® (valbenazine) capsules**
Indication	**Cervical Dystonia**
Marketing Authorization Holder (MAH)	**Neurocrine Continental, Inc. 12780 El Camino Real San Diego, California 92130 USA**
Objectives	**Determine the potential efficacy and safety of valbenazine in reducing pain/spasm and improving quality of life and sleep for patients with cervical dystonia.**
Study Design	**The study will be an open-label, prospective study. Patients with a diagnosis of cervical dystonia will undergo 4 weeks of baseline evaluation, followed by a 12-week treatment period. Subjects will be evaluated in-clinic every 4 weeks. Standardized assessments will be performed at these visits. Data will also be collected from wearable IMUs (inertial measurement units) and analyzed for improvements in involuntary, repetitive movements and postures.**
Number of Patients	**N = 20**
Inclusion Criteria	**1. Male or female patients between 18 and 85 years of age (inclusive) 2. A clinical diagnosis of cervical dystonia (ie, spasmodic torticollis) by investigator for at least six months 3. Moderate to severe head tremor and/or dystonic posturing as judged by the investigator 4. Stable Botulinum Toxin (Botox, Dysport, Xeomin, or Myobloc) therapy dosage for at least 3 months prior to baseline visit**
Exclusion Criteria	**1. Tardive dyskinesia 2. Predominant anterocollis 3. Concomitant use of strong CYP3A4 inhibitors (i.e. itraconazole, ketoconazole, clarithromycin), digoxin, strong CYP2D6 inhibitors (i.e.**

paroxetine, fluoxetine, quinidine), monoamine oxidase inhibitors (i.e. isocarboxazid, phenelzine, selegiline)

4. Myotomy or denervation surgery in the affected muscles (eg, peripheral denervation and/or spinal cord stimulation)
5. Diagnosis of Myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other significant neuromuscular disease which might interfere with the trial
6. Moderate to severe hepatic impartment as determined by a Child-Hugh Score ≥7
7. Marked limitation on passive range of motion that suggests contractures or other structural abnormality, eg, cervical contractures or cervical spine syndrome
8. Any conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study
9. Participation in another interventional study during participation in this study
10. Pregnant or lactating females, or females of child-bearing potential not willing to use an acceptable method of contraception
11. History of hypersensitivity to valbenazine or any components of INGREZZA.
12. Is suicidal at screening as defined by below:

    a. According to the C-SSRS, he or she must not be actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of "yes" to C-SSRS questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 1 year prior to Visit 1 (Screening); OR

    b. The subject is actively suicidal in the Investigator's judgment

Duration of Study	The regular duration of observation and data collection for an individual patient will be a period of 4 weeks of baseline evaluation followed by 12 weeks of on investigational product
Primary Endpoint	Change in incidence rate of pain/spasm as measured by frequency and intensity in subjects prior to and during use of valbenazine as measured by TWSTRS and IMU.
Secondary Endpoints	Changes in Twenty-four-hour pain/spasm/ tightness/range of motion VAS Changes in Neck Pain Disability Index

Changes in Sleep quality (The Pittsburg Sleep Quality Index)

Treatment efficacy as measured by Investigator Global Assessment of Efficacy (IGAE)

Treatment efficacy as measured by Patient Evaluation of Global Response (PEGR)

Procedure	screening /baseline	treatment visit	treatment visit	treatment visit	treatment visit/ET visit
	1	2	3	4	5
Informed Consent	x				
Inclusion and Exclusion Criteria	x				
Demography	x				
Medical History	x				
Medication History	x				
Physical Examination	x				x
Vital Signs	x	x	x	x	x
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)	x	x	x	x	x
Twenty four hour pain/spasm/ tightness/range of motion VAS	x	x	x	x	x
Neck Pain Disability Index	x	x	x	x	x
Urine pregnancy test	x				
12-lead ECG	x				
Clinical Global Impression (CGI)			x	x	x
Patient Global Impression of Change (PGIC)			x	x	x
Sleep quality (The Pittsburg Sleep Quality Index)		x	x	x	x
Investigational Product (IP) dispensing		x			
IP accountability/ collection			x	x	x
Subject IMU dispensing	x	x	x	x	x
Subject IMU collection		x	x	x	x
AE / SAE Recording			x	x	x
Concomitant Medications	x	x	x	x	x
C-SSRS	x				
Blood draw/Lab Prep	x				
INR	x				
Bilirubin (total)	x				
Albumin	x				

1.1. Background

1.1.1. Rationale for Conducting the Study:

Hyperkinetic movement disorders encompass a heterogeneous group of diseases. Many of these disorders involve complex dysregulation of neurochemical activity within the basal ganglia. These include but are not limited to tardive dyskinesia, motor tics, cervical dystonia, bruxism, Parkinson's related dyskinesia, blepharospasm, limb dystonia, essential tremor, and restless leg syndrome.

The on-label success of VMAT2 inhibitors in treating tardive dyskinesia and Huntington's Chorea provides promise for other hyperkinetic disorders that may have a paucity of treatment options. There is some limited experience treating motor tics and research with other movement disorders is lacking1,2,3,4. Exploratory research using valbenazine for treatment of cervical dystonia is suggested on an initial pilot level. The following are potential study objectives, basic study parameters, and outcome measures for pilot research.

2. Objectives

2.1. Primary Objectives

Determine the potential efficacy and safety of valbenazine in reducing pain/spasm and improving quality of life and sleep for patients with cervical dystonia.

3. Investigational Plan

3.1. Primary Endpoint

- Change in incidence rate of pain/spasm as measured by frequency and intensity in subjects prior to and during use of valbenazine as measured by TWSTRS and IMU.

3.2. Secondary Endpoints

- Changes in Twenty-four-hour pain/spasm/ tightness/range of motion VAS
- Changes in Neck Pain Disability Index
- Changes in Sleep quality (The Pittsburg Sleep Quality Index)
- Treatment efficacy as measured by Investigator Global Assessment of Efficacy (IGAE)
- Treatment efficacy as measured by Patient Evaluation of Global Response (PEGR)

3.3. Study Design

The study will be an open-label, prospective study. Patients with a diagnosis of cervical dystonia will undergo 4 weeks of baseline evaluation, followed by a 12-week treatment period. Subjects will be evaluated in-clinic every 4 weeks. Standardized assessments will be performed at these visits. Subjects also may elect to have data collected from wearable IMUs (inertial measurement units) and analyzed for improvements in involuntary, repetitive movements and postures.

Duration of study: 16 weeks

4. Study Population

4.1. Population Base

This study will include 20 subjects with a diagnosis of moderate to severe cervical dystonia.

4.1.1 Patient Inclusion Criteria

1. Male or female patients between 18 and 85 years of age (inclusive)
2. A clinical diagnosis of cervical dystonia (ie, spasmodic torticollis) by investigator for at least six months
3. Moderate to severe head tremor and/or dystonic posturing as judged by the investigator
4. Stable Botulinum Toxin (Botox, Dysport, Xeomin, or Myobloc) therapy dosage for at least 3 months prior to baseline visit

4.1.2. Patient Exclusion Criteria

1. Tardive dyskinesia
2. Predominant anterocollis
3. Concomitant use of strong CYP3A4 inhibitors (i.e. itraconazole, ketoconazole, clarithromycin), digoxin, strong CYP2D6 inhibitors (i.e. paroxetine, fluoxetine, quinidine), monoamine oxidase inhibitors (i.e. isocarboxazid, phenelzine, selegiline)
4. Myotomy or denervation surgery in the affected muscles (eg, peripheral denervation and/ or spinal cord stimulation)
5. Diagnosis of Myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other significant neuromuscular disease which might interfere with the trial
6. Moderate to severe hepatic impartment as determined by a Child-Hugh Score ≥7
7. Marked limitation on passive range of motion that suggests contractures or other structural abnormality, eg, cervical contractures or cervical spine syndrome
8. Any conditions that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study
9. Participation in another interventional study during participation in this study
10. Pregnant or lactating females, or females of child-bearing potential not willing to use an acceptable method of contraception
11. History of hypersensitivity to valbenazine or any components of INGREZZA.
12. Is suicidal at screening as defined by below:
    a. According to the C-SSRS, he or she must not be actively suicidal at Visit 1 (Screening) or Visit 2 (Baseline) (including, an answer of "yes" to C-SSRS

questions 4 or 5 [current or over the last 6 months]) and must not have attempted suicide in the 1 year prior to Visit 1 (Screening); OR

b. The subject is actively suicidal in the Investigator's judgment

4.2. Prior and Concomitant Therapy

Relevant concomitant medications the patient is taking at enrollment and given during the study will be documented at each visit by generic medication name, dose, units, frequency, route, indication and start and end dates. All concomitant medications are at the treating physician's discretion. All medications administered during the study and recorded into the patient's visit note are considered relevant and will be listed in the eCRF. *(see table 1.0 for prohibited medications)*

5. Treatment

Subjects will receive 40 mg valbenazine daily for 4 weeks. Dose will be titrated to 80mg daily beginning at 8 weeks if IP is tolerated by the subjects – if not, the subject will remain or be titrated down to 40mg daily for the duration of the study. Subjects will continue to receive standard botulin toxin injection per their routine standard of care throughout the study.

5.1. Medicinal Product

INGREZZA contains valbenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor, present as valbenazine tosylate salt, with the chemical name, L-Valine, (2R,3R,11bR)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-yl ester, 4-methylbenzenesulfonate (1:2). Valbenazine tosylate is slightly soluble in water. Its molecular formula is C38H54N2O10S2, and its molecular weight is 762.97 g/mol (ditosylate salt).

The molecular formula of valbenazine free base is C24H38N2O4 and its molecular weight is 418.57. INGREZZA capsules are intended for oral administration only. Each capsule contains 73 mg or 146 mg of valbenazine tosylate equivalent to 40 mg or 80 mg of valbenazine free base, respectively. The capsules contain the following inactive ingredients: hypromellose, isomalt, magnesium stearate, pregelatinized starch, and silicified microcrystalline cellulose. The capsule shells contain candurin silver fine, FD&C Blue#1, FD&C Red#40, and gelatin.

The mechanism of action of valbenazine in the treatment of tardive dyskinesia is unknown, but is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release.

Valbenazine inhibits human VMAT2 (Ki ~ 150 nM) with no appreciable binding affinity for VMAT1 (Ki > 10 μM). Valbenazine is converted to the active metabolite [+]-α-dihydrotetrabenazine ([+]-α-HTBZ). [+]-α-HTBZ also binds with relatively high affinity to human VMAT2 (Ki ~ 3 nM). Valbenazine and [+]-αHTBZ have no appreciable binding affinity (Ki > 5000 nM) for dopaminergic (including D2), serotonergic (including 5HT2B), adrenergic, histaminergic or muscarinic receptors.

INGREZZA may cause an increase in the corrected QT interval in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 or CYP3A4 inhibitor. An exposure-response analysis of

clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking an INGREZZA 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean QT prolongation of 11.7 msec (14.7 msec upper bound of double-sided 90% CI) as compared to otherwise healthy volunteers given INGREZZA, who had a mean QT prolongation of 6.7 msec (8.4 msec).

Valbenazine and its active metabolite ([+]-α-HTBZ) demonstrate approximate proportional increases for the area under the plasma concentration versus time curve (AUC) and maximum plasma concentration (Cmax) after single oral doses from 40 mg to 300 mg (i.e., 50% to 375% of the recommended treatment dose).

Following oral administration, the time to reach maximum valbenazine plasma concentration (tmax) ranges from 0.5 to 1.0 hours. Valbenazine reaches steady state plasma concentrations within 1 week. The absolute oral bioavailability of valbenazine is approximately 49%. [+]-α-HTBZ gradually forms and reaches Cmax 4 to 8 hours after administration of INGREZZA. Ingestion of a high-fat meal decreases valbenazine Cmax by approximately 47% and AUC by approximately 13%. [+]-α-HTBZ Cmax and AUC are unaffected.

The plasma protein binding of valbenazine and [+]-α-HTBZ are greater than 99% and approximately 64%, respectively. The mean steady state volume of distribution of valbenazine is 92 L. Nonclinical data in Long-Evans rats show that valbenazine can bind to melanin-containing structures of the eye such as the uveal tract. The relevance of this observation to clinical use of INGREZZA is unknown.

Valbenazine has a mean total plasma systemic clearance value of 7.2 L/hr. Valbenazine and [+]-α-HTBZ have half-lives of 15 to 22 hours.

Valbenazine is extensively metabolized after oral administration by hydrolysis of the valine ester to form the active metabolite ([+]-α-HTBZ) and by oxidative metabolism, primarily by CYP3A4/5, to form monooxidized valbenazine and other minor metabolites. [+]-α-HTBZ appears to be further metabolized in part by CYP2D6. The results of in vitro studies suggest that valbenazine and [+]-α-HTBZ are unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5, or induce CYP1A2, CYP2B6 or CYP3A4/5 at clinically relevant concentrations. The results of in vitro studies suggest that valbenazine and [+]-α-HTBZ are unlikely to inhibit the transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3) at clinically relevant concentrations.

Following the administration of a single 50-mg oral dose of radiolabeled C-valbenazine (i.e., ~63% of the recommended treatment dose), approximately 60% and 30% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 2% was excreted as unchanged valbenazine or [+]-α-HTBZ in either urine or feces.

5.1.1. Method of Administration

INGREZZA is taken orally and can be taken with or without food.

6. Study Conduct

6.1. Study Procedures

6.1.1. Informed Consent and Enrollment

Any patient who provides informed consent (ie, signs and dates the informed consent form) is considered enrolled in the study.

6.1.2. Patient Demographics

At screening visit, the subject's pertinent demographics should be recorded.

6.1.3. Medical History

At screening/enrollment, the subject's medical history will be described for the following body systems including severity or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphocytic; dermatological; and genitourinary. Diagnosis and treatment history of cervical dystonia will also be recorded.

6.1.4. Physical Exam

At screening/enrollment and closeout visit, a physical examination should be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At screening/enrollment, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease, not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

6.1.5. Changes to Health Status

At each visit, any clinically significant changes to the subject's health that may have occurred since the previous visit should be recorded. Clinical significance is determined by the treating physician.

6.1.6. Concomitant Medications

At screening/enrollment visit, infusion visits and close-out visit, all prescription medications, over the counter medications and dietary supplements that the subject is currently taking should be confirmed and recorded.

6.1.7. Vitals

Results from the assessment of vital signs will be collected if routinely performed during clinical practice or indicated based on the clinical judgment of the investigator. Vital signs will include body temperature (°C or °F), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Height (in or cm) and weight (kg) will be reported as available. For each abnormal vital sign value, the investigator will determine whether or not to report an AE. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

6.1.8. Adverse Drug Reactions

All patient reported AEs that occur between visits should be recorded. An AE is defined as any untoward medical occurrence in a subject administered a medicinal product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, rash, pain, discomfort, fever, dizziness, etc.), disease (eg, peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of a medicinal product, whether or not considered causally related to the medicinal product.

It is the responsibility of the treating physician to determine causality of adverse reactions and AEs. The investigator will report causality of all AEs in the source document.

Any serious or unexpected adverse events should be reported to the FDA and sponsor within 24 hours. It is the responsibility of the investigator to report any unexpected or significant events or unacceptable risks to patient safety. The investigator will make the decision to terminate or suspend any portion of the study based on unacceptable risk to the patients in the study.

6.1.9. Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)

TWSTRS Total (scored 0–85), composed of the Severity (0–35), Disability (0–30), and Pain (0–20) subscales, is a validated, disease-specific scale in which higher scores indicate greater impairment. It is commonly used in clinical trials of BoNT for the treatment of Cervical Dystonia.

6.1.10. Twenty-four-hour pain/spasm/ tightness/range of motion VAS

A Visual analog scale will be used to measure subjective responses form subjects based on their perceived levels of pain, spasm, tightness and range of motion from the previous 24 hours.

6.1.11. Neck Pain Disability Index (NPDI)

The NPDI is a patient-completed, condition-specific functional status questionnaire with 10 items including pain, personal care, lifting, reading, headaches, concentration, work, driving, sleeping and recreation. It is the most commonly used self-report measure for neck pain.

6.1.12. The Pittsburg Sleep Quality Index (PSQI)

The PSQI is a patient-completed status questionnaire with 10 items related to the nature and quality of their sleep over the previous 30 days. The questionnaire also includes QOL items related to interruptions to daily routine and general mood due to lack of sleep and/or poor sleep quality.

6.1.13. Clinical Global Impression (CGI)

The CGI is a subjective rating system used by the investigator to measure the subject's overall condition. The CGI consists of 2 7-point scales for severity of illness and amount of change.

6.1.14. Patient Global Impression of Change(PGIC)

The PGIC is a patient-completed descriptive scale ranging from 1(very much improved) to 7(very marked worsening).

6.1.15. Functional characteristics of head movement by 9-DOF positional IMU sensor

Wearable Inertial measurement units will collect data during subject's periods of wakefulness. Data will be analyzed for affects to involuntary, repetitive movements and postures in relation to the IP's and concomitant medications' (primarily BoNT) metabolic lifecycle.

6.1.16. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS, is a suicidal ideation and behavior rating scale. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent and behaviors."

6.1.17. Hematology and Clinical Chemistry

Results from the assessment of hematology and clinical chemistry will be collected. Data collected will consist of INR, bilirubin (total) and albumin.

6.1.18. Urine pregnancy test

Urine pregnancy test will be performed on all females of child-baring potential at the screening visit.

6.1.19. 12-lead ECG

A 12-lead ECG will be performed on all individuals at the screening visit. The primary purpose is to identify subjects who may present QT elongation in order to appropriately assign IP dosage.

Procedure	screening /baseline	treatment visit	treatment visit	treatment visit	treatment visit/ET visit
	1	2	3	4	5
Informed Consent	x				
Inclusion and Exclusion Criteria	x				
Demography	x				
Medical History	x				
Medication History	x				
Physical Examination	x				x
Vital Signs	x	x	x	x	x
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)	x	x	x	x	x
Twenty four hour pain/spasm/ tightness/range of motion VAS	x	x	x	x	x
Neck Pain Disability Index	x	x	x	x	x
Urine pregnancy test	x				
12-lead ECG	x				
Investigator Global Assessment of Efficacy (IGAE)			x	x	x
Patient Evaluation of Global Response (PEGR)			x	x	x
Sleep quality (The Pittsburg Sleep Quality Index)		x	x	x	x
Investigational Product (IP) dispensing		x			
IP accountability/ collection			x	x	x
Subject IMU dispensing		x	x	x	x
Subject IMU collection			x	x	x
AE / SAE Recording			x	x	x
Concomitant Medications	x	x	x	x	x
C-SSRS	x				
Blood draw/Lab Prep	x				
INR	x				
Bilirubin (total)	x				
Albumin	x				

6.2. Study Visits

7. Data Sources

7.1. Source Data

Source data for this study may comprise the following: study-provided paper source documents, hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subject questions, treatment logs or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, medical imaging data (eg, microfiches, photographic negatives, microfilm or magnetic media, x-rays), subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

7.2. Subject Questionnaires

Subjects will be provided with self-completed questionnaires at each visit.

7.3. Data Collection Methods

The investigator is responsible for the procurement of data and for the quality of data recorded in the patient electronic medical records, clinical office charts, treatment logs and evaluation checklists, outcomes reported by subjects, pharmacy dispensing records and laboratory results. Data will be retrieved directly from the sources and aggregated by Quantum.

7.4. Confidentiality

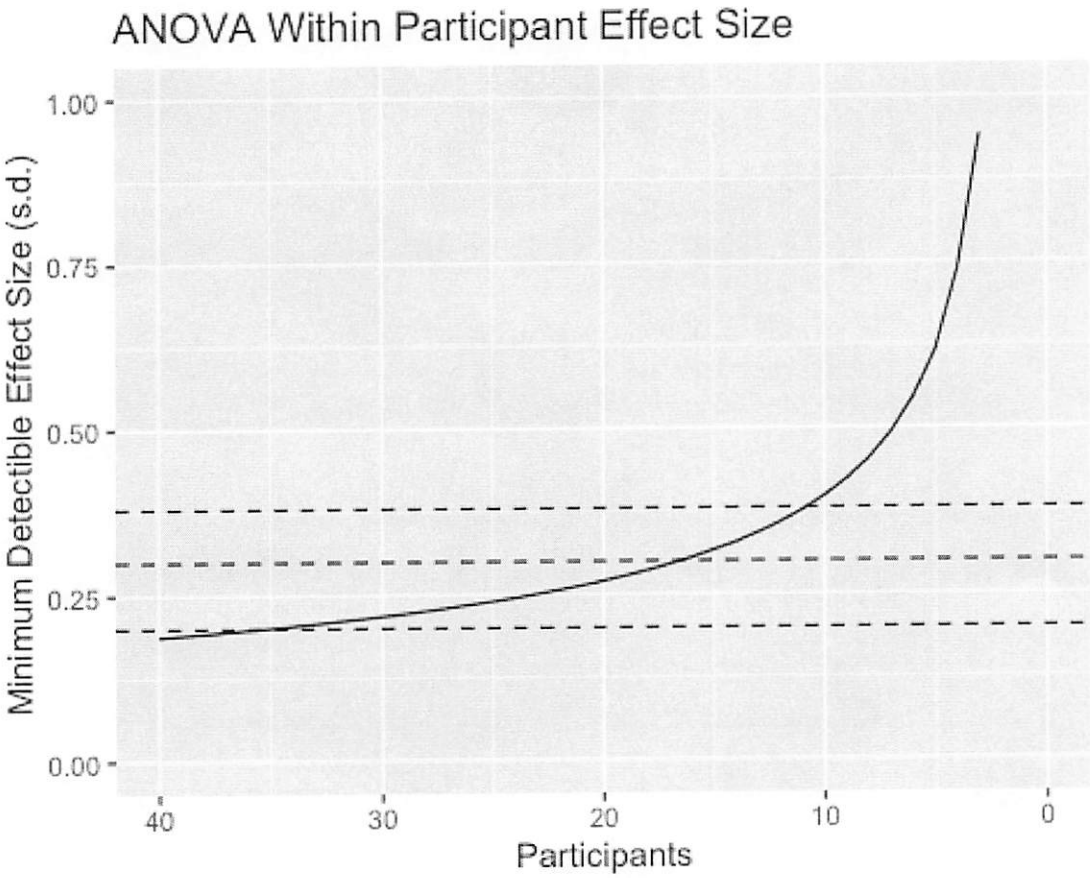
Subjects will be assigned and identified throughout the study by a subject ID number upon entering the study. All study data obtained will be associated to this number and will not include or be associated with any personally identifiable information. No personally identifiable medical information will be collected or stored.

7.5. Software

The software for data management is to be determined.

7.6. Data Methods

The median observed effect size is 0.3 (IQR 0.2 – 0.38). A non-parametric statistical approach will be used.



% of Patients with Improved Outcomes	% of Patients with Negative Outcomes: 0	10	20	30	40
10	40	-	-	-	-
20	20	110	-	-	-
30	14	40	160	-	-
40	10	28	55	223	-
50	8	18	30	72	270
60	7	15	20	39	80
70	6	13	18	23	-
80	5	10	13	-	-
90	5	8	-	-	-
100	4	-	-	-	-

8. Protection of Human Subjects

8.1 Compliance Statement

This study will be conducted in accordance with this protocol and applicable national and local requirements for good pharmacovigilance practices.

8.2 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Non-interventional Trial Agreement.

8.3. Ethics Committee (EC)/Institutional Review Boards and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the Market Authorization Holder (MAH)'s receipt of approval/favorable opinion from the EC and, if required, upon the MAH's notification of applicable regulatory authority(ies) approval, as described in the Trial Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and relevant regulatory authorities, where applicable. The protocol amendment will only be implemented upon the MAH's receipt of approval and, if required, upon the MAH's notification of applicable regulatory authority(ies) approval.

8.4 Informed Consent

Investigators will choose patients for enrollment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source. All patients must sign an informed consent form before entering into the study according to applicable regulatory requirements. Before use, the informed consent form will be reviewed by the MAHand approved by the EC and regulatory authority(ies), where applicable. The informed consent form will include a comprehensive explanation of the study without any exculpatory statements, in accordance with the elements required by applicable regulatory requirements.

Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients agree to the use of their data for the study, unless they withdraw voluntarily or are terminated from the study for any reason.

Table 1.0

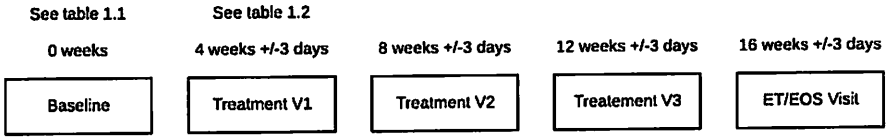


Table 1.1

neurotoxins / neuromuscular blockers (see table 1.1a)	4 weeks s/p
MAOIs (see table 1.1b)	3 weeks s/p
strong CYP3A4 inducers (see table 1.1c)	3 weeks s/p

Table 1.2

Treatment V1 IP dose: 40 mg daily
Treatment V1: Subject will receive standard botulin toxin injection per standard of care
Treatment V2 IP dose: Titrate to 80 mg daily for study duration if tollerated *

*Subjects using strong CYP3A4 inhibitors or strong CYP2D6 inhibitors will stay on 40 mg daily

Table 1.1a

neurotoxins / neuromuscular
onabotulinumtoxinA (Botox)
abobotulinumtoxinA (Dysport)
incobotulinumtoxinA (Xeomin)
rimabotulinumtoxinB (Myobloc)

Table 1.1b

MAOIs
Isocarboxazid (Marplan)
Nialamide (Niamid)
Phenelzine (Nardil, Nardelzine)
Hydracarbazine
Tranylcypromine (Parnate, Jatrosom)
Moclobemide (Aurorix, Manerix)
Rasagiline (Azilect)
Selegiline (Deprenyl, Eldepryl, Emsam, Zelapar)
Safinamide (Xadago)

Table 1.1c

strong CYP3A4 inducers
carbamezepine
phenytoin
rifampicin
fosphenytoin
pentobarbital
phenobarbital
primidone
enzalutamide
lumacaftor
St. John's Wort
mitotane
apalutamide
rimexolone
rifaximin
rifamycin
midostaurin
dexamethasone