A SAFETY TRIAL OF DANTROLENE SODIUM IN PEDIATRIC AND ADULT PATIENTS WITH WOLFRAM SYNDROME

Study Phase: Phase 1b

Product name: Dantrolene Sodium

Indication: Wolfram syndrome

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FDA IND #: 133439

Protocol synopsis

Title	A Safety Trial of Dantrolene Sodium in Pediatric and Adult Patients with Wolfram Syndrome.
Protocol number	
Investigational product	Dantrolene Sodium for oral administration
Study objectives	**The Primary Objective of this study is:** To assess the safety and tolerability of dantrolene sodium administered orally at upper end of therapeutic dose range for 6 months in patients with Wolfram syndrome with an optional extension phase up to 24 months. Patients who express the wish to continue in the optional extension phase on dantrolene sodium will be offered this possibility. **The Secondary Objectives of this study are:** • Determine the effect of dantrolene sodium on remaining beta cell functions using a mixed-meal tolerance test and monitoring base-line C-peptide levels, blood glucose levels, proinsulin/C-peptide ratios, hemoglobin A1c levels, and urine glucose levels. • To determine the efficacy of dantrolene sodium on visual acuity (LogMar scores) • To determine the efficacy of dantrolene sodium on visual functions using Visual Functioning Questionnaire – 25. • To evaluate the efficacy of dantrolene sodium on neurological functions using the Wolfram Unified Rating Scale (WURS) and standard neurological assessments. **The Exploratory Objectives of this study are:** • To further explore potential relationships between predefined biomarkers and endocrine and neurological symptoms, including serum levels of mesencephalic

	astrocyte-derived neurotrophic factor (MANF), myelin basic proteins, and circulating insulin DNA. • To evaluate the effects of dantrolene sodium on functional activities of daily living by assessing health related quality of life using PedsQL (pediatric patients) and SF-36v2 (adult patients).
Study endpoints	**The Primary Endpoint of this study is:** • To assess the safety and tolerability of dantrolene sodium administered orally up to 100 mg b.i.d. (adults) and up to 2 mg/kg b.i.d. (pediatric patients, up to 50 kg) for 6 months with an optional extension phase up to 24 months in patients with Wolfram syndrome. • Safety will be assessed by adverse events (by type and severity) and changes in clinical laboratory testing (including liver function tests). • This will be assessed by monitoring of serum chemistry including liver function tests and ammonia. • Safety will be also assessed by complete physical exam (PE), vital signs (vs)/weight (wt) at each visit **The Secondary Endpoints include:** • Determine the effect of dantrolene sodium on on remaining beta cell functions using a mixed-meal tolerance test and monitoring base-line C-peptide levels, blood glucose levels, proinsulin/C-peptide ratios, hemoglobin A1c levels, and urine glucose levels. • To determine the efficacy of dantrolene sodium on visual acuity (LogMar scores) • To determine the efficacy of dantrolene dosicum on visual functions using Visual Functioning Questionnaire – 25. • To evaluate the efficacy of dantrolene sodium on neurological functions using the Wolfram Unified Rating Scale (WURS) and standard neurological assessments.
Inclusion criteria	Patients must meet all of the following criteria to be eligible for enrolment: 1. The patient has a definitive diagnosis of Wolfram syndrome, as determined by the following: a. Documented functionally relevant recessive mutations on both alleles of the *WFS1* gene or dominant mutation on one allele of the *WFS1* gene based on historical test results (if available) or from a qualified laboratory at screening. 2. The patient is at least 5 years of age (biological age) at the time of written informed consent. 3. The patient, patient's parent(s), or legally authorized guardian(s) must have voluntarily signed an Institutional Review Board/Independent Ethics Committee-approved

	informed consent form after all relevant aspects of the study have been explained and discussed with the patient. The guardians' consent and patient's assent, as relevant, must be obtained.
Exclusion criteria	Patients who meet any of the following criteria are not eligible for this study: 1. The patient has clinically significant non-Wolfram related CNS involvement which is judged by the investigator to be likely to interfere with the accurate administration and interpretation of protocol assessments. 2. The patient has a known defect in oxidative phosphorylation (such as a confirmed mitochondrial myopathy) 3. The patient has abnormal liver function (defined as serum transaminases more than twice the upper limit of normal for the reference laboratory) 4. The patient has a significant medical or psychiatric co-morbidity that might affect study data or confound the integrity of study results. 5. The patient has received treatment with any investigational drug within the 30 days prior to study entry. 6. The patient has received blood product transfusions within 90 days prior to screening. 7. The patient is unable to comply with the protocol, (e.g. has a clinically relevant medical condition making implementation of the protocol difficult, unstable social situation, known clinically significant psychiatric/behavioral instability, is unable to return for safety evaluations, or is otherwise unlikely to complete the study), as determined by the Investigator. 8. The patient has a known history of central apnea and/or ventilation requirements. 9. The patient has a known history of chronic obstructive pulmonary disease, pleural effusion, and/or myocardial disease.
Number of patients planned and duration of study participation	Up to 50 patients (25 adults and 25 children) will be enrolled to provide a total of a) 46 evaluable patients who complete the study (23 adults and 23 children), based on an anticipated drop-out rate of 10%; The planned duration of oral dantrolene sodium administration in this study is 6 months with an optional extension phase up to 24 month. The planned overall duration of each patient's participation in this study is 9 months. For participants who continue in the optional extension phase, the planned overall duration is up to 27 months (screening, study drug dose maximization, outcome measure evaluation, and final safety follow-up).
Treatment administered and treatment schedule	Patients who receive study drug will undergo a run-in period (3 weeks) for dose maximization. **Adults**

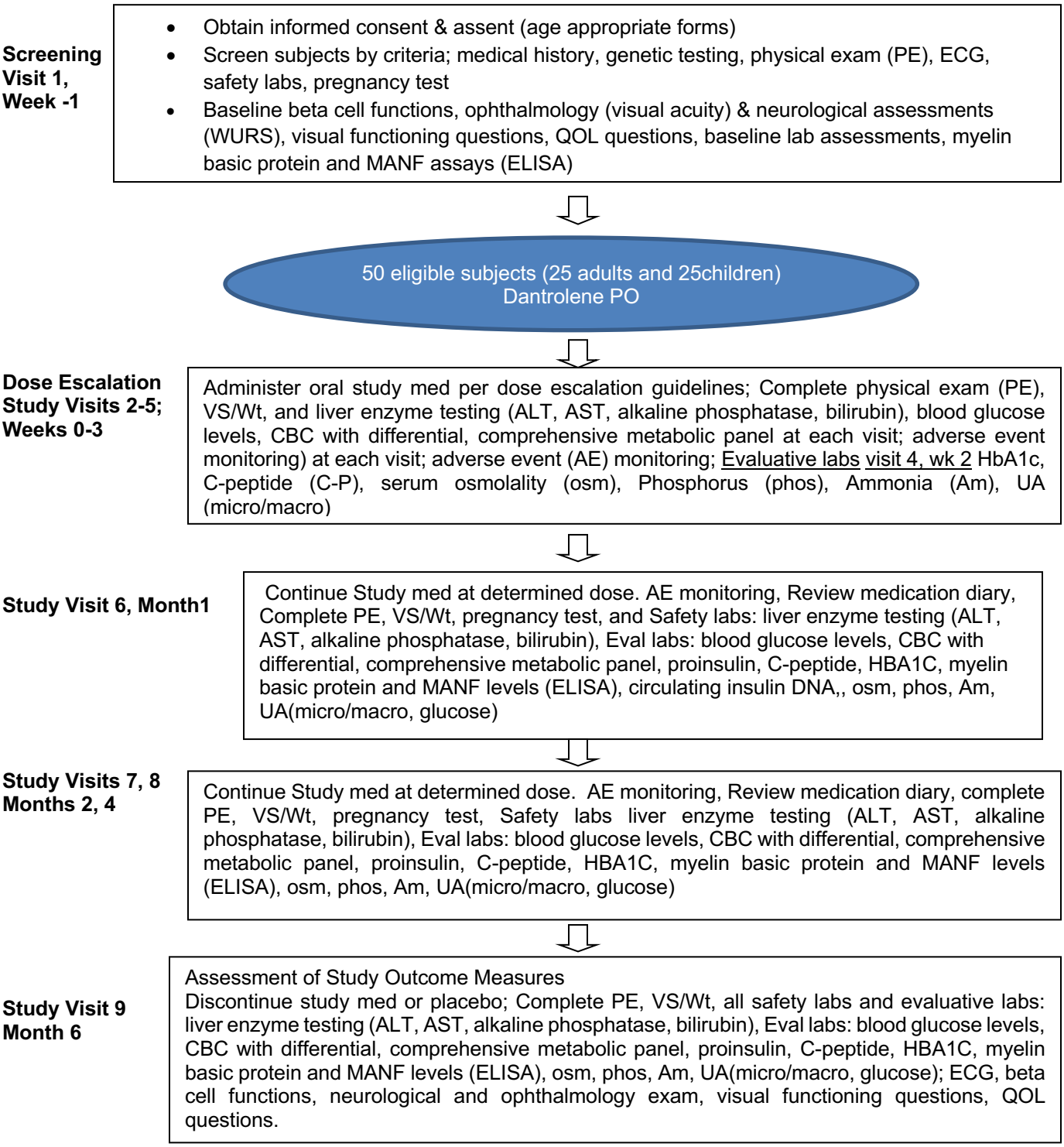
	Up to 25 mg once daily for seven days as prescribed by the physician, then Up to 25 mg b.i.d. for seven days Up to 50 mg b.i.d. for seven days Up to100 mg b.i.d. **Pediatric Patients** (a patient with an age < 18 years) up to 50 kg Up to 0.5 mg/kg once daily for seven days as prescribed by the physician, then Up to 0.5 mg/kg b.i.d. for seven days Up to 1 mg/kg b.i.d. for seven days Up to 2 mg/kg b.i.d. No dose changes if weight change is within ± 3% of the original dosing weight. Dantrolene sodium for oral use will be provided by the Washington University's clinical trials pharmacy
Study duration	The duration of this study will be approximately 9 months. For participants who continue in the optional extension phase, the duration of the study is up to 27 months.
Study methodology	This is a single center, dose-escalation study designed to evaluate the safety, and tolerability of maximal dose level of dantrolene sodium administered orally over 6 months with an optional extension phase up to 24 months in patients with Wolfram syndrome. The study will have 'x' periods as follows: • Baseline and confirmatory screening (all patients): within 56 days prior to treatment. • Dose maximization period (weeks 0-3 for each patient). • Treatment period (weeks 1-) for all patients. • Week 0 through week 3 (+/- 2 days): dose escalation up to the maximum recommended. Assessments for safety at months 1 (+/- 2 days), 2 (+/- 7 days), 4 (+/- 7 days), and 6 (+/- 7 days); and clinical examination, including ophthalmic, neurologic, endocrine, and laboratory assessments at months 0 and 6 (+/- 7 days). For participants who continue in the optional extension phase, additional assessments for safety at months 12 (+/- 7 days), 18 (+/- 7 days), and 24 (+/- 7 days); and additional clinical examinations, including ophthalmic, neurologic, endocrine, and laboratory assessments at months 12 (+/- 7 days), 18 (+/- 7 days) and 24 (+/- 7 days). • Outcome measure evaluations (all patients): month 6 (+/- 7 days) after the last dantrolene sodium administration for participants who complete the study, month 24 (+/- 7 days) after the last dantrolene sodium administration for participants who complete the optional extension phase, and within 28 days (+/- 7 days) after the last dantrolene sodium

	administration for patients who discontinue prior to the end of the study. • Final Safety Follow-Up (all patients): within 28 days (+/- 7 days) following discontinuation of study drug. Patient eligibility will be based on a diagnosis of Wolfram syndrome. Eligibility will be confirmed during the baseline screening visit. Patients who have provided written informed consent/assent to participate in this study will undergo baseline screening procedures, which will include a review of the study entry criteria and standard laboratory tests (serum chemistry, hematology and urinalysis), genetic testing confirmation, ophthalmic examination, standardized neurological and endocrinology evaluations. When central apnea is suspected in a participant, baseline screening will include the confirmation of the absence of central apnea based on the result of most recent polysomnography. Patients who are confirmed eligible based on the results of the baseline screening assessments will be enrolled to receive study drug. Baseline procedures will include complete physical exam, standard clinical laboratory tests (serum chemistry, liver function tests, hematology and urinalysis, bone chemistry), protocol-specific laboratory testing (e.g.), 12 lead ECG. If there are no safety concerns, patients will begin the 3-week dose maximization period of the study drug. We will perform ECG before and 4 hours after the first dose of dantrolene sodium, then again at months 2 and 6. For participants in the optional extension phase, we will also perform ECG at months 12, 18, and 24. All patients will undergo outcome measure evaluations at month 6. Participants in the optional extension phase undergo outcome measure evaluations at months 12, 18, and 24. Outcome measure evaluations will include standard clinical laboratory tests (serum chemistry, haematology and urinalysis), 12-lead ECG, vision assessments, neurological examination, remaining beta cell function assessment (boost test), protocol-specific laboratory testing, and standardized functional activities of daily living tests. A Final Safety Follow-Up visit will be conducted at 28 days (+/- 7 days) after the outcome measure evaluations to collect updated information on adverse events and concomitant medications, therapies and procedures. For patients who discontinue prior to the outcome measure evaluations, this will be conducted within 28 days (+/- 7 days) after the last dantrolene sodium administration.

	Administration of dantrolene sodium will be contingent upon normal results of the relevant safety laboratory tests and measures (i.e., LFTs). All adverse events, safety lab results and use of concomitant medications will be monitored closely by the PI throughout the study and for 30 days following discontinuation of study medication. If any clinically significant laboratory or clinical abnormality occurs, the subjects will be monitored closely until resolution or clinically stable. Study medication will be discontinued if indicated. Progress of the trial will be determined following periodic reviews by a Data and Safety Monitoring Board (DSMB) of the safety data in all previously enrolled patients.
Statistical Methodology	The first aim of the statistical analysis will be to assess safety and tolerability of dantrolene sodium in this patient population. The analysis will be based on all enrolled patients and will not include any formal statistical tests. To evaluate safety, the number and percentage experiencing each adverse event will be tabulated and compared by treatment status. Adverse events will be summarized by severity and by category. Vital signs, and serum chemistries, hematology and urinalysis safety monitoring will be listed for each patient and abnormal values will be flagged. The maximum dose received by patients, duration of treatment and reasons for dose reductions or early withdrawal will be reported to assess tolerability of treatment. The second aim of the statistical analysis will be to assess efficacy in terms of the secondary outcome measures of residual beta cell functions, visual acuity, and neurological function. Each variable will be quantified as a change from the baseline value. The trajectory of change for each variable will be assessed between baseline and 6-month assessments. For participants in the optional extension phase, the trajectory of change for each variable will be assessed between baseline, 6-month, 12-month, 18-month, and 24-month assessments.. As this is a rare disease and the trial involves only a small numbers of patients, statistical inferences will be based on estimation rather than hypothesis testing. Specifically a Bayesian approach to estimation will be used based on both non-informative and informative priors as appropriate. This type of approach has been endorsed for trials of rare diseases. Drop-outs may be replaced, such that an adequate number of evaluable patients complete the study.
Individual stopping criteria	1. If a participant experiences more than a few but not more than 10 diarrhea stools in a single day while taking dantrolene sodium, a temporary withdrawal (48 h or longer) should be discussed with a PI. A patient with Wolfram syndrome tends to

	have diarrhea due to autonomic dysfunction. Thus, the temporary withdrawal is determined by the discretion of the PI. If a patient experiences more than 10 diarrhea stools in a single day, a temporary withdrawal (48 h or longer) should be immediately done. After the temporary withdrawal, a participant should use the previously tolerated dosing regimen. 2. If a participant experiences significant muscle weakness while taking dantrolene sodium, a participant should use the previously tolerated dosing regimen. Muscle weakness is examined at every study visit as part of the physical exam. Muscle weakness is assessed by the following methods. • Rise to stand from floor without using hands. If a participant cannot do this due to neurological dysfunction of Wolfram syndrome, the order in which we would like a participant to attempt is the following: From floor with hands, from a chair without using hands, from a chair with hands. • Hand grip strength using a hand dynamometer, left and right. If a participant cannot rise to stand with the method he/she used or a participant's total hand grip strength (sum of right- and left-hand grip strength) is decreased by more than 20% with the current dosing regimen, a patient should use the previously tolerated dosing regimen. Two failures in either of these two steps would constitute stopping the drug permanently. 3. ALT or AST >8xUpper Limits of Normal (ULN) 4. ALT or AST >5xULN for more than 2 weeks 5. ALT or AST >3xULN and (serum total bilirubin >2xULN or international normalized ratio >1.5) 6. ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
Study stopping criteria	We define the study stopping criteria based on established adverse event criteria, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4. The study may need to be stopped if ≥2 patients on drug develop the same CTCAE Grade 3 or if 1 patient develops a CTCAE Grade 4 or higher.

FIGURE: CLINICAL TRIAL DIAGRAM



For participants who continue in the optional extension phase

Study Visits 10, 11, and 12 Month 12, 18, and 24	Assessment of Clinical Outcome Measures Discontinue study med or placebo; Complete PE, VS/Wt, all safety labs and evaluative labs: liver enzyme testing (ALT, AST, alkaline phosphatase, bilirubin), Eval labs: blood glucose levels, CBC with differential, comprehensive metabolic panel, proinsulin, C-peptide, HBA1C, myelin basic protein and MANF levels (ELISA), osm, phos, Am, UA(micro/macro, glucose); ECG, beta cell functions, neurological and ophthalmology exam, visual functioning questions, QOL questions.

Final Follow up	Safety labs, AE monitoring, complete PE, VS/Wt