Title	Cerebrotendinous Xanthomatosis Registry: Long term Non-Interventional Follow-up of Safety and Effectiveness of Chenodeoxycholic Acid Leadiant.
Protocol Version Identifier	Final 2.0
Date of last version of protocol	30 March 2018
EU PAS register number	Study not registered. To be registered after approval of protocol by PRAC
Active substance	Chenodeoxycholic Acid 250 mg ATC code: A05AA01
Medicinal product	Chenodeoxycholic Acid Leadiant
Product Reference	EU/1/16/1110/001
Procedure number	EMEA/H/C/004061/0000
Marketing authorisation holder	Leadiant Biosciences, Amberley House, Peascod Street, Windsor, SL4 1DN, UK.
Joint PASS	No
Research question and objectives	The objective of the registry study is to collect long-term safety and effectiveness of Chenodeoxycholic Acid Leadiant in the treatment of Cerebrotendinous Xanthomatosis.
Countries of study	All European countries
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Marketing authorisation holder(s)

Marketing authorisation holder(s)	Leadiant GmbH, Liebherrstrasse 22 80538 Munich, Germany.
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2 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomic Therapeutic Chemical classification system
CCDS	Composite Cerebellar Functional Severity score
CDCA	Chenodeoxycholic Acid
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Toxicity Criteria for Adverse Event
CTX	Cerebrotendinous Xanthomatosis
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
EMA	European Medicines Agency
EMG	Electromyography
EVPM	EudraVigilance Post-authorisation Module
FAB	Frontal Assessment Battery
FARS	Friedreich's Ataxia Rating Scale
FAS	Full Analysis Dataset
GCP	Good Clinical Practice
HCP	Health Care Provider
HMG-CoA	3-Hydroxy-3-Methylglutaryl-CoA
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MEPs	Motor Evoked Potentials
MMS	Mini Mental Scale
MRI	Magnetic Resonance Imaging

PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SARA	Scale for the Assessment and Rating of Ataxia
SOP	Standard Operating Procedure
WHO	World Health Organization

3 Responsible parties

Sponsor:

Leadiant Biosciences, Amberley House, Peascod Street, Windsor

Sponsor Signatory:

Dr Surabhi Verma

Chief Medical Officer, Leadiant Biosciences Ltd

Co-investigator(s):

Dr Aad Verrips, Netherlands

Prof. Anotnio Federico, Italy

Study Management:

Leadiant biosciences has contracted with contract research organisation(s) with expertise in observational post-marketing studies, to provide input and to conduct the study. The Contract Research Organisation (CRO) will conduct the study with review and input from the Marketing Authorisation Holder (MAH).

The work will be carried out by the following responsible parties: Protocol writing, study management, data management, biostatistics, statistical programming and reporting of the study will be carried out by CROS NT Ltd, Beechwood, Grove Park, White Waltham, Maidenhead, SL6 3LW, UK and CROS NT SrL, Via Germania 2, 37136 Verona, Italy.

Pharmacovigilance (adverse event (AE) monitoring and reporting) will be undertaken by Leadiant Biosciences Ltd (Amberley House, Peascod Street, Windsor, UK). An audit programme will be developed and managed by seQure, a sister company of CROS NT.

4 Abstract

Title

Cerebrotendinous Xanthomatosis Registry: Long term Non-Interventional Follow-up of Safety and Effectiveness of Chenodeoxycholic Acid Leadiant.

Rationale and background

Cerebrotendinous xanthomatosis (CTX) is a rare genetic metabolic disorder of cholesterol and bile acid metabolism that results in systemic and neurological abnormalities. Typically, the disease begins during early infancy with chronic diarrhoea or neonatal cholestasis. Cataracts become evident in childhood or adolescence, while tendon xanthomas often develop in the second and third decades of life. Significant neurological impairment also occurs: this often includes intellectual disability, seizures, and cerebellar and pyramidal dysfunction. Motor impairment typically begins in the third or fourth decade of life, sometimes earlier, and progresses until death, which is premature if the condition remains untreated. The presentation and course of CTX varies widely, and treatment can dramatically alter the natural history of the condition, especially when started early.

The primary enzymatic defect in CTX is in mitochondrial sterol 27-hydroxylase, a key enzyme in the complicated process of bile acid synthesis from cholesterol. Defects in the enzyme result in decreased synthesis of Chenodeoxycholic Acid (CDCA) and an accumulation of bile acid precursors, including cholestenol, in tissues. Deposition of cholestanol and cholesterol in the central nervous system (brain and spinal cord), muscle (including heart), blood vessels, eye lenses, and tendons results in a degenerative process that worsens over time unless treated.

Treatment with CDCA has been found to normalize bile acid metabolism and to slow, halt, and even reverse problems associated with CTX.

Patients with untreated CTX have a life expectancy into the fifth and sixth decades; however, confirmed deaths have been reported from as early as age 4 months. This is a progressive and terminal disease if left untreated. Treated patients may achieve a normal lifespan.

Research question and objectives

This is a patient registry project that aims to provide information about the long-term effectiveness and safety of CDCA in the CTX patient population. Data will be collected from CTX patients treated with CDCA at centres in Europe during routine clinical practice. The study design is non-interventional with no randomisation or blinding. Some data may be collected retrospectively via retrieval from patient records.

The primary objective is to develop a registry and to monitor the safety and effectiveness of CDCA use in routine care.

The secondary objective is to develop a disease/product registry to serve as a repository on treatment and outcomes for patients with CTX.

Study design

This is a patient registry project which aims to provide information about the long-term effectiveness and safety of CDCA in the CTX patient population. The design is observational, non-interventional, follow-up of CTX patients treated with Chenodeoxycholic Acid Leadiant. Data will be collected from patients treated with Chenodeoxycholic Leadiant at centres in Europe during routine clinical practice. The study design is non-interventional with no randomization or blinding. No additional follow-up or tests will be specified. Data collection will be prospective, with some retrospective data retrieval from patient records where necessary.

Population

The registry population will consist of male and female subjects of any age with a confirmed diagnosis of CTX and who are receiving treatment with Chenodeoxycholic Acid Leadiant.

Study endpoints

Safety endpoints include adverse events and serious adverse events, laboratory tests including liver function tests, pregnancy use, and discontinuations and changes to doses during treatment.

A scientific committee will be responsible for ensuring a consistent approach in the follow-up and assessment of patients.

The effectiveness endpoints are as follows:

Effectiveness endpoints:

- Onset of, or changes from baseline (worsened, stayed the same or improved) in clinical signs and symptoms:

  - Neurological status (Scale for the Assessment and Rating of Ataxia (SARA), Composite Cerebellar Functional Severity score (CCFS), Friedreich's Ataxia Rating Scale (FARS) and/or similar scales will be used)
  - Psychiatric status
  - Diarrhoea
  - Neonatal hepatitis
- Change from baseline in biochemical parameters:
  - Serum cholestanol
  - Urine bile alcohol (collected where possible)
  - Serum 7 alpha C4 (collected where possible)
- Changes (worsened, stayed the same or improved) in:
  - Cognitive performance scales
  - Neurological impairment
  - Disability status (RANKIN scale, Expanded Disability Status Scale (EDSS) and/or similar scales will be used)
  - Cognitive status (Frontal Assessment Battery (FAB), Mini Mental Scale (MMS) or similar assessments will be used)

Data sources

The primary safety and effectiveness outcomes will be collected prospectively from patient's routine care as reported by the treating physicians into the registry database. In cases where the patient has already taken Chenodeoxycholic Acid Leadiant or the previous product Xenbilox, baseline and treatment follow-up data will also be retrieved from patient notes retrospectively where feasible.

Study size

Cerebrotendinous xanthomatosis is a rare genetic metabolic disorder and there are very few centres for research. The sponsor has identified four specialist centres with CTX patients in Europe and will endeavour to find additional centres to participate in the study by liaising with the relevant European Reference Networks, but given the prevalence of this disease, this is unlikely to increase recruitment significantly. The registry will be open to recruitment of interested CTX centres throughout Europe.

Based on the expected diagnostic rate, it is estimated that the registry will be able to recruit between 40 and 60 patients. It is anticipated that this will generate approximately 80-120 years of patient follow-up data.

Data analysis

The primary endpoint of change from baseline in serum cholestanol level will be summarised using descriptive statistics. The mean change from baseline at each post-baseline assessment will be presented with 95% confidence intervals. A paired t-test will be used to test for a significant change from baseline.

A restricted maximum likelihood (REML) based repeated measures approach will also be used to analyse the change from baseline results over time, using all available yearly assessments (based on time windowing).

Secondary effectiveness endpoints will be summarised by time point using descriptive statistics. Further details of the planned summaries and analyses will be provided in the statistical analysis plan.

Adverse events will be summarised using frequency counts and percentages. Laboratory test results will be summarised by time point using descriptive statistics.

Milestones

Milestone	**Planned date**
Start of data collection	September 2018
End of data collection	September 2023
Interim report	December 2020
Final report of study results	March 2024

5 Amendments and updates

Protocol Version Final 2.0 incorporated changes requested by PRAC and was created before the start of data collection.

No substantial amendments or updates have been made to the study protocol since the start of data collection.

6 Milestones

Milestone	Planned date
Start of data collection	September 2018
End of data collection	September 2023
Interim report	December 2020
Final report of study results	March 2024

7 Rationale and background

7.1 Background

Cerebrotendinous xanthomatosis (CTX) is a rare genetic metabolic disorder of cholesterol and bile acid metabolism that results in systemic and neurological abnormalities. Typically, the disease begins during early infancy with chronic diarrhoea or neonatal cholestasis. Cataracts become evident in childhood or adolescence, while tendon xanthomas often develop in the second and third decades of life. Significant neurological impairment also occurs: this often includes intellectual disability, seizures, and cerebellar and pyramidal dysfunction. Motor impairment typically begins in the third or fourth decade of life, sometimes earlier, and progresses until death, which is premature if the condition remains untreated. The presentation and course of CTX varies widely, and treatment can dramatically alter the natural history of the condition, especially when started early.

The primary enzymatic defect in CTX is in mitochondrial sterol 27-hydroxylase, a key enzyme in the complicated process of bile acid synthesis from cholesterol. Defective enzymatic function disrupts bile acid synthesis. Defects in the enzyme result in decreased synthesis of CDCA; this, in turn, disrupts feedback regulation on cholesterol 7-alpha-hydroxylase, which is the rate-limiting step in the classic pathway of bile acid synthesis. Therefore, bile acid precursors accumulate in tissues. Cholestanol is formed in a pathway from the bile acid precursor 7-alpha-hydroxy-4-cholesten-3-one [1]. Deposition of cholestanol and cholesterol in the central nervous system (brain and spinal cord), muscle (including heart), blood vessels, eye lenses, and tendons results in a degenerative process that worsens over time unless treated.

About 300 CTX patients have been reported worldwide, with an estimated prevalence of 1 case per 50,000 individuals in white populations [2, 3]. Genetic islands of increased CYP27A1 mutation frequency exist; for example, there is an estimated disease prevalence of 1:440 for the Druze population in Israel [4].

Experts strongly believe that CTX is seriously underdiagnosed [3, 5]. Cases have been reported in USA, China, Canada, Belgium, Brazil, Saudi Arabia, India, Germany, Taiwan, France, Switzerland, South Africa, Australia, Israel, and Argentina. A large representation has been reported among Spanish [5] and Dutch populations, as well as in Italy and Japan. A founder effect and high rate of consanguinity appear to be responsible for the high prevalence among the Druze population [4, 6].

Morbidity often begins with intractable diarrhoea. Pre-senile cataracts result in vision abnormalities. Xanthomas can cause motor restriction and joint deformities, resulting in various orthopaedic sequelae. Vascular abnormalities such as premature atherosclerosis (especially in the carotid and coronary vessels) can lead to strokes and myocardial infarction. The primary neurological manifestations of the disease are associated with complications that range from treatable seizures to neurological devastation. The severity of disease varies widely between families, but also within single families. Early diagnosis of CTX is imperative, since it is a treatable disease. This early diagnosis depends on recognition of early signs and symptoms, specifically the combination of diarrhoea and cataracts along with personal or family history of infantile hepatitis, prolonged jaundice or early infantile death.

The treatment of choice in CTX is CDCA replacement therapy [11], which was initially used for the treatment of gallstones. CDCA should be considered the mainstay of therapy. If hypercholesterolemia is not controlled with CDCA treatment alone, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors may be added. HMG-CoA reductase inhibitors (statins) have well-established efficacy and safety in patients with hypercholesterolemia and have also been used alone and in combination with CDCA to treat patients with CTX.

A number of studies have evaluated the use of different treatments in patients with CTX. Dotti et al examined treatment with CDCA, simvastatin, and low-density lipoprotein apheresis in several combinations [7]. Although the established treatments performed well, low-density lipoprotein apheresis was not associated with a clinical benefit and possibly put the patient at risk for treatment complications. Verrips et al reported that addition of 40 mg simvastatin daily to 750 mg CDCA was effective to further reduce serum cholestanol, LDL cholesterol, and lathosterol in adult CTX patients treated with long-term CDCA [8]. Cholic acid, has been used occasionally to treat children with CTX [9]. There is insufficient evidence to recommend its routine use and its usefulness for neurological symptoms has not been demonstrated. Other medical treatment modalities typically used in the treatment of disorders of bile and cholesterol metabolism, specifically hydrophilic 7 beta-hydroxy bile acids and cholestyramine, have been shown to be ineffective.[10]

Treatment with CDCA has been found to normalize bile acid metabolism and to slow, halt, and even reverse problems associated with CTX. In several well-documented studies, the bile acids and metabolites in plasma, bile, urine, and cerebrospinal fluid (CSF) concentrations of cholestanol have normalized after as little as 4 months of treatment .[5, 11, 12]. Clinically, neuropsychological and peripheral neurological symptoms improve with CDCA treatment, as do effects on bone mineralization. [12]. In a landmark study, dementia was found to improve in 10 out of 12 CTX patients after initiating treatment with CDCA, with strong improvements in mentation, speech, orientation, and memory [11]. Corresponding improvements were seen in magnetic resonance imaging (MRI) and electroencephalogram (EEG) findings. Xanthoma and cataract development were non-progressive but were not reversed with CDCA administration. Biochemical changes with therapy have included reduced serum cholestanol levels and increased CDCA levels [13, 14]. Further studies have confirmed and expanded on these findings [11, 15-23]. Once significant neurological pathology has been established, pharmacological treatment is recommended [24], but the effects can be limited [17]. A recent study demonstrated that patients who started treatment with CDCA after the age of 25 years had a worse outcome than those who started treatment earlier [25]. Some patients will continue to deteriorate despite treatment [4, 25].

It has been suggested [11] that patients with CTX should undergo an annual examination, which should include a neurological and neuropsychological evaluation, measurement of cholestanol plasma concentrations, brain MRI, electrophysiological examination including electromyography (EMG), motor evoked potentials (MEPs), and EEG in selected cases, echocardiography when indicated and bone mineral density assessment when indicated.

Patients with untreated CTX have a life expectancy into the fifth and sixth decades; however, confirmed deaths have been reported from as early as age 4 months. This is a progressive and terminal disease if left untreated. Treated patients may achieve a normal lifespan.

7.2 Chenodeoxycholic Acid Leadiant

Cerebrotendinous Xanthomatosis results in a deficiency of primary bile acids with a severe deficiency/ virtual absence of chenodeoxycholic acid and a total bile acid pool enriched with cholic acid. Chenodeoxycholic Acid Leadiant is a primary bile acid that has been licensed for the treatment of inborn error of primary bile acid synthesis, due to sterol 27-hydroxylase deficiency presenting as CTX in infants and children aged 1month to 18 years and adults.

A recent retrospective study, which recruited 35 CTX patients at a single centre in The Netherlands, evaluated the ability of CDCA administered orally (750 mg/day or 15 mg/kg/day) to reduce serum levels of cholestanol and, in selected cases, urinary bile alcohols [26]. The study also assessed the impact of CDCA treatment in halting, slowing, improving or stabilizing the clinical disease process through the evaluation of several parameters including disability scores, electrophysiological data, imaging data, laboratory parameters and disease signs and symptoms. The safety and tolerability of CDCA administered orally at doses of 750 mg/day or 15 mg/kg/day was also assessed. Results showed that long-term CDCA treatment (median 9 years, range 2.7-25.1 years) was effective at reducing serum cholestanol and urinary bile alcohols in CTX patients. At the end of treatment, the majority of disease signs and symptoms had stabilised, resolved or improved and there was a stabilisation or improvement of the disability scores in a majority of patients. Long term CDCA treatment was also shown to have a satisfactory safety profile. There were no serious safety concerns with Chenodexycholic Acid Leadiant. There were 3 treatment related adverse reactions. These were constipation of mild intensity (2 AEs in 2 patients, 5.7%) and hepatitis toxic of moderate intensity (1 AE in 1 patient, 2.9%). None of the treatment-related AEs was serious.

8 Research question and objectives

Since the number of patients with CTX is low, the disease is considered rare and CDCA was designated an orphan medicine by the European Medicines Agency (EMA) in December 2014. Chenodeoxycholic acid was recently approved by the EMA for use in the treatment of CTX under “exceptional circumstances” due to the rarity of the disease. In accordance with the terms of this approval, Leadiant Biosciences (the MAH) has agreed to set up a post-authorisation registry to monitor the safety and effectiveness of CDCA in the treatment of patients with CTX. This is the aim of the study described in this protocol.

It was originally planned that the comparator in this study would be a natural historical cohort of untreated patients. However, there is a lack of availability of natural history descriptions in the current literature due to the well established use of CDCA, with the majority of CTX patients being treated with CDCA upon diagnosis. Therefore, a qualitative natural history summary as described by some authors and substantiated by a review of the natural history from the initial publications of untreated series/ patients prior to the introduction of CDCA in 1975 has been prepared by the MAH. Since the natural history of CTX is not currently described in sufficient detail to facilitate its inclusion within the study design, this summary will be used to compare the findings, as a narrative in the final study report.

The primary objective of the study is to develop a registry and to monitor the safety and clinical effectiveness of CDCA use in routine care.

The secondary objective is to develop a disease/product registry to serve as a repository on treatment and outcomes for patients with CTX.

9 Research methods

9.1 Study Design

This is a patient registry project which aims to provide information about the long-term effectiveness and safety of CDCA in the CTX patient population. The design is observational, non-interventional, follow-up of CTX patients treated with Chenodeoxycholic Acid Leadiant. Data will be collected from patients treated with Chenodeoxycholic Leadiant at centres in Europe during routine clinical practice. The study design is non-interventional with no randomization or blinding. No additional follow-up or tests will be specified. Data collection will be prospective, with some retrospective data retrieval from patient records where necessary.

The registry project is expected to run for a minimum of 5 years. Recruitment will be open throughout this time, meaning some patients will be followed up for less than 5 years.

9.1.1 Setting

This registry study will be open to all CTX treatment centres in Europe.

9.1.2 Inclusion Criteria

Patients satisfying the following criteria will be eligible to participate in this registry study:

1. Informed consent obtained from patient or parent/carer as appropriate.
2. Male or female subjects of any age
3. Confirmed diagnosis of CTX
4. Receiving treatment with Chenodeoxycholic Acid Leadiant.

9.1.3 Exclusion Criteria

No formal exclusion criteria are specified. All CTX patients receiving Chenodeoxycholic Acid Leadiant will be eligible, subject to informed consent.

9.1.4 Withdrawal/Stopping criteria

A parent/carer or consented patient may be withdrawn from the registry due to loss to follow-up or withdrawal of consent. All data collected up to the time of withdrawal will be included in the analysis, where permitted by the consent of the patient.

9.1.5 Assessments and procedures

The registry will not require or specify medical interventions outside the standard of care in the treating centre. Baseline, treatment and follow-up data will be captured. It is anticipated that there may be some variability in the length of follow-up and hence time windows will be specified for analysis. Safety and effectiveness data will be captured prospectively. The registry will capture adverse events reported by patients/carers to their healthcare provider at routine follow-up visits. As follow-up visits may be up to a year apart it is anticipated adverse event capture will be incomplete due to recall which will introduce some reporting bias. However, this bias should not apply to serious adverse event reporting due to the supportive care required.

For patients already on Chenodeoxycholic Acid Leadiant or previous product Xenbilox, baseline and treatment follow-up data will be retrieved from patient notes retrospectively where feasible. Where appropriate, follow-up with the Healthcare Provider (HCP) will retrieve data from patient notes to ensure completeness of Case Report Forms (CRFs). In cases on treatment with another CDCA containing product, only baseline pre-treatment data will be included.

The following baseline data will be collected for each patient (where available):

Demography (including, age at disease onset and diagnosis, sex, race/ethnicity, medical history)

Clinical characteristics (including current disease signs and symptoms (diarrhoea, cataracts, xanthomas, cognitive impairment, psychiatric impairment, neurological impairment), previous treatment for CTX)

Laboratory data (including serum cholestanol, serum cholesterol, haematology data, serum 7 alpha C4 and urine bile alcohol)

Treatment information (start/stop dates, treatment source (compounded/CDCA Leadiant), concomitant medications).

The registry project will run for a minimum of 5 years and patients can be recruited at any time during this 5 year period. Recruitment will be open throughout this time, meaning some patients will be followed up for less than 5 years. The registry will accept new patients at any time during this 5 year period regardless of the time of exposure to CDCA. There is no minimum follow-up time. Since data can be collected retrospectively from patient records some patients may have more than 5 years of follow-up data.

9.2 Study endpoints

The following safety and effectiveness endpoints will be evaluated:

Safety endpoints:

- Incidence of AEs and serious adverse events (SAEs)
- Incidence of hepatitis
- Incidence of constipation
- Incidence of liver toxicity (from serum ALT and bilirubin levels if available)
- Changes in laboratory tests (including serum cholesterol and haematology values)
- Pregnancy use
- Discontinuations and changes to doses (including switches from/ to other drugs) during treatment

Effectiveness endpoints:

As this is an observational, non-interventional study, the method of assessment and follow-up of the data for the effectiveness endpoints will be based on the local practices at the study sites. Therefore, for some endpoints there will be a variety of different assessment tools used and the data from these will need to be combined. For this reason, results will be classed as either “worsened”, “stayed the same “or “improved” so that they can be combined even if the actual measurement tools are different. It is also noted that for the biochemical parameters, these can only be evaluated if they are routinely measured at the site.

A Scientific Committee will hold regular meetings to agree a consistent approach in the follow-up and assessment of patients. The Scientific Committee will adjudicate on how the different assessment tools can be compared and will decide what constitutes worsening, stabilisation or improvement for each tool in the context of a CTX patient.

Effectiveness endpoints:

- Onset of, or changes from baseline (worsened, stayed the same or improved) in clinical signs and symptoms:
    - Neurological status (Scale for the Assessment and Rating of Ataxia (SARA), Composite Cerebellar Functional Severity score (CCFS), Friedreich’s Ataxia Rating Scale (FARS) and/or similar scales will be used)
    - Psychiatric status
    - Diarrhoea
    - Neonatal hepatitis
- Change from baseline in biochemical parameters:
    - Serum cholestanol
    - Urine bile alcohol (collected where possible)
    - Serum 7 alpha C4 (collected where possible)
- Changes (worsened, stayed the same or improved) in:
    - Cognitive performance scales
    - Neurological impairment
    - Disability status (RANKIN scale, Expanded Disability Status Scale (EDSS) and/or similar scales will be used)
    - Cognitive status (Frontal Assessment Battery (FAB), Mini Mental Scale (MMS) or similar assessments will be used)

There is currently no standard of care or guidance on how to assess and treat patients with CTX. Any other rating scales used to assess these patients will be included in the assessments of efficacy and safety if possible.

Given the progressive nature of CTX, stabilisation or improvement in neurological status will be considered as a response.

9.3 Data sources

Information about the patient's CTX symptoms, results of tests (including blood tests and any rating scales) and any changes observed in the patient's neurological, cognitive and psychiatric status will be collected prospectively during the patient's routine care by the treating physician and recorded in the patient's notes. The data will also be entered into the registry database. The source data will be the patient's notes. In patients who have previously taken Chenodeoxycholic Acid Leadiant or the previous product Xenbilox, data will also be retrieved from patient notes retrospectively where feasible.

Information recorded in the registry database will include demography, baseline clinical features, symptoms (particularly gastrointestinal and hepatic) adverse events, laboratory parameters (including serum cholestanol, urine bile alcohol and serum 7 alpha C4 levels where possible), imaging data, disability scores, neurological, cognitive and psychiatric status and information relating to the clinical and biochemical response to CDCA treatment and follow-up. Since this is an observational, non-interventional study, only the parameters and assessments recorded in the patient's notes during routine clinical practice will be available for inclusion in the Registry database.

The timing of assessments will be in accordance with standard patient follow-up procedures at the site. Due to the observational, non-interventional design of this study, timing of the assessments cannot be predetermined in the protocol.

9.4 Study size

Cerebrotendinous xanthomatosis is a rare genetic metabolic disorder and there are very few centres for research. The sponsor has identified four specialist centres with CTX patients in Europe and will endeavour to find additional centres to participate in the study by liaising with the relevant European Reference Networks, but given the prevalence of this disease, this is unlikely to increase recruitment significantly. The registry will be open to recruitment of interested CTX centres throughout Europe.

Based on the expected diagnostic rate, it is estimated that the registry will be able to recruit between 40 and 60 patients in these four specialist centres. It is anticipated that this will generate approximately 80-120 years of patient follow-up data.

9.5 Data management

Data management: data validation, management of data discrepancies and queries (for example inconsistencies in the information collected in the various sections of the CRF), coding of medical terms, and creation of the SAS datasets, will be undertaken by CROS NT, Via Germania 2, 37136 Verona, Italy.

The data management processes will be defined in a separate Data Management Plan. To avoid inconsistencies, the data management plan will be written after the protocol and CRF have been finalised.

Medical terms will be coded according to the following dictionaries:

- Medical Dictionary for Regulatory Activities (MedDRA), for medical conditions and AEs.
- World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) Classification System codes, for previous and concomitant medications

9.6 Data analysis

The statistical analysis will be performed by CROS NT, Via Germania 2, 37136 Verona, Italy.

All analysis will be further defined in the Statistical Analysis Plan (SAP). The SAP will be written and reviewed by two independent statisticians from CROS NT.

This is an exposure registry without a comparison group.

9.6.1 Analysis populations

The following analysis populations will be considered:

Full analysis set (FAS) – All enrolled patients with a baseline and at least one post-baseline result.

Safety set – All enrolled patients who took at least one dose of study medication since registry entry.

All baseline and efficacy endpoints will be analysed using the FAS. All safety endpoints will be analysed using the safety set.

9.6.2 Statistical analysis

All statistical analyses and data processing will be performed using SAS® Software (release 9.4) on a Windows 7 operating system.

Descriptive statistics will be provided according to the type of variable. Continuous variables will be summarised using n (sample size), mean, standard deviation, median, minimum and maximum. Categorical variables will be summarised using frequency counts and percentages. All data collected will be presented in listings.

The number of patients with missing categorical data will be presented under a 'Missing' category. Missing values will be included in the denominator count when computing percentages. In the case of continuous data, only non-missing values will be included in the calculation of summary statistics.

Analyses over time will be analysed using a mixed effect model which will handle missing data under a 'missing at random' assumption. Further details on the handling of missing data will be included in the statistical analysis plan.

For inferential analyses, p-values will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value is less than or equal to 0.05. Adjustment for multiple testing is not planned due to the exploratory nature of the trial.

9.6.2.1 Time windows

Time windowing will be used to evaluate patient data at comparable time points. The time windows at each assessment point will be specified in the statistical analysis plan, and will be based on discussions of usual practice at the scientific committee meeting.

Time windows will be applied for all summaries and analyses by time point, unless otherwise specified. Time windowing will also be applied when repeated measures analyses are performed as a categorical time variable is required in this type of modelling.

If more than one result falls into a time window, the result closest to the time point in question will be used. All data will be listed.

9.6.2.2 Primary effectiveness endpoint

The primary endpoint of change from baseline in serum cholestanol level will be summarised using descriptive statistics. The mean change from baseline at each post-baseline assessment (based on the time windows described in Section 9.7.2.1) will be presented with 95% confidence intervals. A paired t-test will be used to test for a significant change from baseline.

A restricted maximum likelihood (REML) based repeated measures approach will also be used to analyse the change from baseline results over time, using all available yearly assessments (based on time windowing). The fixed categorical effects of centre and time point, as well as the continuous fixed covariates of baseline and baseline-by-time point interaction will be included. Further covariates identified during the scientific committee meeting may be added to the model, and will be specified in the statistical analysis plan. An unstructured covariance structure will be used to model the within-patient measurements. If this analysis fails to converge, the following covariance structures will be tested in order: TOEPH, TOEP, AR(1). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Further details of the planned summaries and analyses of the primary endpoint will be provided in the statistical analysis plan.

9.6.2.3 Secondary effectiveness endpoints

Where available, urinary bile alcohols will be categorised into the following categories: elevated, mildly elevated or normal. Shift tables will be used to present the number and percentage of patients with each baseline result against each post-baseline assessment.

Where available, the absolute and change from baseline serum 7 alpha C4 values will be summarised using descriptive statistics at each post-baseline assessment. The absolute and change from baseline values in EDSS, Rankin scale or other performance scale scores will also be summarised using descriptive statistics.

The number and percentage of patients with clinical signs and symptoms will be presented at baseline, and at each post-baseline assessment. If the symptom is present at baseline, the change (for example, improved, stayed the same or worsened) will be presented at each post-baseline assessment. The number and percentage of patients experiencing new symptoms at each post-baseline assessment will also be presented, while the time to onset of symptoms will be explored.

Further details of the planned summaries and analyses will be provided in the statistical analysis plan.

9.6.2.4 Safety endpoints

AEs will be coded using MedDRA. The number of AEs, SAEs, adverse drug reactions (ADRs), AEs leading to discontinuation of study medication, and AEs leading to death will be presented by system organ class and preferred term. The number and percentage of patients experiencing AEs, SAEs, ADRs, AEs leading to discontinuation

and AEs leading to death will also be presented by system organ class and preferred term. Incidence rates will also be used in order to adjust for the number of patient years observed.

Liver toxicity will be defined as a statistically significant doubling (or more) in the incidence of serum alanine aminotransferase (ALT) elevation >3 × the upper limit of normal (ULN); and/or any incidence of serum ALT elevation >9 × ULN; and/or any incidence of serum ALT elevation >3 × ULN accompanied by a serum bilirubin elevation >2 × ULN) [27,28].

Laboratory assessments will be summarised at post-baseline time points using descriptive statistics.

Patients found to be pregnant during the study will be investigated further through detailed listings of all safety data.

9.6.2.5 Other endpoints

The number and percentage of patients permanently discontinuing study medication, or changing their dose will be listed.

9.6.3 Interim analysis

An interim analysis is planned in order to provide an update to the Pharmacovigilance Risk Assessment Committee (PRAC). Key safety and effectiveness data will be summarised descriptively. No formal testing will be performed.

9.6.4 Independent reviews

A Scientific Committee will regularly review the ongoing conduct of the registry along with safety data to assure that the safety of study subjects is protected while the scientific goals of the registry are being met.

The Scientific Committee will provide independent oversight based on a multidisciplinary approach to the diagnosis, treatment, and follow-up of patients with CTX. The Scientific Committee aims to include the following members: independent investigators/clinicians from the participating countries, representative(s) from the Sponsor (Leadiant Biosciences), a geneticist, a chemical pathologist, a metabolist, a neuro radiologist and a specialist nurse.

Regular meetings will be held to agree a consistent approach to the follow-up and assessment of patients. The Scientific Committee will adjudicate on how the different assessment tools can be compared and will decide what constitutes worsening, stabilisation or improvement for each assessment tool in the context of a CTX patient.

9.7 Quality control

Data from each patient will be recorded by the Investigator on a CRF. All of the information requested in the CRF is needed for correct final evaluation of the study patient. The Investigator should ensure the accuracy, completeness and timelines of the data reported in the CRF. Data recorded in the CRF must be consistent with the source documents and any discrepancies should be explained.

The CRF will be developed by CROS NT and will comply with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements and any other requirements specified by the EMA. Data edit checks will be performed as detailed in the Data Management Plan. Data queries will be issued to the clinical sites in order to resolve any discrepancies in the CRF and the sites will update the data accordingly.

The CRF to be used in this study consists of specific forms to record all of the information required by the protocol, such as eligibility and safety assessments, etc. All study site personnel involved in recording information onto the CRF will receive specific training to ensure that they are able to use it properly.

Monitoring of this study will be undertaken by CROS NT or its designees, in accordance with GCP and all applicable CROS NT Standard Operating Procedures (SOPs). The Investigator must agree to undergo regular monitoring visits; the frequency of visits will be determined by patient enrolment rates or other issues such as audits.

A risk based monitoring strategy will be implemented. A risk assessment will be conducted and used to determine data validation and verification strategies for participating centres. Details of the planned data validation processes (such as full site monitoring, remote data validation, etc) will be documented in the Monitoring Plan. Site audits will be performed at centres recruiting larger numbers of patients.

At each visit, the Investigator or a designated member of the study personnel must be available to provide access to all study-related documentation, including the original patient notes, and to make any necessary corrections to the CRF and/or other study documents.

The study monitor will provide the Investigator with all the necessary study materials before the study starts and, during the course of the study, will check at least the following:

- full compliance with GCP procedures, and with the study protocol;
- patient recruitment;

- completeness and accuracy of the CRF data and their consistency with the source data (full source data verification will be conducted on 100% of CRFs);
- continued acceptability of the facilities;
- Investigator's Study File.

The Investigator/Institution must allow the sponsor to conduct the audits as an integral part of the quality assurance process. The audit is an independent verification (separate from monitoring visits) of study activities and documentation to ensure that the activities pertinent to the study were duly carried out and that they were recorded, analysed and transferred in compliance with the protocol, GCP, all relevant SOPs and applicable legislation.

The Investigator/Institution must permit national and foreign regulatory authorities to conduct inspections, if required. An Inspection on behalf of one or more Regulatory Authorities will consist of an official review of the documents, facilities, records and any other resource considered by the authorities to be connected with the study.

9.8 Limitations of the research methods

Collection and analysis of data in an observational setting over a long period of time can be prone to measurement bias. The timing and method of assessments can vary, and the extent of missing data can be high. Statistical analyses will be adjusted for baseline characteristics known to influence outcome measures, while care will be taken to handle missing data in the most appropriate way.

9.9 Ethical issues

The protocol, site-specific informed consent forms (local language and English versions, and other requested documents and any subsequent amendments will be reviewed and approved by the appropriate ethical review bodies for each participating site.

All patient data will handled in accordance with the terms of the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679).

9.10 Other aspects

None.

10 Protection of human subjects

The study will be conducted in accordance with the protocol and the ethical principles defined in the Declaration of Helsinki, the ICH GCP Guidelines (ICH-E6) and all other applicable legislation.

Written approval for the study must be obtained from an independent and appropriately constituted Independent Ethics Committee (IEC) at the facility where the study is due to be performed, prior to the enrolment of any study subjects at that site. The Sponsor and the Investigator will submit all of the documents as required by the IEC. A copy of the IEC approval letter must be provided to the sponsor before initiation of the study. Any amendments to the protocol must be submitted to the IEC for approval prior to implementation and the IEC must also be notified of any administrative changes.

Prior to the initiation of the study at a specific site, the sponsor will obtain written approval to conduct the study from the appropriate regulatory authority in accordance with all local regulatory requirements.

Before entering the study, the investigator (or authorised deputy) will explain the nature and purpose of the study to the subject and each subject will be given a copy of the written study information leaflet. Subjects will then be given the opportunity to ask questions. They will be told that they can withdraw from participation in the study at any time without prejudice. If the subject is happy to participate they (or their legal representative) will be asked to voluntarily sign and date the Informed Consent Form (ICF). Subjects will be given a copy of the signed ICF and all written information for future reference. The written information provided to the subjects and the ICF will be submitted to the IEC for approval prior to the start of the study.

11 Management and reporting of adverse events /adverse reactions

11.1 Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence in a patient administered a medical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of this medicinal product.

An **Adverse Drug Reaction (ADR)** concerns noxious and unintended responses to a medicinal product. A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the medical product and the adverse event is at least a reasonable possibility.

Serious AE/ADR (SAE/SADR):

Preamble: “Serious” and “Severe” are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious”, which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death of the patient.
- Is life-threatening: this refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalisation: an event/reaction that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
- Results in prolongation of existing hospitalisation: an event/reaction that occurs while the study patient is hospitalised and prolongs the patient's hospital stay.
- Is a congenital anomaly/birth defect: an anomaly detected at or after birth, or any anomaly that results in foetal loss.
- Results in persistent or significant disability/incapacity: an event/reaction that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle).
- Is a medically important event or reaction: an important medical event/reaction that may not be immediately life-threatening or result in death or hospitalisation, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e. death of patient, life-threatening, hospitalisation, prolongation of hospitalisation, congenital anomaly/birth defect, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious ADR.

Spontaneous reports: unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Solicited reports: are those derived from organized data collection systems, which includes clinical trial, registries, post-approval named patient use programs, other patient support and disease management programs, survey of patients or healthcare providers or information gathering on efficacy or patient compliance.

11.2 Causality assessment

The HCP will use the following definitions for any adverse event being collected in the study and for all serious adverse events, to assess the relationship of the adverse event to the use of CDCA:

- **Related**: There is a “reasonable possibility” that the AE is related to the study drug. An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another aetiology is unlikely or significantly less likely or a more likely alternative aetiology does not exists.
- **Not related**: There is “not reasonable possibility” that the AE is related to the study drug. An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative aetiology), or an adverse event has little or no temporal relationship to the study drug and/or a more likely alternative aetiology exists.

11.3 Reporting of AEs

11.3.1 Adverse Event reporting: from Investigator to Sponsor

Any information regarding AEs will be recorded by the Investigator in the study CRF.

Non-Serious AE/ADR reporting

All AEs (potentially related or not-related to CDCA) will be recorded in the CRF by the Investigator. The Investigator will be asked to determine the causality to CDCA when adding the AE to the CRF.

Serious AE/ADR reporting

In case of serious AEs (SAEs) the Investigator will register the SAE data in the CRF but will also fill in the SAE form provided, to be transmitted within 24 hours of the Investigator becoming aware of the event to:

Pharmacovigilance (PV) dedicated mailbox:

safety@leadiantbiosciences.com

Or to

Fax: +44 (0)1753 860 328

Vaibhav Gaikwad is available 24 hours/day, 7 days/week for any pharmacovigilance related enquiries via the Safety Phone:

Safety phone number: +44 7387418152

Detailed instructions on the procedure to be followed in reporting Adverse Events are reported in the Study-specific Safety Management Plan.

11.3.2 Adverse Event reporting: from Sponsor to Competent Authorities

For regulatory reporting purposes on post-approval safety data, only ADRs have to be reported to Competent Authorities of the Countries where the study is conducted.

For this reason the Investigator should provide his/her causality assessment possibly at the time of reporting the AE, but in any case as soon as possible.

If an AE is collected in the study CRF (“solicited report”) and either the Investigator or the Sponsor, or both, consider the AE related to the study drug, it meets the definition of an ADR and must be submitted to the concerned Competent Authorities by the MAH.

It may happen that an ADR concerning CDCA , is spontaneously reported (“unsolicited report”) by a patient participating to the study, to the MAH (Leadiant); in this case even if the relationship is unknown or unstated, it meets the definition of an ADR and must be submitted to the concerned Competent Authorities by the MAH.

The clock for the submission of an ADR report from the study, starts as soon as the information has been brought by the Investigator and/or a patient, to the attention of the Sponsor or its representative. It is the first day when the Sponsor or marketing authorisation holder gets knowledge of a valid AE report, irrespective of whether the information is received during a weekend or public holiday. The timelines for submission are based on calendar days.

In order to monitor the safety of the study, a report containing all ADRs will be run from the EDC system every three months and supplied to Leadiant Biosciences Ltd.

The AEs will be reviewed in order to identify eventual safety reports to be submitted to Competent Authorities. For the reports identified during these checks the date of the EDC report should be considered as “day zero” for the ADR reports identified.

Leadiant Biosciences Ltd will notify ADRs to the Competent Authorities through EudraVigilance Post-authorisation Module (EVPM) in the following timelines:

- **Serious** adverse reactions related to CDCA: within **15 calendar days** from day zero.
- **Non-serious** adverse reactions related to CDCA: within **90 calendar days** from day zero.

11.3.3 Adverse Event reporting: from Investigator to Competent Authorities

It will be the Investigator’s responsibility to report any suspected adverse reaction related to products other than CDCA, to the respective marketing authorization holder and/or to the regulatory authorities as per local regulatory requirements.

11.4 Pregnancy reporting

Any pregnancy where the foetus may have been exposed to CDCA through maternal exposure should be notified by the Investigator to Leadiant Biosciences Ltd, by filling in the provided “In-utero exposure Form” and sending it, within 24 hours of its knowledge, to:

PV dedicated mailbox: safety@leadiantbiosciences.com

Or to

Fax: +44 (0)1753 860 328

Outcome of the pregnancy (normal or abnormal) should be followed up and recorded.

Abnormal pregnancy outcome in association with CDCA should be notified on an expedited basis (i.e. within 24 hours of the Investigator becoming aware of the abnormal pregnancy outcome) using the SAE form (see 11.3.1). This refers especially to congenital anomalies in the foetus/child, foetal death and spontaneous abortion, and adverse reactions in the neonate that are classified as serious.

Pregnancy will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils SAE criteria.

12 Plans for disseminating and communicating study results

The results of the study will be presented in a clinical study report based on the final statistical analysis and clinical outcomes. The clinical study report will be written by CROS NT, Beechwood, Grove Park, White Waltham, Maidenhead, SL6 3LW, UK and approved by the sponsor.

The final clinical study report will be submitted to the EMA and the results disseminated via publication(s) in the scientific literature.

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Annex 1: List of stand-alone documents

None

Annex 2: Declaration of Helsinki (October 2013)

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Annex 3: ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Cerebrotendinous Xanthomatosis Registry: Long term Non-Interventional Follow-up of Safety and Effectiveness of Chenodeoxycholic Acid Leadiant.

Study reference number:
2017_LBL_NIS_01

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☐	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Due to the exploratory nature of the study formal hypotheses aren't stated.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.3
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.6.2
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.1
4.2.2 Age and sex?	☒	☐	☐	9.1
4.2.3 Country of origin?	☒	☐	☐	9.1
4.2.4 Disease/indication?	☒	☐	☐	9.1
4.2.5 Duration of follow-up?	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g.	☒	☐	☐	9.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
event or inclusion/exclusion criteria)				

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Treatment discontinuations and interruptions will be collected but dosing information will be limited due to the observational nature of the study.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☒	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Current monitoring and follow-up of CTX patients is highly variable between study centres. Agreement on the definition and measurement of the study outcomes will be agreed by the Scientific Committee.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.8
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.8
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Analyses will be adjusted for baseline covariates, these covariates will be decided following the Scientific Committee.

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

This will be addressed in the SAP following the Scientific Committee.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.2
9.1.3 Covariates?	☒	☐	☐	9.6.2.2
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☒	☐	
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.5
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.6.2
10.2 Are descriptive analyses included?	☒	☐	☐	9.6.2
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.6.2
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.4

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.7

Comments:

Data Management information will be included in a separate Data Management Plan.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	9.8
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.9
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.3 Have data protection requirements been described?	☒	☐	☐	9.9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _Corinne Hedgley_____

Date: 14/11/2017

Signature: