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Protocol Registration and Results System

ID: 20159460 Denosumab for the Treatment of Adult LCH NCT03270020

Protocol Registration Preview

This is a rough approximation of how the Protocol Registration will appear on the ClinicalTrials.gov public web site.

Denosumab for the Treatment of Adult LCH

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03270020

Recruitment Status: Completed
First Posted: *
Last Update Posted: *

* Date not available in PRS

Sponsor:

Hellenic Society for the Study of Bone Metabolism

Information provided by (Responsible Party):

Hellenic Society for the Study of Bone Metabolism

Study Description

Brief Summary:

This study is aiming to evaluate the efficacy of denosumab among adult patients suffering from Langerhans Cell Histiocytosis (LCH).

Condition or disease	Intervention/treatment	Phase
Langerhans Cell Histiocytosis	Drug: Denosumab 70 MG/ML [Xgeva]	Phase 2

Detailed Description:

The majority and diversity of clinical manifestations in LCH are attributed to immunological dysfunction resulting from langerhans cell (LC) derived cytokine secretion both at the lesional and systemic level. In a recent study, Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) was found to be abundantly expressed in cells within diverse LCH lesions from adult patients, especially in inflammatory infiltrates, a finding in line with a previously reported high osteoprotegerin (OPG) and low RANKL levels in the serum of patients with or without bone involvement. RANKL expression was associated with concomitant p65 Nuclear Factor Kappa-B (NFκB) nuclear staining, the main downstream effector of RANKL signaling, suggesting that lesional cell activation may be triggered locally by RANKL. Combining the serum and the lesional results, it can be inferred that there is an ongoing process of countervailing OPG production against lesional RANKL, which could be one of the self defense mechanisms among LCH patients. Therefore, the use of denosumab seems a rational treatment option in LCH in order to support and enhance the defensive OPG action and hopefully control or even interrupt the lesional immunological process.

The primary study objective is to assess the therapeutic efficacy of denosumab 120 mg every 8 weeks (Q8W) sc in adult LCH patients.

Secondary Objectives:

1. To define an uniform treatment approach for LCH patients with mild symptoms and low risk disease.
2. To explore the efficacy of denosumab 120 mg Q8W sc in reducing disease reactivations after treatment completion.
3. To illustrate the safety profile of denosumab in LCH patients. The primary efficacy endpoint is defined as the percentage of patients with progression of disease at Month 8.

Study Design

Study Type:	Interventional
Actual Enrollment:	10 participants
Allocation:	N/A
Intervention Model:	Single Group Assignment
	The investigational arm will recruit patients who will receive denosumab 120mg sc every 2 months. The estimated duration of the recruitment period is 12 months.
	The treatment period would be 6 months (denosumab administration on months: 0, 2, 4, 6) and the follow-up period would be 12 months.
Masking:	None (Open Label)
Primary Purpose:	Treatment

Official Title:	Evaluation of Efficacy of Denosumab in Adult Patients With Langerhans Cell Histiocytosis (LCH): a Multiple-site, Single Arm, Open Label Clinical Trial
Actual Study Start Date:	September 7, 2017
Actual Primary Completion Date:	June 22, 2022
Actual Study Completion Date:	January 14, 2025

Arms and Interventions

Arm	Intervention/treatment
Experimental: Treatment arm This is a single arm study; the study arm include all patients participating in the study who will all receive Denosumab 70 MG/ML [Xgeva]	Drug: Denosumab 70 MG/ML [Xgeva] As already described in arm description Other Names: • Xgeva

Outcome Measures

Primary Outcome Measure:

1. Primary efficacy endpoint: effect of denosumab treatment on the activity status of the disease (Incidence of patients with active disease) [Time Frame: 8 months]

   The primary efficacy endpoint will be measured through the incidence of patients with active disease at Month 8. Given that all patients have active disease at baseline the incidence of patients with active disease at Month 8 will provide the efficacy of denosumab in controlling the disease within this time frame.

Secondary Outcome Measures:

1. Secondary efficacy endpoint: development of disease-related permanent sequelae during the study period (Incidence of disease-related permanent sequelae) [Time Frame: 18 months]

   Incidence of disease-related permanent sequelae, developed during the study, at month 18. In specific, permanent sequelae such as diabetes insipidus, anterior pituitary deficiencies, and pulmonary failure will be assessed at the end of the study in order to evaluate the efficacy of denosumab in preventing those conditions.

Other Pre-specified Outcome Measures:

1. Safety endpoints: Incidence of all Adverse Events during the trial [Time Frame: 18 months]

   Incidence of Adverse Events during the trial. In specific, all adverse events will be assessed at the end of the study period in order to evaluate the safety issues of denosumab treatment in LCH.

2. Safety endpoint: Incidence of all adverse events on bone metabolism following Denosumab treatment and its withdrawal [Time Frame: 30 months]

   Assess the effects of treatment and its withdrawal on bone metabolism, in particular the presence or not of rebound of bone turnover following discontinuation of Denosumab

Eligibility Criteria

Ages Eligible for Study:	18 Years and older
Sexes Eligible for Study:	All
Gender Based:	No
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Adults (>18 years of age)
- Definitive diagnosis of LCH [Based on clinic-pathological evidence with microscopic examination and at least one of the following immunological staining: Langerin (CD 207) positivity, Cluster of Differentiation 1a (CD1a) positivity, Presence of Birbeck granules on electronic microscopy]
- Mild symptoms (symptoms of low intensity; no need for hospitalization) and low risk disease needing first line systemic therapy for LCH because of:
  - single system disease with multifocal lesions, or
  - single system disease with "special site" lesions (vertebral lesions with intraspinal extension, craniofacial bone lesions with soft tissue extension), or
  - multi-system disease without involvement of risk organs [hematopoietic system, spleen, liver, tumorous central nervous system (CNS)].
- Have signed the informed consent form (consent should be taken before any study-specific procedure is performed).
- A patient should undergo a PET-CT imaging test, in order for him to be deemed suitable for the study. The initial PET-CT either may have been carried out, within 3 months prior to visit 1, regardless of the diagnostic center or the type of the device, which has been used for, or may take place in the context of visit 2, at the diagnostic center(s) specialized on Nuclear Medicine, which have been partnered with the Sponsor. Whichever is the case, the initial PET-CT report should be legible and accurate, so that to be assessed by the qualified physician, responsible for the PET-CT test at the partnered diagnostic center(s).

Exclusion Criteria:

- Symptomatic multi system LCH - no risk organs involved.
- Multi-system LCH (with or without symptoms) - risk organs involved.
- Isolated pulmonary LCH disease
- Previous administration of denosumab from clinical trials or other use (e.g. commercial use).
- Current participation in another clinical trial or having received any investigational product within the last 3 months.

- Impaired renal function as determined by an estimated glomerular filtration rate (eGFR) of ≤ 30 mL/min/1,73m2 [using the Chronic Kidney Disease-Epidemiology, (CKD-EPI) formula].
- Patients that have received oral bisphosphonates within 6 months of study enrollment or intravenous bisphosphonates, fluoride and strontium ranelate within 1 year of study enrollment.
- Treatment with immune suppressive agents within 4 weeks from baseline evaluation.
- Patients with severe impairment of clinical condition including: severely impaired pulmonary function [for example total lung capacity (TLC)<60%, forced expiratory volume 1 (FEV1)<30%, diffusing capacity of the lungs for carbon monoxide (DLCO) <30%, partial pressure of oxygen (PaO2)<55 mmHg), long term oxygen therapy or cor pulmonale.
- Known to have a liver failure or chronic hepatic disease e.g. cirrhosis, chronic hepatitis; or elevated transaminases defined as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 fold the upper limit of normal laboratory range.
- Heart failure [New York Heart Association (NYHA) Functional Classification above 2].
- Patients with life expectancy of less than one year.
- Female subjects of childbearing potential who refuse to use a reliable contraceptive method throughout the study, defined as use of 2 highly effective forms of contraception and continuation of use for 7 months after last administration of study drug. Birth control methods that can achieve a failure rate of less than 1% per year, when used consistently and correctly, are considered as highly effective.
- Pregnancy, planning a pregnancy or currently lactating
- Severe concurrent illness which in the investigator's opinion may confound patient evaluation, e.g. malignancy (except basal cell carcinoma, cervical or breast ductal carcinoma in situ) within the last 5 years.
- Known alcohol or drug abuse.
- Parathyroid hormone (PTH), PTH derivatives, teriparatide, odanacatib, anabolic steroids, testosterone, glucocorticosteroids (> 5 mg/day of prednisone equivalent for > 10 days), systemic hormone-replacement therapy, selective estrogen receptor modulators (SERMs), raloxifene, tibolone, calcitonin use within the last 6 weeks.
- Evidence of hyper- or hypothyroidism; patients with an abnormal thyroid stimulate hormone (TSH) level on thyroid treatment (patients on stable thyroid treatment with a normal TSH allowed); current hyper- or hypoparathyroidism; current hyper or hypocalcemia (hypercalcemia based on albumin adjusted serum calcium > 10.40 mg/dL; hypocalcemia based on albumin adjusted serum calcium < 8.5 mg/dL); vitamin D deficiency (25-hydroxy vitamin D level < 20 ng/mL; if the resulted value of the retest is 20 ≥ ng/Ml, after repletion with 50,000 - 100,000 IU of cholecalciferol, subject will be allowed. The retest should be carried out within 30 days post to visit 1(screening)); rheumatoid arthritis; Paget's disease; any known bone disease with osteolytic and/or osteoblastic lesions that would interfere with interpretation of findings.
- Known sensitivity to mammalian cells, denosumab or any components of denosumab 120mg, or any of the products to be administered during the study (e.g., calcium or vitamin D).
- History of any Solid Organ or Bone Marrow Transplant.
- History of osteonecrosis of the jaw, and/or recent tooth extraction or other dental surgery; or planned invasive dental work during the study.
- Intolerance to calcium supplements.
- Malabsorption syndrome; severe malabsorption including Celiac disease, Short Bowel Syndrome, Crohn's disease, Previous Gastric Bypass.

Contacts and Locations

Locations

Greece

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Investigators

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More Information

Publications:

Makras P, Tsoli M, Anastasilakis AD, Thanou M, Kaltsas G. Denosumab for the treatment of adult multisystem Langerhans cell histiocytosis. Metabolism. 2017 Apr;69:107-111. doi: 10.1016/j.metabol.2017.01.004. Epub 2017 Jan 12.

Makras P, Salagianni M, Revelos K, Anastasilakis AD, Schini M, Tsoli M, Kaltsas G, Andreakos E. Rationale for the application of RANKL inhibition in the treatment of Langerhans cell histiocytosis. J Clin Endocrinol Metab. 2015 Feb;100(2):E282-6. doi: 10.1210/jc.2014-2654. Epub 2014 Nov 6.

Makras P, Polyzos SA, Anastasilakis AD, Terpos E, Kanakis G, Schini M, Papatheodorou A, Kaltsas GA. Serum osteoprotegerin, RANKL, and Dkk-1 levels in adults with Langerhans cell histiocytosis. J Clin Endocrinol Metab. 2012 Apr;97(4):E618-21. doi: 10.1210/jc.2011-2962. Epub 2012 Jan 25.

Girschikofsky M, Arico M, Castillo D, Chu A, Doberauer C, Fichter J, Haroche J, Kaltsas GA, Makras P, Marzano AV, de Menthon M, Micke O, Passoni E, Seegenschmiedt HM, Tazi A, McClain KL. Management of adult patients with Langerhans cell histiocytosis: recommendations from an expert panel on behalf of Euro-Histio-Net. Orphanet J Rare Dis. 2013 May 14;8:72. doi: 10.1186/1750-1172-8-72.

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Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Human Subjects Protection Review Board Status: Approved

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No