A Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of IgPro20 (Subcutaneous Immunoglobulin, Hizentra®) in Adults with Dermatomyositis (DM) - The RECLAIIM Study

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Musculoskeletal and connective tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON55228

Source
ToetsingOnline

Brief title
IgPro20_3007 (2102/0079); Immunoglobulin research with dermatomyositis

Condition

- Musculoskeletal and connective tissue disorders NEC
- Epidermal and dermal conditions

Synonym
dermatomyositis, muscle disease

Research involving
Human

Sponsors and support

Primary sponsor: CSL Behring LLC
Source(s) of monetary or material Support: By the study sponsor CSL Behring

Intervention

Keyword: dermatomyositis, immunoglobulin

Outcome measures

Primary outcome

The primary endpoint is the responder status based on the total Improvement

Score (TIS) assessments at Weeks 17, 21, and 25.

Secondary outcome

Key secondary endpoints of the study are:

* TIS at Week 25

* Change from Baseline in Manual Muscle Testing (MMT-8) at Week 25

* Change from Baseline in Cutaneous Dermatomyositis Disease Area and Severity

Index (CDASI) total activity score at Week 25

* Reduction of oral corticosteroid dose at Week 25

Study description

Background summary

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of acquired muscle disorders characterized by muscle weakness, elevated creatine kinase (CK) levels, myopathic electromyographic findings, characteristic histopathological findings, and in certain cases, an association with autoantibodies. IIM are best classified into 4 main subtypes: dermatomyositis (DM), polymyositis (PM), necrotizing myopathy, and inclusion body myositis. The

identification of the correct subtype and the distinction of these diseases from other disorders which have characteristics that mimic them is fundamental to treatment, because each subtype has a different prognosis and response to therapies.
Incidence and prevalence of DM varies greatly across studies. In a nationwide patient register and rheumatology quality register, the average incidence was 11 per 1,000,000 (13 for women and 9.7 for men) while prevalence rate was 14 per 100,000 (17 for women and 11 for men). Both incidence and prevalence rates increased with age with a peak in the 70-79 year range.
Diagnosis of DM is achieved by the evaluation of a combination of clinical and pathological features. Dermatomyositis, with its characteristic skin rash and relatively greater responsiveness to corticosteroids and other immunomodulators than the other IIM subgroups, is quite distinguishable and carries significant morbidity and mortality. If left untreated, muscle weakness leads to ambulation difficulties (restriction to wheel chair or confinement to bed). Within the patients with DM, a subgroup of patients with amyopathic / hypomyopathic DM has been identified. These patients present with characteristic rash but without obvious muscle weakness or elevations in muscle enzyme. This DM subgroup represents about 20% of all DM cases. These patients are at increased risk of breast, lung, and ovarian cancer and may also have systemic involvement such as interstitial lung disease and cardiac disease.
Primary treatment modalities include corticosteroids, intravenous immunoglobulin G (IVIG), plasmapheresis, and other immunomodulators (such as methotrexate, azathioprine, and cyclosporin A). In clinical practice, corticosteroids are usually the first choice medication in DM; however, long-term treatment with corticosteroids has significant side effects and is not well tolerated in patients. One study estimated the 10-year survival rate of 160 DM / PM patients treated with immunomodulators such as corticosteroids, methotrexate, and azathioprine to be 62%, highlighting the continued unmet need in this disease.
The trigger that initiates DM or other IIM subtypes or causes flares is not clearly understood. However, it is known that environmental factors in genetically susceptible individuals can trigger myositis with involvement of several cellular and humoral mechanisms. In DM, inflammatory cells (predominantly CD4+ cells) and perifascicular atrophy, in addition to immune attacks targeting capillaries leading to capillary loss and subsequent ischemia are observed. More recently, the importance of B lymphocytes, macrophages, and dendritic cells and CD4+ CD25+ T-regulatory cells have been described as having a different role and weight in DM versus PM (where inflammatory cells [predominantly CD8+ cells] are noted in the perimysium and in perivascular areas).
Because of the heterogeneity of IIM as mentioned above, and the possibility of different clinical outcome among subtypes, this study will enroll only subjects with DM, including (clinically) amyopathic DM and adults first diagnosed with DM as juveniles (< 18 years old), to evaluate the safety and efficacy of IgPro20.

Study objective

The primary objective of this study is to assess the efficacy of IgPro20 0.5 g/kg weekly subcutaneous (SC) doses in comparison to placebo in adult subjects with DM, as measured by responder status based on the Total Improvement Score (TIS) assessments at Weeks 17, 21, and 25.

The secondary objectives of the study are:
• To assess the efficacy, with additional clinical outcome measures, of IgPro20 in comparison to placebo
• To assess the safety of IgPro20 in comparison to placebo
• To assess the safety and efficacy of IgPro20 at Week 53
• To assess the safety of IgPro20 after Week 53 to end of study participation

Study design

This is a phase 3, multicenter, randomized, placebocontrolled, double-blind study of IgPro20 (subcutaneous immunoglobulin G [SCIG]) treatment in adult subjects with dermatomyositis (DM) with or without muscle weakness.

After screening, subjects will be randomized 1:1 to 1 of 2 treatment sequences:
Sequence A: 0.5 g/kg IgPro20 for 24 weeks (study period 1) followed by 0.5 g/kgIgPro20 for 28 weeks (study period 2)
OR
Sequence B: placebo for 24 weeks (study period 1) followed by 0.5 g/kg IgPro20 for 28 weeks (study period 2).

Subjects with demonstrated treatment benefit at the End of Period 2 (EOP2) (Total Improvement Score [TIS] >= 20 points at Week 49) will be eligible to continue long term treatment with IgPro20 for up to 3 years in Study Period 3.

Intervention

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All IgPro20 will be administered by SC infusions as weekly doses.
The total dose / volume of IgPro20 will be calculated on the basis of the body

weight.

Study burden and risks

Please refer to section 6. 'Possible side effects and discomforts' in the subject information sheet for an overview of the risks and side effects.

Contacts

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CSL Behring LLC

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Capable of providing written informed consent by signing an informed consent form and willing and able to adhere to all protocol requirements
• Age >= 18 years

• Diagnosis of at least probable idiopathic inflammatory myopathies per European League
Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria: minimum aggregate score of 5.5 without and 6.7 with muscle biopsy (historical muscle biopsy is acceptable) which includes confirmation of DM rash / skin manifestation (present or by history [historical skin biopsy is required for amyopathic DM subjects])
• Disease activity defined by:
• Presence of DM rash / skin manifestation (eg, Gottron's papules / sign, heliotrope rash, periorbital edema, V sign, Shawl sign) at Screening Visit OR
• One objective disease activity measure within 3 months before Baseline:
o Magnetic resonance imaging showing active inflammation (edema) of a proximal skeletal muscle - OR -
o Electromyogram showing acute changes such as spontaneous activity not explained by other disease - OR -
o Muscle biopsy with perivascular or perimysial inflammation - OR -
o CK > 4 x upper limit of normal (ULN)
• Disease severity defined by a minimum value of 2 cm on a 10 cm Physician Global Disease Activity Visual Analog Scale and:
o MMT-8 <= 142 OR
o CDASI total activity score >= 14
• Subject has failed other DM treatment or is on DM treatment such as immunosuppressants and/or antimalarials on a stable dose >= 3 months before Baseline; and/or oral corticosteroids (<= 20 mg/day prednisolone equivalent and/or topical) on a stable dose >= 1 month before Baseline

Exclusion criteria

• Cancer-associated myositis, defined as the diagnosis of myositis within 2 years of the diagnosis of cancer
• Evidence of malignancies diagnosed within the previous 5 years. Note: Subjects with a history of carcinoma in situ of the cervix that has been excised and cured with >= 5 years since excision or subjects with documented history of treated basal or squamous cell skin cancer may be enrolled into the study..
• Physician Global Damage Assessment >= 3 on a 5-point Likert scale where a score of 3 represents severe damage
• Clinically relevant improvement between Screening Visit and Baseline, defined by >= 2 cm improvement on a 10 cm Physician Global Disease Activity Assessment Visual Analog Scale
• Known or suspected hypersensitivity or other severe reactions to IgPro20 or to any of its excipients, or other immunoglobulins (Igs)or severe reactions to blood products
• Other significant medical conditions that could increase the risk to the subject, eg:

o History of allogeneic bone marrow / stem cell transplant / solid organ transplant
o Cardiac insufficiency (New York Heart Association Class III or IV) or unstable ischemic heart disease
o Chronic kidney disease stage IV or V
o Recent surgery requiring general anesthesia within the previous 4 weeks before Screening
o Known hyperprolinemia type I or type II
o Documented thrombophilic abnormalities including blood hyperviscosity, protein C or protein S deficiency, anti-thrombin-III deficiency, plasminogen deficiency, antiphospholipid antibodies, Factor V Leiden mutation, dysfibrinogenemia, or prothrombin G20210A mutation
o History of documented thrombotic episode, eg, pulmonary embolism, deep vein thrombosis, myocardial infarction, or thromboembolic stroke at any time
o More than 3 of the following specified risk factors for thromboembolic events (documented and current conditions) occurring concurrently: atrial fibrillation, coronary disease, diabetes mellitus, dyslipidemia, hypertension, obesity (body mass index >= 30 kg/m2), recent significant trauma and immobility (wheelchairbound or bedridden)
o Uncontrolled, severe, or rapidly progressive interstitial lung disease which will prevent the subject from successful participation in the study
o Severe skin disease at planned infusion sites that would make subcutaneous (SC) infusions infeasible
o Medical conditions whose symptoms and effects could alter protein catabolism and or Immunoglobulin G (IgG) utilization (eg, protein-losing enteropathies, nephrotic syndrome, known Immunoglobulin A [IgA] deficiency with antibodies to Immunoglobulin A)
• Other conditions which would prevent correct assessment or lead to impaired muscle strength (eg, other neurological disorders including, but not limited to, Parkinson*s disease or severe musculoskeletal conditions like severe osteoarthritis or deformities)
• Laboratory exclusions at Screening:
o positive result for any of the following human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV)
o Creatinine > 1.5 × ULN or Blood Urea Nitrogen (BUN) > 3 × ULN
• Any of the following therapies:
o Within 1 month before Baseline: intramuscular, intravenous, or intra-articular corticosteroids including adrenocorticotropic hormone (any dose), doses > 20 mg/day prednisolone equivalent (any route), or any change to physiotherapy
o Within 2 months before Baseline: IgG (Note: subject may enroll < 2 months after stopping IgG therapy if clinical deterioration is experienced after withdrawal)
o Within 3 months before Baseline: plasma exchange or plasmapheresis
o Within 6 months before Baseline: Cyclophosphamide or alkylating agents
o Within 6 months or 5 half-lives of the drug, whichever is longer, before Baseline: other biologic therapies including investigational agents

o Within 9 months before Baseline: Rituximab or evidence of persistent B cell depletion after stopping therapy
• Male subject or female subject of childbearing potential either not using or not willing to use a medically reliable method of contraception (see protocol section 7.4.2), not sexually abstinent during the study, or not surgically sterile before study enrollment
• Pregnant or breastfeeding
• Alcohol, drug, or medication abuse within 1 year of providing informed consent
• Previously received investigational medicinal product (IMP) in this study or failed screening more than 1 time in this study
• Involved in the planning and/or conduct of the study (applies to CSLB staff, staff at the study site, and third-party vendors)
• Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study or unable to comply with study procedures, eg inability to self-administer IMP or by aid through a caregiver

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hizentra

Generic name:	immunoglobulin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-08-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003171-35-NL
ClinicalTrials.gov	NCT04044690
CCMO	NL69702.018.19

Study results

Date completed: 19-07-2023

Actual enrolment: 0

Summary results
Trial never started