A MULTICENTER, OPEN-LABEL STUDY TO ESTIMATE THE EFFECT SIZES OF HRCT ENDPOINTS IN RESPONSE TO GLUCOCORTICOID INDUCTION THERAPY IN SUBJECTS WITH PULMONARY SARCOIDOSIS

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Primary Objectives* To estimate the effect size, at 4 and 8 weeks, of change from baseline in high- resolution computed tomography (HRCT)-based measurements of lobar volumes at functional residual capacity (FRC) and total lung capacity (TLC) in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Observational invasive

Summary

ID

NL-OMON48613

Source
ToetsingOnline

Brief title
NDS-CP-001 (0451/0268) Celgene

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
known as granulomas that can affect how lungs work and breathing., sarcoidosis; growth and accumulation of cells of immune system (white blood cells) in lungs

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene cooperation

Intervention

Keyword: glucocorticoids (prednisone or prednisolone), high-resolution computed tomography (HRCT), Open-label, PULMONARY SARCOIDOSIS

Outcome measures

Primary outcome

Primary Endpoint: HRCT

Description:

* HRCT-based metrics of Sarcoid activity and progression, lobar volumes at TLC

and FRC, and airway wall volumes

Secondary outcome

Exploratory Endpoint: HRCT

Description:

* Lung volumes at FRC and TLC

* (specific) CFD- based Airway resistance at FRC and TLC

* (specific) Airway volume down to generation 8-10 at TLC

* (specific) Airway volume down to generation 4-5 at FRC

* Air Trapping at FRC

* Internal airflow distribution based on lobar expansion

* Emphysema score on lobar level

Exploratory Endpoints: Pulmonary Function Tests (PFTs)

Description:

* forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1),

diffusing capacity of lung for carbon monoxide (DLCO), total lung capacity

(TLC) and functional residual capacity (FRC), six-minute walk test (6MWT)

For other Exploratory Endpoints see protocol under Table 2: Study Endpoints

Study description

Background summary

Sarcoidosis is a multisystemic disorder characterized by the formation of granulomas. It affects people of all racial and ethnic groups and occurs at all ages, although it usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years. The lung parenchyma and the mediastinal lymph nodes are affected in > 90% of patients, often resulting in dyspnea, dry cough, and chest pain. Of the patients diagnosed with pulmonary sarcoidosis (PS), approximately 9% to 37% have concurrent skin involvement (cutaneous sarcoidosis [CS]) presenting as maculopapular lesions erupting on the face, trunk and/or the extremities. Although little is known about the causes of the pathologic inflammatory response seen in sarcoidosis, it is characterized by an accumulation of activated lymphocytes, predominantly expressing the helper T cell Type 1 (Th1) phenotype, as well as macrophages, resulting in the formation of granulomas. While it is generally accepted that T cell activation is required for the initiation of this process, granuloma formation involves other cell types, including macrophages, epithelioid cells, and multinucleated giant cells.
Macrophage colony stimulating factor (M-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) induce alveolar macrophage proliferation, differentiation, and multinucleated giant cell formation, which is integral to granuloma formation. The alveolar macrophage is a major source of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-*) in the lung, which are strongly linked to the pathogenesis of sarcoidosis. Additionally, there is clinical evidence that inhibition of TNF-* may be an effective treatment for sarcoidosis.
Although remission occurs within three years in more than 50% of patients diagnosed with sarcoidosis, approximately one-third of patients develop damage

in a number of organs. Patients with lung, heart, or brain involvement, or with lupus pernio, a sarcoidosis-related disfiguring skin condition that does not remit spontaneously, are at greater risk of less favorable outcomes. While sarcoidosis often responds to corticosteroids and other immunosuppressive or immuno- modulatory drugs, the latter are not curative and relapses frequently occur. Drugs used to date in current clinical practice include glucocorticoid, hydroxychloroquine, methotrexate, thalidomide, and infliximab. Nevertheless, the precise role of immunosuppressive drugs and anti-TNF agents in the treatment of sarcoidosis remains uncertain, and, with the exception of glucocorticoids, there are no products approved for sarcoidosis by the European Medicines Agency (EMA) or the Food and Drug Administration (FDA). Because of the chronic nature of the disease and the toxicities often associated with these drugs, there is an unmet medical need for more effective treatments.

The assessment of sarcoidosis has been significantly aided by recent imaging technology. Standard chest radiography is typically employed to evaluate and classify patients with suspected pulmonary sarcoidosis. High resolution computed tomography (HRCT) is superior to conventional chest radiography and can identify characteristic features of sarcoidosis. Certain HRCT features may also differentiate active inflammation from fibrosis which may help guide treatment. This study will investigate the ways that certain HRCT-based measures can serve.

Study objective

Primary Objectives
* To estimate the effect size, at 4 and 8 weeks, of change from baseline in high- resolution computed tomography (HRCT)-based measurements of lobar volumes at functional residual capacity (FRC) and total lung capacity (TLC) in response to glucocorticoid induction therapy (eg, prednisone or prednisolone) in subjects with pulmonary sarcoidosis.
* To estimate the effect size, at 4 and 8 weeks, of change from baseline in HRCT-based measurements of airway wall volume in response to glucocorticoid induction therapy in subjects with pulmonary sarcoidosis.

Exploratory Objectives
* To estimate the effect size, at 4 and 8 weeks, of change from baseline in total lung volumes, airway resistance, airway volume at FRC and TLC, air trapping at FRC, internal airflow distribution based on lobar expansion, and emphysema score in response to glucocorticoid induction therapy in subjects with pulmonary sarcoidosis, as measured by HRCT.
* To estimate the effect size, at 4 and 8 weeks, of change from baseline in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), diffusing capacity of lung for carbon monoxide (DLCO), the inhalation (TLC) and exhalation capacity (FRC), and six-minute walk test (6MWT) in response to glucocorticoid induction therapy in subjects with pulmonary sarcoidosis.
* To estimate changes, at 4 and 8 weeks, from baseline in pharmacodynamic (PD)

biomarkers in response to glucocorticoid induction therapy in subjects with pulmonary sarcoidosis.
* To estimate changes from baseline in patient-reported pulmonary endpoints using the St. George's Respiratory Questionnaire (SGRQ), baseline/transition dyspnea indices (BDI/TDI) and King*s Sarcoidosis Questionnaire in response to glucocorticoid induction therapy for 4 and 8 weeks in subjects with pulmonary sarcoidosis.
* To describe AE frequency and type in symptomatic pulmonary sarcoidosis patients receiving glucocorticoid treatment.

Study design

This is a multicenter, single-arm, unblinded/open-label study in subjects with a diagnosis of pulmonary sarcoidosis with dyspnea and evidence of disease on chest radiograph (Stage II or III) who are not receiving initial induction treatment for their disease.
This study will evaluate the effect of glucocorticoid therapy on functional respiratory imaging (FRI) parameters and also pulmonary function tests (PFTs) during treatment with glucocorticoid in patients with pulmonary sarcoidosis. The study follows a multiple dose design with 24 subjects receiving glucocorticoid (* 30 mg/day prednisone or prednisolone).

Length of Study
The estimated duration of the study from first-subject-first-visit (FSFV) to last-subject-last-visit (LSLV), is approximately 12 months.
The estimated duration of each subject*s participation in the study, from screening through the follow-up phone call is approximately 4 months.
The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Intervention

Geen onderzoeksmedicatie

Study burden and risks

This study evaluates the effect size in response to standard treatment, operational ease, and general suitability of high resolution computed tomography (HRCT)-based variables as endpoints. Certain HRCT features may also differentiate active inflammation from fibrosis which may help guide treatment. This study will investigate the ways that certain HRCT-based measures can serve.The standard treatment for sarcoidosis in the lungs is prednisone or prednisolone. There is always a risk when taking medication. However, the

subjects will be carefully monitored for any problems that may arise during the treatment.

Please refer to ICF for more details.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject are male or female * 18 and * 65 years of age, inclusive, at the time of signing the informed consent form (ICF)., 2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted., 3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements., 4. Subject has not received glucocorticoid as initial sarcoidosis therapy (* 20 mg/day prednisone or

prednisolone) or other sarcoidosis therapy for at least 3 months or 5 PK half-lives, whichever is longer, prior to enrollment., 5. Subjects have a diagnosis of pulmonary sarcoidosis:, a. According to the ATS/ERS/WASOG (Appendix J) statement, supported by clinical presentation and biopsy-proven noncaseating granulomatous inflammation with no alternative cause of the granulomas;, b. With radiographic stage II or III disease;, c. With dyspnea (MRC grade * 1);, d. With an FVC as follows - * 45% and * 80% of predicted normal value at screening (for at least 10 subjects) - * 45% and * 90% of predicted normal value at screening (for no more than 14 subjects);, e. With or without concurrent extra-pulmonary sarcoidosis;, f. Without clinically significant neurosarcoidosis or cardiac sarcoidosis;, g. Without history of resistance or refractoriness to glucocorticoid induction therapy., 6. Subject is in good health (except for sarcoidosis) as determined by a physical examination at screening., a. Stable and mild syndromes associated with normal ageing, that are not expected to affect safe participation or data interpretation are allowed. Examples include, but are not limited to, systemic hypertension, hypothyroidism, prostatic hypertrophy, etc., 7. Contraception Requirements: Must comply with the following acceptable forms of contraception. All FCBP1 must use one of the approved contraceptive options as described below while participating in the study and for at least 28 days after the last study visit., At the time of study entry, and at any time during the study when a FCBP*s contraceptive measures or ability to become pregnant changes, the Investigator will educate the subject regarding contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy. All FCBP must have a negative pregnancy test at screening, Baseline (Day 1/Visit 1), Visit 3 and Visit 5. All FCBP subjects who engage in activity in which conception is possible must use one of the approved contraceptive options described below:, Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner*s vasectomy; OR, Option 2: Male or female condom (latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]); PLUS one additional barrier(c) contraceptive sponge with spermicide. Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (latex or non-latex condoms NOT made out of natural [animal] membrane [for example, polyurethane]) while on the study and for at least 28 days after the last study visit., 8. Subject has body mass index (BMI) * 17 and * 40 kg/m2 at screening., 9. Subject has clinical laboratory safety test results that are within normal limits or acceptable to the Investigator. Platelet count, absolute neutrophil count, and absolute lymphocyte count must be above the lower limit of normal at screening., 10. Subject is afebrile, with supine systolic blood pressure (BP) * 90 and * 150 mmHg, supine diastolic BP * 50 and * 90 mmHg, and pulse rate * 40 and * 110 bpm at screening., 11. Subject has a normal or clinically acceptable 12-lead ECG at screening.

Exclusion criteria

1. Subject has any significant medical condition, laboratory abnormality, neurological disease or psychiatric illness that would prevent the subject from safely completing the study. Prior evidence of neurological disease must be documented., 2. Subject has any condition that confounds the ability to interpret data from the study., 3. Subject is a pregnant or a nursing female., 4. Subject has received another interventional investigational drug for sarcoidosis within the 3 months prior to screening or 5 PK half-lives, whichever is longer*., 5. Subject has clinically significant lung disease, other than sarcoidosis, such as asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) or lung cancer., a. Subject has a history of significant (greater than a wedge) lung resection., 6. Subject is receiving therapy for sarcoidosis associated pulmonary hypertension, or has an indication for such therapy., 7. Subject has uncontrolled diabetes and/or other contraindications to glucocorticoid therapy., 8. Subject has a history of listeriosis, coccidioidomycosis, histoplasmosis, blastomycosis, treated or untreated tuberculosis or exposure to individuals with tuberculosis., 9. Subject is an active smoker or has > 10 pack-year smoking history. Previous smokers must have discontinued smoking for at least 1 year., 10. Subject is unable to perform any study-related procedure or maneuver., 11. Subject has had any biologic anti-tumor necrosis factor (anti-TNF) therapy within the previous year., 12. Subject has active infection requiring treatment within 30 days prior to screening*., 13. Subject has a positive QuantiFERON-TB Gold tuberculosis test., a. In case of an indeterminate result, the test may be repeated once. The repeat result must be negative to permit entry into the study., 14. Subject has active fungal infection (other than candidiasis of the urinary tract*) or active infection with hepatitis B or hepatitis C or a history of either HCV infection or chronic HBV infection., 15. Subject has a history of congenital and/or acquired immunodeficiencies (eg, common variable immunodeficiency, HIV, etc.)., 16. Subject has aspartate transaminase (AST), alanine aminotransferase (ALT) or total bilirubin > 2 x the upper limit of normal at screening (unless the increase is considered to be due to sarcoidosis by the Investigator and/or Sponsor*s medical monitor)., 17. Subject has a serum creatinine level > 1.8 mg/dL (> 159.12 *mol/L), 18. Subject has clinically significant organic heart disease (eg, congestive heart failure), myocardial infarction requiring initiation or change in medical treatment within six months prior to screening., 19. Subject has QTcF of > 450 milliseconds or findings on electrocardiogram (ECG) at screening (eg, an arrhythmia, heart block, etc.) that suggest either significant cardiac sarcoidosis or significant risk of cardiac adverse event over the duration of this study., 20. Subject has a history of malignancy within 5 years (except basal cell carcinoma of the skin that is surgically cured, remote history of cancer now considered cured or positive pap smear with subsequent negative follow-up)., 21. Subject is expecting to have elective surgery in the time interval between screening and 10 weeks after the last study visit if the

surgery would be expected to confound evaluation of study endpoints or AE assessment., *Candidate subjects having these conditions may be re-evaluated upon resolution and entered into the study if all other criteria are met.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-10-2018
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	20-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
CCMO	NL63613.078.18
Other	SF NIHR CRN reference: RESP 35694