A randomized, double-blind, placebo-controlled, multicentre proof-of-concept trial of IVA337 in the treatment of diffuse cutaneous systemic sclerosis

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Connective tissue disorders (excl congenital)
Study type	Interventional

Summary

ID

NL-OMON45927

Source
ToetsingOnline

Brief title
IVA337 SSC POC

Condition

- Connective tissue disorders (excl congenital)
- Epidermal and dermal conditions

Synonym
Scleroderma, Systemic Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Inventiva SA
Source(s) of monetary or material Support: Inventiva SA;30 Rue de Dijon;21121 Daix;France

Intervention

Keyword: dcSSc, diffuse cutaneous systemic sclerosis, IVA337, scleroderma

Outcome measures

Primary outcome

Primary outcome is the mean change of the MRSS from baseline to week 48

Secondary outcome

At the time points specified in the Schedule of Study Procedures:

EFFICACY

• MRSS response rates; improvers are defined by a reduction >=5 points and >=25 % of MRSS

• Overall progression of the disease: defined as absence of rescue therapy and absence of severe organ involvement (see definition below)

• Change in pulmonary function (FVC% predicted and cDLCO% predicted)

• Changes in patient reported outcomes (SHAQ, UCLA SCTC GIT, PROMIS29, SF36)

• Digital ulcer net burden (defined as total number of ulcers at a certain time point minus number of ulcers at baseline) and proportion of patients who do not develop new ulcers

• Cochin Hand Function Scale

• Physician and patient global assessments of disease activity over the past week (VAS)

• Change in the Combined Response Index for Systemic Sclerosis (CRISS), consisting of five variables: MRSS, FVC % predicted, physician and patient global assessments, and HAQ-DI score (from SHAQ patient reported outcome)

• Need for escape therapy (% patients)

• Severe organ involvement (% patients) defined by

• new renal crisis OR

• new or worsened clinically symptomatic and significant heart disease, considered secondary to DcSSc OR

• Relative decline in FVC % predicted by >= 10% or relative decline in FVC % predicted between 5 to < 10% with associated relative decline in DLCO % predicted by >= 15%, provided that the decline in FVC results in FVC <75% of predicted OR

• New or worsening of gastrointestinal disease requiring hospitalization or new requirement for parenteral nutrition OR

• Critical ischaemia of the extremities promoting necrosis and/or gangrene OR

• New development of pulmonary hypertension associated with pulmonary fibrosis - defined by a mean pulmonary arterial pressure of 25 mmHg or more at right heart catheterization

SAFETY

• Frequency and type of AEs

• Lab tests: mean change and frequency of values outside the normal range

OTHER

• Changes in Raynaud phenomenon (Raynaud*s condition score)

• Mean changes in activity biomarkers

• Population pharmacokinetics

• Follow-up: There is a follow-up visit to evaluate any changes that might

occur within 4 weeks after completion of the treatment. The performed

assessments listed in the Schedule of Study Procedures refer to safety.

• Evaluate the changes of Ssc activity index.

Study description

Background summary

Systemic sclerosis (SSc), or scleroderma is a connective tissue disease of autoimmune origin. It is a life-threatening orphan disease with severe physical and psychosocial consequences. There is currently no cure for this debilitating disease.
IVA337 has strong potential for becoming a breakthrough therapeutic option for SSc patients. IVA337 has been shown in several preclinical models of fibrotic disorders that it can prevent the development of skin fibrosis and reverse established skin fibrosis in curative settings

Study objective

The primary objective of this study is to evaluate in patients suffering from diffuse cutaneous SSc (DcSSc) the effect of 800mg and 1200mg IVA337 daily on the skin compared to placebo. The modified Rodnan Skin Score (MRSS) will be used to determine the changes in skin.
Secondary objectives include additional efficacy evaluations (details in the protocol), assessment of adverse events (AEs), and determination of population PK parameters of IVA337 in patients.

Study design

Randomized, double-blind, placebo-controlled, multicentre proof-of-concept trial of IVA337 in the treatment of early DcSSc.

Intervention

Patients take 6 capsules per day (3 capsules twice daily with food) and thus receive either 800 mg or 1200 mg IVA337 or placebo, the control intervention.

Study burden and risks

The flow chart of the study is described on page 12 of the Protocol. The duration of the study is as follows: screening period of 1 to 4 weeks prior to the administration of medication; treatment period of 60 weeks. A total of 15 visits are performed. The screeningvisit may take more than 2 hours, but thereafter each visit will not take more than 1 hour. If optional PK blood samples are taken then it is possible that the patient is admitted to the hospital. This differs per center. The patient will otherwise stay in the hospital during the day.
Bloodsamples for safety analysis are taken during 11 visits. In addition, during 4 visits blood samples will be collected for biomarker analysis. Optional pharmacokinetics samples are taken during 2 visits. Physical examination will take place during each visit, a total of 15 times. The patient will also be asked whether he wants to undergo a skinbiopsy during visit 1 and 14. The biopsy takes place on the forearm and is voluntary.
At visit 1, 8, 14 and 15 patients are requested to answer questionnaires. The patient could perceive these as confrontational. The questionnaires are : SHAQ, PROMIS29, GIT and SF36. On visit 0, 4 and 8, the patient is asked to write down the symptoms of Raynaud's in a patient diary during one week.The Cochin hand function scale is carried on Visit 0, visit 1, visit 5, visit 8, visit 10, visit 14 and visit 15.

The risk-benefit analysis of IVA337 in the current study is as follows:

IVA337 potentially offers a new therapeutic approach for SSc for which no curative treatment is available: patients with SSc suffer from a high risk of premature mortality and have considerable morbidity from their disease due to skin fibrosis and excessive collagen deposition in various organs including the lungs, kidney, heart and gastrointestinal tract. There is no cure for SSc, there are only treatments for some of the symptoms. Hence there is a high unmet medical need for new treatments.
IVA337 has been shown in non-clinical models to inhibit the effects of the main fibrogenic cytokines, TGFβ and PDGF in vitro on fibroblasts trans-differentiation into myofibroblasts and on fibroblasts proliferation respectively. In vivo, IVA337 displayed antifibrotic activity in bleomycin-induced fibrosis in the skin or lung and in CCL4-induced fibrosis in the liver. In the skin, IVA337 was active in both preventive as well as curative mode, thus providing evidence for an anti-fibrotic effect in established fibrotic disease.

Risks
IVA337 has not yet been evaluated in systemic sclerosis and therefore there are no expected events for IVA337 in this indication.

IVA337 has been evaluated in healthy volunteers and diabetic patients, and the following adverse reactions have been observed:
Table 1: Frequencies of adverse reactions (AEs considered by the investigator as related to IVA337) in healthy volunteers and diabetic patients who received IVA337.

System Organ Class Description Severity Frequency

Healthy volunteers N=100

Gastrointestinal disorders:
constipation-Severity;mild, Frequency;1
epigastric discomfort-Severity;mild, Frequency;1
dysphagia-Severity; moderate, Frequency;1
nausea-Severity;mild, Frequency;2
vomiting-Severity;moderate, Frequency;1

General disorders
feeling hot-Severity; mild, Frequency;1

Nervous system disorders
dizziness-Severity;mild, Frequency;3
dizziness postural-Severity;mild, Frequency;7
lethargy-Severity;mild, Frequency;3
headache -Severity;mild, Frequency;3
somnolence-Severity;mild, Frequency;2

Psychiatric disorders
abnormal dreams-Severity;mild, Frequency;1

Renal and urinary disorders
pollakiuria-Severity;mild, Frequency;1

Vascular disorders
hot flush-Severity;mild, Frequency;1

Diabetes mellitus N=47

Blood and lymphatic system disorders
hypochromic anaemia-Severity;mild, Frequency;1

Nervous system disorders
headache -Severity; severe, Frequency;1

Gastrointestinal disorders
constipation-Severity;mild, Frequency;1

Urinary tract infections
urinary tract infection-Severity;mild, Frequency;1

IVA337 belongs to the group PPAR agonists. Even though it differs from other PPARγ and PPARα agonists, one cannot yet exclude the following risks known for some of these products:
- Hypoglycaemia, especially when combined with hypoglycaemic agents of sulfonylurea class or insulin therapy,
- Fluid retention, pedal oedema and congestive heart failure , a risk shared by the PPARγ and dual PPARα/γ agonists that cannot be excluded at this stage of the clinical development of IVA337 despite an improved preclinical profile,
- Weight gain,
- Haematological changes i.e. small reductions in mean haemoglobin and haematocrit,
- Liver enzyme increases,
- Myalgia and creatine phosphokinase increase,
- Ovulation resumption in special population,
- Bone fractures, increase of incidence in particular in women,
- Macular oedema,
- Cholelithiasis,
- Carcinogenicity: A review of the data on rodent carcinogenicity studies on PPAR agonists by the European authorities has shown that epithelial cell carcinomas in the bladder of rats and haemangiosarcomas in mice can occur. It is not possible to determine the relevance of this data to humans.

The risks are mitigated by comprehensive and frequent monitoring of the patients.

Conclusion

There is a positive risk-benefit balance in favour of IVA337. The serious nature of systemic sclerosis, the unmet medical need, and the good tolerability of IVA337 so far, justify further investigation of IVA337 in this rare disease.

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

• Systemic sclerosis according to ACR/EULAR 2013 criteria
• Diffuse cutaneous SSc subset (LeRoy*s criteria)
• Diagnosis within the past 3 years as defined by the first non-Raynaud*s symptom
• MRSS between 10 and 25
Patients on stable treatment (for >3 months) with prednisone <= 10 mg, methotrexate<= 20 mg/w, azathioprine <= 150 mg/d, mycophenolate mofetil <= 2g/d, or leflunomide <= 20 mg/d may be included in the study; therapy to be maintained as background therapy.
A complete list of criteria is provided in Section 7.1 of the protocol.

Exclusion criteria

• Cyclophosphamide during the past 3 months
• Requirement of IV prostanoids for pulmonary hypertension in the last 3 months
• Renal insufficiency defined by a creatinine clearance of less than 30 ml/min (CKD-EPI or MDRD formula) and/or past/current renal crisis
• Hepatic impairment i.e. primary biliary cirrhosis and unexplained persistent liver function abnormality,
• Gallbladder disease (Cholelithiasis is not an exclusion criterion)
• Diabetic ketoacidosis
• Severe cardiac (LVEF <45%) and/or pulmonary disease (FVC < 50% or pulmonary hypertension proven by right heart catheterisation)

• History of heart failure, symptomatic coronary artery disease, significant ventricular tachyarrhythmia, stent placement, coronary artery bypass surgery, and/or myocardial infarction.
• Recipient of solid organ transplant
• Gastrointestinal involvement preventing oral administration of study drug
• Chronic infections, positive serology for infection with hepatitis B or C
• Pregnancy, Lactation. Woman of childbearing potential unwilling to use a medically acceptable form of birth control (see 7.1.3)
• History of malignancy within the last 5 years, except for resected basal or squamous cell carcinoma of the skin, treated cervical dysplasia, or treated in situ cervical cancer
• A recent history of alcohol or drug abuse, non-compliance with other medical therapies
• Participation in a clinical study involving another investigational drug or device within the past 4 weeks or during the study
• Laboratory parameters at the pre-treatment visit showing any of the following abnormal results: transaminases > 2x the upper limit of normal (ULN) and/or bilirubin > 2x ULN; neutrophil count < 1,500/mm3; platelet count < 100,000/mm3; haemoglobin < 9 g/dL.
• Known hypersensitivity or allergy to class of drugs or the investigational product.
• Any condition or treatment, which in the opinion of the investigator, places the subject at unacceptable risk as a patient in the trial.
• Co-therapy with biologics. Wash-out period: Any anti-TNF agent in the last 3-months: adalimumab, certolizumab, etanercept, golimumab, infliximab, abatacept and tocilizumab in the last 3 months; rituximab in the last 6 months
• Any other significant heart disease or any clinically significant ECG abnormality reported by central ECG reading.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	20-04-2017
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IVA337
Generic name:	IVA337

Ethics review

Approved WMO Date:	06-04-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-06-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	27-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2018
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
EudraCT	EUCTR2015-001617-27-NL
CCMO	NL56540.078.16
Other	NTC02503644