FCBHEALTH

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Actemra
(tocilizumab)

October 2017

Systemic Sclerosis (SSc)

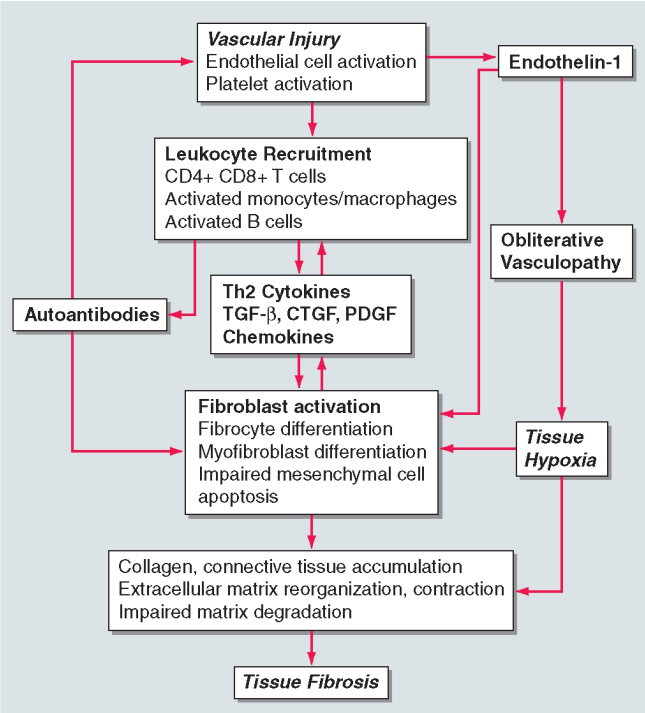
Disease Overview and Management

Brief overview

- SSc is an autoimmune connective tissue disorder
- Cause of disease is unknown
  - Possible genetic: 1.6% of SSc patients have first-degree relative with SSc. Incidence among Choctaw Indians is also high
  - Environmental factors: exposure to silica dust or petroleum-based products increases risk
- Characterized by thickening of the skin (known as scleroderma) and affects multiple organ systems, such as the lungs, GI tract, heart and kidneys
- Estimated about 300,000 Americans have SSc – a rare disease
  - Affects all races, with predominance among females and age range of 30-50 years
  - Incidence is higher among blacks than whites
- There is no cure
  - Current treatment guidelines aim to slow the progression of the disease and alleviate symptoms

Pathogenesis

- Generally accepted that vascular injury kickstarts the process
- Many different processes that lead to fibroblast activation, including the formation of autoantibodies targeting the body
- Fibroblast activation causes collagen and connective tissue accumulation
- Ultimately leading to tissue fibrosis, or excessive fibrous connective tissue, across many organ systems



Diagnostic criteria

Enough to diagnose SSc

2013 ACR / EULAR Criteria For The Classification Of Systemic Sclerosis (Scleroderma)*

Item	Sub-items(s)	Weight/score †
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere 3 Anti–topoisomerase I Anti–RNA polymerase III	3

* The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

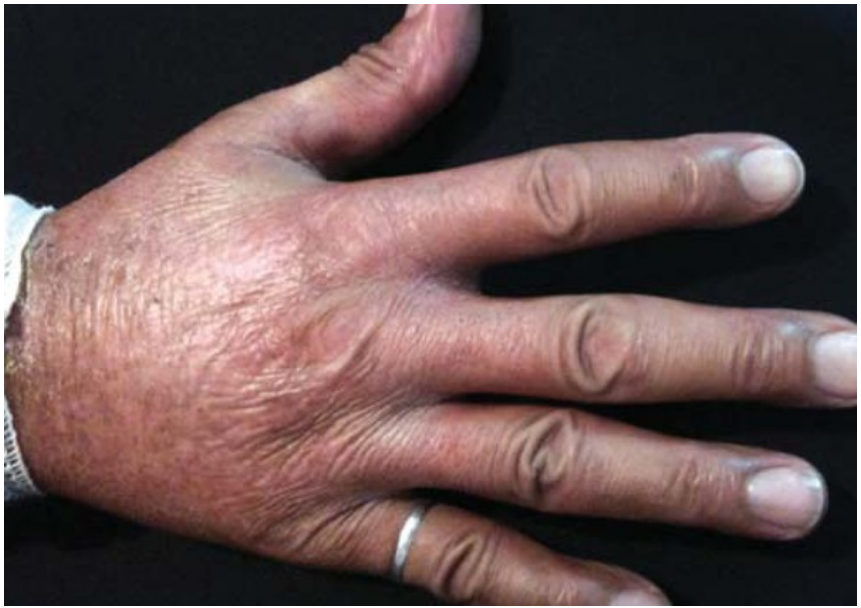
† The total score is determined by adding the maximum weight (score) in each category.
Patients with a total score of ≥ 9 are classified as having definite scleroderma.

Sensitivity 91% Specificity 92%

Van den Hoogen et al. 2013 Classification Criteria for Systemic Sclerosis. Arthritis and Rheumatism. Vol. 65, No. 11, November 2013, pp 2737–2747

Clinical manifestations

Skin features



- Skin thickening across the body is a hallmark feature of SSc
- Starts in the fingers, then advances throughout the body
- Skin is firm, coarse and thickened, and may be darkly pigmented
- Thickening can result in immobility of fingers, wrists, elbows and knees, leading to muscle atrophy and joint weakening

Raynaud's phenomenon

- Vasoconstriction, or reduced blood flow, affecting the fingers and sometimes the toes
- Occurs in episodes (comes and goes) and is triggered by
  - exposure to cold
  - decrease in temperature
  - emotional stress
  - vibration
- Attacks start with affected area turning white, then blue
- When blood returns, area turns red and burns

Pulmonary features

- Interstitial Lung Disease (ILD)
  - 16-43% of SSc patients
  - Causes restrictive pulmonary defect, impairing gas exchange in the lungs
  - High-resolution CT is often needed to confirm diagnosis of ILD

- Pulmonary arterial hypertension (PAH)
  - 15% of SSc patients, either with ILD or isolated
  - Associated with right sided heart failure
  - At first patient is asymptomatic
  - Initial sign is dyspnea (shortness of breath) and decrease in exercise ability
  - Progression of PAH includes angina and syncope, and elevated mean pulmonary arterial pressure.

Gastrointestinal features

- Upper GI
  - Xerostomia (dry mouth), reduced oral aperture, gum disease, and resorption of mandibular condyles (surfaces that connect the jaw to the skull via a joint)
  - Gastroesophageal reflux disease (GERD) symptoms occur
    - Heartburn, regurgitation, dysphagia
  - Gastroparesis (delayed or impaired stomach emptying) can also occur
- Lower GI
  - SSc patients may have impaired intestinal motility, resulting in malabsorption and bacterial overgrowth
  - Colonic involvement may cause constipation, fecal incontinence, and rectal prolapse

Renal features

- Occurs in 10-15% of SSc patients
- Characteristically present with accelerated hypertension and progressive renal insufficiency
  - Headache, blurred vision, and chest pain may accompany blood pressure elevation
- Renal failure eventually develops over several days

Disease progression

- Most symptoms begin to appear in the early years of the disease (first 5 years)
  - Skin thickening being the earlier and prominent symptom to appear
- At a certain point, skin thickening reaches a plateau and shows a slow regression
- New organ involvement is rare after skin involvement has reached its peak

treatment

Treatment guidelines

- Most current guidelines for treatment of systemic sclerosis come from European League against Rheumatism (EULAR)
  - American College of Rheumatology does not have their own guidelines
- Address treatment of SSc-related organ complications.
- Immunosupressants are used to slow progression or severity of SSc complications
  - Should start early treatment before disease worsens
    - Actemra's potential place in therapy
  - Important to be diagnosed early
- Treatment is highly effective in alleviating symptoms and slowing down progression of disease

Treatments by organ systems

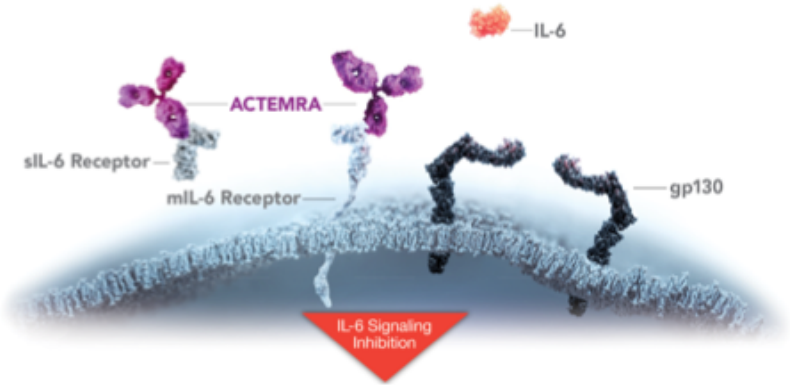
- GI Complications
  - Proton pump inhibitors for GERD and prokinetic drugs for motility issues
- PAH
  - Endothelin receptor antagonists (ambrisentan, bosentan), PDE-5 inhibitors (sildenafil, tadalifil) or riociguat are recommended for treatment of SSc-related PAH
- ILD
  - Cyclophosphamide is recommended
- Renal Complications
  - Prompt recognition of symptoms are required to initiate short-acting ACE inhibitor
- Skin Features (focus)
  - Methotrexate and cyclophosamide have both been recommended
  - Both immunosuppresants – important as tocilizumab is one as well
  - Current phase 3 trial involving tocilizumab has primary endpoint as change in modified Rodnan skin score
    - Rodnan skin score measures extent and severity of skin thickening

Source: Kowal-bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327-1339.

Actemra
(tocilizumab)

Mechanism of action

- Actemra works by binding to soluble and membrane-bound IL-6 receptors, preventing IL-6 binding and signal inhibition
- Serum IL-6 levels are correlated with the extent of skin fibrosis and are found to be elevated in SSc patients
- In addition, IL-6 help induce T helper 17 differentiation from naïve CD4 T cells, which are pro-inflammatory
- Lastly, IL-6 promotes fibrosis by inducing collagen formation through fibroblasts
- These mechanisms make IL-6 a possible novel target for SSc therapy



Source: Sakkas LI. Spotlight on tocilizumab and its potential in the treatment of systemic sclerosis. Drug Des Devel Ther. 2016;10:2723-8.

Dosing and indications

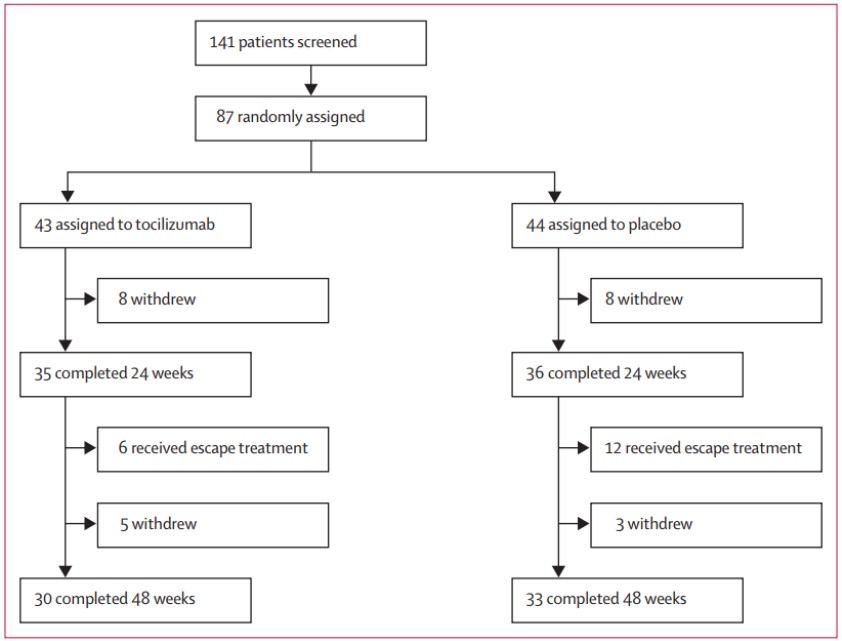
- Dosing
  - As Actemra is currently in clinical trials (phase III) for use in SSc, there is no official dosing yet
  - However, a completed phase II study and the current ongoing phase III study are using a dose of 162 mg given subcutaneously once a week
- Indication
  - Current clinical trials have had a primary endpoint of improved modified Rodnan skin scores
  - Indication could be to treat skin-related symptoms of SSc
  - Secondary endpoint in current phase III trial is change in forced vital capacity (FVC)
    - Possible that Actemra may target lung-related symptoms as well

Boxed warning

- Actemra is an immunosuppressant, and there is an increased risk of serious infections as a result
- Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to starting Actemra
- Viral reactivation can also occur, and cases of herpes zoster exacerbation were observed in clinical studies with Actemra (for use in rheumatoid arthritis)

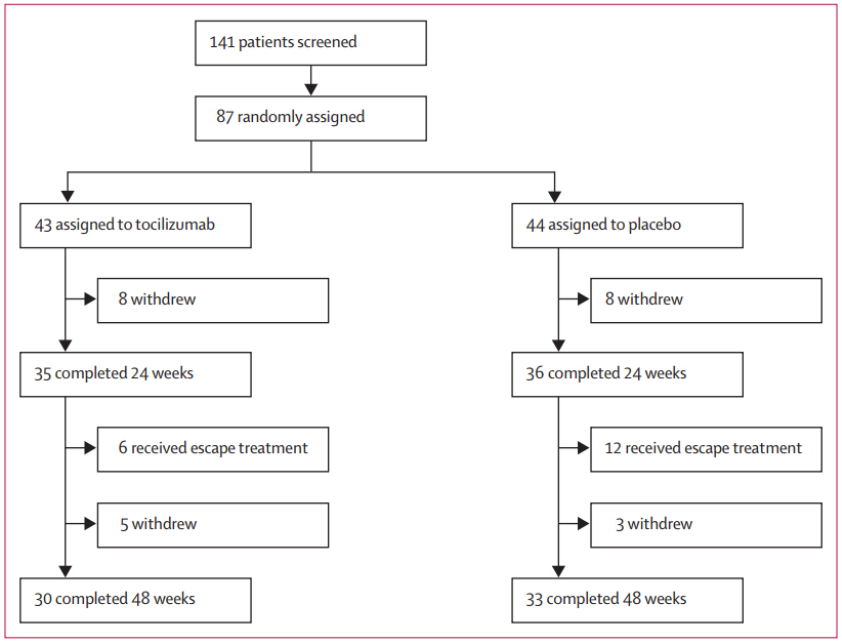
trials

Phase ii (completed)



- Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate)
- Double blind, placebo controlled. Patients were randomly assigned (1:1) either SQ Actemra 162 mg or placebo
- Patients enrolled had progressive SSc of 5 years or fewer from first non-Raynaud's sign or symptom
- Primary endpoint was difference in mean change from baseline in modified Rodnan skin score at 24 weeks
  - An exploratory endpoint defined a minimal clinically important difference as a difference of 4.7

Phase ii (completed)

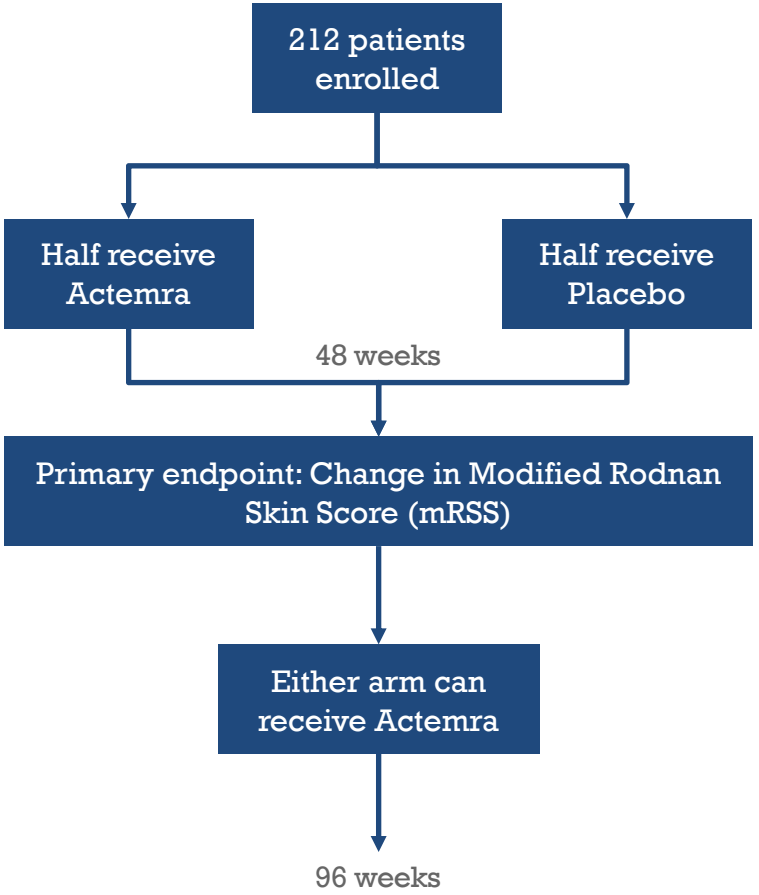


- Serious infections were more common in the Actemra group than in placebo group. One patient died in relation to Actemra treatment.
- Study did not detect a significant difference between Actemra and placebo
  - Difference was 2.7, p = 0.0915
  - Skin profile decreased more in the Actemra group

Source: Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. 2016;387(10038):2630-40

Phase iii (ongoing)

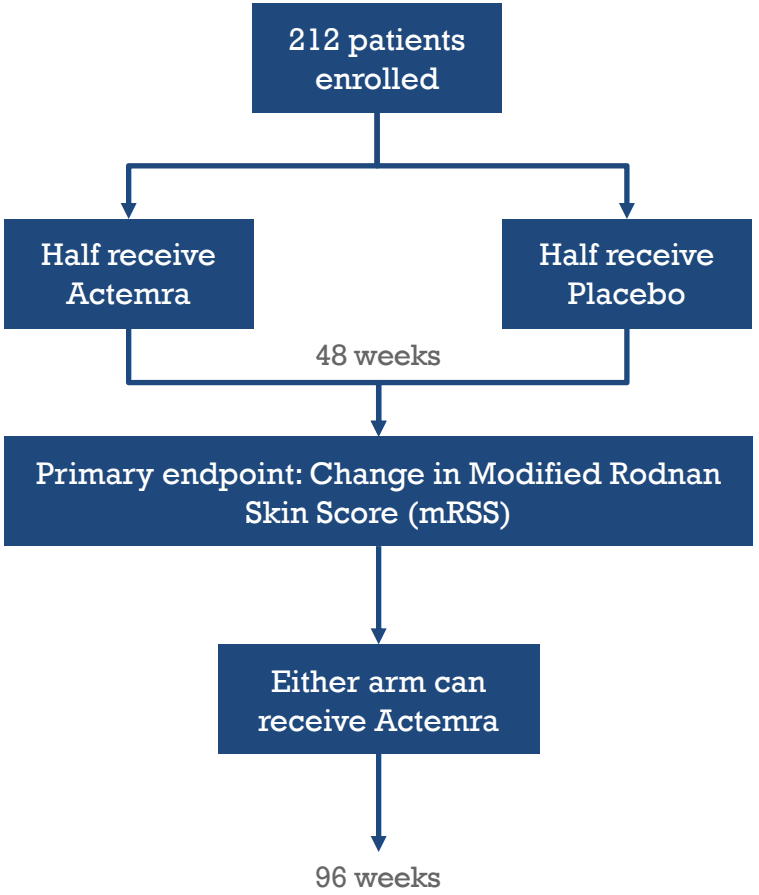
- A Study of the Efficacy and Safety of Tocilizumab in Participants With Systemic Sclerosis (SSc) (focuSSced)
- Double blind, placebo controlled. Patients were randomly assigned (1:1) either SQ Actemra 162 mg or placebo from baseline to 47 weeks.
  - Weeks 48-96, either arm can get open-label Actemra
- Patients enrolled must have SSc for 5 years or less, and a modified Rodnan skin score of 10-35 units



Source: Hoffmann-La Roche. A Study of the Efficacy and Safety of Tocilizumab in Participants With Systemic Sclerosis (SSc) (focuSSced). Available from: https://clinicaltrials.gov/ct2/show/NCT02453256. NLM identifier: NCT02453256. Accessed September 22, 2017.

Phase iii (ongoing)

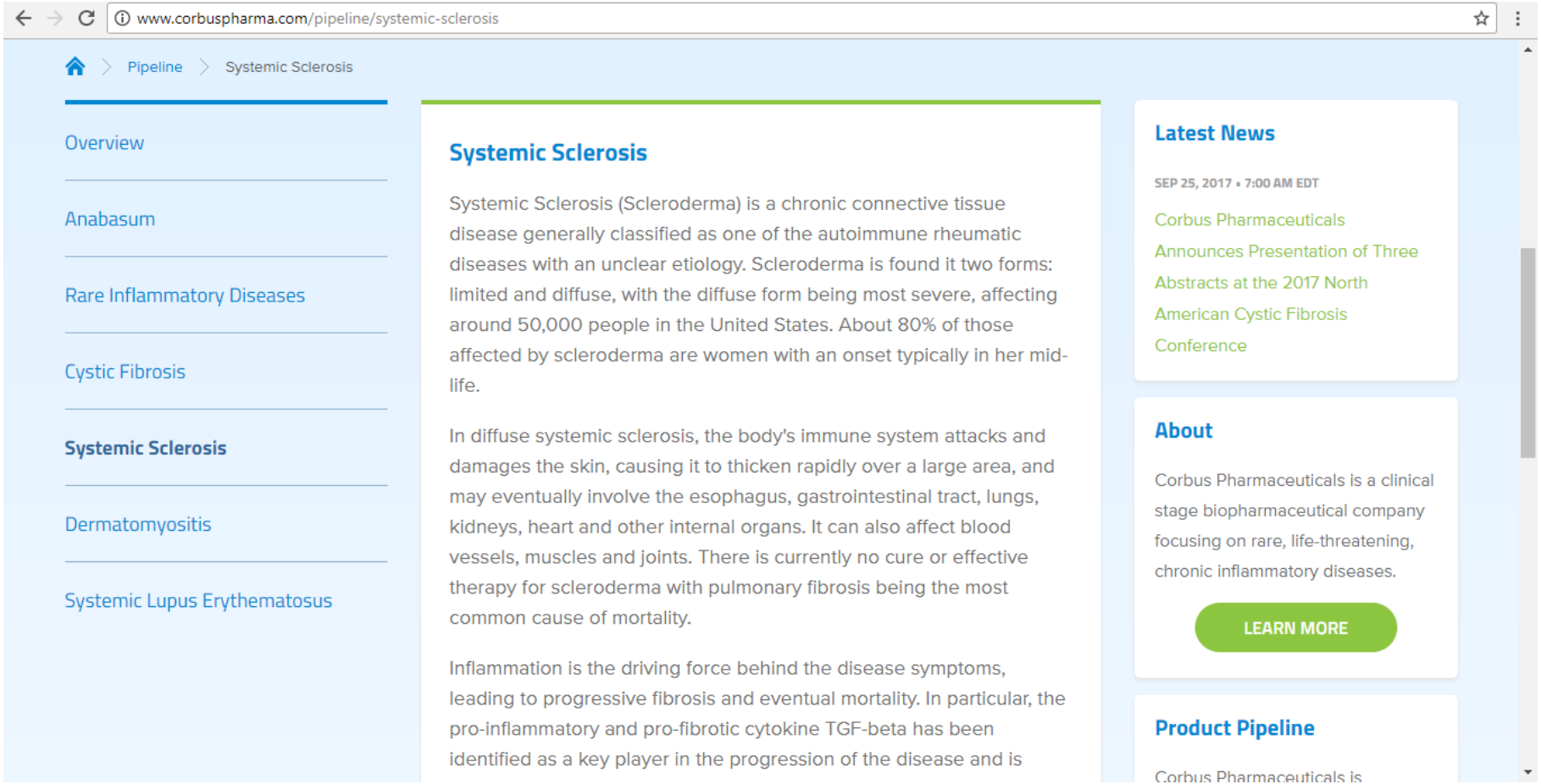
- Primary endpoint is change in modified Rodnan skin score from baseline to week 48
  - A secondary endpoint is change in forced vital capacity from baseline to week 48
- Estimated to be completed in January 2018



Competitors

Anabasum/resunab (Corbus pharmaceuticals)

- Synthetic oral drug mimicking effects of endocannabinoids
- Triggers production of mediators that activate a cascade leading to reduced inflammation and stopping fibrosis
  - Designed to do so without immunosuppression
- Estimated completion of current Phase 2 trial is December 2017 (final data collection)
  - Trial identifier: NCT02465437
- Phase 3 trial to commence in the fourth quarter of 2017


www.corbuspharma.com/pipeline/systemic-sclerosis
Pipeline
Systemic Sclerosis
Overview
Anabasum
Rare Inflammatory Diseases
Cystic Fibrosis
Systemic Sclerosis
Dermatomyositis
Systemic Lupus Erythematosus
Systemic Sclerosis
Systemic Sclerosis (Scleroderma) is a chronic connective tissue disease generally classified as one of the autoimmune rheumatic diseases with an unclear etiology. Scleroderma is found it two forms: limited and diffuse, with the diffuse form being most severe, affecting around 50,000 people in the United States. About 80% of those affected by scleroderma are women with an onset typically in her mid-life.
In diffuse systemic sclerosis, the body's immune system attacks and damages the skin, causing it to thicken rapidly over a large area, and may eventually involve the esophagus, gastrointestinal tract, lungs, kidneys, heart and other internal organs. It can also affect blood vessels, muscles and joints. There is currently no cure or effective therapy for scleroderma with pulmonary fibrosis being the most common cause of mortality.
Inflammation is the driving force behind the disease symptoms, leading to progressive fibrosis and eventual mortality. In particular, the pro-inflammatory and pro-fibrotic cytokine TGF-beta has been identified as a key player in the progression of the disease and is
Latest News
SEP 25, 2017 • 7:00 AM EDT
Corbus Pharmaceuticals Announces Presentation of Three Abstracts at the 2017 North American Cystic Fibrosis Conference
About
Corbus Pharmaceuticals is a clinical stage biopharmaceutical company focusing on rare, life-threatening, chronic inflammatory diseases.
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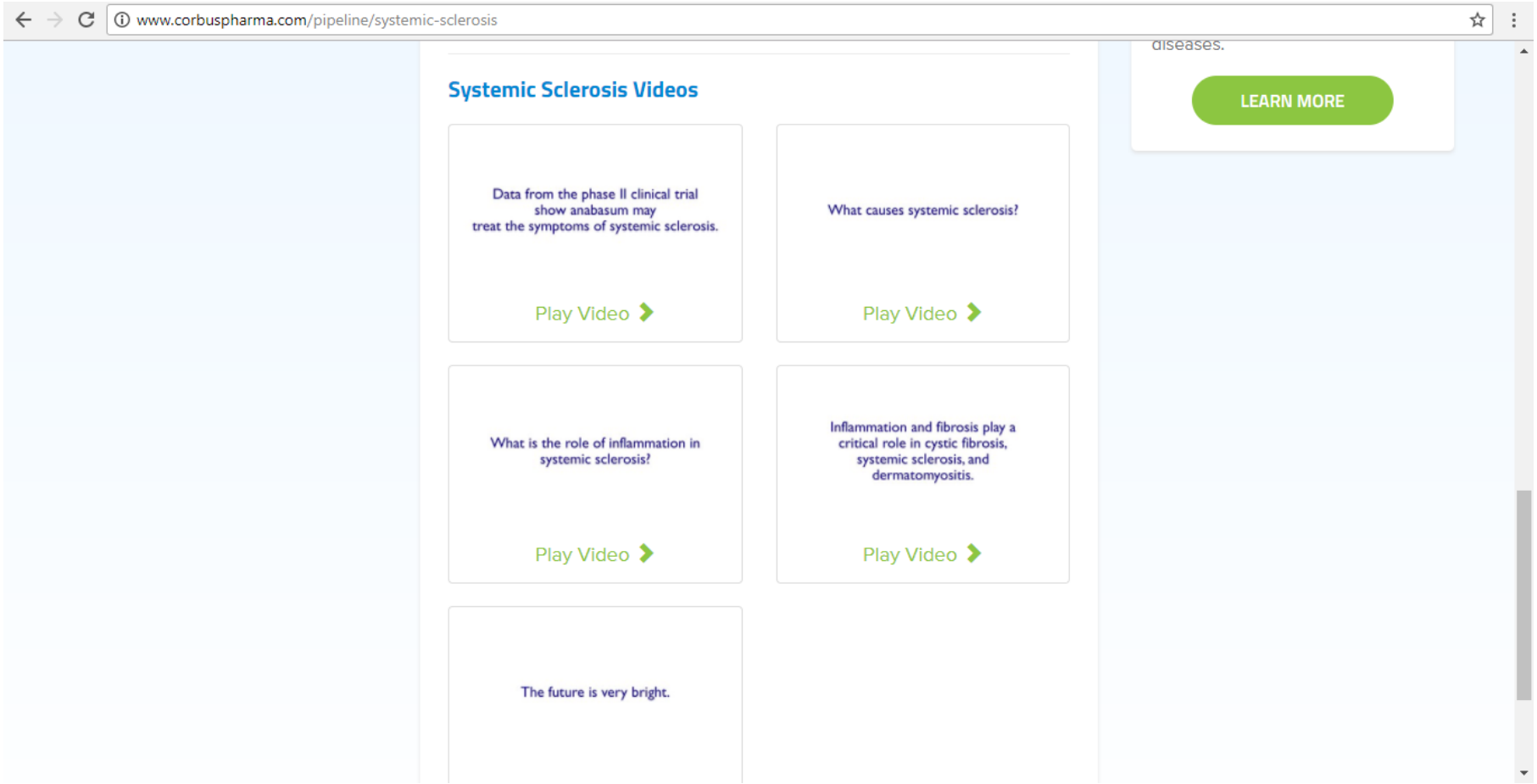
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Data from the phase II clinical trial show anabasum may treat the symptoms of systemic sclerosis.
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Inflammation and fibrosis play a critical role in cystic fibrosis, systemic sclerosis, and dermatomyositis.
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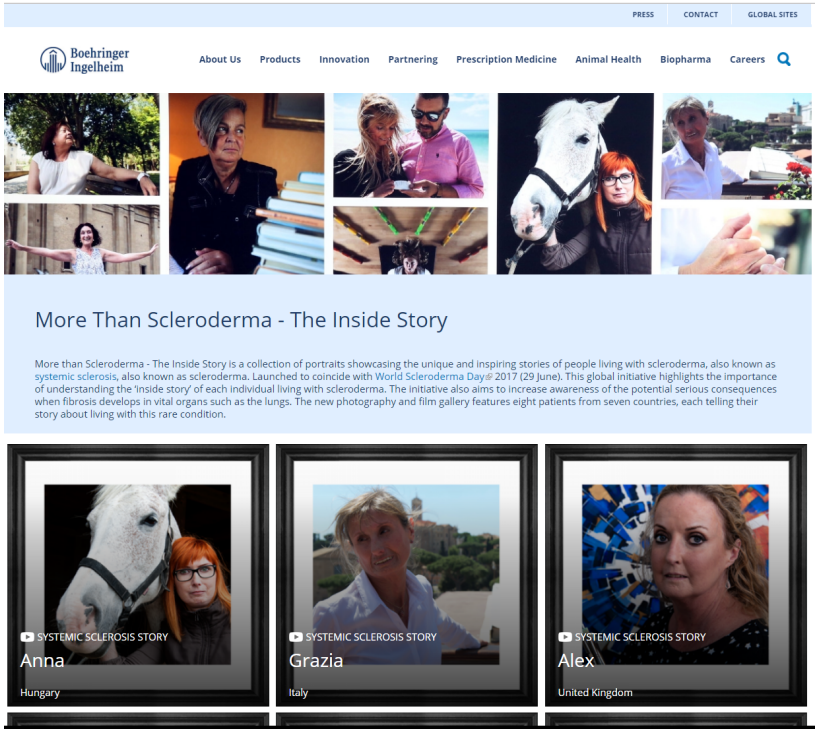
The future is very bright.

Nintedanib (Boehringer ingelheim)

- Tyrosine kinase inhibitor previously approved for treatment of idiopathic pulmonary fibrosis
- Inhibition of tyrosine kinase receptors decreases release of growth factor and growth factor receptors involved in the proliferation, migration and transformation of fibroblasts
  - Possible benefit in SSc may be to decrease fibrosis
- Received Orphan Drug Designation in September 2016 for treatment of systemic sclerosis
- Phase 3 study is currently recruiting participants
  - Primary outcome measure is rate of decline in FVC in patients
  - A secondary outcome measure is change from baseline in skin scores
  - Estimated to be completed in December 2018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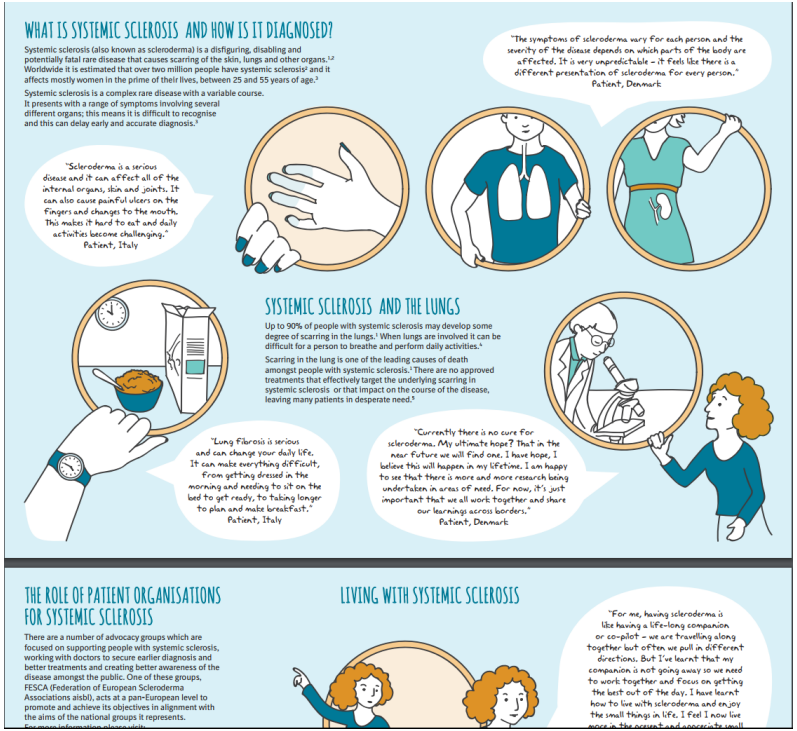
More Than Scleroderma - The Inside Story
More than Scleroderma - The Inside Story is a collection of portraits showcasing the unique and inspiring stories of people living with scleroderma, also known as systemic sclerosis, also known as scleroderma. Launched to coincide with World Scleroderma Day 2017 (29 June). This global initiative highlights the importance of understanding the 'inside story' of each individual living with scleroderma. The initiative also aims to increase awareness of the potential serious consequences when fibrosis develops in vital organs such as the lungs. The new photography and film gallery features eight patients from seven countries, each telling their story about living with this rare condition.
SYSTEMIC SCLEROSIS STORY
Anna
Hungary
SYSTEMIC SCLEROSIS STORY
Grazia
Italy
SYSTEMIC SCLEROSIS STORY
Alex
United Kingdom


WHAT IS SYSTEMIC SCLEROSIS AND HOW IS IT DIAGNOSED?
Systemic sclerosis (also known as scleroderma) is a disfiguring, disabling and potentially fatal rare disease that causes scarring of the skin, lungs and other organs.[1,2] Worldwide it is estimated that over two million people have systemic sclerosis[2] and it affects mostly women in the prime of their lives, between 25 and 55 years of age.[3]
Systemic sclerosis is a complex rare disease with a variable course. It presents with a range of symptoms involving several different organs; this means it is difficult to recognise and this can delay early and accurate diagnosis.[3]
"The symptoms of scleroderma vary for each person and the severity of the disease depends on which parts of the body are affected. It is very unpredictable – it feels like there is a different presentation of scleroderma for every person."
Patient, Denmark
"Scleroderma is a serious disease and it can affect all of the internal organs, skin and joints. It can also cause painful ulcers on the fingers and changes to the mouth. This makes it hard to eat and daily activities become challenging."
Patient, Italy
SYSTEMIC SCLEROSIS AND THE LUNGS
Up to 90% of people with systemic sclerosis may develop some degree of scarring in the lungs.[1] When lungs are involved it can be difficult for a person to breathe and perform daily activities.[4]
Scarring in the lung is one of the leading causes of death amongst people with systemic sclerosis.[1] There are no approved treatments that effectively target the underlying scarring in systemic sclerosis or that impact on the course of the disease, leaving many patients in desperate need.[5]
"Lung fibrosis is serious and can change your daily life. It can make everything difficult, from getting dressed in the morning and needing to sit on the bed to get ready, to taking longer to plan and make breakfast."
Patient, Italy
"Currently there is no cure for scleroderma. My ultimate hope? That in the near future we will find one. I have hope, I believe this will happen in my lifetime. I am happy to see that there is more and more research being undertaken in areas of need. For now, it's just important that we all work together and share our learnings across borders."
Patient, Denmark
THE ROLE OF PATIENT ORGANISATIONS FOR SYSTEMIC SCLEROSIS
There are a number of advocacy groups which are focused on supporting people with systemic sclerosis, working with doctors to secure earlier diagnosis and better treatments and creating better awareness of the disease amongst the public. One of these groups, FESCA (Federation of European Scleroderma Associations aisbl), acts at a pan-European level to promote and achieve its objectives in alignment with the aims of the national groups it represents.
LIVING WITH SYSTEMIC SCLEROSIS
"For me, having scleroderma is like having a life-long companion or co-pilot – we are travelling along together but often we pull in different directions. But I've learnt that my companion is not going away so we need to work together and focus on getting the best out of the day. I have learnt how to live with scleroderma and enjoy the small things in life. I feel I now live more in the present and appreciate small

Advocacy

The Scleroderma foundation

- Non-profit in the US
- Raises funds for support, education and research
- Support
  - Patient centered, helps with coping through support programs, peer counseling, physician referrals and education information
- Education
  - Promotes public awareness and educations through seminars, literature, and publicity campaigns
- Research
  - Stimulates and support research to improve treatment and ultimately find a cure
- www.scleroderma.org