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ECCS-50 (Cytori stem cell therapy) for moderate to severe hand dysfunction due to Scleroderma

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LAY SUMMARY

Scleroderma is a condition where the body's immune system becomes overactive and targets and damages healthy body tissue. The symptoms of scleroderma vary for each person, and the severity depends greatly on which parts of the body are affected. Symptoms include hardening of the skin, swelling of the hands and feet, joint pain and stiffness, Raynaud's phenomenon (RP) (where fingers and toes turn white in response to cold) and distal ulcers (skin ulcers which develop on the fingers and toes).

RP and distal ulcers can cause great pain and disability in the hands of people with scleroderma. There is no cure for scleroderma and current treatments focus on symptoms and include looking after your skin, protecting your joints, managing RP and preventing development of distal ulcers.

ECCS-50 (Cytori stem cell therapy) is a new treatment intended for the treatment of moderate to severe hand problems in people with scleroderma. It involves taking stem cells (a cell with the potential to become any cell type) from patient's fat tissue and reinjecting these cells into the hands. Clinical trials on ECCS-50 are currently being conducted to determine if this treatment could improve hand symptoms and function in people with scleroderma.

If ECCS-50 was licenced in the UK, it could provide a new treatment option for people with moderate to severe hand problems due to scleroderma, which may improve hand symptoms and function.

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TARGET GROUP

Hand dysfunction due to Scleroderma: mild to moderate

TECHNOLOGY

DESCRIPTION

ECCS-50 (ADCs, Cytori Therapeutics; adipose stem cells, Cytori Therapeutics; adipose-derived stem and regenerative cells, Cytori; ADRCs; autologous adipose-derived stem cells, Cytori; DCCT-10; ECCI-50; ECCO-50; ECCS-50; Habeo; OICH-D3; stem cell therapy, Cytori Therapeutics) are adipose derived stem and regenerative cells (ADRCs) taken from the patient's own tissue and prepared using Cytori's cellulation system before administration.[1] ADRCs can be used to repair and regenerate a range of damaged or diseased tissue types by differentiation of the ASRCs along the specific cell lineage, thereby replacing the damaged or missing tissue.[2] Cytori cell therapy is intended for the treatment of hand dysfunction due to scleroderma. Treatment with the Cytori cell therapy system involves the processing of the patients own ADRCs using the cellulation device. 40,000,000 ADRCs are then administered via subcutaneous injection, two injections per digit, on both hands.[3]

ECCS-50 does not currently have Marketing Authorisation in the EU for any indication.

ECCS-50 is currently in phase III trials for scleroderma and urinary incontinence and phase II trials for general ischaemia and osteoarthritis.

INNOVATION and/or ADVANTAGES

If licensed, ECCS-50 will offer an additional treatment option for severe hand dysfunction due to systemic sclerosis with the potential to improve symptoms and hand function in patients with hand dysfunction due to systemic sclerosis.

DEVELOPER

Cytori Therapeutics

AVAILABILITY, LAUNCH or MARKETING

ECCS-50 is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Scleroderma is an autoimmune condition where the immune system targets and damages the connective tissue in the skin, internal organs and blood vessels. This leads to the overproduction of collagen by connective tissue cells, causing scaring and thickening of the tissue. There are two types of scleroderma, localised scleroderma (affecting just the skin) and systemic sclerosis (SS) (affecting the whole body). Systemic sclerosis can be further subdivided into limited SS (where fibrosis is confined to below the elbows and knees and the face) and diffuse SS (where fibrosis is more widespread on the

body and affects internal organs).[4, 5] The symptoms of scleroderma vary but generally include hardening of the skin, swelling of the hands and feet, joint pain and stiffness and Raynaud's phenomenon (RP) (where fingers and toes turn white in response to cold). RP is very common and affects 95% people with scleroderma,[6] causing pain and disability. RP is also a contributing factor to the development of digital ulcers (necrotic lesions of the fingers and toes affecting approximately 30% of scleroderma patients) which significantly increase pain and disability, and can lead to serious infection resulting in the need for amputation.[4]

The causes of scleroderma are not fully understood, however it is thought that environmental triggers and risk factors may lead to the development of the disease in genetically susceptible people. Risk factors for scleroderma development include gender and pregnancy. Females are four times more likely than men to develop scleroderma,[6] however men have a worse prognosis. Pregnancy also increases scleroderma risk by 2.8 times when compared to those who have never been pregnant.[4] In addition to this several small genetic changes (SNPs) and certain Human Leukocyte Antigen (HLA) alleles (gene responsible for encoding the major histocompatibility complex cell surface protein which regulates the immune system) have been associated with increased risk of systemic sclerosis (SS).

CLINICAL NEED and BURDEN OF DISEASE

For the UK in 2014, the prevalence of SS in adults above 18 years was 4,948. The prevalence of RP in those with SS was 4765 (96% of the SS population) and the prevalence of distal ulcers in those with SS was 1781 (36% of the SS population) in the UK in 2014.[4]

In 2015, there were 3,293 admissions for Systemic Sclerosis (ICD-10 M34) in England, resulting in 3491 bed days and 3,467 finished consultant episodes.[7]

According to a systematic review of worldwide data, survival rates in SS from diagnosis to 5 years was 75% and from diagnosis to 10 years was 63%.[8]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- Evidence Summary. Skin Involvement in systemic sclerosis: rituximab (ES7). March 2017.
- Evidence Summary. Digital Ulcers: sildenafil (ESUOM42). March 2015.
- Evidence Summary. Scleroderma: oral mycophenolate (ESUOM32). July 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Dermatology Services (All Ages). A12/S/a.

- NHS England. Clinical Commissioning Policy: Sildenafil and Bosentan for the Treatment of Digital Ulceration in Systemic Sclerosis.

CURRENT TREATMENT OPTIONS

There is no cure for scleroderma and treatment focuses mainly on managing and preventing symptoms. These can include blood pressure medications (to dilate blood vessels), immunosuppressant medications (to ease SS symptoms), steroids (to relieve joint and muscle symptoms), antacid medication (to reduce acid reflux), antibiotics (to prevent infections) and painkillers. Non-pharmacological strategies may also be used to relieve symptoms including moisturising the skin (to keep it supple and relieve itching), physiotherapy (to keep muscle supple and loosen tight skin), keeping hands and feet warm (for those with RP) and eating healthily, exercising and stop smoking (to control blood pressure and improve circulation).[5, 9]

Specifically regarding hand dysfunction, mainly due to Raynaud's phenomenon and digital ulcers, in scleroderma, current treatment options include:[4]

First line treatments:

- Calcium channel blockers e.g. nifedipine – used as first line treatment to all patients with SS and RP
- Phosphodiesterase 5 Inhibitors e.g. sildenafil – used for severe RP and digital ulcers in SS patients
- Prostacyclins e.g. iloprost – used in SS patients with severe RP and distal ulcers
- Angiotensin receptor blockers e.g. losartan – used in SS patients with severe RP and distal ulcers
- Selective Serotonin Reuptake Inhibitors (SSRIs) e.g. fluoxetine - used in SS patients with RP

Second line treatments:

- Bosentan – used SS patients with multiple distal ulcers after failure with calcium channel blockers and prostanoid therapy
- Phosphodiesterase 5 Inhibitors e.g. sildenafil –used in SS patients with RP who have not responded to calcium channel blockers

EFFICACY and SAFETY

Trial	NCT02558543, SCLERADEC II, Scl104, EudraCT Number: 2014-003321-17, TrialTroveID-253616; scleroderma affecting the hands and fingers; ECCS-50 vs Placebo; phase II/III trial	NCT02396238; STAR; TrialTroveID-222535; scleroderma affecting the hands and fingers; ECCS-50 vs placebo; phase III trial
Sponsor	Cytori Therapeutics	Cytori Therapeutics
Status	Ongoing	Complete and published in abstract
Source of Information	trial registry [10]	trial registry [11], poster [12]
Location	France	USA
Design	Randomised, placebo-controlled controlled	Randomised, placebo controlled, double blind, crossover

Participants	n=40 (planned); aged above 18 years; scleroderma affecting the hands and fingers, diagnosed systemic sclerosis	N=88, aged 18 to 70 years, scleroderma affecting the hands and fingers, diagnosed diffuse cutaneous scleroderma or limited cutaneous scleroderma, symptoms of Raynaud's phenomenon.
Schedule	Participants are randomly allocated to 1 of 2 treatment arms at 1:1 ratio. Active treatment arm involved injection of ECCS-50 into the sub-dermic plan on the side faces of the fingers distal and proximal or 4 times 0.25ml per finger (total 1ml) for every finger. Placebo group received the same treatment schedule except Ringer lactate solution is injected. Placebo participants will crossover to active treatment arm after 24 weeks follow up.	Patients are randomly allocated (at 1:1 ratio) to receive a single treatment of ECCS-50 or placebo treatment. Those receiving placebo are eligible for crossover to ECCS-50 treatment after patients have completed the 12 months follow up. Participants receive a subcutaneous administration of placebo (sterile lactated ringers solution and a small amount of the participants blood) or ECCS-50 (containing 40 million ADRCs) of two injections per digit on both hands.
Follow-up	After administration of treatment, follow up visits were scheduled for 1, 3 and 6 months	After administration of treatment, follow up visits were scheduled for 1, 4, 12, 24, 36 and 48 weeks.
Primary Outcomes	Cochin Hand Function Scale (measure of hand function) at 3 months	Cochin Hand Function Scale (measure of hand function) at 6 months
Secondary Outcomes	Raynaud's Condition Score, modified Rodnan Score, functional hand assessment, capilliaroscopy, Adverse Events (AEs), EVA Pain scale (measure of pain in the hands), scleroderma health assessment questionnaire, hand mobility in Scleroderma, grip strength and pinch strength, finger tactile sensitivity, trouble trophicity, monitoring of existing digital ulcers and onset of new digital ulcers, severity of Raynaud's phenomenon, vascular suppression score.	Raynaud's condition score, Scleroderma health assessment questionnaire, physician and patient global assessment, hand mobility in Scleroderma, digital ulcer count, modified rodnan score, grip strength and pinch strength, finger circumference (with hand volume), 1^{st} corner distance and sum of 2^{nd}, 3^{rd} and 4^{th} corner distances, EuroQOL five dimensions questionnaire (EQ-5D), adverse events, serious adverse events, VAS, functional hand assessment.
Key Results	-	Interim results for blinded baseline measures presented 28-09-2016. Baseline cochin score was 42.2 (±14.2) and 73% and 39% patients had digital ulcers. Mean adipose tissue harvest was 293 (±50) ml and mean ADRC yield was 120.6 (±66) $x10^6$ cells. ADRC viability was 89.1 (±2.7)%.

Adverse effects (AEs)	-	Liposuction related AEs were experienced including discomfort and ecchymosis. No cell related or serious adverse events were reported.
Expected reporting date	25-07-2018	Not reported

ESTIMATED COST and IMPACT

COST

The cost of ECCS-50 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☒ Need for new services: administration of liposuction for ADRC yield and administration of ECCS-50 by subcutaneous injection.

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: cost of liposuction, ADRC preparation and administration of ECCS-50 by subcutaneous administration.

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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