# A phase 2 multicentre randomized controlled comparative efficacy and safety study of Tiscover and AS210 in chronic (arterio-)venous ulcers

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Determine the safety and efficacy of Tiscover compared to AS210 (acellular donor dermis, construct Tiscover is cultured on) for the treatment of chronic, therapy resistant (arterio-) veneus leg/foot ulcers in an out patient setting.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON40033

**Source**
ToetsingOnline

**Brief title**
Autologous skin substitutes or donordermis for chronic leg/foot ulcers

### Condition

- Other condition
- Skin vascular abnormalities

**Synonym**
chronic lower leg and foot wounds; hard to heal ulcers

**Health condition**

been en voet ulcera door (arterio)-veneuze insufficientie

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum
**Source(s) of monetary or material Support:** Agentschap NL;Internationaal Innoveren en Samenwerken subsidie;ZONmw,A-SKIN Nederland BV ,Ministerie van Volksgezondheid, Welzijn en Sport (VWS)

## Intervention

**Keyword:** Autologous or donor, Chronic wounds, Leg ulcers, Skin substitute

## Outcome measures

**Primary outcome**

1. Safety

- Assessed by describing the number and type of adverse events; any untoward

medical occurrence in a trial participant, even if it does not

necessarily have a causal relationship with the treatment, will be reported.

2. Efficacy; assessed by determining:

- Time to heal (in weeks)

- Number and percentage of closed wounds, within 26 weeks after application

of Tiscover or AS210

Complete wound closure is defined as total epithelialization with no wound

exudate being present. Digital photographs will record wound closure.

- Wound size reduction

The percentage of reduction in wound area within 26 weeks after

application of Tiscover or AS210 in week 12 and week 26. Wound size is measured

with Visitrak® wound measurement system (Smith & Nephew) and wound digital photographs.

**Secondary outcome**

1. Recurrence

- Number and percentage of closed wounds at 3 and 6 months.

2. Quality of the healed skin

- Closed wounds will be visually assessed regarding to scarring.

3. Quality of life

- Quality of life measured at baseline, when closed and at 3 and 6 months follow up.

Quality of life will be assessed using:

i) SF36; Quality of life score

ii) Numeric pain rating scale for experienced pain (VAS scale)

Take rate of individual Tiscover and AS210 patches.

Number and percentage of Tiscover or AS210 patches present on the wound after weekly wound care at weeks 2 - 26

# Study description

**Background summary**

Chronic wounds (venous-, arterio-venous and diabetic foot- ulcers) represent a major problem in our society (Grey et al. 2006; Vileikyte 2001). These ulcers

occur with high incidence and exist for long periods of time despite standard therapy creating a large financial burden to society (Matricali et al. 2006; Mekkes et al. 2003) and also a large personal burden to the patients involved (Phillips et al. 1994; Vileikyte 2001). prevalence numbers vary between 1 and 5%, increasing with age. Characteristics of ulcers include a loss of skin or underlying tissue and resistance to conventional types of treatment. Wound healing stagnates resulting in ulcers remaining open for prolonged periods (>12 weeks * 50 years recurring). In western societies approximately 1% of the total health care budget is spent on wound care. Most leg ulcers are located between on the lower leg and are caused by venous insufficiency (45*60%), arterial insufficiency (10*20%), diabetes (15*25%) or combinations of these (10*15%).

Standard therapies for ulcer treatment are described by the Kwaliteitsinstituut voor de Gezondheidszorg CBO (Guidelines ulcus cruris) and are co- written by dedicated top medical specialist in the field. The Dutch guidelines are in accordance with European and American guidelines. In short the standard wound care consists of wound cleaning, creation of an optimal (moist) wound environment, and adequate compression therapy.
More advanced wound care therapies which are infrequently available require hospitalization and/or operation. These advanced treatments include autograft (punch biopsies, split skin) and negative pressure therapy (VAC®).

Until now the more advanced treatments (as mentioned above) do not results in high success rates in healing a therapy resistant ulcer. For these reasons new advanced therapies, such as application of living skin substitutes are being developed. The advantage of living skin substitutes above acellular dressings is now widely accepted: they provide an immediate cover but above all they continuously secrete a cocktail of cytokines, chemokines and growth factors which promote wound healing. These factors improve wound healing by stimulating angiogenesis, granulation tissue formation and epithelialisation.

We have developed an autologous full thickness skin substitute for healing therapy resistant chronic wounds. The autologous skin substitute (Tiscover) consists of an acellular dermail matrix and both cultured autologous fibroblasts and keratinocytes forming an epidermal and dermal layer, resembling histology of normal healthy skin.

The advantage of autologous cell constructs is that they are not rejected. They serve as an immediate cover for the wound and incorporate in the wound bed, so continuously secrete growth factors and cytokines to accelerate wound closure. Additionally the advantage of any cultured skin substitute above a native autograft is that less donor skin is required.

Since 2004 our first generation cultured skin substitute, Tiscover I, has been applied to a variety of chronic wounds in the hospitalized and out-patient (multi-centre) setting.
EU regulation require skin transplants using autologous cell culture to comply

with the DG Sanco *Tissue Directives* which regulates the quality and safety of advanced tissue products.
As of January 1ste 2009 the situation of non harmonized EU regulation, with respect to market authorization which allows for free trade among member states, was dissolved. This resulted in a amendment of the pharmaceutical directive 2001/83/EU with regards to Advanced Therapy Medicinal Products regulation.
In order to comply with the new National and European legislation (regarding GMP, GCP, labelling, packaging) Tiscover I has been adjusted with extensive change control procedures. The culture ingredients not in line with legislation have been omitted or replaced by clinical grade or GMP grade products. This has resulted in a second generation full thickness autologous skin substitute, known as second generation Tiscover.

**Study objective**

Determine the safety and efficacy of Tiscover compared to AS210 (acellular donor dermis, construct Tiscover is cultured on) for the treatment of chronic, therapy resistant (arterio-) veneus leg/foot ulcers in an out patient setting.

**Study design**

A prospective, multi centre, open randomized controlled phase II study in which patients with hard to heal (chronic) therapy resistant (arterio-) venous leg/foot ulcers are treated in an out patient setting with Tiscover (test group) or AS210 (control group). Tiscover (autologous cultured skin substitute) is constructed from small skin biopsies (diameter 3 mm) from unaffected skin as described previously (Gibbs et al, 2006). The required number of skin biopsies will be sufficient to culture Tiscover patches to cover 125% of the total wound surface.
In week -2 keratinocytes and fibroblasts are isolated from the skin biopsies and seeded into As210. The autologous skin cells and As210 are co-cultured for approximately 3 weeks, after which Tiscover is ready for application.
The protocol for treatment of ulcers with Tiscover of AS210 consists of two consecutive applications.
First appliction week 0: minimal approximally 1/4 of the total ulcer surface is covered with Tiscover or AS210.
Week 1: After 1 week all Tiscover or AS210 is removed. The complete ulcer surface is covered with new Tiscover or AS210, which will be held in place until ingrowth.

Tiscover of AS210 are, after both applications, covered and held in place with wound dressings and bandages. Each patient is seen weekly for wound care, cleaning, debridement and bandage changes until complete wound closure or until the end of the study at 26 weeks. After complete closure patients are seen for follow up at 3 and 6 months to assess possible ulcer recurrence.

### Study burden and risks

The burden for the participating patient is minimal (S. Gibbs et. al., 2006).
The study protocol consists of standard wound care which is supplemented with application of Tiscover or AS210. Patients receive ambulatory standard wound care during their weekly out patient wound control visits. The evaluation of the wounds and dressing changes will take approximately 30 minutes instead of the usual 12 minutes. Our experience from case studies and the multicenter trial with Tiscover I, consisting of cultured autologous skin cells seeded into a human acellular dermis, strongly support the statement that burden to the patient is minimal. Patients experience minor inconvenience during removal of biopsies and blood. Biopsies are removed under local anaesthesia.
A possible risk is intolerance or an allergic reaction to Tiscover or AS210. However, until now over 100 patients have been treated with Tiscover I in pilot studies, case studies as well as in a multicenter trial, without showing any related adverse events. Over 10 hospitals and out patient clinics have been participating without reporting any serious adverse reactions.
Compared to the culture procedure used for first generation Tiscover, for second generation Tiscover most of the culture medium ingredients have now been omitted and some have been replaced according to a validated change control process, which reduces the already minimal risk to adverse events even more. These validated controlled changes have resulted in a second genration Tiscover which now complies with EU legislation (in place since January 1st 2009) for ATMP.
We anticipate that the experimental treatment will activate the inert ulcer wound bed resulting in decrease in ulser size and wound closure. This will result in a new ambulant treatment for hard to heal leg ulcers.

## 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

Presence of confirmed venous or arterio-venous ulcer.
Patients age over 18 years
Ulcer duration over 12 weeks and less than 15 years consecutively
<30% ulcer size reduction in 4 weeks prior to inclusion
Ulcer is between 1-40 cm2 in size
Ankle brachial pressure index (ABPI) * 0.6 and * 1.3
Ulcer depth <1 cm
Mobile, at least able to walk with medical walker, and able to return for required treatments and study evaluations
(Legially) capable to give informed consent
Able to understand and comply with requirements of study protocol

## Exclusion criteria

Ulcer chronicity < 12 weeks
Severe co-morbidity reducing life expectance to < 1 year
Use of oral corticosteroids and/or cytostatics >20 mg/per day;
Allergy to Gentamycin (which is used in the tissue media), or the used local wound treatments
Severe infection of ulcer, active cellulitis, osteomyelitis
Expected non compliance with compression therapy, protocol treatment or no informed consent
Severe malnutrition
Uncontrolled diabetes mellitus, HbA1c > 12% (108 mmol/mol)
Anaemia Hb <6 mmol/l

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Observational invasive |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 22-08-2012 |
| Enrollment: | 49 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Generic name: | Somatic cells autologous |

# Ethics review

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|---|---|
| Approved WMO Date: | 21-11-2011 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 19-01-2012 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

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|---|---|
| Approved WMO Date: | 12-06-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 20-11-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 13-12-2012 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 17-10-2013 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 12-11-2013 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 13-02-2014 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 15-05-2014 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 18-12-2014 |
| Application type: | Amendment |

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|---|---|
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 23091
Source: Nationaal Trial Register
Title:

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2010-021797-10-NL |
| ISRCTN | ISRCTN86386707 |
| CCMO | NL32502.000.11 |
| OMON | NL-OMON23091 |