National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: June 2017

VF-001 (VitroGro ECM) for venous leg ulcer

NIHRIO (HSRIC) ID: 13402

NICE ID: 9394

LAY SUMMARY

Leg ulcers are long-lasting wounds that can take more than six weeks to heal, usually developing on the inside of the leg, just above the ankle. The most common type are venous leg ulcers, which account for the majority of cases identified. Venous leg ulcers also become increasingly common with age and can impact a patient physically and psychologically.

VF-001 is a new drug that enables and accelerates chronic wound repair by providing cell attachment sites and stimulating cell activity. Consequently, skin cells are able to attach, migrate and increase rapidly to restore the wound healing process.

VF-001 is applied to the wound weekly, and fits with standard care for chronic wounds. The wound closes, breaking the cycle of inflammation, and leaving healthy, functional tissue.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Venous leg ulcer in adults (above 18 years old) – adjunctive treatment

TECHNOLOGY

DESCRIPTION

VF-001 is under development for the treatment of venous leg ulcers. The drug is administrated topically and is a fusion protein composed of vitronectin, conjugated to growth factor through a linker. Vitronectin binds to alpha v beta 3 also known as vitronectin receptor. VF-001 binds to the vitronectin receptor and delivers the growth factor to the wound site. The growth factor promotes cell adherence, cell migration and wound healing.[1]

VF-001 is currently in phase II clinical trials for venous leg ulcers; patients with venous leg ulcer aged 18 years or older are randomized to receive either the VF-001 at a dose of 14 micrograms per treatment as an adjunct to standard care (Mepitel and Coban2) (low dose), or at a dose of 140 micrograms per treatment as an adjunct to standard care (Mepitel and Coban2) (high dose), or the control treatment group (placebo plus SC) for up to 12 weeks.[2]

Current phase II trials of VF-001 are ongoing in:[3]

- Cardiovascular Disease
- Skin Ulcers
- Dermatological Disorders
- Leg Ulcers
- Varicose Ulcers
- Ulcers (Gastrointestinal)

VF-001 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, VF-001 will offer a novel additional treatment option for venous leg ulcer.

DEVELOPER

Factor Therapeutics Ltd.

GROUP

BACKGROUND

Venous leg ulcers (VLUs) are defined as open lesions between the knee and ankle joint that occur in the presence of venous disease.[4] They account for 60-80% of all leg ulcers, therefore are the most

common cause.[5] It is estimated that 33-60% of VLUs persist for more than 6 weeks and are consequently referred to as chronic VLUs.[6] These ulcers represent the most advanced form of chronic venous disorders like varicose veins and lipodermatosclerosis.[7]

A number of factors can increase the risk of developing a venous leg ulcer. These include older age, female sex, obesity, trauma, immobility, congenital absence of veins, deep vein thrombosis (DVT), phlebitis, and factor V Leiden mutation.[8,9]

Patients with venous leg ulcers experience multiple symptoms, including pain, depression, discomfort from lower leg inflammation and wound exudate the presence of co-occurring symptoms may have a negative effect on wound healing and quality of life (QOL).[10]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, population prevalence rates generally fall in the range of 1.2–3.2 per 1,000 people, which means there are 70,000–190,000 individuals in the UK with a venous leg ulcer at any time.[11] Prevalence increases markedly with age; a UK study found that in a local population, crude prevalence of venous ulceration was 0.3/1,000 in men and 0.5/1,000 in women whilst in those aged over 85, rates were 8.29/1,000 (men) and 8.06/1,000 (women).[12]

In Scotland, 83% of cases of leg ulcer care were completed entirely in the community whereas in 12% of cases it was a collaborative effort between hospital and the community. A further 5% of cases were hospital inpatients.[13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Venous leg ulcers – new treatments (ID394). In development.
- NICE medtech innovation briefing. UrgoStart for chronic wounds (MIB82). October 2016.
- NICE medtech innovation briefing. Woundchek Protease Status for assessing elevated protease status in chronic wounds (MIB83). October 2016.
- NICE medtech innovation briefing. The Juxta CURES adjustable compression system for treating venous leg ulcers (MIB25). March 2015.
- NICE medtech innovation briefing. Oxyzyme and Iodozyme 2-layer hydrogel wound dressings with iodine for treating chronic wounds (MIB11). November 2014.
- NICE medical technologies guidance. The Debrisoft monofilament debridgement pad for use in acute or chronic wounds (MTG17). March 2014
- NICE medical technologies guidance. The MIST Therapy system for the promotion of wound healing (MTG5). July 2011.

- NICE evidence summary. Chronic wounds: advanced wound dressings and antimicrobial dressings (ESMPB2).
- NICE clinical guideline. Varicose veins: prevention and management (CG168). July 2013.
- NICE Clinical Knowledge Summaries (CKS): Leg ulcer-venous. February 2016.
- NICE key therapeutic topic. Wound care products (KTT14). January 2017.

NHS ENGLAND and POLICY GUIDANCE

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

OTHER GUIDANCE

- SIGN clinical guideline. The Care of Patients with Chronic Leg Ulcer (SIGN CPG 120). 2010.[4]
- AAWC guideline. Association for the Advancement of Wound Care (AAWC) venous ulcer guideline. 2010.[14]
- Guideline for Diagnostics and Treatment of Venous Leg Ulcer. 2016.[15]
- ESVS guideline. Management of Chronic Venous Disease, Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). 2015.[16]

CURRENT TREATMENT OPTIONS

The aim of treatment is to improve venous return by increasing velocity flow in the deep veins, and to reduce any oedema, by decreasing the pressure difference between capillaries and the tissue using compression therapy to promote healing.[17]

SIGN guideline for management of chronic venous leg ulcers recommends the following treatments:[4]

- Assessment:
    - Leg ulcer patients with dermatitis/eczema should be considered for patch-testing using a leg ulcer series.
- Treatment:
    - A simple non-adherent dressings are recommended in the management of venous leg ulcers.
    - A high compression multicomponent bandaging should be routinely used for the treatment of venous leg ulcers.
    - A use of pentoxifylline (400 mg three times daily for up to six months) to improve healing should be considered in patients with venous leg ulcers.

If a leg ulcer is associated with signs of venous hypertension (eg varicose veins), NICE recommends referral to a vascular service.[18]

- Assessment

- Use duplex ultrasound to confirm the diagnosis of varicose veins and the extent of truncal reflux, and to plan treatment for people with suspected primary or recurrent varicose veins.

- Interventional treatment
  - For people with confirmed varicose veins and truncal reflux:
    - Offer endothermal ablation (see Radiofrequency ablation of varicose veins [NICE interventional procedure guidance 8] and Endovenous laser treatment of the long saphenous vein [NICE interventional procedure guidance 52]).
    - If endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy (see Ultrasound-guided foam sclerotherapy for varicose veins [NICE interventional procedure guidance 440]).
    - If ultrasound-guided foam sclerotherapy is unsuitable, offer surgery.

      If incompetent varicose tributaries are to be treated, consider treating them at the same time.
  - If offering compression bandaging or hosiery for use after interventional treatment, do not use for more than 7 days.
- Non-interventional treatment
  - Do not offer compression hosiery to treat varicose veins unless interventional treatment is unsuitable.

Management during pregnancy

- Give pregnant women presenting with varicose veins information on the effect of pregnancy on varicose veins.
- Do not carry out interventional treatment for varicose veins during pregnancy other than in exceptional circumstances.
- Consider compression hosiery for symptom relief of leg swelling associated with varicose veins during pregnancy.

EFFICACY and SAFETY

Trial	NCT02973893, VF00102,GDCT0276630; adults with venous leg ulcers; VF-001 (low dose) vs VF-001 (high dose) vs placebo all in combination with standard care; phase II
Sponsor	Factor Therapeutics Ltd.
Status	Ongoing, recruiting
Source of Information	Trial registry[2]
Location	USA
Design	Randomised, placebo-controlled, double-blind study
Participants	n=168 (planned), aged 18 and over; chronic venous leg ulcers; Ankle-Brachial Pressure Index (ABI) ≥0.80; previously treated with standard care; moderate severity
Schedule	Participants are randomized to receive one of three intervention arms:

	-control treatment (placebo and standard care) - VF-001 (low dose) at a dose of 14 micrograms per treatment in combination with standard care (Mepitel and Coban2) - VF-001 (high dose) at a dose of 140 micrograms per treatment in combination with standard care (Mepitel and Coban2). Treatments were delivered in 1ml syringes (containing 0.5ml treatment) for up to 12 weeks during the treatment phase.
Follow-up	Active treatment for 12 weeks, follow-up 12 weeks
Primary Outcomes	The percentage reduction in the study ulcer area in each treatment group over the 12-week Treatment Phase
Secondary Outcomes	The proportion of patients with complete study ulcer closure within the 12-week Treatment Phase - 12-weeks, time to complete study ulcer closure within the 12-week Treatment Phase - 12-weeks, time to first instance of no study ulcer pain (i.e., pain score less than 5 mm on Visual Analog Scale [VAS) within the 12-week Treatment Phase - 12-weeks, time to clinically meaningful study ulcer pain reduction (33% reduction on VAS) within the 12-week Treatment Phase - 12-weeks, change in Quality-of-Life metrics Euro Quality-of-Life Questionnaire EQ-5D-5L - Up to 24-weeks, change in Quality-of-Life metrics Patient Benefit Index - wound version PBI-W - Up to 24-weeks, the incidence of adverse events (AEs), including overall AEs, AEs related to the IP and study-ulcer-associated AEs. - Up to 24-weeks
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date is reported as November 2017

ESTIMATED COST and IMPACT

COST

The cost of VF-001 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: improved Efficacy, Safety and quality of life for carers

☐ 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

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] Global data. *VF-001*. Available from: https://pharma.globaldata.com/ClinicalProductsView.aspx?id=Drug&ClinicalID=o3LnQHkIg8iYBxZsmZpMNg==. [Accessed 4 June 2017, log-in required]

[2] Global data. Clinical Trial Profile Overview. *VF-001*. Available from: https://pharma.globaldata.com/ClinicalProductsView.aspx?ClinicalID=o3LnQHkIg8iYBxZsmZpMNg==.[Accessed 4 June 2017, log-in required]

[3] Global data. Clinical trials. *VF-001*. Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=279804 [Accessed 4 June 2017, log-in required]

[4] Management of chronic venous leg ulcers. A national clinical guideline. SIGN Publication. 2010. Available from: http://www.sign.ac.uk/sign-120-management-of-chronic-venous-leg-ulcers.html [Accessed 2 June 2017]

[5] O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev. 2014 Jan 1;1(1).

[6] Briggs M, Flemming K. Living with leg ulceration: a synthesis of qualitative research. Journal of Advanced Nursing. 2007 Aug 1;59(4):319-28.

[7] Fowkes FG, Evans CJ, Lee AJ. Prevalence and risk factors of chronic venous insufficiency. Angiology. 2001 Aug;52(1_suppl):S5-15.

[8] Abbade LP, Lastória S. Venous ulcer: epidemiology, physiopathology, diagnosis and treatment. International journal of dermatology. 2005 Jun 1;44(6):449-56.

[9] Etufugh CN, Phillips TJ. Venous ulcers. Clinics in dermatology. 2007 Feb 28;25(1):121-30.

[10] Edwards H, Finlayson K, Skerman H, Alexander K, Miaskowski C, Aouizerat B, Gibb M. Identification of symptom clusters in patients with chronic venous leg ulcers. Journal of pain and symptom management. 2014 May 31;47(5):867-75.

[11] Graham ID, Harrison MB, Nelson EA, Lorimer K, Fisher A. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. Advances in skin & wound care. 2003 Nov 1;16(6):305-16.

[12] Moffatt CJ, Franks PJ, Doherty DC, Martin R, Blewett R, Ross F. Prevalence of leg ulceration in a London population. QJM: An International Journal of Medicine. 2004 Jul 1;97(7):431-7. M

[13] Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. Br Med J (Clin Res Ed). 1985 Jun 22;290(6485):1855-6.

[14] O'Donnell TF, Passman MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, Lurie F, Henke PK, Gloviczki ML, Eklöf BG, Stoughton J. Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. J Vasc Surg. 2014 Aug 1;60(2 Suppl):3S-59S.

[15] Neumann M, Cornu-Thénard A, Jünger M, Mosti G, Munte K, Partsch H, Rabe E, Ramelet AA, Streit M. Evidence based (S3) guidelines for diagnostics and treatment of venous leg ulcers. Im Internet: http://www. euroderm. org/edf/index. php/edf-guidelines/category/5-guidelines-miscellaneous. 2016 Aug 1.

[16] Wittens CD, Davies AH, Bækgaard N, Broholm R, Cavezzi A, Chastanet S, De Wolf M, Eggen C, Giannoukas A, Gohel M, Kakkos S. Editor's choice–management of chronic venous disease: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). European Journal of Vascular and Endovascular Surgery. 2015 Jun 30;49(6):678-737.

[17] Clinical Knowledge Summaries. *Leg Ulcer – Venous – Management 2016*. Available from: cks.nhs.uk/leg_ulcer_venous. [Accessed 4 June 2017]

[18] Varicose veins: diagnosis and management. Clinical guideline [CG168] 2013. Available from: https://www.nice.org.uk/guidance/cg168/chapter/1-Recommendations. [Accessed 4 June 2017]