National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: June 2018

Granexin gel for diabetic foot ulcers

NIHRIO (HSRIC) ID: 12177 NICE ID: 9803

LAY SUMMARY

Diabetes mellitus can cause serious foot problems as a result of diabetic neuropathy (loss of normal nerve function) and peripheral vascular disease (loss of normal circulation). These two conditions can lead to diabetic foot ulcers, as the nerves that usually carry pain sensation to the brain from the feet do not function as well and it is possible for unintentional foot damage to occur. Wearing tight shoes, cuts, blisters and bruises can all develop into diabetes foot ulcers. In a person with diabetes, a foot ulcer is defined as a patch of broken skin usually on the lower leg or feet. Diabetic foot ulcers can affect people with both type 1 and type 2 diabetes.

When blood sugar levels are high or fluctuate regularly, as in people with diabetes, skin that would normally heal may not properly repair itself because of nerve damage. As a result, even a mild injury can start a foot ulcer. Granexin gel contains the peptide ACT1, which possesses potential anti-inflammatory and regenerative properties when administered topically to diabetic foot ulcers. If licensed, granexin gel may offer an additional therapy option for diabetic foot ulcers which are a particularly difficult-to-treat chronic wound type.

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

Diabetic foot ulcers (DFUs)

TECHNOLOGY

DESCRIPTION

Granexin gel (Granexin; ACT1), under development for diabetic foot ulcers (DFUs), is a 25 amino acid novel bioengineered synthetic peptide that acts through a multi-mechanism effect. While the pathophysiology and impaired wound healing response of DFUs is complex and multi-factorial, a growing number of pre-clinical studies have identified the gap junctional (GJ) protein, connexin43 (Cx43), as a novel therapeutic target in diabetic wound healing. Cx43 has roles in dermal wound healing and targeting Cx43 signalling accelerates wound reepithelialisation.[1]

Granexin gel containins the carboxy-terminal PDZ binding domain of Cx43 linked to a 16 amino acid long antennapedia cell internalization sequence embedded in a hydroxyethyl-cellulose hydrogel for topical application.[1,2] The molecular mechanism of granexin gel involves modulation of the interaction between Cx43 and its C-terminal binding partners, mediated increases in size and stability of GJ channel aggregates, and a reduction in non-junctional (hemichannel) communication.[1] Targeting Cx43 with granexin gel, a peptide mimetic of the carboxyl-terminus of Cx43, accelerates fibroblast migration and proliferation, and wound reepithelialization. [3]

In phase III clinical trials (NCT02667327, NCT02666131), granexin gel comprised of 100 µM aCT1 peptide plus hydroxyethyl cellulose is applied topically to DFUs once a week for 12 weeks or until wound closure, whichever comes first. This is in addition to standard of care which includes cleaning and irrigating of ulcers, non-surgical debridement, pain management, ulcer dressing, off-loading, and nutritional assessment.[4,5]

Granexin gel does not currently have Marketing Authorisation in the EU for any indication.

According to the company website, granexin gel is currently in phase III clinical development for cutaneous radiation injury and phase II development for scar reduction (post-surgical/keloids).[6]

INNOVATION and/or ADVANTAGES

Current biomedical approaches for advanced wound care aim at providing antimicrobial protection to the open wound together with a matrix scaffold (often collagen-based) to boost reestablishment of the skin tissue.[2] DFUs that remain refractory to conventional treatment protocols may develop soft tissue infection, osteomyelitis, and tissue necrosis leading to lower-extremity amputation, lengthy hospital stays and costly treatments.[1]

Incorporation of granexin gel with standard of care protocols may represent a well-tolerated, highly effective therapeutic strategy that expedites diabetic foot ulcer healing by treating the underlying pathophysiology through Cx43-mediated pathways.[3] If licensed, granexin gel will offer an additional treatment option for DFUs that may provide a high degree of convenience and long-term compliance through once weekly topical administration.[7]

DEVELOPER

FirstString Research, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

EU/UK regulatory information/marketing plans by the company are currently unknown.

PATIENT GROUP

BACKGROUND

Diabetes is a chronic disease that stems from pancreas dysfunction, impairing normal production of insulin which leads to high, and also fluctuating, blood glucose levels. This in turn leads to an imbalance in the homeostatic regulation of the body, causing serious health problems including blindness, kidney failure, heart disease, venous insufficiency and peripheral neuropathy. A combination of these latter two conditions leads to loss of sensitivity in the feet of diabetic patients, which facilitates chronically-infected lesions known as diabetic foot ulcers (DFUs). DFUs can affect people with both type 1 (when the body is unable to produce insulin) and type 2 (where the level of glucose in the blood becomes too high) diabetes.[11,8,9] DFUs may ultimately lead to limb amputation.[2]

With neuropathy being the underlying cause of ulceration, many diabetes patients complain of burning, tingling, or numbness of the feet on presentation. The ulcer is usually on the plantar foot, most commonly under the great toe or first metatarsal head. Because of pressure, it is often surrounded by a rim of hyperkeratotic tissue, which may even cover the ulcer and give the illusion that the ulcer has healed, when it in fact has not. Infected ulcers may be associated with cellulitis, lymphangitis, adenopathy, calor, oedema, foul odour, and purulent drainage. Systemic signs such as fever and chills may be related, but are often absent, even in the presence of severe infection. There may be foot deformity or prominent areas of pressure associated with the ulcer.[10]

People who have diabetes for a longer period or manage their diabetes less effectively are more likely to develop foot ulcers. Smoking, not taking exercise, improper footwear, being overweight, and having high cholesterol or blood pressure can all increase risks of DFUs.[11] Keeping people on their feet, walking and mobile is fundamental to preventing the progression of lifestyle related diseases. People will not walk if they have pain, balance issues, or fear they are doing more damage to their feet; and they are unable to walk if they have open ulcers on the plantar surface. Once these problems arise, people often become increasingly sedentary. With decreased physical activity, short and long-term blood glucose levels will increase resulting in possible weight gain and overall health decline.[12]

CLINICAL NEED and BURDEN OF DISEASE

The diabetic foot is a major medical, social and economic problem worldwide. However, the reported frequency of ulceration and amputation varies considerably. This may be due to differences in diagnostic criteria as well as regionally specific social, economic and health related factors. The prevalence of active foot ulceration varies from approximately 1% in certain European and North American studies to more than 11% in reports from some African countries.[12]

In 2013, there were almost 2.9 million people in the UK diagnosed with diabetes. By 2025, it is estimated that more than 5 million people in the UK will have diabetes. In England, the number of people diagnosed with diabetes has increased by approximately 53% between 2006 and 2013, from 1.9 million to 2.9 million. The life expectancy of people with diabetes is shortened by up to 15 years.[13] The 2014-2016 National Diabetes Foot Care Audit for England and Wales notes more than 60,000 people with diabetes in England are thought to have foot ulcers at any given time. Between July 2014 and April 2016, 11,073 patients underwent first expert assessment for a total of 13,034 recorded new ulcer episodes at 173 specialist foot care services.[14]

Diabetes is the most common cause of non-traumatic limb amputation, with DFUs preceding more than 80% of amputations. After a first amputation, people with diabetes are twice as likely to have a subsequent amputation as people without. Mortality rates after diabetic foot ulceration and amputation are high, with up to 70% of people dying within 5 years of amputation and approximately 50% dying within 5 years of developing a diabetic foot ulcer.[13] DFUs are the most common reason for hospitalization of people with diabetes, with one in six diabetes patients developing at least one foot ulcer during their lifetime.[2]

Foot problems in people with diabetes have a significant financial impact on the NHS through primary care, community care, outpatient costs, increased bed occupancy and prolonged stays in hospital. A report published in 2012 by NHS Diabetes estimated that around £650 million (or £1 in every £150 the NHS spends) is spent on foot ulcers or amputations each year.[13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Diabetic foot ulcers – new treatments (ID381). Expected date of issue to be confirmed.
- NICE quality standard. Diabetes in adults (QS6). August 2016.
- NICE guideline. Type 2 diabetes in adults: management (NG28). May 2017.
- NICE guideline. Type 1 diabetes in adults: diagnosis and management (NG17). July 2016.
- NICE guideline. Diabetic foot problems: prevention and management (NG19). August 2015.
- NICE guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). August 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology Services (Adult). A03/S/a.

OTHER GUIDANCE

- NHS Digital. *National Diabetes Audit*, 2016-17[15]
- NHS England. *National diabetes treatment and care programme*, 2016[16]
- NHS England. *Action for Diabetes*, 2014[17]

- Diabetes UK. *NHS Diabetes commissioning documents & guidance*, 2013[18]

CURRENT TREATMENT OPTIONS

Management of DFUs is most advantageous through prevention, as ulceration is difficult to heal once developed. Prevention may include policies for foot inspection and use of custom therapeutic footwear to prevent ulceration.

Management of DFU requires good knowledge of their complexity for a correct classification of stage and severity; for instance, it is important to distinguish sloughy and necrotic tissues (severe infection) from granulation and epithelializing ulceration (healing wounds) as treatment regimens will vary accordingly.[2]

NICE recommends one or more of the following as standard care for treating diabetic foot ulcers: offloading, control of foot infection, control of ischaemia, wound debridement and/or wound dressings.[19]

EFFICACY and SAFETY

Trial	GAIT 1, NCT02667327; granexin gel plus standard of care vs vehicle gel plus standard of care vs no intervention plus standard of care; phase III
Sponsor	FirstString Research, Inc.
Status	Ongoing
Source of Information	Trial registry
Location	USA
Design	Randomised, parallel assignment, double-blind
Participants	n=552(planned); aged ≥18 years; diagnosis of diabetes mellitus (type I or II); glycosylated hemoglobin (HbA1c) value < 10.0%; diagnosis of neuropathic foot ulcer by 10g monofilament test, tuning fork (128 Hz), cotton wisp, or quantitative sensory test; designated foot ulcer meets the following criteria at both the screening and baseline visits: a. Present for at least 4 weeks; b. Full-thickness cutaneous ulcer below the ankle surface; c. University of Texas grade A1; d. Diameter (after debridement) 1 to 40.0 cm2; e. Viable, granulating wound (investigator discretion); ankle brachial index 0.7 to 1.3 at both the screening and baseline visits
Schedule	Randomised to receive granexin gel (100 µM aCT1 peptide plus hydroxyethyl cellulose) along with standard of care (includes cleaning and irrigating ulcer, non-surgical debridement, pain management, ulcer dressing, off-loading, and nutritional assessment); or placebo comparator (hydroxyethyl cellulose without active pharmaceutical ingredient) plus standard of care; or no intervention, standard of care once a week for up to 12 weeks or until wound closure, whichever comes first
Follow-up	Participants will have an additional 12 week follow-up period beyond the treatment period to assess durability of wound closure
Primary Outcomes	• Incidence of complete wound closure at week 12 based on investigator assessment

Secondary Outcomes	• Time in days to first complete wound closure of the target ulcer based on investigator assessment over the 12 week treatment period
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as December 2019.

Trial	GAIT 2, NCT02666131; granexin gel versus vehicle gel; phase III
Sponsor	FirstString Research, Inc.
Status	Ongoing
Source of Information	Trial registry
Location	USA
Design	Randomised, parallel assignment, double-blind
Participants	n=368 (planned); aged ≥18 years; diagnosis of diabetes mellitus (type I or II); glycosylated hemoglobin (HbA1c) value < 10.0%; diagnosis of neuropathic foot ulcer by 10g monofilament test, tuning fork (128 Hz), cotton wisp, or quantitative sensory test; designated foot ulcer meets the following criteria at both the screening and baseline visits: a. Present for at least 4 weeks; b. Full-thickness cutaneous ulcer below the ankle surface; c. University of Texas grade A1; d. Diameter (after debridement) 1 to 40.0 cm2; e. Viable, granulating wound (investigator discretion); ankle brachial index 0.7 to 1.3 at both the screening and baseline visits
Schedule	Randomised to receive granexin gel (100 µM aCT1 peptide plus hydroxyethyl cellulose) along with standard of care (includes cleaning and irrigating ulcer, non-surgical debridement, pain management, ulcer dressing, off-loading, and nutritional assessment); or placebo comparator (hydroxyethyl cellulose without active pharmaceutical ingredient) plus standard of care once a week for up to 12 weeks or until wound closure, whichever comes first
Follow-up	Participants will have an additional 12 week follow-up period beyond the treatment period to assess durability of wound closure
Primary Outcomes	• Incidence of complete wound closure at Week 12 based on investigator assessment
Secondary Outcomes	• Time in days to first complete wound closure of the target ulcer based on investigator assessment over the 12 week treatment period
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as December 2019.

ESTIMATED COST and IMPACT

COST

The cost of granexin gel is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ 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

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☒ None identified

REFERENCES

[1] Grek CL, Prasad GM, Viswanathan V et al. Topical Administration of a Connexin43-based peptide Augments Healing of Chronic Neuropathic Diabetic Foot Ulcers: A Multicenter, Randomized Trial. *Wound Repair and Regeneration*. 2015 Mar; 23(2): 203-212. Available from: https://dx.doi.org/10.1111%2Fwrr.12275

[2] Gomes A, Teixeira C, Ferraz R et al. Wound-Healing peptides for Treatment of Chronic Diabetic Foot Ulcers and Other Infected Skin Injuries. *Molecules*. 2017; 22(10): 1743. Available from: https://doi.org/10.3390/molecules22101743

[3] Ghatnekar GS, Grek CL, Armstrong DG et al. The Effect of a Connexin43-Based Peptide on the Healing of Chronic Venous Leg Ulcers: A Multicenter, Randomized Trial. *The Journal of Investigative Dermatology*. 2015 Jan; 135(1): 289-298. Available from: https://dx.doi.org/10.1038%2Fjid.2014.318

[4] ClinicalTrials.gov. *A Study of Granexin Gel in the Treatment of Diabetic Foot Ulcer*. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02667327 [Accessed 29th May 2018] Last updated 7th February 2018

[5] ClinicalTrials.gov. *A Study of Granexin Gel to Treat Diabetic Foot Ulcer*. Available from: https://www.clinicaltrials.gov/ct2/show/record/NCT02666131 [Accessed 29th May 2018] Last updated 7th February 2018

[6] FirstString Research. *Pipeline*. Available from: https://firststringresearch.com/pipeline/ [Accessed 22nd June 2018]

[7] Relief Therapeutics. *Relief Therapeutics Holding AG – Addressing diabetes and respiratory disease*. Available from: https://www.researchdynamics.ch/reports/465/ [Accessed 30th May 2018]

[8] NHS Choices. *Type 2 diabetes*. Available from: https://www.nhs.uk/conditions/type-2-diabetes/ [Accessed 15th June 2018]

[9] NHS Choices. *Type 1 diabetes*. Available from: https://www.nhs.uk/Conditions/Diabetes-type1/Pages/Causes-old.aspx [Accessed 15th June 2018]

[10] Boike A, Maier M, and Logan D. *Prevention and Treatment of Leg and Foot Ulcers in Diabetes Mellitus, Cleveland Clinic Centre for Continuing Education*. Available from: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/prevention-treatment-diabetic-leg-and-foot-ulcers/ [Accessed 4th June 2018]

[11] Diabetes.co.uk. *Foot ulcers*. Available from: https://www.diabetes.co.uk/diabetes-complications/diabetic-foot-ulcers.html [Accessed 30th May 2018]

[12] International Diabetes Federation. *IDF Clinical Practice Recommendations on the Diabetic Foot – 2017*. Available from: https://www.idf.org/component/attachments/attachments.html?id=1151&task=download [Accessed 29th May 2018]

[13] National Institute for Health and Care Excellence. *Diabetic foot problems: prevention and management – NICE guideline [NG19]*. Available from: https://www.nice.org.uk/guidance/ng19/chapter/introduction [Accessed 4th June 2018] Last updated January 2016

[14] NHS Digital. *National Diabetes Foot Care Audit – 2014-2016*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-footcare-audit/national-diabetes-foot-care-audit-2014-2016 [Accessed 29th May 2018]

[15] NHS Digital. *National Diabetes Audit (NDA) 2016-17*. Available from: http://content.digital.nhs.uk/nda [Accessed 15th June 2018]

[16] NHS England. *National Diabetes Treatment and Care Programme*. Available from: https://www.england.nhs.uk/wp-content/uploads/2016/12/diabetes-call-to-bid.pdf [Accessed: 19th January 2018]

[17] NHS England. *Action for Diabetes*. Available from: https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2016/08/act-for-diabetes-31-01.pdf [Accessed 19th January 2018]

[18] Diabetes UK. *NHS Diabetes commissioning documents*. Available from: https://www.diabetes.org.uk/professionals/position-statements-reports/nhs-diabetes-commissioning-documents-guidance [Accessed: 19 January 2018]

[19] National Institute for Health and Care Excellence. *Diabetic foot problems: prevention and management – NICE guideline [NG19], 1.5 Diabetic foot ulcer.* Available from: https://www.nice.org.uk/guidance/ng19/chapter/1-Recommendations#diabetic-foot-ulcer [Accessed 29th May 2018]