

Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers

- **Objective:** To compare hard-to-heal venous leg ulcers treated with compression therapy alone versus compression therapy with amelogenin protein. Parameters used were: percentage reduction in wound size, number of improved ulcers, pain related to the disease and at dressing changes, amount and nature of exudate, and the safety and tolerability of the two treatments.
- **Method:** This was an open randomised comparative parallel group multicentre investigation with a three-week run-in period. Inclusion criteria included adult, mobile patients with hard-to-heal venous leg ulcers that had been treated with compression therapy for at least one month prior to screening. The ulcers had to be at least six months old, with a surface area at inclusion of 10–30cm², and not demonstrating excessive exudate or signs of infection. At the end of the run-in period, additional criteria for eligibility, such as change in wound area of $\pm \geq 50\%$ and a wound area between 8cm² and 36cm² were applied. Patients were randomised to treatment with amelogenin plus high compression bandaging or high compression bandaging alone. All participants received high compression bandaging therapy one month prior to and during the three-week run-in period, as well as throughout the 12 weeks of active treatment.
- **Results:** Eighty-three patients were randomised and received treatment: 42 with high compression plus amelogenin (amelogenin group) and 41 to high compression therapy alone (control group). The amelogenin group had a greater percentage reduction in ulcer size (mean -33.11%) compared with the control group (mean -11.07%) from baseline to the last visit ($p=0.06$). The number of improved ulcers was significantly greater ($p=0.01$) in the amelogenin group than in the control group. Compensating for baseline characteristics by multiple regression resulted in a statistically significant ($p=0.03$) larger reduction in change in ulcer size in the amelogenin group. Statistically significant differences in favour of the amelogenin group were also found for reduction in ulcer-related pain ($p=0.01$), reduction in pain at dressing changes ($p=0.02$) and the proportion of patients with 'none' or 'low' levels of exudate ($p=0.01$).
- **Conclusion:** The combination of amelogenin with high compression promotes the healing process in hard-to-heal ulcers. Application of amelogenin as an adjunct to compression results in a significant reduction in ulcer size, improvement in the state of ulcers, reduced pain and a larger proportion of ulcers with low levels of exudate. The results of this study are statistically and clinically significant.
- **Declaration of interest:** This study was funded by Mölnlycke Health Care, Gothenburg, Sweden.

amelogenin; extracellular matrix protein; compression therapy; venous leg ulcers

Approximately 1–2% of the whole population,¹ and 3–5% of the population aged over 65 years will have a leg ulcer during their lifetime,² with the prevalence increasing to 20:1000 of the population at the age of 80.³ This number is likely to increase as the ageing population rises.

Clinical trials have shown modest improvements in healing times with modern dressings, and greatest efficacy has been reported with high compression bandaging — healing rates in the region of 50% at 12 weeks.⁴ However, over 20% remain unhealed after one year.⁵

Extracellular matrix (ECM) proteins define the extracellular environment of living cells. Inappro-

priate matrix remodelling in chronic wounds results from the imbalance of proteinases and their endogenous inhibitors; this may compromise the function of the ECM, especially with respect to the sequence of filling the dermal defect.^{6,7}

Therapy using amelogenin, an ECM-biocompatible protein that provides a temporary matrix for cell attachment and promotes wound healing, has been shown to be successful in the treatment of periodontal wounds.^{8,9} Vowden et al.'s study on patients with venous leg ulcers indicated the potential for amelogenin proteins to assist the healing of 'hard-to-heal' chronic wounds.¹⁰

Subsequent case studies have been conducted on a cohort of patients with venous leg ulcers in rou-

P. Vowden, MD, FRCS, Consultant Vascular Surgeon, Professor of Wound Healing Research, Vascular Unit, Bradford Royal Infirmary, Bradford, UK;
M. Romanelli, MD, PhD, Consultant Dermatologist, Department of Dermatology, University of Pisa, Pisa, Italy;
P. Price, PhD, Professor of Health Sciences, Wound Healing Research Unit, Cardiff, UK;

continued overleaf

on behalf of the European
Xelma Clinical
Investigation team.
Email: peter.vowden@
blueyonder.co.uk

References

1 Anderson, I. Aetiology, assessment and management of leg ulcers. *Wound Essentials* 2006; 1: 20-36.
2 Mekkes, J.R., Loots, M.A., van der Wal, A.C. et al. Causes, investigation and treatment of leg ulceration. *Br J Dermatol* 2003; 148: 3, 388-401.
3 Nelson, E.A., Cullum, N., Jones, J. Venous leg ulcers. *Clinical Evidence* 2006. [www.clinicalevidence.com/wnd/1902/1902.jsp](http://www.clinicalevidence.com/ceweb/conditions/wnd/1902/1902.jsp) (accessed 14 Feb 2007).
4 Franks, P.J., Moody, M., Moffatt, C.J. et al. Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration. *Wound Repair Regen* 2004; 12: 2, 157-162.
5 Barwell, J.R., Davies, C.E., Deacon, J. et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet* 2004; 363: 1854-1859.

tine clinical practice, and the clinical outcomes mirrored those recorded in controlled clinical trials.¹¹ In a study involving 36 patients with hard-to-heal venous leg ulcers, three different amelogenin treatment regimens (three, six and 12 weeks) were compared. The highest reduction in wound size was achieved in patients treated for 12 weeks (72%) when compared with six (46%) and three weeks (22%).¹²

This clinical study evaluated the effect of Xelma (Mölnlycke Health Care), a sterile ECM protein for topical application, consisting of amelogenin proteins dissolved in a propylene glycol alginate vehicle and water, on hard-to-heal venous leg ulcers. Its efficacy and safety in conjunction with compression therapy, versus compression therapy alone, was evaluated. Parameters measured included:

- Percentage reduction in wound size from baseline
- Percentage of improved ulcers
- Pain related to the disease
- Pain at dressing changes
- Amount and nature of exudate.

Safety and tolerability were also determined in relation to recorded adverse events.

Ethics committee approval was obtained in all participating centres. The study was conducted according to the European Standard EN ISO: 14155 Clinical Investigations with Medical Devices.

Method

This was an open randomised comparative parallel group multicentre investigation with a three-week run-in period. The run-in period ensured that a true population of non-healing ulcers had been enrolled as after this only patients with an ulcer size of 8–36cm² and who did not have a change in wound area of $\pm \geq 50\%$ were continued in the study.

One ulcer per patient was included. If there was more than one ulcer, the largest was chosen provided it was in the size range of 8–36cm².

The five variables for efficacy were: wound status; ankle circumference; area tracing of ulcer (cm²); viable tissue (granulation) and non-viable tissue (necrotic, fibrin and/or slough or black and/or yellow necrotic tissue), each measured as a percentage of the actual ulcer area; exudate levels and nature of exudate; wound odour.

Suitable patients were screened for inclusion and exclusion criteria at the screening visit at -3 weeks and were included in the run-in period after ulcer tracing and photography had been performed.

Inclusion criteria

- Venous leg ulcer treated with compression for one month
- Ankle brachial pressure index (ABPI) ≥ 0.8 or TcPO₂ ≥ 40 mmHg
- Ulcer duration of over six months
- Ulcer size 10–30cm²
- Both genders and age over 18 years
- Signed consent form.

Exclusion criteria

- Highly exuding ulcers
 - Clinical signs of wound infection
 - Other causes of ulceration
 - Non-controlled diabetes
 - Treatment with systemic steroids — except occasional doses or doses less than 10mg prednisolone a day or equivalent
 - Atrophic skin due to long-term use of steroids
 - Significant underlying disease
 - Known allergy/hypersensitivity to any of the components of the products included in the study
 - Totally confined to bed or wheelchair
 - Physical and/or mental conditions meaning the patient would not be expected to comply with the investigation
 - Participation in other clinical investigation(s) involving drugs or wound dressings with active substances (such as silver) within one month prior to the run-in period
 - Previously randomised to this investigation.
- Additional exclusion criteria after the run-in period were:
- Wound reduction or enlargement of $\geq 50\%$ in the three-week run-in period
 - Ulcer area $< 8\text{cm}^2$ or $> 36\text{cm}^2$.

Treatment allocation and outcome measures

Patients who continued in the study after the run-in period were randomised to receive high compression therapy alone or high compression therapy with amelogenin added.

Patients randomised to the amelogenin group

Table 1. Number of patients screened (n=101) and enrolled into the study

	Amelogenin	Control
Randomised	42	41
Intention to treat	42 (100%)	41 (100%)
Per protocol	30 (71%)	25 (61%)
Discontinued*	9 (21%)	15 (37%)
Wound enlargement not reported as adverse event	1 (2%)	0 (0%)
Two-week interval in the treatment period	1 (2%)	0 (0%)
Discontinuation, incomplete data†	1 (2%)	1 (2%)

* Healing not counted as discontinuation
† Information still at site at the time of writing

received one application per week. A secondary dressing combination of Mepitel and Mesorb or Mepilex (all Mölnlycke Health Care) was used to manage exudate and protect the wound. Medications considered necessary for the patient's well-being were given at the discretion of the investigator and recorded in the case-report form.

Clinical photographs were taken to provide a visual record of wound progress. Patients were free to discontinue at any time, and without prejudice to further treatment; those who discontinued were asked the reason(s) for this and about the occurrence of any adverse event or adverse device effect, and were assessed by an investigator/nurse.

The primary efficacy variable was the percentage change in ulcer size from baseline to the last visit in the investigation and an associated improvement in ulcers. The last visit was either the final visit at 12 weeks or the visit at which the patient healed or was discontinued prematurely. The last observation carried forward technique was used to achieve consistency of the data.

Statistical evaluation

The sample size needed was calculated with reference to the primary endpoint (comparing the reduction in wound size as measured by the mean percentage decrease from baseline to the last visit). Assuming a 32% difference in favour for patients treated with amelogenin, a power of 80%, a significance level of 95% (two-sided) and a standard deviation of 50%, it was calculated that 42 patients were needed in each treatment group.

The primary endpoint was analysed using the non-parametric Wilcoxon Mann-Whitney U test, as was the analysis of pain related to the disease and experienced at dressing change. The rate of healed and improved patients and comparisons of exudate levels were analysed using Fisher's exact test between the groups at the final time point.

To adjust the main efficacy analyses for measured covariates at baseline, multiple logistic regression was calculated. The primary efficacy variable was considered the main variable in the model; the group variable was the dependent variable; wound size, wound duration, viable tissue, ankle circumference, exudate level, body mass index (BMI) and maceration were included as independent covariates. In this way the two treatment groups were adjusted for these baseline variables. The result of the adjusted analysis is the expected result if all covariates were adjusted to have the same mean in the two treatment groups at baseline. For the safety population, the number of subjects with an adverse effect, adverse device effect, serious adverse event or serious adverse device event were analysed using a log-rank test, and pain was analysed using the Wilcoxon Mann-Whitney U test.

Table 2. Baseline demographic and clinical characteristics

	Amelogenin (n=42)	Control (n=41)
Age	68.5 (13.7) 71.0 (25.6–91.2)	72.7 (12.9) 75.5 (33.5–93.4)
Male	17 (41%)	15 (37%)
Caucasian	41 (98%)	41 (100%)
Height (cm)	169.1 (10.2) 168.0 (148.0–204.0)	168.2 (10.2) 168.0 (147.0–195.0)
Weight (kg)	89.6 (26.4) 80.0 (50.0–170.0)	80.5 (20.1) 76.0 (50.0–137.0)
BMI (kg/m ²)	31.3 (9.0) 28.3 (19.9–57.5)	28.4 (6.3) 27.4 (17.9–43.0)
Systolic blood pressure (mmHg)	138.7 (18.2) 140.0 (100.0–190.0)	136.0 (16.9) 135.0 (104.0–197.0)
Diastolic blood pressure (mmHg)	82.3 (12.8) 80.0 (59.0–140.0)	78.6 (10.8) 80.0 (50.0–100.0)
Pulse (BPM)	75.1 (12.5) 76.0 (51.0–108.0)	73.6 (6.7) 72.0 (64.0–86.0)
Medical history		
Underlying diseases	28 (67%)	30 (73%)
Surgical interventions	12 (29%)	17 (42%)
Diabetes	4 (10%)	4 (10%)
ABPI	41 (100%)	39 (95%)

BMI = body mass index; BPM = beats per minute; ABPI = ankle brachial pressure index
Data are presented as mean (SD) and median (minimum–maximum)

Table 3. Wound history at baseline

Amelogenin (n=42)		Control (n=41)	
Ulcer duration (months)	Ulcer size (cm ²)	Ulcer duration (months)	Ulcer size (cm ²)
55.3 (62.7)	17.0 (9.1)	32.4 (27.8)	18.0 (9.0)
30.0 (6.0–240.0)	14.3 (8.7–59.4)	24.0 (6.0–120.0)	17.4 (5.5–46.1)

Data are presented as mean (SD) and median (minimum–maximum)

Results

Eighty-three of the 101 screened patients were randomised and entered the treatment phase (Table 1). The intention-to-treat population included all patients who received at least one treatment.

Forty-two patients were treated with amelogenin plus compression therapy, and 41 with compression alone. The per-protocol populations were amelogenin

6 Gailit, J., Clark, R.A. Wound repair in the context of extracellular matrix. *Curr Opin Cell Biol* 1994; 6: 717-725.

7 Tomic-Canic, M., Agren, M.S., Alvarez, O.M. Epidermal repair and the chronic wound. In: Rovee, D.T., Maibach, H.I. (eds). *The Epidermis in Wound Healing*. CRC Press, 2004.

8 Hoang, A.M., Klebe, R.J., Steffensen, B. et al. Amelogenin is a cell adhesion protein. *J Dent Res* 2002; 81: 497-500.

9 Okubo, K., Kobayashi, M., Takiguchi, T. et al. Participation of endogenous IGF-I and TGF-beta 1 with enamel matrix derivative-stimulated cell growth in human periodontal ligament cells. *J Periodontol Res* 2003; 38: 1-9.

10 Vowden, P., Romanelli, M., Peter, R., Bostrum, A. et al. The effect of amelogenins (Xelma) on hard-to-heal venous leg ulcers. *Wound Repair Regen* 2006; 14: 3, 240-246.

11 Hultdt, T., Helge, J., Dufour, N. et al. Treatment of hard to heal chronic venous ulceration with amelogenin: the Norwegian experience. *SAR* 2006; 4.

Table 4. Number of subjects with adverse events and/or adverse device events per treatment

System organ class/ preferred term	Amelogenin (n=42)				Control (n=41)			
	Not serious		Serious		Not serious		Serious	
	AE	ADE	SAE	SADE	AE	ADE	SAE	SADE
Cardiac disorders:								
• cardiomyopathy					1 (2%)		1 (2%)	
• cardiovascular disorder	1 (2%)		1 (2%)					
General disorders and administration-site conditions:								
• ulcer	1 (2%)							
Infections and infestations:								
• bronchitis					1 (2%)			
• cellulitis	1 (2%)				1 (2%)	1 (2%)	1 (2%)	
• erysipelas					1 (2%)			
• eye infection						1 (2%)		
• infection						1 (2%)		
• influenza	2 (5%)							
• paronychia	1 (2%)							
• skin infection					1 (2%)	1 (2%)		
• wound infection	3 (7%)	2 (5%)		1 (2%)	3 (7%)	1 (2%)		
Injury, poisoning and procedural complications:								
• procedural complication			1 (2%)	1 (2%)				
• wound					2 (5%)	1 (2%)		
• wound complication	2 (5%)	3 (7%)			5 (12%)	1 (2%)		
Musculoskeletal and connective tissue disorders:								
• arthralgia						1 (2%)		
• joint swelling	1 (2%)							
• muscle spasms		1 (2%)						
Nervous system disorders:								
• headache		1 (2%)			1 (2%)			
Skin and subcutaneous tissue disorders:								
• eczema			1 (2%)				2 (5%)	
• erythema					1 (2%)			
• pruritus						1 (2%)		
• venous ulcer pain					1 (2%)	1 (2%)		
Vascular disorders:								
• thrombophlebitis	1 (2%)							

Each subject is counted only once per system organ class/preferred term
 AE = adverse event; ADE = adverse device event; SAE = serious adverse event; SADE = serious adverse device event

group n=30; control group n=25. Descriptive statistics for patient demographics, clinical characteristics and medical history are presented in Table 2. Wound duration and sizes at baseline and their descriptive statistics are presented in Table 3.

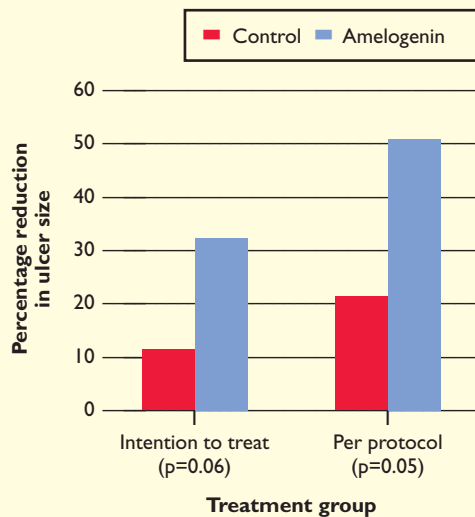
Nine patients in the amelogenin group and 15 in the control group discontinued the investigation for various reasons excluding healing during the treatment period. Most did so because of adverse effects

(seven patients in both groups). In the control group three patients withdrew consent and four were lost to follow-up. No patients in the amelogenin group withdrew consent; discontinuation was due to low concordance (Table 4).

Statistical analysis

The primary efficacy analysis was the difference in the percentage change in ulcer size from baseline to

Fig 1. Statistical comparison (control versus amelogenin) of the final reduction in ulcer size



the last visit between the two treatment groups (Fig 1). The results (intention-to-treat data) show that the mean percentage change for the amelogenin group was -33.11% (SD 49.69%) and for the control group -11.07% (SD 46.55%) (p=0.06).

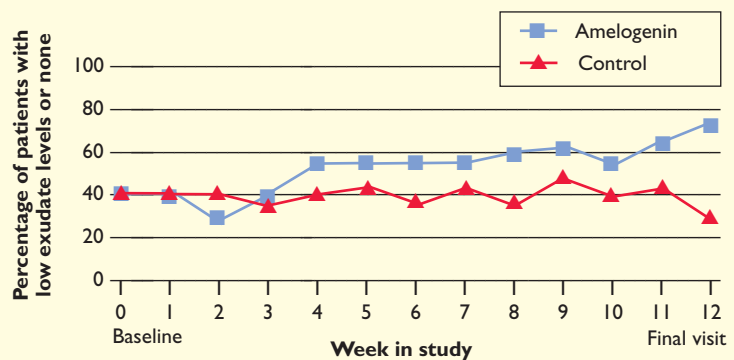
The data relating to the reduction in ulcer size showed more wounds with reductions of 50–100% in the amelogenin group and, conversely, more wounds with increases of 50–100% in the control group. The overall healing rate was greater in the amelogenin group. The percentage of improved ulcers at the final visit was statistically significantly higher — 47.5% in the amelogenin group compared with 19.5% in the control group (p=0.01).

Compensating for baseline characteristics by using a multiple regression test revealed a statistically significant (p=0.03) reduction in percentage change in ulcer size in the amelogenin group. The mean and 95% confidence interval (CI) for the difference between the amelogenin and the control group was -22.04% (-43.08 to -1.01%) (p=0.03) (intention-to-treat data).

Similar results were seen for the per-protocol data: amelogenin group reduction in ulcer area -50.33% (SD 41.86%) and control -21.16% (SD 50.54%) (p=0.03).

Pain was estimated using an ordinal scale with 11 step, from 0 = none to 10 = unbearable pain.¹³ The results showed that reductions in disease-related pain and pain at dressing changes were more apparent in the amelogenin group. Statistical analysis showed that the amelogenin group had significantly greater ulcer pain reduction (p=0.01); the mean and 95% CI for the difference in pain reduction between

Fig 2. Percentage of patients with low levels of exudate or none in the amelogenin and control groups per week



the amelogenin and control groups at the final visit was -1.59 (-2.84 to -0.34).

The level of exudate was estimated as ‘none’, ‘low’, ‘moderate’ or ‘high’. In the amelogenin group, ‘none’ and ‘low’ exudate levels were recorded for 28 patients (66%), compared with 15 patients in the control group (37%) (Fig 2). There were more patients in the amelogenin group with ‘none’ or ‘low’ exudate levels for much of the treatment period. Comparison of ‘moderate’ or ‘high’ exudate levels between the two treatment groups over the course of the 12-week study shows that a significant (p=0.01) reduction in the higher levels of wound exudate occurred in the amelogenin group, but not in the control group.

Discussion

The personal suffering and financial costs involved in the treatment of venous leg ulcer are high: in the UK the annual cost is £400–600 million.¹⁴

High compression bandaging is recognised as the ‘gold standard’ treatment. Alternative approaches such as growth factors and artificial skin have projected greater efficacy than traditional dressings, with significantly greater costs, but results to date have been mixed.¹⁵

This highlights the need for new advanced treatments that can stimulate non-healing chronic wounds into a healing process. Amelogenin provides a surrogate ECM protein that aids healing, and has been demonstrated to promote healing in patients with hard-to-heal venous leg ulcers.¹⁰

In this study the Wilcoxon Mann-Whitney U test, when applied to the primary efficacy (intention-to-treat) data, gave a p value of 0.06 in favour of the amelogenin group. The results (intention-to-treat data) show that the mean percentage change in wound size from baseline to the last visit for the amelogenin group was -33.11% (SD 49.69%) and for the control group -11.07% (SD 46.55%) (p=0.06).

12 Ellervee, T., Jarve, H., Kaha, E. et al. Enamel matrix proteins (EMP) in hard-to-heal venous leg ulcers, an open regime investigation. Poster presented at the 8th Annual Symposium on Advanced Wound Care and Medical Research Forum on Wound Repair (SAWC), San Diego, 2005.

13 Hartrick, C.T., Kovan, J.P., Shapiro, S. The numeric rating scale for clinical pain measurement: a ratio measure. *Pain Pract* 2003; 3: 4, 310-316.

14 Bosanquet, N. Cost of venous ulcers from maintenance therapy to investment programme. *Phlebol* 1992; 1 (Suppl): 44-46.

15 Khan, M.N., Davies, C.G. Advances in the management of leg ulcers — the potential role of growth factors. *Int Wound J* 2006; 3: 2, 113-119.

16 Margolis, D.J., Allen-Taylor, L., Hoffstad, O. et al. The accuracy of venous leg ulcer prognostic models in a wound care system. *Wound Repair Regen* 2004; 12: 2, 163-168.

17 Douglas, V. Pain in venous leg ulcers and its impact on quality of life. In: White, R., Harding, K., (eds). *Trauma and Pain in Wound Care*. Wounds UK, 2006.

18 European Wound Management Association. Position document: Pain at Wound Dressing Changes. MEP, 2002.

19 Independent Advisory Group. Best Practice Statement: Minimising Trauma and Pain in Wound Management, 2004. www.wounds-uk.com (accessed 14 February 2007).

20 World Union of Wound Healing Societies. Principles of Best Practice: Minimising Trauma and Pain at Wound Dressing-Related Procedures. A consensus document, 2004. www.wuwhs.org/datas/2_1/2/A_consensus_document (accessed 14 February 2007).

Wound area measurements substantiate these results, showing more patients with a 50–100% reduction in wound size in the amelogenin group ($p=0.01$).

Further analysis was undertaken using multiple logistic regression,¹⁶ which allowed for the inclusion of the baseline variables of wound size, wound duration, viable tissue, ankle circumference, level of exudate, BMI and maceration. This gave p values of 0.03 in favour of the amelogenin group for both the intention-to-treat and per-protocol population data.

These results show the amelogenin group to have significant benefits, statistically and clinically, over the control group.

It is noteworthy that the patient population in this study had difficult-to-heal ulcers, some wounds with a very long duration (10 years or more) and mean ages of 55.3 months (SD 62.7) versus 32.4 months (SD 27.8), and mean sizes of 17.0cm² (SD 9.1) versus 18.0cm² (SD 9.0) for the amelogenin and control groups respectively. This underlines the significant clinical benefit of amelogenin therapy in this patient population.

In any evaluation, wound area measurements or percentage changes in ulcer size are only superficial measurements of healing as they fail to take wound depth into account. The photographs taken while the current study was in progress provide an important record and allow a qualitative evaluation of healing progress in each of the groups.

A series of photographs of a venous leg ulcer treated with amelogenin is provided (Figs 3–6). This 83-year-old, female, Caucasian patient presented with an ulcer of eight months' duration on the left leg; there was no other underlying disease. At the start of the run-in period the wound area was 17.9cm², reducing to 0.02cm² by week 9, when it had effectively healed.

The photographs demonstrate the progression of healing as the wound fills with granulation tissue and epithelial cells cover the wound bed. At the final time point complete healing has occurred and visually the scar tissue was good with no evidence of hypertrophy or contracture.

Significant differences in favour of the amelogenin group were also found for the following secondary variables:

- Reduction in pain at dressing changes
- The proportion of patients with 'none' or 'low' levels of exudate.

Pain is a considerable problem for patients with venous leg ulcers, and a major concern when treating patients.¹⁷⁻²⁰ Thus, the fact that amelogenin therapy, in a way as yet undetermined, significantly reduced pain in these patients in this study is noteworthy and perhaps requires further investigation.

The results have also demonstrated more patients treated with amelogenin had no or low exudate lev-



Fig 3. Ulcer at beginning of the run-in period (15 November 2005): large clean wound (17.9cm²)



Fig 4. Ulcer at baseline (7 December 2005): still a large clean wound after the run-in period



Fig 5. Ulcer at four weeks' treatment (5 January 2006): significant healing with re-epithelialisation and granulation tissue formation. No maceration and skin adjacent to wound appears very healthy



Fig 6. Ulcer at 12 weeks' treatment (4 February 2006): qualitatively, an excellently healed wound, with little scar tissue or contracture

els, which may correlate with better healing and/or reduced infection.

No other secondary variables, such as viable tissue, ankle and calf circumference and wound odour, showed any significant difference between the two treatment groups.

The total number of adverse events in the two groups was similar; investigation of vital signs, weight and BMI did not reveal any safety issues. The most commonly reported serious adverse event/serious adverse device event was reported under the heading 'cardiac disorders' and 'infections and infestations', with single reports under each heading in both treatment groups. No consistent pattern of adverse events evolved in the investigations, suggesting good safety of the two treatments.

Conclusion

These results support other clinical studies¹⁰⁻¹² that have demonstrated that the combination of amelogenin with high compression bandaging is significantly beneficial to the healing of hard-to-heal venous leg ulcers in the following areas:

- Reduction in ulcer size
- Improvement in the state of ulcers
- Reduction of pain between visits and at dressing change
- Larger proportion of ulcers with low levels of exudate.

The investigation indicates that amelogenin (Xelma) is safe and effective in the treatment of hard-to-heal venous leg ulcers that have failed to heal with

standard therapy.

The ulcers in this study present the worst-case scenario in this indication, in that some patients had presented with their wounds many years previously and no treatment was effective in initiating or maintaining a healing response.

This study also highlights the importance of applying amelogenin to a clean/non-infected wound bed, preferably in association with high compression therapy.

Although the mechanism by which the amelogenin initiates healing is not yet fully understood, it is thought the protein acts as a surrogate ECM within a wound that is lacking components normally required to support cell proliferation, growth and maturation. Thus, cell adhesion to the amelogenin matrix may enable the wound-healing response to be initiated and proceed in a more normal fashion. Further work is needed to clarify this mechanism so that the product can be used in an optimal way.

This study has also shown that Xelma significantly reduced the level of pain associated with venous ulceration. This is a clinically significant finding and the mechanism by which this occurs needs to be elucidated in future studies. ■