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The Potential Role for a Painless Enzymatic Debridement Gel in Wound Bed Preparation for Venous Leg Ulcers—A Dose Escalation Study

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ABSTRACT

Venous leg ulcers (VLUs) are painful wounds that require thorough debridement to optimise their chances of healing. We sought to assess the impact on debridement pain from the use of tarumase gel in a prospective Phase IIA open-label, multi-centre, dose escalation study and comparing this to historical pain scores derived from a review of surgical and mechanical debridement within similar chronic wound populations. With tarumase gel, no increase in pain over baseline was observed, irrespective of whether pain was assessed 15–30 min after administration or whether the gel had been resident on the wound for 48–72 h. At the highest concentration of tarumase tested [11 U/mL], all reported NRS scores were below 2.90 (categorised as slight pain) with small trends towards a reduction in the pain score from as early as the first application. By contrast, from previous literature, surgical and mechanical debridement, when used without anaesthesia, commonly resulted in pain scores in excess of 50 mm on 100 mm visual analogue scales (VAS), categorised as moderate to severe pain. Pain from surgical/mechanical debridement can be reduced by topical anaesthetic creams; however, this requires at least 30–60 min of application and subsequent removal prior to debridement, making it impractical to use in busy clinic facilities.

1 | Introduction

Chronic wounds are defined as wounds characterised by delayed healing, typically by more than 6–12 weeks or by wounds that do not heal at all [1, 2]. Although aetiologies vary between venous leg ulcers (VLUs), diabetic foot ulcers (DFU) and pressure ulcers (PU), symptomology, notably excess wound exudate, necrotic/sloughy wounds, wound infection, wound odour and/or wound pain remain common [3]. In this context, debridement is a key aspect of the now well-established TIME paradigm within wound bed preparation, used to remove non-viable material from the wound, reduce potential bioburden and restore the viability of the wound base with a view to accelerating healing.

Repeated debridement of chronic wounds during the healing process has been shown to be clinically beneficial. In one retrospective cohort study reported by Wilcox et al. [4] and involving 525 wound care centres (representing 154 644 with 312 744 wounds of all causes), the authors report that in regard to time to heal, a significantly higher proportion of wounds that received weekly or more frequent surgical debridement ($p < 0.001$) healed in a shorter period of time. Similarly, Cardinal et al. [5], performed a retrospective analysis of two controlled prospective randomised trials of topical wound treatments and noted that centres where patients were debrided more frequently were associated with higher rates of wound closure in both clinical studies ($p = 0.007$ VLU, $p = 0.015$ DFU).

Summary

- The study highlights that tarumase gels up to 11 U/mL did not result in any increase in pain to the patient above baseline levels whether assessed shortly after administration or after having been left on the wound for 48–72 h.
- Surgical and mechanical wound debridement is a painful procedure and whilst this can be reduced by topical administration of local anaesthesia prior to debridement, this is not routinely performed due to the long wait times needed for onset of anaesthesia.

Debridement, especially by surgical or mechanical means which remains the most common standard of care in the US, can however be a painful experience for many patients, especially where the ulcer is not neuropathic. Leg ulcers are particularly noted to be frequently painful [6–9] and in one study [10] pain was found to be the key symptom of VLU leading patients to seek medical attention for their ulcers. It is therefore unsurprising that VLU studies also indicate that patients typically have a poorer quality of life compared with age-matched controls [11–14].

Krasner [15] conducted interviews with 14 people with VLU's to explore the meaning of the experience of living with venous ulcers. Eight key themes were identified and one of these themes was concern over the aspect of starting the pain all over again through [repeated] painful debridement. Green et al. [16] also carried out initial unstructured interviews with nine patients suffering with a leg ulcer which revealed significant issues for the patients including the dominance of pain, issues relating to exudate and odour, social isolation and psychological effects. Pain was reported by all nine participants and formed the very core of each interview. Pain dominated the patients' lives and limited their functioning. All spoke of their reluctance to take analgesia, often because they were already taking a cocktail of medications for their comorbidities.

Pain is clearly an overriding symptom in VLU, with ongoing concerns raised about the need for repeated painful, surgical or mechanical debridement to aid healing. In this context, there is a medical imperative to ensure that effective debridement procedures do not add to the patient's pain burden, and indeed where possible, can help reduce pain through e.g., cooling effects of gels or creams when added to the wound. Whereas autolytic techniques of achieving debridement have been shown to be largely painless [17], the rate of debridement is significantly slower. By contrast, surgical and mechanical debridement effect more rapid debridement but are often associated with significant pain.

This study sought to compare the potential for debridement pain and/or pain on application arising from the use of a new enzymatic debridement treatment (tarumase in combination with a proprietary hydrogel) and compared these data against historical pain scores experienced by patients during and/or after surgical or mechanical debridement. Additional qualitative and quantitative information in relation to pain (and other side-effects) is provided for other enzymes used now or in the past for removing devitalised tissue from chronic wounds and burns.

2 | Materials and Methods

2.1 | Phase IIA Clinical Trial of Tarumase Gel

The clinical study reported here was a prospective, open-label, multi-centre, dose escalation study that was conducted in accordance with the requirements of the International Council on Harmonisation Good Clinical Practice (ICH GCP) and in accordance with national regulations and guidance of the United Kingdom, Hungary and the USA across a total of eight clinical centres using 43 patients with sloughy VLUs.

Patients enrolled to the study were required to be ≥ 18 years of age, to have provided written informed consent, to be in a good general state of physical and mental health, as assessed by the investigator and to have a confirmed VLU (2–50 cm^2 in size) present for less than 2 years, that contained sufficient non-viable tissue requiring clinical debridement. Exclusions included abnormal blood laboratory and/or vital signs; clinical signs of infection during screening (including use of oral or IV antibiotics); bleeding disorders and/or use of anti-thrombotic therapy in the screening period; deep ulcers (i.e., exposed tendons, ligaments, muscle or bone); wounds with high levels of exudate; prior skin graft, use of negative pressure wound therapy (NPWT), systemic or cutaneously applied growth factors, use of other enzymatic debriding agents or live maggot therapy within 2 weeks before screening; and pregnant or breastfeeding women.

Patients attended visits every 2–3 days for dressing changes, and re-application of the tarumase gel was made at each dressing change through to the end of 4 weeks. Application of the gel occurred after wound cleansing and was performed without any anaesthesia or mandated wound edge protection. Five cohorts of patients were to be enrolled sequentially. Cohort 1 (five patients) was dosed with the hydrogel vehicle (placebo); Cohorts 2–5 utilised increasing concentrations of tarumase in the vehicle at 1 U/mL, 2 U/mL, 6 U/mL and 11 U/mL and recruited 9, 10, 9 and 10 patients per cohort, respectively. There was no stratification of patients, and patients were enrolled sequentially provided they met the inclusion/exclusion criteria.

As part of the clinical study, assessments of pain were collected at each visit using an 11-point numerical rating scale (NRS), where 0 = no pain and 10 = worst pain imaginable. At each visit, pain assessments were performed (i) prior to the wound dressing change, (ii) within 5 min of the dressing change and (iii) within 15–30 min of applying the tarumase gel. In this context, all aspects of pain during the course of treatment with tarumase gel were considered.

Differences in mean pain scores (End of Treatment Pain [before dressing removed] – Baseline pain [before dressing removed]) was tested using a Student's *t*-test for paired data.

2.2 | Literature Review

A systematic search strategy involving PubMed/Medline, Cochrane Library, Google Scholar and clinical trial databases (ClinicalTrials.gov and EudraCT) was conducted to identify potentially relevant published clinical studies relating to

surgical and mechanical debridement. Specific keywords and Medical Subject Heading (MESH) terms using Boolean operators; terms included: 'surgical', 'sharp', 'mechanical', 'wet-to-dry', in combination with references to 'debridement pain' and 'chronic wounds' [leg ulcer, pressure ulcer, diabetic foot ulcer]. All randomised controlled trials (RCTs), systematic review articles, and/or non-randomised, cohort controlled studies in the English language that evaluated debridement pain as a reported primary or secondary endpoint and published through to 31 January 2024 were included in the review. Laboratory studies, animal-related studies and clinical studies that were performed exclusively in neuropathic ulcers were excluded from the analysis. Supplementing this analysis, a qualitative commentary on pain-related adverse events associated with the use of other enzymatic debridement was performed.

Both authors carried out screening of potential papers by independently reading titles and abstracts to exclude literature that obviously did not conform to the inclusion criteria. In the case of systematic reviews, featuring multiple studies in a single published work, clinical data on study contents were extracted as needed. Manuscripts with significant unresolvable differences of opinion were excluded from the analysis.

3 | Results

3.1 | Phase IIA Clinical Trial of Tarumase

Overall, 43 patients were recruited to the clinical study and 39/43 (91%) completed all assessments through to week 4 of the clinical study. Mean age of patients was 68.6 ± 14.75 years, 57/43% were male/female and had a mean wound size of 13.92 ± 12.71 cm^2 at baseline. The median age of the wounds included in the study fell in the range of 3–6 months, with only 12% of participants having a wound greater than 1 year.

Mean (±SD) pain scores derived at each of the visits are summarised in Table 1, and show that the addition of increasing concentrations of tarumase to the wound bed over the four-week period did not add to the patient's baseline pain scores at any time point. Indeed, even at the highest concentrations of tarumase applied (11 U/mL), the mean pain score throughout the four-week period of the study was always reported at or below the baseline pain score of 2.9 ± 1.5 (categorised as slight pain). When tested, there was no statistical significance between baseline pain score (before dressing was removed) and end of treatment (also before dressing was removed) ($p > 0.05$) however, small numerical trends towards reduction in pain scores were observed across all tarumase treated groups from as early as the first application.

3.2 | Literature Review

The literature search performed initially identified a total of 551 publications. After application of the inclusion/exclusion criteria, a total of 10 references were identified as providing relevant information in respect of pain during surgical/sharp debridement (eight publications; $n = 570$) or mechanical debridement (two references; $n = 110$) (See Figure 1).

3.2.1 | Surgical/Sharp Debridement

Seven prospective RCTs [18–24] and one retrospective cohort controlled study [25] that assessed pain during surgical/sharp debridement across a range of venous, arterial and mixed aetiology leg ulcers, as well as DFU wounds were included in the analysis. The mean age of the patients across these studies ($n = 8$) was 68 ± 3 years and included wound sizes of 35.4 ± 59 cm^2. Wound sizes were heavily influenced by one study reported by Mosti et al. [25] in a series of mixed aetiology wounds; excluding these data, wound sizes were reduced to 10.4 ± 8.1 cm^2.

In six of the studies, the primary aim was a consideration of the efficacy of local anaesthesia (EMLA Cream) to reduce debridement pain. In two studies [19, 25], pain was a secondary measure whilst assessing the comparative efficacy of surgical with laser debridement and hydrosurgical with autolytic debridement, respectively. No studies reported baseline pain scores prior to debridement.

In all eight of the reported studies, a 100 mm self-reported visual analogue scale (VAS) was used as a means to assess pain in patients where 0 mm = no pain and 100 mm = worst pain possible. Scores were reported as either median scores in five studies and a mean score in three studies. Additional pain assessments were included in four of the reported studies, and these comprised four-point categorical scales (No pain, mild or slight pain, moderate pain and severe pain); an investigator 100 mm VAS was also used in one study.

Due to the heterogeneity of reporting data, no formal meta-analysis could be performed on the reported studies; however, a qualitative analysis of these studies indicates that surgical debridement without anaesthesia consistently results in significantly higher VAS (i.e., worse pain), typically in the region of 50 mm but up to a reported maximum of 88 mm in VLU (i.e., severe pain) (Table 2). Topically applied anaesthesia, as expected, did have a significant effect on reducing the pain experienced by patients during surgical debridement; however, it is notable that topical application of EMLA Cream for at least 20 min (and ideally 60 min) prior to debridement is needed to have any significant effect on reducing pain [24, 25]. The pain reported with a hydrosurgical device (Versajet) by Mosti et al. [25] was also within the same range as that reported for use of a scalpel (43 mm), although the authors note that pain could be reduced by altering the power level according to the patient's tolerance; even so, some form of anaesthesia was given to 25/68 (37%) patients complaining of very painful ulcers prior to debridement.

3.2.2 | Mechanical Debridement

Only two RCTs were included within the context of mechanical debridement; both described the use of a curette as a scraping tool to remove non-viable tissue from the wounds [26, 27]. Other studies involving mechanical debridement were excluded from the analysis due to poor quality and/or lack of controls. In both included studies, self-reported pain using a 100 cm VAS was the primary efficacy analysis. One study (Lok et al. [26]) considered the efficacy of anaesthesia (EMLA Cream) on mechanical debridement vs. placebo, and in the other study (Claeys et al.

TABLE 1 | Mean (±SD) reported pain scores in the tarumase phase IIA clinical trial in venous leg ulcers.

	Control (Vehicle) ($n=5$)	1 U/mL ($n=9$)	2 U/mL ($n=10$)	6 U/mL ($n=9$)	11 U/mL ($n=10$)
Baseline					
Before dressing removed	2.40 ± 1.517	3.11 ± 1.054	3.40 ± 1.506	3.11 ± 2.713	2.90 ± 1.524
After dressing removed	2.60 ± 0.894	2.89 ± 1.269	3.60 ± 1.430	3.22 ± 2.906	2.80 ± 1.619
After first application					
15–30 min post dose	2.00 ± 0.707	2.67 ± 1.414	2.80 ± 1.398	3.00 ± 2.784	2.70 ± 1.889
After 3× applications (Wk 1)					
Before dressing removed	1.40 ± 0.894	2.13 ± 1.727	2.44 ± 1.236	4.00 ± 3.464	2.40 ± 1.838
After dressing removed	1.60 ± 1.342	2.63 ± 1.768	2.78 ± 1.394	3.78 ± 2.949	2.50 ± 2.014
15–30 min post dose	1.40 ± 1.517	2.38 ± 1.598	2.67 ± 1.323	3.56 ± 2.877	2.11 ± 1.691
After 6× applications (Wk 2)					
Before dressing removed	1.40 ± 0.894	2.13 ± 1.727	2.44 ± 1.878	2.89 ± 3.333	2.29 ± 1.380
After dressing removed	1.20 ± 1.095	2.63 ± 1.847	2.78 ± 1.563	2.89 ± 2.571	2.86 ± 2.035
15–30 min post-dose	1.00 ± 0.707	2.25 ± 1.982	2.33 ± 1.323	1.86 ± 2.268	1.67 ± 1.862
After 9× applications (Wk 3)					
Before dressing removed	2.00 ± 2.236	2.14 ± 1.464	3.44 ± 3.005	2.20 ± 2.864	1.14 ± 1.215
After dressing removed	1.60 ± 1.517	2.29 ± 1.496	2.33 ± 1.936	2.40 ± 2.881	1.86 ± 2.035
15–30 min post-dose	1.20 ± 1.095	2.00 ± 1.732	2.22 ± 1.394	3.00 ± 2.646	1.29 ± 1.380
End of treatment (Wk 4)					
Before dressing removed	1.00 ± 0.707	2.22 ± 1.563	2.50 ± 2.506	2.13 ± 2.748	2.20 ± 1.619
Differences between baseline and end of treatment					
(Before dressing removed)	−1.4	−0.89	−0.9	−0.98	−0.70
p-value	0.134	0.137	0.214	0.149	0.225

[27]) the effects of two anaesthetics (Nitrous Oxide Mixture vs. EMLA) were compared.

Results indicated that mechanical debridement without anaesthesia produced a median pain score of 50 mm, largely comparable with that noted for surgical debridement. Where locally applied anaesthesia was used (EMLA) pain was reduced in one study to a median of 23 mm and in the other a reported mean of 36.8 mm. The use of Nitrous Oxide mixture did not, however, have a clinically beneficial effect and in this context reported a mean pain of 52.9 mm on the self-reported VAS.

4 | Discussion

Review of the literature indicates that surgical and/or mechanical debridement of chronic ulcers, without topical anaesthesia, routinely results in higher pain scores, typically > 50 mm on a VAS scale and which could be categorised as moderate to severe pain.

Although most wounds from the reported studies were noted as either VLU wounds only or mixed aetiology wounds (reported as a single measure), one small study [19] did provide differential data between VLU and DFU pain scores, with an

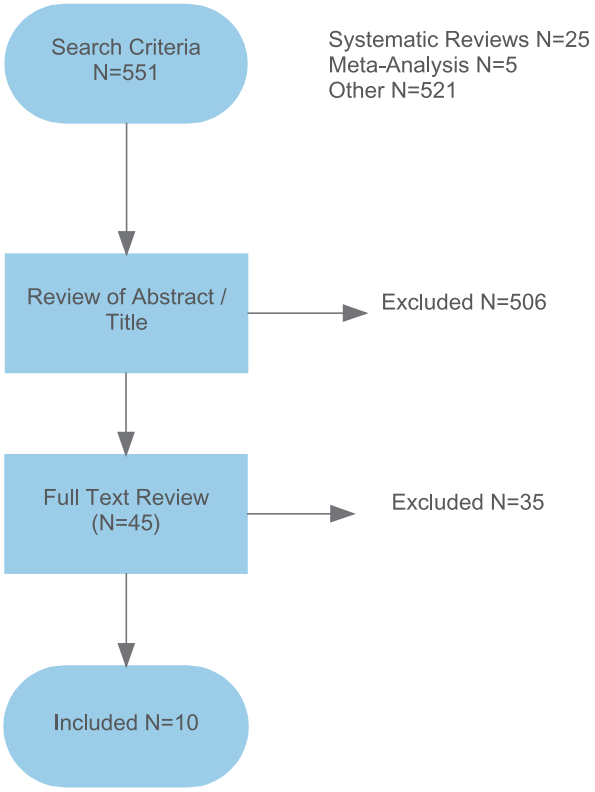

FIGURE 1 | Flow-chart showing exclusions.

indication that DFU wounds are likely less painful to debride, presumably due to the presence of some neuropathy at the wound site.

4.1 | Enzymatic Debridement

A recent systematic peer-reviewed analysis of the history and current practice of the use of enzymes in wound care [28] showcased three decades of clinical and laboratory study of the use of many different enzymes to effect wound bed cleansing, and potentially also to promote healing [28]. Historically, collagenases, ureases, papain, bromelain, and several other proteolytic enzymes have been tried in clinical studies and in patient populations [28]; there have been reports of both local and systemic toxicities with various enzymes in clinical use, which have, as with papain-urea, completely curtailed their current use [28]. There is a necessary balance to strike in the choice of enzyme between speed and completeness of action against wound bed devitalised tissue versus ensuring a lack of local or systemic toxicities resulting from these powerful agents in clinical use. In the acute burn setting, the prioritisation of rapid removal of eschar means that pain from debridement (enzymatic or otherwise) has to be catered for if the agent used is capable of robust debridement. Equally, in chronic indolent wounds, there is more flexibility available clinically, and clinicians and patients are not necessarily in a precipitate rush to debride chronic wounds as fast as surgical approaches can.

The use of concentrated pineapple-stem enzyme preparations such as Bromelain without analgesia has a significant pain-inducing effect in acute burn patients, necessitating enhanced protocols of analgosedation and/or locoregional anaesthesia during Bromelain-based debridement [29]. Pain in the acute burn situation can be dealt with more effectively by sedation as these patients are often very unwell, especially if frail or elderly. This choice would be much less clinically safe to adopt in a home-care or outpatient setting with elderly frail patients with diabetic, pressure or chronic VLUs.

The same enzymatic substrate (bromelain) has been studied in the chronic wound setting. For example, in the 2018 report [30] from a selection of chronic wound patients who had 10% bromelain applied to the wound bed the statement 'peri-procedural pain was reported in five of the 24 patients (21%), and injury of the peri-wound skin was reported in four of the 24 patients'; while VAS scores were apparently measured in all patients reported in this study, these data were not presented in this manuscript.

In a later similar follow-on study again in chronic wounds of diverse aetiology, Shoham et al. [31] tested 5% bromelain based debridement versus hydrogel. Here, VAS pain scores were reported, though the range of score seen in vehicle and treatment-arm subjects was very wide (approximately 1–7 on the VAS scale), with high score for vehicle treated subjects even before treatment was delivered. For example, VAS pain scores before the first study application were 2.9 ± 2.9 in the Bromelain group and 3.4 ± 3.0 in the Gel group. After the first, second, and third study applications, the VAS pain scores were 2.8 ± 2.4, 3.9 ± 3.2 and 3.5 ± 3.1 in the Bromelain group and 2.8 ± 3.1, 3.3 ± 3.4 and 2.9 ± 2.9 in the Gel group accordingly. Pain scores tended to be slightly higher in the VLU subgroup—for example, the VAS pain scores in the VLU subgroup before the first study application were 3.5 ± 3.5 in the bromelain group and a very high value (severe pain) of 6.7 ± 2.4 in the Gel group, After the first, second, and third study applications, they were 3.3 ± 2.9, 5.4 ± 2.8 and 4.6 ± 3.6 in the bromelain group and 5.5 ± 3.5, 6.8 ± 2.9 and 5.4 ± 3.0 in the Gel group accordingly (again, significantly higher scores than seen in the comparator Bromelain group, pre or post treatment administration). Additionally, and critically, 57% of the ESX group patients and 46% of the Gel group patients received an analgesic in addition to the recommended pre-application treatment with a topical anaesthetic. This renders a comparison with the tarumase treated patients nearly impossible, as none of the tarumase-treated patients received any systemic or local analgesia chronically or acutely in relation to the application of their debridement treatment.

The use of topical anaesthesia, notably EMLA Cream, is clearly an effective means to reduce pain during surgical and/or mechanical debridement of painful wounds, and it is noted that this cream is widely licensed for this clinical indication. The data do however confirm that increasing the length of exposure to topical EMLA Cream is an important parameter in reducing procedural pain; short exposures of 10 min or less only have a minimal effect on surgical or mechanical debridement pain. In this context it is notable that the approved prescribing information recommends application of EMLA Cream for 30–60 min prior to initiation of debridement. Although achievable in some hospital or clinic settings, this length of wait largely precludes EMLA's wider use in the community setting, where there is a limited time available to achieve suitable anaesthesia. Similar

TABLE 2 | Overview of pain scores derived from surgical/sharp debridement, with ancillary study treatments.

References	Population	Study treatment	*N*	Median debridement pain (VAS)	Mean debridement pain (VAS ± SD)	Other pain score
Agrifoglio et al. [18]	VLU only	EMLA cream	54	16.5 mm	NR	No pain ($n = 33$); mild pain ($n = 16$); moderate pain ($n = 2$); severe pain ($n = 3$)
		Placebo	56	52.0 mm		No pain ($n = 12$); mild pain ($n = 22$); moderate pain ($n = 12$); severe pain ($n = 9$)
Bowen et al. [19]	VLU	Er: Yag laser	6	NR	34 mm ± 12	NR
		Surgery	6	NR	59 mm ± 12	
	DFU	Er: Yag laser	4	NR	12.5 mm ± 8.3	NR
		Surgery	4	NR	10.0 mm ± 1.1	
Cuomo et al. [23]	VLU	EMLA cream	25	NR	6.34	NR
		Lidocaine spray	25	NR	6.48	
Hansson et al. [20]	VLU only	EMLA cream	22	4.0 mm	NR	Pain reported in 20/161 visits (12%)
		Placebo	21	33.0 mm		Pain reported in 96/156 visits (62%)
Holm et al. [21]	Mixed aetiology	EMLA cream	16	18.5 mm	NR	No pain ($n = 3$); slight pain ($n = 8$); moderate pain ($n = 3$); severe pain ($n = 2$)
		Placebo	14	84 mm		No pain ($n = 0$); slight pain ($n = 4$); moderate pain ($n = 2$); severe pain ($n = 8$)
Holst and Kristofferson [24]	VLU	EMLA 10 min	19	41 mm	NR	NR
		EMLA 20 min	20	20 mm		
		EMLA 60 min	20	8 mm		
Mosti et al. [25]	Mixed aetiology	Versajet	68	NR	4.3 ± 1.6	NR
		Autolytic MW dressings	99		NR	
Rosenthal et al. [22]	Mixed aetiology	EMLA	51	18.0 mm	NR	Investigator VAS: 20 mm

considerations are relevant to other clinical situations where significant local or systemic analgesia is mandated.

Nonetheless, there remains a clear need to achieve clinically acceptable and pain-free debridement that allows for more rapid complete wound bed preparation, especially in the community setting, where many painful leg ulcers are treated. Less painful alternatives to surgical or mechanical debridement for hospital and clinic use are becoming available, and these include ultrasonic devices and lasers [19, 32, 33]. These devices, however, remain expensive pieces of equipment and are not easily transportable into the community where a nurse or clinician may be calling on several different patients in a working day.

As a consequence, despite several advances, autolytic debridement remains the mainstay of standard-of-care for painful chronic wounds in the community setting. Autolytic debridement includes products such as Medihoney or other hydrogels and includes advanced wound care dressings. Generally, these products are reported to be largely pain-free [34–37], but are recognised as slow at debriding, requiring repeated applications over many weeks to achieve clinically-significant debridement.

A clinical alternative currently in development is tarumase wound gel; an enzymatic debridement product. Although early in clinical development, this gel has shown in its first clinical trial a dose-dependent trend towards accelerated debridement [38]. Importantly, like autolytic hydrogels, this product can be readily applied to painful VLU wounds without the need for prior anaesthesia or analgesia, making it highly suitable for community-based use.

The use of tarumase at concentrations up to 11 U/mL has indicated no evidence of pain on application above that reported at baseline, nor when the gel is repeatedly left in contact with the wound over a period of 48–72 h over a four-week period. Moreover, the lack of any reported increase in wound pain on application suggests that there is potential to increase the concentration of tarumase in the wound, in order to further accelerate the debriding effect. We hypothesise that the pain profile of this enzyme is in large part due to the parasitic maggot from which the enzyme was originally identified and cloned, and which has sought through evolution to minimise its impact on the host.

The completed tarumase clinical study [38] is accepted to have limitations. As a first-in-human clinical trial, this study was neither blinded, randomised, nor stratified in any way, and as a consequence, patients and clinicians knew what was being applied to the wounds. The study was primarily focused on safety, not efficacy, and so the amount of debridement achieved in this phase IIa study was incomplete in terms of an active drug in clinical use. Encouragingly, there was clear evidence of partial debridement, and even when patients knew they were receiving higher concentrations of tarumase, there was no evident increase in wound pain. Thus, as we seek to expand the use of tarumase gel into larger, randomised and blinded clinical trials, we are encouraged that pain from debridement is unlikely to be a limiting factor in its intended clinical use.

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Ethics Statement

This previously-published clinical study was a prospective, open-label, multi-centre, dose escalation study that was conducted in accordance with the requirements of the International Council on Harmonisation Good Clinical Practice (ICH GCP) and in accordance with national regulations and guidance.

Conflicts of Interest

David Goldsmith is a shareholder and David Fairlamb is an employee and shareholder of SolasCure Ltd.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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