Sickle cell disease (SCD) is an intractable haematologic condition most commonly affecting patients of African ancestry. It is a serious global public health concern as over 300,000 babies are born annually with SCD, with up to 75% residing in sub-Saharan Africa. Chronic leg ulcers occur in 20–70% of SCD patients, although 75% of Jamaican patients that are homozygous for haemoglobin S are affected. Systemic therapies such as hydroxyurea and red blood cell transfusions have dramatically increased the life span of SCD patients and as a result more patients are reaching adulthood, where they are at greatest risk of developing leg ulcerations. SCD leg ulcers are very resistant to heal and are associated with significant pain, disability, and negative psychosocial and economic impacts. Although the mechanism of ulcer development has yet to be fully elucidated, the pathogenesis is believed to be a result of vaso-occlusion following intracellular precipitation of the sickle haemoglobin. This promotes endothelial dysfunction, a hypercoagulable state, inflammation, ischaemia reperfusion injury and associated tissue necrosis.

There is no effective standard treatment for SCD leg ulcers, and thus, healing rates are dismal. The most published experimental topical treatments involve RGD peptide and sodium nitrite. To date, positive outcomes in terms of wound closure and analgesia are reported but higher levels of evidence are still lacking. However, concern has been raised about the potential carcinogenic effects of sodium nitrite, as well as the potential apoptotic effects on normal cell lines by RGD peptide. The endocannabinoid system (ECS) is a chemical signalling system that holds a ubiquitous presence in all mammalian organ systems. Furthermore, the ECS is embodied throughout all levels, components and appendages of the integumentary system, both cutaneous and mucous membranes. ECS signalling goes beyond the classic cannabinoid receptors, CB1 and CB2, by involving other surface membrane receptors such as TRPV, GPR, and 5-HT, as well as acting on nuclear receptors such as PPAR. It has been theorized that dysregulated ECS signalling is central to the pathophysiology of integumentary and wound conditions. Together with a robust preclinical literature that reports the ability of cannabis extracts to promote wound healing and analgesia, human evidence is beginning to accrue demonstrating that cannabis-based medicines containing cannabinoids, terpenes and flavonoids are showing promise in the most challenging and “orphaned” diseases such as epidermolysis bullosa, pyoderma gangrenosum and calciphylaxis, both uraemic and non-uraemic.

Topical cannabis-based medicines (TCBMs) are a family of proprietary mixtures containing cannabinoids, terpenes and flavonoids that are emerging as novel treatments for integumentary diseases and wounds; there are 2 formats, one compounded in aloe vera and hyaluronic acid gels that facilitate absorption into lipophilic wound beds, while the other is compounded in liposomal base that facilitates absorption into peri-wound tissues through the relatively impervious stratum corneum. TCBMs have been formulated to address the key pathophysiological stigmata that underpin non-healing wounds, namely, hyper-inflammation, and tissue hypoxia, both of which are occurring within both the wound bed and peri-wound tissues. TBCM is completely non-invasive, may be combined with existing evidence-based practices and may be self-administered. Disease-specific variations of TCBM may evolve for application to the full spectrum of acute and chronic integumentary wounds. Although data on systemic absorption are not available, the authors theorize that TCBM largely operates through local mechanisms within the integumentary system.

Our open-label clinical trial (ISRCTN16488940; William Osler Health System REB 18-0038) demonstrated wound closing trends in up to 90% of the 33 complex patients with refractory non-healing integumentary wounds of over 6 months of duration; no clinically relevant adverse reactions, neither systemic nor local, were reported. We are reporting the results of a 44-year-old woman of African-Jamaican ancestry with a 12-year history of chronic recurrent ulcerations involving both lateral ankles and her left medial ankle that were continuously open for at least 3 years. She was chronically ill, with a palliative performance scale score of 60% (healthy persons score 100%) and an M3 multimorbidity index of 3.35 (two-thirds of persons from typical populations score zero). She also presented with right ventricular heart failure and peripheral vascular disease; her haemoglobin ranged between 65 and 75 g/L, while her oxygen saturation was consistently less than 90%. Prior to enrolling into the trial, she was already employing inelastic leg bandaging. Her pre-trial medications included hydroxyurea 500 mg bid, pentoxifylline 400 mg bid, furosemide 20 mg qd and hydromorphone 8–10 mg per day. Our protocol involved daily topical application of TCBM (Table 1), VS-21 to the wound beds and VS-22 to a 4–6 cm radial cuff of peri-wound integument. Both VS-21 and VS-22 contain delta-9 tetrahydrocannabinolic acid, which is a strong agonist of PPARy, a key nuclear receptor that is highly influential in integumentary
Importantly, both VS-21 and VS-22 contain high levels of beta-caryophyllene that enhances wound healing through multiple routes, particularly through agonism at CB2. Tissues were then covered with one layer each of Jelonet® and Mesorb®, followed by spiral bandaging of her lower limbs, sequentially, using gauze kling roll, Comprilan® and Easifix®. Smartphone photography was used daily to estimate wound size. On day 0 of treatment, the three wound sites located at right lateral ankle, left medial ankle and left lateral ankle were estimated to be 11.0, 1.8 and 5.4 cm², respectively. The left medial ankle wound was completely closed on day 24. On day 45, the right and left lateral wounds were 97% and 98.5% closed (Figure 1). Then, the patient stopped the treatment and was lost to follow-up until day 97 when she was admitted to hospital with sepsis from cholecystitis. Her left medial ankle wound had remained closed, but the other two deteriorated to the point that they were larger than on day 0. The patient agreed to resume the same daily treatments. After another 53 days, the left medial ankle wound closed completely from 11.14 cm² and the left lateral ankle wound also closed completely from 7.46 cm². Images are shown in Figure 1.

TABLE 1 Composition of topical cannabis-based medicines

<table>
<thead>
<tr>
<th>Components</th>
<th>VS-21 applied to wound bed</th>
<th>VS-22 applied to peri-wound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASE</strong></td>
<td>Hyaluronic acid + Aloe Vera Gel 50/50 v/v</td>
<td>liposomal base</td>
</tr>
<tr>
<td>Cannabidiol (CBD)a</td>
<td>2.5 mg/ml</td>
<td>2.5 mg/ml</td>
</tr>
<tr>
<td>Delta-9 Tetrahydrocannabinol (THC)a</td>
<td>&lt;1 mg/ml</td>
<td>&lt;1 mg/ml</td>
</tr>
<tr>
<td>Delta-9 Tetrahydrocannabinolic Acid (THCA)a</td>
<td>2.65 mg/ml</td>
<td>2.65 mg/ml</td>
</tr>
<tr>
<td>Quercetinb</td>
<td>31.25 mg/ml</td>
<td>31.25 mg/ml</td>
</tr>
<tr>
<td>Diosminb</td>
<td>25.31 mg/ml</td>
<td>25.31 mg/ml</td>
</tr>
<tr>
<td>Hesperidinb</td>
<td>2.5 mg/ml</td>
<td>2.5 mg/ml</td>
</tr>
<tr>
<td>Beta-caryophyllene²</td>
<td>101.79 mg/ml</td>
<td>101.79 mg/ml</td>
</tr>
</tbody>
</table>

aCannabinoids.  
bFlavonoids.  
²Terpenes.  

**FIGURE 1** Images of all three wounds before and after the first and second treatments
Scientific advancements involving the endocannabinoid system that have been catalysed by progressive global legalization of medical cannabis, coupled with a global opioid crisis, will continue to generate innovative and targeted therapies utilizing cannabis-based medicines. SCD leg ulceration is an "orphaned" condition that causes untold suffering and reduced quality of life. In such chronically ill, complex and compromised patients, complete wound closure is extremely difficult to achieve, yet this patient’s three wounds healed within an average of 43.3 days by adding TCBM to existing best practices. The observed results raise speculation that TCBM may become a future viable and non-invasive option for SCD leg ulcers, thus, warranting further investigations through controlled clinical trials.

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This study is approved by William Osler Health System, Brampton, Ontario, Canada: REB 18-0038. ISRCTN registry (Study ID # ISRCTN16488940).

CONFLICT OF INTEREST
VM is the President & CEO of VinSan Therapeutics Inc. which holds intellectual property and patents related to the formulae and methodology used in this study. RS, FF and LP declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
VM: Study design; data collection; analysis design; manuscript drafting; manuscript review. RS: Analysis design; statistical analysis; manuscript drafting; manuscript review. FF: Analysis design; manuscript drafting; manuscript review. LZ: Study design; Analysis design; manuscript drafting; manuscript review.

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REFERENCES