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A Prospective Cohort Study of Hard-to-Heal Chronic Foot and Leg Wounds Followed for up to 20 Weeks After Initiation of ReGenerating Tissue Agents (RGTA) Technology as an Add-on to Optimal Local Care

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ABSTRACT

ReGenerating Tissue Agents (RGTA, trade name CACIPLIQ20) contain a structural analogue of heparan sulfates (HSs) that promotes tissue regeneration in hard-to-heal chronic wounds resistant to the best standard of care for 6 months or longer. The MATHCOW study aimed to evaluate the real-life performance and safety of RGTA administered in addition to optimal treatment in diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and leg ulcers with an ischemic component (arterial ulcers). The primary outcome measure was the rate of ulcer closure within the first 20 weeks of treatment. A total of 191 patients were recruited; 173 signed informed consent and constituted the intention-to-treat (ITT) analysis set. The per-protocol (PP) population included 114 patients. The primary endpoint was 50 wound closures at 20 weeks in the ITT analysis (28.9%) and 46 wound closures in the PP analysis (40.4%). Closure rates varied according to ulcer type: 43.7% for VLUs, 46.2% for DFUs, and 14.6% for arterial ulcers. Other endpoints also improved, including clinician global impression, pain, and ulcer area. Adverse events were recorded in 4% of cases. This open-label study confirms the performance and tolerability of RGTA in a population of patients with particularly hard-to-heal chronic ulcers.

1 | Introduction

A chronic wound is defined as a break in skin continuity persisting for more than 4 weeks [1]. Most chronic wounds can be classified into the following categories: diabetic ulcers, pressure ulcers, and vascular ulcers (venous or arterial) [2–4]. Approximately 70% of leg ulcers are caused by venous disease, and roughly 20% are caused by arterial insufficiency or mixed arteriovenous disease. Approximately 85% of foot ulcers are caused by diabetic peripheral neuropathy, often complicated by arterial disease [4]. Despite differences in aetiology, chronic wounds share several common molecular features, including excessive levels of pro-inflammatory cytokines, proteases, reactive oxygen species, and senescent cells, as well as persistent infection and deficiency or dysfunction of stem cells [2]. The result is a hostile environment characterized by downregulation of protease inhibitors and direct damage to extracellular matrix (ECM), cellular components, and protective growth factors such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).

General principles of chronic wound treatment include wound debridement, infection control, application of dressings, and treatment of underlying conditions such as diabetes mellitus and peripheral arterial disease. In addition, compression therapy is recommended for venous leg ulcers (VLUs); restoration of local

Key Points

- OTR4120 is a heparane sulfate mimetic which is indicated for chronic skin ulcers resistant to the best standard of care.
- This post marketing clinical follow-up study confirms good tolerance and suggests efficacy in a particularly difficult-to-treat population.

blood flow by revascularization is the most effective treatment for arterial ulcers, and off-loading is mandatory for pressure ulcers and diabetic foot ulcers (DFUs) [5–7]. If a wound does not respond to standard care—typically defined as a reduction in wound size of 30% for VLUs and 50% for DFUs within 4 weeks after treatment initiation—advanced care and referral to a wound specialist are indicated [4].

Advanced wound therapies include negative-pressure wound therapy, hyperbaric oxygen therapy, biophysical treatments such as electrical stimulation, acellular matrices, bioengineered allogeneic cellular therapies, stem cell therapies, and other approaches such as sucrose octasulfate, hyaluronan, or platelet-rich plasma. However, despite increasing knowledge and the development of numerous interactive wound care products, healthcare professionals continue to encounter wounds in which healing is prolonged or never achieved [8]. According to Frykberg and Banks [2], only 50% of all leg ulcers heal within 1 year while Guest et al. [9] estimated that only 37% of VLUs and 52% of DFUs heal within 1 year. Accordingly, in large clinical trials, 20%–30% of VLUs and DFUs healed within 20 weeks in the standard-of-care groups, whereas fewer than 50% healed with advanced therapies [10–17]. There is therefore a major unmet medical need for ulcers that remain unhealed for at least 6 months despite best available treatment.

ReGenerating Tissue Agent (RGTA OTR4120) has been CE-marked since 2008 under the name CACIPLIQ20 with the following indication: chronic cutaneous ulcers caused by pressure (bedsores), peripheral arterial disease (e.g., Stage IV Leriche and Fontaine classification), or diabetes (including post-amputation wounds), showing no tendency to heal after 6 months of standard care, or still unhealed after 12 months. The active principle of RGTA is alpha 1–6 polyglucose carboxymethyl sulfate (also called OTR4120), a heparan sulfate (HS) mimetic, at a concentration of 100 μg/mL in saline solution [18, 19]. OTR4120 mimics HSs in their biological functions, including: (1) organization of the extracellular matrix scaffold, (2) protection of matrix proteins, and (3) binding and protection of signalling peptides. OTR4120 differs from endogenous HS in its resistance to glycanases [18]. Because its primary mode of action is mechanical rather than pharmacological, OTR4120 is regulated as a medical device in Europe. However, it is considered a drug in the United States, where the definition of medical devices differs.

When introduced at the site of injury, OTR4120 replaces destroyed HS and restores their functions. This enables restoration of matrix architecture and the cellular microenvironment, thereby facilitating cell survival and tissue recovery at the site of injury [18]. OTR4120 is eliminated by endocytosis and catabolized in lysosomes during extracellular matrix turnover.

In many skin wound models, the addition of OTR4120 improved tissue regeneration and repair and ultimately led to better tissue organization and increased skin strength [20–24]. OTR4120 treatment was associated with an increased collagen I/collagen III ratio, decreased inflammation, and increased angiogenesis [20, 21, 25–27]. Skin growth factors such as VEGF, PDGF, and transforming growth factor beta-1 were increased after OTR4120 treatment [27]. Thus, OTR4120 triggers four important biological processes that are fundamental to tissue healing: downregulation of inflammation, extracellular matrix repair, growth factor protection, and promotion of angiogenesis.

The beneficial effects of OTR4120 have been reported in humans in several publications, including one randomized controlled trial [28], three prospective open-label studies [29–31], and several case reports or retrospective clinical series [32–39]. In all these studies, RGTAwas used as a last resort in ulcers that had remained resistant to best available therapy for 6 months or longer. Despite the selection of a very difficult-to-treat population, RGTA treatment was associated with high rates of complete healing (range, 22% to 100%), decreased wound area over time, pain improvement, increased granulation tissue, improved odour, and lower amounts of exudate and fibrin. Improvement in biomarkers of inflammation, ECM repair, and angiogenesis has also been reported at the histological level [28].

Most evidence regarding the performance and tolerability of RGTA comes from relatively small clinical studies. The main objective of the MATHCOW post marketing follow-up (PMCF) study was therefore to prospectively and systematically collect clinical data in a relatively large cohort of patients in order to assess the performance and tolerability of RGTA under real-life conditions.

2 | Methods

2.1 | Study Design and Participants

This was a PMCF prospective cohort study conducted by clinicians experienced in wound management. Patient inclusion and follow-up were conducted in collaboration with each patient's healthcare team and with physicians and expert nurses from the Cicat-Occitanie network, a regional telemedicine system providing expertise and care coordination in wound management. This network relies on secure and validated teleconsultation tools. Inclusion in the cohort did not modify the usual functioning of the network. The data recorded for the purpose of the study were identical to the information routinely collected in the CICAT-Occitanie data management system, including high-quality digital wound photographs. A specific study number was assigned to each patient recruited into the MATHCOW study, and this identifier contained no personal information. Variables required for study analyses were extracted using specific queries, while strict anonymization was maintained. Two hundred eligible subjects were expected to be included in a single-arm cohort study. Patients were followed until closure of the target wound or for a maximum of 20 weeks if no event occurred during this period requiring treatment interruption. Clinical evaluations and local care were performed according to usual professional practice.

The study was approved by a national ethics committee (comité de protection des personnes Ile de France II), under the reference 2021-A01910-41. The study protocol was registered at ClinicalTrials.gov under NCT05170984 before study initiation. Patients were eligible if all of the following main conditions were met: (1) age ≥ 18 years and treatment with RGTAdeemed appropriate by the care provider; (2) target chronic wound showing no sign of improvement during the 6 months preceding inclusion; (3) target wound located below the knee; and (4) target wound meeting one of the following definitions: (i) a leg ulcer predominantly of venous origin (ankle-brachial pressure index [ABPI] ≥ 0.8) with an area > 10 cm^2 and/or a duration of at least 5 months, referred to here as a VLU; (ii) a leg ulcer of any size or duration associated with documented lower limb ischemia (ABPI < 0.8), referred to here as an arterial ulcer; or (iii) a foot ulcer of any size or duration documented as a DFU. If more than one eligible wound was present, investigators were required to select the largest wound as the target wound or, if wounds were of similar size, the ulcer considered by the investigator to be the most severe. The exclusion criteria were female patients who are pregnant, or lactating, bedridden patients unable to spend at least 1 h per day sitting in a chair, patients suffering from severe cognitive problems precluding any voluntary participation to the study, patients with, according to the investigator's opinion, a very poor life expectancy, patients with leg or foot ulcerations which are not of venous, arterial or diabetic origin (e.g., Martell's ulcer and related ulcers, pressure ulcers, traumatic wounds or burns), patients whose target wound is located on an amputation stump, patients presenting with a fungating wound at the time of inclusion, patients in an emergency situation and unable to give consent, patients intolerant to one of the study device components or to heparinoids.

2.2 | Procedures

This study did not involve any examinations or procedures beyond those performed as part of standard care. Patients who met the eligibility criteria were included upon initiation of RGTA treatment. Each CACIPLIQ20 bottle contains 7 mL of a solution of OTR4120 (RGTA) at a concentration of 100 μg/mL. Each spray delivers 14 μg (140 μL) of RGTA, corresponding to approximately 50 sprays per bottle. RGTA (CACIPLIQ20 spray) treatment was applied twice weekly (every 3–4 days), generally by a nurse. Treatment was administered after wound debridement, cleaning, disinfection, rinsing with sterile physiological saline, and drying, ideally at the time of dressing changes. One spray was applied per 7–9 cm^2 of affected wound area. Following application, wounds were dressed according to the standard of care. The maximum treatment duration was 20 weeks.

2.3 | Outcomes

The primary endpoint was the rate of wound closure within 20 weeks after treatment initiation, defined as 100% re-epithelialization, including:

- Confirmed complete closure (CCC), defined as wound closure reported by the investigator and confirmed by an independent reviewer based on wound photographs;
- Possible complete closure (PCC), defined as wound closure reported by the investigator without confirmation by the independent reviewer, either because no photograph was available, the photograph was of insufficient quality, or the image did not allow unequivocal confirmation. The primary endpoint comprised both CCC and PCC. The main secondary endpoints were: (1) the rate of adverse events (AEs) and device deficiencies (DDs); (2) the rate of wound closure according to closure type (CCC or PCC) and wound type (VLU, arterial ulcer, or DFU); (3) clinician global impression of change (CGI), a 7-point clinician-rated scale assessing overall change in the patient's clinical condition from baseline; (4) time to wound closure; (5) change in pain numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain); and (6) identification of predictive factors associated with wound closure.

2.4 | Statistical Analysis

The main objective of the study was to estimate the prevalence of wound closure. A closure rate above 40% was considered a strong indicator of efficacy. A total sample size of 200 patients was considered sufficient to estimate a prevalence of at least 40% with a precision of ±7% points at the 95% confidence level, based on Cochran's sample size formula. As this was a single-arm cohort study, no between-group comparisons were planned. Descriptive statistics, were used to describe the primary and secondary outcomes. The safety population was defined as all patients who received at least one application of RGTA. The intention-to-treat (ITT) population was defined as all patients included in the study who signed informed consent for use of their data. The per-protocol (PP) population was defined as all ITT patients without major protocol deviations. Major protocol deviations included premature treatment discontinuation (i.e., before wound closure or before completion of the 20-week follow-up), loss to follow-up, and situations in which the primary endpoint was not assessable. Other unexpected major protocol deviations were defined and approved by the scientific committee.

3 | Results

From January 2022 to June 2024, 191 patients were treated with RGTA and constituted the safety population. Among them, 173 signed informed consent for the use of their data and constituted the ITT population, including 71 patients with VLUs, 89 with arterial ulcers, and 13 with DFUs. The per-protocol set comprised 114 patients, including 50 with venous ulcers, 55 with arterial ulcers, and nine with DFUs. Reasons for exclusion from the per-protocol population are shown in Figure 1. Baseline demographic characteristics are presented in Table 1 and Figure 2.

For the overall ITT population, the median [Min; Max] age at inclusion was 81.4 years [73; 102], the male-to-female ratio was 1.05, the median [Min; Max] BMI was 26.2 kg/m^2 [15.6; 57.4], the median ulcer duration at inclusion was 9 months, and the mean ± SD ulcer area was 10 ± 17 cm^2. Concomitant local treatments used in addition to RGTA corresponded to best standard of care in France and included, depending on ulcer type, active dressings (Urgostart), hydrophobic antimicrobial

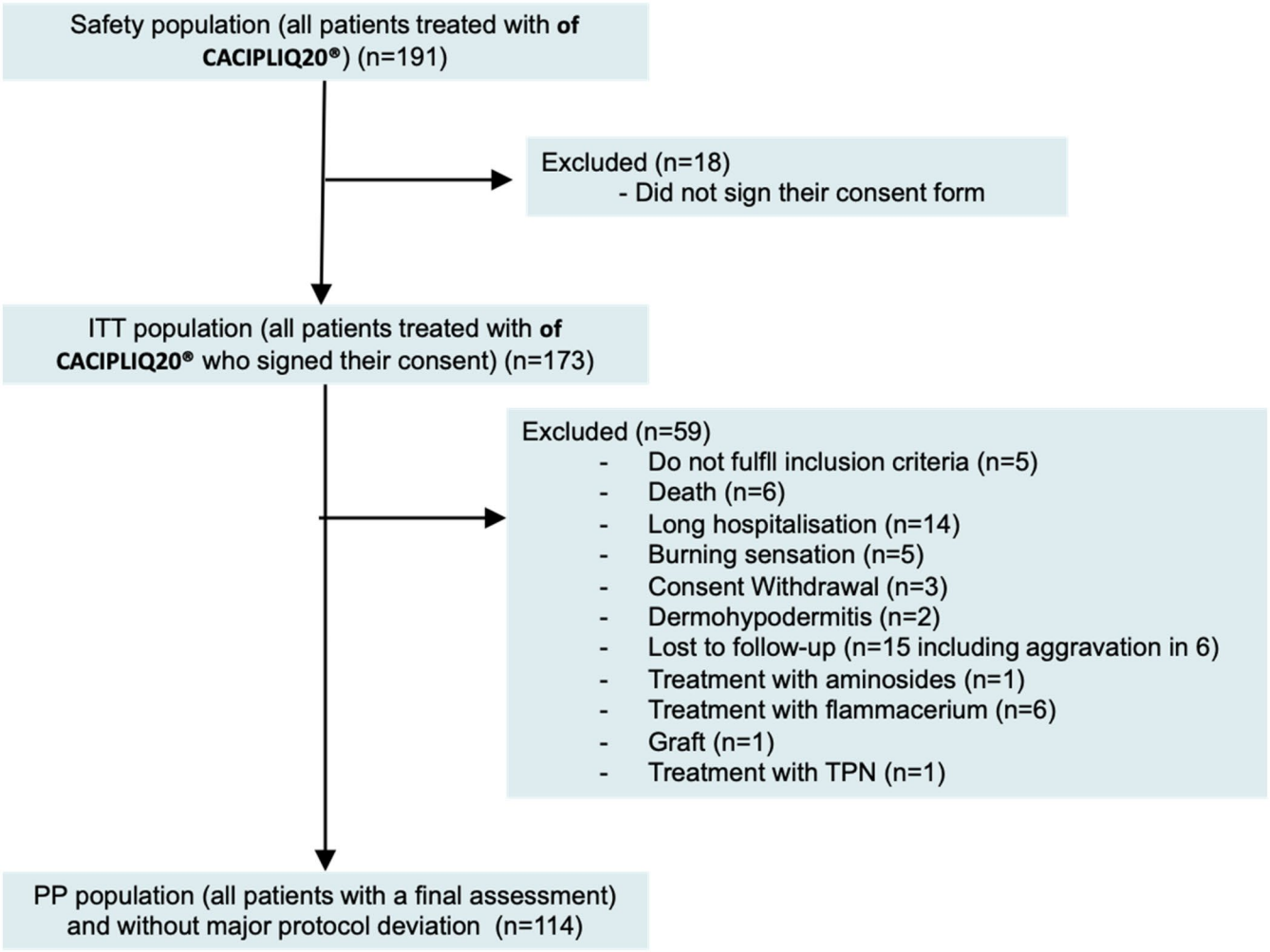

FIGURE 1 | Study flowchart. TPN, Negative pressure therapy.

TABLE 1 | Demographic characteristics—ITT population.

Variables		VLUs ($N=71$)	Arterial ulcers ($N=89$)	DFUs ($N=13$)	Total ($N=173$)
Age (years)	Mean	77	81	80	79
Gender	M/F ratio	0.73	1.28	2.25	1.05
BMI (kg/m^2)	Mean ± SD	29.4 ± 9.1	26.7 ± 5.8	25.6 ± 4.9	27.8 ± 7.5
Ulcer area at baseline (cm^2)	Mean ± SD	11 ± 20	11 ± 14	1.3 ± 1.6	10 ± 17
Ulcer duration at baseline (months)	Median	9	12	6	9

agents (Sorbact), wound debridement when feasible, compression bandaging, off-loading devices, therapeutic shoes, and various types of dressings (alginate, hydrocellular, hydrocolloid, fibre, and absorbent dressings). The primary endpoint included 50 wound closures in the ITT analysis (28.9%, IC95 [22.2; 35.7]) and 46 wound closures in the PP analysis (40.4%, IC95 [33.1; 50.9]).

There were 7 adverse device events (ADEs) reported in the study (3.7%), including 1 serious adverse device event (SADE; 0.5%). Five patients experienced burning sensations or pain after the first applications of RGTA, leading to early treatment discontinuation. One 30-year-old patient with a chronic venous ulcer developed a blister containing blood and lymph after application of RGTAspray to the wound. Treatment was stopped after one application; the symptoms did not recur, and no sequelae were reported. The single SADE was reported in a patient with an arterial ulcer who experienced wound bleeding 24 h after RGTA application, requiring urgent hospitalization. This patient had chronic arteriopathy and was receiving dual antiplatelet therapy.

Main pre-planned efficacy endpoints are presented in Table 2.

There were marked differences in wound closure rates according to ulcer type. In the ITT analysis set, 43.7% (31/71) of venous ulcers and 46.2% (6/13) of DFUs were considered closed within 20 weeks, whereas only 14.6% (13/89) of arterial ulcers had closed.

In the PP analysis set, 54.0% (27/50) of venous ulcers and 66.7% (6/9) of DFUs were considered closed within 20 weeks, whereas only 23.6% (13/55) of arterial ulcers had closed.

The median CGI of change was 3 ("minimally improved"), with a mean score of 3.2. Overall, after introduction of CACIPLIQ20, 45.1% of patients were considered improved, 69.4% were stable or improved, and 11.0% worsened. Most wound closures (90.0%, 45/50) occurred at least 39 days after treatment initiation, whereas only 10.0% (5/50) occurred within the first month. Fifty percent of closures occurred after 75.5 days. Pain was evaluated using a Numerical Pain Rating Scale (NPRS) ranging from 0 (no pain) to 10 (maximal pain), assessed during treatment sessions for all ulcers and by ulcer category. Comparison of pre-treatment values (i.e., pain during the last treatment session before RGTAinitiation) with the average of post-treatment values showed an overall decrease in pain. Considering all ulcers, the mean NPRS score decreased from 1.5 ± 2.6 before treatment to 0.74 ± 1.4 after treatment ($p = 0.0001$, Wilcoxon signed-rank test). To identify predictive variables associated with wound closure, a binary logistic regression model was built using wound closure as the dependent variable and ulcer duration, wound area, wound type, sex, and age as explanatory variables. Wound area was inversely associated with the probability of wound closure (odds ratio [OR] = 0.8; 95% CI, 0.6871–0.9047; $p = 0.002$). Venous ulcer type was positively associated with the probability of wound closure (OR = 8.1; 95% CI, 2.6–28.9; $p < 0.0001$). The other variables (ulcer duration, sex, and age) were not associated with wound closure. In a post hoc analysis, percentage change in ulcer area from baseline was evaluated in the ITT population. All ulcer categories showed overall improvement. The mean percentage area reduction ± SD was 54% ± 83 for all ulcers, 59% ± 101% for venous ulcers, 76% ± 43% for DFUs, and 46% ± 65% for arterial ulcers.

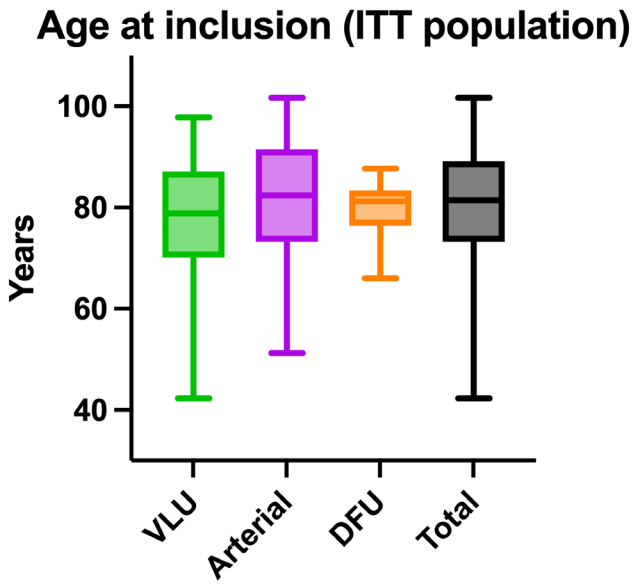

FIGURE 2 | Age of patients at inclusion. Lines indicate median values, boxes represent the interquartile ranges (IQR), and whiskers indicate the minimum and maximum values.

4 | Discussion

Patients included in the study had hard-to-heal ulcers with no signs of improvement during the 6 months preceding inclusion. The median ulcer duration at inclusion was 9 months, longer than in most published large clinical trials in chronic skin ulcers, in which ulcer duration is usually below 6 months [10–12, 15, 17]. Ulcer size was also substantial, with a mean ± SD baseline

TABLE 2 | Pre-planned secondary efficacy endpoints (based on ITT population).

Variables	VLUs ($N = 71$)	Arterial ulcers ($N = 89$)	DFUs ($N = 13$)	Total ($N = 173$)
Total rate of wound closures by ulcer type (primary endpoint)	31 (43.7%) IC95 [32.1; 55.2]	13 (14.6%) IC95 [7.3; 21.9]	6 (46.2%) IC95 [19.1; 73.2]	50 (28.9%) IC95 [22.2; 35.7]
Rate of wound closures confirmed by an adjudication committee (based on available good quality photographs)	23 (32.4%)	11 (12.4%)	3 (23.1%)	37 (21.4%)
Clinical impression of change (CGI) (mean (SD))	3.3 (1.1)	3.2 (1)	3.3 (1.7)	3.2 (1.1)
Time to wound closure (median time for ulcers that healed)	80	135	92	75.5
Changes in the pain numerical rating scale (mean ± SD scores before treatment compared to mean ± SD scores post treatment) p-value (Wilcoxon signed rank test)	1.6 ± 2.7 vs. 0.6 ± 1.1 ($p = 0.0015$)	1.4 ± 2.3 vs. 0.89 ± 1.70 ($p = 0.0685$)	2.6 ± 3.7 vs. 0.44 ± 0.81 ($p = 0.14$)	1.5 ± 2.6 vs. 0.74 ± 1.4 ($p = 0.0001$)

area of $10 \pm 17\,cm^2$ overall. Patients included in the study were relatively old (median age, 81.4 years [73; 102]). These patients were expected to have comorbidities likely to negatively affect wound healing and increase the risk of loss to follow-up. The distribution of ulcer types suggests that the MATHCOW cohort was enriched in arterial ulcers, which are particularly difficult to heal. In the general population, approximately less than 20% of leg ulcers are caused by arterial insufficiency or mixed arteriovenous disease [4, 9]. In contrast, in the MATHCOW ITT population, 51% had arterial ulcers (including mixed arteriovenous disease).

There were 50 wound closures in the ITT analysis (28.9%) and 46 in the PP analysis (40.4%). As expected, differences were observed between types of closure: confirmed closures assessed by an independent adjudication committee versus possible closures assessed by investigators. These discrepancies likely reflect the fact that investigators considered the totality of evidence, including both clinical examination and photographs, whereas the adjudication committee relied only on photographs, which were sometimes not available or of insufficient quality to support a definite conclusion.

The low closure rate observed in patients with arterial ulcers was not unexpected and may be explained by two main factors. First, the study included patients who had shown no improvement during the 6 months before inclusion, which likely excluded patients who had recently undergone successful revascularization and whose ulcers would have been expected to improve. Second, the study was conducted in an outpatient setting, where debridement was not performed by surgeons. In early studies with RGTA, higher closure rates in severe ischemic wounds were reported when debridement was performed by trained surgeons [29, 30]. Nevertheless, other endpoints indicate that arterial ulcers did benefit from CACIPLIQ20 as well: the clinician global impression of change (CGI) showed that patients with arterial ulcers were considered "improved" in average. Similarly, the mean Numerical pain rating scale (NPRS) value before treatment was 1.4 ± 2.3 compared to 0.89 ± 1.70 after treatment, $p = 0.0685$. Also, the mean percentage area reduction after introduction of CACIPLIQ20 was 46% for these ulcers. Overall, it can be concluded that arterial ulcers did benefit from treatment in terms of clinical global impression, pain reduction and decrease in wound area. Based on these observations, patients with arterial ulcers who show delayed or insufficient healing despite appropriate standard of care may represent a population in whom CACIPLIQ20 could be considered, provided that arterial perfusion has been appropriately assessed and managed.

The protocol stated that, based on the literature, a wound closure rate around 40% would be considered a strong sign of treatment efficacy. This assumption was based on published clinical trials in hard-to-heal ulcers of venous or diabetic origin, in which closure rates in best standard-of-care groups are usually below 30% [10–17]. Importantly, these expectations were based on DFU and VLU trials and did not account for the fact that arterial ulcers ultimately represented 51% of the cohort. In addition, the large number of patients lost to follow-up or with a non-assessable endpoint (59/173, 34%) diluted the observed closure rate in the ITT population. In the PP analysis, 40.4% of all ulcers healed, which appears notable given the severity of the population and the predominance of arterial ulcers.

The overall safety profile suggests that the product is generally well tolerated, except for a few mostly minor events consisting of burning sensations after the first applications, which resolved after treatment discontinuation. The rate of device-related adverse events was assessed in the safety population ($n = 191$). There were 7 ADEs (3.7%), including 1 SADE (0.5%) consisting of serious wound bleeding requiring hospitalization in a patient already receiving dual antiplatelet therapy for chronic arteriopathy. A pharmacological interaction between clopidogrel, aspirin, and OTR4120 leading to increased bleeding risk cannot be completely excluded. However, such a case of wound bleeding has been reported only once since RGTAwas commercialized in 2008.

This study has several limitations. First, it was an open-label prospective PMCF study rather than a randomized, double-blind controlled trial. Second, a substantial number of patients were lost to follow-up, which may be explained by the advanced age and comorbidity burden of the included population, leading to death, hospitalization, or discontinuation of follow-up. Third, the number of arterial ulcers was unexpectedly high compared with the literature, and the number of DFUs was too small to allow firm conclusions regarding this subgroup.

5 | Conclusions

This open-label PMCF study confirms the performance and tolerability of RGTA in a real-life population of patients with particularly hard-to-heal chronic ulcers.

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Ethics Statement

The study obtained ethical approval from the Comité de Protection des Personnes Île-de-France II, Hôpital universitaire Necker Enfants malades, Carré Necker, 149 rue de Sèvres, Porte N2, 1er étage, 75015 Paris, France (e-mail: cppidf2@gmail.com), under reference 21.01439.000026. The study was approved by the French regulatory authority (ANSM, DMCDIV/DAPTEC/AE/2021-A01910-41).

Consent

All participants included in the intention-to-treat analysis signed informed consent for participation and use of their data. Written informed consent was obtained from patients.

Conflicts of Interest

Denis Barritault is co-inventor and co-owner of the patents describing RGTA technology and its applications. He is the founder, president, and a shareholder of OTR3, the company that manufactures and markets CACIPLIQ20. Frédéric Sedel and Martin Inizan are employees and shareholders of OTR3. Luc Téot has a consultancy agreement with

OTR3. The other authors declare no conflicts of interest related to this work.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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