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ORIGINAL RESEARCH

Xioglican Cream in Italian Patients with Chronic Venous Disease: A Post-Marketing Study Investigating Effects on Clinical and Cutaneous Signs and Symptoms

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ABSTRACT

Introduction: The progression of chronic venous disease (CVD) is characterized by edema of the legs and/or venous ulcers of the lower limbs in association with cutaneous signs and/or skin alterations, such as hyperpigmentation, corona phlebectatica, telangiectasia, eczematous dermatitis, lipodermatosclerosis, atrophie blanche, cellulitis, and induration. Xioglican cream is a galactosaminoglycan polysulfate and hyaluronic acid-containing medical device with strong hydrophilic, moisturizing, and soothing properties. This post-marketing observational study evaluated topical Xioglican cream in the amelioration of skin manifestations and clinical signs and symptoms in patients with CVD treated in routine clinical practice.

Methods: Adult patients (18–75 years) with a clinical diagnosis of C2–C3 CVD according to Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) classification who received 12 weeks of treatment with Xioglican (applied up to 3 times daily), according to investigator decision (and consistent with conventional clinical practice and established standard of care), were enrolled from two study sites in Italy. A range of endpoints were used to evaluate efficacy, safety, effect on patient quality of life (QoL), and patient satisfaction with topical application of Xioglican cream in the physiological restoration of skin signs and symptoms.

Results: In patients with CVD ($n = 30$), Xioglican cream reduced CVD-related skin manifestations and associated symptoms, with significant reductions in leg circumference [mean ± standard deviation (SD): -3.21 ± 3.39 cm for left and -2.92 ± 2.70 cm for right legs, both $p < 0.0001$] and local edema (-5.52 ± 7.94 cm, $p = 0.0034$) and significant improvement in Venous Clinical Severity Scores (mean 0.52 ± 1.94 decrease from baseline, $p = 0.1952$) observed after 12 weeks. Skin burning, pain, aching or tiredness, and QoL were also significantly improved. There was no change in CEAP classification. Globally, 92.0% of patients were "Very satisfied" or "Satisfied" with the product.

Conclusions: Topical treatment with Xioglican cream improves the signs, symptoms, and QoL of patients with CVD class C2–C3.

Keywords: Chronic venous disease; Lower limb venous disorders; Skin changes; Venous insufficiency

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Key Summary Points

Why carry out this study?

Chronic venous disease (CVD) manifests as leg pain, itching, edema, telangiectasia, reticular or varicose veins, and as various cutaneous signs and/or skin alterations (e.g., hyperpigmentation, corona phlebectatica, telangiectasia, eczematous dermatitis, lipodermatosclerosis, atrophie blanche, cellulitis, and induration).

Xioglican, a topical preparation composed primarily of galactosaminoglycan polysulfate and hyaluronic acid, is a widely used topical treatment for CVD-related skin conditions, promoting physiological hydration of the skin and preventing local edema and appearance of skin alterations.

This post-marketing study assessed the effects of Xioglican cream on skin signs and symptoms in patients with CVD treated in Italian routine clinical practice.

What was learned from the study?

Xioglican cream significantly reduced leg circumference and local edema, improved Venous Clinical Severity Scores, skin burning, pain, and aching or tiredness; patient QoL improved significantly, and most patients were 'Very satisfied' or 'Satisfied'.

Topical treatment with Xioglican cream improves the signs, symptoms, and QoL of CVD patients, supporting the recommendations of the International Guidelines for CVD management, which recognize the importance to patients of relieving the pain, heaviness, discomfort, and swelling related to CVD, together with ameliorating skin changes and improving QoL.

INTRODUCTION

Chronic venous disease (CVD) is a common global pathology that imposes a considerable socioeconomic impact, particularly from its more severe manifestations [1–4]. Cosmetic consequences associated with varicose veins, telangiectasias, and reticular veins also negatively affect patient quality of life (QoL) and should not be dismissed [3–5]. Across the spectrum of symptoms (from varicose veins to venous ulceration), the socioeconomic impact of CVD is dramatic, hampering individuals' ability to participate in everyday social and occupational activities, imposing financial constraints, and reducing QoL.

A more advanced stage of CVD, defined as chronic venous insufficiency (CVI), encompasses functional abnormalities of the venous system, including cutaneous signs and/or skin alterations, such as hyperpigmentation, corona phlebectatica, telangiectasia, eczematous dermatitis, lipodermatosclerosis, atrophie blanche, cellulitis, induration, edema of the legs, and/or venous ulcers of the lower limbs [2, 4–7].

Differences in evaluation methods, the criteria adopted for definition, and the geographic regions considered when studying CVD epidemiology have resulted in greatly varying estimates of the prevalence and incidence of CVD. Globally, it is widely recognized that the number of affected people is high, with some estimates reporting that up to 60–70% of all adults, or even higher, experience some form of the disease, depending on the population studied [8, 9]. CVI also shares several risk factors with cardiovascular disease; individuals are at a higher risk of developing cardiovascular disease with increasing severity of CVD, including CVI with skin changes [9]. Additionally, CVI is a strong predictor of all-cause mortality [hazard ratio 1.51, 95% confidence interval (CI) 1.11–2.05, $p = 0.009$], independent of clinical profile or cardiovascular medication.

Appropriate CVD management is aimed at relieving symptoms, reducing the visible signs of venous disease, preventing disease progression, and improving patient QoL [4]. Conservative management of CVD relies heavily on

compression therapy, which is used in combination with lifestyle adaptations (e.g., weight loss from physical exercise targeting lower limb muscle strength and mobility, leg elevation at rest, and avoidance of prolonged standing or sitting), medication to improve vein function, and topical agents to ameliorate skin changes and promote wound healing [2, 4, 10–12]. Conservative treatment with various topical agents may be useful in managing CVD, particularly in patients with specific wound characteristics, although robust evidence on efficacy is currently lacking [4, 13–15]. Surgical approaches may provide more effective relief of symptoms and improve patients' QoL more than conservative treatment with compression hosiery and lifestyle modifications, particularly in patients with uncomplicated varicose veins [13, 16, 17]. Furthermore, newer minimally invasive alternatives, such as cryostripping and endovenous laser therapy, have been shown to be safe and effective in CVD, reducing the trauma of conventional stripping procedures while reducing complications and recurrences [18]. Various pharmacological treatment interventions have also been used over the years, with a range of natural and synthetic venoactive drugs administered orally or applied topically aimed at repairing the endothelium, decreasing capillary permeability, reducing the release of proinflammatory mediators, and improving venous tone,. However, the place of pharmacological therapies in CVD management is somewhat unclear, and high-quality evidence from controlled trials is needed to fully define the efficacy and risk/benefit aspects of venoactive agents in CVD [4, 14].

Glycosaminoglycans (GAGs) or mucopolysaccharides (MPS) comprise long, unbranched polysaccharides with repeating disaccharide units. Found most commonly in the vertebrate extracellular matrix, their highly-polar chemical structure permits considerable hydrogen bonding with adjacent water molecules, effectively hydrating the surrounding tissue through their strong water-retaining capabilities [19–21]. Xioglican cream is a topical formulation composed primarily of the GAG galactosaminoglycan polysulfate (PSGAG) and the sodium salt of hyaluronic acid (HA; hyaluronan, hyaluronate). Galactosaminoglycan polysulfate is a hydrophilic film-forming agent which is not absorbed systemically and exerts its action locally. As it does not achieve its principal intended action by a pharmacological, immunological, or biochemical mechanism of action, it is categorized as a medical device. The strongly hydrophilic nature of the cream, and its considerable moisturizing and soothing properties, have led Xioglican to become a widely established topical treatment for CVD-related skin conditions. The cream promotes physiological hydration of the skin and is helpful in the local prevention and treatment of skin alterations (e.g., dystrophies, dyschromias, xerosis, peeling, and dryness) associated with CVD (i.e., varicose veins, phlebitis, and superficial thrombophlebitis). Xioglican cream may also be applied for the local treatment of edema and hematomas induced by trauma and superficial bruises.

The aim of this post-marketing study was to assess the efficacy and safety profile of Xioglican cream in the physiological restoration of cutaneous signs and symptoms in patients with CVD treated in Italian routine clinical practice.

METHODS

This study (XIO/09/2020) was designed to evaluate the efficacy, safety, and effects on patient QoL of Xioglican topical cream for the physiological restoration of skin alterations (desquamation, dystrophies, dyschromias, xerosis, and hyperkeratosis) and symptoms (burning, itching, and pain) in patients with C2–C4b CVD according to the Clinical, Etiologic, Anatomical, and Pathophysiological (CEAP) classification system, 2020 revision [22].

Study Design and Objectives

This was a multicenter, prospective, observational, post-marketing study conducted at two study sites, the Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone", Palermo, Italy, and the Ospedale "Riccardo Guzzardi", Ragusa, Italy. A study period of 18 months from the patients' enrollment was planned, with

each patient followed up for 12 weeks. Initiation of Xioglican was based on an investigator's decision after assessing patient suitability consistent with conventional clinical practice; all medical procedures were performed per standard of care.

The investigator used an electronic data capture system and case report forms to collect all the data required by the protocol.

Ethical Considerations

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki of 1964 and its later amendments, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline on the Structure and Content of Clinical Trial Reports on Good Clinical Practice (GCP), ISO14155:2020, the European Union Medical Device Regulation MDR 2107/475, and following all other local Italian laws. Registration of the study with the European Union Clinical Trials Register (EudraCT) was not required.

Before the study was conducted, the clinical investigation plan and any subsequent amendments were submitted to and approved by the relevant Ethics Committees: Comitato Etico Palermo 1, Azienda Ospedaliero Universitaria Policlinico "Paolo Giaccone", Palermo, Italy, and the Comitato Etico Catania 1, Azienda Ospedaliero Universitaria Policlinico "G. Rodolico-San Marco", Catania, Italy. Written informed consent was collected from all patients at enrollment. A progressive unique numerical code was assigned to each patient, and data relating to that patient were kept anonymized throughout the study.

Project management, protocol and report medical writing, and monitoring study activities were carried out by the Contract Research Organization (CRO), UNIFARM Research Centre, Catania, Italy. Latis Srl, Genova, Italy, was responsible for the statistical analysis and for preparing the statistical analysis report.

Trial Population

A total of 30 patients were to be recruited with competitive enrollment at the study sites. Patients were included if they were adults aged 18–75 years with a clinical diagnosis of C2–C4b CVD according to CEAP classification, revision 2020 [22]. Patients had to be able to provide informed consent, comprehend the full nature and purpose of the study, including the possible risks and side effects, be able to cooperate with the investigator, and comply with all study requirements.

Key exclusion criteria were: CVD classified as CEAP C0, C1, C4c, C5, and C6; decompensated cardiac insufficiency; edema not due to venous disease of the legs; known or potential hypersensitivity and/or history of allergic reactions to one of the components of the topical medical device; peripheral arterial disease; current acute phlebitis or thrombosis; insulin-dependent diabetes mellitus, neuropathies, hyper- or hypocalcemia, and presence of malignancies; anamnestic indications of diabetic microangiopathy or polyneuropathy, or a history of alcohol or drug abuse. Participation in a clinical trial within the previous 30 days was not allowed. Patients with evidence of severe or uncontrolled systemic disease or any other significant disorders that did not allow participation in the study or could compromise the results were excluded.

Concomitant treatments taken according to current medical practice were allowed, except for topical or systemic therapies that might interfere with the evaluation of Xioglican. Patients who were wearing elastic compression hosiery prior to study enrollment were permitted to continue using compression treatment during the observation period.

Study Procedures

Xioglican topical cream is a marketed Commission Européene (CE)-certified medical device consisting of PSGAG, HA (sodium salt), and a variety of other components (i.e., cetostearyl alcohol type A, medium chain triglycerides, myristic alcohol, isopropyl myristate,

bentonite, isopropyl alcohol, imidazolidinyl urea, phenoxyethanol, lavender essence, and purified water). The preparation (lot number "003"), manufactured by Neopharmed Gentili, Milan, Italy, is a cream of white or off-white color, packaged in 50-g tubes, and produced via a long-established standard production process.

Patients were treated for 12 weeks and evaluated by routine clinical practice during four scheduled visits: baseline (visit 1; day 0), 10 days post-initial administration (visit 2), 6 weeks post-initial administration (visit 3; day 42), and at 12 weeks post-initial administration (study termination visit; day 84). A window of ± 1 day was allowed for all scheduled visits. Patient compliance to ensure correct treatment with the medical device and use of other medication was monitored by the CRO study staff during visits and evaluated by the investigator.

Patients were informed about the study aims and procedures during the baseline visit and provided written informed consent for inclusion. All precautions, warnings, and side effects of the preparation were clearly reported to the patients in the instructions for use. Inclusion/exclusion criteria were checked, and the patient's demographic data were collected. Self-assessment questionnaires were provided to patients, and treatment commenced (topical application of 2–4 cm of cream on the surface of the skin to be treated and surrounding areas, up to thrice daily, gently massaging until complete absorption, for 12 weeks). Patients were informed that treatment should be continued until the symptoms disappeared, at which time the number of daily applications could be reduced progressively.

At all visits, patients' medical history and drug history were recorded (to monitor the use of concomitant medications), a general physical examination/vital sign assessment was performed, clinical signs and symptoms of CVD were assessed, and instrumental and laboratory tests based on current clinical practice were conducted. Additionally, at visits 2–4, any reported adverse events were evaluated. The investigator performed all assessments they deemed necessary and could suspend treatment with the Xioglican cream if required. At visit 4 (study termination), the self-evaluation questionnaires were collected, and any remaining Xioglican cream was returned.

Outcome Measures

The primary study objectives were to (1) evaluate the efficacy of topical application of Xioglican cream in the physiological restoration of skin manifestations (desquamation, dystrophies, dyschromias, xerosis, and hyperkeratosis) and CVD symptoms (burning, itching, and pain); (2) evaluate the safety profile of the medical device Xioglican cream; and (3) assess the QoL and the degree of patient satisfaction.

The secondary objectives were to (1) evaluate the efficacy of Xioglican cream in improving edema and hematoma (if present), and (2) evaluate the efficacy of the Xioglican cream at week 12.

The Investigator Global Assessment of Safety Global (IGAS) scale, CEAP classification [22], and the Venous Clinical Severity Score (VCSS) [23] were used to assess the clinical efficacy of the medical device. A change in CEAP clinical class is a validated and internationally-accepted standard for describing patients with CVD that has been used for reporting clinical research findings. CEAP classification was calculated at each visit based on current clinical practice. In addition, VCSS was used to evaluate changes in CVD severity over time and in response to treatment. Finally, a patient-evaluated visual analog scale (VAS) was used to assess the symptoms of venous insufficiency, including pain, cramps, heaviness, paresthesia, and a feeling of swelling (edema).

Primary endpoints were (1) improvement of signs and symptoms by ≥ 1 CEAP class (i.e., responder); (2) assessment of Xioglican global efficacy using VCSS ranging from 0–30 (0 = absent, 30 = severe); (3) evaluation of CVD associated symptoms (burning, itching, and pain) on a VAS ranging from 0 to 10; (4) evaluation of any reported adverse events and Xioglican cream safety using the IGAS (4-point scale: 1 = very good safety, 2 = good safety, 3 = moderate safety, and 4 = poor safety) evaluated at visit 4 (week 12); and (5) patient QoL according to the Chronic Venous Insufficiency

Quality of Life Questionnaire (CIVIQ-20 questionnaire) [24], assessed at baseline and week 12. The CIVIQ-20 questionnaire (min score: 20, max score: 100) provides a global index and outline of four QoL dimensions: "pain" (4 items), "physical" (4 items), "psychological" (9 items), and "social" (3 items), with each item scored between 1 and 5.

Secondary endpoints were (1) resolution of edema and hematoma (if present), assessed via improvements in the circumference of the affected leg(s) (in cm), and blood flow in the affected area at baseline and week 12, and (2) evaluation of the Xioglican cream medical device at baseline and week 12.

Sample Size

Patients were considered "responders" if their CEAP classification decreased by at ≥ 1 point; "non-responders" were patients whose CEAP classification remained stable or increased. It was estimated that for the study to have 80.0% power to detect a statistically significant proportion (75.0%) of responders against a referent 50.0% proportion using the exact binomial test, 29 patients would be required. Similarly, it was estimated that enrollment of 27 patients would provide 80.0% power to detect a statistically significant difference of 2 points [standard deviation (SD) of 3.5] between baseline and treatment VAS and VCSS. As this was an observational study, no adjustment for multiplicity was made in the sample size estimation. According to these considerations, 30 patients were to be enrolled.

Statistical Methods

All the enrolled patients were included in the statistical analysis. Continuous variables were reported as minimum, maximum, average, SD, and medians. Categorical variables were reported as absolute rates and percentages. The proportion of responders according to change in CEAP was compared to a 50.0% proportion using the exact binomial test. Changes from baseline in continuous variables were tested using the paired *t* test. The corresponding non-parametric Wilcoxon signed-rank test was used when appreciable deviation from normality was detected. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS® Software version 9.4 for Windows (SAS Institute, Cary, NC, USA). The last observation carried forward approach was employed for missing data in post-baseline performance endpoints.

Demographic characteristics (e.g., age, sex, and race) and baseline values were summarized utilizing descriptive statistics. For the safety population, all enrolled patients who received ≥ 1 dose of Xioglican cream were included in the analysis.

RESULTS

The first visit of the first patient was on May 27, 2021, and the last visit of the last patient was on October 20, 2022. There was a final close-out visit on October 25, 2022.

Demographics

Thirty-two patients were screened and began treatment with Xioglican. Two patients who did not apply Xioglican were excluded. Of the 30 patients who applied the cream, five discontinued prematurely and 25 completed the study. The efficacy and safety populations comprised 30 and 25 patients, respectively. The disposition of patients through the study is shown in Fig. 1. Baseline demographic and clinical characteristics are shown in Table 1. All patients had CVD and were Caucasian; 50.0% had a C2 CEAP classification, and 50.0% were C3. No patient had CEAP C2r, C4a, or C4b CVD (Table 1).

Effects on Clinical Signs and Symptoms and Skin Manifestations

There was a reduction in CVD-related clinical signs and symptoms and cutaneous manifestations at the end of the observation period (Table 2), with a statistically significant reduction in leg circumference (mean ± SD:

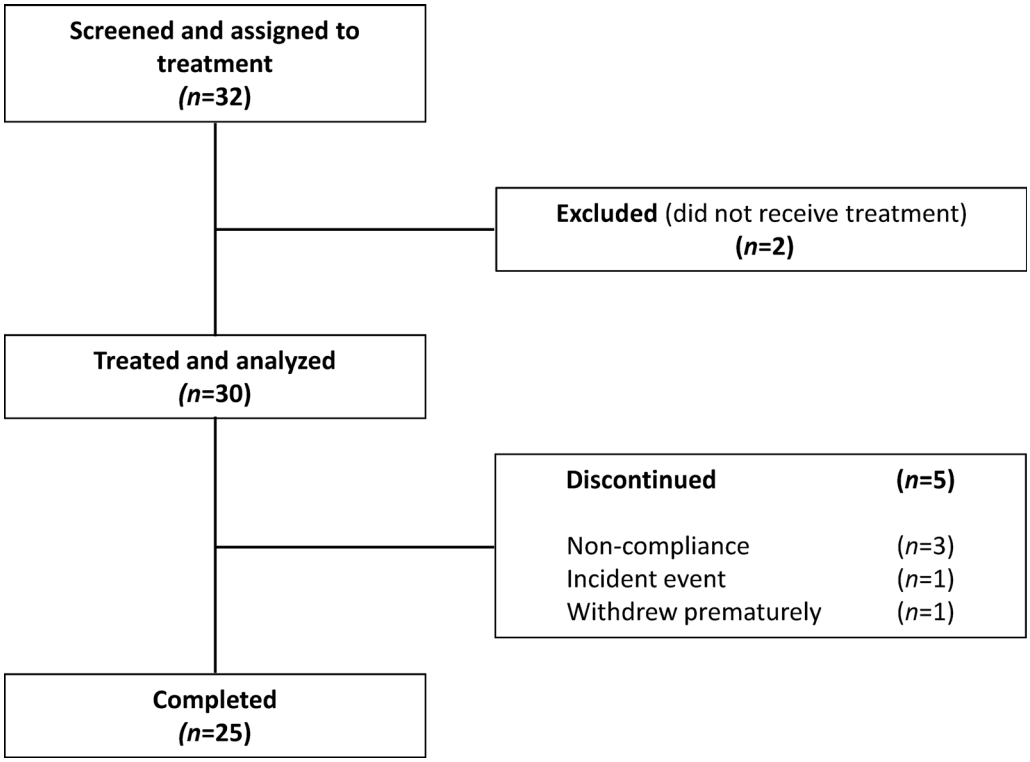

Fig. 1 Patient disposition throughout the study

-3.21 ± 3.39 for left and -2.92 ± 2.70 cm for right legs, both $p < 0.0001$) and in local edema (-5.52 ± 7.94 cm, $p = 0.0034$). Treatment was not associated with a change of ≥ 1 CEAP class (Table 3), i.e., treatment failure was observed in all patients. When the proportion of treatment failure (100.0%) was compared to a referent proportion (50.0%) using the exact binomial test, the analysis showed that the difference was statistically significant ($p < 0.0001$).

VCSS, assessed by the same research nurse at each visit, improved with Xioglican cream with a mean ± SD decrease of -0.52 ± 1.94 from baseline to the termination visit ($p = 0.1952$; Table 3). The improvement in total VCSS was driven by reductions in pain, varicose veins, and venous edema.

As shown in Table 3, skin burning, pain, and aching or tiredness significantly decreased from baseline to the end of treatment ($p = 0.0043$, $p = 0.0039$, and $p = 0.0008$, respectively), and patient QoL significantly improved ($p = 0.0061$). Swelling decreased slightly from baseline to the end of treatment (mean ± SD -0.50 ± 1.98 cm); however, this difference was not statistically significant ($p = 0.2133$). Flaking or itching skin slightly decreased from baseline to the end of treatment (-0.38 ± 1.28 cm), but the difference did not reach statistical significance ($p = 0.1644$). Inferential analysis was not performed on stasis ulcers or leathery-looking skin, as the VAS assessment for both endpoints was 0 cm for all patients at both baseline and Visit 4.

Hyperkeratosis and leathery-looking skin were not present in any patient at baseline or after treatment.

Satisfaction with Treatment

Globally, almost all patients (23/25, 92.0%) were "Very satisfied" or "Satisfied" with the use of the product. Two patients were neither satisfied nor dissatisfied. The degree of satisfaction with Xioglican cream reported by patients at

Table 1 Baseline demographic and clinical characteristic ($n = 30$)

Characteristic	Xioglican cream
Age, years	
Mean ± SD	60.77 ± 9.90
Median (range)	62.00 (33–74)
Sex, *n* (%)	
Female	26 (86.7)
Male	4 (13.3)
Height, cm	162.54 ± 7.44
Weight, kg	78.86 ± 15.07
Blood pressure, mmHg	
Systolic	121.83 (12.00)
Diastolic	75.83 (10.01)
Heart rate, bpm	72.40 (7.68)
CVD manifestations[a]	
C2	15 (50.00)
C3	15 (50.00)
C2r, C4a, or C4b	0 (0.00)
Extent of edema on palpation, cm	12.17 ± 9.00
General physical examination normal, *n* (%)	28 (93.3)

Unless otherwise indicated, data are presented as mean ± SD. Data for height, weight, and general physical examination were not available for 2 patients

BPM beats per minute, *CEAP* Clinical, Etiologic, Anatomical and Pathophysiological, *CVD* chronic venous disease, *SD* standard deviation

[a]According to CEAP classification: *C2* varicose veins > 3 mm, *C3* edema, *C2r* recurrent varicose veins, *C4a* secondary pigmentation, eczema, or both, *C4b* lipodermatosclerosis, white atrophy, or both

12 weeks is shown in Fig. 2. At least 92.0% of patients were very satisfied or satisfied with skin sensation after application, the ease of application, the speed of absorption of the cream, and the pleasantness of the cream.

Safety

Overall, two adverse events were reported during the study; severe itch (grade 3) in one patient, considered related to the study medical device, and suspected mild (grade 1) phlebitis in another patient, not considered related to the treatment. Neither adverse event was considered serious. At the study end, the IGAS of the preparation was rated as "Very good" in all 25 patients (100.0%) in the safety population.

DISCUSSION

In this prospective observational study, the efficacy and safety of Xioglican cream in patients (aged 18–75 years) with CEAP class C2–C3 CVD were evaluated. At the end of the observation period, topical treatment with Xioglican cream was associated with stabilizing or reducing some CVD-related skin signs and symptoms (edema, burning, itching, pain, and swelling). However, as expected, there was no change in CEAP classification. There was a statistically significant reduction in the circumference of the legs (i.e., local edema) and an improvement in subjective measures of CVD, including VCSS scores and patients' QoL, suggesting that Xioglican was associated with stabilization of the disease. Of note, although CEAP is established as the clinical standard for confirming and classifying the disease, it is less suited for assessing therapeutic efficacy, as measurements in each class are static [25, 26]. In this regard, the VCSS is a validated measure designed to complement the CEAP by providing a dynamic score with additional sensitivity. VCSS scores are consistent with a CEAP diagnosis, with favorable inter- and intra-observer variability and reliability coefficients [23, 27]. The 10-item, 30-point VCSS instrument's construction includes nine clinical characteristics most indicative of therapeutic changes supporting QoL assessments [23, 27]. The tenth category of the VCSS relates to the use of compression garments [27]. The mean total VCSS score was 3.93 ± 1.14 at baseline and 3.28 ± 1.95 at the study termination visit, representing a mean score improvement of

Table 2 Change from baseline in leg circumference and extent of edema ($N = 30$)

Characteristic	Xioglican cream
Left leg	
Affected by CVD at visit 1 (baseline), *n* (%)	30 (100.0)
Leg circumference at baseline, cm	$n = 30$
Mean ± SD	27.13 ± 4.13
Median (range)	27.00 (20.00, 40.00)
Affected by CVD at visit 4 (end of treatment), *n* (%)	$n = 25$[a]
No	1 (4.0)
Yes	24 (96.0)
Leg circumference at visit 4, cm	$n = 24$[a]
Mean ± SD	24.04 ± 4.11
Median (range)	24.00 (18.00, 32.00)
Change from baseline	$n = 24$[a,b]
Mean ± SD	− 3.21 ± 3.39
Median (range)	− 3.00 (− 13.00, 3.00)
Right leg	
Affected by CVD at visit 1 (baseline), *n* (%)	30 (100.0)
Leg circumference at baseline, cm	$n = 30$
Mean ± SD	26.53 ± 4.01
Median (range)	26.00 (20.00, 38.00)
Affected by CVD at visit 4 (end of treatment), *n* (%)	$n = 25$[a]
No	1 (4.0)
Yes	24 (96.0)
Leg circumference at visit 4, cm	$n = 24$[a]
Mean ± SD	23.92 ± 3.76
Median (range)	23.00 (18.00, 30.00)
Change from baseline	$n = 24$[a,b]
Mean ± SD	− 2.92 ± 2.70
Median (range)	− 3.00 (− 8.00, 4.00)
Extent of edema (cm)	
Visit 1 (baseline), *n* (%)	$n = 30$
Mean ± SD	12.17 ± 9.00
Median (range)	10.00 (0.00, 32.00)
Visit 4 (end of treatment), *n* (%)	$n = 25$[a]
Mean ± SD	7.64 ± 8.02
Median (range)	7.00 (0.00, 30.00)
Change from baseline	$n = 25$[a,c]
Mean ± SD	− 5.52 ± 7.94
Median (range)	− 6.00 (− 22.00, 12.00)

CVD chronic venous disease, *SD* standard deviation
[a]Five patients discontinued prematurely, [b]$p < 0.0001$, [c]$p = 0.0034$

0.52 ± 1.94. As the VCSS captured the physician's evaluation of CVD symptoms, the results suggest that treatment with Xioglican cream promoted stabilization of clinical symptoms.

Only two adverse effects were reported during the treatment period, neither serious, and only one of which was considered related to the study medical device. This corroborates the good safety profile of Xioglican cream. Furthermore, patient satisfaction related to the use of Xioglican cream showed that almost all patients (92.0%) were "Very satisfied" or "Satisfied" with the use of the product.

CVD is characterized by "morphological and functional abnormalities of the venous system of long duration" [7], manifesting as a wide range of signs and symptoms that may severely reduce a patient's QoL and warrant investigation and treatment. While most

Table 3 Changes from baseline in efficacy endpoints ($n = 30$)

Endpoint	Xioglican cream
CEAP classification at Visit 1 (baseline)	
C2 ($n = 15$)	15 (50.0)
C3 ($n = 15$)	15 (50.0)
CEAP classification at Visit 4 (end of treatment)	
C2 ($n = 12$)	12 (48.0)
C3 ($n = 13$)	13 (52.0)
Venous Clinical Severity Score	
Visit 1 (baseline) ($n = 30$)	3.93 ± 1.14
Visit 4 (end of treatment) ($n = 25$)	3.28 ± 1.95
Change from baseline ($n = 25$)	− 0.52 ± 1.94[a]
Skin burning VAS (cm)	
Visit 1 ($n = 30$)	2.17 ± 3.17
Visit 4 (end of treatment) ($n = 25$)	0.52 ± 1.42
Change from baseline ($n = 25$)	− 1.40 ± 2.22[b]
Pain VAS (cm)	
Visit 1 (baseline) ($n = 30$)	2.80 ± 2.28
Visit 4 (end of treatment) ($n = 25$)	1.40 ± 1.76
Change from baseline ($n = 25$)	− 1.24 ± 1.90[c]
Aching or tiredness VAS (cm)	
Visit 1 (baseline) ($n = 30$)	3.37 ± 2.13
Visit 4 (end of treatment) ($n = 25$)	1.48 ± 1.85
Change from baseline ($n = 25$)	− 1.80 ± 2.36[d]
CIVIQ-20 score	
Visit 1 (baseline) ($n = 30$)	43.38 ± 23.98
Visit 4 (end of treatment) ($n = 25$)	30.85 ± 20.08
Change from baseline ($n = 25$)	− 9.65 ± 16.05[e]

Unless otherwise indicated, data are mean ± SD

CEAP Clinical, Etiologic, Anatomical, and Pathophysiological, *C2* varicose veins > 3 mm, *C3* edema, *CIVIQ-20* Chronic Venous Insufficiency Quality of Life Questionnaire-20 item, *SD* standard deviation, *VAS* visual analog scale

[a]$p = 0.1925$ [b]$p = 0.0043$ [c]$p = 0.0039$ [d]$p = 0.0008$ [e]$p = 0.0061$

pharmacological approaches to CVD aim to prevent or resolve the more serious complications of the disease, patients with early-stage disease can also experience daily discomfort that negatively impacts their QoL. Moreover, it is known that skin health may be compromised by circulatory pathologies, leading to a state of excessive dryness, which, if left untreated, can lead to painful symptoms and skin tears, supporting the role of moisturizing and emollient creams such as Xioglican in maintaining skin health and adequately hydrated skin [2]. Maintaining or restoring skin health and preventing CVD-related complications such as infections and ulceration is also important [2, 4, 10]. As the treatment options for CVD continue to evolve, clinicians need to have access to effective therapeutic products that benefit patients in their everyday lives.

To this end, the medical device, Xioglican cream, has strong moisturizing and soothing capabilities, and has an established role in the topical treatment of CVD-related skin alterations and symptoms. GAGs (e.g., PSGAG and HA), as principal components of Xioglican cream, are characterized by a strong hydrophilic character and a sizable moisturizing power due to their remarkable hygroscopic properties [19–21]. The great hydrophilicity of GAGs has led to their widespread use in medical disciplines and the pharmaceutical industry, where they have been used for decades as anti-inflammatory and antithrombotic agents in treating osteoarthritis, thrombophlebitis, thromboembolism prophylaxis, skin hematomas, sports injuries, wound healing, ophthalmology, and edema [19–21, 28]. Systemic administration of the GAG mesoglycan has been shown to improve cutaneous blood flow in patients with CVD [29], and HA is a known structural and functional component in the vertebrate cutaneous extracellular matrix [20, 21, 28]. HA's strongly hydrophilic properties make it capable of attracting and retaining approximately 1000 times its weight in water, highlighting its importance for maintaining the structure and volume of tissues [21].

Exogenous GAGs have also been shown to increase hydration by stimulating the synthesis of endogenous hyaluronate, thus increasing the water binding capacity and viscoelasticity of the skin, enhancing the RNA levels of key extracellular matrix molecules (including endogenous GAGs and proteoglycans), protecting cells from membrane disruption, reducing the levels of

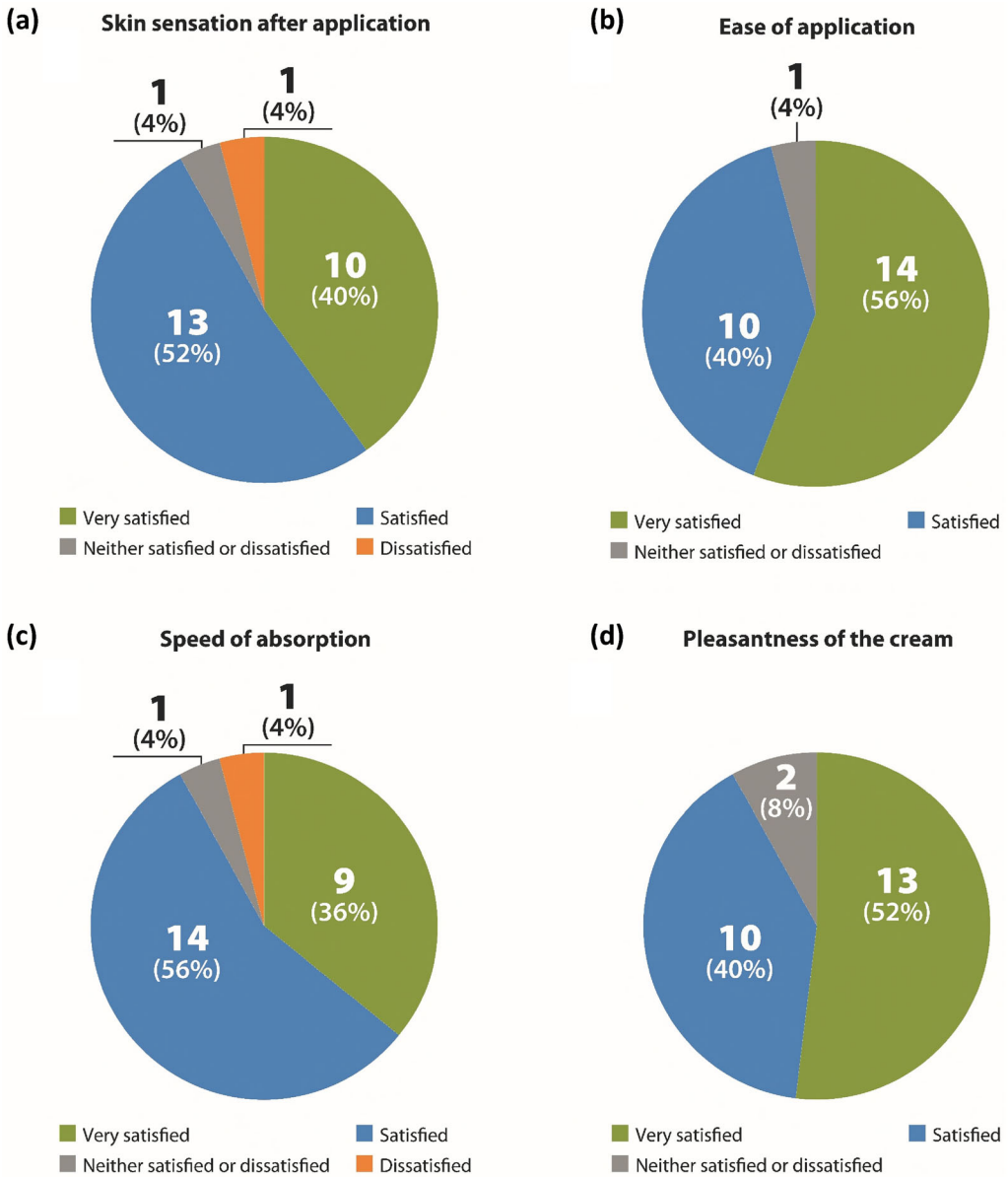

Fig. 2 Degree of satisfaction with Xioglican cream at the end of treatment for **a** skin sensation after application, **b** ease of application, **c** speed of absorption, and **d** pleasantness of the cream

pro-inflammatory cytokine tumor necrosis factor-α, and inhibiting apoptosis by enhancing membrane stability and promoting cell survival [19, 28, 30].

Although Xioglican cream does not exhibit a pharmacological or biochemical mechanism of action, it has a strong local soothing and moisturizing activity. As with other commercially available topical formulations of PSGAG and HA, Xioglican cream is a non-invasive medical device for external use only and should not be applied in case of bleeding, on open wounds and mucous membranes, or sites of infections or in the case of suppurative processes.

Data from randomized, controlled studies of topical venoactive agents in the treatment of CVD-related skin conditions are limited [14]. Topical application of HA assisted in healing venous leg ulcers in patients, significantly

improving the appearance and dimensions of the ulcers, and was significantly more effective than topical dextranomer (the product of choice in France at the time) in decreasing edema [31]. There is also some evidence for the benefits of other topical treatments, such as *O*-(β-hydroxyethyl)-rutosides. In two studies in patients with CVI, topical application of an *O*-(β-hydroxyethyl)-rutosides gel significantly improved lower leg circumference and symptoms [32], and significantly improved the response to oral *O*-(β-hydroxyethyl)-rutosides alone [33]. Of interest, Dwyer and colleagues enrolled 32 patients with CEAP C4a (89.0%), C4b (6.0%), C3 (2.0%), and C1 (3.0%) CVD, who underwent treatment with a natural health varicose vein cream containing 10.0% witch-hazel as the active ingredient as well as horse chestnut and rutin [34]. After 6 weeks of treatment, 66.0% of treated legs showed a decrease in severity, from a mean total VCSS score of 10.0 ± 3.0 at baseline to 8.0 ± 1.9 at 6 weeks, a score improvement of 2.0 points.

Our study suggests that Xioglican cream may have an adjuvant effect against CVD skin manifestations, although differences in patient characteristics and study design limit comparisons with other studies. Specifically, in the sample studied by Dwyer and colleagues [34], all of the legs had pigmentation, and 52.0% had signs of inflammation, both of which are characteristics of C4 CVD. In our study, all legs had varicose veins and edema, characteristics of C2 and C3 CVD, respectively.

Additionally, the significant and progressive deterioration of general and health-related QoL in patients with CVD, related not just to the physical aspects of pain, swelling, leg discomfort, and severe skin changes but also to emotional or mental health, suggests that improvement of QoL better captures the burden of CVD and should be viewed as the main therapeutic outcome measure [35].

This study has some limitations, including the small number of patients enrolled. Also, as a single-arm, observational study that did not include a control group, it shares the limitations of open-label studies, including the possibility of selection bias. Although these efficacy and safety data may, therefore, be affected by confounding factors caused by population selection by the investigators and inability to objectively evaluate treatment adherence, the appropriate assessment and outcome measures were included, both patient-reported and investigator assessments were reported, and stringent inclusion and exclusion criteria were applied. As a prospective observational study, the medical device was prescribed in the usual manner following the terms of the marketing authorization. The decision to initiate Xioglican in a patient was not decided in advance according to the study protocol, but was determined as part of routine clinical practice; the prescription of the medicine was separated from the decision to include the patient in the study.

Our experience with Xioglican is promising. However, larger, controlled multicenter studies are needed to confirm and expand on these findings. Finally, the investigation of Xioglican in combination with other active pharmacological agents is a potential direction for future research into safe and effective therapeutic strategies for managing venous disease.

CONCLUSIONS

Topical treatment with Xioglican cream improves the signs, symptoms, and QoL of CVD patients (CEAP class C2–C3). These results confirm that this clinical approach can be effectively and safely adopted into the routine care of patients with CVD. The results of this real-world study support the recommendations of international guidelines for managing CVD, which recognize the importance to patients of relieving the pain, heaviness, discomfort, and swelling related to CVD, along with ameliorating skin changes and improving QoL.

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Data Availability. The data generated/analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Ida Maria Muratori, Francesco Contorno, and Corrado Amato declare that they have no competing interests, nor have they received grants related to the study.

Ethical Approval. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki of 1964 and its later amendments, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline on the Structure and Content of Clinical Trial Reports on Good Clinical Practice (GCP), ISO14155:2020, the European Union Medical Device Regulation MDR 2107/475, and following all other local Italian laws. Registration of the study with the European Union Clinical Trials Register (EudraCT) was not required. Before the study was conducted, the clinical investigation plan and any subsequent amendments were submitted to and approved by the relevant Ethics Committees: Comitato Etico Palermo 1, Azienda Ospedaliero Universitaria Policlinico "Paolo Giaccone", Palermo, Italy, and the Comitato Etico Catania 1, Azienda Ospedaliero Universitaria Policlinico "G. Rodolico-San Marco", Catania, Italy. Written informed consent was collected from all patients at enrollment. A progressive unique numerical code was assigned to each patient, and data relating to that patient was kept anonymized throughout the study. Project management, protocol and report medical writing, and monitoring study activities were carried out by the Contract Research Organization (CRO), UNIFARM Research Centre, Catania, Italy. Latis Srl, Genova, Italy, was responsible for the statistical analysis and for preparing the statistical analysis report.

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