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Real-World Evidence of Crizanlizumab Showing Reductions in Vaso-Occlusive Crises and Opioid Usage in Sickle Cell Disease

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ABSTRACT

Objective: Access to crizanlizumab, a disease-modifying therapy for sickle cell disease (SCD), was provided through a managed access program (MAP, NCT03720626). The present analysis evaluated the impact of 12 months of crizanlizumab treatment on vaso-occlusive crises (VOCs), and on the use of opioids for VOC-related pain relief, in patients with SCD from the MAP.

Methods: From June 2018 to January 2023, 112 patients with a history of recurrent VOCs completed 12 months of crizanlizumab (5 mg/kg) treatment and were monitored for adverse events (AEs).

Results: Crizanlizumab led to reductions of 18.0% and 36.2% in the proportions of patients having ≥ 1 home- and ≥ 1 healthcare-managed VOCs. Median absolute changes (interquartile range) from baseline in the rates of home- and healthcare-managed VOCs were −3.0 (−6.0, −1.0) and −2.0 (−4.0, 0), respectively. Data stratified by genotype and prior hydroxyurea use showed similar reductions in VOC rates. A 35.5% reduction in the proportion of patients requiring opioids was noted. AEs were consistent with earlier reports, and no new safety concerns were identified.

Conclusions: Crizanlizumab demonstrated potential benefits in attenuating VOC episodes, irrespective of SCD genotype and prior hydroxyurea use, and in lowering opioid usage. The safety of crizanlizumab was consistent with earlier reports.

Trial Registration: The MAP has been registered at ClinicalTrials.gov with the ID, NCT03720626

1 | Introduction

Sickle cell disease (SCD), a group of hereditary hematological disorders, impacts millions of lives globally and triggers significant public health concerns [1–4]. It affects approximately 0.5 million births per year worldwide, with a high disease burden in sub-Saharan Africa, India, the Middle East, and the Caribbean regions [1, 4, 5]. The disease is caused by mutations in the β-globin gene resulting in the production of sickle hemoglobin (HbS) [1, 2] and is characterized by chronic hemolytic anemia, vaso-occlusive crises (VOC), and an increased risk of end-organ dysfunction, often resulting in premature death [3, 4, 6, 7]. The multi-system clinical manifestations of SCD are presented as either acute complications, including acute pain crises, acute

chest syndrome (ACS), acute hepatic sequestration, splenic sequestration, cholelithiasis, priapism, and stroke, or chronic complications such as chronic kidney disease, chronic pulmonary hypertension, cardiomegaly, cardiopulmonary dysfunction, functional asplenia, long-term complications of priapism, retinopathy, avascular necrosis (AVN), and skin ulcers [6–9]. Vaso-occlusion contributes to VOCs, the clinical hallmark of SCD, and can impact various organs, often leading to debilitating chronic pain from leg ulcers, AVN, and/or neuropathy [10]. Overall, recurrent, unpredictable pain crises profoundly reduce a patient's quality of life (QoL) and are the primary reason for visits to emergency departments or frequent hospitalizations [3, 10, 11].

The complex nature of SCD demands a multidisciplinary approach to the management of its symptoms and complications [10]. Several pharmacological and non-pharmacological therapies have been recommended for pain management in SCD depending on the disease severity and phenotype, along with integrative therapeutic interventions individualized for patient needs [12, 13]. However, the mainstay of treatment remains disease-modifying therapies (DMTs) [12, 13]. Among potential DMTs, hematopoietic stem cell transplantation is the only curative therapy for SCD and can have an 85%–90% success rate in some pediatric patients [10]. However, its use can be limited by a lack of fully matched sibling donors, limited resource-rich facilities, an increased risk of graft-versus-host disease, and mortality occurring in almost 5%–20% of patients, depending on age [10, 14, 15]. Furthermore, chronic blood transfusions, which can result in more frequent healthcare facility visits and interactions with healthcare professionals, carry the risks of transfusional hemosiderosis, alloimmunization, and end-organ damage, potentially reserving it for serious complications, such as ACS, splenic sequestration, aplastic crisis, and cerebral infarction [8, 10]. Hydroxyurea (HU), or hydroxycarbamide (HC), is well established as the primary DMT for SCD [16], although some patients might not demonstrate a significant or sustained response to the drug due to noncompliance, decreased marrow reserve preventing adequate dosage, and genetic factors [17, 18]. HU is not routinely indicated for the HbSC genotype, and monitoring the drug response in such patients can be challenging [19]. Therapy with HU can lead to myelosuppression, the most common manifestation being neutropenia, which necessitates close monitoring of blood parameters [18]. Moreover, HU treatment frequently results in reversible oligo- and azoospermia in men [18], which might hinder compliance, especially while planning for conception [13]. Concerns about potential side effects, cost, limited availability of HU, and the need for regular blood testing and monitoring can be significant barriers to its acceptance and patient adherence [20].

The unmet need for alternative DMTs has driven research into SCD pathophysiology, identifying potential therapeutic targets, and introducing novel molecules, thus expanding the therapeutic landscape of SCD. Among recent DMTs, the amino acid L-glutamine plays a key role in regulating oxidative stress, which contributes to SCD; studies with the commercial formulation of L-glutamine (Endari) showed a 25% reduction in median VOC events, with fewer hospitalizations, compared with placebo [21]. Another potent target is P-selectin, a key driver of multicellular adhesion in SCD; its blockade has shown promise in reducing adhesion, improving microvascular blood flow velocities, and potentially alleviating VOCs [22–25]. Crizanlizumab, a first-in-class humanized monoclonal antibody that binds to P-selectin, blocking interaction with its ligands including P-selectin glycoprotein ligand 1, was identified as a potential DMT based on the findings of the SUSTAIN trial [25]. The phase 2 trial (NCT01895361) demonstrated a 45.3% reduction in annual VOC rates in patients with SCD, irrespective of their genotype or concomitant HU use, and prolonged the median time to the first and second VOC [25]. Furthermore, a post hoc analysis demonstrated crizanlizumab's ability to increase the likelihood of being VOC event-free and delay time-to-first VOC [26]. On this basis, crizanlizumab received United States Food and Drug Administration (US FDA) approval on November 15, 2019, for the reduction in frequency of VOCs in patients with SCD aged ≥ 16 years [27].

In this report, we provide an analysis of the real-world outcomes of crizanlizumab treatment in patients with SCD who participated in a managed access program (MAP) [28]. Our objective was to assess the impact of 12 months of crizanlizumab treatment on VOCs managed in both home and healthcare settings, as well as on the utilization of opioids for VOC-related pain relief.

2 | Methods

2.1 | Novartis MAP for Access to Crizanlizumab

A MAP, also known as "compassionate use" or "expanded access" program, allows pre-approval access to locally unauthorized medicine for patients with serious or life-threatening conditions with no satisfactory alternative treatment available, who are ineligible for clinical trials, and if explicitly allowed by the local laws and regulations of the country of request origin. Initiating a MAP requires sufficient scientific evidence, ideally phase 2b/3 data, to support a positive benefit–risk profile for the product. Novartis established a MAP for crizanlizumab (NCT03720626) [28] based on the SUSTAIN study results, with the intention of allowing access to crizanlizumab for eligible patients with SCD to prevent or reduce the frequency of VOCs. Unsolicited requests were received from physicians via the Novartis Managed Access System. Each request was reviewed by Novartis' clinicians and approved, provided the request was in line with applicable MAP criteria and local laws and regulations. Requesting physicians were guided for treatment and monitoring of their patients. The physicians filled out the initial and resupply request forms using patient information gathered during their clinical visits, including medical histories, hospital records, insurance claims, prescription refills, and consultations, among other sources. The patient information included demographics, disease characteristics, treatment history, ethnicity, physical metrics, VOC frequency, hospitalization history, and opioid usage details.

The present analysis utilized patient records from countries such as Brazil, Italy, Spain, Canada, and Israel. Data from France were excluded as the requests were received outside of the Novartis Managed Access System. Due to the data cut-off for patients who had received crizanlizumab for at least 12 months, patients from Greece and Germany were not included in this dataset and analysis.

2.2 | Patients

Patients were eligible for the MAP if they were aged ≥16 years (≥18 years for Italy), with a confirmed diagnosis of SCD (any genotype) by Hb electrophoresis or high-performance liquid chromatography, and a history of recurrent VOCs as determined by the treating physician, despite receiving HU/HC, L-glutamine (Endari), erythropoietin-stimulating agents, or other preventative therapies. Concomitant treatment with such preventative therapies was allowed. VOC leading to healthcare visit was defined as a VOC with any visit to a medical facility such as an emergency room, hospital, and/or office visit, which included pain management of that VOC in situ. VOC managed at home was defined as a VOC with no visit to any medical facility and/or healthcare professional to receive treatment for VOC. Further, patients were eligible for inclusion only if they were considered ineligible for alternative treatment options, had discontinued them due to unfavorable benefit–risk profiles, or were ineligible for crizanlizumab clinical trials, as determined by their treating physicians. The eligibility criteria have been detailed in Table S1.

2.3 | Treatment and Dosing

All assessments and treatment decisions, along with drug requests and reporting of relevant safety data, were at the discretion of treating physicians and in accordance with applicable local laws and regulations. The dosage and administration of crizanlizumab (Adakveo, Novartis Pharmaceuticals) were according to the MAP treatment plan. Each patient received an intravenous infusion of crizanlizumab 5 mg/kg on Day 1 of Weeks 1 and 3, followed by every 4 weeks. The dosing scheme was identical to that recommended by the US FDA product information and the European Medicines Agency (EMA) summary of product characteristics [27, 29]. For patients who could not tolerate this dosing schedule, crizanlizumab dose interruptions were either recommended or mandated. Dose reductions were not allowed. All possible efforts to maintain the patient on the planned dosing schedule were encouraged. Treatment was discontinued in conditions such as pregnancy and lactation, a significant risk to the patient's safety (e.g., grade 3 and 4 infusion-related reactions [IRRs]), patient's or guardian's decision, unacceptable toxicity, use of prohibited medication, or decisions based after reviewing the safety of the drug or a change in its benefit–risk profile.

2.4 | Patient Monitoring Parameters and Assessments

Patients were assessed during their visits for vital signs, height, weight, electrocardiogram, hematology, chemistries, concomitant medications, dosing, and compliance and monitored for adverse events (AEs). Bleeding events and coagulation were monitored for patients receiving therapeutic anticoagulation or antiplatelet therapy. Further tests were performed before infusions and in the case of IRRs. Pregnancy tests were performed prior to treatment, on the days of the infusions, and at the end of treatment (Table S2).

2.5 | Monitoring and Management of AEs

AEs were assessed using the NCI CTCAE v5.0 (National Cancer Institute Common Terminology Criteria for Adverse Events) grading scale and monitored continuously from consent. All AEs were to be reported by the treating physician, including serious AEs (SAEs) within 24 h. Safety information was to be reported to the local health authority and/or to the ethics committee or institutional review board according to local laws and regulations, and to the respective Novartis local patient safety department according to the agreement letter. In the event of drug-induced toxicities, patients were closely monitored, and treatment continuation or discontinuation was decided at the next visit. On missing two consecutive doses due to suspected drug-related AEs, treatment was permanently stopped. Recommendations for dose interruption and reinitiation of crizanlizumab were provided for adverse drug reactions, including IRRs, neutropenia, thrombocytopenia, elevated direct bilirubin and ALT levels, and infections, as outlined in Table S3. Possible drug-induced liver injury was reported as an SAE in patients with increased ALT and direct bilirubin while ensuring that liver test elevations were not due to cholestasis.

2.6 | Ethics

The treating physicians obtained written informed consent from all participants or their representatives prior to the start of treatment, in accordance with the local laws and regulations and in line with the ethical principles outlined in the Declaration of Helsinki. Confirmation of informed consent was communicated to Novartis through the Managed Access System prior to the treatment initiation.

2.7 | Statistical Methods

Data from the Novartis Managed Access System were summarized using the Statistical Analysis System (SAS 9.4) software. Categorical variables were summarized by counts and percentages. Continuous variables were summarized with means, medians, interquartile ranges (IQRs), and absolute ranges.

3 | Results

3.1 | Baseline Demographics and Clinical Characteristics

Between June 2018 and January 2023, 183 patients with SCD had their initial and resupply requests approved; however, 82 requests were closed for reasons such as discontinuation of treatment ($n=24$), transition to commercial supply ($n=19$), medication not initiated ($n=17$), and others ($n=22$). Among the patients who stopped treatment, seven had reported AEs. Events (preferred terms [PTs]) leading to study treatment discontinuation are presented in Table S4. Events (PTs) leading to study treatment discontinuation in ≥2 patients are presented in Table S1. Patient disposition is shown in Figure 1A. Overall, 112 patients with SCD from Brazil ($n=90$), Italy

(*n* = 15), Spain (*n* = 3), Canada (*n* = 2), and Israel (*n* = 2), aged 16–70 years (18–70 years for Italy), who completed 12 months of crizanlizumab treatment, were included in this analysis (Figure 1B).

The baseline characteristics of the patients are presented in Table 1. The median age of the patients was 35 years, 55.4% were female and 50.9% were African American. Most of the patients had sickle cell anemia (SCA; HbSS, 82.1%). Data regarding HU usage were available for only 76 patients, of which 73.7% reported using HU during their participation in the MAP.

3.2 | Incidence of VOCs

At baseline, 111/112 (99.1%) and 105/112 (93.8%) patients with ≥1 VOC were managed at home and in healthcare facilities, respectively; the proportion decreased to 91/112 (81.3%) and

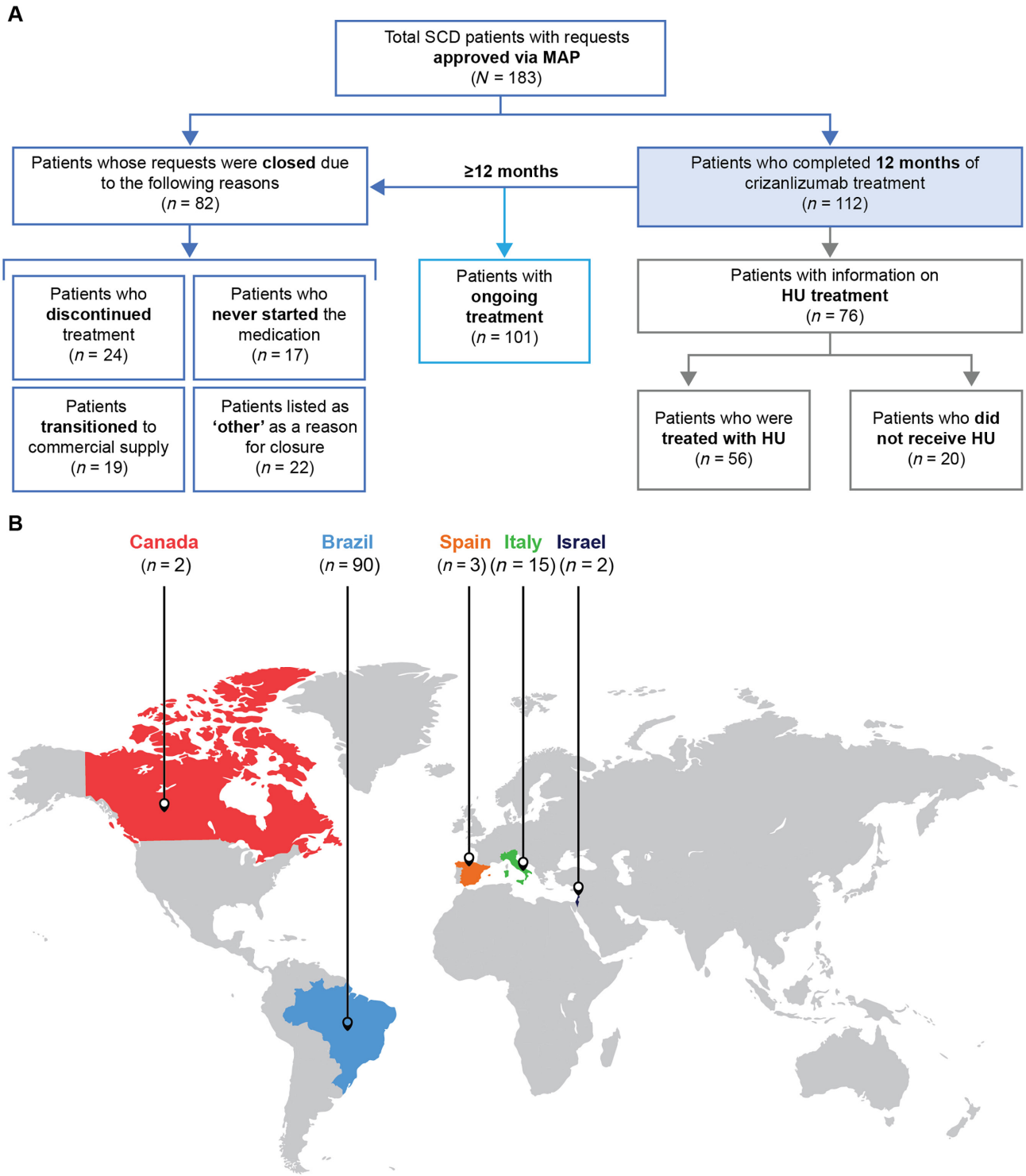

FIGURE 1 | (A) Patient disposition. (B) Worldwide distribution of patients involved in this analysis, and the numbers of participants. HU, hydroxyurea; MAP, managed access program; SCD, sickle cell disease.

TABLE 1 | Characteristics and baseline values of patients with SCD from the MAP, treated with crizanlizumab for 12 months.

Characteristics	Patients ($N=112$)
Age, years	
Median (IQR)	35 (27.5–42.5)
Gender, *n* (%)	
Female	62 (55.4)
Male	50 (44.6)
Ethnicity/race, *n* (%)	
African American	57 (50.9)
Caucasian	10 (8.9)
Hispanic/Latino	19 (17.0)
Other	26 (23.2)
Genotype, *n* (%)	
HbSS	92 (82.0)
HbSC	7 (6.3)
HbSβ^+ thal	6 (5.4)
HbSβ^0 thal	7 (6.3)
HU use, *n* (%)	
Yes	56 (73.7)
No	20 (26.3)
Not reported	36
Patients hospitalized for complications related to SCD in the last 12 months (prior to infusion), *n* (%)	96 (85.7)
Complications related to SCD in the last 12 months (prior to infusion), Median (IQR)	2.5 (2–4)

Abbreviations: HbSβ^0-thal, sickle beta zero thalassemia; HbSβ^+-thal, sickle beta plus thalassemia; HbSC, sickle cell hemoglobinopathy; HbSS, sickle cell anemia; HU, hydroxyurea; IQR, interquartile range; MAP, managed access program; SCD, sickle cell disease.

67/112 (59.8%) following 12 months of crizanlizumab treatment (Figure 2A), corresponding to an overall decrease of 18.0% and 36.2%, respectively. Consistently, the proportion of patients free of home- and healthcare-managed VOCs increased with crizanlizumab treatment when compared with baseline (21/112 [18.8%] and 45/112 [40.2%] vs. 1/112 [0.9%] and 7/112 [6.3%], respectively), which was also reflected in the subgroups defined by genotype and HU use (Figure 2B). The overall frequencies of home- and healthcare-managed VOCs also decreased with crizanlizumab treatment (from 873 to 353 and 473 to 218, respectively). Crizanlizumab treatment resulted in a median absolute change (IQR) from baseline in the rates of home- and healthcare-managed VOCs (−3.0 [−6.0 to −1.0] and −2.0 [−4.0 to 0], respectively) (Figure 2C). Similar reductions in VOC rates were observed when the data were stratified by SCD genotype and prior HU use (Figure 2C).

3.3 | Opioids for VOC-Related Pain Relief

At baseline, 107/112 (95.5%) patients used opioids for pain relief due to VOCs. After 12 months of crizanlizumab treatment, this decreased to 69/112 (61.6%) patients, representing a 35.5% reduction in the proportion of patients requiring opioids. The most frequently prescribed opioid was morphine, followed by tramadol and codeine (Figure 3A). The frequency of opioid use is described in Figure 3B. Crizanlizumab led to a noticeable reduction in opioid use, with opioids being taken infrequently, once daily, or weekly.

3.4 | Tolerability

Overall, AEs were consistent with those reported in other crizanlizumab studies, and no new safety concerns were identified. Of the 112 patients, 58 (51.8%) experienced at least one AE. In Novartis safety database, the most common reported AEs by PT, reported in ≥5% of the patients were: SCA with VOC (17.0%), pain (13.4%), pyrexia (11.6%), arthralgia (7.1%), and pain in extremity (5.4%). The incidence of IRR was 3% (three patients). One patient experienced an IRR during the first dose, leading to crizanlizumab discontinuation. Another developed an IRR after the third dose, with recurrent IRRs in subsequent doses, also resulting in discontinuation. The third patient had an IRR after the eleventh dose, but the action taken on treatment remains unknown. Ten SAEs resulted in fatal outcomes in patients treated for VOC; these were severe acute respiratory syndrome and coronavirus 2 ($n=2$), hepatic failure ($n=1$), VOC with respiratory arrest ($n=1$), cerebrovascular accident ($n=1$), gastrointestinal infection ($n=1$), pneumonia ($n=1$), and unknown causes at the time of the current analysis ($n=3$). None of the deaths were reported as related to the crizanlizumab treatment.

4 | Discussion

The real-world data gathered from the MAP revealed notable decreases in the occurrence of VOCs managed at home and in healthcare settings, regardless of the SCD genotype or prior HU use. The data also demonstrated a decrease in opioid usage for VOC-related pain relief and confirmed the tolerability of crizanlizumab to be consistent with previous clinical trial findings. While the primary objective of the MAP was to provide access to crizanlizumab for patients, the data collected from this MAP can offer robust evidence of the drug's effectiveness in the real-world setting and the benefits in the global SCD population, complementing the published data from SUSTAIN and SOLACE clinical trials.

The reduction in the rates of VOCs with crizanlizumab observed in the current analysis resonates with the outcomes of both the SUSTAIN and SOLACE-Adults clinical trials [25, 26, 30]. SUSTAIN was the pivotal study for crizanlizumab (5 mg/kg) in patients with SCD ($N=198$; age ≥16 years) [25, 26]. It demonstrated a 45.3% reduction in the annual rate of VOCs or sickle cell-related pain crises with crizanlizumab (5 mg/kg) versus placebo (1.63 vs. 2.98, $p=0.01$) [25]. The post hoc analysis revealed that more patients were VOC-free when treated with

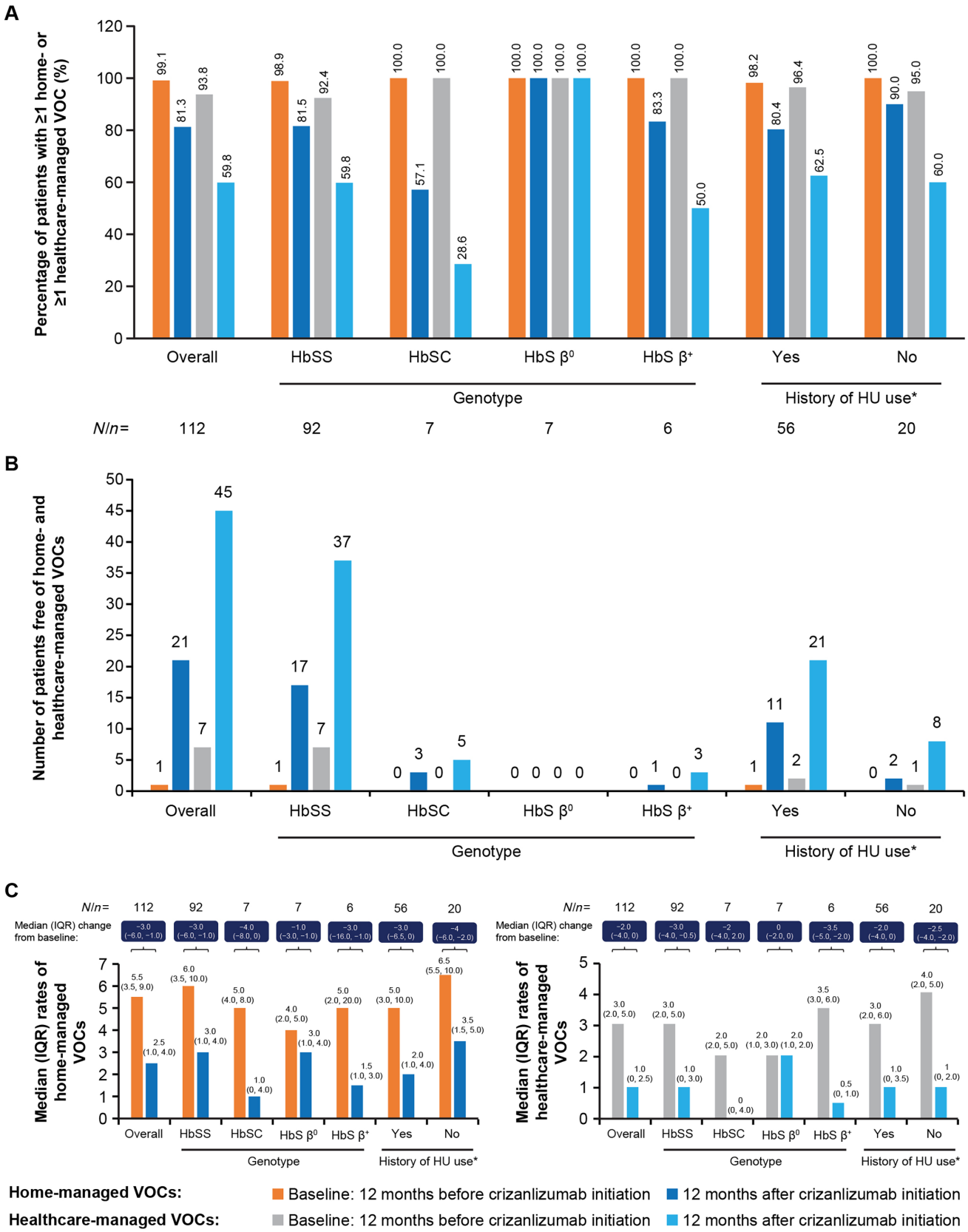

FIGURE 2 | (A) Percentage of patients with ≥1 home- and healthcare-managed VOCs at baseline (12 months before crizanlizumab initiation) and 12 months after crizanlizumab initiation. (B) Number of patients free of home- and healthcare-managed VOCs at baseline (12 months before crizanlizumab initiation) and 12 months after crizanlizumab initiation. (C) Rates of home- and healthcare-managed VOCs, overall and stratified by SCD genotype and history of HU use. *Data on prior HU use were available for only 76/112 patients. HbSβ^0, sickle beta zero thalassemia; HbSβ$^+$, sickle beta plus thalassemia; HbSC, sickle cell hemoglobinopathy; HbSS, sickle cell anemia; HU, hydroxyurea; IQR, interquartile range (Q1, Q3); SCD, sickle cell disease; VOC, vaso-occlusive crisis.

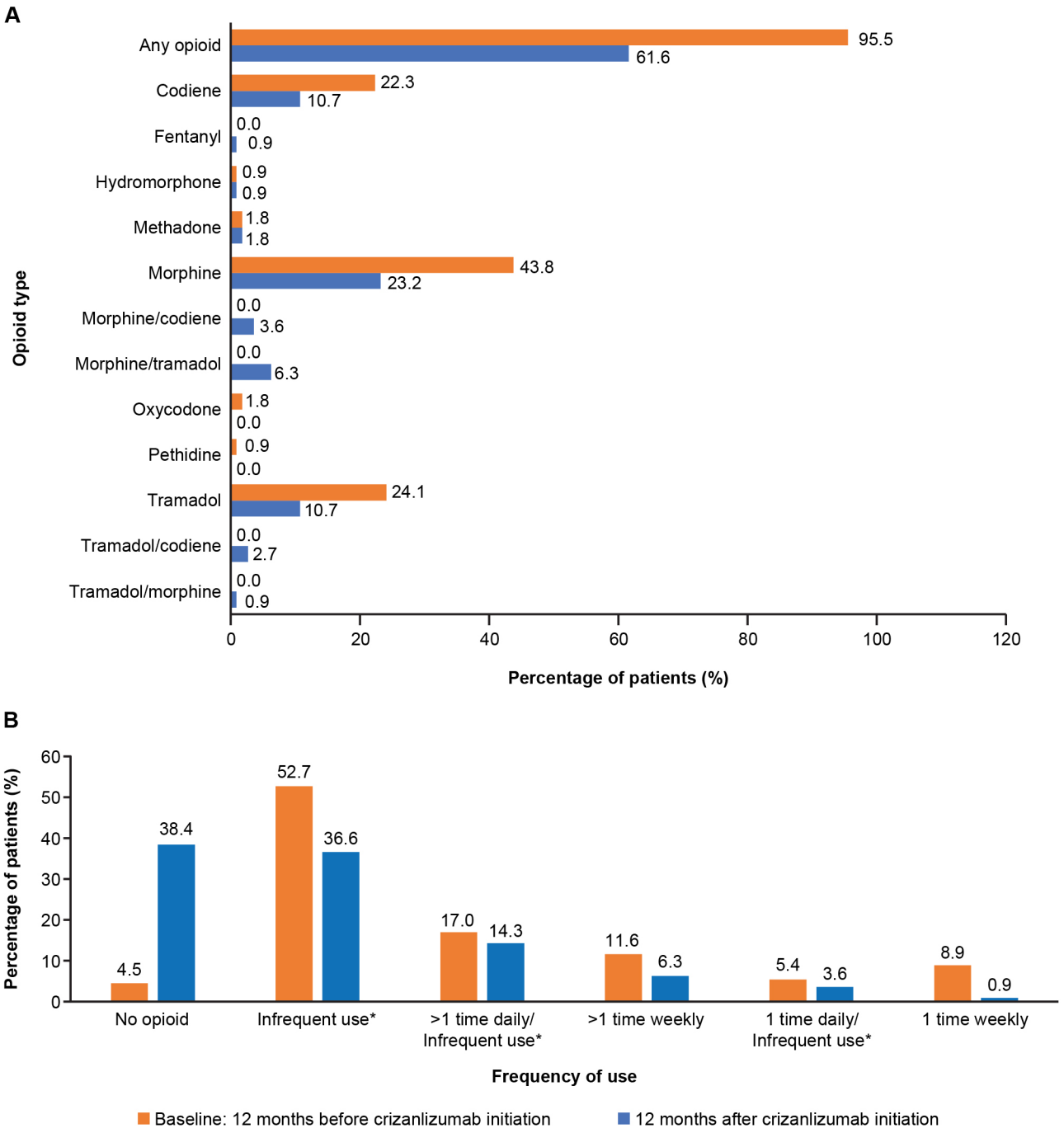

FIGURE 3 | (A) Percentage of patients receiving different opioid types at baseline (12 months before crizanlizumab initiation) and 12 months after crizanlizumab initiation. (B) Frequency of opioid use among those receiving opioids at baseline (12 months before crizanlizumab initiation) and 12 months after crizanlizumab initiation. *Infrequent use, for example, less than four times in a month. The percentages are based on the options of opioid usage frequencies selected by physicians during the submission of requests via the Novartis Managed Access System.

crizanlizumab than placebo, irrespective of frequent prior VOCs (i.e., 5–10; 28.0% vs. 4.2%), HbSS genotype (31.9% vs. 17.0%), and/or concomitant HU use (33.3% vs. 17.5%) [26]. Consistent with the SUSTAIN trial, interim data from SOLACE-Adults trial (phase 2, open-label, NCT03264989) in patients with SCD ($N = 57$; age ≥ 16 years) demonstrated similar efficacy and a favorable safety profile with 12 months of crizanlizumab treatment (5.0 and 7.5 mg/kg) [30]. In the SOLACE-Adults trial, the median (range) absolute reduction from baseline in the annualized rate of VOCs leading to a healthcare visit with crizanlizumab 5 mg/kg treatment was −0.88 (−14.7, 13.3) [30]. Similarly, the MAP data showed reductions in rates of home- and healthcare-managed VOCs (median [IQR] absolute change from baseline, −3.0 [−6.0, −1.0] and −2.0 [−4.0, 0], respectively), as well as in the proportions of patients with ≥ 1 home- (18.0%) and healthcare-managed VOC (36.2%) with 12 months of crizanlizumab (5 mg/kg) treatment. The current analysis demonstrated the effectiveness of crizanlizumab in real-world clinical practice, and the data corroborated the findings of the SUSTAIN and SOLACE-Adults clinical trials.

Based on the SUSTAIN study results, crizanlizumab received conditional marketing authorization from the European Commission on October 28, 2020, for preventing painful crises in patients with SCD aged ≥16 years, following the EMA's scientific assessment [29]. However, on August 3, 2023, the European Commission issued a legally binding decision to revoke the conditional marketing authorization of the drug for the aforementioned indication, after reviewing the primary analysis results of the ongoing phase 3 STAND study [31]. These results did not demonstrate a statistically significant difference between crizanlizumab 5 or 7.5 mg/kg and placebo in the annualized rates of VOCs leading to a healthcare visit during the first year following randomization in a population of adolescent and adult patients with SCD. The efficacy outcomes in the STAND study were inconsistent with those in the SUSTAIN and SOLACE-Adults trials [31, 32]. The safety results were consistent with the known safety profile of crizanlizumab, and no new safety concerns were reported.

In the current MAP data, the rate of home-managed VOCs reported by patients with the HbSβ^+ genotype (mean, 9.7) was high, despite its heterozygous genotype that historically gives rise to a less severe phenotype [33]. In contrast, patients with the HbSβ^0 genotype who typically are noted to have a more severe clinical course resembling SCA, due to the absence of HbA, were reported to experience fewer VOCs (mean, 4.6). While acknowledging the limitations of a small dataset and the inadequate population size within each subgroup to establish significant relationships, the data in this real-world setting point toward contrasting phenotypes when mapped against the genotypes of SCD. However, there are some reports of severe clinical presentations, such as VOCs, ACS, sepsis, AVN, stroke, and osteonecrosis, being associated with the HbSβ^+ genotype [33, 34]. HbSβ^+ thalassemia is clinically heterogeneous, with variable residual amounts of HbA depending on the underlying mutation [33]. Mild to severe manifestations with HbSβ^+ have been attributed to mutations such as intervening sequence (IVS) 1–5 (G → C) and IVS-1 (−2) (A → C) or associated α thalassemia and XmnI polymorphism [35, 36]. Such genetic factors potentially lead to anomalous disease severity, as characterized by the VOC rates in the current group of psickle cell patients.

Studies have shown that VOC episodes are often underreported, as patients usually manage them at home. A lower documented prevalence of VOCs might not reflect the actual burden or severity and cause likely misclassification, miscommunication, and undertreatment of the condition [3, 37]. The current report clearly indicates a higher incidence of VOCs managed at home (mean, 7.8) than at a hospital (mean, 4.2), suggesting that the actual frequency of VOCs might be nearly twice as high as the hospital visits indicate. Earlier surveys have also described managing VOC episodes at home, though the rates are possibly underreported. The international Sickle Cell World Assessment Survey of 2145 patients, showed a mean of 5.3 (standard deviation, 6.8) VOCs reported over the prior year, with 24% being managed at home [38, 39]. Even in high-income countries, 31% of VOCs were managed at home [38]. The most common reasons for managing VOCs at home were poor prior experience at emergency departments or hospitals, assuming that medical assistance was not required, and believing that healthcare professionals do not understand SCD [38, 39]. In a US survey of 303 adults 51% of participants who experienced ≥1 VOC in the 12 months preceding survey completion reported managing VOCs at home [40]. Besides being acquainted with treating their pain crises, and symptoms often being mild, patients preferred home-based VOC management due to expensive treatment elsewhere, others' incapability or unwillingness to treat VOCs, limited or no access to other treatments, and difficulty in commuting to treatment centers [40]. More frequent home-managed VOCs in the MAP data might suggest a deficit in SCD-related healthcare utilization and possibly a need for timely interventions with home management pain plans, as instructed by the primary healthcare practitioner, for early resolution of VOCs.

VOCs are generally associated with acute, abrupt, unpredictable, and severe pain due to skeletal or soft tissue infarction [41]. Chronic pain in SCD typically starts in childhood and continues into adulthood, persisting for most days, lasting over 6 months; 29% of adult patients reported pain on up to 95% of days [42]. Chronic pain can result from either a continuation of painful VOC episodes, from complications such as AVN of various joints, bone infarcts, and leg ulcers, or even from non-SCD etiologies including degenerative joint disease [41, 42]. Therefore, SCD-related pain can be acute, chronic, or a combination of both, which can have a substantial impact on the patient's QoL and is typically managed with opioids, often leading to an alarming increase in their usage or even dependence [41]. There are concerns about opioid abuse, which often arises from self-medication, possibly due to inadequate treatment and the potential harm caused by long-term opioid usage in SCD, including depression and tolerance to opioids [42–44]. Such factors demand the use of alternative therapies aimed at resolving the underlying disease mechanisms, along with the associated pain and morbidity. The current analysis showed a 35.5% reduction in the proportion of patients requiring opioids. Such a favorable outcome in a real-world setting adds value to the understanding of VOC management.

In the current MAP, a female Brazilian patient with SCA presented with chronic leg ulcers and recurrent VOCs for almost 15 years [45]. Although she was initially treated with HU and multiple therapies, including topical ulcer treatments, antibiotics, and opioids, the ulcers worsened; HU discontinuation for the ulcers resulted in recurrent VOC-related hospitalizations [45]. One year of treatment with crizanlizumab significantly improved her leg ulcers and VOC episodes [45]. This provides a new perspective on crizanlizumab's potential to benefit patients with SCD beyond reducing their VOCs. Further long-term related studies are needed to generate evidence substantial enough to advocate such benefits.

We acknowledge the limitation of the small datasets and inadequate population size within each subgroup to establish comparative analyses. Unlike RCTs, these programs are not conducted in a controlled environment and may be susceptible to potential biases, such as dependence on patient data from consultations, hospital records, and insurance claims. However, these findings provide valuable insights into the characteristics of the target population in real-world settings and have the potential to generate sufficient data for confirmatory, prospective, and controlled trials. It should be noted

that the lack of a comparator or control group is a limitation owing to the nature of the MAP, the purpose of which is to provide treatment, with sufficient clinical data prior to approval, to patients with serious diseases when other therapy options have been exhausted [46, 47]. Moreover, this report emphasizes the outcomes of patients treated in Brazil, where 80% of the patients received their care. It is essential to consider the differences in the availability of medical resources, treatment guidelines, and attitudes toward pain management when interpreting the data. Nonetheless, such findings can help inform clinical management decisions in all countries where crizanlizumab is available.

The real-world data presented here revealed a high burden of VOCs and other SCD complications along with opioid usage at baseline, despite prior treatment with HU in many patients. The analysis demonstrated a reduction in VOC rates and opioid usage with the administration of crizanlizumab, regardless of SCD genotype and prior HU use. These findings, along with the consistent tolerability of the drug, provide real-world evidence to support the use of crizanlizumab in SCD management. To continue to build the body of evidence on crizanlizumab, additional data from clinical trials, as well as longitudinal studies with large sample sizes, are warranted to explore the therapeutic impact of crizanlizumab in different healthcare settings for widespread clinical adoption and timely care for the global SCD community.

Author Contributions

L.D. contributed to conceptualization, methodology, supervision, funding acquisition, and project administration. V.J. contributed to software, validation, and formal analysis of data, and data curation. A.C.S.P., R.C., A.P., F.A., and R.D.C. contributed to the investigation and resources. S.S. contributed to conceptualization, methodology, and visualization. R.S. contributed to software, validation, and formal analysis of data. W.S. contributed to conceptualization, methodology, validation, and formal analysis of data, and data curation. All authors critically reviewed and revised the manuscript and approved the final version for submission. All authors had full access to all the data in the program and took final responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit the manuscript for publication.

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Ethics Statement

The treating physicians obtained written informed consent from all participants or their representatives prior to the start of treatment, in accordance with the local laws and regulations and in line with the ethical principles outlined in the Declaration of Helsinki. Confirmation of informed consent was communicated to Novartis through the Managed Access System prior to the treatment initiation.

Conflicts of Interest

L.D. is an employee of Novartis Pharmaceuticals Corporation (NPC) and holds stocks in NPC. V.J. is an employee of Novartis Healthcare Pvt. Ltd. and holds stocks in Novartis Pharma AG and Sandoz. A.C.S.-P. reports consultancy in the past 2 years with honoraria for Novartis, Global Blood Therapeutics (GBT)/Pfizer, Chiesi, EMS, and Masters. R.C. is a member of the advisory board or reports consultancy for Novartis, Vertex, GBT/Pfizer, Addmedica, Forma Therapeutics, Novo Nordisk, and Agios. R.D.C., A.P., and F.A. declare no conflicts of interest. S.S. is an employee of Novartis Pharma AG and owns Novartis Pharma AG shares. R.S. is an employee of Novartis Healthcare Pvt. Ltd. W.S. is an employee of Novartis Saudi Ltd.

Data Availability Statement

For original data, please contact laurie.debonnett@novartis.com.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.