Research

CLINICAL INVESTIGATION

Real-World Effectiveness of MIGSPRAY: A Dual-Action Nasal Spray for Migraine Prevention Through Mechanical Barrier and Osmotic Sinus Decongestion

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Abstract

Background: Migraine is a common neurological disorder affecting over 10% of the global population and is a leading cause of disability. Various triggers, including environmental and chemical irritants, are known to activate the trigeminal system, contributing to the onset of migraines. MIGSPRAY, a nasal spray composed of natural filmogen glycerol and plant-based polymers, has been developed as a novel treatment to prevent migraines. Its dual mechanism of action includes forming a protective barrier on the nasal mucosa to block triggers and exerting strong osmotic properties to naturally decongest the sinuses.

Objective: To evaluate the effectiveness of MIGSPRAY in reducing the frequency, intensity, and duration of migraines in a real-world population, and to confirm the findings from a previous randomized clinical trial.

Methods: This observational study followed 322 patients with a history of migraines over a 3-month period. Eligible patients were between 12 and 55 years old and experienced at least five migraine days per month. MIGSPRAY was administered twice daily. The primary outcome was the change in the number of migraine days per month. Secondary outcomes included changes in migraine intensity, duration, and disability scores as measured by HIT-6 and MIDAS.

Results: After three months of treatment, patients experienced a significant reduction in migraine days (-1.9 ± 0.2 days; 26% reduction, $p<0.001$), as well as decreases in migraine intensity (-1.1 ± 0.2 on the VAS, $p<0.001$) and duration (-1.1 ± 0.1 hours, $p<0.001$). Significant improvements were also observed in HIT-6 and MIDAS scores ($p<0.001$), indicating reduced migraine-related disability. These results confirm the findings of a previous randomized clinical trial, demonstrating the consistent efficacy of MIGSPRAY in both controlled and real-world settings.

Conclusion: MIGSPRAY is a safe and effective non-pharmacological treatment for preventing migraines. By combining mechanical barrier protection and osmotic sinus decongestion, MIGSPRAY significantly reduces migraine frequency, intensity, and disability. The findings from this real-world study confirm the results of prior clinical trials, suggesting MIGSPRAY as a valuable option for migraine management.

Keywords:Migraine prevention • MIGSPRAY • Nasal spray • Children • Osmotic decongestion • Non-pharmacological treatment • Trigeminal system • Real-world study • HIT-6 • MIDAS

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Introduction

Migraine is a prevalent and disabling neurological disorder, affecting approximately 12% of the global population. It is characterized by recurrent episodes of moderate to severe headache, often accompanied by nausea, vomiting, and heightened sensitivity to light, sound, and smells [1]. The exact pathophysiology of migraine remains complex, involving multiple mechanisms such as neurogenic inflammation, central sensitization, and cortical spreading depression [2]. One of the critical systems involved in migraine is the trigeminal system, which is activated by a range of triggers, including sensory stimuli and environmental factors like odors and chemical molecules [3]. This trigeminal activation plays a central role in the development of migraine symptoms, highlighting the need for interventions targeting these pathways.

■ Nasal mucosa and its barrier function in migraine prevention

The nasal mucosa serves as a critical interface between the external environment and the trigeminal system. Chemical irritants and odors can pass through the nasal passage, directly triggering the trigeminal nerves and leading to the onset of migraine [4]. The activation of the trigeminovascular system through the nasal mucosa can initiate a cascade of neuropeptide release, such as Calcitonin Gene-Related Peptide (CGRP), contributing to neurogenic inflammation and migraine onset [2]. To mitigate these effects, the concept of creating a protective barrier within the nasal mucosa has been proposed. Such barrier systems, including nasal sprays and gels, could potentially block the access of migraine-inducing molecules to the trigeminal system, thus offering a novel preventive approach for individuals prone to migraines [2].

■ The role of nasal congestion in migraine

Nasal congestion has been increasingly recognized as a common symptom in individuals suffering from migraine, with studies indicating that a substantial proportion of migraineurs report nasal congestion during attacks [5]. The relationship between migraine and nasal congestion is thought to stem from shared pathways involving the trigeminovascular system. During a migraine episode, the trigeminal nerve can release vasoactive neuropeptides, such as CGRP and substance P, which contribute to mucus secretion, leading [6]. Additionally, central sensitization, a hallmark of migraine pathophysiology, may also influence the development of nasal congestion, further complicating the clinical picture for migraine sufferers [3].

In this context, MIGSPRAY, a novel nasal spray composed of natural filmogen glycerol and plant-based polymers, offers a promising solution by mechanically blocking triggers at the nasal mucosal level. By preventing the entry of environmental and chemical triggers into the nasal passage, MIGSPRAY reduces the activation of the trigeminal system, thereby lowering the frequency and intensity of migraine attacks. In addition to its barrier function, MIGSPRAY also possesses strong osmotic properties that naturally help to decongest the sinuses, further relieving pressure and mitigating factors that can contribute to migraine onset. Previous randomized clinical trials have already demonstrated the efficacy of MIGSPRAY in reducing migraine days and improving patient-reported outcomes. This article presents the results of a real-world observational study, which confirms and extends those findings by evaluating the effectiveness of MIGSPRAY in a larger population under routine clinical conditions [7].

Materials and Methods

This is a 3 months observational clinical follow-up, performed in France between January and May 2022. The study was conducted in a context of routine practice. The clinical study is a post-market trial on the population authorised under the CE mark for this medical devices. The trial complied with the International Conference on Harmonisation Guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and relevant national and local regulations. At the time of screening, participants signed consent forms. Data were anonymized before analysis [8]. The trial sponsor, VITROBIO SAS, provided the trial medication. Statistical analysis was independently subcontracted to the Naturveda Research Center (Clermont-Ferrand - France).

■ Trial medication

MIGSPRAY is a class IIa medical device composed of glycerol, Migcyanidin (polymeric extract from Tanacetum parthenium, Salix alba, Vitis vinifera, curcuma longa and Mentha piperita), potassium sorbate, citric acid, sodium benzoate, potassium sorbate and thickening gums. It comes in a 15 ml nasal spray. Use two sprays per nostril three times a day [9].

■ Inclusion criteria

Patients eligible for this study were required to meet the following criteria: They had to be between 12 and 55 years old, male or female, and diagnosed with migraine with or without aura according to the International Classification of Headache Disorders, 3rd edition. Additionally, they must have been diagnosed with migraines for more than one year, experienced at least five migraine days per month, and had each migraine attack lasting at least two hours [10].

■ Exclusion criteria

Patients were excluded from the study if they had used a new treatment for migraines within six months prior to the study, were diagnosed with medication overuse headaches, had allergies to salicylates or hypersensitivity to the study medication, or had a history of drug abuse or dependency. Other exclusion criteria included chronic psychiatric or systemic diseases, being pregnant or breastfeeding, and use of neuroleptics, anxiolytics, or new prophylactic treatment for migraines within three months before the start of the study [11]. Study participants were

asked to maintain their usual treatments, so that the only variation was the use of MIGSPRAY.

■ Trial end points

The primary evaluation criterion was the number of migraine days after 3 month of product use (T3). A migraine day was defined as any day on which the patient had a migraine or probable migraine. Defined as a calendar day in which headache pain lasted, at least, 2 consecutive hours and met criteria for migraine or probable migraine (subtype in which only one migraine criterion is absent), or a day in which acute migraine specific medication was used to treat a headache of any duration.

Secondary endpoints were pain intensity ratings on an analog scale of 0 to 10, where 0 is no pain and 10 is intolerable pain. Then the evaluation of the duration of migraines in hours was analyzed. This is defined by the duration of the headache and the migraine aura (if it exists), without any crisis treatment being taken [12].

Other secondary end points included the mean change in the score on the six-item Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS). HIT-6 and MIDAS tests were designed to provide a global measure of adverse headache impact. HIT-6: scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability. MIDAS scores are interpreted as grade I =0-5 (minimal or infrequent disability), grade II =6-10 (mild or infrequent disability), grade III =11-20 (moderate disability), grade IVa =21-40 and higher (severe disability), grade IVb =41 and higher (very severe disability) with higher scores indicating greater disability and decreased scores consistent with improvement. Safety and side-effect profiles were evaluated according to reported adverse events based on the material safety form provided to patients.

■ Study design

Patients were received via videoconference by the Naturveda investigation center to confirm their eligibility criteria, sign consent forms and provide study instructions. 322 patients satisfying all the International Classification of Headache Disorders (ICHD) inclusion criteria and none of the exclusion criteria were enrolled. Data collection was done after consent through an online evaluation form. Migraine diary assessment, HIT-6 and MIDAS were collected anonymously online before the start of treatment (T0) and 3 months after use (T3). 322 patients completed the first migraine assessment questionnaire, and 310 patients completed the second after 3 months of treatment (Figure 1). A material safety hotline has been set up to allow patients to report any incidents or side effects [13].

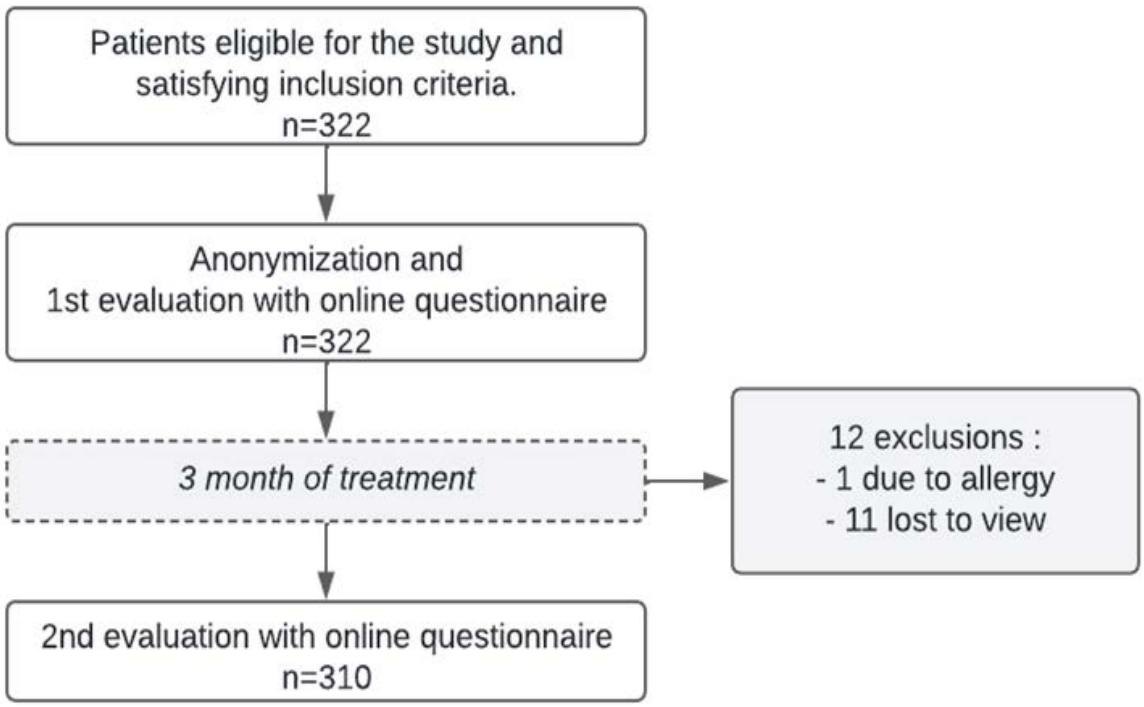

Figure 1: Study flow

Statistical analysis

The descriptive data are presented as mean ± SD between T0 (before starting the treatment) and T3 (after 3 months of treatment). A Q-Q plot was used to assess the suitability of the adjustment of the distribution. The Agostino and pearson normality test was employed to reject the hypothesis of a normal distribution. A non-parametric Wilcoxon Signed Rank test was used to assess the difference observed between time T0 and T3. A p-value less than 0.05 was considered as statistically significant, with a confidence interval (CI) of 95%. Statistical analyses were performed in GraphPad Prism 9.1 (GraphPad Software, Inc., CA, USA).

Results

Primary endpoint

A total of 322 patients received the treatment and completed the first migraine assessment questionnaire. 12 patients were unable to complete the second questionnaire. 1 patient due to allergy and 11 other patients were lost to follow-up. 310 episodic migraine patients were analyzed. Demographic and baseline data are presented in (Table 1).

Table 1: Baseline characteristics of patients. Quantitative parameters are presented as mean ± SD

Male, n (%)	108 (35)
Female, n (%)	202 (65)
Mean age, years	37.2 ± 2.2
Mean weight, kg	64 ± 9.4
Mean height, cm	171 ± 8.8
Mean no. of migraine days at T0	7.4 ± 2.1
Mean VAS score intensity (/10) at T0	7.1 ± 2.0
Mean migraine duration (hours) at T0	5.8 ± 2.1
Mean HIT-6 score at T0	54.2 ± 9.3
Mean MIDAS score (score; grade) at T0	21.4 ± 9.8 (IVa)

MIGSPRAY showed a significant decrease in the number of migraine days -1.9 ± 0.2 (95%CI - 2,20 to -1,50); p<0.001, this represents 26% reduction in migraine days per month, with 56% of patients responding (Table 2).

Table 2: Primary and secondary end points

	T0	T+3 month	p-value	IC95
Migraine Days				
Mean value	7.4 ± 2.1	5.5 ± 2.3	<0,001	(-2.21 to -1.50)
Difference T0 *vs.* T3	- 1,9 ± 0.2			
Intensity				
Mean value	7.1 ± 2.0	5,9 ± 2.3	<0,001	(-1.52 to -0.84)
Difference T0 *vs.* T3	-1.1 ± 0.2			
Duration				
Mean value	5.8 ± 2.1	4.7 ± 2.3	<0,001	(-1.43 to -0.73)
Difference T0 *vs.* T3	-1.1 ± 0.1			
HIT 6				
Mean value	54.2 ± 9.3	45.7 ± 5.1	<0,001	(-9.62 to -7.27)
Difference T0 *vs.* T3	-8.4 ± 0.6			
MIDAS				
Mean value	21.4 ± 9.8	16.1 ± 6.5	<0,001	(-6.59 to -3,99)

The primary endpoint was the change in the number of migraine days per month from time T0 to time T+3 months of treatment (T3) (Figure 2).

If we compare the frequency distribution of migraine days between T0 and T3, we see that initially the distribution is predominantly centered in the interval (5;10). This is followed by a tail in the interval (10;13). After three months of treatment,

the distribution shifted towards the interval (2;6) with the tail attenuating over the interval (8;12). In other words, treatment has been beneficial in reducing the number of migraine days, revealing a new interval (1;4).

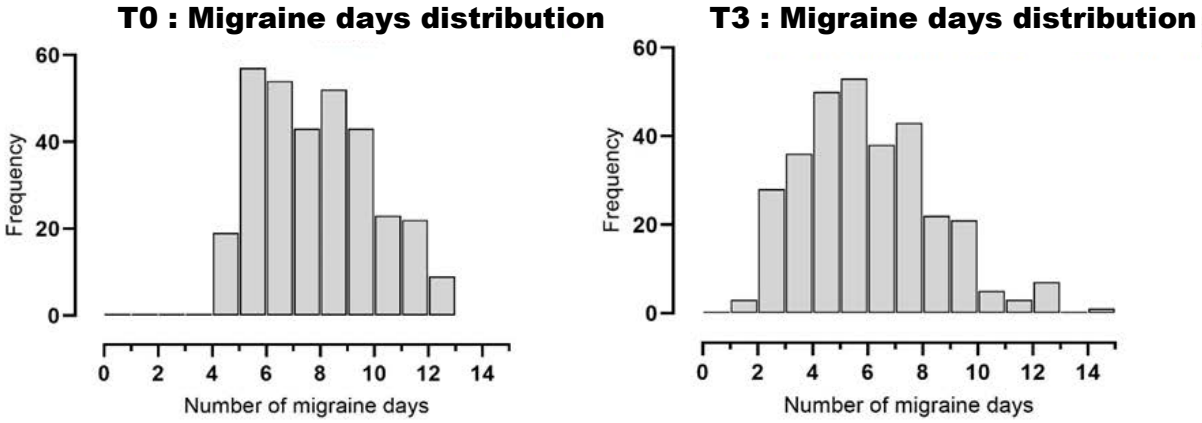

Figure 2: Distribution of the number of migraine days at time T0 and T3. The frequency is expressed in number of patients

■ Secondary end point

Concerning migraine duration in hours, the histogram at T0 shows a frequency distribution predominantly centered on the interval (4;8), with an initial tail on the interval (2;4) and a final tail on the interval (8;12). Mean migraine duration was 5.8 ± 2.1 hours before starting treatment. After three months of treatment, mean migraine duration fell to 4.7 hours ± 2.3 hours, a significant difference of -1.1 ± 0.1 (95% CI -1.43 to -0.73), p<0.001, representing an improvement of around 19%. The T3 histogram shows a distribution centered on the interval (2;6), reduced on the interval (6;8) and with a final tail on the interval (8;13) (Figure 3).

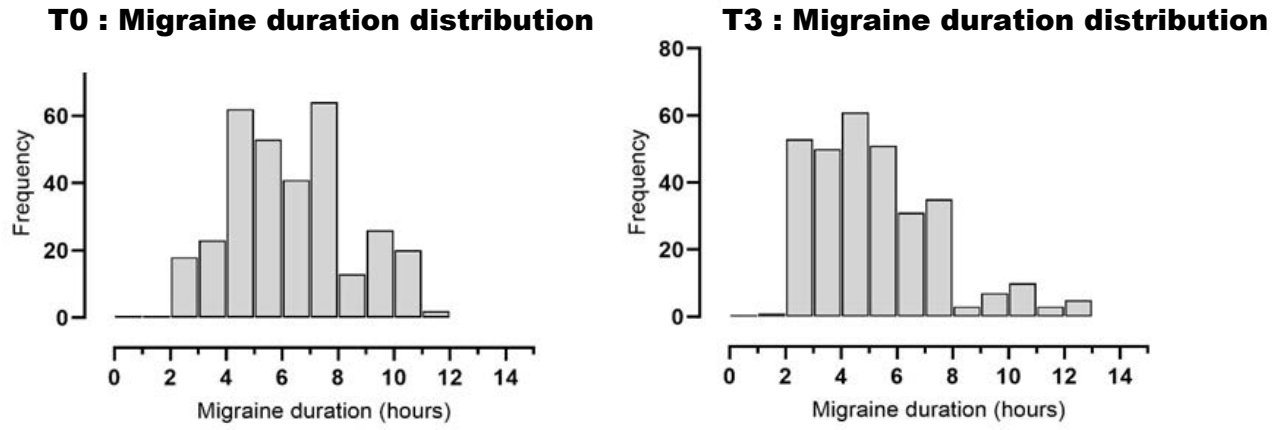

Figure 3: Distribution of the migraine duration in hours at time T0 and T3. The frequency is expressed in number of patients

In the same way, the intensity score of a migraine was evaluated. The evolution between the time of T0 and T3 shows a significant decrease of -1.1 ± 0.2 ({95% CI – 1.52 to -0.84} ; p<0.001). These results are corroborated by the HIT-6 values, with a significant reduction of 8.4± 0.6 ({95% CI -9.62 to -7.27}; p<0.001) points on the total score. Minimally important change (MIC) and Minimally Important Difference (MID) for HIT-6 were defined at -2.5 to -6 points for MIC and -1.5 points for MID. Although no MIC has been established for MIDAS, a preliminary analysis based on 25% change in monthly headache days estimated that an increase or decrease of 5 days of migraine-related disability per 3 months represents meaningful within-patient change [10]. MIDAS test decrease of -5.3 ± 0.7 ({95% CI – 6.59 to -3.99}; p<0.001). days in treated patients compare to time T0 and T3.

■ Safety

A total of 1 patient reported mild allergy symptoms, that occurred within the first week of treatment. These adverse events were transient and self-limiting, resolving within 2 days without any treatment. It

should be noted that 52% of patients reported a side effect consisting of a tingling sensation in the nose following application of the product, which subsides within a few minutes. No serious adverse effects have been reported [14].

Discussion

This study provides compelling evidence for the efficacy and safety of MIGSPRAY as a novel treatment for reducing migraine frequency, intensity, and duration in patients with episodic migraines [15]. Over a three-month period, MIGSPRAY demonstrated significant improvements across all primary and secondary endpoints, supporting its potential as an alternative or complementary therapy in migraine management.

■ Efficacy of migspray in reducing migraine frequency

The primary endpoint of the study the number of migraine days per month showed a significant reduction of 1.9 days on average, representing a 26% decrease. This reduction is clinically meaningful as fewer migraine days translate directly into improved quality of life for patients [16]. The histogram analysis revealed a shift in the distribution of migraine days from higher ranges (5 days -10 days) at baseline to a lower range (2 days-6 days) after treatment. This finding highlights MIGSPRAY's ability to reduce not only the frequency but also the intensity of migraine attacks across a wide patient population. Compared to existing treatments, these results position MIGSPRAY as a viable option for individuals seeking non-pharmacological approaches to migraine prevention.

■ Impact on migraine duration and intensity

In addition to reducing migraine frequency, MIGSPRAY also decreased the average duration of migraine episodes by 1.1 hours (19% reduction), along with a significant reduction in pain intensity by 1.1 points on a 10-point scale. These findings are notable because shorter and less intense migraines can substantially decrease the disruption caused by migraines in patients' daily lives. By addressing both the frequency and severity of attacks, MIGSPRAY shows promise in providing holistic relief for migraine sufferers. These improvements are particularly relevant when compared to other barrier interventions that aim to prevent migraines by targeting the nasal mucosa, further validating the efficacy of the mechanical barrier approach [17].

■ Reduction in HIT-6 and MIDAS scores

MIGSPRAY led to substantial reductions in both HIT-6 and MIDAS scores, which are widely used to assess the impact of migraines on daily functioning and quality of life. The HIT-6 score decreased by 8.4 points, which exceeds the Minimally Important Difference (MID) threshold of 1.5 points and is far greater than the Minimally Important Change (MIC) threshold of 2.5 to 6 points. The MIDAS score also showed a meaningful decrease of 5.3 points, reflecting significant improvement in migraine-related disability [18]. These results suggest that MIGSPRAY not only reduces the physical symptoms of migraine but also alleviates the broader functional impairments associated with the condition.

■ Mechanism of action of MIGSPRAY

MIGSPRAY's effectiveness is likely linked to its mechanical barrier action on the nasal mucosa, which prevents migraine triggers, such as chemical molecules and odors, from activating the trigeminal system. By forming a protective layer over the nasal mucosa, MIGSPRAY may reduce the entry of irritants that are known to activate the trigeminovascular system, thus reducing the occurrence of neurogenic inflammation [16]. This is consistent with the pathophysiological mechanisms of migraine, where the trigeminal nerve plays a central role in migraine onset and progression. Similar approaches, such as other barrier-based treatments, have shown promise, but MIGSPRAY's use of a natural composition offers an additional benefit for patients seeking non-pharmacological options [19].

■ Nasal congestion and its role in migraine

The relationship between nasal congestion and migraines is well-established, with studies suggesting that the trigeminovascular system plays a role in both phenomena [5]. MIGSPRAY's ability to alleviate migraine symptoms may also be linked to its effect on nasal congestion. Although nasal congestion was not a primary outcome in this study, the barrier-forming action of MIGSPRAY may have additional benefits in reducing congestion, further contributing to its overall efficacy in preventing migraines. Future studies could explore this potential dual action, assessing how reducing nasal congestion might improve migraine outcomes.

■ Safety and tolerability

MIGSPRAY was well-tolerated by the majority of patients, with no serious adverse effects reported. One patient experienced a mild allergic reaction, which resolved without intervention, and over half of the participants reported a brief tingling sensation in the nose following application, which subsided

within minutes. These side effects are minor compared to the more serious side effects associated with many pharmacological migraine treatments, suggesting that MIGSPRAY is a safe option for long-term use. The absence of significant adverse events underscores its potential as a first-line or adjunctive therapy, particularly for patients seeking a non-systemic treatment approach.

■ Future directions and clinical implications (revised)

The findings of this real-world observational study align closely with the results from a previous randomized, double-blind, placebo-controlled clinical trial, further supporting the efficacy and safety of MIGSPRAY. The prior randomized trial demonstrated significant reductions in migraine days, HIT-6, and MIDAS scores in a controlled environment, providing robust evidence for the clinical benefits of this treatment. This current study extends those findings to a larger, more diverse population in real-world settings, confirming that MIGSPRAY consistently reduces migraine frequency, duration, and severity across a broad patient base.

The consistency of the results across both controlled and real-world conditions strengthens the case for MIGSPRAY as a reliable, non-invasive treatment for migraine prevention. These real-world data provide additional insights into the product's practicality, tolerability, and safety when used in routine clinical practice, further reinforcing its role as a promising alternative or adjunctive therapy for patients with migraines.

■ Limitations and strengths of the current study

While the observational design of this study lacks the placebo control found in the previous randomized clinical trial, the large sample size and real-world setting increase the external validity and generalizability of the results. The confirmation of similar outcomes in a non-controlled environment highlights the robustness of MIGSPRAY's efficacy. However, the absence of a control group in this study leaves some room for placebo effects or biases in patient-reported outcomes. Future research could focus on longer-term studies and include further real-world trials to continue validating the findings over extended periods and in varied populations. Also, the high responder rate may be biased by the absence of a placebo group [20].

Conclusion

The data from this real-world study confirm and extend the findings from previous controlled trials, establishing MIGSPRAY as an effective and safe option for migraine prevention. By acting as a mechanical barrier on the nasal mucosa, MIGSPRAY significantly reduces migraine frequency and severity, while also improving disability scores (HIT-6 and MIDAS). This treatment represents a novel, multi-target approach that provides a non-pharmacological and well-tolerated solution for patients seeking migraine relief. The alignment between clinical trial data and real-world evidence solidifies MIGSPRAY's potential as an important tool in the broader management of migraines.

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