

# Intranasal Civamide for the Treatment of Episodic Cluster Headaches

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**Objective:** To evaluate the safety and efficacy of intranasal civamide solution for preventive treatment during an episodic cluster headache period.

**Subjects and Methods:** This was a multicenter, double-blind, randomized, vehicle-controlled study with a 7-day treatment period and a 20-day posttreatment period performed at 14 headache/neurology centers in the United States. Twenty-eight subjects were randomized to receive civamide or its vehicle in a 2:1 ratio; 18 received civamide and 10 received the vehicle. Subjects received 100  $\mu$ L of 0.025% civamide (25  $\mu$ g) or 100  $\mu$ L of the vehicle to each nostril via dropper once daily for 7 days. The total daily dose of civamide was 50  $\mu$ g.

**Main Outcome Measures:** The number of cluster headaches per week during the treatment and posttreatment periods, pain intensity, presence of associated symptoms, and the incidence of adverse events were assessed.

**Results:** Subjects in the civamide group had a significantly greater percent decrease in the number of headaches from baseline to posttreatment during days 1 through

7 (–55.5% vs –25.9%;  $P = .03$ ) and a trend toward significance during days 8 through 14 (–66.9% vs –32.3%;  $P = .07$ ) and days 15 through 20 (–70.6% vs –34.9%;  $P = .07$ ), as well as a near-significant decrease during the entire posttreatment period (days 1 through 20 [ $P = .054$ ]) compared with the vehicle group. There were larger decreases in the number of headaches per week during the posttreatment period in the civamide-treated group, with trends toward significance during posttreatment days 8 through 14 (–8.6 vs –3.6;  $P = .09$ ) and days 15 through 20 (–8.9 vs –3.6;  $P = .07$ ). There were no significant differences between groups in cluster headache pain intensity, number of severe headaches, or associated symptoms. The most common adverse events included nasal burning (14 of 18 civamide-treated subjects, 1 of 10 vehicle-treated subjects;  $P = .001$ ) and lacrimation (9 of 18 civamide-treated subjects, 0 of 10 vehicle-treated subjects;  $P = .01$ ).

**Conclusion:** Intranasal civamide solution at a dose of 50  $\mu$ g may be modestly effective in the preventive treatment of episodic cluster headache.

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**C**LUSTER HEADACHES are severe, unilateral headaches often accompanied by ipsilateral lacrimation, conjunctival hyperemia, and nasal congestion. Nausea is not commonly associated with cluster headaches as it is with migraine headaches. Cluster headaches are usually brief (15-180 minutes) but involve intense pain from the outset in and around the orbit. Most subjects have episodic rather than chronic cluster headaches. They have 1 or more headaches daily for several weeks to several months, often at the same time each day, but the headaches then disappear and may not return for many months or years.

The etiology of cluster headaches is poorly understood. Neuropeptide release from central and peripheral endings of trigeminal neurons, particularly substance P (SP) and calcitonin gene-related peptide (CGRP), has been suggested to be a cause.<sup>1-3</sup> The role of nitric oxide, both centrally (hypothalamic) and distally (trigeminal nerve), has also been

suggested,<sup>4</sup> and plasma nitrates are increased in both the active and remission phases of episodic cluster headaches.<sup>5</sup>

Calcitonin gene-related peptide and SP-containing trigeminal afferent nerves innervate the pial and dural cephalic vessels.<sup>6</sup> The release of CGRP and SP results in dilation of pial arteries, increases in vascular permeability, and activation of an inflammatory response.<sup>7</sup> When CGRP and SP are released by the trigeminal nerve into the walls of the cerebral blood vessels, headache results. Increases in CGRP concentrations in external jugular blood have been observed during a migraine headache<sup>8</sup> and interictally in the peripheral circulation.<sup>9</sup> The intravenous administration of CGRP has also been shown to induce migraines in patients with migraines without aura.<sup>10</sup> Cluster headache has also been ascribed to the release of CGRP and SP from both central (causing pain) and peripheral (causing rhinorrhea, lacrimation, and conjunctival hyperemia) endings of trigeminal neurons.<sup>11</sup>

## SUBJECTS AND METHODS

The protocol was approved by the institutional review board at each center and informed consent was obtained from each subject prior to enrollment. Subjects were 18 years or older with at least a 2-year history of cluster headaches and had 1 to 3 cluster headache periods during the previous 2 years, with at least 1 cluster headache daily on each of the 3 days prior to study entry. Headaches had to meet slightly modified International Headache Society Diagnostic Criteria for episodic cluster headache<sup>20</sup>: 1 to 4 attacks per day of severe, unilateral, orbital, supraorbital, and/or temporal pain lasting 15 to 240 minutes untreated, associated with at least 1 of the following: conjunctival hyperemia, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, or eyelid edema. Subjects were otherwise in generally good health and had normal electrocardiogram results at baseline. Subjects were excluded from the study if they were pregnant or lactating; had a history of alcohol or drug abuse within the past year; had clinical, historical, or laboratory evidence of significant cardiovascular, renal, gastrointestinal, pulmonary, hepatic, endocrine, or other neurological or systemic disease; or had taken preventive medication for cluster headaches within 2 days of starting the study.

This was a randomized, double-blind, vehicle-controlled study designed to assess the safety and efficacy of intranasal civamide for the preventive treatment of episodic cluster headaches. Civamide and the vehicle were supplied in identical packaging and assigned to subjects in a ratio of 2 civamide to 1 vehicle according to a computer-generated randomization code. Subjects and investigators were blinded to drug assignment throughout the treatment and posttreatment periods of the study.

### SUBJECTS

Subjects were treated with either 100  $\mu$ L of 0.025% civamide (25  $\mu$ g) or 100  $\mu$ L of the vehicle delivered into each nostril once daily for the 7-day treatment period. Treatments were self-administered using a calibrated dropper. Following the treatment period, subjects were then monitored for a 20-day posttreatment period. During the entire study, subjects were allowed abortive treatment of individual headaches after 15 minutes with 100% oxygen, dihydroergotamine mesylate injection, subcutaneous or oral sumatriptan, oral zolmitriptan, and opiate or nonopiate analgesics.

Subjects recorded details of their cluster headaches daily in a diary for the 27 days of the study. The frequency of headaches, rating of cluster headache pain intensity, presence or absence of symptoms associated with cluster headaches, and the need for abortive therapies were recorded. The investigator evaluated subjects at 4 visits (on day 1,

day 7, day 17, and day 27). Evaluations included a nasal mucosa examination, odor detection test, serum chemistry and hematologic assessment, and urinalysis. Adverse experiences were monitored and recorded throughout the study.

The primary efficacy end point was the change in frequency of cluster headaches per week during the posttreatment period. Secondary efficacy end points included the change in frequency of headaches experienced during each approximately 1-week period of the posttreatment period, pain intensity (0-3), presence or absence of associated symptoms, and use of abortive therapies. Safety outcomes included the incidence of adverse events and treatment-related adverse events, odor detection tests, nasal mucosa examinations, laboratory tests, and electrocardiogram results. Adverse events were classified according to the preferred term and body system.

### STATISTICAL ANALYSES

The population analyzed for efficacy included all randomized subjects who had a diagnosis of cluster headaches, had received at least 3 days of study medication, and did not receive any disallowed concomitant medications. All subjects who took at least 1 dose of study medication were included in the safety analyses. All comparisons of the treatment groups were performed using 2-sided tests at a .05 overall level of significance ( $\alpha = .05$ ). The null hypothesis for all analyses was that there is no difference between the treatment groups.

Demographic and baseline variables were compared between treatment groups by a 2-sample *t* test for continuous variables and by the Fisher exact test for discrete variables. Baseline headache frequency was calculated from a retrospective report by the subject of the number of cluster headaches experienced during the 3 days prior to treatment, and this number was then adjusted to represent a weekly (7-day) rate. Efficacy end points, including the total number of headaches per week, the number of severe headaches per week, mean pain intensity, and the number of headaches requiring abortive therapy during the treatment and posttreatment periods were compared between treatment groups by 2-sample *t* tests. The change and percent change in the total number of headaches from treatment to posttreatment and from baseline to the specified periods were also compared by 2-sample *t* tests. The subject's assessment of drug effectiveness was compared by the Fisher exact test. The number of headaches associated with specific symptoms was compared between treatment groups by the Wilcoxon rank sum test. No adjustments for multiplicity of testing were made for the secondary efficacy end points. Safety results, including the incidence of adverse events, odor detection test results, nasal mucosa examination results, and laboratory test results were compared between treatment groups by the Fisher exact test.

Capsaicin is a derivative of homovanillic acid found in hot peppers. It is a known neuropeptide depletor that has been shown to cause the release of SP and other neuropeptides from primary sensory neurons,<sup>12</sup> with eventual desensitization by depletion of SP and CGRP from nerve terminals. On this basis, studies of intranasal capsaicin have been performed and have demonstrated some

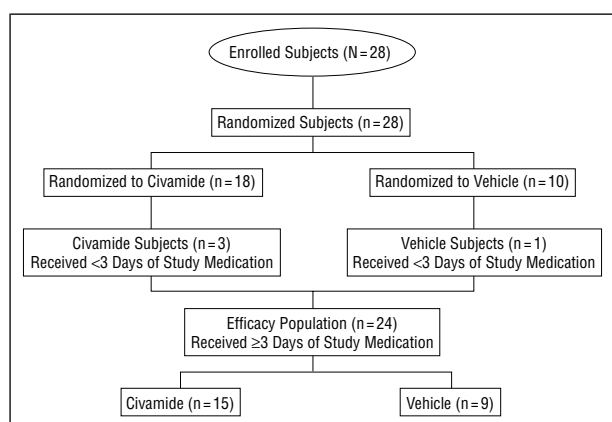
effectiveness in relieving cluster headaches.<sup>11,13,14</sup> Capsaicin's extreme irritant effects, however, have limited the clinical use of this therapy.

Civamide (*cis*-8-methyl-*N*-vanillyl-6-nonenamide), a synthetic isomer of capsaicin, is a vanilloid receptor agonist and a neuronal calcium channel blocker<sup>15</sup> that inhibits the neuronal release of excitatory neuro-

**Table 1. Demographic and Baseline Variables**

	Civamide (n = 18)	Vehicle (n = 10)	P Value*
Age, mean ± SD (range), y	45.1 ± 10.5 (22-64)	43.9 ± 16.3 (23-83)	.81
Weight, mean ± SD (range), kg	86.6 ± 20.1 (61.4-150.5)	87.7 ± 14.6 (65.9-109.5)	.88
Sex, No. (%)			> .99
Male	16 (89)	9 (90)	
Female	2 (11)	1 (10)	
Race, No. (%)			.63
Black	2 (11)	0	
White	14 (78)	9 (90)	
Asian	1 (6)	0	
Hispanic	0	1 (10)	
No. of cluster headache periods per year, mean ± SD (range)	1.8 ± 0.73 (1-3)	2.0 ± 0.94 (1-4)	.49
Length of current episode, mean ± SD (range), d	38.9 ± 30.4 (3-90)	44.5 ± 59.2 (3-180)	.79
No. of cluster headaches during last 3 days, mean ± SD (range)	5.1 ± 2.0 (3-9)	4.9 ± 3.2 (3-13)	.87

\*P values are from the 2-sample *t* test for continuous variables and the Fisher exact test for discrete variables.

**Figure 1.** Study flow chart.

transmitters,<sup>16</sup> including CGRP and SP, and depletes neurons of their neurotransmitter content.<sup>2</sup> When civamide is applied intranasally to the mucosa, the release of neurotransmitters by the trigeminal plexus centrally to meningeal and dural blood vessels should be decreased. This would then result in less vasodilation, plasma extravasation, and histamine/serotonin release, with a potential for the amelioration of neurogenic inflammation and cluster headache pain.

Civamide has been demonstrated to be significantly more potent at depleting SP and CGRP than capsaicin,<sup>17,18</sup> as well as significantly less irritating than capsaicin.<sup>19</sup> This study was designed to assess the safety and efficacy of intranasal civamide vs vehicle control for preventive treatment of cluster headaches during an episodic cluster period.

## RESULTS

### SUBJECT DISPOSITION AND CHARACTERISTICS

Twenty-eight subjects, 18 subjects randomized to receive civamide and 10 to receive the vehicle, were enrolled at 14 headache centers in the United States. Most subjects were men (90%) and white (82%); the mean age

for all subjects was 44.7 years (22-83 years) (**Table 1**). There were no significant differences between treatment groups for any demographic or baseline variables.

A total of 24 subjects received at least 3 days of study medication and were included in the efficacy analysis (**Figure 1**): 15 subjects in the civamide group (13 subjects received 7 days, 1 subject 6 days, and 1 subject 5 days of treatment) and 9 subjects in the vehicle group (9 subjects received 7 days of treatment). The 4 subjects who were not included received just 1 day of study medication: 3 subjects (17%) in the civamide group who withdrew owing to an adverse event and 1 subject (10%) in the vehicle group who withdrew owing to lack of improvement.

During the posttreatment period, 3 subjects (17%) in the civamide group withdrew from the study due to lack of improvement and one subject (10%) in the vehicle group was lost to follow-up. Posttreatment data from 3 subjects were excluded from the efficacy analysis from the time they took other prohibited preventive medications.

### EFFICACY VARIABLES

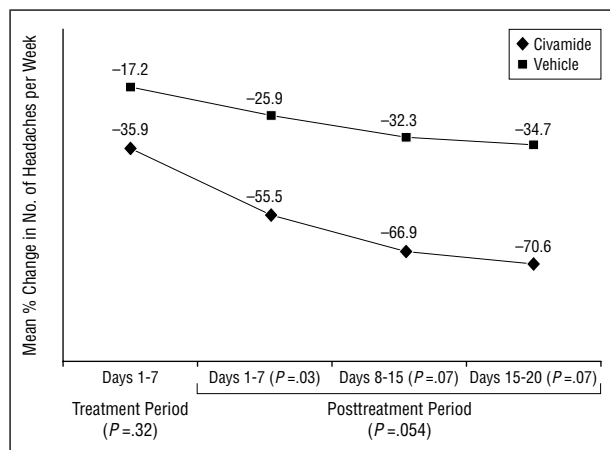
Subjects in the civamide group had a significantly greater percent decrease in the number of headaches from baseline to posttreatment days 1 through 7 ( $-55.5$  vs  $-25.9$ ;  $P=.03$ ) and a trend toward significance during days 8 through 14 ( $-66.9$  vs  $-32.3$ ;  $P=.07$ ) and days 15 through 20 ( $-70.6$  vs  $-34.9$ ;  $P=.07$ ), as well as a near-significant decrease during the entire posttreatment period (days 1 through 20 [ $P=.054$ ]) compared with the vehicle group (**Table 2** and **Figure 2**). Greater decreases in the number of headaches per week during the posttreatment period were observed in the civamide-treated group, with trends toward significance during posttreatment days 8 through 14 ( $-8.4$  vs  $-3.6$ ;  $P=.09$ ) and days 15 through 20 ( $-8.9$  vs  $-3.6$ ;  $P=.07$ ) (**Table 2** and **Figure 3**).

There were no significant differences between the treatment groups in the number of severe headaches, mean cluster headache pain intensity, the presence or absence of associated symptoms, or the requirement for abortive medications at any visit.

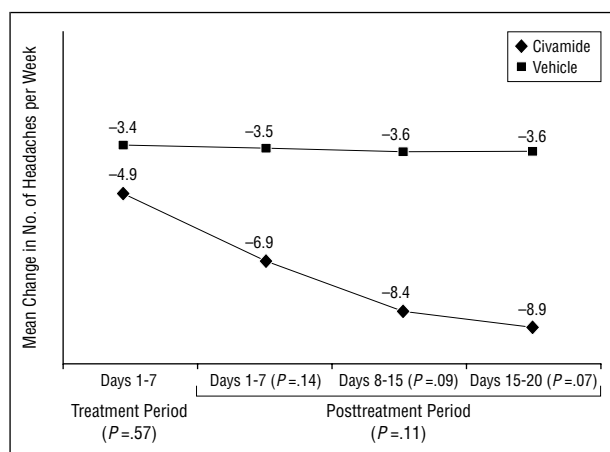
**Table 2. Change and Percent Change in the Number of Cluster Headaches per Week**

Days (Active/Vehicle)	Civamide			Vehicle			P Value*	
	No. per Week	Δ No.	Δ%	No. per Week	Δ No.	Δ%	Δ No.	Δ%
Baseline period (15,9)	12.5			10.8				
Treatment period								
Days 1-7 (15,9)	7.2	-4.9	-35.9	7.8	-3.4	-17.2	.57	.32
Posttreatment period								
Days 1-20 (15,9)	4.9	-7.6	-61.4	7.2	-3.6	-30.9	.11	.05
Days 1-7 (14,8)	5.6	-6.9	-55.5	7.3	-3.5	-25.9	.14	.03
Days 8-14 (14,8)	4.1	-8.4	-66.9	7.2	-3.6	-32.3	.09	.07
Days 15-20 (11,8)	4.2	-8.9	-70.6	7.2	-3.6	-34.7	.07	.07

\*P values are from the Fisher exact test.



**Figure 2.** Percent change in the mean number of headaches per week from baseline to treatment and posttreatment periods. P values from 2-sided t tests.



**Figure 3.** Change in the number of headaches per week from baseline to treatment and posttreatment periods. P values from 2-sided t tests.

### SAFETY RESULTS

Most subjects (17/18 [94%] in the civamide-treated group and 7/10 [70%] in the vehicle group) had 1 or more adverse events during the study (**Table 3**). The initial onset of most adverse events was on treatment day 1 for most civamide-treated subjects. There were no serious adverse events reported. The most common events were nasal burning and lacrimation. At least 1 treatment-related episode of nasal burn-

**Table 3. Incidence of Common Adverse Events**

Body System	No. (%)		P Value
	Active (n = 18)	Vehicle (n = 10)*	
Central and peripheral nervous system			
Nasal burning	14 (78)	1 (10)	.001
Respiratory system			
Any adverse event	9 (50)	2 (20)	.23
Pharyngitis	8 (44)	1 (10)	.10
Rhinorrhea	6 (33)	1 (10)	.36
Vision			
Any adverse event	10 (56)	0	<.001
Lacrimation	9 (50)	0	.01

\*P values are from the Fisher exact test.

ing was reported for 14 of 18 subjects (78%) in the civamide group and 1 of 10 subjects (10%) in the vehicle group ( $P = .001$ ). Most nasal burning was moderate or severe and was transient, lasting less than 20 minutes after application. Significantly more subjects in the civamide group also had lacrimation ( $P = .01$ ) than in the vehicle group.

There were no clinically significant changes in systolic or diastolic blood pressure, heart rate, respiration rate, or oral temperature during the study. All subjects could detect the test odor at both visits and there were no clinically significant differences between the treatment groups with respect to the examination of the nasal mucosa. No subjects in either treatment group had clinically significant abnormalities on results of their electrocardiograms or laboratory tests.

### COMMENT

This pilot study has shown that intranasal civamide may hold promise as a preventive therapy for episodic cluster headaches during active cluster periods. There are no medications for the prevention of cluster headaches currently approved by the Food and Drug Administration, and subcutaneous sumatriptan is the only approved medication for abortive therapy of individual cluster headache attacks.<sup>21-23</sup> Since cluster headaches are among the most severe headaches known and result in significant disability during active cluster periods, any therapy that can reduce their frequency would be valuable.

### Intranasal Civamide Study Group

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Our results demonstrate an early, significant decrease in cluster headache frequency in subjects receiving civamide compared with those receiving the vehicle in the first 7 days of the posttreatment period following as few as 5 days of active therapy. During each of the subsequent posttreatment follow-up weeks and during the entire 20-day posttreatment follow-up period, the decrease in frequency trended toward significance despite the small number of subjects. Other efficacy parameters, including headache severity and rescue medication use, were not significantly different throughout the study within or between groups without any indications that headaches of different severity were affected differently. The small number of subjects may have contributed to the lack of significance of the secondary efficacy parameters.

The safety data indicate that while tolerated by most, most active-treated subjects in our study experienced transient nasal burning, rhinorrhea, and lacrimation. Although during the study the subjects did not know for certain whether the vehicle solution produced similar symptoms as the active solution, in our future studies of this medication, several modifications will be made for better blinding. A spray pump will be used to deliver 100  $\mu$ L of a less concentrated (0.01%) solution of civamide to decrease the incidence and severity of burning.<sup>24</sup> The spray will be administered twice daily so the total amount of delivered drug each day (40  $\mu$ g) will be approximately equal to the daily dose used in this study (50  $\mu$ g). Additionally, the vehicle may be modified to produce some burning in vehicle-treated patients.

Our results provide tentative support to the putative role of CGRP and SP in the pathogenesis of cluster headaches. The adverse effect profile that was observed can be understood as part of the mechanism of action of intranasal civamide, ie, there is a distal release of neuropeptides SP, CGRP, etc, by the terminal branches of the trigeminal nerve in the nasal mucosa.

Study design and rigorous inclusion and exclusion criteria made enrollment difficult in this study despite the number of centers. Our future studies will have more subjects since the protocol will permit them to continue stable doses of other preventive medications and be enrolled if they are still experiencing a significant number of cluster headaches. A prospective rather than retrospective baseline will be determined using diaries. Additionally, there will be a longer posttreatment period to evaluate continued responses to therapy and to help evaluate a necessity for a second course.

In conclusion, the results of this study demonstrate that intranasal civamide significantly decreases the frequency of cluster headaches during the first 7 days of the posttreatment period with a continued decrease during the entire 20-day posttreatment period. Intranasal civamide use was not associated with any systemic adverse effects; however, local adverse effects limited tolerability for some subjects. This study offers early support for the possible value

of intranasal civamide as a safe and effective preventive treatment for episodic cluster headache.

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**Author contributions:** Study concept and design (Drs Saper, Mathew, Rapoport, Phillips, Bernstein); acquisition of data (Drs Klapper, Mathew, Rapoport); analysis and interpretation of data (Drs Phillips, Bernstein); drafting of the manuscript (Drs Saper, Rapoport, Phillips); critical revisions of the manuscript for important intellectual content (Drs Klapper, Mathew, Rapoport, Phillips, Bernstein); obtained funding (Drs Phillips, Bernstein); administrative, technical, and material support (Drs Rapoport, Phillips, Bernstein); study supervision (Drs Saper, Mathew, Phillips, Bernstein).

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