A Randomized, Double-Blind, Placebo-Controlled Study of Breath Powered Nasal Delivery of Sumatriptan Powder (AVP-825) in the Treatment of Acute Migraine (The TARGET Study)

Roger K. Cady, MD; Peter J. McAllister, MD; Egilius L.H. Spierings, MD, PhD; John Messina, PharmD; Jennifer Carothers, ScD; Per G. Djupesland, MD, PhD; Ramy A. Mahmoud, MD, MPH

This research was funded by the developer of the product. The developer of the product provided financial and material support, monitoring, and data management and analysis to the authors and investigators.

Reprinted from HEADACHE, Vol. 55, No. 1, May 2015

Headache
© 2014 The Authors. Headache published by Wiley Periodicals, Inc. on behalf of American Headache Society.
ISSN 0017-8748
doi: 10.1111/head.12472
Published by Wiley Periodicals, Inc.

Research Submission

A Randomized, Double-Blind, Placebo-Controlled Study of Breath Powered Nasal Delivery of Sumatriptan Powder (AVP-825) in the Treatment of Acute Migraine (The TARGET Study)

Breath Powered and Bi-Directional are trademarks of OptiNose US

Roger K. Cady, MD; Peter J. McAllister, MD; Egilius L.H. Spierings, MD, PhD; John Messina, PharmD; Jennifer Carothers, ScD; Per G. Djupesland, MD, PhD; Ramy A. Mahmoud, MD, MPH

Objective.—To evaluate the efficacy and safety of AVP-825, a drug–device combination of low-dose sumatriptan powder (22 mg loaded dose) delivered intranasally through a targeted Breath Powered device vs an identical device containing lactose powder (placebo device) in the treatment of migraine headache.

Background.—Early treatment of migraine headaches is associated with improved outcome, but medication absorption after oral delivery may be delayed in migraineurs because of reduced gastric motility. Sumatriptan powder administered with an innovative, closed-palate, Bi-Directional, Breath Powered intranasal delivery mechanism is efficiently absorbed across the nasal mucosa and produces fast absorption into the circulation. Results from a previously conducted placebo-controlled study of AVP-825 showed a high degree of headache relief with an early onset of action (eg, 74% AVP-825 vs 38% placebo device at 1 hour, $P < .01$).

Methods.—In this double-blind, placebo-controlled, parallel-group study in adults with a history of migraine with or without aura, participants were randomized via computer-generated lists to AVP-825 or placebo device to treat a single migraine headache of moderate or severe intensity. The primary endpoint was headache relief (defined as reduction of headache pain intensity from severe or moderate migraine headache to mild or none) at 2 hours post-dose.

Results.—Two hundred and thirty patients (116 AVP-825 and 114 placebo device) were randomized, of whom 223 (112 and 111, respectively) experienced a qualifying migraine headache (their next migraine headache that reached moderate or severe intensity). A significantly greater proportion of AVP-825 patients reported headache relief at 2 hours post-dose compared with those using the placebo device (68% vs 45%, $P = .002$, odds ratio 2.53, 95% confidence interval [1.45, 4.42]). Between-group differences in headache relief were evident as early as 15 minutes, reached statistical significance at 30 minutes post-dose (42% vs 27%, $P = .03$), and were sustained at 24 hours (44% vs 24%, $P = .002$) and 48 hours (34% vs 20%, $P = .01$). Thirty-four

From the Headache Care Center, Springfield, MO, USA (R.K. Cady); New England Institute for Neurology and Headache, Stamford, CT, USA (P.J. McAllister); Craniofacial Pain Center, Tufts University School of Dental Medicine; Headache & Face Pain Program, Tufts Medical Center, Boston, MA, USA (E.L.H. Spierings); OptiNose US Inc., Yardley, PA, USA (J. Messina, J. Carothers, R.A. Mahmoud); OptiNose AS, Oslo, Norway (P.G. Djupesland).

Address all correspondence to R.K. Cady, 3805 S. Kansas Expressway, Springfield, MO 65807, USA, email: rcady@banyangroupinc.com

Accepted for publication September 8, 2014.

percent of patients treated with AVP-825 were pain-free at 2 hours compared with 17% using the placebo device ($P = .008$). More AVP-825 patients reported meaningful pain relief (patient interpretation) of migraine within 2 hours of treatment vs placebo device (70% vs 45%, $P < .001$), and fewer required rescue medication (37% vs 52%, $P = .02$). Total migraine freedom (patients with no headache, nausea, phonophobia, photophobia, or vomiting) reached significance following treatment with AVP-825 at 1 hour (19% vs 9%; $P = .04$). There were no serious adverse events (AEs), and no systemic AEs occurred in more than one patient. Chest pain or pressure was not reported, and only one patient taking AVP-825 reported mild paresthesia. No other triptan sensations were reported.

Conclusions.—Targeted delivery of a low-dose of sumatriptan powder via a novel, closed-palate, Breath Powered, intranasal device (AVP-825) provided fast relief of moderate or severe migraine headache in adults that reached statistical significance over placebo by 30 minutes. The treatment was well tolerated with a low incidence of systemic AEs.

Key words: migraine, Bi-Directional nasal delivery, Breath Powered nasal delivery, intranasal delivery, sumatriptan powder, AVP-825

Abbreviations: AE adverse event, AVP-825 Breath Powered delivery of low-dose sumatriptan powder, CGRP calcitonin gene-related peptide, CO_2 carbon dioxide, ECG electrocardiogram, e-diary electronic diary, FAS full analysis set, GTN glyceryl trinitrate, NO nitric oxide, PK pharmacokinetic, SS Safety Set

(*Headache* 2015;55:88-100)

Triptans are first-line treatments for moderate-to-severe migraine headaches, and sumatriptan (a 5-$HT_{1B/1D}$ receptor agonist) is the most commonly prescribed drug in this class.[1] The efficacy and safety profiles of various routes of sumatriptan delivery, including subcutaneous, intranasal, transdermal, oral, and rectal, have been extensively characterized in clinical trials, and multiple formulations are in widespread use.[1] Although oral administration is the most common route used for triptans, variability in gastric emptying during migraine and the resulting delay in absorption may contribute to inconsistent effectiveness, including delayed onset and reduced magnitude of relief.[2] In an effort to overcome the limitations of oral delivery while maintaining a similar level of convenience, intranasal delivery (in the form of nasal sprays) aims at improving the speed and consistency of drug absorption while avoiding issues associated with self-administering an injection (eg, pain and aversion).[3-5]

Currently available intranasal treatments employ standard single-dose nasal-spray pumps that characteristically deposit a substantial fraction of the liquid dose along the floor of the nasal cavity, proximal to the nasal valve.[6,7] A substantial portion of the dose delivered through liquid sprays either drips out of the nose and is wiped away, or accumulates at the floor of the nasal cavity, and is sniffed toward the pharynx and swallowed.[8] Active sniffing during actuation further narrows the slit-like nasal valve and results in additional drug being sucked along the floor of the nasal cavity toward the oropharynx and swallowed. The

Financial Statement: This research was funded by OptiNose AS Norway. OptiNose provided financial and material support, monitoring, and data management and analysis to the authors and investigators.

Clinical Trial Registration: The TARGET Study was registered at ClinicalTrials.gov (NCT01462812).

Conflict of Interest: Dr. Messina, Dr. Carothers, Dr. Djupesland, and Dr. Mahmoud are employees of OptiNose and own stock or stock options in OptiNose. Dr. Djupesland is a member of the Board of Directors at OptiNose.

Dr. Cady is a consultant for Allergan Inc., Boston Scientific Corporation, Merck & Co., Inc., Novartis AG, OptiNose US Inc., Pfizer, Inc., Amgen Inc., Avanir Pharmaceuticals, Inc., Evidera, Transcept Pharmaceuticals, Inc., and Zogenix, Inc.; is on the speaker bureau for Allergan Inc., Impax Laboratories, Inc., Merck & Co., Inc., Novartis AG, and Zogenix, Inc.; and has received research grants from Allergan Inc., Avanir Pharmaceuticals, Inc., Tian Medical, Fortis Spectrum, GlaxoSmithKline plc., Nico Worldwide, Inc., Questcor Pharmaceuticals, and Primary Care Education.

Dr. McAllister is on the speaker's bureau for Zogenix, Inc. and Allergan Inc., and has received research support from Allergan Inc., OptiNose US, Inc., Amgen Inc., Questcor Pharmaceuticals, and AstraZeneca plc.

Dr. Spierings has served as an investigator for OptiNoseUS Inc. studies and has received research support from OptiNose US Inc.

swallowed portion of the dose is then subject to the same challenges of variable intestinal absorption associated with oral delivery. This "dual route" of absorption from standard liquid nasal-spray delivery is shown in pharmacokinetic (PK) studies of sumatriptan.[9-12] A small peak in plasma concentration is observed at ~20 minutes post-dose (nasal absorption), followed by a delayed peak at ~90 minutes post-dose (intestinal absorption).

AVP-825 (formerly "OptiNose Sumatriptan") is an investigational drug–device combination containing sumatriptan powder that is being developed by Avanir Pharmaceuticals, Inc., for the acute treatment of migraine with and without aura. It employs a novel closed-palate, Breath Powered intranasal drug-delivery system (OptiNose US, Inc., Yardley, PA, USA) designed to take advantage of specific features of nasal anatomy and physiology in order to overcome the deficiencies of conventional liquid nasal sprays. Closure of the soft palate and opening of the nasal valve during AVP-825 intranasal delivery of sumatriptan powder allows targeted deposition deep into and throughout the nasal cavity while helping to avoid sumatriptan deposition in the oropharynx or lungs.[12,13] The device includes a mouthpiece for exhalation, connected to a device body, and a nosepiece, designed to seal the nasal opening to improve the extent and reproducibility of drug dosing.[7,11,14] Exhalation into the device causes air flow resistance and positive air pressure in the oropharynx that naturally elevates the soft palate, separating the nasal and oral cavities. The shaped, sealing nosepiece redirects the exhaled air into the nasal cavity, without creating obstructive compression by soft tissues, to balance the pressure across the soft palate and gently expand the narrow, slit-like nasal passages, including the nasal valve. Under balanced pressure, a pathway located deep in the nasal cavity behind the nasal septum remains open between the two nostrils. With these dynamic circumstances, powdered drug particles emitted into the airflow enter via one nostril and are deposited deeply throughout the nasal cavity before the air delivering the particles exits through the other nostril (Bi-Directional delivery).[6,7]

Drug deposition studies in humans using radiolabeled lactose powder delivered using the closed-palate, Breath Powered device have demonstrated significantly greater delivery to the deeper nasal regions beyond the nasal valve, compared with radiolabeled liquid delivered with a conventional nasal spray-pump (Fig. 1).[6,7] Greater initial deposition to more superior and posterior regions of the nasal cavity beyond the nasal valve following Breath Powered delivery of powder is consistent with decreased anterior drip-out and less swallowed drug.[6,10]

The advantages of this delivery method have been demonstrated in a phase 1 bioavailability cross-

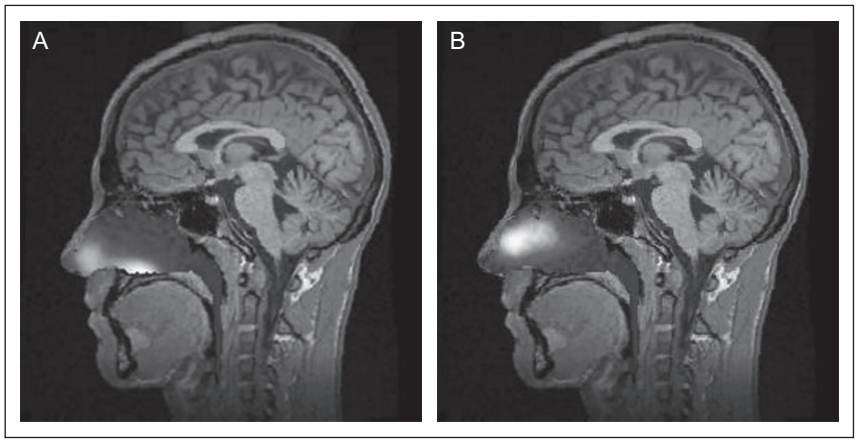

Fig 1.—Gamma camera image of deposition 2 minutes after delivery of a solution of $^{99m}TcO_4$ in saline using a conventional liquid spray device (A) and ^{99m}Tc-labeled lactose powder delivered using the Breath Powered device (B). The image of the nasal cavity is superimposed on the corresponding sagittal MRI section. The images were from the same subject after each method of administration.

over study in 20 healthy participants where AVP-825 (delivered dose 16 mg) produced a greater and earlier peak plasma concentration and significantly higher systemic drug exposure within the first 30 minutes than sumatriptan nasal spray (delivered dose 20 mg sumatriptan) and significantly lower systemic drug exposure than Imitrex oral (100 mg) or subcutaneous injection (6 mg) (Imitrex Nasal Spray and Imitrex Tablet, GlaxoSmithKline, Research Triangle Park, NC, USA).[10,12] The delivery method benefits were observed in a phase 2 placebo-controlled study in 117 patients with acute migraine, where AVP-825 produced high and sustained pain relief, relief of migraine-associated symptoms, and no reported systemic triptan-related adverse events (AEs).[13] Taken together, the randomized comparative PK study and the initial placebo-controlled efficacy study showed that AVP-825 may address unmet needs of migraine sufferers by efficiently delivering a low dose of sumatriptan deep into the nasal passages, which may provide fast and sustained migraine relief with a low potential for systemic AEs.

This phase 3 study (the TARGET study, NCT01462812) was designed to expand the clinical data in a larger patient cohort by comparing the efficacy and safety of AVP-825 with a placebo-containing Breath Powered device (placebo device) in adults with migraine headache with or without aura.

METHODS

The TARGET study was a randomized, double-blind, parallel-group (1:1 allocation) comparison of AVP-825 to an identical device delivering lactose powder (placebo device) in the treatment of a single moderate or severe migraine headache in adult outpatients, conducted at 15 outpatient centers focusing on neurological conditions throughout the USA.

Patients.—Male and female migraineurs 18-65 years of age, diagnosed at least 1 year prior to screening with episodic migraine with or without aura according to The International Classification of Headache Disorders, 2nd Edition (1st revision, May 2005), were recruited to participate in the study. Subjects were recruited from the clinics of investigators where they were receiving care, and in some instances via advertising or referral from other clinics. Eligible patients must have reported experiencing between 1 and 8 migraine headaches/month in the 12 months prior to screening and have verified airflow through both nostrils, ability to close the soft palate (eg, ability to inflate a balloon), and demonstrated ability to use the Breath Powered device.

Patients with hemiplegic or basilar migraine; a history or symptoms or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes; uncontrolled hypertension or seizures; or a history of headache of any kind ≥15 days per month, were excluded. A history of hypersensitivity or intolerance to sumatriptan (or any of its components or sulfonamides), history of resistance to sumatriptan, or non-response to an adequate dose and duration of treatment with two or more other triptans, use of any excluded concomitant medications or use of an investigational medication within 4 weeks before randomization rendered patients ineligible for participation. Patients with known nasal obstruction due to severe nasal septum deviation, polyposis, severe mucosal swelling, or any other reason, current uncontrolled nasopharyngeal illness, or known velum insufficiency were also excluded. Moderate nasal congestion (eg, due to common cold or allergic rhinitis) was not a reason for exclusion.

Protocol Approvals, Registrations, and Patient Consents.—The TARGET study was conducted in accordance with the Declaration of Helsinki, all relevant US federal regulations, and in compliance with the International Conference on Harmonization guideline for Good Clinical Practice. The study protocol, informed consent forms, and any other appropriate study-related documents were reviewed and approved by an Institutional Review Board/Ethics Committee at each center. Written informed consent was obtained from each patient prior to any protocol-related activities. All authors had full access to study data.

Eligible patients were randomized in a 1:1 ratio using an interactive web-based response system to either AVP-825 or placebo device. Randomization sequences were computer generated in blocks of four. The patients, investigators, sponsor, and staff involved in the clinical trial remained blinded during the conduct of the study. Randomization codes

were maintained within the interactive web-based response system.

Following randomization, patients were instructed to treat their next migraine headache when it was moderate or severe in intensity (qualifying migraine). If a patient was unable to treat the first headache with study medication, the patient was instructed to treat the next one. To maintain study blinding, the placebo device was identical to AVP-825. Study medication was provided in disposable nose pieces containing capsules identical in appearance. The active treatment capsule contained an 11 mg base equivalent (15.4 mg of the succinate salt) of sumatriptan powder and the placebo capsule contained lactose powder. At the time of treatment, patients inserted one new nose piece onto the body of the Breath Powered device and administered the study medication or placebo into the nostril on the side of the headache. Following administration, the nosepiece was replaced with a new one and the contents of the second nosepiece were administered into the opposite nostril (total loaded dose of active treatment in the two nosepieces was 22-mg sumatriptan base equivalent). It should be noted that this dose has been reported as nominally 20 mg in previous literature, which was based on *in vitro* studies of delivered dose.[10,13] Use of triptans (other than study drug) and other 5-HT_1 receptor agonists was prohibited from 48 hours prior to the use of study medication until 2 hours post-dose. The use of ergot medications, opioid analgesics, medications for migraine prophylaxis (unless the patient was on a stable dose for at least 30 days prior to the screening visit), monoamine oxidase A inhibitors, antipsychotics, and investigational study drugs was prohibited prior to the use of study medication and for 48 hours after administration. Patients who had taken any monoamine oxidase A inhibitors, antipsychotics, or investigational drug prior to screening were required to have a minimum washout period of 4 weeks. For patients whose migraine headache persisted or worsened after treatment, rescue medication (excluding ergot medications and opioids) was allowed starting 2 hours after treatment with study medication.

Patients recorded treatment time, efficacy assessments, and any rescue medication use in an electronic diary. Efficacy assessments were made immediately before study medication dosing (baseline) and at multiple time points up to 2 hours after administration and at 24 and 48 hours post-dose. Electronic diaries with time alerts were employed for recording of patient reported outcomes. Patients recorded the headache severity score (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain), functional disability score (0 = no disability, able to function normally, 1 = performance of daily activities mildly impaired, can still do everything but with difficulty, 2 = performance of daily activities moderately impaired, unable to do some things, 3 = performance of daily activities severely impaired, cannot do all or most things, bed rest may be necessary), and the presence or absence of the migraine-associated symptoms of nausea, phonophobia, photophobia, and vomiting. Achievement of meaningful pain relief based on individual patient interpretation was also recorded. The patient-reported data for the 2-hour assessment were captured prior to use of any rescue medication. Any patient not experiencing a qualifying headache within 8 weeks of randomization was withdrawn from the study. Patients returned for follow-up evaluations 48 hours to 7 days after treatment.

Outcome Measures.— The primary efficacy endpoint for statistical hypothesis testing was the percentage of patients in each group with headache relief, defined as a reduction in headache intensity from moderate or severe (grade 2 or 3) to mild or none (grade 1 or 0) at 2 hours. Secondary endpoints included headache relief at other time points, pain freedom, relief of migraine-associated symptoms (ie, nausea, phonophobia, photophobia, and vomiting), clinical disability scale score, patient self-assessment of meaningful pain relief, rescue medication use, and maintenance of headache response (patients with headache relief at 2 hours who had no headache recurrence and no rescue medication use) at 24 and 48 hours post-dose. Additionally, maintenance of pain freedom (patients who were pain-free at 2 hours and had no recurrence and no rescue medication use) at 24 and 48 hours and total migraine freedom (no pain and no migraine-associated symptoms) at 2 hours were calculated post hoc. Safety assessments included

AEs, laboratory variables (hematology, serum chemistry, and urinalysis), physical examination, vital signs, and ECG recording.

Statistical Analysis.— Sample size calculations for this study were based on headache response data from a prior study with AVP-825.[13] It was assumed that 35.9% of placebo patients would report headache response at 2 hours. Thus, a sample size of 100 patients per treatment group was required to provide 90% power with a two-sided chi-square test at $\alpha = 0.05$ when the odds ratio was 2.5, exclusive of allowances for drop-out or failure to experience a qualifying migraine. The study was not powered to detect efficacy on secondary endpoints. Tables and listings were produced using SAS@ Version 9.3 (SAS Institute Inc., Cary, NC, USA).

The Full Analysis Dataset (FAS) included all randomized patients who recorded a baseline pain assessment of moderate or severe intensity, administered study drug, and recorded at least one post-treatment assessment of pain intensity. The FAS was used for the analysis of efficacy. The Safety Set (SS) included all randomized patients who received study drug.

The primary and secondary efficacy endpoints (ie, headache relief, pain freedom, relief of migraine-associated symptoms, meaningful pain relief, rescue medication use, and maintenance of headache response) were compared using a chi-square test (continuity corrected). Time to meaningful pain relief was analyzed with a log-ranked test. In all cases, statistical significance was accepted for $P < .05$.

RESULTS

A total of 230 patients (116 AVP-825, 114 placebo device) were randomized, 223 (112 and 111) received study medication (SS), and 212 (108 and 104) were included in the FAS (Fig. 2). Patients were enrolled and assessed between December 2011 and May 2012. Demographics and baseline migraine characteristics were comparable between groups (Table 1). At the time of treatment, 83% of patients in the FAS reported moderate pain and 17% severe pain.

Based on an evaluation of used nosepieces, 96.4% of patients in both treatment groups who reported dosing actually administered medication.

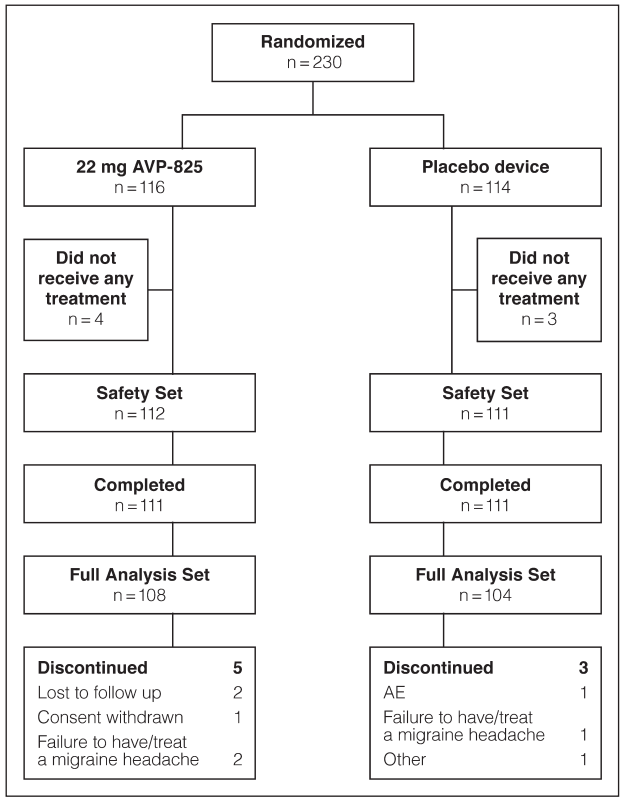

Fig 2.—Patient disposition. The Safety Analysis Dataset includes all patients who received at least one dose of the study drug. The Full Analysis Dataset includes all patients who received at least one dose of the study drug and recorded at least one post-treatment assessment of pain severity.

Laboratory analysis of drug residuals in returned devices showed that the mean amount of sumatriptan delivered to the patients from two nosepieces (containing a total of 22 mg of sumatriptan) was approximately 15 mg, an amount similar to the delivered doses in the prior phase II and PK trials.[10,13]

Efficacy.— Headache relief at 2 hours after treatment (the primary outcome) was reported by significantly more patients taking AVP-825 compared with placebo device (67.6% vs 45.2%, $P = .002$, OR 2.53, 95% CI [1.45, 4.42]). Between-group differences in headache relief appeared as early as 15 minutes (19.4% AVP-825 vs 14.4% placebo device) and were significant at 30 minutes (41.7% vs 26.9%, $P = .03$; Fig. 3). Patients treated with AVP-825 also reported significant differences in maintenance of headache relief at 24 hours (44.4% vs 24.0%, $P = .002$) and 48 hours (34.3% vs 20.2%, $P = .01$) compared with

Table 1.—Patient Demographics and Baseline Characteristics (FAS)

	22 mg AVP-825 (n = 108)	Placebo (n = 104)	Total (n = 212)
Age (years), mean (SD)	41.9 (10.3)	42.0 (10.7)	42.0 (10.5)
Male, n (%)	17 (15.7)	18 (17.3)	35 (16.5)
Female, n (%)	91 (84.3)	86 (82.7)	177 (83.5)
Race, n (%)			
White	90 (83.3)	92 (88.5)	182 (85.8)
Black	15 (13.9)	9 (8.7)	24 (11.3)
Asian	1 (0.9)	1 (1.0)	2 (0.9)
Other	2 (1.9)	2 (1.9)	4 (1.9)
Height (cm), mean (SD)	167 (8.4)	165 (9.5)	166 (8.9)
Weight (kg), mean (SD)	79.6 (20.4)	79.1 (18.7)	79.4 (19.6)
Attacks per month, mean (SD)	4.3 (1.9)	4.8 (1.9)	4.5 (1.9)
Baseline characteristics of treated migraine headache, n (%)			
Moderate pain	90 (83.3)	86 (82.7)	176 (83.0)
Severe pain	18 (16.7)	18 (17.3)	36 (17.0)
Migraine type, n (%)			
Aura only	1 (0.9)	0	1 (0.5)
With aura	41 (38.0)	34 (32.7)	75 (35.4)
Without aura	85 (78.7)	87 (83.7)	172 (81.1)
Presence of (past 6 months)†			
Nausea	90 (83.3)	91 (87.5)	181 (85.4)
Vomiting	42 (38.9)	30 (28.8)	72 (34.0)
Photophobia	106 (98.1)	101 (97.1)	207 (97.6)
Phonophobia	101 (93.5)	92 (88.5)	193 (91.0)
Clinical disability scale, n (%)			
None	2 (1.9)	4 (3.8)	6 (2.8)
Daily activity mildly impaired	44 (40.7)	43 (41.3)	87 (41.0)
Daily activity moderately impaired	55 (50.9)	48 (46.2)	103 (48.6)
Daily activity severely impaired	7 (6.5)	9 (8.7)	16 (7.5)

†Patients may have had more than one of the listed symptoms.

placebo device (Fig. 3). Twice as many patients using AVP-825 vs placebo device were pain-free at the 2-hour endpoint (34.3% vs 17.3%, $P = .008$). At 24 hours, 27.8% of patients in the AVP-825 group maintained pain freedom vs 11.5% in the placebo device group ($P = .005$), and 20.4% vs 8.7% were pain-free at 48 hours ($P = .02$). Significant differences favoring treatment with AVP-825 were also seen in the percentage reporting meaningful pain relief (70.4% vs 45.2%, $P < .001$). Additionally, the time to meaningful pain relief was significantly faster for AVP-825 patients (median 47.5 minutes) compared with placebo device where the median was not achieved prior to the 2 hour endpoint ($P < .001$). Rescue medication use at or after the initial 2-hour assessment period was also reported by significantly fewer AVP-825 patients compared with placebo device patients (37.0% vs 51.9%, $P = .02$). Rescue medication most commonly consisted of aspirin/acetaminophen/caffeine combinations, NSAIDs, and triptans.

At baseline, the mean (SD) clinical disability scores were 1.6 (0.6) and 1.6 (0.7) for the AVP-825 and placebo–device groups, respectively, with 57.4% and 54.9% of patients reporting at least moderate impairment of daily activity, and only 1.9% and 3.8% reporting no impairment (Table 1). Following study medication dosing, clinical disability scores improved at successive time points, with significant differences between groups emerging at 45 minutes post-dose (mean change from baseline of –0.5 AVP-825 vs –0.3 placebo device, $P = .03$). At the 2-hour endpoint, mean (SD) change scores were twice as large for AVP-825 (–0.8) as placebo device (–0.4, $P = .005$); categorical responses were also significantly different

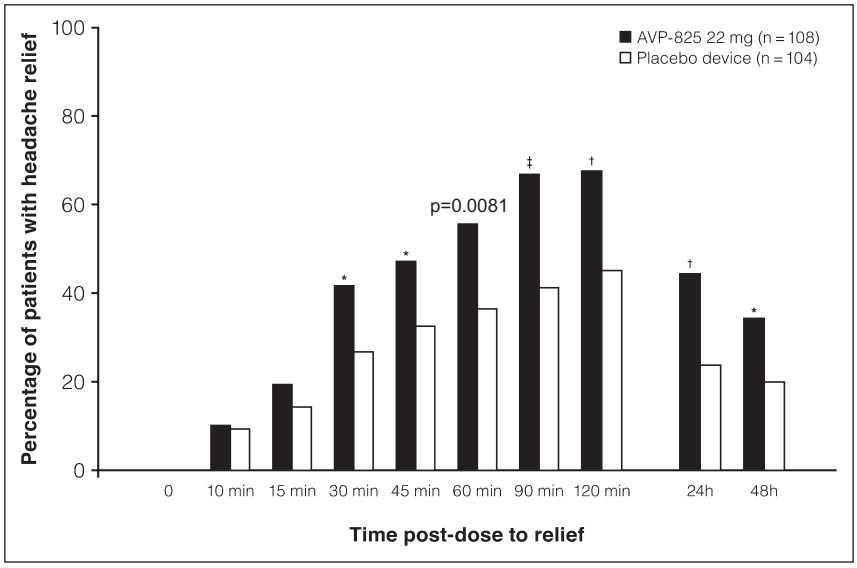

Fig 3.—Patients with headache relief up to 120 minutes and sustained relief at 24 and 48 hours (FAS). *$P < .05$;†$P < .01$;‡$P < .001$. Headache relief = reduction from severe (grade 3) or moderate (grade 2) headache pain to mild (grade 1) headache pain or none (grade 0). Sustained relief at 24 or 48 hours was calculated for patients with headache relief at 120 minutes and required that patients had no recurrence of headache, or rescue medication usage during that timeframe.

($P = .04$) with fewer AVP-825 patients reporting at least moderate disability (19.4%) vs placebo–device patients (34.6%), and more AVP-825 patients reporting no disability (41.7% vs 26.9% placebo device).

Although reductions in migraine-associated symptoms (nausea, phonophobia, photophobia, and vomiting) were also observed, the between-group difference for most symptoms did not reach statistical significance. At the 2-hour endpoint, the incidence of nausea had decreased by 25.9% for AVP-825 and 20.1% for placebo device. A similar trend was observed for photophobia, although significant between-group improvement was seen at 90 minutes, with decreases from 77.8% at baseline to 50.0% for the AVP-825 group and from 78.8% to 64.4% for the placebo–device group ($P = .048$). Likewise, the incidence of phonophobia decreased from 64.8% at baseline to 32.4% at 2 hours following treatment with AVP-825 and from 64.4% to 44.2% for treatment with placebo device, but there were no significant differences at any time point. A low incidence of vomiting in both treatment groups precluded meaningful comparisons. The post-hoc calculation of percentage of patients with total migraine freedom reached significance at 1 hour (19.4% vs 8.7%; $P = .04$); at 2 hours, 29.6% on AVP-825 vs 17.3% placebo device experienced total migraine freedom; $P = .05$.

Safety and Tolerability.—No serious AEs were reported during the study, and a single patient (placebo device) withdrew due to AEs. There were no unanticipated AEs and no reported technical device issues. There were few systemic AEs, and none were reported by more than one patient. The most commonly reported AEs (≥2% in any treatment group) were abnormal product taste (22% AVP-825 vs 4% placebo device), nasal discomfort (13% vs 2%), rhinorrhea (5% vs 3%), and rhinitis (3% vs 0%). One patient using AVP-825 reported mild dizziness and another reported mild paresthesia; no other patients reported abnormal sensations or other systemic AEs typically associated with triptan use. There were no reports of chest pain or pressure. Almost all AEs were mild or moderate in intensity. Only four patients in the AVP-825 group reported an AE of severe intensity: one patient each reported rhinitis, sinus headache, and abnormal product taste, all of which were considered related to treatment and transient, and a fourth reported influenza which was considered unrelated. One patient using the placebo device experienced a severe AE (toothache) that was considered

unrelated to treatment. No clinically significant changes were noted in laboratory values, vital signs, or ECGs.

DISCUSSION

This study confirms findings from a previous phase 2 study demonstrating a clear clinical and statistical benefit of AVP-825 22 mg (Breath Powered delivery of low-dose sumatriptan powder) compared with placebo in the acute treatment of migraine headache. A large fraction of AVP-825-treated patients (42%) reported headache relief by 30 minutes, with over two-thirds reporting relief at 2 hours post-dose, and over one-third of patients reported sustained headache relief at 48 hours, despite the low delivered dose. The 42% rate of response at 30 minutes, in particular, is substantial in the context of other commonly used triptans.[15-22] For sumatriptan, 30-minute pain-relief rates reported in previous clinical trials range from 10% to 20% of patients for high-dose (100 mg) oral sumatriptan and from 20% to 30% of patients for the traditional sumatriptan liquid nasal spray (20 mg).[23] Notably, the 30-minute response rate for AVP-825 approached that reported in multiple studies with sumatriptan subcutaneous injection (~50% of patients).[3,23,24] Despite the high response rate with AVP-825 at 30 minutes in this trial relative to results with other sumatriptan formulations, it must be kept in mind that direct comparisons of data across trials are difficult to interpret due to a number of factors, including differences in study design, patient population, and placebo response rates. In addition, it should be noted that statistical adjustments for multiple comparisons for secondary endpoints, including the non-primary time points for pain relief, were not made in this study.

The rapid onset of effect with AVP-825 seen in this study is consistent with the quick systemic absorption of sumatriptan powder delivered by the Breath Powered device.[10] The rapid systemic absorption is presumed to occur because the Breath Powered device delivers drug deep in nasal passages where the ciliated respiratory epithelium is richly vascularized.[10,11,24,25] Delivery of a powdered drug may offer advantages over liquid formulations that include increased stability, reduced need for excipients, and slower clearance from the ciliated regions of the mucosa.[26] In addition, those regions of the nasal cavity are extensively innervated by the branches of the trigeminal nerve and also in part by the olfactory nerve.[6,25] Therefore, it is possible that migraine relief observed with AVP-825 is also partially mediated by local effects at trigeminal nerve endings in the nasal mucosa[27,28] and direct transport of sumatriptan to brain (via olfactory and trigeminal nerves),[29] to the trigeminal ganglion,[25] and to the pterygopalatine ganglion,[30,31] all of which have been implicated in the pathophysiology of migraine. In addition, it is possible that sumatriptan action at serotonin receptors on the nerve could have a direct role in modulating migraine-associated inflammation.[32] Other effects related to the device may also have a role in migraine relief. The air exhaled through the device delivers CO_2 deep into the nasal cavity and may provide an effect (discussed further later).[11,23] Whether any of these additional mechanisms contribute to the clinical effects of AVP-825 has not been determined and is beyond the scope of this study.

In addition to providing rapid headache relief, AVP-825 demonstrated broad clinical benefit as shown by a consistent effect across other efficacy measures. "Meaningful pain relief," a patient-reported outcome, provides a comprehensive, clinically relevant appraisal of treatment benefit and has been widely used in non-migraine pain studies.[33] A high proportion of patients in the AVP-825 treatment group in this study reported meaningful pain relief during the first 2 hours, a rate that is similar to the previous phase 2 study of AVP-825 for the treatment of migraine headache (70% in this trial vs 71% in the phase 2 study).[13] The median time to meaningful pain relief was also significantly faster in the AVP-825 treatment group than in the placebo–device group (48 minutes vs > 120 minutes). Maintenance of headache relief and pain freedom data further support the clinical benefit of treatment with AVP-825, as significantly more patients who reported headache relief or pain freedom at 2 hours did not experience headache recurrence or use a rescue medication through 24 and 48 hours in the AVP-825 group than the placebo–device group. Sustained efficacy is particularly notable in light of the low dose of sumatriptan

delivered through AVP-825 (averaged emitted dose is 15-16 mg), showing a delivery method that is very efficient. Further substantiating the clinical relevance of the treatment effect, AVP-825 significantly improved patient function on the clinical disability measure as early as 45 minutes post-dose.

Reductions in the percentage of patients experiencing migraine-associated symptoms of nausea, phonophobia, photophobia, and vomiting were numerically larger for AVP-825, but did not reach statistical significance over placebo at most time points nor at the 2-hour endpoint. Despite the lack of significance, overall reductions in the percentage of patients experiencing these symptoms appeared generally consistent with reductions seen in published migraine trials.[34] Although this study was not powered to assess the effect on migraine-associated symptoms, this result was unexpected, particularly in the context of the robust and significant symptom-related response seen in the AVP-825 phase 2 study. The results could be a consequence of the combination of high placebo response for these symptoms coupled with the low baseline incidence of some symptoms, such as nausea. To further evaluate effects on migraine-associated symptoms, we conducted a post-hoc analysis to evaluate total migraine freedom, defined as no headache pain and no migraine-associated symptoms. Patients in the AVP-825 treatment group experienced improved total migraine freedom that was significant at 1 hour and approached the level of significance ($P = .05$) at the 2-hour time point. Collectively, these results demonstrate that AVP-825 22 mg, using closed-palate Breath Powered technology to deliver a low dose (mean 15 mg delivered) of sumatriptan powder, provides a high level of treatment efficacy that is rapid, clinically meaningful, and sustained over time.

The 2-hour response rates in the placebo group and the percentage achieving freedom from pain were greater than those typically observed in similar migraine trials.[35] Response to placebo treatment is sensitive to several aspects of the experimental intervention, including patient expectation of benefit, investigator bias, characteristics of the disease among participants (eg, headache intensity), and, particularly important in this case, factors related to the intervention being tested, such as the use of a device.[36,37] It is also conceivable that patient expectations of relief were influenced by the use of a medication (sumatriptan) known to be effective for the treatment of migraine; in fact, 27% of patients in this trial had an ongoing prescription for sumatriptan. Additionally, there may be a higher expectation of success in patients treated with innovative devices or new formulations[38] as well as bias introduced from investigator expectations based on efficacy observed in the previous trial. For example, placebo response rates for headache relief at 2 hours of 42-46%, comparable to those observed in this study, were reported with the rapidly dissolving sumatriptan tablet[39] and the oral calcitonin gene-related peptide (CGRP) antagonist, telcagepant.[40]

Another factor that could theoretically contribute to placebo (and potentially active drug) response may be related to neurochemical effects of CO_2 delivery and/or removal of NO at the trigeminal nerve endings within the nasal cavity. Since AVP-825 redirects exhaled air deep into the nasal cavity, it has an added advantage of broadly exposing deep intranasal structures innervated by the first branch of the trigeminal nerve to positive pressure and high airflow of exhaled air.[23,41,42] The increased Bi-Directional airflow (in one nostril, out the other) may locally replace the elevated levels of NO found in this region with exhaled air containing 5-6% CO_2.[43] NO is known to stimulate release of CGRP, a key mediator in the pathophysiology of migraine, whereas increases in local CO_2 concentration causes a decrease in pH that mediates intracellular reactions that ultimately inhibit CGRP release from the trigeminal neurons, which may be beneficial in migraine modulation.[44-46] In the context of this study, it is important to recognize that all patients used the Breath Powered device and any purely device-related benefits would have accrued to both the active and placebo treatment groups.

AVP-825 showed a favorable safety profile in this trial, with no serious AEs, and no atypical sensations (the so-called triptan effects) other than mild paresthesia reported by just one patient; there were no reports of chest, jaw, or neck tightness. Common AEs were limited to the site of administration, such as

abnormal product taste and nasal discomfort, which were both generally mild and transient.

Despite the availability of multiple triptans with varied formulations, dissatisfaction with migraine treatment persists for many patients.[47] Oral tablets, although commonly prescribed and easy to use, can provide relatively slow onset of relief and inconsistent treatment response owing to delayed intestinal absorption during migraine headache.[2] Swallowing tablets also may not be tolerated during migraine headaches associated with nausea or vomiting. Furthermore, a high tablet dosage relative to other routes of administration is required to overcome poor drug bioavailability, and higher overall drug exposure may increase risk for triptan-related AEs.[48,49] Subcutaneous injection of sumatriptan offers the greatest speed and magnitude of headache relief; however, injections are inconvenient, painful to administer, and associated with a high frequency of both local and systemic side effects.[24] Conventional intranasal methods of drug delivery were developed in an attempt to complement and address the shortcomings of other routes of delivery. However, liquid nasal sprays have achieved limited use, potentially in part because patients have not perceived clinically relevant advantages over oral products. Shortcomings of conventional liquid nasal-spray technology contribute to the difficulties in achieving the promise of nasal delivery. Conventional nasal-spray delivery is associated with variable loss of drug due to drip-out with nasal-spray devices, exacerbated by the broad plume delivered into the anterior non-ciliated region of the nasal cavity due to the physical barrier of the narrow nasal valve. Much of the drug dose with these conventional nasal sprays, as PK data show, is ultimately swallowed and subject to delayed and variable gastric emptying and intestinal absorption during a migraine headache.[8,24] The novel AVP-825 delivery system of sumatriptan powder can offer an important therapeutic and practical alternative for migraine treatment by efficiently delivering sumatriptan powder beyond the nasal valve to the highly absorptive surface of the nasal cavity and to cranial nerve structures potentially relevant for migraine therapy.

Conclusions.— In this study, AVP-825 (using closed-palate Breath Powered delivery of low-dose sumatriptan powder) provided fast and sustained migraine relief, was well tolerated, and had a low rate of triptan-related AEs. This study confirms previous safety and efficacy results from a phase 2 trial.

Acknowledgments: Statistical analysis was provided by Hsi-Wen Liao of inVentiv Health Inc. Manuscript preparation, including editing and formatting the manuscript, incorporating author comments, preparing tables and figures, and coordinating submission requirements, was provided by Apurva Davé, PhD, and Jennifer Hepker, PhD, of Prescott Medical Communications Group (Chicago, IL). This editorial support was funded by Avanir Pharmaceuticals, Inc. Joao Siffert, MD, and Andrea Formella, PharmD of Avanir Pharmaceuticals, Inc. (Aliso Viejo, CA) provided clinical review, scientific advisement, and substantive revision of the manuscript for intellectual content.

REFERENCES

1. Thorlund K, Mills EJ, Wu P, et al. Comparative efficacy of triptans for the abortive treatment of migraine: A multiple treatment comparison meta-analysis. *Cephalalgia*. 2014;34:258-267.
2. Aurora SK, Kori SH, Barrodale P, McDonald SA, Haseley D. Gastric stasis in migraine: More than just a paroxysmal abnormality during a migraine attack. *Headache*. 2006;46:57-63.
3. Silberstein SD, Marcus DA. Sumatriptan: Treatment across the full spectrum of migraine. *Expert Opin Pharmacother*. 2013;14:1659-1667.
4. Rapoport A. New frontiers in headache therapy. *Neurol Sci*. 2011;32(Suppl. 1):S105-S109.
5. Rapoport AM. The therapeutic future in headache. *Neurol Sci*. 2012;33(Suppl. 1):S119-S125.
6. Djupesland PG, Skretting A. Nasal deposition and clearance in man: Comparison of a bidirectional powder device and a traditional liquid spray pump. *J Aerosol Med Pulm Drug Deliv*. 2012;25:280-289.
7. Djupesland PG, Skretting A, Winderen M, Holand T. Breath actuated device improves delivery to target sites beyond the nasal valve. *Laryngoscope*. 2006;116:466-472.
8. Aggrawal R, Cardozo A, Homer JJ. The assessment of topical nasal drug distribution. *Clin Otolaryngol*. 2004;29:201-205.
9. Duquesnoy C, Mamet JP, Sumner D, Fuseau E. Comparative clinical pharmacokinetics of single

doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. *Eur J Pharm Sci*. 1998;6:99-104.
10. Obaidi M, Offman E, Messina J, Carothers J, Djupesland PG, Mahmoud RA. Improved pharmacokinetics of sumatriptan with Breath Powered nasal delivery of sumatriptan powder. *Headache*. 2013;53:1323-1333.
11. Djupesland PG, Messina JC, Mahmoud RA. Breath powered nasal delivery: A new route to rapid headache relief. *Headache*. 2013;53(Suppl. 2):72-84.
12. Luthringer R, Djupesland PG, Sheldrake CD, et al. Rapid absorption of sumatriptan powder and effects on glyceryl trinitrate model of headache following intranasal delivery using a novel bi-directional device. *J Pharm Pharmacol*. 2009;61: 1219-1228.
13. Djupesland PG, Docekal P. Czech Migraine Investigators Group. Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: A randomised, placebo-controlled study. *Cephalalgia*. 2010;30:933-942.
14. Djupesland PG, Skretting A, Windern M, Holand T. A novel concept for nasal delivery of aerosols can prevent lung inhalation. *Aerosol Med*. 2004;17:249-259.
15. MAXALT (rizatriptan benzoate) tablets [Prescribing Information], Merck & Co., Inc. (Whitehouse Station, NJ) 2013. http://www.merck.com/product/usa/pi_circulars/m/maxalt/maxalt_pi.pdfh (Accessed February 28, 2014).
16. RELPAX (eletriptan hydrobromide) tablets [Prescribing Information]. Roerig, Division of Pfizer Inc. (New York, NY) 2013. (Accessed February 28, 2014).
17. FROVA (frovatriptan succinate) tablets [Prescribing Information]. Endo Pharmaceuticals Inc. (Malvern, PA) 2013. http://www.endo.com/File%20Library/Products/Prescribing%20Information/FROVA_Prescribing_Information.html
18. Goadsby PJ. Therapeutic prospects for migraine. *Ann Neurol*. 2013;74:423-434.
19. Goadsby PJ, Zanchin G, Geraud G, et al. Early vs non-early intervention in acute migraine-"Act when Mild (AwM)." A double-blind, placebo-controlled trial of almotriptan. *Cephalalgia*. 2008;28:383-391.
20. AMERGE (naratriptan hydrochloride) tablets [Prescribing Information]. GlaxoSmithKline (Research Triangle Park, NC) 2013. (Accessed February 28, 2014).
21. ZOMIG (zolmitriptan) nasal spray [Prescribing Information]. Astrazeneca, distributed by Impax Pharmaceuticals (Hayward, CA) 2013. (Accessed February 28, 2014).
22. ZOMIG (zolmitriptan) tablets [Prescribing Information]. Astrazeneca, distributed by Impax Pharmaceuticals (Hayward, CA) 2012. (Accessed February 28, 2014).
23. Tepper SJ. Clinical implications for breath-powered powder sumatriptan intranasal treatment. *Headache*. 2013;53:1341-1349.
24. IMITREX (sumatriptan succinate) Injection [Prescribing Information]. GlaxoSmithKline (Research Triangle Park, NC) 2012. https://www.gsksource.com/gskprm/htdocs/documents/IMITREX-INJECTION-PI-PPI.PDF
25. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective-a review. *Drug Deliv Trans Res*. 2013; 3:42-62.
26. Illum L. Nasal drug delivery – Possibilities, problems and solutions. *J Control Release*. 2003;87:187-198.
27. Ivanusic JJ, Kwok MM, Jennings EA. Peripheral targets of 5-HT(1D) receptor immunoreactive trigeminal ganglion neurons. *Headache*. 2011;51:744-751.
28. Ivanusic JJ, Kwok MM, Ahn AH, Jennings EA. 5-HT(1D) receptor immunoreactivity in the sphenopalatine ganglion: Implications for the efficacy of triptans in the treatment of autonomic signs associated with cluster headache. *Headache*. 2011;51:392-402.
29. Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases – An anatomic, physiologic, and delivery technology overview. *Ther Deliv*. 2014;5:709-733.
30. Goadsby PJ. Sphenopalatine (pterygopalatine) ganglion stimulation and cluster headache: New hope for ye who enter here. *Cephalalgia*. 2013;33:813-815.
31. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study. *Cephalalgia*. 2013;33:816-830.
32. Sarrouilhe D, Dejean C, Mesnil M. Involvement of gap junction channels in the pathophysiology of migraine with aura. *Frontiers Physiol*. 2014;5:78.

33. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149-158.
34. Dahlof C. Sumatriptan nasal spray in the acute treatment of migraine: A review of clinical studies. *Cephalalgia*. 1999;19:769-778.
35. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: A meta-analysis of 53 trials. *Lancet*. 2001;358:1668-1675.
36. Autret A, Valade D, Debiais S. Placebo and other psychological interactions in headache treatment. *J Headache Pain*. 2012;13:191-198.
37. Olanow CW. Double-blind, placebo-controlled trials for surgical interventions in Parkinson disease. *Arch Neurol*. 2005;62:1343-1344.
38. Diener HC. Placebo effects in treating migraine and other headaches. *Curr Opin Investig Drugs*. 2010;11:735-739.
39. Sheftell FD, Dahlof CG, Brandes JL, Agosti R, Jones MW, Barrett PS. Two replicate randomized, double-blind, placebo-controlled trials of the time to onset of pain relief in the acute treatment of migraine with a fast-disintegrating/rapid-release formulation of sumatriptan tablets. *Clin Ther*. 2005;27:407-417.
40. Ho TW, Mannix LK, Fan X, et al. Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. *Neurology*. 2008;70:1304-1312.
41. Suren M, Kaya Z, Ozkan F, Erkorkmaz U, Arici S, Karaman S. Comparison of the use of the Valsalva maneuver and the eutectic mixture of local anesthetics (EMLA(R)) to relieve venipuncture pain: A randomized controlled trial. *J Anesth*. 2013;27:407-411.
42. Wallasch TM, Beckmann P, Kropp P. Cerebrovascular reactivity during the Valsalva maneuver in migraine, tension-type headache and medication overuse headache. *Funct Neurol*. 2011;26:223-227.
43. Djupesland PG, Chatkin JM, Qian W, et al. Aerodynamic influences on nasal nitric oxide output measurements. *Acta Otolaryngol*. 1999;119:479-485.
44. Shusterman D, Avila PC. Real-time monitoring of nasal mucosal pH during carbon dioxide stimulation: Implications for stimulus dynamics. *Chem Senses*. 2003;28:595-601.
45. Spierings ELH, Cady RK, Goldstein J, Klapper JA, Rozen T. Abortive treatment of migraine headache with non-inhaled, intranasal carbon dioxide: A randomized, doubleblind, placebo-controlled, parallel-group study [abstract]. *Headache*. 2005;45:809.
46. Vause C, Bowen E, Spierings E, Durham P. Effect of carbon dioxide on calcitonin gene-related peptide secretion from trigeminal neurons. *Headache*. 2007; 47:1385-1397.
47. Walling AD, Woolley DC, Molgaard C, Kallail KJ. Patient satisfaction with migraine management by family physicians. *J Am Board Fam Pract*. 2005; 18:563-566.
48. Tepper S, Rapoport A. The triptans: A summary. *CNS Drugs*. 1999;12:403-417.
49. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24(Suppl. 1):9-160.

Signature Page for TARGET reprint with cover page PP-ONZ-US-0016 v1.0

Marketing Approval	Patty Pound Marketing 15-Oct-2015 23:28:02 GMT+0000

Legal Approval	Will Pedranti Legal 15-Oct-2015 23:32:38 GMT+0000

Medical Approval	Ken Shulman Medical 16-Oct-2015 00:02:59 GMT+0000

Legal Approval	Aneta Ferguson Legal 19-Oct-2015 16:37:56 GMT+0000

Regulatory Approval	Art Rosenthal Regulatory 01-Dec-2015 21:05:05 GMT+0000

Signature Page for TARGET reprint with cover page PP-ONZ-US-0016 v1.0