

# Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: A randomised, placebo-controlled study

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**PG Djupesland<sup>1</sup>, P Dočekal<sup>2</sup> and the Czech Migraine Investigators Group**

## Abstract

**Introduction:** Intranasal sumatriptan is an option for the treatment of migraine; however, nasal delivery using conventional spray pumps is suboptimal.

**Methods:** Adult subjects ( $n = 117$ ) with migraine were enrolled in a multicentre, randomised, double-blind, parallel group, placebo-controlled study. A single migraine attack was treated in-clinic with sumatriptan 10 mg, sumatriptan 20 mg or placebo administered intranasally by a novel bi-directional powder delivery device when migraine was moderate or severe.

**Results:** A greater proportion of subjects who received sumatriptan were pain-free at 120 minutes compared with those who received placebo (10 mg/20 mg sumatriptan vs. placebo = 54%/57% vs. 25%,  $P < .05$ ). Significant benefits were also observed for pain relief at 120 minutes (84%/80% vs. 44%,  $P < .001/.01$ ) and as early as 60 minutes (73%/74% vs. 38%,  $P < .01$ ) and for 48 hours sustained pain-free ( $P < .05$ ). Treatment-related adverse events were rare, with a metallic taste being the most commonly reported (10%/13%).

**Conclusions:** Sumatriptan nasal powder administered using the new device during a migraine attack was effective and well tolerated.

## Keywords

Sumatriptan, migraine, bi-directional nasal delivery

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## Introduction

Migraine is a recurrent headache of moderate-to-severe intensity that is associated with gastrointestinal, neurological and autonomic symptoms. During migraine attacks, gastric emptying is delayed, and as a consequence oral treatments may have a delayed onset of effect. Furthermore, patients may suffer from nausea and vomiting, which may make taking an oral tablet difficult. Intranasal formulations of some triptans, including sumatriptan, have been developed with the intent of achieving a faster onset of action, while avoiding the need to inject the drug. Clinical studies have shown that intranasal sumatriptan delivered by conventional liquid spray pumps is an effective means of relieving migraine (1–3).

A recent review of the pharmacokinetics and clinical effects of different sumatriptan formulations describes the tradeoff between fast onset offered by subcutaneous (SC) injection compared with the more favorable adverse-event profile and patient acceptability offered by oral and nasal sumatriptan (4). For patients, a barrier exists related to difficulties using the conventional

<sup>1</sup>OptiNose AS, Oslo, Norway.

<sup>2</sup>Department of Neurology, Charles University in Prague, Czech Republic.

## Corresponding author:

PG Djupesland OptiNose AS, Oslo Innovation Center (Forskningsparken), Gaustadalleen 21, 0349 Oslo, Norway.  
Email: pgd@optinose.no

nasal devices, which may also cause variability in the clinical effects (5). However, intranasal delivery is considered the most attractive route for patients with nausea and/or vomiting, particularly if the speed of onset and reliability can be improved (4).

Current nasal sprays deposit the drug mainly in the non-ciliated part of the nasal passage anterior to the nasal valve. To avoid drip-out, the patient typically sniffs, which rapidly moves the concentrated drug along the floor of the nose to the oral cavity, often resulting in a bitter taste (3). The bi-directional delivery system used in the powder delivery device (OptiNose) has documented significantly improved deposition to the respiratory and olfactory mucosa (6), which is essential for rapid systemic absorption and for potential direct transport from the nose to the brain (N2B) (5). Bi-directional delivery uses two aspects of nasal anatomy to improve the extent and reproducibility of dosing while avoiding the risk of lung inhalation (6,7). First, during exhalation against a resistance the soft palate closes due to positive pressure, separating the nasal and oral cavities. Consequently, it becomes possible to use smaller particles in a nasal spray and avoid lung deposition by exhalation through the mouth during nasal administration. Second, during closure of the soft palate there is a communication pathway between the two nostrils, located behind the wall separating the two passages. Under these circumstances, it is possible for air flow to enter via one nostril and leave by the other. Indeed, a recent phase I study with the same device and sumatriptan formulation used in this study showed a faster and more extensive systemic absorption across the nasal mucosa than the existing sumatriptan liquid spray pump, and also suggests some degree of N2B transport or local action via the olfactory and trigeminal nerves, which innervate the nasal mucosa (8).

The aim of this study was to evaluate the efficacy and safety of two doses of a powder formulation of sumatriptan delivered intranasally with the novel device in comparison with placebo.

## Methods

### Study design

This randomised, double-blind, placebo-controlled, dose-ranging, parallel group study enrolled adult subjects with a history of migraine headache at 10 centres in the Czech Republic. Nine centres were in hospital neurology clinics, and one centre was a private clinic. All subjects gave written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki and the principles of

Good Clinical Practice. The study was approved by both a central ethics committee and local ethics committees at each site.

Inclusion criteria were age 18–65 years; a developing or established attack of migraine with or without aura according to the International Headache Society (IHS) criteria, of moderate (grade 2) or severe (grade 3) intensity and no improvement in the attack at the time of assessment; migraine present for at least one year, with a three-month, well-documented retrospective history; 48 hours of freedom from headache between attacks of migraine; age at first diagnosis of migraine less than 50 years; an average of  $\geq 1$  and  $\leq 6$  migraine attacks per month for the past six months; reporting the migraine attack and attending the clinic within four hours of the onset of the attack; verified air flow through both nostrils and an ability to close the soft palate; and the ability to trigger the breath-actuation mechanism of a device in accordance with the instructions for use. Exclusion criteria included an inability to distinguish other headaches from migraine; other headaches at a frequency of more than six days per month; subjects who use drugs excessively for headache (i.e. who use medication for acute headache more than 10 days each month); resistance to migraine drugs; use of ergotamine, ergot-type medications or any 5-HT<sub>1</sub> agonist or narcotic analgesics within the previous 24 hours before treatment; current use of drugs for migraine prophylaxis; use of any analgesic within 12 hours before treatment; treatment with monoamine oxidase A (MAO-A) inhibitors or attending for treatment within two weeks of discontinuation of MAO-A inhibitor therapy; treatment with selective serotonin-reuptake inhibitors; using a decongestant within six hours of attendance at the clinic on the treatment day; hemiplegic or basilar migraine; a history, symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes or uncontrolled hypertension (systolic blood pressure  $>140$  mmHg and/or diastolic blood pressure  $>95$  mmHg); known nasal obstruction due to nasal deviations, polyposis, severe mucosal swelling or any other reason; current uncontrolled nasopharyngeal illness; known velum insufficiency; and extensive nasal and/or sinus surgery.

At the screening visit, eligible subjects underwent a physical examination, 12-lead electrocardiogram (ECG), measurement of vital signs after the subject had been sitting for five minutes and blood and urine sampling for clinical laboratory tests. Nasal patency and ability to close the soft palate were checked. Each subject was trained in the use of the device, and their ability to achieve a suitable outflow was established. Subjects were instructed to telephone the clinic at the onset of their first migraine attack.

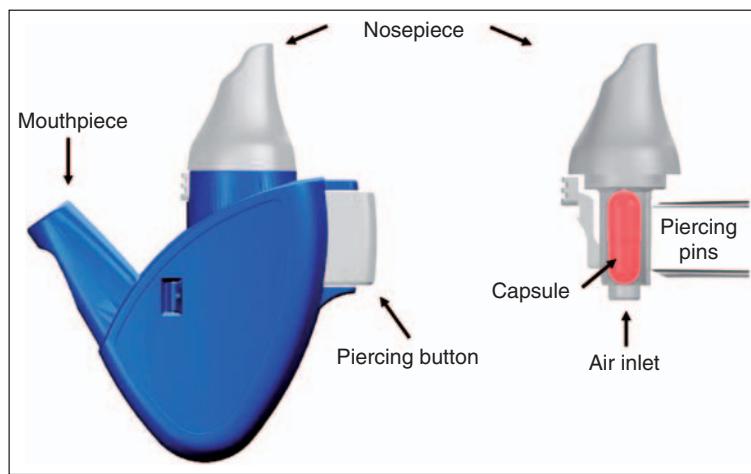
There was a single treatment day. Subjects were transported to the clinic as soon as they reported a migraine attack. Continued compliance with inclusion/exclusion criteria was checked. A pregnancy test was conducted on all female subjects of childbearing potential. The subjects' vital signs were recorded after they had been sitting for five minutes, a 12-lead ECG was recorded and blood and urine samples taken for safety evaluation. Baseline details of each subject's migraine attack were recorded. The subjects were instructed again in the use of the device and then randomly allocated to treatment, either 10 mg sumatriptan, 20 mg sumatriptan or placebo. Efficacy and safety assessments were made for 120 minutes after administration. The OptiNose powder device is shown in Figure 1. Prior to each administration, the capsule inside the device was punctured by pressing the piercing button once. The subject placed the sealing nosepiece into the nostril selected for administration and the mouthpiece into their mouth. To effect the administration, the subject took a deep breath with the mouth open, then closed the lips around the mouthpiece and exhaled into the device, delivering the powdered drug into the nose via the nosepiece. For the 10 mg dose, one device was provided containing the 10 mg dose and the subject performed the administration to one nostril. For the 20 mg dose, two devices were provided, each containing a 10 mg dose and the subject performed the administration to both nostrils, in rapid succession. In the placebo group, one-half of the subjects administered one placebo device and one-half of the subjects administered two placebo devices (one to each nostril) to maintain blinding in the same manner. The devices were identical in appearance and therefore neither the study staff nor the study subjects were aware of whether active treatment or placebo

was being administered. Where the treatment consisted of a single device (active or placebo), the administration was to the nostril on the same (ipsilateral) side as the migraine headache occurred. If the headache was bilateral, the single administration could be made to either side. The administration(s) were supervised by the investigator or a designee.

Each capsule contained the active ingredient sumatriptan succinate at a dose of 10 mg base equivalent (14 mg of the succinate salt) with a mean particle size of 15  $\mu$ . The device was provided pre-filled. The residuals of sumatriptan in the capsules were measured using a high-performance liquid chromatography method. The placebo device was identical in external appearance to the active device, but contained an empty capsule.

### Efficacy assessments

On attending the clinic, patients had the pre-treatment details of the migraine attack recorded. Headache severity score (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain); the level of functional disability (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 migraine-associated symptoms (nausea, vomiting, phonophobia, photophobia) were recorded immediately prior to dosing and 15, 30, 60, 90 and 120 minutes post-dose. Subjects measured time to meaningful relief using a stopwatch. Meaningful relief was defined subjectively by the patient. If the subject was not pain-free at the 120-minute assessment,



**Figure 1.** The OptiNose powder delivery device.

the subject was permitted to take rescue medication. The sustained pain-free (SPF) status (defined as pain-free within 120 minutes with no use of rescue medication or relapse within 48 hours) of the subject was recorded at the follow-up visit.

### Safety assessments

Safety assessments included adverse events, laboratory tests, vital signs, 12-lead ECG and physical examination. Details of all reported adverse events were recorded throughout the study, with severity graded as mild, moderate or severe, and a relationship to treatment assigned based on the judgment of the investigator. Blood and urine sampling for laboratory tests and recording of a 12-lead ECG were performed at screening, before dosing on the treatment visit and at follow-up. The following haematological parameters were assessed: haemoglobin concentration, total red blood cell count, erythrocyte sedimentation rate, mean corpuscular volume, total white cell count, neutrophils, lymphocytes, eosinophils, monocytes, basophils and platelets. The following blood biochemical parameters were assessed: hepatic function (total bilirubin, alkaline phosphatase, gamma-glutamyltransferase, aspartate transferase, alanine transferase), renal function (urea, creatinine) and clinical chemistry (sodium, potassium, calcium, albumin, total protein, glucose). Urine analysis consisted of pH, glucose, protein, occult blood, ketones, specific gravity, bilirubin and urobilinogen. Measurement of vital signs (blood pressure and pulse rate) and physical examination were performed at screening and follow-up. In addition, vital signs were measured prior to treatment and after 15, 30, 60, 90 and 120 minutes on the treatment day.

### Statistical analysis

It was initially planned that a modified intent-to-treat analysis would be performed on all subjects who presented with a migraine, received study medication and had a post-dose primary efficacy evaluation. A review of blinded data listings prior to database lock found that 13 subjects were major protocol violators: 12 subjects with a headache severity score of 1 (mild) at baseline on the treatment day and one subject who received rescue medication within 120 minutes of study treatment administration. Therefore a per-protocol analysis excluding these major violators was included in the statistical analysis plan. This change to the planned analysis was made prior to database lock and unblinding of the study. This paper presents the results for the per-protocol population.

All statistical tests were performed using SAS version 8.2 software (SAS Institute Inc., USA). The level of

significance, alpha ( $\alpha$ ), for this study was 0.05. The primary end point was the proportion of subjects pain-free at 120 minutes after treatment. Secondary end points were relief of headache (defined as a decrease in headache intensity from severe [grade 3] or moderate [grade 2] to mild [grade 1] or none [grade 0]), time to meaningful relief, level of functional disability, incidence of associated symptoms (nausea, vomiting, photophobia phonophobia), need for rescue medication and SPF status. Calculation of the recently introduced end point, sustained pain-free and no adverse events (SPFNAE), encompassing a combination of parameters of what the patients desire of their medication for migraines, was also performed, using  $\text{SPFNAE} = \text{SPF}(1-\text{AE})$  (9).

The primary efficacy analysis was Fisher's exact test comparing the proportion of subjects treated with sumatriptan in each dose group who were pain-free at 120 minutes post-dose to those on placebo who were pain-free at 120 minutes. Fisher's exact test was also used to capture differences between each sumatriptan group and the placebo group at different time points for relief of headache, incidence of associated symptoms, rescue medication use and SPF status. Time to meaningful relief was estimated using Kaplan-Meier survival analysis and analysed using log-rank test for treatment difference between the sumatriptan groups and the placebo group. Data were censored at 120 minutes post-dose. The level of functional disability, measured at 15, 30, 60, 90 and 120 minutes, was analysed using log-linear models.

Sample size calculations were based on proportions of subjects pain-free at 120 minutes of 11% for placebo and 41% for sumatriptan 20 mg, as predicted from published studies (1,2). A sample size of 40 subjects per treatment group allowed 80% power to detect this difference at the 5% level (two-sided).

## Results

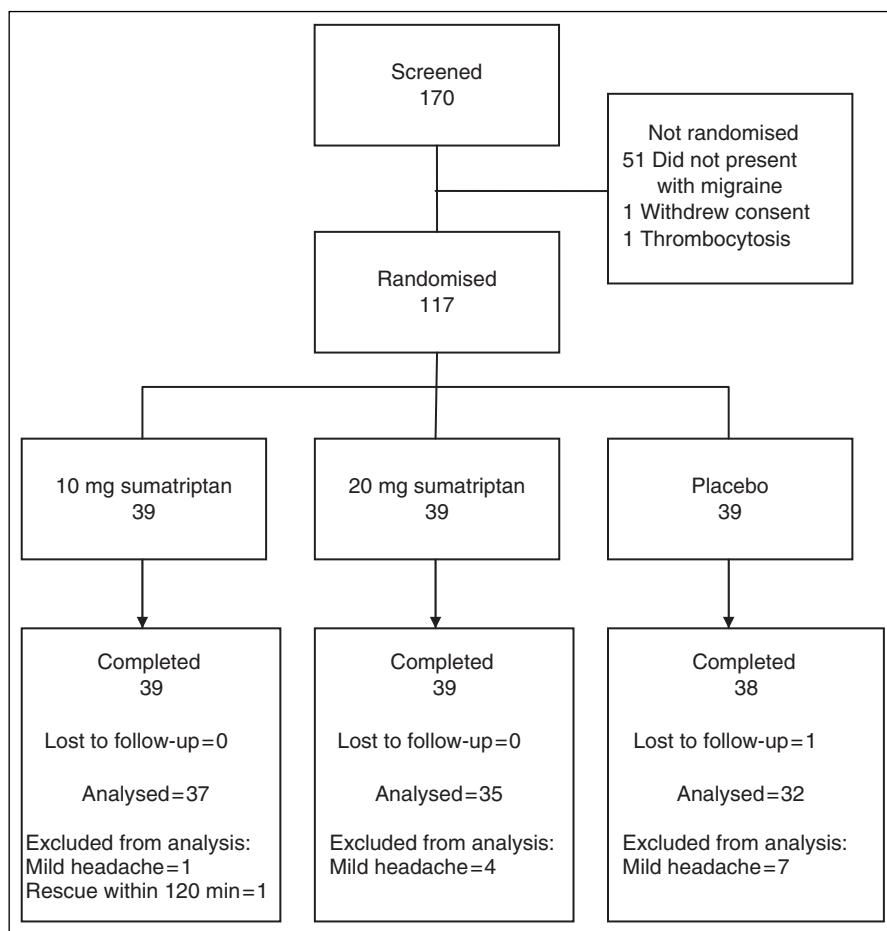
### Subject characteristics

Subjects were recruited from April 2007 to September 2007. A total of 117 subjects (100 females, 17 males) were randomised to treatment. Demographics and baseline characteristics of treated migraines were similar among all treatment groups (Table 1). Apart from one subject in the placebo group who was lost to follow-up, all subjects completed the study. All subjects were included in the safety population. One subject in the 10 mg sumatriptan group, four subjects in the 20 mg sumatriptan group and seven subjects in the placebo group had only mild headache on treatment. In addition, one subject in the 10 mg group took rescue medication within 120 minutes of dosing. All these subjects were major protocol violators and were excluded from

**Table 1.** Demographics, migraine history and characteristics of pre-treatment headache

Demographics	10 mg sumatriptan (n = 39)	20 mg sumatriptan (n = 39)	Placebo (n = 39)
Mean age (years)	40.6	42.7	42.8
Range	21.0–59.0	18.0–58.0	21.0–64.0
Race, n (%) Caucasian	39 (100)	39 (100)	39 (100)
Gender, n (%)			
Male	7 (17.9)	4 (10.3)	6 (15.4)
Female	32 (82.1)	35 (89.7)	33 (84.6)
Mean height (cm)	168.8	167.3	168.7
Range	156.0–187.0	156.0–182.0	156.0–193.0
Mean weight (kg)	69.1	63.3	68.3
Range	53.0–112.0	45.0–85.0	52.0–97.0
Migraine history			
Mean duration of migraine (years)	18.0	18.9	18.6
Range	4.0–38.0	1.0–45.0	1.1–46.0
Migraine attacks usually with aura, n (%)	3 (7.7)	4 (10.3)	5 (12.8)
Mean frequency of migraine attacks/month	2.7	2.9	3.7
Range	1.0–7.0	1.0–5.0	1.0–6.0
Mean age at first diagnosis (years)	23.0	23.1	24.6
Range	10.0–40.0	8.0–46.0	6.0–48.0
Sumatriptan use for migraine, n (%)			
Subcutaneous	0 (0.0)	1 (2.6)	0 (0.0)
Intranasal	3 (7.7)	2 (5.1)	5 (12.8)
Oral	33 (84.6)	32 (82.1)	35 (89.7)
Pre-treatment headache			
Migraine type			
Usually with aura	4 (10.3)	4 (10.3)	2 (5.1)
Without aura	35 (89.7)	35 (89.7)	37 (94.9)
Duration of migraine attack before study medication			
<4 hours	38 (97.4)	38 (97.4)	38 (97.4)
>4 hours	0 (0.0)	1 (2.6)	0 (0.0)
Not recorded	1 (2.6)	0 (0.0)	1 (2.6)
Presence of*			
Nausea	32 (82.1)	35 (89.7)	30 (76.9)
Vomiting	2 (5.1)	2 (5.1)	1 (2.6)
Phonophobia	25 (64.1)	22 (56.4)	23 (59.0)
Photophobia	35 (89.7)	35 (89.7)	28 (71.8)
Headache severity			
Mild	1 (2.6)	4 (10.3)	7 (17.9)
Moderate	35 (89.7)	30 (76.9)	29 (74.4)
Severe	3 (7.7)	5 (12.8)	3 (7.7)
Functional disability score			
No disability	4 (10.3)	3 (7.7)	3 (7.7)
Daily activities mildly impaired	5 (12.8)	4 (10.3)	10 (25.6)
Daily activities moderately impaired	28 (71.8)	29 (74.4)	23 (59.1)
Daily activities severely impaired	2 (5.1)	3 (7.7)	3 (7.7)

\*A subject may have had more than one of the listed symptoms.



**Figure 2.** Disposition of subjects and numbers analysed.

the per-protocol population. Figure 2 presents a flow diagram showing the progress of subjects through the study, including the numbers analysed. All treatment administrations were made in the clinic in the presence of the investigator or designee, and compliance was 100%. An audible rattle (due to the capsule in the device spinning around) was recorded on each administration made, indicating that each device had actuated correctly. There were no device failures, and the majority of patients found the powder device easy and intuitive to use despite only one rehearsal before self-administration during the moderate-to-severe migraine attack. Measurements of residuals showed that a mean  $\pm$  standard deviation (SD) of  $77 \pm 11\%$  was emitted from the device, yielding a mean delivered sumatriptan dose of 7.7 mg and 15.4 mg, respectively, from the 10 mg and 20 mg nominal doses.

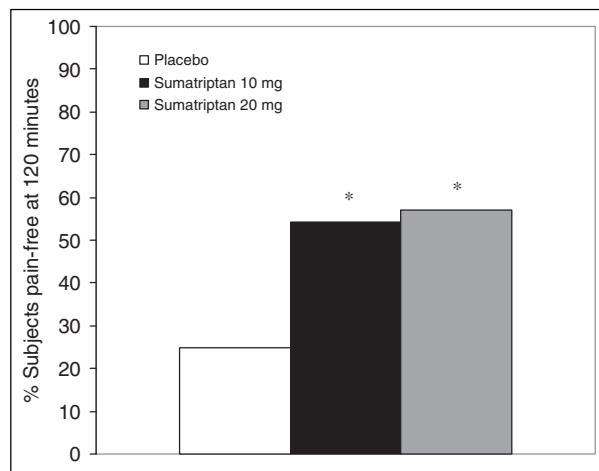
### Efficacy

A significantly greater proportion of subjects in both the 10 mg sumatriptan (54% vs. 25%;  $P < .05$ ) and 20 mg sumatriptan (57% vs. 25%;  $P < .05$ ) groups were

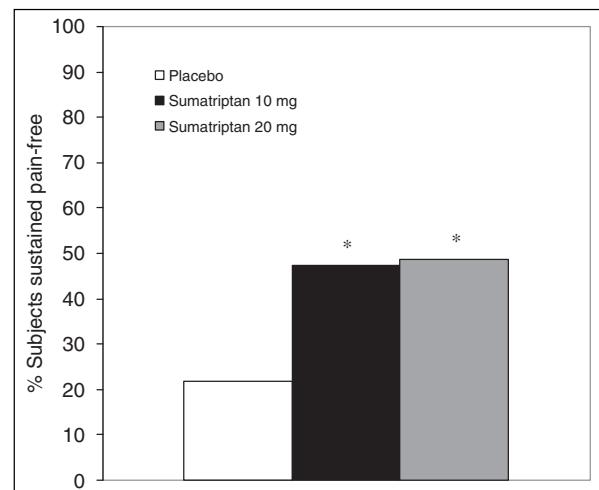
pain-free at 120 minutes compared with placebo (Figure 3). For both the 10 mg and 20 mg sumatriptan doses, the proportion of subjects with relief of headache was significantly greater than placebo at 60 minutes (10 mg 73% vs. 38%,  $P < .01$ ; 20 mg 74% vs. 38%,  $P < .01$ ), 90 minutes (10 mg 78% vs. 41%,  $P < .01$ ; 20 mg 77% vs. 41%,  $P < .01$ ) and 120 minutes (10 mg 84% vs. 44%,  $P < .001$ ; 20 mg 80% vs. 44%,  $P < .01$ ) post-dose (Figure 4).

The median time to meaningful relief was 54 minutes for 10 mg sumatriptan ( $P < .05$ ) and 50 minutes for 20 mg sumatriptan ( $P < .05$ ), with both times significantly faster than the median time of 120 minutes for placebo (data for the survival analysis were censored at 120 minutes and therefore a median time longer than 120 minutes for the placebo group was not possible). A significantly greater proportion of subjects in both the 10 mg sumatriptan (76% vs. 44%;  $P < .05$ ) and 20 mg sumatriptan (71% vs. 44%;  $P < .05$ ) groups had meaningful relief compared with placebo.

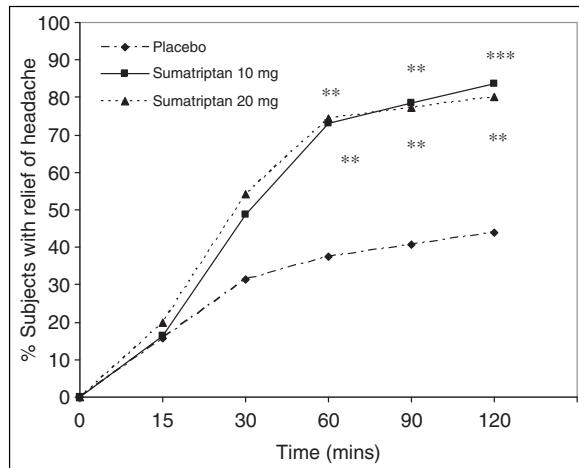
At baseline, the majority of subjects had daily activities moderately or severely impaired (see Table 1). At 90 minutes post-dose, no disability was reported in



**Figure 3.** Proportion of subjects pain-free at 120 minutes after treatment. \* $P < .05$  vs. placebo using Fisher's exact test.



**Figure 5.** Proportion of subjects sustained pain-free up to 48 hours after treatment. Sustained pain-free is defined as pain-free within 120 minutes with no use of rescue medication or relapse within 48 hours. \* $P < .05$  vs. placebo using Fisher's exact test.



**Figure 4.** Proportion of subjects with relief of headache at various time points after treatment. Relief of headache is defined as a decrease in headache intensity from severe (grade 3) or moderate (grade 2) to mild (grade 1) or none (grade 0). \*\* $P < .01$ , \*\*\* $P < .001$  vs. placebo using Fisher's exact test.

60% of subjects in the 10 mg group and 54% in the 20 mg group compared with 31% in the placebo group ( $P < .05$ ). Similar differences were observed at 120 minutes post-dose (10 mg 65% vs. 31%,  $P < .05$ ; 20 mg 63% vs. 31%,  $P < .05$ ). Additionally, at 60 minutes post-dose, 46% of subjects in the 10 mg sumatriptan group had no disability compared with 25% in the placebo group ( $P < .05$ ).

There were marked reductions in the incidence of nausea, photophobia and phonophobia compared to baseline in both the 10 mg and 20 mg sumatriptan groups between 60 and 120 minutes post-dose. For the 10 mg sumatriptan group, the incidence of phonophobia was significantly lower than placebo at 90 minutes (13% vs. 34%;  $P < .05$ ) and the incidence of

photophobia was significantly lower than placebo at both 90 minutes and 120 minutes post-dose (16% vs. 41%;  $P < .05$ ). The reductions in the incidence of phonophobia or photophobia for 20 mg sumatriptan were not, however, significantly lower than placebo at any time point. For nausea, the reductions were not statistically significant compared with placebo for either the 10 mg or the 20 mg dose. The incidence of vomiting was very low in all three treatment groups, and no significant treatment effects were observed.

The proportion of subjects who required rescue medication at 120 minutes post-dose was significantly lower in the 10 mg sumatriptan group compared with placebo (11% vs. 38%;  $P < .05$ ). A smaller, non-significant reduction was observed between the 20 mg sumatriptan group and placebo (26% vs. 38%).

A significantly greater proportion of subjects were SPF from 120 minutes up to 48 hours post-dose (European Medicines Agency "Guideline on the clinical investigation of medicinal products for treatment of migraine") (10) in both the 10 mg (47% vs. 22%;  $P < .05$ ) and 20 mg (49% vs. 22%;  $P < .05$ ) sumatriptan groups compared with placebo (Figure 5).

The SPFNAE calculated from the SFP and AE rates were 39% and 37% for 10 mg and 20 mg sumatriptan, respectively.

## Safety

In total, seven subjects (18%) in the 10 mg sumatriptan group, nine subjects (23%) in the 20 mg sumatriptan group and two subjects (5%) in the placebo group experienced at least one adverse event. The incidence of treatment-related adverse events was higher in both

sumatriptan groups than in the placebo group (six subjects [15%] in both the 10 mg and 20 mg sumatriptan groups vs. one subject [3%] in the placebo group). The most common adverse event following administration of 10 mg or 20 mg sumatriptan was dysgeusia, reported as a bitter or metallic taste, in 10% subjects receiving the 10 mg dose and 13% receiving the 20 mg dose. There were no cases of chest discomfort or pain, paresthesia or asthenia in the active treatment groups. One subject in the placebo group experienced oral paresthesia. No adverse events resulted in the withdrawal of a subject from the study. There were no serious adverse events in the study. There were no clinically significant findings in relation to vital signs, 12-lead ECG or clinical laboratory test results for any of the treatment groups.

## Discussion

Sumatriptan powder in 10 mg and 20 mg doses administered intranasally using the bi-directional delivery device was highly effective in treating a single migraine attack.

### *Pain freedom and pain relief*

The proportions of subjects pain-free were 54% for 10 mg and 57% for 20 mg sumatriptan compared to 26–42% at two hours post-dose for the liquid sumatriptan nasal spray (11) and zolmitriptan nasal spray (35.6%) (12). The mean pain-free rate for 12 studies with the 100 mg oral dose was 28%, which is very similar to the pain-free rate for six oral triptans of 29% (11,13) and the new calcitonin gene-related peptide (CGRP) antagonist (14,15). The proportions of subjects with headache relief at two hours were 84% and 80% for the 10 mg and 20 mg treatments, respectively. Headache relief rates ranging from 50–78% have been reported for the liquid 20 mg sumatriptan nasal spray, oral 100 mg sumatriptan, the sumatriptan-naproxen combination, the new CGRP-antagonist and other oral triptans (11,13,15,16). As described in the statistical analysis, the current study used a per-protocol analysis, excluding major protocol violators (mostly subjects with a mild [grade 1] headache at baseline); caution should therefore be exercised when interpreting the comparative data with earlier studies, which may have handled protocol violators differently.

### *The placebo effect*

The placebo effect in the present study for both pain relief (44%) and pain freedom (25%) is high, reducing the two-hour therapeutic gain (TG) for pain relief to 40% and 36% and to 29% and 32% for pain freedom

for 10 and 20 mg OptiNose powder, respectively. Similar placebo rates of 42–46% at two hours have, however, been reported for pain relief in studies with nasal sprays (placebo = 42%, TG = 32%) (11), the new rapid-dissolving formulation of sumatriptan (placebo = 46%, TG = 26%) (17) and the CGRP antagonist telcegepant (placebo = 46.3%, TG = 21.7%) (14). Despite lower pain-free placebo rates at two hours for the conventional triptan nasal sprays (4,12), the CGRP antagonist (15) and the sumatriptan-naproxen combination (16), ranging from 8–18%, these treatments also have lower pain-free TG rates than the OptiNose powder device. The TG rates for the highest doses of oral triptans were lower or similar to the OptiNose powder device (11,13). Only SC injection of sumatriptan has a higher TG than the OptiNose powder device for pain relief at two hours (placebo = 19%, TG = 50%) (11).

Higher patient expectancy for new formulations or technologies may be one factor explaining the high placebo rates in studies with new formulations such as the rapidly dissolving sumatriptan tablet (17), the new CGRP antagonist (14) and our new sumatriptan powder drug-device combination.

### *Early onset*

Many studies fail to show significant improvement at time points earlier than two hours, and data on one hour are often not reported. In our relatively small phase II study, the one-hour pain relief rates for 10 mg and 20 mg doses of 73% (TG = 36%) and 74% (TG = 37%) are higher than the published data on sumatriptan oral 100 mg tablets, the oral sumatriptan rapidly dissolving tablets and the 20 mg sumatriptan nasal spray with relief rates of 49–52% (TG = 20–22%) (11,16,17). This is achieved with a sumatriptan dose more than 10 times lower than the oral 100 mg tablet and less than one-half of the marketed 20 mg sumatriptan nasal spray. The 6 mg SC injection is the only formulation with similar one-hour pain relief rates of 69–73% (11). SC injection shows better TG at one and two hours, but the  $C_{max}$  is almost 10 times higher than that of 10 mg OptiNose sumatriptan powder (8,11).

### *Sustained pain freedom*

Despite the 48-hour time interval in the current study, the SPF rates for both 10 mg (47%, TG = 26%) and 20 mg (49%, TG = 27%) sumatriptan groups are high. For the 100 mg oral, 20 mg nasal and 6 mg SC sumatriptan, the sumatriptan-naproxen combination and nasal zolmitriptan 5 mg, the absolute SPF rates vary between 23% and 30% and the TG is at 15–20% (10,11,14). The absolute SPF rates of the highest dose marketed oral triptans, vary between 19% and 26% (9).

It is possible that the differences between the present study and earlier studies may be a reflection on how the data were collected. The earlier studies collected data using diary cards, whereas the current study collected SPF data at a visit to the clinic.

### Adverse events

The most common adverse event in the present study was bitter or metallic taste, reported in four subjects (10%) and five subjects (13%) in the 10 mg and 20 mg treatments groups, respectively. Higher rates of bitter or bad taste have been reported following administration of sumatriptan liquid spray by the nasal route, occurring in about 25% of patients receiving the 20 mg dose with a liquid spray (3) and in 17.9% of patients using zolmitriptan nasal spray (12). When patients are asked specifically about taste, the incidence of bitter taste with the 20 mg liquid nasal spray may be as high as 68% (12,18). A traditional spray delivers most of the dose of the drug to the anterior, non-ciliated segment and subjects commonly sniff to avoid drip-out, causing the concentrated drug to be sucked posterior along the nasal floor to reach taste buds at the base of the tongue, recording bitter taste. A broader mucosal distribution and different clearance pattern will dilute the drug and minimise the amount reaching the “bitter” taste buds at the base of the tongue (6).

### Sustained pain-free plus no adverse events

Calculation of SPFNAE from a single, relatively small study must of course be interpreted with great caution. Nevertheless, it is noteworthy that the SPFNAE rates in the present study of 39% and 37% for 10 mg and 20 mg nasal, respectively, of OptiNose sumatriptan are three times higher than the median value reported in a large meta-analysis which included the six major marketed oral triptans (median 12%, range 7–22%) (9).

### Mechanisms of action

It has been suggested that it is the rate of absorption, not the extent, which explains the onset of action of triptans (19). The superior efficacy of subcutaneous versus oral administration of sumatriptan and naratriptan was also considered most likely due to a quicker rise in blood concentrations following subcutaneous administration (20). Delivery of sumatriptan powder by the OptiNose device provides more rapid and extensive direct absorption across the nasal mucosa to the blood, resulting in a much earlier median  $t_{max}$  at 20 minutes compared to a median  $t_{max}$  of 1.5 hours for the marketed nasal sumatriptan spray (8,21). The fraction absorbed from the nose following delivery with the

doses and device used in this study is estimated to be 30% compared to 10% for the marketed sumatriptan spray, resulting in a more pronounced, two-tiered absorption pattern with initial rapid nasal absorption and a slower delayed gastrointestinal absorption (3,4,8,21). The comparable efficacy of the 10 mg and 20 mg doses in our study with the same  $t_{max}$  but different  $c_{max}$  (8) also supports the hypothesis that rate of absorption is more important than extent of absorption, but these observations may simply reflect a dose response ceiling for delivery of nasal sumatriptan powder by the bi-directional delivery device.

The broader distribution of the sumatriptan powder formulation following bi-directional delivery to the nasal mucosa may not only increase systemic absorption compared with conventional liquid sprays, but potentially could also result in enhanced direct or reflex-mediated actions of nasally delivered sumatriptan on the trigeminal nerve, the ganglion and associated cerebral structures involved in the pathogenesis of migraine (5,6,8). This provides an alternative explanation for high efficacy despite low systemic exposure and the similar efficacy of the 10 mg dose delivered to the side of the migraine as 20 mg divided between the two nostrils. However, the present study design does not allow for any conclusions, and a more comprehensive discussion of the potential role of N2B transport mechanism or direct actions on or via the trigeminal nerve and ganglion is outside the scope of this paper.

Convenience mostly drives the preference of patients for tablets, whereas the speed of onset and the efficacy are the key drivers for preference for the nasal spray. Among patients having tried two oral (regular tablet and fast-dissolving tablet) and the nasal zolmitriptan formulation, as many as 40% preferred the nasal zolmitriptan spray (22). Thus, it is likely that the faster onset of action, higher rate of sustained pain freedom and lower rate of adverse events with low rate of bitter taste will make users more attracted to the new sumatriptan powder device combination.

### Conclusions

Sumatriptan at doses of 10 mg or 20 mg administered using the new bi-directional powder delivery device was effective, safe and well tolerated in treating a single migraine attack. The performance of the new device was good and there were no device failures.

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