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Research Submissions

Efficacy, Tolerability, and Safety of DFN-15 (Celecoxib Oral Solution, 25 mg/mL) in the Acute Treatment of Episodic Migraine: A Randomized, Double-Blind, Placebo-Controlled Study

Richard B. Lipton, MD; Sagar Munjal, MD; Elimor Brand-Schieber, PhD; Stewart J. Tepper, MD; David W. Dodick, MD

Objective.—The objective of this study was to evaluate the efficacy, tolerability, and safety of 120 mg DFN-15 vs placebo for the acute treatment of migraine.

Background.—Certain nonsteroidal anti-inflammatory drugs (NSAIDs) are guideline-recommended therapies for the acute treatment of migraine, but patients who use them may have issues with gastrointestinal tolerability. Celecoxib, a selective inhibitor of cyclooxygenase-2, produces analgesia similar to nonselective NSAIDs. DFN-15 is an oral, ready-made liquid solution of celecoxib being investigated for the acute treatment of migraine.

Methods.—A randomized, double-blind, placebo-controlled, efficacy, tolerability, and safety study in adults with migraine was conducted. Subjects treated a single migraine attack with 120 mg DFN-15 or placebo as soon as possible after the onset of pain of moderate to severe intensity. The 2 independent coprimary efficacy endpoints were the proportion of subjects with freedom from pain and the absence of the most bothersome symptom (MBS) at 2 hours postdose. A second double-blind treatment period followed the first, but did not contribute to the primary outcomes and will be reported elsewhere.

Results.—There were 622 subjects randomized (1:1) to double-blind treatment with either 120 mg DFN-15 or placebo, and 567 (91.2%) treated a migraine with study drug (n = 285 DFN-15; n = 282 placebo). Groups were balanced in demographic characteristics; the mean age was 40, and most subjects were female (87% [494/567]). At 2 hours postdose, DFN-15 was significantly superior to placebo for pain freedom (35.6% [98/275] vs 21.7% [57/263], $P < .001$), with an odds ratio (95% CI) of 2.00 (1.36, 2.94) and for freedom from the MBS (57.8% [134/232] vs 44.8% [104/232], $P = .007$), with an odds ratio (95% CI) of 1.68 (1.17, 2.43). A total of 13.3% (38/285) of DFN-15-treated subjects and 8.9% (25/282) of placebo-treated subjects reported a treatment-emergent adverse event (TEAE). Study drug-related TEAEs were reported by 9.1% (26/285) of DFN-15 subjects and 6.0% (17/282) of placebo subjects, the most common of which were dysgeusia (4.2% [12/285] vs 1.4% [4/282]) and nausea (3.2% [9/285] vs 1.8% [5/282]). No subjects treated with DFN-15 reported TEAEs that were severe or led to withdrawal, and no serious TEAEs or deaths were reported in the study.

Conclusions.—DFN-15 was significantly more effective than placebo for the acute treatment of migraine, with a generally favorable tolerability and safety profile.

Key words: migraine, acute treatment, nonsteroidal anti-inflammatory drug, oral, celecoxib

From the Albert Einstein College of Medicine, Bronx, NY, USA (R.B. Lipton); Dr. Reddy's Laboratories, Princeton, NJ, USA (S. Munjal and E. Brand-Schieber); Geisel School of Medicine at Dartmouth, Hanover, NH, USA (S.J. Tepper); Mayo Clinic, Scottsdale, AZ, USA (D.W. Dodick).

Address all correspondence to R.B. Lipton, Albert Einstein College of Medicine, Bronx, NY, USA, email: Richard.Lipton@einstein.yu.edu

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Abbreviations: AE adverse event, CI confidence interval, COX cyclooxygenase, GI gastrointestinal, ICHD International Classification of Headache Disorders, LOCF last observation carried forward, MBS most bothersome symptom, NSAID nonsteroidal anti-inflammatory drug, PPMQ-R Patient Perception of Migraine Questionnaire-Revised, TEAE treatment-emergent adverse event

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INTRODUCTION

Inflammatory mediators have been implicated in the pathophysiology of migraine.[1-10] Certain nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, diclofenac, ibuprofen, and naproxen, which inhibit the synthesis of prostaglandins by blocking the effects of cyclo-oxygenase (COX)-1 and COX-2 on arachidonic acid,[11] are established as effective for the acute treatment of migraine and are recommended by evidence-based guidelines.[12,13] However, the use of NSAIDs has been associated with an increased risk of adverse gastrointestinal (GI) events that are sometimes serious.[14-16]

Celecoxib, a selective COX-2 inhibitor that produces analgesia similar to other NSAIDs, has shown a significantly lower risk of GI events than naproxen (P = .01) or ibuprofen (P = .002) and a significantly lower risk of renal events than ibuprofen (P = .004) in a large study (N = 24,081) comparing them for long-term use for osteoarthritis and rheumatoid arthritis.[17,18] Celecoxib is indicated for the treatment of acute pain in patients with ankylosing spondylitis, osteoarthritis, primary dysmenorrhea, and rheumatoid arthritis. The oral capsule form of celecoxib (Celebrex®; Pfizer Inc., New York, NY, USA) has previously been assessed as an acute treatment for migraine. In an open-label study comparing 400 mg celecoxib oral capsules with naproxen sodium 550 mg (Synflex®; F. Hoffmann-La Roche Ltd), celecoxib and naproxen sodium

Conflict of Interest: Richard B. Lipton serves on the editorial board of Neurology and Cephalalgia and as senior advisor to Headache but is not paid for his roles on Neurology or Headache. He has received research support from the NIH. He also received support from the Migraine Research Foundation and the National Headache Foundation. He received research grants from Allergan, Amgen, Dr. Reddy's Laboratories, and Novartis. He has reviewed for the NIA and NINDS and serves as consultant, advisory board member, or has received honoraria from Alder, Allergan, Amgen, Autonomic Technologies, Avanir, Biohaven, Boston Scientific, CoLucid, Dr. Reddy's Laboratories, electroCore, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Merck, Novartis, Teva, and Vedanta. He received royalties from Wolff's Headache (8th Edition, Oxford Press University, 2009) and Informa. He holds stock options in eNeura Therapeutics and Biohaven Pharmaceuticals.

Sagar Munjal and Elimor Brand-Schieber are employed by and own stock in Dr. Reddy's Laboratories.

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significantly improved migraine headache pain with no efficacy difference between them, although naproxen sodium caused significantly more gastric pain than celecoxib ($P = .029$).[19] While preliminary results suggest comparable efficacy but better tolerability than widely used and guideline-recommended NSAIDS, celecoxib is not currently approved for migraine.

DFN-15 is an oral liquid solution of celecoxib being developed for the acute treatment of migraine in adults. In comparison with the oral capsule formulation of celecoxib under fasting conditions, 120 mg DFN-15 (50 mg/mL) demonstrated a faster median time to peak concentration (within 1 hour vs 2.5 hours).[20] The faster time to maximum plasma concentration could translate into more rapid onset of pain relief, which is a treatment priority for people with migraine.[20,21] In addition, DFN-15 120 mg had a relative bioavailability of 144% (ie, 44% greater) compared with a 400 mg dose of celecoxib oral capsules.[20] Higher bioavailability could result in lower dose requirements and, in turn, greater GI safety and tolerability.

A proof-of-concept study[22] demonstrated the numerical superiority of DFN-15 over placebo for acute treatment; because no difference in efficacy was observed between DFN-15 120 and 240 mg, the 120 mg dose was selected for further development. We hypothesized that a 120 mg dose of DFN-15 would be more effective than placebo for the acute treatment of migraine. The objectives of this single attack, acute treatment trial were to compare the efficacy, tolerability, and safety of 120 mg DFN-15 with placebo for the acute treatment of migraine.

METHODS

Ethics.—This study was conducted according to the Guidelines of the World Medical Association Declaration of Helsinki in its revised edition (WMA Brazil, 2013), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and the U.S. Food and Drug Administration's Code of Federal Regulations, as well as the demands of national drug and data protection laws and other applicable regulatory requirements. The protocol (available by reasonable request), the subject information and informed consent forms, and other relevant study documentation were reviewed and approved by an Institutional Review Board at each study center before initiation of the study. Investigators ensured that subjects were informed about the nature and purpose of the study, the conditions of participation/termination, and the risks and benefits of treatment, and subjects provided written informed consent to participate before undergoing any study-related examination or activity.

Study Conduct.—This randomized, double-blind, placebo-controlled study (ClinicalTrials.gov Identifier: NCT03006276) was conducted at multiple US study centers. Male and female subjects aged 18 to 75 years (inclusive) with at least a 12-month prescreening medical history of episodic migraine with or without aura as defined by International Classification of Headache Disorders, third edition (beta version) (ICHD-3 beta)[23], no signs of medication overuse, 2 to 8 migraine attacks (with or without aura) per month, 14 or fewer headache days per month, and 48 hours of headache-free time between migraine attacks who met all inclusion criteria and successfully completed all screening procedures were randomized in a 1:1 ratio by an interactive web response system to DFN-15 or matching placebo to treat a migraine attack with moderate to severe headache (Figure 1).

A single migraine attack was treated with study drug as soon as possible (and no more than 1 hour after) experiencing pain of moderate to severe intensity. Subjects then returned to the study site within 2 to 7 days of the first treatment. Although subjects were re-randomized to treat a second attack, the primary efficacy endpoints are based on the first double-blind treatment period, which is the focus of this report.

Study drugs were only used to treat new migraine attacks, not recurrences, and only after at least 48 hours of pain and symptom freedom from a previous attack had elapsed. After randomization, the total duration of each subject's participation in the study was up to 10 weeks.

Data regarding the study drug effect and the associated impact on migraine pain, symptoms, functional disability, and subjects' satisfaction with treatment were entered by the subjects in real-time in an electronic diary. After study completion or discontinuation,

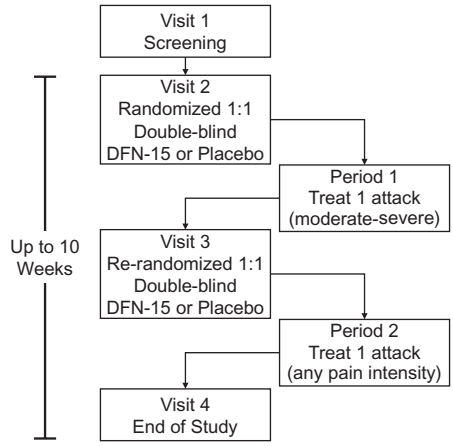

Fig. 1.—Study schema. Data are presented for Period 1 only.

subjects were referred to their usual healthcare professional to resume their prestudy standard of care.

Subjects.—To be eligible for participation, subjects had to be able to read, speak, and understand English proficiently; provide written informed consent; and be male or female, 18 to 75 years of age, inclusive, at screening. Females had to have a negative serum pregnancy test at screening, not plan to become pregnant during the study, and not be lactating, and they had to have a negative urine pregnancy test at all subsequent study visits after the screening visit and, unless surgically or otherwise sterile or postmenopausal for more than 1 year, agree to practice a reliable form of contraception or abstinence during the study (eg, implants, injectables, combined oral contraceptives, an intrauterine device, a bilateral tubal ligation, a vasectomized partner, an exclusively female partner, and double-barrier methods); males had to agree to practice a reliable form of contraception or abstinence. Subjects also had to have at least a 12-month history of episodic migraine characterized by 2 to 8 attacks per month, with no more than 14 monthly headache days and at least 48 hours of headache-free time between attacks, an age of onset before age 50 years, and a usual untreated migraine pain intensity of moderate or severe (ie, 2 or 3 on a scale of 0 to 3). For the duration of the study, subjects had to be able to evaluate and record pain, migraine symptoms, and study drug effectiveness information, as well as each instance of the use of study drug and rescue medication, in real-time using an electronic diary and comply with all other study procedures and scheduling requirements.

Subjects were excluded if they had prior exposure to DFN-15; had taken opioids, opioid-barbiturate fixed combinations, triptans, or ergot alkaloids on at least 10 days or NSAIDs or other simple medications on more than 14 days per month during the 90 days before screening; had been treated with onabotulinumtoxinA for migraine within 4 months before screening; were on unstable dosages of migraine preventive medications within 30 days before and through screening; had taken mini-prophylaxis for menstrual migraine; or were on chronic warfarin sodium or equivalent. Subjects were also excluded if they had a history of any condition that might interfere in any way with the study conduct, outcomes, or interpretation of results.

Treatments.—Each subject was given a single-dose bottle of DFN-15 120 mg or matching placebo containing 4.8 mL liquid. They were instructed to drink the entire contents of the bottle to ensure complete consumption of study medication. In order to blind the study treatment, study drug kits with identical labeling appearance were assigned unique kit numbers by an interactive web response system. To ensure that site staff and investigators were blinded, the kits were assembled centrally (The Coghlan Group, Bastrop, TX, USA) and distributed to the sites before the start of dosing.

Subjects who did not experience sufficient or any pain relief from the study drug were permitted to take rescue medication, if needed, at least 2 hours after taking the study drug and only after completing the 2-hour postdose assessments in the electronic diary. Specific rescue medications were chosen by investigators and subjects and could be adjusted as needed.

To comply with guidelines for clinical trials of migraine medications,[24] as well as to allow comparison of results with those of earlier research, subjects were instructed to treat a single migraine attack as soon as (and no later than 1 hour after) their pain reached at least moderate intensity (2 or 3 on a 0 to 3 scale) in the first double-blind period. At the time of the treated attack, subjects were prompted by the eDiary to confirm that they were reporting a migraine attack prior to entering predose data.

Assessments.—*Primary Efficacy Endpoints*.—Two independent coprimary efficacy endpoints were used to compare DFN-15 with placebo. One coprimary endpoint was the proportion of subjects with pain freedom at 2 hours postdose. The other coprimary endpoint was the proportion of subjects free of their MBS 2 hours postdose. Pain freedom was defined as a reduction from predose moderate (Grade 2) or severe (Grade 3) pain to none (Grade 0). The MBS was selected from the choices of nausea, photophobia, and phonophobia at the time of the screening migraine history. Subjects were asked if they experienced nausea, photophobia, or phonophobia with their headaches. If only 1 of the 3 symptoms was reported at screening that symptom was designated as the MBS. If more than 1 symptom was present, subjects identified the symptom they considered most bothersome. For the coprimary MBS analysis, the symptom(s) collected predose had to include the symptom identified as MBS at screening.

Secondary Efficacy Endpoints.—Secondary efficacy endpoints included the proportion of subjects who were free from nausea, photophobia, and phonophobia at 15, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 hours postdose; the proportion of subjects with pain relief at 2 hours postdose; the proportion of subjects who were pain free at 15, 30, and 45 minutes and 1, 1.5, 4, and 24 hours postdose; the proportion of subjects free from their screening MBS at 15, 30, and 45 minutes and 1, 1.5, 4, and 24 hours postdose; change in functional disability score at 2, 4, and 24 hours postdose; and treatment satisfaction at 2 and 4 hours postdose; treatment satisfaction at 24 hours postdose as measured by the Patient Perception of Migraine Questionnaire-Revised (PPMQ-R); sustained pain freedom at 2 to 24 hours postdose; and sustained pain relief at 2 to 24 hours postdose.

Freedom from nausea, photophobia, and phonophobia was defined as having these symptoms predose and being free from them at the prespecified postdose time points. Pain relief was defined as a reduction from predose pain of moderate or severe intensity to postdose pain of mild or no intensity. Functional disability was measured on a 4-point scale on which 0 = no disability and 3 = performance of daily activities severely impaired, cannot do all or most things, bed rest may be necessary. Treatment satisfaction at 2 and 4 hours postdose was measured on a 7-point scale where 1 = very satisfied and 7 = very dissatisfied (ie, a lower score means greater satisfaction).

The PPMQ-R was used at baseline (prerandomization) to assess subjects' satisfaction with their usual prestudy migraine treatment, and was also used to assess study treatment satisfaction at 24 hours postdose. Items that evaluated treatment satisfaction were scored on a 7-point Likert-type scale from 1 (very satisfied) to 7 (very dissatisfied); items that evaluated tolerability of side effects (ie, how bothersome were the side effects) were scored on a 5-point Likert-type scale from 1 (not at all) to 5 (extremely). Subscale scores and total scores (except the total raw score) were transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale, and multiplying by 100. The 3 individual global items were not transformed. The total score comprised the composite of efficacy, function, and ease of use subscale scores. For the transformed results, a higher score meant greater satisfaction. For nontransformed PPMQ-R results, a lower score meant greater satisfaction. If a response was missing, the particular subscale or global item was considered nonevaluable. If a subscale or global item was deemed nonevaluable or missing, the corresponding total score was also considered nonevaluable and assigned as missing.

Sustained pain freedom from 2 to 24 hours postdose was defined as pain free at 2 hours postdose, with no use of rescue medication and no recurrence of headache pain within 2 to 24 hours postdose. Sustained pain relief from 2 to 24 hours postdose was defined as pain relief at 2 hours postdose, with no use of rescue medication and no worsening of headache pain within 2 to 24 hours postdose.

Safety Endpoints.—Safety endpoints included tolerability as assessed by adverse events (AEs) and safety as assessed by clinical laboratory tests, vital signs, physical examinations, and electrocardiograms. Safety assessments included AEs (from signing of informed consent until completion or discontinuation); concomitant medication review; physical examinations and suicidality check; pregnancy tests in female subjects of childbearing potential; measurement of vital signs (sitting systolic and diastolic blood pressure, pulse rate, and body temperature); clinical laboratory examination

(hematology, chemistry, and urinalysis); and 12-lead electrocardiogram. All AEs were coded using the Medical Dictionary for Regulatory Activities, version 19.0.

Statistical Methods.—Unless specified otherwise, statistical testing and confidence intervals (CIs) were 2-sided and performed using a significance (alpha) level of .05. All statistical analyses were conducted with the SAS® software package (version 9.3).

Efficacy Analyses.—*Coprimary Efficacy* Endpoints.—The pain freedom rate at 2 hours postdose was calculated as the number of subjects who were pain free at 2 hours postdose divided by the number of subjects with nonmissing assessments at 2 hours postdose. Missing primary efficacy endpoint data were imputed using last observation carried forward (LOCF). For the analysis of freedom from the MBS at 2 hours postdose, the subject's symptom that was identified as the MBS at screening had to be present as a symptom also at predose. Subjects who took rescue medication prior to the data collection of the 2-hour postdose time point (inclusive; LOCF) were excluded, as were those who had mild or no predose pain.

A closed sequential testing procedure was employed to test for statistical significance of the coprimary efficacy endpoints. Specifically, if the first coprimary endpoint (pain freedom) was statistically significant at a 5% (2-sided) level of significance, the second coprimary endpoint (freedom from the MBS) was tested at a 5% (2-sided) level of significance. If results on the first coprimary endpoint were nonsignificant versus placebo, the second endpoint was not tested. The study had to show a significant statistical benefit at a 5% (2-sided) level of significance on both coprimary endpoints to be considered statistically successful.

For the comparisons between treatment groups for the proportion of subjects with pain freedom; freedom from nausea, photophobia, and phonophobia; pain relief; and freedom from the screening MBS; *P* values were computed from Fisher's exact test.

For the comparison between treatment groups for changes in functional disability score, *P* values were computed from the Wilcoxon rank-sum test. *P* values were computed from the Wilcoxon signed-rank test for the change from baseline within each treatment group. The following levels of change from baseline in functional disability score were compared between DFN-15 and placebo: 3-, 2-, and 1-point increase; 0-point change; and 1-, 2-, and 3-point decrease.

The subject-rated treatment satisfaction score at 2 and 4 hours postdose and the baseline PPMQ-R response for the same question were compared for the DFN-15 group only; *P* values for this comparison were computed from the Wilcoxon rank-sum test.

The difference between the subject-rated treatment satisfaction score at 2 and 4 hours postdose and the baseline PPMQ-R response for the same question was summarized by treatment group. *P* values from the Wilcoxon rank-sum test were computed for the comparison between overall treatment satisfaction score at 2 and 4 hours postdose and baseline PPMQ-R response for the DFN-15 group only. *P* values from the Wilcoxon signed-rank test were computed for the difference between baseline and postbaseline PPMQ-R for the DFN-15 group only.

For the comparison between treatment groups for subject-rated treatment satisfaction at 24 hours postdose (PPMQ-R), *P* values were computed from the Wilcoxon rank-sum test. The change from baseline to 24 hours for each subscale score, each global item score, the total score, and the total raw score were also analyzed using the Wilcoxon signedrank test. Baseline and 24-hour postdose total scores and total raw scores were compared for the DFN-15 group only, and *P* values from the Wilcoxon rank-sum test were computed for those 2 comparisons.

No hierarchy was assigned to secondary endpoints, and there were no adjustments for multiple comparisons.

Sample Size.—A sample size of approximately 600 subjects was planned. It was based on the assumption that, with a study population of 600 subjects, 17.6% of placebo-treated and 29.2% of DFN-15-treated subjects would be pain free at 2 hours postdose, providing 88% power to detect the assumed difference at a 5% (2-sided) level of significance and with a 15% dropout rate.

RESULTS

Subjects.—The first subject was enrolled on December 13, 2016, and the last subject completed the study on October 6, 2017. The disposition of subjects is presented in Table 1.

Demographics were similar in the DFN-15 and placebo treatment groups (Table 2). Of the 567

Table 1.—Disposition of Subjects

	Placebo n (%)	DFN-15 n (%)	Overall n (%)
Randomized	311	311	622
Analyzed for safety†	282 (90.7)	285 (91.6)	567 (91.2)
Analyzed for efficacy‡	280 (90.0)	283 (91.0)	563 (90.5)
Completed	266 (85.5)	265 (85.2)	531 (85.4)
Discontinued	43 (13.8)	42 (13.5)	85 (13.7)
Primary reason for discontinuation			
No migraine attack	11 (3.5)	7 (2.3)	18 (2.9)
Withdrawal by subject	7 (2.4)	9 (2.9)	16 (2.7)
Lost to follow-up	5 (1.6)	8 (2.6)	13 (2.1)
Other	4 (1.2)	6 (1.9)	10 (1.8)
Protocol deviation	4 (1.3)	4 (1.3)	8 (1.3)
Use of nonpermitted medication	1 (0.3)	4 (1.3)	5 (0.8)
Noncompliance with study drug	2 (0.6)	2 (0.6)	4 (0.6)
Adverse event	3 (1.0)	0 (0)	3 (0.5)
Study terminated by sponsor	3 (1.0)	0	3 (0.5)
Physician decision	0	2 (0.6)	2 (0.3)
Pregnancy	2 (0.6)	0	2 (0.3)
Investigator request	1 (0.3)	0	1 (0.2)

†Subjects who took a dose study drug in the first treatment period and recorded it in their electronic diary.
‡Randomized subjects who took a dose of study drug and had at least 1 postbaseline efficacy time point assessment for either pain or the most bothersome symptom (among nausea, photophobia, phonophobia) in the first treatment period.

subjects, most were female, non-Hispanic, and comparable in mean age, weight, and body mass index. Approximately three quarters of subjects had never smoked. The most common MBS at screening was photophobia, with rates slightly higher among those treated with placebo than with DFN-15 (59.9% [161/269] vs 49.1% [136/277]); nausea and phonophobia were about half as common and slightly less prevalent among subjects treated with placebo than with DFN-15. Approximately three quarters of the population had pain of moderate intensity at predose (73.1% [198/271] vs 68.1% [190/279] for placebo and DFN-15, respectively).

Efficacy.—*Coprimary Efficacy Endpoints*.—At 2 hours postdose (Fig. 2), DFN-15 was significantly superior to placebo for pain freedom (35.6% [98/275] vs 21.7% [57/263], $P < .001$) using LOCF. Results were also significant in favor of DFN-15 over placebo in the observed case analysis of 2-hour pain freedom (35.8% [97/271] vs 22.1% [57/258]), $P < .001$). The odds ratios for pain freedom at 2 hours postdose (95% CI) were 2.00 (1.36, 2.94) for the LOCF analysis and 1.97 (1.34, 2.89) for the observed case analysis.

For freedom from the MBS (Fig. 2), DFN-15 was significantly better than placebo at 2 hours postdose (57.8% [134/232] vs 44.8% [104/232], $P = .007$) using LOCF. The difference favoring DFN-15 over placebo at 2 hours postdose was also significant in the observed case analysis (58.3% [133/228] vs 45.4% [103/227], $P = .007$). The odds ratios for MBS freedom at 2 hours postdose (95% CI) were 1.68 (1.17, 2.43) for the LOCF analysis and 1.69 (1.16, 2.44) for the observed case analysis.

To further assess the results of the primary analyses conducted using the LOCF and observed cases methodologies, a post hoc sensitivity analysis, where subjects who did not have evaluable data at 2 hours postdose were considered nonresponders, was conducted. As in the primary analysis, the sensitivity analysis showed that DFN-15 was significantly more effective than placebo on the coprimary endpoints of 2-hour freedom from pain (34.3% [97/283] vs 20.4% [57/280], $P < .001$) and the MBS (47.0% [133/283] vs 36.8% [103/280], $P = .017$), indicating robustness of study results.

Secondary Efficacy Endpoints.—The proportion of subjects with pain relief in the DFN-15 was significant-

Table 2.—Demographics and Baseline Characteristics

	Placebo N = 282	DFN-15 N = 285
Age, mean (SD), y	40 (12)	41 (11)
Sex, n (%)		
Female	242 (85.8)	252 (88.4)
Male	40 (14.2)	33 (11.6)
Ethnicity, n (%)		
Not Hispanic/Not Latino	243 (86.2)	242 (84.9)
Hispanic or Latino	38 (13.5)	40 (14.0)
Not reported	1 (.4)	3 (1.1)
Race, n (%)		
White	219 (77.7)	198 (69.5)
Black or African American	50 (17.7)	75 (26.3)
Asian	6 (2.1)	5 (1.8)
Native Hawaiian or Other Pacific Islander	0	2 (.7)
American Indian or Alaska Native	0	1 (.4)
Other	7 (2.5)	4 (1.4)
Height, mean (SD), cm	166.2 (8.6)	165.9 (8.5)
Weight, mean (SD), kg	83.0 (22.5)	84.1 (22.6)
BMI, mean (SD), kg/m^2	30.0 (7.9)	30.6 (7.8)
Smoker or nicotine product user, n (%)		
Never	216 (76.6)	216 (75.8)
Former	40 (14.2)	35 (12.3)
Current	26 (9.2)	34 (11.9)
Years of use,† mean (SD)	14 (11)	18 (10)
Cigarettes/nicotine products smoked,† mean (SD), n	7.5 (5.3)	7.3 (5.6)
Screening MBS‡		
Nausea	66 (24.5)	82 (29.6)
Photophobia	161 (59.9)	136 (49.1)
Phonophobia	42 (15.6)	59 (21.3)
Predose pain intensity§		
Mild	3 (1.1)	1 (0.4)
Moderate	198 (73.1)	190 (68.1)
Severe	70 (25.8)	88 (31.5)

†Among former and current smokers.
‡DFN-15 n = 277; placebo n = 269.
§DFN-15 n = 279; placebo n = 271.
BMI = body mass index; MBS = most bothersome symptom; SD = standard deviation.

ly superior to placebo at 1 hour (56.8% [155/273] vs 45.1% [116/257], $P = .009$); 1.5 hours (70.0% [191/273] vs 55.2% [143/259], $P < .001$); and 2 hours postdose (74.5% [205/275] vs 60.5% [159/263], $P < .001$). Results at 2 hours after treatment are shown in Table 3.

Mean overall satisfaction scores for subjects in the DFN-15 and placebo groups were significantly different at 2 hours (3.3 vs 3.9, $P < .001$, Table 3) and 4 hours postdose (3.2 vs 3.7, $P = .002$). For the PPMQ-R administered at 24 hours postdose, the comparison between treatment groups at 24 hours postdose showed that DFN-15-treated subjects had significantly greater treatment satisfaction than placebo subjects for total score ($P = .011$), total raw score ($P = .008$), the subscales for efficacy ($P = .008$) and function ($P = .009$), and the global items for medication effectiveness ($P = .003$) and overall satisfaction ($P = .004$). No statistically significant differences were found for the subscales ease of use ($P = .585$), tolerability ($P = .343$), and the global item of side effects ($P = .972$). For the comparison between 24 hours postdose and baseline PPMQ-R, subjects had significantly greater satisfaction with DFN-15 than with their usual migraine medication in total score ($P = .031$), the subscales for function ($P = .002$), ease

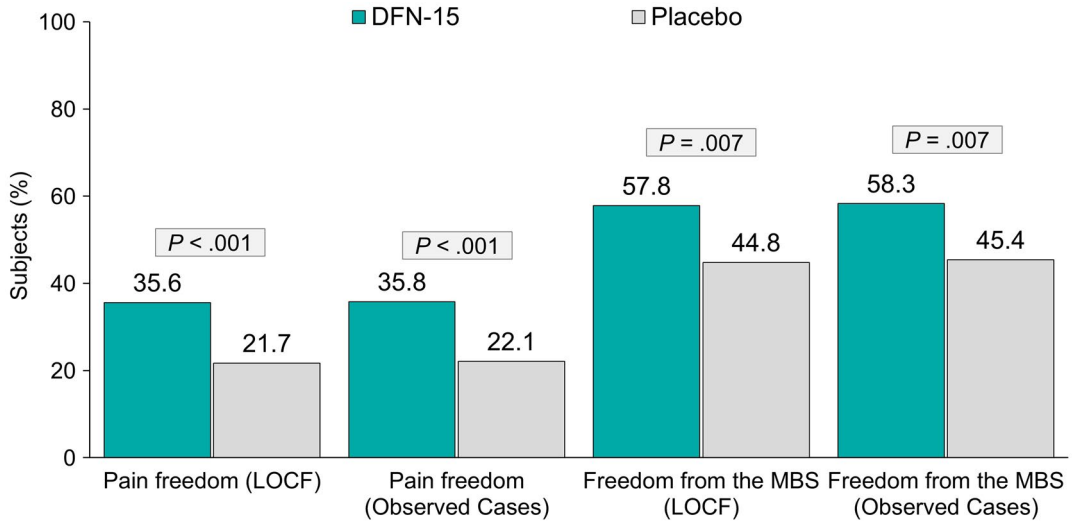

Fig. 2.—DFN-15 efficacy vs placebo at 2 hours postdose: pain freedom and freedom from the MBS. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3.—DFN-15 Efficacy vs Placebo: Secondary Efficacy Endpoints

Parameter	Placebo N = 280	DFN-15 N = 283	*P* Value
Nausea freedom, 2 hours, n_1/n_2† (%)	92/148 (62.2)	100/148 (67.6)	.394
Photophobia freedom, 2 hours, n_1/n_2† (%)	106/239 (44.4)	137/235 (58.3)	.002
Phonophobia freedom, 2 hours, n_1/n_2† (%)	109/200 (54.5)	118/193 (61.1)	.186
Pain relief, 2 hours, n_1/n_2† (%)	159/263 (60.5)	205/275 (74.5)	<.001
Pain freedom, 1 hour, n_1/n_2† (%)	33/257 (12.8)	49/273 (17.9)	.118
Use of rescue medication, 2-24 hours, n_1/n_2† (%)	81/269 (30.1)	44/278 (15.8)	<.001
Change in functional disability, 2 hours, mean, 0-3 scale	−.7	−.9	.004
Treatment satisfaction question, 2 hours, 1-7 scale‡	3.9	3.3	<.001
Treatment satisfaction (PPMQ-R Total Score), 24 hours, 0-100 scale§	59.7	65.8	.011
Sustained (2-24 hours) pain freedom,¶ n_1/n_2†††‡‡ (%)	36/212 (17.0)	55/205 (26.8)	.018
Sustained (2-24 hours) pain relief,¶ n_1/n_2†† (%)	92/212 (43.4)	113/205 (55.1)	.019

†n_1 = number of responders; n_2 =number of assessments.
‡Lower scores indicate greater satisfaction.
§Based on a composite transformed scale (0-100) where a higher score means greater satisfaction.
¶Endpoints were prespecified but reanalyzed post hoc due to an error in statistical methodology.
††n_1 = number of subjects with pain freedom at 2 hours postdose (LOCF), no use of rescue medication between 2 hours and 24 hours postdose, and no recurrence of headache pain within 2 to 24 hours postdose; n_2 = number of subjects with nonmissing pain assessment at 2 hours (LOCF), 4 hours (Observed), and 24 hours (Observed) postdose.
‡‡n_1 = number of subjects with pain relief at 2 hours postdose (LOCF), no use of rescue medication between 2 hours and 24 hours postdose, and no worsening of headache pain within 2 to 24 hours postdose; n_2 = number of subjects with nonmissing pain assessment at 2 hours (LOCF), 4 hours (Observed), and 24 hours (Observed) postdose.
MBS = most bothersome symptom.

of use ($P = .036$), and tolerability ($P < .001$), and the global item for side effects ($P < .001$).

The mean changes from baseline in respective functional disability scores for DFN-15 and placebo were −.9 and −.7 at 2 hours (Table 3), −1.3 and −1.1 at 4 hours, and −1.7 and −1.8 at 24 hours postdose, and the comparison between treatment groups at 2 hours postdose was significant for DFN-15 over placebo ($P = .004$).

For sustained pain freedom from 2 to 24 hours, DFN-15 was significantly superior to placebo (26.8%

Table 4.—Summary of Adverse Events Occurring in ≥2% of Subjects Who Treated a Migraine Attack with DFN-15 or Placebo

Event	Placebo N = 282 n (%)	DFN-15 N = 285 n (%)
Dysgeusia	4 (1.4)	12 (4.2)
Nausea	5 (1.8)	9 (3.2)

[55/205] vs 17.0% [36/212], $P = .018$). DFN-15 was also significantly superior to placebo for sustained pain relief (55.1% [113/205] vs 43.4% [92/212], $P = .019$). Note that sustained endpoints were prespecified but had to be reanalyzed post hoc due to an error in statistical methodology.

All other secondary efficacy endpoints are reported in Table 3.

Tolerability and Safety.—In total, 63 subjects reported 76 TEAEs: 38 subjects/44 TEAEs in the DFN-15 group and 25 subjects/32 TEAEs in the placebo group. TEAEs were reported by 13.3% (38/285) of DFN-15 subjects and 8.9% (25/282) of placebo subjects, and study drug-related TEAEs were reported by 9.1% (26/285) of DFN-15 subjects and 6.0% (17/282) of placebo subjects. As shown in Table 4, the most common TEAEs were dysgeusia (4.2% [12/285] vs 1.4% [4/282]) and nausea (3.2% [9/285] vs 1.8% [5/282]).

One of the 282 placebo-treated subjects (0.2%) discontinued study drug after experiencing a TEAE of vomiting. Another of the 282 subjects in the placebo group (0.2%) had a severe TEAE of diarrhea; the outcome was reported as recovered/resolved, and the subject completed the study. No serious TEAEs or deaths were reported.

DISCUSSION

This randomized, double-blind, placebo-controlled study was conducted to compare DFN-15, an oral solution of celecoxib, with placebo for the acute treatment of migraine. DFN-15 was significantly more effective than placebo on the coprimary endpoints of freedom from pain and MBS at 2 hours postdose. DFN-15 was also significantly superior to placebo on multiple secondary efficacy endpoints, including pain relief, change in functional disability from baseline, relief of photophobia, 24-hour satisfaction with treatment, use of rescue medication, and sustained pain relief and pain freedom. The tolerability and safety of DFN-15 were generally favorable, with mostly mild AEs that are characteristic of the known profile of celecoxib, and there were no clinically significant changes in vital signs or laboratory values.

Although both oral forms of celecoxib appear to be effective for the acute treatment of migraine, the pharmacokinetics of DFN-15 compares favorably with that of celecoxib oral capsules. Previous research has shown that DFN-15 produces higher peak plasma concentrations, is more rapidly absorbed, and has a shorter time to maximal concentration (T_{max}) than celecoxib 400 mg oral capsules.[25] Although DFN-15 was studied and will be used on acute basis, in clinical practice there are cardiovascular risks associated with long-term use of NSAIDs, including COX-2 selective drugs such as DFN-15, and they should be used with caution in patients with cardiovascular risk factors.[26]

Given the widespread use of NSAIDs and oral triptans for the acute treatment of migraine, a new COX-2 inhibitor that is effective and rapidly absorbed could provide an important new option for a wide range of patients. Though cross-study comparisons are problematic, the current results for DFN-15 indicate that its efficacy is similar to that of NSAIDs and small-molecule calcitonin gene-related peptide receptor antagonists (gepants), based on placebo-subtracted rates pain freedom in acute treatment trials (14-21%).[27-32] DFN-15 may also be useful among triptan users, who are at elevated risk of medication-overuse headache[33] and for whom TEAEs within 24 hours postdose are common.[34] Relative to triptans, NSAIDs appear to be protective against the development of medication-overuse headache among those with low to moderate attack frequency (<10 days per month), and the incidence of TEAEs related to DFN-15 in this study was 9%. The form and delivery system of DFN-15 – a ready-to-use solution in a 4.8-mL single-use bottle – may support patient adherence.

The secondary endpoint results need to be interpreted with caution given that the prespecified analysis plan did not assign a hierarchy, and there was no adjustment for multiple comparisons. However, meeting the coprimary endpoints and the overall weight of the evidence, as well as the large sample size of a population representative of likely users of DFN-15, provide an important early assessment supporting the efficacy and safety of DFN-15 for the acute migraine treatment.

Limitations.—This study has several limitations. First, the placebo response rates in this trial were robust, even considering the recent trend of increasing placebo rates in acute migraine trials.[31] Perhaps the novelty of a ready-made oral solution, which has not been previously tested for the acute treatment of migraine, also contributed to the placebo response. A slightly higher rate of subjects with moderate predose pain in the placebo group may also has been a contributing factor. Finally, this study does not address treatment during mild pain or consistency of treatment across multiple attacks.

CONCLUSIONS

DFN-15, acutely administered for the treatment of a migraine attack, was significantly superior to placebo on the coprimary endpoints of freedom from pain and freedom from the MBS at 2 hours postdose. DFN-15 was also significantly superior to placebo on multiple secondary 2-hour endpoints, including freedom from photophobia, pain relief, change in functional disability from baseline, overall and 24-hour satisfaction with treatment, and use of rescue medication. No new safety or tolerability issues, other than those previously associated with single doses of celecoxib, were identified. DFN-15 has the potential to become a reliable and convenient acute therapeutic option for patients with migraine.

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Richard B. Lipton, Sagar Munjal, Elimor Brand-Schieber

(b) Acquisition of Data
Sagar Munjal, Elimor Brand-Schieber

(c) Analysis and Interpretation of Data
Richard B. Lipton, Sagar Munjal, Elimor Brand-Schieber, Stewart J. Tepper, David W. Dodick

Category 2

(a) Drafting the Manuscript
Richard B. Lipton, Elimor Brand-Schieber

(b) Revising It for Intellectual Content
Richard B. Lipton, Sagar Munjal, Elimor Brand-Schieber, Stewart J. Tepper, David W. Dodick

Category 3

(a) Final Approval of the Completed Manuscript
Richard B. Lipton, Sagar Munjal, Elimor Brand-Schieber, Stewart J. Tepper, David W. Dodick

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