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Efficacy and safety of single-dose DFN-15 for treatment of acute postsurgical dental pain: a randomized, double-blind, placebo-controlled study

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Abstract

The analgesic efficacy and safety of DFN-15, a new oral liquid formulation of celecoxib with more rapid absorption than the capsule, were evaluated in the treatment of acute pain in adult patients after dental surgery. In this randomized, double-blind, placebo-controlled, dose-ranging study, 120 otherwise healthy adults who underwent the extraction of bilateral impacted mandibular third molar teeth and experienced moderate to severe pain postsurgery were randomly assigned, in a 1:1:1:1 ratio, to receive one dose of either placebo or DFN-15 at 3 doses: 62.5, 125, and 250 mg. Participants were evaluated at prespecified time points over 8 hours after study drug administration, using several instruments, including the 11-point Numerical Pain Rating Scale, 5-point Pain Relief Scale, and 5-point Treatment Satisfaction Scale. Rescue analgesic (oxycodone / acetaminophen) was permitted. The primary endpoint was the summed pain intensity difference (SPID) over the 6-hour postdose period (SPID6), which was compared between each DFN-15 dose and placebo using analysis of covariance. Other assessments of pain relief, use of rescue medication, and safety were also analyzed. All 3 doses of DFN-15 were significantly superior to placebo in SPID6 (least square mean difference over placebo: −756.6, −1120.7, and −1355.1, $P < 0.0001$ for all comparisons). In addition, DFN-15 was generally superior to placebo in other endpoints, including reduction of pain intensity, speed and magnitude of pain relief, treatment satisfaction, and rescue medication use. DFN-15 was similar to placebo in the incidence of adverse events with no apparent dose-related effects.

Keywords: Celecoxib, Dental pain, Analgesia

1. Introduction

To treat acute pain after dental surgeries, a variety of analgesic medications are commonly used. It has been reported that approximately 12% of all opioid prescriptions in the Unites States are related to dental procedures,[8] and opioids are prescribed 27.5% of the time when analgesics are necessary after dental procedures.[23] However, nonsteroidal anti-inflammatory drugs (NSAIDs) may be as effective as opioids in this indication. In a systematic review of published studies of single-dose oral analgesics, celecoxib 400 mg was as effective as or more effective than some opioids and maintained a long duration of action (8 hours) for painful dental procedures, such as third molar extraction.[15] Furthermore, NSAIDs produce meaningful analgesia without opioid-associated side effects, such as sedation, nausea and vomiting, and have a low risk of abuse and dependence.[1,13] Selective inhibitors of the type 2 cyclooxygenase isoenzyme (COX-2), such as celecoxib, are safer than other NSAIDs for their lack of effects on the mucosal barrier of the gastrointestinal (GI) tract.[3]

Celecoxib is a selective COX-2 inhibitor approved for the management of acute pain in adults.[5] Celecoxib is associated with a lower incidence of upper GI ulcers and bleeds and less GI symptoms than nonselective NSAIDs.[9,11,14,20] When used as perioperative analgesic treatment, selective COX-2 inhibitors may be safer than nonselective NSAIDs, especially regarding the risk of bleeding,[10,19] incisional wound hematomas, and GI ulceration,[22] with no known effects on bone fusion and wound healing.[19]

In addition to the magnitude of pain relief (PR), the time to onset of analgesic effect is an important consideration in the management of acute pain. Rapid onset of PR is highly desirable for patients and can reduce the likelihood of taking additional medications that may lead to adverse events.[4,7]

DFN-15 is a liquid oral formulation containing the active ingredient celecoxib at a concentration of 25 mg/mL and formulated in a proprietary delivery system that allows for a more rapid absorption rate than the capsule formulation, leading to a higher peak plasma concentration within 1 hour.[18] The partial areas under the plasma concentration-over-time curve (pAUCs) within the interval from 15 minutes to 2 hours after a 120-mg dose of DFN-15 were at least 3-fold greater than the pAUCs after a dose of 400-mg oral capsule.

We conducted this clinical study to evaluate the efficacy and safety of 3 doses of DFN-15 (62.5, 125, and 250 mg), orally

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administered as a single dose, for the treatment of acute, moderate to severe pain after the extraction of bilateral impacted (either partial or full bony impaction) mandibular third molar teeth. The efficacy evaluations included both the magnitude of analgesia and the time to PR.

2. Methods

This was a single-center, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of DFN-15 (celecoxib oral solution), given as a single dose, to treat acute postdental surgery pain in adult patients. This study was conducted from June 19, 2018, through August 20, 2018.

2.1. Study participants

Generally healthy adults (aged between 18 and 60 years) who were scheduled to undergo elective bilateral mandibular third molar extraction under local anesthesia were enrolled into this study. This extraction had to involve a full or partial bony impaction confirmed by panoramic X-ray. Participants were required to have been able to understand and willing to comply with study procedures and requirements and provide informed consent. Women were eligible to participate if they were not pregnant or lactating and were committed to avoiding pregnancy during the entire study.

Those with contraindications to the use of NSAIDs (eg, risk of thrombovascular events, renal insufficiency) or a history of allergy or hypersensitivity to celecoxib, NSAIDs, or other prespecified perioperative medications were excluded. Specific exclusion criteria ruled out participants with a history of migraine headaches, low back pain or other acute or chronic pain conditions that might affect evaluations in the study, and those who regularly took medications in the pharmacological classes of hypnotics, sedatives, monoamine oxidase inhibitors, sympathomimetic amines, benzodiazepines, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, or anticonvulsants, all of which are known to act on the central nervous system to modulate pain. Participants with GI conditions that could potentially have an impact on celecoxib absorption, such as recent gastric bypass procedure, gastroduodenal ulceration, and dysphagia, were also excluded. To avoid interference with study assessments, participants who had routine use of pain medications, including opioids, NSAIDs, and selective COX-2 inhibitors, or cannabinoids, within 4 weeks before the surgery were excluded.

2.2. Randomization, blinding, and study treatment

On the day of surgery and study drug administration, before undergoing the procedure, participants were screened again and educated on the pain assessment tools used in the study. Participants then underwent bilateral mandibular third molar extractions. Removal of any maxillary third molars, if necessary, was permitted but not required. Local anesthesia with lidocaine 2% with epinephrine (up to 20 mL) was given. Nitrous oxide and benzocaine gel were also allowed. Sedation, long-acting local anesthetics (eg, bupivacaine and ropivacaine), or steroids were prohibited.

Participants who experienced acute postoperative pain of moderate to severe intensity on a 4-point pain intensity (PI) scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and a PI of at least 5 on an 11-point Numerical Pain Rating Scale (NPRS; 0 = no pain and 10 = worst imaginable pain) within 6 hours postsurgery were randomized for study treatment. A computer-generated randomization scheme assigned eligible participants, at a ratio of 1:1:1:1, to 4 treatment groups: DFN-15 62.5 mg, DFN-15 125 mg, DFN-15 250 mg, and placebo. The 4 study treatment solutions were identical in appearance. Within 15 minutes of meeting the postoperative PI criteria, each randomized participant received a single dose (10 mL) of the assigned study drug by mouth in a double-blind manner with blinding to both the study staff and participants. The time of the study drug administration was designated as T0.

After the administration of study drug (DFN-15 or placebo), participants were encouraged to wait at least 2 hours, if possible, before receiving any rescue medication. The rescue medication allowed in this study was 1 or 2 tablets of oxycodone / acetaminophen 5 mg/325 mg every 4 hours as needed. Participants were observed at the study center for at least 8 hours after the study drug administration, during which time they were not allowed to use ice packs. After being discharged from the center, participants were asked to return 7 (±3) days postsurgery for follow-up evaluation of safety and well-being.

2.3. Pain and other assessments in the study

Pain intensity was measured using the 11-point NPRS, and PR was measured using a 5-point categorical PR scale (ranging from 0 = no PR to 4 = complete PR) at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after T0. To assess their overall level of satisfaction with the study drug, participants were asked to respond to the following query: "Please rate how well your pain has been controlled since you received study medication? (0-poor, 1-fair, 2-good, 3-very good, or 4-excellent)." The query was administered at 8 hours postdose, before discharge from the study center.

If a participant required rescue medication or was discontinued from the study within 8 hours postdose, the NPRS, PR, and treatment satisfaction were assessed and recorded at least 5 minutes before the first dose of rescue medication (ie, "pre-rescue" scores) or on early discontinuation from the study.

In addition, the time to perceptible PR and time to meaningful PR were assessed using the "two-stopwatch" method. Two stopwatches were started immediately after T0. Each participant was given the first stopwatch and instructed to stop it when they first perceived PR, and this time was recorded as the time to perceptible PR. Once the first watch was stopped, the second stopwatch was given with the instruction to stop it when they first experienced meaningful PR, and this time was recorded as time to meaningful PR.

Safety assessments included monitoring of adverse events, clinical laboratory tests, vital signs, 12-lead electrocardiograms, and physical and oral examinations. Abnormal laboratory results that were deemed clinically significant by the investigator, regardless of causal relationship, were reported as adverse events.

2.4. Endpoints

The primary endpoint of this study was the summed PI difference (SPID) over the first 6 hours after T0 (SPID6). The PID score was calculated as the difference between the NPRS score at baseline (ie, the last recorded score before T0) and each postdose time point. Summed PI difference for any postdose duration was calculated by summing the time-weighted PID scores using the area under the PID curve within the corresponding time period. The same calculation was used to calculate the total PR (TOTPAR) values by replacing the PID score with the PR score.

The other efficacy endpoints were (1) TOTPAR values over 2, 4, 6, and 8 hours after T0; (2) SPID at 2, 4, and 8 hours after T0; (3)

time to confirmed perceptible PR and time to meaningful PR; (4) treatment satisfaction score; (5) use of rescue medication; (6) PID at each time point (15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after T0); (7) peak PR score, defined as the maximum postdose PR score within 8 hours after T0 or before rescue medication use; and (8) time to peak PR.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.

2.5. Statistical analysis

Efficacy analyses were performed on the modified intent-to-treat (mITT) analysis set, defined as all participants who were randomized, received the study drug (DFN-15 or placebo), and recorded at least one postdose NPRS score. Demographics and safety analyses were performed on the safety analysis set, defined as all participants who received a dose of the study drug.

For primary analysis, SPID6 was compared between each of the 3 DFN-15 doses and placebo. All SPID endpoints were analyzed using analysis of covariance (ANCOVA) with treatment as the main effect and baseline NPRS score and body mass index as covariates.

For other efficacy analyses, TOTPAR was analyzed using a method similar to SPID. Pain relief scores at each time point were descriptively summarized for each treatment group. Peak PR score, a rough indicator of the magnitude of analgesic effect, was summarized descriptively. The times to perceptible and meaningful PR, time to first dose of rescue medication, and time to peak PR were all analyzed using Kaplan–Meier curves and compared between each DFN-15 dose and placebo using the log-rank test. Perceptible PR was summarized only for participants who also achieved meaningful PR (ie, confirmed perceptible PR). The proportion of participants satisfied with study treatment, defined as those who reported treatment satisfaction scores of $\geq$2 on the 5-point scale, and the proportion of participants who received rescue medications were analyzed using the Cochran–Mantel–Haenszel χ^2 test or, alternatively, a Fisher exact test if there were $<$5 participants in any group.

In participants who required rescue medications, all scheduled PI and PR scores within 4 hours after the rescue medication administration were replaced by the "prerescue" scores in the efficacy analysis (ie, the "windowed last observation carried forward" imputation method). Any other scheduled PI and PR scores that were missing intermittently (outside the 4-hour window after rescue medication) were imputed using linear interpolation between adjacent observed values. Any missing PI or PR scores due to study discontinuation were imputed as follows: (1) If the participant had discontinued because of an adverse event, the score was imputed using the "baseline observation carried forward" method. (2) If the participant had discontinued for other reasons, the score was imputed using the "last observation carried forward" method. If a participant's baseline PI score was missing, any postdose PI scores were excluded from the analysis.

Treatment-emergent adverse events (TEAEs), defined as adverse events that occurred after the study drug administration, were summarized descriptively by treatment group.

No statistical comparisons between the DFN-15 doses were conducted.

All statistical analyses were prespecified in the statistical analysis plan before the data were unblinded.

2.6. Compliance with ethical standards

The study was conducted according to the International Conference on Harmonization Guideline for Good Clinical Practice E6, the U.S. FDA Code of Federal Regulations Title 21 (parts 50, 54, and 56), and applicable principles of the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects[24] at a single clinical study site (JBR Clinical Research) in Salt Lake City, UT. The study protocol, the informed consent documents, and relevant supporting information were submitted to Aspire Institutional Review Board (IRB) for review and were approved before the study was initiated. The study was registered at http://www.clinicaltrials.gov (ClinicalTrials.gov identifier NCT03554772) before commencement of enrollment.

3. Results

3.1. Demographics

Overall, 247 adults were screened; 118 (47.8%) were screen failures, 9 (3.6%) were not enrolled because the planned number of participants had been reached, and 120 eligible adults were enrolled and randomized in the study. Of the randomized participants, 30 were randomized to the placebo group, and 30, 29, and 31 were randomized to the 62.5-mg, 125-mg, and 250-mg DFN-15 groups, respectively. All participants completed the 8-hour observation period postdose and nearly all completed the study, except 2 participants in the DFN-15 250 mg group who were lost to follow-up. The CONSORT flowchart for study participants is published in the online version.

All 120 participants received the study treatment as assigned and recorded at least one postdose NPRS score. Therefore, the mITT and safety data sets were identical and consisted of all 120 randomized participants. Demographic and baseline characteristics of the study participants are summarized in **Table 1**.

The demographic characteristics were generally similar across the treatment groups. Overall, half of the participants were male. The majority were White and not Hispanic or Latino. The mean (standard deviation, SD) age was 19.8 (2.37) years, the mean (SD) weight was 73 (14.5) kg, and the mean (SD) body mass index was 25.8 (4.51) kg/m^2.

Baseline characteristics were generally similar across all groups. As planned, all participants had at least moderate postoperative pain at baseline, and 63.3% participants had severe pain. The 3 DFN-15 dose groups had slightly higher percentages of participants with moderate pain, ranging from 37.9% to 43.3% than the placebo group (26.7%). The mean NPRS baseline score was 7.4 (range 5-10) for all participants: 7.6 for the placebo group and ranging from 7.1 to 7.5 for the DFN-15 dose groups.

3.2. Primary efficacy: Summed Pain Intensity Difference over the first 6 hours

The mean PID scores over time in the placebo group and DFN-15 dose groups are displayed in **Figure 1**. All groups showed a decrease in PI postdose, but the DFN-15 groups showed greater decreases in PI from baseline compared with placebo.

The SPID6 values, calculated as the area under the curve of PID score vs time from study drug administration (T0) to 6 hours postdose, and comparison between each DFN-15 dose and placebo are summarized in **Table 2** and displayed in **Figure 2**.

The least square (LS) mean differences compared with placebo in SPID6 values for the 62.5, 125, 250-mg, and combined DFN-15 groups were −756.6, −1120.7, −1355.1, and −1076.9, respectively, which were statistically highly significant for all comparisons ($P < 0.0001$, ANCOVA model).

Table 1

Summary of demographic and baseline characteristics—modified intent-to-treat population.

	Placebo, N = 30	DFN-15 62.5 mg, N = 30	DFN-15 125 mg, N = 29	DFN-15 250 mg, N = 31	Total, N = 120
Age					
Mean (SD)	19.9 (2.70)	19.6 (2.45)	19.2 (1.64)	20.5 (2.45)	19.8 (2.37)
Median	18	18	19	20	19
Range (min, max)	(18, 27)	(18, 28)	(18, 23)	(18, 25)	(18, 28)
Sex, n (%)					
Male	14 (46.7)	16 (53.3)	12 (41.4)	18 (58.1)	60 (50.0)
Female	16 (53.3)	14 (46.7)	17 (58.6)	13 (41.9)	60 (50.0)
Race, n (%)					
White	28 (93.3)	26 (86.7)	22 (75.9)	28 (90.3)	104 (86.7)
Black or African American	1 (3.3)	1 (3.3)	0	0	2 (1.7)
Asian	0	1 (3.3)	0	0	1 (0.8)
American Indian or Alaska Native	0	0	1 (3.4)	0	1 (0.8)
Native Hawaiian or other Pacific Islander	1 (3.3)	0	2 (6.9)	0	3 (2.5)
Multiple	0	1 (3.3)	2 (6.9)	1 (3.2)	4 (3.3)
Other	0	1 (3.3)	2 (6.9)	2 (6.5)	5 (4.2)
Ethnicity, n (%)					
Hispanic or Latino	6 (20.0)	6 (20.0)	4 (13.8)	7 (22.6)	23 (19.2)
Non-Hispanic or Latino	24 (80.0)	24 (80.0)	25 (86.2)	24 (77.4)	97 (80.8)
Height (cm)					
Mean (SD)	167.9 (10.25)	167.5 (10.54)	167.0 (7.08)	170.6 (9.28)	168.3 (9.39)
Median	169	169	166	171	168
Range (min, max)	(150, 191)	(141, 183)	(158, 182)	(156, 191)	(141, 191)
Weight (kg)					
Mean (SD)	74.7 (15.12)	76.6 (18.33)	69.8 (10.19)	70.9 (12.47)	73.0 (14.45)
Median	71	76	70	70	71
Range (min, max)	(52, 114)	(48, 109)	(52, 92)	(54, 99)	(48, 114)
BMI (kg/m^2)					
Mean (SD)	26.4 (4.15)	27.1 (5.03)	25.1 (4.11)	24.4 (4.41)	25.8 (4.51)
Median	26	27	25	23	25
Range (min, max)	(19, 34)	(20, 35)	(20, 33)	(19, 34)	(19, 35)
Qualifying (baseline) categorical pain score					
0 = No pain	0	0	0	0	0
1 = mild pain	0	0	0	0	0
2 = moderate pain	8 (26.7)	13 (43.3)	11 (37.9)	12 (38.7)	44 (36.7)
3 = severe pain	22 (73.3)	17 (56.7)	18 (62.1)	19 (61.3)	76 (63.3)
Qualifying (baseline) NPRS score					
Mean (SD)	7.6 (1.28)	7.1 (1.11)	7.3 (1.14)	7.5 (1.18)	7.4 (1.17)
Median	8	7	7	7	7
Range (min, max)	(5, 10)	(5, 10)	(6, 9)	(6, 10)	(5, 10)

BMI, body mass index; kg, kilogram; max, maximum; min, minimum; NPRS, Numerical Pain Rating Scale.

Therefore, the primary endpoint was met, and DFN-15, at all doses, was superior to placebo in pain reduction through 6 hours postdose.

3.3. Other efficacy results

The mean TOTPAR values, calculated as the sum of the area under the curve of PR scores vs time, were higher for each of the DFN-15 doses and for the combined DFN-15 group, compared with placebo, at each time point at which TOTPAR was estimated. At 2, 4, 6, and 8 hours postdose, the least square mean differences between each DFN-15 dose and placebo were all statistically highly significant with $P < 0.0001$, except the 62.5-mg DFN-15 group vs placebo comparison at 8 hours postdose with $P = 0.0033$. The analysis of TOTPAR values at 6 hours (TOTPAR6) is summarized in **Table 2**.

At 2, 4, and 8 hours postdose, the SPID values at all doses of DFN-15 and for the combined DFN-15 group were statistically significantly superior (ie, a greater reduction of PI) to placebo ($P \leq 0.0076$).

The percentage of participants who reached confirmed perceptible PR was 56.7%, 82.8%, and 87.1% in the 62.5, 125, and 250-mg DFN-15 dose groups, respectively, compared with 33.3% in the placebo group. The median times to confirmed perceptible PR for the 125-mg (15 minutes) and 250-mg (20 minutes) DFN-15 dose groups were statistically significantly shorter than placebo ($P < 0.0001$). (Note: The median time for the placebo group could not be estimated as two-thirds of the observations were censored; the lower bound of 95% CI of the median time was 101.4 minutes.) The median time for the 62.5-mg DFN-15 dose group (32 minutes) was not significantly different from placebo ($P = 0.0529$).

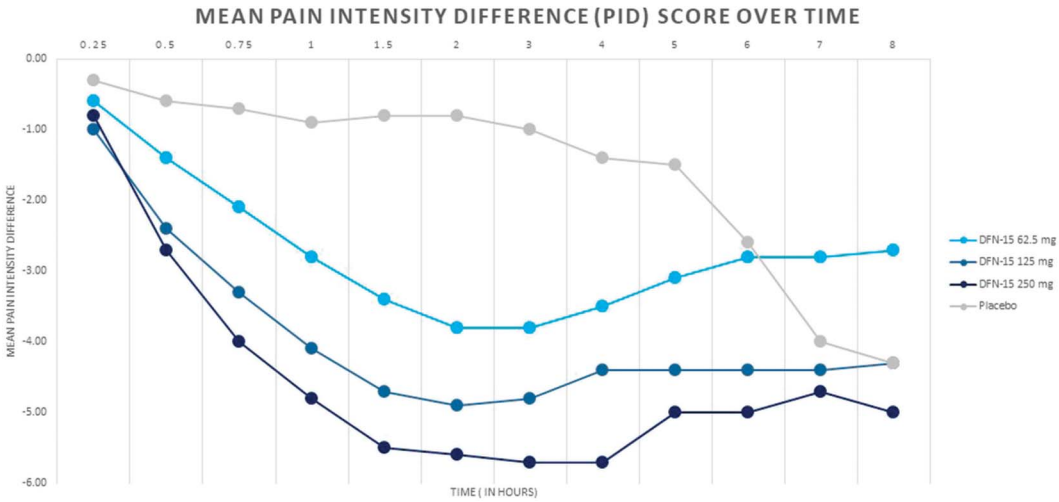

Figure 1. Mean pain intensity difference (PID) scores over time (mITT population). mITT, modified intent-to-treat.

The percentage of participants who reached meaningful PR was the highest (87.1%) in the 250-mg DFN-15 dose group, compared with 33.3% in the placebo group (**Table 2**). The median times to meaningful PR for the 125-mg (59 minutes) and 250-mg (42 minutes) DFN-15 dose groups were statistically significantly shorter than placebo ($P < 0.0001$). (Note: The median time for placebo could not be estimated as two-thirds of the observations were censored; the lower bound of 95% CI of the median time was 231.6 minutes.) Similar to confirmed perceptible PR, the median time to meaningful PR for the 62.5-mg DFN-15 dose group (114 minutes) was not significantly different from placebo ($P = 0.0895$). The Kaplan–Meier curve for time to meaningful PR is shown in **Figure 3**.

A large majority of participants (77% to 93%) reported satisfaction with their treatment in the DFN-15 dose groups compared with 23% in the placebo group. The mean (SD)

Table 2

Analyses of key endpoints (mITT population).

	Placebo, N = 30	DFN-15 62.5 mg, N = 30	DFN-15 125 mg, N = 29	DFN-15 250 mg, N = 31
SPID6				
N	30	30	29	31
Mean (SD)	−420.2 (716.42)	−1101.0 (570.74)	−1509.0 (805.29)	−1771.7 (646.10)
ANCOVA results [1]				
LS means	−392.6	−1149.2	−1513.2	−1747.7
LS mean difference [2]		−756.6	−1120.7	−1355.1
95% CI [3]		(−1172.3, −340.9)	(−1538.0, −703.3)	(−1767.8, −942.4)
Dunnett *P* value [4]		<0.0001	<0.0001	<0.0001
TOTPAR6				
N	30	30	29	31
Mean (SD)	309.5 (357.18)	680.4 (285.71)	869.8 (334.13)	956.1 (244.29)
ANCOVA results [1]				
LS means	314.0	687.3	865.9	948.7
LS mean difference [2]		373.3	551.9	634.6
95% CI [3]		(180.9, 565.7)	(358.8, 745.0)	(443.7, 825.6)
Dunnett *P* value [4]		<0.0001	<0.0001	<0.0001
Time to meaningful PR (minutes)				
Subjects reaching meaningful pain relief, n (%)	10 (33.3)	17 (56.7)	24 (82.8)	27 (87.1)
Censored observations, n (%) [5]	20 (66.7)	13 (43.3)	5 (17.2)	4 (12.9)
Mean time (SD mean)	192.2 (13.69)	232.6 (34.22)	126.5 (27.33)	70.2 (10.73)
Median time	NE	114	59	42
95% CI of median time	(231.6, NE)	(66.4, NE)	(33.1, 94.3)	(32.4, 59.3)
Log-rank *P* value [6]		0.0895	<0.0001	<0.0001

PID were defined as NPRS at hour x−baseline NPRS, therefore negative PID indicates less pain and larger negative SPID indicates larger benefit. Header N indicates the number of mITT participants randomized to the treatment arm, whereas row n indicates the number of nonmissing values used in the calculation.

[1] ANCOVA model included treatment as main effect, and baseline NPRS and baseline BMI as covariates. [2] Least square mean difference = LS mean of active−LS mean of placebo. [3] CI = confidence interval of the LS mean difference. [4] Dunnett adjusted (for individual treatment arms, but not total) *P* value comparing each dose group to placebo. [5] Subjects receiving rescue medication or discontinuing study before reporting meaningful pain relief were censored at 8 hours. Perceptible pain relief was summarized only for participants who also achieved meaningful pain relief (confirmed perceptible pain relief). [6] *P* value was obtained using the log-rank test comparing active with placebo.

ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; LS, least squares; mITT, modified intent-to-treat; NE, not evaluable; NPRS, Numerical Pain Rating Scale; PID, pain intensity difference; SPID, summed pain intensity difference; TOTPAR6, total pain relief at 6 hours postdose.

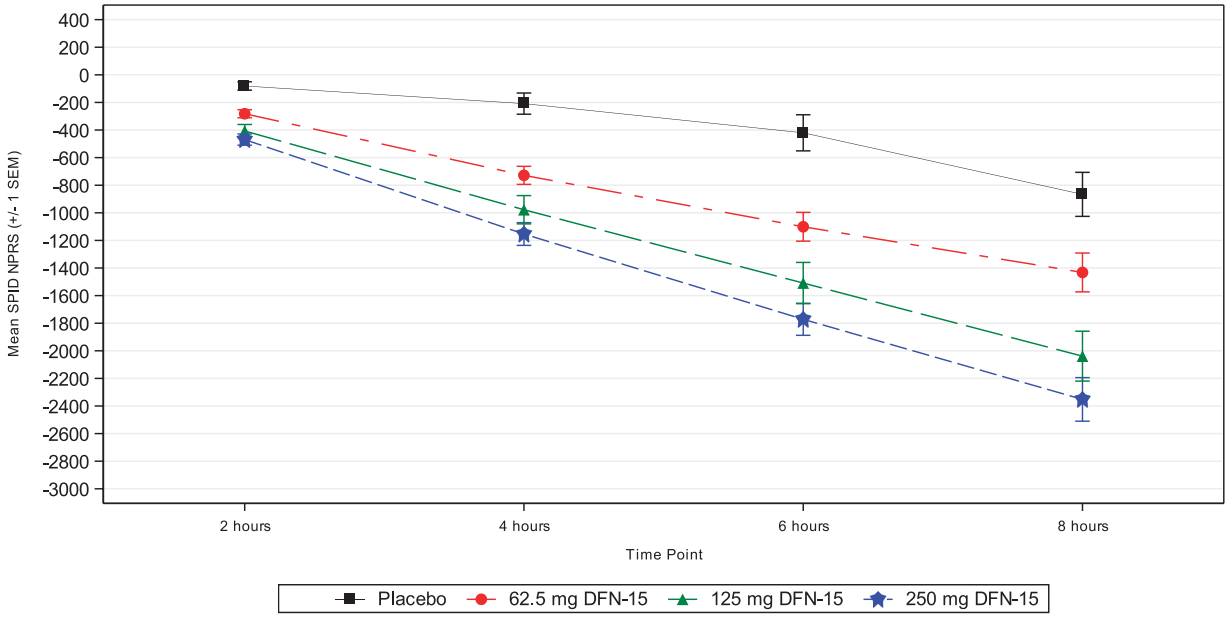

Figure 2. Mean SPID values from T0 through 2, 4, 6, and 8 hours postdose (mITT population). mITT, modified intent-to-treat; NPRS, Numerical Pain Rating Score; PID, pain intensity difference; SPID, summed pain intensity difference; T0, time of study drug administration. PID were defined as NPRS at hour x−baseline NPRS, therefore negative PID indicates less pain and larger negative SPID indicates larger benefit.

satisfaction scores were 2.1 (1.06), 2.9 (1.07), and 3.2 (0.96) in the 62.5, 125, and 250-mg DFN-15 dose groups, respectively, compared with 0.8 (1.10) in the placebo group. The differences compared with placebo were statistically significant at all DFN-15 doses ($P < 0.0001$ for all comparisons).

The number and proportion of participants who received rescue medication during the 8-hour postdose period are summarized by treatment group in **Table 3**. In the 62.5, 125, and 250-mg DFN-15 dose groups, 23.3%, 10.3%, and 6.5% participants used at least one dose of rescue medication, compared with 53.3% in the placebo group. The odds ratio of using rescue medication in the 62.5, 125, and 250-mg DFN-15 dose groups relative to the placebo group was 0.27, 0.10, and 0.06, respectively, which were statistically significant ($P = 0.0178$, $P = 0.0006$, and $P < 0.0001$, respectively).

The mean (SD) time to first use of rescue medication was 395.9 (15.48), 414.7 (13.70), and 321.6 (0.54) minutes in the 62.5, 125, and 250-mg DFN-15 dose groups, respectively, compared with 197.6 (17.45) minutes in the placebo group. All 3 DFN-15 doses had statistically significant separation from placebo ($P \leq 0.0012$, log-rank test).

The PID scores were statistically significantly lower in all DFN-15 dose groups compared with placebo at all postdose time points between 30 minutes and 5 hours, with $P \leq 0.0419$, $P < 0.0001$, and $P < 0.0001$ for the 62.5-, 125-, and 250-mg DFN-15 dose groups, respectively (**Fig. 1**). The statistical significance vs placebo extended to 15 minutes and 6 hours postdose time points for the 125-mg dose group and to 6 hours postdose for the 250-mg dose group. The PID value for the combined DFN-15 group was also statistically significant compared with the placebo group between 15 minutes and 6 hours postdose ($P \leq 0.0288$).

The mean (SD) peak PR score was 2.6 (0.83), 3.2 (0.79), and 3.3 (0.69) for the 62.5, 125, and 250-mg DFN-15 dose groups, respectively, compared with 2.4 (1.11) for the placebo group. More important, the median times (95% CI) to peak PR score were 76 (60, 120), 61 (60, 120), and 90 (60, 120) minutes for the 62.5, 125, and 250-mg DFN-15 dose groups. These data compared favorably against the placebo group, for which the median time to peak PR could not be estimated because half of the observations were censored because of participants not reporting a positive PR score (the lower bound of the 95% CI was 180 minutes) ($P < 0.001$ for all comparisons, log-rank test).

3.4. Adverse events

No participant in any group discontinued the study because of adverse events. No serious adverse event was reported by any participant.

Among the 120 participants in the study, 28 TEAEs were reported in 18 (15.0%) participants (**Table 4**). In the combined DFN-15 dose groups, 14 (15.6%) participants had at least one TEAE, compared with 4 (13.3%) participants in the placebo group. Sixteen of the 18 participants had mild TEAEs, and none had severe TEAEs. All related TEAEs, reported by 11 of the 18 participants, were of mild intensity.

The most frequently reported TEAEs were nausea (4 [4.4%] participants in the combined DFN-15 group and 1 [3.3%] in the placebo group), blood bilirubin increased (3 [3.3%] in the combined DFN-15 group), and epistaxis (2 [2.2%] in the combined DFN-15 group). Although the events of "blood bilirubin increase" and "epistaxis" were not reported in the placebo group, "alveolar osteitis" (dry socket) and "dizziness" were reported in one participant each in the combined DFN-15 dose and placebo groups. There was no apparent dose-related trend in the incidence or the types of adverse events across the 3 doses of DFN-15 evaluated.

4. Discussion

In this study, a newly developed oral liquid formulation of celecoxib, DFN-15, was compared with placebo in the treatment

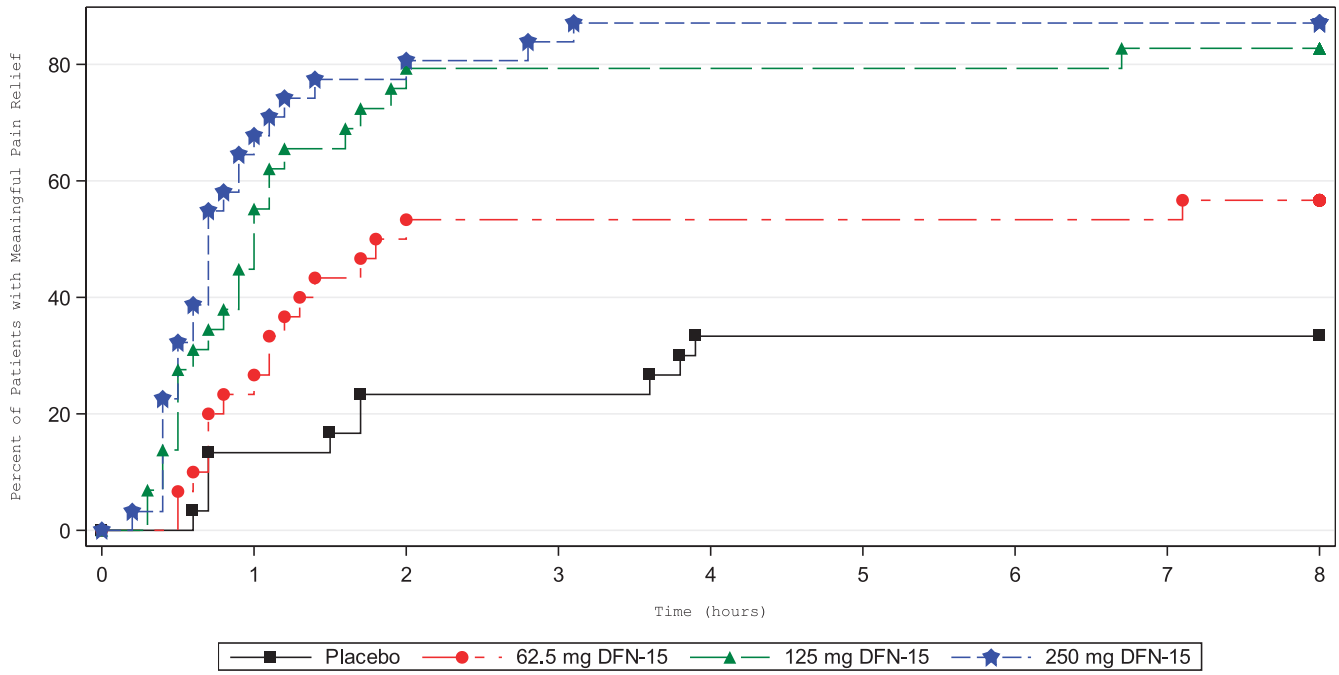

Figure 3. Kaplan–Meier curve for time to meaningful pain relief (mITT population). mITT, modified intent-to-treat. Subjects receiving rescue medication or discontinuing the study before reporting meaningful pain relief were censored at 8 hours.

of acute moderate to severe pain after a major dental surgery in otherwise healthy adults. This oral liquid formulation has been shown to result in more rapid absorption of celecoxib than CELEBREX (celecoxib) capsules.[18] In a pharmacokinetic study, the bioavailability of DFN-15 was 1.4 times of that of CELEBREX capsules under fasted state. The speed of celecoxib absorption from DFN-15, based on the time to maximum blood concentration of less than 1 hour of ingestion and the pAUCs from 15 minutes to 2 hours, was at least 3 times higher than the capsules.[18] These data suggest that DFN-15 could provide good PR to patients earlier during the course of acute pain, compared with most solid oral formulations of analgesic medications in general, particularly celecoxib. The results of the current study showed that a single dose of celecoxib as low as 62.5 mg in DFN-15 was significantly superior to placebo in pain reduction over the first 6 hours postdose, whereas larger (and statistically significant) differences from placebo were demonstrated at doses of 125 and 250 mg.

The effectiveness of DFN-15 in treating acute postsurgical dental pain was supported by consistently significant superiority in several of the PI and PR measures, participants' satisfaction with treatment, and the time to the use of rescue medications. In the 250-mg DFN-15 group (the highest dose given in the study), only 6.5% participants needed rescue treatment with oxycodone/acetaminophen 5 mg / 325 mg, which was significantly lower compared with more than half (53.3%) of the participants in the placebo group who needed the medication. Significantly lower rates of rescue medication use compared with placebo were also observed in the 62.5 (23.3%) and 125-mg (10.3%) dose groups, underscoring the effectiveness of DFN-15 in providing adequate acute PR across a wide range of doses and a meaningful reduction in the need of remedication and rescue medication.

The time to the onset of analgesia, defined as the median time to confirmed perceptible PR, is an important endpoint in clinical trials that evaluate the efficacy of medications for dental and other types of acute pain. For example, fast-acting formulations of

Table 3

Proportion of participants using rescue medication (mITT population).

	Placebo, N = 30	DFN-15 62.5 mg, N = 30	DFN-15 125 mg, N = 29	DFN-15 250 mg, N = 31
Subjects using any rescue medication [1] n (%)	16 (53.3)	7 (23.3)	3 (10.3)	2 (6.5)
Doses of rescue medication				
1 dose, n (%)	13 (43.3)	6 (20.0)	3 (10.3)	2 (6.5)
2 doses, n (%)	3 (10.0)	1 (3.3)	0	0
Analysis results [2]				
Odds ratio [3]		0.27	0.10	0.06
95% CI [4]		(0.09, 0.81)	(0.02, 0.46)	(0.01, 0.33)
P value [5]		0.0178	0.0006	<0.0001

Header N indicates number of mITT participants randomized to the treatment arm, whereas row n indicates the number of nonmissing values for the specific row.

[1] The expected rescue medication in this study was 1 to 2 oxycodone 5 mg or acetaminophen 325 mg every 4 hours as needed. Subjects were counted as receiving rescue if they used any rescue medication during the 8 hours inpatient period. [2] Analysis comparing each active dose with placebo individually. [3] An odds ratio > 1 indicated the active group was more likely to receive rescue than the placebo group. [4] CI was the confidence interval of the odds ratio; if the CI did not contain 1, it indicated that the ratio was statistically significant. [5] *P* value was from a χ^2 test if the expected cell counts were all at least 5, otherwise the Fisher exact *P* value was displayed.

CI, confidence interval; mITT, modified intent-to-treat.

Table 4

Treatment-emergent adverse events reported by >1 participant in either placebo or combined DFN-15 group (safety population).

System organ class preferred term	Placebo, N = 30	DFN-15 62.5 mg, N = 30	DFN-15 125 mg, N = 29	DFN-15 250 mg, N = 31	DFN-15 combined, N = 90
Subjects with at least 1 TEAE, n (%)	4 (13.3)	5 (16.7)	4 (13.8)	5 (16.1)	14 (15.6)
Gastrointestinal disorders					
Nausea	1 (3.3)	2 (6.7)	1 (3.4)	1 (3.2)	4 (4.4)
Investigations					
Blood bilirubin increased	0	1 (3.3)	0	2 (6.5)	3 (3.3)
Respiratory, thoracic, and mediastinal					
Epistaxis	0	0	0	2 (6.5)	2 (2.2)

TEAE, treatment-emergent adverse events.

ibuprofen have been shown to achieve significantly better analgesia over 6 hours and reduce the need for remedications than standard formulations of ibuprofen at the same dose without any increased safety risks.[16] Currently, there are no fast-acting formulations of celecoxib being marketed in the United States.

In this study, the time to onset of analgesia was significantly shorter in DFN-15 groups compared with placebo. The median (95% CI) time to confirmed perceptible PR was 15 minutes (13.9, 24.2) in the 125-mg DFN-15 group. To note, the estimated median (95% CI) times to onset of analgesia were 54 minutes (48, 66) for CELEBREX 400 mg (two 200-mg capsules) in a study by Malmstrom et al.[12] and 28 minutes (22, 33) for one CELEBREX 400 mg capsule in another study by Cheung et al.[6] The median time (95% CI) to meaningful PR (an indicator of the time required to reach effective analgesia levels) with 125-mg dose of DFN-15 in our study was 59 minutes (33.1, 94.3). The median time (95% CI) to meaningful PR was 84 minutes (64, 100) after one capsule of CELEBREX 400 mg in the Cheung et al. study. Both of these studies used the postsurgical dental pain model standardized for acute pain of moderate to severe intensity, although direct comparisons with the current study cannot be made.

This study demonstrates that DFN-15 single-dose treatment is safe and well tolerated at doses up to and including 250 mg, the highest dose used in the study. The adverse events reported in DFN-15-treated participants were similar, in frequency and in type, to placebo-treated participants. The higher dose of 250 mg was not associated with any evidence of higher safety risks.

In summary, DFN-15, as an oral solution formulation of celecoxib, offers potential therapeutic advantages in terms of a more rapid onset of analgesia and early pain relief with greater magnitudes than solid oral formulations, which are attributable to its proprietary self-microemulsifying drug delivery system that generates a unique pharmacokinetic profile. Fast-acting analgesics are desirable in various moderate to severe painful conditions of acute onset, such as acute musculoskeletal injuries (sprains and fractures), and breakthrough pain of various etiologies, as well as in emergency medicine settings. As it belongs to the selective COX-2 inhibitor class of NSAIDs, DFN-15 is devoid of the common safety concerns including respiratory depression, excessive sedation, and dependence and abuse liabilities associated with opioids. Furthermore, the doses of celecoxib evaluated in this study (125 and 62.5 mg) through the liquid DFN-15 were lower than doses commonly used, whereas the pain relief appeared to be adequate. Although these lower doses might lead to better safety profiles,[2,17,21] this hypothesis requires further study.

A limitation of this study is the lack of active comparator. As such, any efficacy comparisons vis-à-vis CELEBREX capsules or ibuprofen tablets are indirect and suggestive at best. Another limitation was that no statistical comparisons were made between the 3 DFN-15 doses for any of the efficacy endpoints to allow for any conclusions regarding possible dose–response relationships. Finally, the sample size was selected empirically, based on other similar studies, without a formal calculation of statistical power.

In conclusion, a single dose of DFN-15, at 62.5 mg to 250 mg, is effective and safe in treating moderate to severe pain after a dental surgery.

Conflict of interest statement

N. Singla and T. Bertoch received payments from Dr. Reddy's Laboratories to conduct this study. S. Shenoy and S. Munjal are employees of Dr. Reddy's Laboratories.

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References

[1] Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH, Senay EC, Woody GE. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage 2006;31:465–76.
[2] Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, Brophy JM. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ 2017;357: j1909.
[3] Borer JS, Simon LS. Cardiovascular and gastrointestinal effects of COX-2 inhibitors and NSAIDs: achieving a balance. Arthritis Res Ther 2005; 7(Suppl 4):S14–22.
[4] Brain P, Leyva R, Doyle G, Kellstein D. Onset of analgesia and efficacy of ibuprofen sodium in postsurgical dental pain: a randomized, placebo-controlled study versus standard ibuprofen. Clin J Pain 2015;31:444–50.
[5] Celebrex. [Package Insert]. New York: Pfizer, 2018.

[6] Cheung R, Krishnaswami S, Kowalski K. Analgesic efficacy of celecoxib in postoperative oral surgery pain: a single-dose, two-center, randomized, double-blind, active- and placebo-controlled study. Clin Ther 2007; 29(Suppl):2498–510.
[7] Cooper SA, Voelker M. Evaluation of onset of pain relief from micronized aspirin in a dental pain model. Inflammopharmacology 2012;20:233–42.
[8] Denisco RC, Kenna GA, O'Neil MG, Kulich RJ, Moore PA, Kane WT, Mehta NR, Hersh EV, Katz NP. Prevention of prescription opioid abuse: the role of the dentist. J Am Dent Assoc 2011;142:800–10.
[9] Goldstein JL, Silverstein FE, Agrawal NM, Hubbard RC, Kaiser J, Maurath CJ, Verburg KM, Geis GS. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. Am J Gastroenterol 2000;95:1681–90.
[10] Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. J Clin Pharmacol 2000;40: 124–32.
[11] Lefkowith JB, Geis GS, Silverstein F. Safety of celecoxib vs other nonsteroidal anti-inflammatory drugs. JAMA 2000;284:3123–4.
[12] Malmstrom K, Fricke JR, Kotey P, Kress B, Morrison B. A comparison of rofecoxib versus celecoxib in treating pain after dental surgery: a single-center, randomized, double-blind, placebo- and active-comparator-controlled, parallel-group, single-dose study using the dental impaction pain model. Clin Ther 2002;24:1549–60.
[13] Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology 2005;102:1249–60.
[14] Moore RA, Derry S, Makinson GT, McQuay HJ. Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from company clinical trial reports. Arthritis Res Ther 2005;7:R644–665.
[15] Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. Cochrane Database Syst Rev 2011:CD008659.
[16] Moore RA, Derry S, Straube S, Ireson-Paine J, Wiffen PJ. Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. PAIN 2014;155:14–21.
[17] Nissen SE, Yeomans ND, Solomon DH, Luscher TF, Libby P, Husni ME, Graham DY, Borer JS, Wisniewski LM, Wolski KE, Wang Q, Menon V, Ruschitzka F, Gaffney M, Beckerman B, Berger MF, Bao W, Lincoff AM, Investigators PT. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016;375:2519–29.
[18] Pal A, Shenoy S, Gautam A, Munjal S, Niu J, Gopalakrishnan M, Gobburru J. Pharmacokinetics of DFN-15, a novel oral solution of celecoxib, versus celecoxib 400-mg capsules: a randomized crossover study in fasting healthy volunteers. Clin Drug Investig 2017;37:937–46.
[19] Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000;91:1221–5.
[20] Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247–55.
[21] Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, Adenoma Prevention with Celecoxib Study I. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352: 1071–80.
[22] Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci U S A 1999;96:7563–8.
[23] Wong YJ, Keenan J, Hudson K, Bryan H, Naftolin F, Thompson VP, Craig RG, Vena D, Collie D, Wu H, Matthews AG, Grill AC, Curro FA. Opioid, NSAID, and OTC analgesic medications for dental procedures: PEARL network findings. Compend Contin Educ Dent 2016;37:710–18.
[24] World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4.