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Selection of 12-Hour Sustained-Release Acetaminophen (Paracetamol) Formulation Through Comparison of Pharmacokinetic Profiles of 4 Sustained-Release Prototype Formulations and Standard Acetaminophen Formulation: An Open-Label, Randomized, Proof-of-Principle Pharmacokinetic Study

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Abstract

Acetaminophen (APAP; paracetamol), a widely used analgesic and antipyretic, is available in modified-release and immediate-release (IR) formulations requiring 3- or 4-times-daily dosing. This phase 1 open-label crossover study compared pharmacokinetic profiles of single 2000-mg doses of 4 different sustained-release (SR) formulations of APAP (designed to allow twice-daily dosing) against two 1000-mg doses (taken 6 hours apart) of standard IR APAP in 14 healthy volunteers. The primary end point was duration of time that plasma APAP concentration exceeded a plasma concentration (T_C) of 4 μg/mL. Of the 4 SR APAP formulations studied, a single 2000-mg dose of a bilayer SR formulation had the longest mean $T_{C>4\mu g/mL}$ (8.1 hours), similar to that of 2 doses of IR APAP (8.3 hours). Mean $T_{C>4\mu g/mL}$ was 7.3 hours with a single-layer SR APAP, 7.5 hours with another single-layer SR APAP formulation using a different excipient, and 7.1 hours with an enteric-coated SR APAP coupled with a fast-dissolving IR APAP. Secondary pharmacokinetic analyses showed a similar extent of absorption and lower peak concentration for the bilayer SR formulation compared with IR APAP. Adverse events were all mild. Based on these results, the bilayer SR APAP formulation was selected for further development.

Keywords

acetaminophen, pharmacokinetics, 12-hour sustained-release formulation, minimal therapeutic plasma concentration

Acetaminophen (APAP), also known as paracetamol (N-acetyl-para-aminophenol), is an analgesic/antipyretic drug available without prescription and used extensively for the treatment of pain associated with various musculoskeletal and other painful disorders. APAP is recommended in multiple international guidelines as initial pharmacotherapy for mild to moderate pain associated with knee and hip osteoarthritis (OA),[1–5] treatment of low back pain,[6–9] as a component of multimodal therapy for postoperative pain management,[10,11] treatment of

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Table 1. Study Formulations

Treatment Group	Formulation	Dose and Administration			
		Number of Tablets	APAP Dose[a] per Tablet	Dosing Frequency	Total Dose
1. Bilayer SR APAP	Bilayer IR (10%)/SR (90%, with 5% hypromellose) modified-release APAP tablets[18,19]	2	1000 mg	Single dose	2 × 1000 mg
2. Single-layer SR APAP #1	SR APAP tablets with 5% hypromellose	2	1000 mg	Single dose	2 × 1000 mg
3. Single-layer SR APAP #2	SR APAP tablets with 6% Kollidon	2	1000 mg	Single dose	2 × 1000 mg
4. Enteric-coated SR APAP + FD IR APAP	Enteric-coated SR tablet[b] with 5% hypromellose *plus* FD IR APAP tablets[c]	1	1000 mg	Single dose	1000 mg +
		2	500 mg	Single dose	2 × 500 mg
5. Standard IR APAP	Standard IR APAP tablets[d]	2	500 mg	2 doses, 6 hours apart	2 × 500 mg every 6 hours × 2

APAP, N-acetyl-para-aminophenol; FD, fast disintegrating; IR, immediate release; SR, sustained release.
[a]All patients received a total dose of 2000 mg APAP.
[b]The enteric coating results in a slow release of APAP in the intestine, the main site of APAP absorption.
[c]Commercially available as Panadol Advance, GlaxoSmithKline Consumer Healthcare.
[d]Commercially available as Panadol, GlaxoSmithKline Consumer Healthcare.

persistent pain in older persons,[12] and treatment for mild to moderate pain conditions.[13]

The recommended daily dosage in persons 12 years and older for immediate-release (IR) extra-strength APAP is 500 to 1000 mg every 4 to 6 hours.[14,15] In some countries, extended-release (ER) formulations of APAP are available that reduce the dosing frequency to 3 times per day instead of 4 times per day, such as Panadol Extend (GlaxoSmithKline, Brentford, United Kingdom), which is a modified-release product containing both immediate- and slow-release layers. The decreased frequency of administration is preferred by many patients with OA and associated with greater treatment satisfaction.[16] It is possible that further reductions in dosing frequency will have additional benefits. In a review of patient adherence studies published from 1986 to 2000, Claxton et al demonstrated that adherence to treatment regimens was inversely related to the number of doses per day.[17] Adherence with twice-daily dosing was significantly higher than with 4-times-daily dosing. A twice-daily sustained-release (SR) formulation of APAP could potentially enhance compliance, resulting in improved pain management.

A series of 4 investigational SR APAP formulations was designed to allow twice-daily dosing. These included a bilayer SR tablet,[18,19] 2 single-layer SR tablets (referred to hereafter as single-layer SR APAP #1 and single-layer SR APAP #2, which differed with regard to the excipients used in the formulations), and an enteric-coated SR tablet given in combination with a fast-disintegrating (FD) IR formulation (Table 1). The primary objective of this proof-of-principle study was to evaluate the duration of time that plasma APAP levels remained above a threshold of 4 μg/mL ($T_{C>4\mu g/mL}$)[20–23] with 4 new SR APAP formulations compared with 2 standard 1000-mg doses of IR APAP taken 6 hours apart. Secondary objectives were to compare the extent of absorption, other pharmacokinetic (PK) parameters, and safety of a single dose of the SR APAP formulations with 2 doses of IR APAP taken 6 hours apart in a semifed state.

Methods

Study Design and Procedures

In this phase 1 single-center, open-label, randomized, 5-way crossover PK study, healthy subjects received single doses of the 4 new SR formulations or 2 doses, 6 hours apart, of standard IR APAP tablets (Panadol Advance; GlaxoSmithKline Consumer Healthcare, Dungarvan, Ireland; Table 1) in random sequence (based on William's square design) during an 11-day confinement period at the study site (MDS Pharma Services, Tempe, Arizona). Adjacent treatments were separated by a washout period of 48 hours for the SR formulations and 42 hours for standard IR APAP. The 4 SR APAP formulations were all manufactured by GlaxoSmithKline Consumer Healthcare.

Table 2. Subject Demographics

Variable	n = 14
Age, mean (SD), years	29.43 (6.11)
BMI, mean (SD), kg/m^2	25.43 (1.77)
Sex, n (%)	
Male	8 (57.1)
Female	6 (42.9)
Race, n (%)	
White	13 (92.9)
Black	1 (7.1)

BMI, body mass index; SD, standard deviation.

Each treatment was administered in a semifed state (approximately 2 hours after a standardized breakfast) with 150 mL of water; fluid consumption was otherwise restricted for 2 hours before and after treatment. A semifed state was used because the stomach returns to a "fasting state" about 4 hours after eating, and a standard IR APAP dosing schedule is every 4 hours. Thus, during actual use, administration is likely to occur while the stomach is in transition between fed and fasted states, and the study was designed to mimic these conditions. All meals were standardized, and alcohol and caffeine consumption was prohibited during the study.

The study protocol was reviewed and approved by MDS Pharma Services Institutional Review Board (Lincoln, Nebraska), and all subjects provided written informed consent prior to initiation; the study was conducted in a manner compliant with the principles of the Declaration of Helsinki.

Study Population

Potential subjects were screened for eligibility within 21 days prior to treatment. Healthy male and female volunteers aged 18 through 50 years with a body mass index of 19–28 kg/m^2 were enrolled. Women who were pregnant or breastfeeding were excluded, and women of childbearing potential had to be using reliable contraception. Exclusion criteria included intolerance of or hypersensitivity to any of the study drug ingredients, medical conditions that could affect the action of the study drugs or the person's ability to complete the study, use of any medications within 14 days of the start of the study, and regular use of any drugs known to induce or inhibit hepatic drug metabolism within 30 days prior to study dosing. Additional exclusion criteria included vegetarian diet, hepatitis or human immunodeficiency virus infection, alcohol or substance abuse within the last 5 years, use of nicotine-containing products within the past 3 months, significant blood loss or donation within 56 days of the baseline visit, and hemoglobin ≤12 g/dL.

Assessments and Outcomes

Sampling procedures. Blood samples were collected once prior to treatment and at defined times posttreatment (0.5, 1, 2, 4, 5, 6, 7, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 15, and 18 hours). Samples were centrifuged at approximately 4°C for 15 minutes at 3000 revolutions per minute. The separated plasma was transferred to labeled polypropylene screw-top tubes and frozen at approximately −20°C within 1 hour of sampling until shipped to the central laboratory (Celerion, Lincoln, Nebraska) for assay.

Bioanalytic methods and validation. Plasma samples were analyzed by validated methods. Plasma concentrations of acetaminophen were determined by validated high-performance liquid chromatography–mass spectrometry, with d_4-acetaminophen as the internal standard, in an assay developed by Celerion (Lincoln, Nebraska). Liquid–liquid extraction was performed with methyl tertbutyl ether as the extraction solvent, and sample extracts were injected into an isocratic reversed-phase chromatography system using an Aquasil C18 (50 × 3 mm, 5 μm; Thermo Electron Corporation, Beverly, Massachusetts) and a polar organic mobile phase (15:85 acetonitrile:1% HCOOH in water). An API 4000 (Applied Biosystems/MDS Sciex, Foster City, California) was used for the detection of positive ions in multiple-reaction monitoring mode. The m/z transitions were 152.1→110.2 for acetaminophen and 156.1→114.1 for the d_4-acetaminophen internal standard. The assay's lower limit of quantitation was 50.0 ng/mL. The intrabatch accuracy range (% bias) was −2.4% to 6.0%, and the precision range (% coefficient of variation) was 1.9% to 6.8%. The interbatch accuracy range was 0.4% to 3.6%, and the precision range was 2.2% to 6.4%.

Pharmacokinetic analyses. The primary PK end point was the period during which each APAP formulation plasma concentration ($T_{C>4\mu g/mL}$) was elevated above a threshold of 4 μg/mL. Previous studies, conducted primarily in febrile children, indirectly suggested that a paracetamol plasma concentration of 3 to 5 μg/mL might be the minimum therapeutic concentration.[20,21] The United Kingdom Over-the-Counter monograph for acetaminophen also recognizes a threshold of 3 to 5 μg/mL as the likely minimum therapeutic concentration for analgesic effect.[22] For the purposes of the current study, 4 μg/mL was selected to allow for a comparison of the SR properties of the new SR formulations relative to 2 doses of standard IR APAP.

Secondary PK end points included area under the plasma concentration-versus-time curve from zero to 6 hours (AUC_{0-6}), AUC from zero to 12 hours (AUC_{0-12}), AUC from zero to time t when the formulation remained detectable (AUC_{0-t}), AUC from

Table 3. Mean Duration of Time Above a Plasma Acetaminophen Concentration of 4 μg/mL ($T_{C>4\mu g/mL}$) With Single Doses of 4 SR APAP Formulations and 2 Doses of Standard IR APAP

	Bilayer SR APAP	Single-Layer SR APAP #1	Single-Layer SR APAP #2	Enteric-Coated SR APAP + FD IR APAP	Standard IR APAP
$T_{C>4\mu g/mL}$, h					
Mean	8.1	7.3	7.5	7.1	8.3
Range	5.0–12.0	5.0–10.5	3.0–14.0	3.0–17.5	5.5–12.0
CV	25.2	22.5	34.1	50.3	21.8

APAP, N-acetyl-para-aminophenol; CV, coefficient of variation; FD, fast disintegrating; IR, immediate release; SR, sustained release.
n = 14.

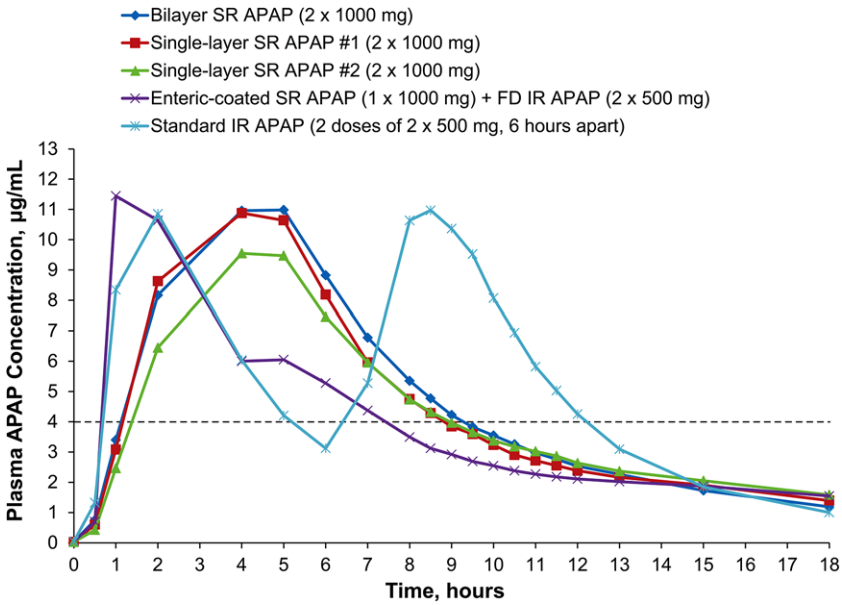

Figure 1. Adjusted mean plasma APAP concentrations over time (n = 14). Dashed line indicates the 4 μg/mL threshold used in the primary end point. Adjusted mean plasma paracetamol concentration for each time was calculated as the mean of individual adjusted plasma paracetamol concentration. Individual adjusted plasma concentrations for each subject were calculated as difference of observed (unadjusted) plasma paracetamol concentration at each point with plasma paracetamol concentration at time 0 (baseline). APAP, N-acetyl-para-aminophenol; FD, fast disintegrating; IR, immediate release; SR, sustained release.

zero and extrapolated to infinity (AUC_{0-inf}), maximum plasma concentration (C_{max}), elimination rate (K_{el}), time to C_{max} (T_{max}), and half-life of elimination ($T_{1/2}$).

Values for $T_{C>4\mu g/mL}$, C_{max}, and T_{max} were taken directly from observed plasma concentration data. AUC end points were derived from plasma concentrations and the elapsed time data using the linear trapezoidal method of noncompartmental model analysis. The $T_{1/2}$ was estimated by nonlinear regression of the terminal-phase plasma-concentration curve.

Safety

All treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were recorded, with safety monitoring continuing through 5 days after the last of the 5 treatments. TEAEs were categorized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities version 12, graded by severity, and assessed for relationship to study treatment.

Statistical Analysis

The safety population was defined as all subjects randomized in the study. The intent-to-treat (ITT) population was defined as all subjects who had evaluable data for at least 1 treatment period. The per-protocol (PP) population was defined as all subjects who fully complied with all study procedures.

Descriptive statistics (mean [or median for T_{max}], range, and coefficient of variation [CV]) were used to summarize each PK parameter and characterize the PK profiles of each formulation. Descriptive statistics and graphics were used to assess $T_{C>4\mu g/mL}$. No imputations

Table 4. Summary of Secondary PK End Points With Single Doses of 4 SR APAP Formulations and 2 Doses of Standard IR APAP

PK Parameters	Bilayer SR APAP	Single-Layer SR APAP #1	Single-Layer SR APAP #2	Enteric-Coated SR APAP + FD IR APAP	Standard IR APAP
AUC_{0-12}, μg·h/mL					
Mean	75.2	72.1	65.2	64.9	82.3
Range	45.1–143.6	48.6–111.2	36.7–102.8	40.4–103.6	50.7–128.7
CV	33.8	26.2	28.7	27.3	27.2
AUC_{0-t}, μg·h/mL					
Mean	85.6	83.4	77.5	76.0	95.2
Range	49.9–161.0	55.8–126.7	44.5–126.8	47.1–127.2	59.9–144.8
CV	32.6	24.5	27.6	30.1	25.9
AUC_{0-inf}, μg·h/mL					
Mean	97.0	98.5	94.9	83.4	99.4
Range	51.4–178.4	63.3–149.3	49.9–168.6	49.0–114.8	62.5–151.9
CV	32.3	27.4	28.7	29.6	25.7
C_{max}, μg/mL					
Mean	11.7	12.1	9.9	12.9	14.2
Range	6.8–21.4	7.6–17.4	6.2–16.2	8.5–19.9	8.0–24.5
CV	34.0	28.0	31.2	23.8	33.3
T_{max}, h					
Median	4.5	4.0	4.5	1.0	2.0, 2.0[a]
Range	2.0–5.0	2.0–5.0	2.0–5.0	0.5–2.1	1.0–4.0, 1.0–3.5[a]
CV	24.9	33.5	19.3	45.2	48.1, 35.7[a]
$T_{1/2}$, mean, h					
Mean	5.2	6.3	7.1	6.2	2.9[b]
Range	2.7–8.7	3.0–8.6	2.9–9.0	3.8–8.5	2.2–3.7
CV	35.1	25.9	25.9	29.5	12.6
K_{el} (1/h)					
Mean	0.15	0.12	0.11	0.12	0.24
Range	0.08–0.26	0.08–0.23	0.08–0.24	0.08–0.18	0.19–0.31
CV	38.8	35.2	46.5	30.8	12.5

APAP, N-acetyl-para-aminophenol; AUC, area under the plasma concentration-versus-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; FD, fast disintegrating; IR, immediate release; K_{el}, elimination rate; PK, pharmacokinetic; SR, sustained release; T_{max}, time to C_{max}; $T_{1/2}$, half-life of elimination.

The full intent-to-treat population consisted of 14 subjects; however, sample sizes for the individual end points varied because of missing data at some points for some outcomes.

[a]Calculated separately for each dose of IR APAP.

[b]$T_{1/2}$ calculated for first dose of IR APAP.

were made for missing data. Plasma concentrations below the limit of quantitation were entered as zero and included in the calculations of the means.

Results

Study Population

A total of 59 subjects were screened for the study, and 14 met eligibility criteria and were randomized to treatment. All 14 randomized subjects completed the study and were included in the safety, ITT, and PP populations. The mean age of the study population was 29.4 years, and 43% were female (Table 2).

Pharmacokinetic Outcomes

Results on the primary end point, $T_{C>4\mu g/mL}$, are shown in Table 3. Of the 4 SR formulations, bilayer SR APAP resulted in the longest elevation of plasma APAP concentration above a concentration of 4 μg/mL (mean $T_{C>4\ \mu g/mL}$, 8.1 hours), a duration that was closest to that of 2 doses of standard IR APAP (mean $T_{C>4\mu g/mL}$, 8.3 hours). Standard IR APAP reached the 4 μg/mL concentration 1 hour postdose, but fell below the threshold during the sixth hour (ie, at the end of the first dosing interval) such that the plasma APAP concentration was 3.1 μg/mL at hour 6 (Figure 1). In contrast, bilayer SR and single-layer SR APAP #2 maintained APAP concentrations above the 4 μg/mL threshold for approximately 9 hours postdose (Figure 1).

Key secondary PK end points are shown in Table 4. Single doses of bilayer SR APAP and single-layer SR APAP #1 produced AUC_{0-12}, AUC_{0-t}, and AUC_{0-inf} values that were greater than the other 2 SR

Table 5. Treatment-Emergent Adverse Events With Single Doses of 4 SR APAP Formulations and 2 Doses of Standard IR APAP

MedDRA v12 Preferred Term	Bilayer SR APAP	Single-Layer SR APAP #1	Single-Layer SR APAP #2	Enteric-Coated SR APAP + FD IR APAP	Standard IR APAP
Subjects with ≥1 TEAE	1 (7.1)	2 (14.3)	1 (7.1)	2 (14.3)	2 (14.3)
Pruritus generalized	1 (7.1)	1 (7.1)	0	0	1 (7.1)
Erythema	0	0	0	0	1 (7.1)
Abdominal pain upper	0	1 (7.1)	0	0	0
Diarrhea	0	0	1 (7.1)	0	0
Stomach discomfort	0	1 (7.1)	0	0	0
Joint swelling	0	0	0	0	1 (7.1)
Pain in extremity	0	0	0	1 (7.1)	0
Headache	1 (7.1)	0	0	1 (7.1)	0
Skin laceration	0	0	1 (7.1)	0	0
Epistaxis	0	0	0	1 (7.1)	0

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
n = 14; data presented as number (%) of subjects.

formulations and closest to results with 2 doses of standard IR APAP. C_{max} was similar for the SR formulations. Mean (range) $AUC_{0–6}$ was 46.7 μg·h/mL (27.0–93.3 μg·h/mL) with bilayer SR APAP, 46.4 μg·h/mL (24.9–74.3 μg·h/mL) with single-layer APAP #1, 39.1 μg·h/mL (21.1–66.1 μg·h/mL) for single-layer APAP #2, 45.8 μg·h/mL (29.2–67.6 μg·h/mL) with enteric-coated SR APAP plus FD IR APAP, and 38.1 μg·h/mL (21.9–63.3 μg·h/mL) with standard IR APAP.

Safety

Four subjects experienced 13 TEAEs over the duration of the study (Table 5). These included 3 TEAEs in 2 subjects after treatment with single-layer SR APAP #1, 2 TEAEs in 1 subject after treatment with bilayer SR APAP, 2 TEAEs in 1 subject after single-layer SR APAP #2, 3 TEAEs in 2 subjects after treatment with enteric-coated SR APAP plus FD IR APAP, and 3 TEAEs in 2 subjects during the 2 doses of standard IR APAP. All TEAEs were mild, and none were serious. One subject experienced treatment-related TEAEs, which included headache after bilayer SR APAP and generalized pruritus after single-layer SR APAP #1, after bilayer SR APAP, and during the 2 doses of standard IR APAP.

Discussion

This study compared the PK profile of single doses of 4 investigational SR formulations of APAP and 2 doses (6 hours apart) of standard IR APAP. Among the SR formulations, a single dose (2 × 1000 mg) of bilayer SR APAP tablet resulted in the longest time (~8 hours) with plasma APAP concentration >4 μg/mL, which may approximate a minimum therapeutic effect based on limited data in children.[20,21] This duration was similar to results with 2 doses of a standard IR APAP formulation, but without the temporary decrease below this threshold seen at hour 6 (ie, the end of the first dosing interval) with standard IR APAP.

Among the SR formulations, single doses of bilayer SR APAP and single-layer SR APAP #1 were the most comparable to 2 doses of standard IR APAP with regard to extent of absorption across the 12-hour period following administration ($AUC_{0–12}$) and as measured by $AUC_{0–t}$ and $AUC_{0–inf}$. In this study, C_{max} of the bilayer SR APAP was somewhat lower than that of 2 doses of standard IR APAP (11.7 vs 14.2 μg/mL), indicating that there was no dose-dumping effect observed with the bilayer SR APAP formulation. The C_{max} of standard IR APAP was similar after the first and second 1000-mg doses, consistent with previously published literature.[24,25] T_{max} was longest with bilayer SR APAP and single-layer SR APAP #2, which supports the SR profile of these formulations. Also consistent with an SR profile, all the SR formulations had longer half-lives compared with the first dose of the IR formulation. However, it must be noted that the half-life observed for SR formulations is dependent on absorption rate as well as elimination rate, so slower absorption of the SR formulations may also have contributed to the differences in half-life.

This small proof-of-principle single-dose PK study confirmed the acceptable PK profile of the bilayer SR APAP formulation. The sample size of this study did not allow for statistical comparison of the SR formulations with each other or with the 2 doses of standard IR APAP; therefore, only descriptive statistics were used. Based on these results, the PK profile of the bilayer SR formulation warranted investigation in larger single-dose studies. In addition, because this formulation was designed for twice-daily dosing, the PK profile at steady

state after repeated dosing over several days also warranted investigation.

We have since conducted 2 single-dose PK studies demonstrating that the bilayer SR tablet (2 × 1000 mg) had comparable bioavailability but greater SR characteristics compared with IR (2 × 500 mg) and ER (2 × 665 mg) APAP formulations and maintained plasma concentrations at or above 4 μg/mL for a longer duration than either IR or ER APAP.[18]

Availability of an APAP formulation with reduced daily dosing frequency may offer patients improved convenience over other APAP regimens requiring up to 4-times-daily dosing to control chronic or persistent forms of pain. Furthermore, current evidence indicates that patient adherence and satisfaction with treatment regimens improve with decreasing daily doses.[16,17] Therefore, further consideration is warranted to determine whether the twice-daily dosing formulations improve patient adherence to treatment and pain control.

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Declaration of Conflicting Interests

Yong Yue was an employee of GlaxoSmithKline Consumer Healthcare at the time of this study. D. Jeffery Liu is an employee of GlaxoSmithKline.

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