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Efficacy and tolerability studies evaluating a sleep aid and analgesic combination of naproxen sodium and diphenhydramine in the dental impaction pain model in subjects with induced transient insomnia

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SUMMARY

Study Objectives: The aim of this study was to evaluate the efficacy and tolerability of novel combination naproxen sodium (NS) and diphenhydramine (DPH) in subjects with postoperative dental pain along with transient insomnia induced by 5 h sleep phase advance. The present studies aimed to demonstrate the added benefit and optimal dosages of the combination product over individual ingredients alone in improving sleep and pain. **Methods:** Each of the two studies was a two-centre, randomised, double-blind and double-dummy trial. In the first study, subjects were randomised into one of the following treatment arms: NS 440 mg/DPH 50 mg, NS 220 mg/DPH 50 mg, NS 440 mg or DPH 50 mg. In the second study, subjects received either NS 440 mg/DPH 25 mg, NS 440 mg or DPH 50 mg. The co-primary end-points in both studies were wake time after sleep onset (WASO) and sleep latency (SL) measured by actigraphy. Other secondary sleep and pain end-points were also assessed. **Results:** The intent-to-treat population included 712 and 267 subjects from studies one and two, respectively. In the first study, only the NS 440 mg/DPH 50 mg combination showed significant improvements in both WASO vs. NS alone (−70.3 min $p = 0.0002$) and SL vs. DPH alone (25.50 and 41.50 min respectively, $p < 0.0001$). In the second study, the NS 440 mg/DPH 25 mg combination failed to show any significant improvements vs. either component alone. **Conclusions:** Only the NS 440 mg/DPH 50 mg combination demonstrated improvement in both sleep latency vs. DPH 50 mg and sleep maintenance (WASO) vs. NS 440 mg. There were no serious or unexpected adverse events reported in either study. **Clinical Trial Registration**: NCT01280591 (study 1); NCT01495858 (study 2)

What's known

Transient insomnia affects many adults and can be resolved by removing precipitating factors such as acute pain. Combination analgesic/sleep-aid products have been used over-the-counter (OTC) to help relieve transient insomnia associated with acute pain. While studies of currently marketed OTC analgesic/sleep-aid combinations assessed Total Sleep Time as the primary endpoint they did not assess sleep latency or sleep maintenance as primary endpoints.

What's new

This article reports on the first two studies to assess the benefits of the combination of a long-acting analgesic, naproxen sodium and a sleep aid, diphenhydramine HCl, in improving sleep and pain. These are the first studies of a combination analgesic/sleep-aid product to assess SL and WASO as co-primary endpoints. The combination naproxen sodium 440 mg/diphenhydramine 50 mg showed improvement in both primary sleep parameters, demonstrating benefit in SL and sleep maintenance.

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Disclosures

Both studies were sponsored by Bayer HealthCare Consumer Care. Irene Laurora, Yuan Wang, Palak Venkataraman and Robert An are employees of Bayer HealthCare Consumer Care. Dr Roth has served as consultant for Abbott, Accadia, AstraZenca, Aventis, AVER, Bayer, BMS, Cypress, Ferrer, Glaxo Smith Kline, Impax, Intec, Jazz, Johnson and Johnson, Merck, Neurocrine, Novartis, Proctor and Gamble, Pfizer, Purdue, Shire, Somaxon, Transcept. He has received research support from Cephalon, Merck and Transcept. He has served on speakers bureaus for Purdue. Dr Stephen A. Cooper has served as a consultant to many pharmaceutical companies in past years and formerly was Senior VP for Global Scientific Affairs at Wyeth Consumer Healthcare. He currently is an independent consultant to the pharmaceutical industry.

Introduction

Insomnia or disturbed sleep affects around 30% of adults and can be characterised as chronic or transient. Transient insomnia, which occurs in about one in four adults complaining of insomnia (1) is a transient sleep disturbance in patients with a history of normal sleep patterns that can be caused by a wide variety of conditions and situations such as acute pain (2,3). Some of the commonly reported insomnia-related complaints include feeling drowsy during waking hours, waking in the middle of the night, difficulty falling asleep and difficulty falling back asleep (1). Pain and sleep disturbance are inter-related conditions: increased pain can lead to sleep disturbance, which in turn leads to a lower pain threshold. In a polysomnographic study, increased pain along with other variables resulted in increased wakefulness or insomnia (4). Many individuals who suffer an acute pain episode also have difficulty with falling asleep and staying asleep. In many cases, transient insomnia is resolved by removing the precipitating factors, for example by relieving pain (2,5,6). In a 1999 National Sleep Foundation study, approximately 40% of respondents reported self-medicating to treat their insomnia (1). The present studies were designed to evaluate an analgesic/sleep aid combination that would relieve acute pain and improve sleep.

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Naproxen sodium (NS) is available without a prescription in at least 38 countries around the world in strengths of 220–550 mg. It is approved in the USA for the temporary relief of minor aches and pains with a dose of 220 or 440 mg every 8–12 h for a maximum of 660 mg in 24 h. A single 220 mg dose can provide pain relief for up to 12 h. Diphenhydramine (DPH) is shown to be an effective hypnotic (7–9) and is available in several countries globally. In the USA, DPH is indicated for the relief of occasional sleeplessness, taken as 50 mg at bedtime. The combination of NS and DPH is hypothesised to provide added benefit over the individual ingredients taken alone and the convenience of taking a single dosage form.

To demonstrate the added benefit of the combination over the single ingredients alone, two pivotal efficacy studies were conducted using the dental impaction pain model (DIPM) to induce transient insomnia. The DIPM has been widely used since the mid-1970s in the evaluation of analgesics for a number of reasons. It is a versatile model that can be used to assess analgesic efficacy, onset of effect and PK/PD parameters among others. Dental surgical procedures can be easily standardised and the population of subjects is usually relatively healthy and homogenous. Subjects can be screened in advance of the elective surgery thus allowing potential confounding treatments to be minimised. Furthermore, the DIPM is unique among pain models used to study analgesics as the time and intensity of pain onset, as well as duration of pain are predictable and other confounding factors are well controlled. Unlike most other pain models and conditions, the control over the surgical procedure provides for a wider dynamic range of postsurgical pain which facilitates differentiation of analgesic efficacy (assay sensitivity) between drugs and different doses of the same drug. There are many published studies in the archival literature substantiating the usefulness of the dental pain model in demonstrating the efficacy of a wide range of analgesics (10–12).

The dental pain model was adapted, using a sleep phase advance, to simultaneously assess both pain and transient insomnia. To accomplish this, the dental surgery was performed in the early afternoon and subsequently subjects were required to go to bed approximately 5 h earlier than usual. Utilising this phase advance model produces a shift in circadian bedtime, which causes a disruption to 'normal' sleep, resulting in transient insomnia (2,3). A larger magnitude shift from normal bedtime correlates to a larger sleep disturbance for those patients (13). In the present studies, the sleep phase advance was done so that the timing for the transient insomnia corresponded to the postsurgical pain episode. Sleep parameters were measured using wrist actigraphy, which has been shown to correlate well with polysomnography (14). The first study was designed to establish the efficacy of varying doses of NS using the FDA monograph sleep-aid dose of DPH (50 mg), while the second study was designed to assess efficacy of a lower dose (25 mg) of DPH in combination with the established effective analgesic dose of NS 440 mg from the first study. The comparators were the single entities NS and DPH, at the currently approved dosages for OTC use (440 and 50 mg, respectively)

These two studies evaluated three different dose combinations of NS and DPH (440/50 and 220/50 in the first study, and 440/25 in the second study) to determine the most effective dose combination in subjects with postoperative dental pain along with transient insomnia induced by a phase advance. The studies were designed to demonstrate the differential benefit of NS/DPH over the individual ingredients taken alone and to determine the optimal dosage for the combination product.

Methods

Study design

The two randomised, double-blind and double-dummy studies were each conducted at two centres. They were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. The study protocols were approved by a central Institutional Review Board, IntegReview. All study medications were over-encapsulated and matching placebos were used to maintain blinding. Subjects were kept under observation at a clinical research centre overnight and their sleep was phase advanced approximately 5 h from their usual bedtime. The actual bedtime was determined by when subjects reached at least moderate pain between 4:00 and 6:30 pm on the day of surgery. Subjects were then required to stay in bed for 10 h. The objective sleep variables were measured by wrist actigraphy; the devices were set to capture activity continuously for 10 h or until the subject awoke and subsequently data were transferred to study computers for analysis.

Patient population

The key inclusion criteria for both studies included otherwise healthy subjects who were scheduled to undergo surgical removal of a minimum of 2 third molars, of which at least one had to be an impacted mandibular third molar (varying from partial to full bony impaction). However, subjects with two full bony mandibular impactions were excluded. In

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addition, subjects must have experienced moderate to severe postoperative pain on the Categorical Pain Rating Scale (score of ≥ 50 mm on the 100 mm Pain Severity Visual Analog Scale or VAS). The main exclusion criteria included history of gastrointestinal bleeding or other bleeding disorders, alcoholism or drug abuse, insomnia within the last month, glaucoma and chronic antihistamine use. Subjects were also excluded if they received a score of > 11 on the Epworth Sleepiness Scale (15) or had done rotating, evening or night shift work over the past month. Subjects were prohibited from taking any medicine other than oral contraceptives, prophylactic antibiotics or routine medications to treat benign conditions for 5 days before oral surgery. Written informed consent from the subject and/or representative was obtained before enrolment in each study.

Randomisation and dosing

Eligible subjects underwent dental surgery between 1:30 and 3:30 pm on the day of admission. Subjects were randomised to receive a single dose of the combination NS/DPH, NS alone, or DPH alone after experiencing moderate to severe postsurgical pain (> 50 mm on the 100-mm Pain Severity VAS). Randomisation was computer-generated using a block design for each site. Subjects were assigned to a treatment group based on the randomisation schedule. The subjects, investigators and study staff involved in study conduct or data management were blinded to the identity of the treatment assignments throughout the course of the study. The first study had four treatment arms: NS 440 mg/DPH 50 mg, NS 220 mg/DPH 50 mg, NS 440 mg and DPH 50 mg. Subjects were randomised in a 2:2:2:1 ratio. The second study had three treatment arms: NS 440 mg/DPH 25 mg, NS 440 mg and DPH 50 mg. Subjects in this study were randomised in a 2:2:1 ratio. The dosages for the NS and DPH comparator arms were chosen based on the FDA approved OTC doses for pain and sleep. The lowest effective analgesic dose from study 1 was used to determine the analgesic dose in the combination product for study 2.

Assessments and outcome measures

The co-primary efficacy end-points were wake time after sleep onset (WASO) for the NS/DPH combination compared with NS alone and sleep latency (SL) for the NS/DPH combination compared with DPH alone. In the first study, both of the combination formulations were compared for each of the co-primary end-points. Actigraphy data for the co-primary and objective sleep end-points were recorded throughout the 10 h of bed time after administration of the investigational product. Upon awakening, the secondary end-points, which included objective and subjective sleep and pain parameters, were assessed. The secondary objective sleep parameters included TST and sleep efficiency (SE). The secondary subjective sleep parameters included the Karolinska Sleep Diary and a Global Assessment of the study medication as a sleep aid. The pain parameters were rescue medication use, time to rescue medication and pain intensity and relief scores upon awakening or at 10 h postdose. Subjects who did not experience adequate pain relief after administration of the investigational product were allowed to use rescue medication. The rescue medication given for additional pain relief was hydrocodone 5 mg/acetaminophen 500 mg tablets. Subjects were able to request rescue medication at any time after administration of the investigational product, however, they were encouraged to wait at least 60 min. Change in pain intensity was assessed using a four-point categorical Pain Rating Scale, and pain relief was measured using a five-point categorical Pain Relief Rating Scale. Investigators also administered a Global Assessment of the study medication as a pain reliever. Finally, study staff conducted follow-up calls within 2–5 days after the end of the dosing period. This end-of-trial assessment included assessment of occurrence or persistence of AEs, review of medications taken and assessment of adequate treatment and follow-up (Figures 1–4).

Statistical analysis

The sample sizes in both studies were estimated to provide 90% power to detect clinically meaningful differences in WASO and SL. All statistical tests were made at the two-sided significance level of 0.05. In both studies, the analysis population includes the intent-to-treat (ITT) population for efficacy and the safety population for safety assessments. The ITT population consisted of all subjects who were randomised, had taken at least one dose of study drug, and provided at least one postdose observation on an efficacy parameter. The safety population consisted of all subjects who were randomised and had taken at least one dose of the study drug.

In the first study, the hierarchical testing procedure was used to adjust for multiplicity to control type 1 error. The treatment comparisons were each tested sequentially for two co-primary end-points in the following order:

Wake time after sleep onset

- NS 440 mg/DPH 50 mg vs. NS 440 mg
- NS 220 mg/DPH 50 mg vs. NS 440 mg
- NS 440 mg/DPH 50 mg vs. NS 220/DPH 50 mg

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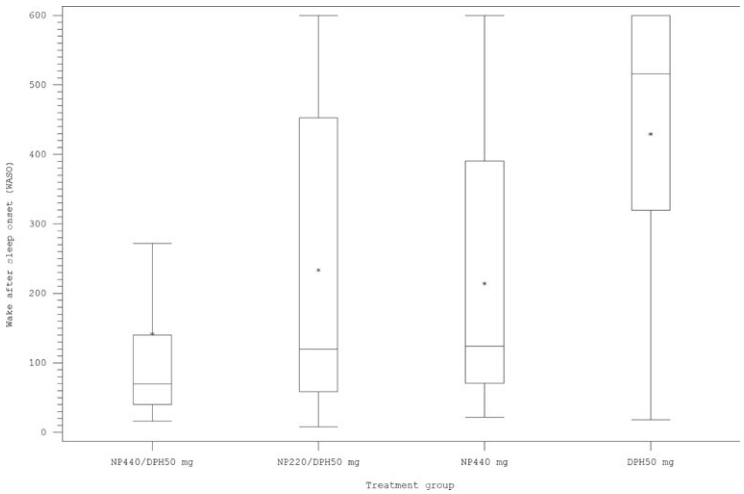

Figure 1 Box plot for wake after sleep onset in study 1 (intent-to-treat population)

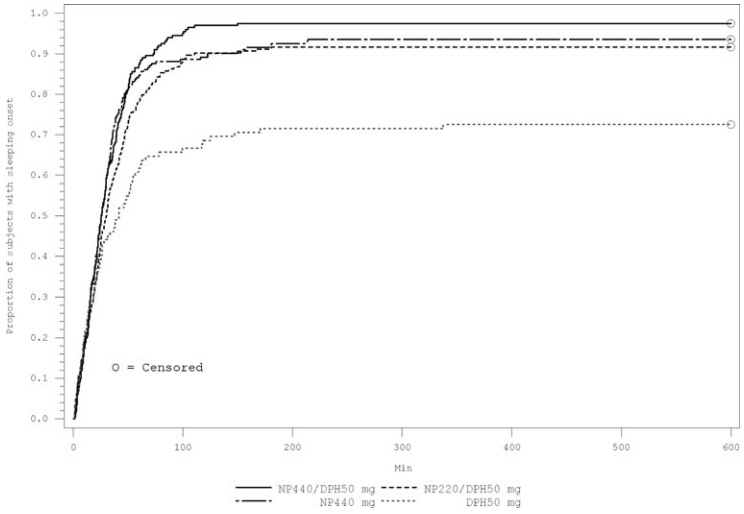

Figure 2 Time to sleep onset in study 1 (intent-to-treat population)

Sleep latency

- NS 440 mg/DPH 50 mg vs. DPH 50 mg
- NS 220 mg/DPH 50 mg vs. DPH 50 mg
- NS 440 mg/DPH 50 mg vs. NS 220 mg/DPH 50 mg

If a comparison was not found to be statistically significant at the level of 0.05, all subsequent comparisons were not technically eligible to be declared significant. All treatment comparisons were still made regardless of eligibility to present the complete outcome.

The second study compared WASO for NS 440 mg/DPH 25 mg vs. NS 440 mg and SL for NS 440 mg/DPH 25 mg vs. DPH 50 mg. Both tests had to be statistically significant at $p \leq 0.05$ for the combination to be declared efficacious.

In both studies, sleep data from subjects who rescued were censored following the use of the rescue medication when applicable. If the subject rescued before sleep onset, both SL and WASO were set to 600 min (the full 10 h of in-bed time). Subjects who rescued after sleep onset were considered to be awake for the remainder of the study duration and the SL was unaffected. Sensitivity analyses were performed to assess the robustness of the efficacy results to account for potential bias in the analyses.

In both studies, WASO was assessed using an analysis of covariance (ANCOVA) model. Least squares (LS) means were calculated for each treatment group and the mean differences were determined for each comparison listed above. SL was assessed using the Kaplan–Meier method and log-rank test. For the secondary end-points, the Cochran–Mantel–Haenszel

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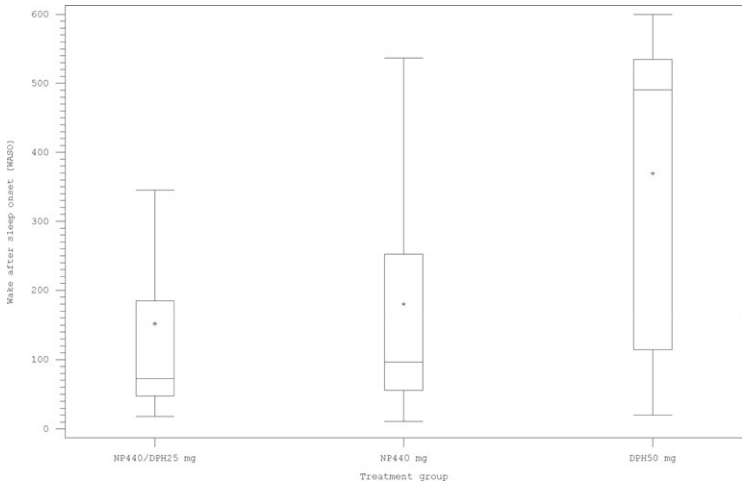

Figure 3 Box plot for wake after sleep onset in study 2 (intent-to-treat population)

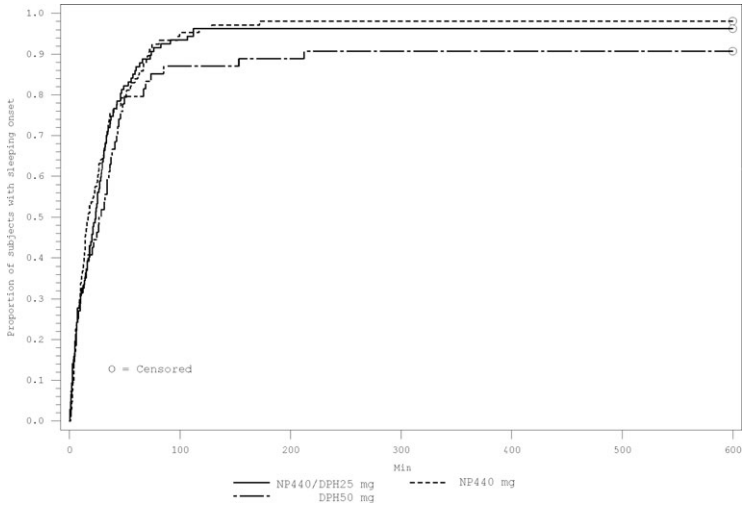

Figure 4 Time to sleep onset in study 2 (intent-to-treat population)

(CMH) test was used to evaluate the subjective sleep parameters, Global Assessment of study medication as a sleep aid and the Karolinska Sleep Diary. Pain intensity scores were assessed using the ANCOVA model, while the Global Assessment of study medication as a pain reliever and pain relief scores were assessed using the CMH test. Time to rescue was assessed using the Kaplan–Meier method. Adverse events for both studies were recorded and tabulations were generated by treatment group.

Results

Subject disposition/baseline characteristics

Across the two studies, a total of 979 subjects (712 and 267 subjects for Study 1 and 2, respectively) were randomised and included in the ITT and safety analysis populations. The baseline demographics were generally comparable between treatment groups in each study; the mean age was 21.2 years, most of the subjects were Caucasian and a slightly higher percentage were female (see Table 1). Three subjects in study 1 did not complete the study and all subjects in study 2 completed the study. Of the three subjects who discontinued in study 1, two discontinued at the request of the subject or legally acceptable representative and one did not meet inclusion criteria.

Study 1 results

Only the NS 440 mg/DPH 50 mg combination showed significant improvement in both WASO and SL when compared with the individual components alone. The NS 440 mg/DPH 50 mg combination had a significantly shorter WASO than NS alone

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Table 1 Demographic summary for the pivotal efficacy studies (safety populations)

Demographic	Study 1 (*N* = 712)	Study 2 (*N* = 267)
Age (years)		
Mean	21.2	21.2
SD	4.70	5.25
Gender (*n*, %)		
Male	309 (43.4)	94 (35.2)
Female	403 (56.6)	173 (64.8)
Ethnicity (*n*, %)		
Hispanic or Latino	153 (21.5)	55 (20.6)
Not Hispanic or Latino	559 (78.5)	212 (79.4)
Race (*n*, %)		
White	634 (89.0)	234 (87.6)
Black or African American	27 (3.8)	17 (6.4)
Asian	20 (2.8)	10 (3.7)
Other	23 (3.3)	3 (1.1)
Multiracial	8 (1.1)	3 (1.1)
Baseline pain intensity (categorical scale)		
Moderate pain	494 (69.4)	160 (59.9)
Severe pain	218 (30.6)	107 (40.1)
Baseline pain intensity (VAS in mm)		
Mean	72.4	75.6
SD	12.31	10.26

SD, standard deviation; VAS, visual analog scale.

(−70.3 min, p = 0.0002). It also had a significantly shorter SL than DPH alone (25.50 min for 440 mg combination and 41.50 min for DPH, p < 0.0001). The NS 220 mg/DPH 50 mg combination failed to meet both primary end-points; it had a significantly longer WASO compared with NS alone (16.9 min more, p = 0.03627) and significantly longer SL compared with DPH alone (p = 0.0003). When comparing the two combination formulations, NS 440 mg/DPH 50 mg was significantly better than NS 220 mg/DPH 50 mg for both WASO (−87.1 min, p < 0.0001) and SL (25.50 for the 440 mg combination and 30.25 for the 220 mg combination, p = 0.0096; Table 2). The results from the sensitivity analyses supported the findings from the primary analysis, indicating that efficacy results were consistent and robust regardless of which data imputation method was used.

The secondary efficacy outcomes supported the findings from the primary end-points. For the objective secondary sleep end-points, only the NS 440 mg/DPH 50 mg formulation showed a significant improvement over NS alone in both TST and SE. The NS 220 mg/DPH 50 mg formulation failed to show a significant difference from NS alone (Table 3). For the pain parameters, both combination formulations consistently showed significant differences in pain intensity and pain relief compared with DPH alone. The NS 440 mg/DPH 50 mg arm had the lowest proportion of subjects taking rescue medication over the time course of the study (43 subjects or 21.2%) at the final time point (Table 4).

Study 2 results

In study 2, there were only small differences among the three treatment arms. The NS 440 mg/DPH 25 mg combination had a shorter WASO vs. NS and shorter SL vs. DPH but neither was statistically significant [−24.83 min (p = 0.3047) and 23.5 min for combination, 27.5 min for DPH (p = 0.1677), respectively; Table 2]. The results of the objective secondary sleep end-points were similar to the results of the co-primary end-points; neither TST nor SE was significantly improved for the combination compared with NS (Table 3). Some of the subjective

Table 2 Comparison of co-primary efficacy end-points from the two pivotal efficacy studies (intent-to-treat population)

	Study 1				Study 2		
	NS 440 mg/ DPH 50 mg *N* = 203	NS 220 mg/ DPH 50 mg *N* = 204	NS 440 mg *N* = 203	DPH 50 mg *N* = 102	NS 440 mg/ DPH 25 mg *N* = 107	NS 440 mg *N* = 106	DPH 50 mg *N* = 54
WASO (mean time in minutes)	142.2	233.6	214.3	429.5	152.13	180.12	369.54
p-value vs. NS 440	0.0002	0.3627			0.3047		
p-value vs. 220/50	<0.0001						
Sleep latency (median time in minutes)	25.50	30.25	25.75	41.50	23.50	16.75	27.50
p-value vs. DPH 50	<0.0001	0.0003			0.1677		
p-value vs. 220/50	0.0096						

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Table 3 Comparison of the objective sleep parameters from the two pivotal efficacy studies (intent-to-treat populations)

	Study 1		Study 2
	NS 440 mg/DPH 50 mg *N* = 203	NS 220 mg/DPH 50 mg *N* = 204	NS 440 mg/DPH 25 mg *N* = 107
Secondary efficacy measures			
Total sleep time[†]			
vs. NS 440 mg[‡]	70.4*	−18.1	26.3
vs. NS 220 mg/DPH 50 mg[‡]	88.5*		
Sleep efficiency[†]			
vs. NS 440 mg[‡]	11.7*	−3.0	4.4
vs. NS 220 mg/DPH 50 mg[‡]	14.7*		

[†]Mean time in minutes; [‡]LS mean treatment difference; *Statistically significant ($p < 0.05$).

Table 4 Comparison of subjective pain assessments from the pivotal studies (intent-to-treat populations)

	Study 1				Study 2		
Assessments	NS 440 mg/DPH 50 mg *N* = 203	NS 220 mg/DPH 50 mg *N* = 204	NS 440 mg *N* = 203	DPH 50 mg *N* = 102	NS 440 mg/DPH 25 mg *N* = 107	NS 440 mg *N* = 106	DPH 50 mg *N* = 54
Pain intensity*							
vs. NS 440 mg	−0.3 (−0.4, −0.1)[†]	0.2 (0.0, 0.4)[†]			−0.09 (−0.3, 0.1)[‡]		
vs. DPH 50 mg	−1.2 (−1.5, −1.0[†]	−0.8 (−1.0, −0.6)[†]			−0.67 (−1.0, −0.4)[†]		
vs. NS 220 mg/DPH 50	−0.5 (−0.6, −0.3)[†]				Na		
Pain relief[§]	2.4 (1.47)	1.7 (1.58)	2.0 (1.58)	0.6 (1.14)	2.3 (1.44)	2.2 (1.52)	0.9 (1.29)
vs. NS 440 mg	0.0047	0.0268			0.3707		
vs. DPH 50 mg	< 0.0001	< 0.0001			< 0.0001		
vs. NS 220 mg/DPH 50	< 0.0001				Na		
IP as pain reliever[¶]	2.9 (0.93)	2.6 (0.99)	2.8 (0.94)	1.8 (1.05)	2.8 (0.86)	2.7 (0.82)	2.2 (1.08)
vs. NS 440 mg	0.2734	0.2841			0.3765		
vs. DPH 50 mg	< 0.0001	0.0014			0.0273		
vs. NS 220 mg/DPH 50	0.0342						

*Categorical Pain Rating Scale (four-point scale) as LS mean treatment difference from baseline and 95% CI for the LS mean treatment difference. [†]Statistically significant ($p < 0.05$). [‡]Not statistically significant ($p < 0.05$). [§]Pain Relief Rating Scale (five-point scale) as mean (standard deviation) by treatment group; p-values are provided. [¶]Global Assessment of Investigational Product as a Pain Reliever Scale (five-point scale) as mean (standard deviation) by treatment group; p-values are provided.

sleep endp-oints were improved vs. DPH but not against NS. Similarly for the pain end-points, the combination product was significantly improved compared with DPH but not NS. With regard to use of rescue medication, the NS 440 mg/DPH 25 mg arm had a significantly longer time to rescue than the DPH arm ($p = 0.0273$). Finally, the DPH arm had the highest proportion of subjects that required rescue medication over the time course of the study (35 subjects or 64.8%).

Safety

There were no serious adverse events or deaths reported in either study. The most commonly reported events were from the system organ classes of nervous system and gastrointestinal disorders. The most commonly reported adverse events (> 2% of subjects in either study) were nausea, vomiting, dizziness, headache and cold sweat (Table 5). No individual treatment emergent adverse events (TEAEs) were reported in greater than 10% of subjects in any

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Table 5 Most commonly reported treatment emergent adverse events (occurring in > 2% of subjects)

	Study 1				Study 2		
	NS 440/DPH 50 *N* = 203	NS 220/DPH 50 *N* = 204	NS 440 *N* = 203	DPH 50 *N* = 102	NS 440/DPH 25 *N* = 107	NS 440 *N* = 106	DPH 50 *N* = 54
Vomiting, *n* (%)	2 (1.0)	5 (2.5)	6 (3.0)	4 (3.9)	1 (0.9)	0	1 (1.9)
Nausea, *n* (%)	15 (7.4)	12 (5.9)	14 (6.9)	10 (9.8)	6 (5.6)	4 (3.8)	2 (3.7)
Headache, *n* (%)	12 (5.9)	13 (6.4)	16 (7.9)	8 (7.8)	6 (5.6)	3 (2.8)	10 (18.5)
Dizziness, *n* (%)	9 (4.4)	8 (3.9)	6 (3.0)	4 (3.9)	9 (8.4)	9 (8.5)	2 (3.7)
Cold sweat, *n* (%)	0	0	0	0	3 (2.8)	0	1 (1.9)

treatment group. In study 1, most of the reported TEAEs were mild or moderate in nature. Three subjects experienced severe TEAEs (presyncope, vomiting, headache) in the NS 440 mg/DPH 50 mg, NS 220 mg/DPH 50 mg and NS 440 mg groups, respectively. In study 2, all of the TEAEs were reported to be mild in nature. There were no reports of somnolence after once-daily nighttime dosing with any of the combination doses used in these studies. None of the subjects in these two studies discontinued the investigational product because of an adverse event.

Table 6 Comparison of topline results from sleep-aid/analgesic combination products

Sleep parameter	Aleve PM	Advil PM	Tylenol PM	
			Study 1	Study 2
SL for combo vs. DPH alone	*	NS	N/A	N/A
WASO for combo vs. analgesic alone	*	*	N/A	N/A
TST for combo vs. analgesic alone	*	*	*	NS
TST for combo vs. DPH alone	*	N/A	*	*

*Statistically significant improvement; NS, non-statistically significant difference. Aleve PM study secondary end-point was TST, Advil PM study secondary end-points were SL and WASO.

Discussion

Transient insomnia is a condition that is often treated by relieving the precipitating factors. In the case of pain as the precipitating factor for insomnia, effective and rapid analgesic action is indicated. The combination of an analgesic and a sleep aid has previously been shown to be effective for occasional sleeplessness associated with minor aches and pains (7,16–18); however, this is the first combination product to contain the long-acting analgesic naproxen sodium. In studies of other currently marketed OTC sleep-aid/analgesic combinations, the primary end-point was TST. TST however does not differentiate between improvements in SL vs. sleep maintenance. In a study comparing ibuprofen 400 mg/diphenhydramine 50 mg with ibuprofen 400 mg alone, TST (measured by actigraphy) in the combination arm was significantly longer than the ibuprofen alone arm. However, for the secondary end-points, only WASO was significantly lowered compared with ibuprofen alone while SL was not (16). In addition, there were two pivotal studies comparing acetaminophen 1000 mg/diphenhydramine 50 mg to the individual components for the primary end-point of TST. Of these, one study showed a significant improvement in TST with the combination product vs. acetaminophen alone. Both studies showed a significant improvement in TST for the combination vs. diphenhydramine alone. The secondary end-points were not published (18) (Table 6). These studies demonstrate an overall increase in TST, but they were not designed to assess how much of the increase is attributed to an improvement in SL vs. sleep maintenance. It should be noted that there have been no published pivotal head-to-head trials comparing the combination of naproxen sodium 440 mg and diphenhydramine 50 mg to the currently marketed combination analgesic/sleep-aid products to date.

The NS 440 mg/DPH 50 mg combination in Study One showed an improvement in both the co-primary end-points, SL and WASO, in addition to the other sleep parameters studied. Both combination products in Study 1 showed a separation from the DPH arm in decreasing SL, which suggests that the NS provides additional benefit in sleep onset over DPH alone. Subjects with mild to moderate pain and transient insomnia would benefit from the addition of a long-lasting analgesic to DPH since the analgesic is important in driving sleep onset improvement in this population. With respect to sleep maintenance (WASO), the combination NS 440 mg/DPH 50 mg arm had a significantly reduced mean wake time during sleep than the NS 440 mg alone arm

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(−70.3 min vs. NS 440 mg, p = 0.0002). The improvement with the 440 mg combination vs. NS alone supports the hypothesis that DPH is an important contributor to the improvement in sleep maintenance for the combination product. In contrast, the NS 220 mg/DPH 50 mg arm had an increased mean wake time during sleep in comparison to the NS alone arm (+16.9 min vs. NS 440 mg, p = 0.3627), supporting the concept that increased analgesia results in faster sleep onset and sustained sleep maintenance. In the second study, the combination product (NS 440 mg/DPH 25 mg) failed to reach significance for either co-primary end-point against the individual ingredients alone.

The combination products in each of the two studies were generally well tolerated. There were no serious adverse events or any adverse events leading to discontinuation. Furthermore, there were no unexpected adverse events as compared with the single ingredients' safety profiles. The NS 440 mg/DPH 50 mg combination product was also shown to be well tolerated after 10 consecutive days of use in a randomised, double-blind, placebo-controlled safety study in subjects with occasional sleeplessness because of minor pain (19). The risks and benefits of NSAIDs have been extensively studied and are well known. As with all NSAIDs, naproxen sodium may cause GI bleeding and this risk increases with increased dose and duration of use or if the patient has certain risk factors such as a history of stomach ulcers or bleeding problems, increased age (60 or older), daily consumption of alcoholic beverages or concurrent use with a blood thinner or steroid drugs. Products containing NSAIDs, including NS/DPH, continue to carry label warnings regarding gastrointestinal and cardiovascular risks with use of NSAIDs.

Rebound insomnia is the worsening of sleep after discontinuation of certain hypnotics. It has been associated with sleep aids with a short half-life, such as short-acting benzodiazepines, and at higher doses (20,21). There were no reports of rebound insomnia in these two studies, but they were not designed to assess this phenomenon. There are several published studies that assess DPH as a sleep aid at various doses including 50 mg. In one previous study of DPH, seven of 15 elderly subjects (ages 70–89) were reported to have rebound insomnia after 14 days of treatment. Subjects were determined to have rebound insomnia if the subjective sleep parameters were rated as worse on the first, second or third night after treatment discontinuation compared with baseline (22). Conversely, there are several studies of DPH as a sleep aid administered in both single and multiple-dose regimens, including elderly subjects, that had no reports of rebound insomnia (8,23–27). The majority of the data seems to indicate that there is little concern for rebound insomnia following the use of DPH 50 mg when used for 14 days or less.

While a fixed-dose combination has the potential advantages of increased compliance, convenience and cost savings, it may also have the disadvantage of reduced flexibility in dosing. However, based on the data from the two efficacy studies, the lower dose combination (naproxen 220 mg with DPH 50 mg, and naproxen 440 mg with DPH 25 mg), did not show a significant benefit vs. the single ingredients alone. Researchers have simulated transient acute sleep disturbances in the laboratory and have demonstrated that the response to these laboratory conditions parallels the effects in 'real life' (2,9,28–30). Sleep phase advance, the model used in these studies, is shown to cause a disruption in sleep parameters such as those for sleep maintenance (WASO, TST and SE) and sleep onset (31–36). However, it is important to keep in mind that the sleep phase advance is an induced insomnia model and will not exactly mimic a natural transient insomnia for a variety of reasons. With respect to pain relief, the dental pain model causes an induced somatic pain. The results from dental pain models can be extrapolated to other somatic pain states, but may not adequately represent pain that is not somatic in nature. Subjects with non-somatic pain could also experience transient insomnia as a result of unrelieved pain. Finally, in subjects who took rescue analgesic, subsequent sleep measures were censored, as is usual in clinical assessments of analgesics, but unique for assessment of sleep. However, sensitivity analyses were performed to address these data handling procedures and the resulting sleep assessments were unaffected.

Based on these two studies, it can be concluded that the combination of naproxen sodium 440 mg and diphenhydramine 50 mg is well tolerated and effective for the treatment of occasional insomnia associated with minor aches and pains. This combination helps to improve both sleep onset and sleep maintenance; two commonly reported sleep complaints (1) that previously were not addressed together by any one FDA-approved OTC product.

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Irene Laurora design, interpretation, critical revision of article; Stephen Cooper design, interpretation, critical revision of article; Yuan Wang design, interpretation, critical revision of article; Palak Venkataraman design, interpretation, critical revision of article; Robert An statistics, critical revision of article; Thomas Roth design, interpretation, critical revision of article.

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