DNP CLINICAL REVIEW

Application Type	NDA
Application Number(s)	N 205,352
Priority or Standard	Standard
Submit Date(s)	3/20/13
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PDUFA Goal Date	1/20/14
Collaborative Division	DNP/ODE1
Lead Division	DNCE/ODE4
Reviewer Name(s)	Veneeta Tandon
Review Completion Date	1/10/14
Established Name	Naproxen Sodium+Diphenhydramine hydrochloride
(Proposed) Trade Name	ALEVE PM
Therapeutic Class	NSAID+Sleep Aid
Applicant	Bayer
Formulation(s)	Tablets
Dosing Regimen	2 tablets taken orally
Indication(s)	Relief of occasional sleeplessness associated with minor aches and pains
Intended Population(s)	Adults and children $\geq$ 12 years

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1 Recommendations

1.1 Efficacy

The primary efficacy variables for the assessment of treatment of sleepless associated with pain in dental pain/phase advance sleep models were 'Wake After Sleep Onset' (WASO) and 'Sleep Latency' derived from actigraphy. Assessment of pain relief from Aleve® PM was one of the secondary efficacy variables. Pain relief was assessed through categorical pain rating scale, pain relief rating scale, global assessment and time to recue medication. Although, secondary efficacy pain variables were included, the efficacy for pain was indirectly measured primarily by sleep latency as pain from tooth extraction would be disruptive to sleep.

The evidence of effectiveness of the naproxen 440 mg+diphenhydramine 50 mg combination dose was based on one phase 3 study, a single dose, double blind, parallel group study (#14837). The primary endpoint, WASO, was significantly shorter (Δ= -70 minutes) for NP440/DPH50 than for NP440 alone (p=0.0002). The co-primary endpoint, Sleep Latency, was significantly shorter (Δ= -15.9 minutes) for NP440/DPH50 than DPH50 alone (P=<0.0001). The results suggested that benefit on sleep latency was from the analgesic and not from DPH, whereas DPH contributed towards sleep maintenance. The results are statistically positive based on pre-specified analyses agreed to by FDA during development (see OTC clinical review for the regulatory history), although the interpretation of the results are problematic due to imputed values of WASO and sleep latency in high percentages of subjects taking rescue pain medication. Also, the severity of post-surgical pain in the dental pain/ phase advance sleep model could raise concern about the generalizability of this model to the actual clinical population that would be taking this OTC product.

A lower analgesic dose, naproxen 220 mg, in the combination NP220/DPH50 was not statistically superior to NP440 alone (p=0.3627) for WASO, but was statistically superior to DPH50 alone for Sleep Latency (p=0.0003). A post surgical dental pain model may not be a good model for understanding the efficacy of a lower naproxen dose in the OTC setting due to the greater pain severity in this model. A lower analgesic dose in the combination could be effective in relieving sleeplessness associated with minor aches and pains associated with common cold, headache etc. Naproxen 220 mg has been found by FDA to be effective in the OTC setting, and labeling recommends using the smallest effective dose. Given that, it might be considered that the lowest effective combination dose could be a rational choice for the combination product as well.

A lower diphenydramine dose, 25 mg, in the combination NP440/DPH25 mg was not statistically superior to either NP440 or DPH50 alone for WASO or Sleep Latency, but this study (#15881) was underpowered, with half the number of subjects than the study evaluating the other two combination doses (NP440/DPH50 and NP220/DPH50), such that no conclusion about the efficacy of 25 mg diphenhydramine can be made.

There was no replication of efficacy findings for the combination treatment doses evaluated and hence the proposed dose. This was agreed upon in prior communications with the sponsor (in a teleconference on April 2012). A single study in this case appears to be acceptable for efficacy as individually, naproxen sodium and DPH are effective at the doses proposed for use in the combination, and this use is for the same indications, pain and insomnia, respectively. A single study also appears acceptable on the grounds of a statistically very persuasive finding (P=0.0002) that NP440/DPH is superior to the individual ingredients based on pre-specified comparisons on both WASO (p=0.0002) and Sleep Onset (p=<0.0001). In addition the secondary endpoints, Total sleep time, Sleep efficiency, global assessment as sleep aid, and Karolinska Sleep Dairy supported the superiority of NP440/DPH50.

1.2 Safety

No new or unexpected adverse events were discovered in the course of the development program for this combination product compared to the individual components (naproxen sodium and diphenhydramine) that have been marketed in the United States for the same indications (pain and insomnia). The current studies may not have power to identify new safety issues. In the 10 day safety study, subjects ≥ 60 years (7.7%) had a higher rate of dizziness than younger subjects (2.6%) compared to none in either placebo group. Dizziness is not mentioned as an adverse event with other OTC products approved for the treatment of sleeplessness associated with pain and may be considered a new adverse event for NP440/DPH50 combination product. Dizziness is listed as common adverse event with an incidence rate of 3-9% for prescription naproxen without mention of incidence rate in placebo. Common Adverse events seen after single dose (in the tooth-extraction setting) were nausea, headache, dizziness and vomiting. Somnolence was not observed in the efficacy studies, but 38% of subjects on NP440/DPH50 in the PK study had somnolence, compared to 6.7% in the NP440 group and 48% in the DPH alone group. About a third to half of the subjects in combination (27%) or DPH alone (42%) group had somnolence that lasted 6-10 hours, with one subject in the NP440/DPH50 fed group that had somnolence up to 14 hours. Drowsiness is also a common adverse event for prescription naproxen.

Each of the individual ingredients, naproxen sodium and DPH, are currently marketed OTC products at the doses proposed for Aleve® PM; naproxen sodium as an analgesic and DPH as a sleep aid and antihistamine. DPH has been a monograph drug since 1982.

Recently, concerns have been raised about the safety of diphenhydramine as a sleep aid (and for other indications as well). Some published reports suggest a risk of next-day residual impairment with the use of diphenhydramine 50 mg. Concerns have also been raised about the anticholinergic effects of diphenhydramine, particularly in the elderly. These data suggest that the balance of benefit to risk may be unfavorable for diphenhydramine. These concerns were previously discussed in detail in Dr. Ronald Farkas's review of Tylenol PM (2009). A more recent article by Katayose et al[1] (2012) found significant subjective and objective sleepiness and

[1] Katayose et al. 2012. Carryover effect on next day sleepiness and psychomotor performance of nighttime administered antihistamine drugs: a randomized trial. Hum. Psychopharmacol Clin Exp 27: 428-436

suppression of psychomotor performance the day after administration of DPH. The authors suggest a risk of carryover effects even after blood levels would have dropped to half the peak concentration in the morning. Also, large discrepancies have been reported between blood kinetics and receptor occupancy of antihistamine receptors in the brain. The receptor occupancy was 56% at 1.5 h after DPH administration (Tashiro et al., 2008[2]) but remained as high as 45% even after 12 h (Zhang et al., 2010[3]). These findings suggest that carryover effects might be present even after blood drug levels have decreased.

All OTC labels containing diphenhydramine have the following warnings: When using this product "drowsiness will occur", "do not drive a motor vehicle and operate machinery". The labels also say "do not use unless you have time for a full night's sleep". The effectiveness of labeling for mitigating risk was not directly addressed by the sponsor in this submission, and may be a concern.

FDA requested Bayer to evaluate a lower diphenhydramine dose, 25 mg. The study with DPH25 failed to show superiority to individual components, but it was underpowered. The sponsor's sample size calculations did not reflect the standard deviation of the clinical endpoints observed in the previous study. Hence, the possible effectiveness of DPH25 remains poorly understood. The 10-day multiple dose safety study only evaluated the combination that contained DPH 50 mg, hence the relative safety of the lower DPH dose also remains poorly understood. Sunshine et. al. (1978)[4] reported that both 25 and 12.5 mg diphenydramine were effective for insomnia using subjective endpoints. Well established evidence of 25 mg DPH as a sleep aid using objective endpoints is not available at the present time.

Many similar products containing diphenyhydramine hydrochloride are marketed as OTC products (eg. Tylenol® PM, others such as Advil® PM, Motrin® PM and Bayer® PM contain diphenhydramine citrate 38 mg, which is equivalent to diphenhydramine hydrochloride 25 mg). Diphenyhydramine is also the only ingredient in many OTC sleep aid products. [See OSE review for post marketing safety of diphenydramine containing products].

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Bayer has proposed a routine risk minimization plan that includes

- comprehensive label information to health care professionals and consumers
- post-marketing surveillance
- reporting

[2] Tashiro M, Mochizuki H, Sakurada Y, et al. 2006. Brain histamine H1receptor occupancy of orally administered antihistamines measured by positron emission tomography with (11)C-doxepin in a placebo-controlled crossover study design in healthy subjects: a comparison of olopatadineand ketotifen. Br J Clin Pharmacol 61: 16–26.

[3] Zhang D, Tashiro M, Shibuya K, et al. 2010. Next-day residual sedative effect after nighttime administration of an over-the-counter antihistamine sleep aid, diphenhydramine, measured by positron emission tomography.J Clin Psychopharmacol 30: 694–701.

[4] Sunshine A et.al. Hypnotic activity of diphenhydramine, methapyriline and placebo. J. Clin Pharmacol, 1978; 18:425-31

1.4 Recommendations for Postmarket Requirements and Commitments

No recommendations for postmarket studies are made.

2 Introduction and Regulatory Background

Bayer's proposed nighttime analgesic/sleep-aid product combines 2 OTC approved products, naproxen sodium and diphenydramine. Naproxen sodium is a non-steroidal anti-inflammatory drug (NSAID). It inhibits prostaglandin synthesis by decreasing the activity of the enzyme cyclooxygenase, which in turn reduces the formation of prostaglandin chemical precursors. DPH is a first generation antihistamine, an H1-antagonist of the ethanolamine class used for a variety of OTC indications, including as an antitussive, a nighttime sleep-aid and an antihistamine for allergy symptoms.

There are several OTC analgesic + nighttime sleep-aid combination products available in the US indicated for pain accompanied by sleeplessness (See Table 1). All the currently available OTC analgesic/sleep aid combination products contain diphenhydramine or diphenhydramine citrate as the sleep-aid component combined with ibuprofen, aspirin, or acetaminophen as the analgesic component. Diphenhydramine hydrochloride and citrate salts have been marketed under the Monograph for Nighttime Sleep-Aid Drug Products for OTC Human Use since April 23, 1982. It was subsequently codified in 21CFR338 for use by adults and children 12 years of age or older at a dose of 50 mg at bedtime for the relief of occasional sleeplessness.

2.1 Product Information

The drug product is a tablet containing a fixed-combination of naproxen sodium 220 mg and diphenhydramine hydrochloride (DPH) 25 mg per tablet for over-the-counter (OTC) use.

The target indication is:

- For the relief of occasional sleeplessness associated with minor aches and pains
- Helps you fall asleep and stay asleep

The proposed directions for use are:

- Adults and children 12 years and older, take 2 caplets at bedtime

The propose dose is 2-tablet taken before bedtime for no more than 10 consecutive days.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently available treatments

OTC Products	Analgesic+night time sleep aid	Dose
Advil® PM	ibuprofen 200 mg + diphenhydramine citrate 38	2 tablets

	mg,	
Motrin PM	ibuprofen 200 mg + diphenhydramine citrate 38 mg,	2 tablets
Tylenol® PM	acetaminophen 500 mg + diphenhydramine HCl 25 mg,	2 tablets
Bayer® PM	aspirin 500 mg + diphenhydramine citrate 38 mg	2 tablets
Excedrin® PM	acetaminophen 500 mg + diphenhydramine citrate 38 mg,	2 tablets

2.3 Availability of Proposed Active Ingredient in the United States

Currently, there are no OTC analgesic + nighttime sleep-aid combination products available in the US that combine naproxen sodium with DPH.

Naproxen sodium has been marketed in prescription form since 1976 under the brand name Naprosyn®. Naproxen sodium under the brand name of Aleve® has been marketed as an OTC product in the US since 1994 at doses of 220 and 440 mg and is currently approved for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, and backache; for the minor pain of arthritis; for the pain of menstrual cramps; and for the reduction of fever.

Aleve dosage from Label: Take one tablet, caplet, gelcap, or capsule every 8 to 12 hours while symptoms last. For the first dose, you may take 2 tablets, caplets, gelcaps, or capsules within the first hour. Do not exceed 2 tablets, caplets, gelcaps or capsules in any 8- to 12-hour period and do not exceed 3 tablets, caplets, gelcaps, or capsules in a 24-hour period. The smallest effective dose should be used.

(Note: Underlines added here for emphasis)

The Drug Facts Label instructs consumers not to take OTC naproxen sodium for more than 10 days for pain relief or more than 3 days for fever reduction unless otherwise directed by a physician.

Diphenhydramine hydrochloride, under the brand name Benadryl®, received marketing approval in the US in 1946 for use as a prescription antihistamine. Diphenhydramine hydrochloride and citrate salts have been marketed as an OTC sleep-aid since 1982 under the Monograph for Nighttime Sleep-Aid Drug Products for OTC Human Use. It has been codified in 21CFR 338 for use by adults and children 12 years of age or older at a dose of 50 mg at bedtime for the relief of occasional sleeplessness.

2.4 Important Safety Issues With Consideration to Related Drugs

Next day residual effects that could affect activities requiring alertness, such as driving have been a major concern for prescription sleep drugs. The residual effects could depend on factors such as drug dose, dosage form and individual patient characteristics. Driving studies to assess risk of car crashes by measuring standard deviation of lateral position and lapses of attention during driving are used evaluating driving impairment for prescription sleep drugs.

In addition, gender difference has also been observed for prescription sleep drugs, where females have higher drug concentration, thereby requiring a lower dose of the sleep drug.

Other safety issues are discussed in Section 7, Review of Safety.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

OTC review will cover this section.

2.6 Other Relevant Background Information

See section 2.1-2.5.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sponsor's application was generally compliant with eCTD and CDISC SDTM standards. There were a few errors in the formatting of the safety dataset set, which was rectified by the sponsor during the review cycle. AEs for the efficacy studies were reviewed by the physicians' and their diagnosis was entered into the CRF.

Patients' verbatim terms were not available and were requested from the sponsor. The sponsor provided these from the progress notes on the patient. The patient name was redacted from the progress notes, which was sent to the data management group for double data entry. The verbatim terms were then linked to the reported term using the subject number. Upon review of these it appears that the progress notes were most likely written by the physicians and did not capture the patients' verbatim complaints. In the progress notes there were terms like paresthesia, epistaxis, presyncope, emesis, aleveolitis/dry socket that are likely recorded by the physicians. Since the pivotal studies were single dose in-patient studies, it appears the AEs were assessed and recorded by the physician at study site.

Regarding the efficacy data, the sleep parameters from the actigraph were calculated based on a computer algorithm and the data was transferred electronically into a spreadsheet. The sponsor no longer had the actigraphs. Hence, the reconciliation between the actigraph and the electronic

spreadsheet data or the CRF's could not be done. Other aspects of the clinical trial were inspected.

Results of clinical site audits by the Office of Compliance, Division of Scientific Investigations for this submission are reviewed in 3.2, below. The reviewer concludes that the data generated in support of clinical efficacy appears to be reliable and there are no other questions related to the integrity of the data submitted (from Review of Dr. El-Hage).

3.2 Compliance with Good Clinical Practices

The Sponsor affirms that all studies in the clinical development program of Aleve® PM were approved by ethics committees or institutional review boards, in line with International Conference on Harmonization and Good Clinical Practice guidelines E6, the Sponsor's Standard Operating Procedures (SOPs) and according to the Declaration of Helsinki, version 1996. Written informed consent was obtained from all patients prior to any study related procedure.

The Sponsor certifies that it did not use any debarred investigators.

The clinical site audits by the Office of Compliance, Division of Scientific Investigations included inspection of the medical records/source data for subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, sponsor correspondence, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings.

Three minor protocol deviations (use of ibuprofen, use of acetaminophen and one missed dose) were observed at one of the inspected site of the multiple dose safety study 15560 (Dr. Lynn Webster) that were not included in the list of protocol deviations. Overall, Dr. El-Hage concludes that the data submitted are reliable to support this application.

3.3 Financial Disclosures

The sponsor states that they do not have any financial arrangement with the listed investigators, where the value of the compensation to the investigator could affect the outcome of the study as defined in 21CFR 54.2(a). The investigators were also required to disclose if they had any proprietary interest in the product. No such disclosures were made. The sponsor also certified that no significant payments of other sorts were made to the investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

None have been identified; however, final reviews from related disciplines have not been incorporated into this clinical review at the time of its writing.

4.1 Chemistry Manufacturing and Controls

From a CMC perspective, the NDA is recommended for approval. There are no Phase 4 commitments from CMC. Over-encapsulated product was used in all efficacy studies for blinding purposes. According to the ONDQA Biopharmaceutics reviewer, the dissolution studies do not suggest that any appreciable differences in absorption of the dosage form are likely to result due to over-encapsulation of the product.

4.2 Clinical Microbiology

No investigations of clinical microbiology are submitted.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was provided as both naproxen and diphenhydramine are approved drugs.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of naproxen sodium includes inhibition of COX and lipoxygenase enzymes involved in the synthesis of prostaglandins and leukotrienes there by reducing the formation of prostaglandin chemical precursors. It is a nonselective COX inhibitor, affecting both the COX-1 and COX-2 isoenzymes.

Diphenhydramine hydrochloride is an inverse agonist of the histamine H_1 receptor. By blocking histamine in the capillaries, DPH reduces the intensity of allergic symptoms. It also crosses the blood-brain barrier and antagonizes the H_1 receptors centrally, causing drowsiness.

4.4.2 Pharmacodynamics

In anti-inflammatory models, naproxen shows inhibitory effects on prostaglandin and leukotriene synthesis, antibradykinin activity, and a stabilizing action on lysosomal membranes. Naproxen also inhibits platelet aggregation.

DPH is used as a sedative, hypnotic, antihistamine, antitussive, and antiemetic agent in OTC products.

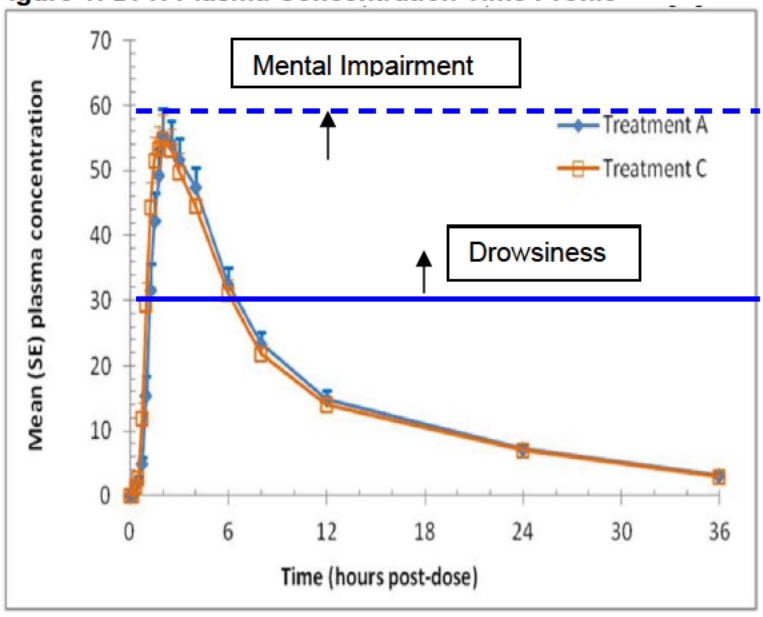
The probability of pharmacodynamic interaction between naproxen sodium and DPH is likely to be low based on their modes of action.

4.4.3 Pharmacokinetics

General Pharmacokinetics: Differences in drug pharmacokinetics of a drug between individuals can affect both efficacy and safety of sleep drugs. The variable pharmacokinetics of DPH, a first generation antihistamine known to cause sedation, is one of the main concerns in assessing the safety of DPH. The pharmacokinetics of DPH as found in literature suggest that the Tmax is around 2-3 hours. Similar tmax was obtained for DPH in the combination in the PK study conducted by the sponsor [mean Tmax 2.5 hours (range 1-6 hours)]. The t1/2 of DPH reported in the literature is 9 hours in the young subjects. The mean t1/2 of DPH observed in the study was 10.83 hours (range 7.75-19.49 hours). This suggests that some subjects may have higher exposure even several hours after dosing. The t/2 of DPH reported in the literature for the elderly is about 13 hours, suggesting a longer elimination in the elderly. This application does not have any PK data in the elderly. Given the variability in the observed PK in the young subjects in the study conducted by the sponsor raises concerns regarding plausible longer elimination in the elderly. The Merck Manual categorizes diphenydramine as a "drug of concern" in the elderly in part because of the long half life in the elderly.

The mean PK profile of DPH from Study 16135 after the administration of the Combination and DPH alone is given in the following Figure 1. These PK profiles show that mean Cmax of DPH is 67.64 ng/ml under fasted conditions and 78.17 under fed conditions (range 29.3-184.2 ng/ml under fed or fasted conditions).

Figure 1: DPH Plasma Concentration Time Profile

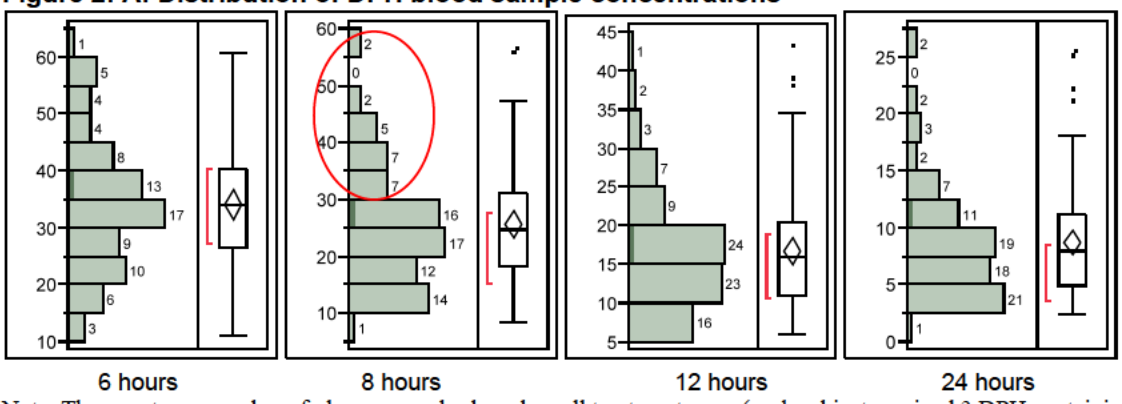


Concentrations associated with Drowsiness and mental impairment

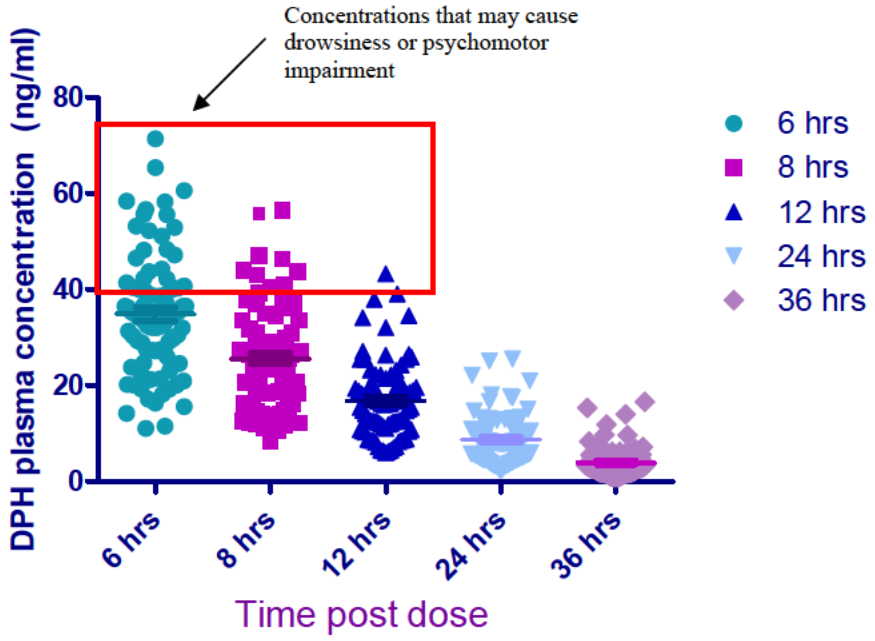
A: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fasted conditions
C: 2 x Allergy Relief® (DPH HCl 25 mg tablet) under fasted conditions

Gengo et.al[5] have suggested that DPH concentrations that produce subjective drowsiness (on a visual analogue scale) are 30.4 to 41.5 ng/ml and those producing mental impairment (assessed with an automobile driving simulator and digit symbol substitution scores) are higher, 58.2 to 74.4 ng/ml. I examined the distribution of DPH blood levels in the PK study. The following Figure 2 A and B, show that some subjects can have blood levels that may lead to drowsiness/mental impairment even after 8-12 hours of dosing.

Figure 2: A: Distribution of DPH blood sample concentrations



Note: The counts are number of plasma samples based on all treatment arms (each subject received 3 DPH containing treatment in a crossover design.



Note: The symbols are plasma concentrations across all treatments

[5] Genco FM et al. Clin Pharmacol Ther, 1989. 45(1):p 15-21

Morning diphenhydramine concentrations in some individuals are close to 80% of the average population Cmax. I further looked at the number of patients that had a DPH concentration > 40 ng/ml at 8 hours post dose. The following Table 2 shows subjects that had concentrations of DPH >40 ng/ml in any treatment arm. The DPH concentrations in an individual subject have been reported for all treatment arms in the study to show the intra-individual variability given the same diphenhydramine dose on different occasions. Four subjects were African Americans. Given the limited sample size and the large inter-individual variability, an effect of race on high DPH concentrations is not interpretable.

Table 2: DPH Plasma Concentrations >40 ng/ml

Subject No.	Treatment A Combination fasted	Treatment C DPH alone	Treatment D Combination fed
1026: F: African Am	57	47	56
1004: M: African Am	36	32	44
1017: F: African Am	28	34	41
1028: F: Hispanic	34	43	44
1030: M: African Am	38	41	46

Please see discussion on page 84-85] regarding the duration of somnolence observed in the PK study.

According to the Clinical Pharmacology review, females appear to have 15-30% higher DPH plasma concentrations than males at 8 hours post dose in the Aleve PM fed/fasted dose group. This mean percent increase appears to be driven by one female that had a high concentration of 57 ng/ml under fed conditions and 56ng/ml under fasted conditions (see subject number 1026 in Table 2 above. The relatively small *average* increase in DPH concentrations in females may therefore represent a clinically meaningful gender effect if it represents a greater risk that a proportion of women vs. men will have unacceptably high next-day DPH levels. However, the small sample size of this study precludes reliable conclusions.

Drug Interaction: Study 16135 demonstrated that there was no significant interaction between naproxen and diphenhydramine.

Food Effect: High-fat meal had no effect on AUC of naproxen or DPH. There is a delay in the rate of absorption for naproxen with a lower (19%) Cmax and prolonged Tmax [median (range): 3.0 (0.75 – 6.0) vs. 1.25 (0.33 – 3.0) hrs] in the presence of food. The Tmax of DPH was similar [2.5 (1.25 – 6.0) vs. 2.5 (1.0 – 4.0) hrs]. The Cmax of DPH was higher (13%) with food.

5 Sources of Clinical Data

The development program for Aleve® PM (Naproxen sodium 220 mg/Diphenhydramine 25 mg) to be taken as two tablets, consisted of 1 pilot study (Study 13053) and two pivotal studies (Study 14837 and 15881) in which single doses of the combination product were compared to

the individual components for efficacy. The two pivotal studies were identical in study design. The only difference was that the second study evaluated the efficacy of a lower dose of DPH (25 mg), in the combination product.

In addition to these there was a 10-Day multiple dose study with once daily dosing (Study 15560) evaluating the safety and tolerability of Aleve® PM.

5.1 Tables of Studies/Clinical Trials

The tabular listing of Clinical Studies is given in Table 3.

Table 3: Tabular listing of Clinical Trials

Study No./ Phase/ Study Type	Study Design/ Control Type	Study Objectives	Test Products; Dosage Regimen	Number of Subjects	Healthy Subjects or Diagnosis of Patients
13053 Phase 4 Proof of Concept	Randomized, double-blind, parallel-group, single-center study	To evaluate the efficacy of a single oral dose of naproxen sodium and DPH combinations when compared to naproxen sodium alone, DPH alone, and an ibuprofen and diphenhydramine citrate combination (Advil PM)	NS 440 mg + DPH 50 mg; single dose NS 220 mg + DPH 50 mg; single dose NS 440 mg; single dose NS 220 mg; single dose DPH 50 mg; single dose Ibuprofen 400 mg/diphenhydramine citrate 76 mg; single dose	27 27 27 27 27 27	Healthy subjects, ages 16 to 45 years, with moderate to severe postoperative dental pain
14837 Phase 3 Efficacy	Randomized, double-blind, parallel-group, multicenter study	To evaluate the efficacy and safety of a single oral dose of 2 dose combinations of naproxen sodium 440 mg/DPH 50 mg and naproxen sodium 220 mg/DPH 50 mg relative to naproxen sodium 440 mg alone and DPH 50 mg alone (active controls) in subjects with postsurgical dental pain and phase-advanced sleep	NS 440 mg/DPH 50 mg; single dose NS 220 mg/DPH 50 mg; single dose NS 440 mg; single dose DPH 50 mg; single dose	203 204 203 102	Healthy subjects, ≥12 years of age, with moderate to severe postoperative dental pain
15881 Phase 3 Efficacy	Randomized, double-blind, parallel-group, multicenter study	To evaluate the efficacy and safety of a single oral dose of naproxen sodium 440 mg/DPH 25 mg combination relative to naproxen sodium 440 mg alone and DPH 50 mg alone (active controls) in subjects with postsurgical dental pain and phase-advanced sleep	NS 440 mg/DPH 25 mg; single dose NS 440 mg; single dose DPH 50 mg; single dose	107 106 54	Healthy subjects, ≥12 years of age, with moderate to severe postoperative dental pain

Note: In the pilot study (Study 13053), the commercial products Aleve® (naproxen sodium 220 mg tablets) and Benadryl® (DPH 25 mg tablets) were administered concomitantly; the new combination product was not taken by any subject in this study.

Study No./ Phase/ Study Type	Study Design/ Control Type	Study Objectives	Test Products; Dosage Regimen	Number of Subjects	Healthy Subjects or Diagnosis of Patients
15560 Phase 3 Safety	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study	To evaluate the safety and tolerability of naproxen sodium 440 mg/DPH 50 mg compared with placebo when used for 10 consecutive days in a population representative of OTC users of analgesic/nighttime sleep-aid combination products	NS 440 mg/DPH 50 mg; once daily at bedtime for 10 consecutive days Placebo; once daily at bedtime for 10 consecutive days	217 109	Subjects, ≥12 years of age, with a history of occasional sleeplessness associated with minor aches and pains (≥2 times, but not continually for >14 days per month, in ≥2 of the past 3 months)
16135 Phase 1 PK	Randomized, open-label, 4-way crossover, single-center study	To determine and compare the PK profile (specifically AUC and C_{max}) of a single oral dose of naproxen sodium 440 mg/DPH 50 mg combination relative to the currently marketed single ingredient products containing naproxen sodium or DPH under fasting conditions To determine and compare the PK profile (specifically AUC and C_{max}) of a single oral dose of naproxen sodium 440 mg/DPH 50 mg combination under fasting and fed conditions To assess the safety and tolerability of naproxen sodium 440 mg/DPH 50 mg combination	NS 440 mg/DPH 50 mg; single dose; under fasting conditions NS 440 mg; single dose; under fasting conditions DPH 50 mg; single dose; under fasting conditions NS 440 mg/DPH 50 mg; single dose; under fed conditions	32 (27 PK evaluable)	Healthy subjects, ages 18 to 55 years, with a BMI of approximately 18 to 30 kg/m² and a total body weight >50 kg (110 lb)

5.2 Review Strategy

The applicant submitted the NDA and subsequent amendments using the eCTD format, which was accessed through the GlobalSubmit Review application. Although the primary source of the clinical data was the applicant's NDA submission, I also reviewed secondary sources of clinical data (i.e., labels and literature) in assessing the safety and efficacy of Aleve PM.

The efficacy (Sleep endpoints) and safety of controlled studies (listed in Table 3) were reviewed by me (DNP). The secondary pain endpoints were reviewed by Clinical Reviewer in DAAAP. The post marketing safety was reviewed by OSE. The remaining safety was reviewed by the Clinical Reviewer in DNCE.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study 14837:

Title: A Multicenter, Randomized, Double-Blind, Parallel-Group Trial Assessing the Efficacy and Safety of Naproxen Sodium and Diphenhydramine Combination in Postsurgical Dental Pain with Phase Advanced Sleep

Study Dates: 22 Oct 2010 to 03 Feb 2011

Objectives: To evaluate the efficacy and safety of a single oral dose of 2 dose combinations of naproxen sodium (NP) and diphenhydramine hydrochloride (DPH) to demonstrate that the NP/DPH combination provides added clinical benefit to sleep improvement than either single ingredient (NP or DPH) alone in subjects with post-surgical dental pain and phase-advanced sleep.

Study Design/Population: This was a multicenter, randomized, double-blind, parallel group, pivotal efficacy study conducted in subjects 12 and older with postoperative pain and phase-advanced sleep. The study included a Screening Visit (28 days), dosing period (2 days) and an End of Trial (EOT) assessment (follow up 2-5 days). Subjects who had undergone dental surgical extraction of impacted third molars between 13:30h and 15:30h and experienced at least moderate severity (>50 mm on VAS scale) were randomized to 1 of the 4 treatment groups. Eligible subjects were required to go to bed approximately 5 hours earlier than usual. Subjects went to bed between 4 and 6.30 PM. The effect on sleep was evaluated objectively using actigraphy (by Respironics-Philips: Actiwatch devices). Actigraphy data was recorded throughout the in-bed time period. It was required that subjects had a fixed in-bed time of 10 hours. At the end of the 10-hour in bed period, subjects were awakened by the study coordinator, unless they had already awoken earlier. Actigraphs were placed on the nondominant arm of the subjects. Each actigraph was set to capture activity every 30 seconds. If adequate pain relief was not achieved, subjects were permitted to take rescue medication.

Treatments administered: Single dose of 1 of the 4 treatments:

1. naproxen sodium/DPH 440 mg/50 mg (as 2 Naproxen sodium 220 mg/DPH 25 mg tablets)
2. naproxen sodium/DPH 220 mg/50 mg (1 Naproxen sodium 220 mg/DPH 50 mg tablet and 1 matching placebo capsule
3. Naproxen sodium 440 mg (as 2 Aleve® 220 mg tablets)
4. DPH 50 mg (as 2 Benadryl® 25 mg tablets)

Subjects would be randomized in a 2:2:2:1 ratio to 4 treatment groups.
All investigational products were over encapsulated and were packaged in single subject bottles according to the randomization code.

Centers/Investigators**:** The study was conducted at two centers in the United States.
William L. Buchanan, MD, DDS: PPD Development, LP (PPD Dental Pain Research Clinic) (Study Site 14001), Austin, TX

Patrick R. Brain, DDS: Jean Brown Research, Inc. (Study Site 14002), Salt Lake City, UT

Assessment Schedule**:** The assessment schedule before, during and after surgery is given in Table 4.

Table 4: Schedule of Assessments (Study 14837)

Protocol Activities	Screening Visit (within 28 days before Dosing Period)	Dosing Period *Inpatient*		End of Trial within 2-5 (± 2) days
		Day 1	Day 2	
Written Informed Consent	x			
Inclusion/Exclusion Reviewed	x	x		
Epworth Sleepiness Scale [a]		x		
Medical/Medication History	x	x		
Physical Examination (at Screening or day of surgery)	x			
Vital Signs [b]	x	x	x	
Urine for Drug Screen and Breath Alcohol Test	x	x		
Urine Pregnancy Test (if applicable)	x	x		
Admission to Unit		x		
Dental Surgery (1330-1530 h)		x		
Randomization Number Assigned		x		
Actigraphy		x	x	
Investigational Product Administration (1600-1830 h)		x		
Pain Severity Visual Analog Scale [c]		x		
Categorical Pain Rating Scale [c,d,e]		x	x	
Categorical Pain Relief Scale [d,e]		x	x	
Global Assessment of Pain Reliever [d,e,f]			x	
Subjective Sleep Questionnaire [d,f]			x	
Karolinska Sleep Diary [d,f]			x	
Global Assessment of Sleep-Aid [d,f]			x	
Concomitant Medications		x	x	x
Adverse Events Assessed		x	x	x
Discharge from Clinical Research Unit (morning of Day 2)			x	
End of Trial				x

[a] Epworth Sleepiness Scale was performed before surgery.
[b] Vital signs included sitting blood pressure, pulse rate, and respiration after sitting for 5 minutes, and were performed at the Screening Visit, on Day 1, and on Day 2.
[c] To have been completed within 5 minutes prior to administration of investigational product.
[d] After randomization occurred, to have been completed upon awakening.
[e] If rescue occurred, scales were to have been completed within ± 1 minute of the time rescue medication was taken.
[f] If rescue occurred after sleep onset, additional assessments were to have been completed within ± 1 minute before rescue medication was taken.

Key Inclusion criteria:

- Healthy male or females, 12 years and above.
- Scheduled to undergo surgical removal of a minimum of 2 third molars, of which at least 1 had to be a mandibular third molar. The mandibular extraction(s) required by each subject were to have met one of the following scenarios: 1) 1 full bony impaction; 2) 2 partial bony impactions; 3) 1 full bony impaction and 1 partial bony impaction; 4) 1 full bony impaction and 1 soft tissue impaction; 5) 1 full bony impaction and 1 erupted third

molar. Two full bony mandibular impactions were not allowed. Maxillary third molars were removed regardless of impaction level.
- Use of a short-acting local anesthetic (lidocaine or mepivacaine) with or without vasoconstrictor and nitrous oxide.
- Had not taken any form of medication within 5 days of admission. Had not consumed alcoholic beverages or foods and beverages containing xanthines since 0800 h on the day of surgery and agreed not to consume any of these foods or beverages throughout the evaluation period.
- Had moderate to severe postoperative pain score of ≥ 50 mm on the 100-mm Pain Severity VAS between 1600 h and 1830 h on the day of surgery.

Key exclusion criteria:
- Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years.
- Current or past history of gastrointestinal bleeding or other bleeding disorder
- Chronic use of antihistamines
- Habituation to analgesic drugs
- History of regularly going to bed earlier than 2200 h
- A score of > 11 on the Epworth Sleepiness Scale.
- Habitually spent less than 6.5 hours in bed.
- Had difficulty falling asleep or staying asleep most nights of the week in the last month.
- Chronic or severe sleep problems that did not respond to OTC medication and required a prescription hypnotic or sedative.
- Travel across time zones within 1 week prior to surgery or did rotating shift work
- On treatment for depression
- Use of alcoholic beverages

Rescue Medication: Rescue medication for pain was allowed, although subjects were encouraged to wait 60 minutes after administration to allow time for the investigational product to take effect. Rescue medication was Lortab® 5 (hydrocodone 5 mg/acetaminophen 500 mg) tablet(s) or other appropriate analgesics at investigators discretion. Subjects were required to complete pain assessments immediately before the first administration of rescue medication. Rescue medication could be administered again if pain returned. (*Reviewer's note: all subjects only took Lortab5*)

The time rescue medication was taken was recorded. This could occur before or after sleep onset. Actigraphic recording continued regardless of whether or not rescue medication was taken. See Table for Schedule of assessments.

Premature patient withdrawals and study drug discontinuations:
End of Treatment assessments were to be done at premature discontinuation.
Subjects could be withdrawn from the study for any reason, including any of the following. Subjects withdrawn were not replaced.
- At their own request or sponsor's request or investigators request

- AE or serious AE (SAE)
- Pregnancy
- Intercurrent illness
- Major clinical violation
- Noncompliance

Efficacy Outcome Measures

Primary efficacy variables
The primary efficacy variables were derived from actigraphy data:
- WASO (naproxen sodium/DPH versus naproxen sodium alone)
- Sleep latency (naproxen sodium/DPH versus DPH alone)

In this protocol, the sponsor does not specify that both endpoints need to be met.

Secondary efficacy variables
The secondary efficacy variables were both for Sleep and as well as Pain Relief. The pain relief variables are discussed in a separate review.

- Sleep variables
  - Objective secondary sleep variables derived from actigraphy data were:
    - Total sleep time
    - Sleep efficiency
  - Subjective secondary sleep variables included the following:
    - Global Assessment of Investigational Product as a Sleep-Aid
    - Karolinska Sleep Diary
    - Subjective Sleep Questionnaire

- Pain variables:
  - Categorical Pain Rating Scale
  - Pain Relief Rating Scale
  - Global Assessment
  - Secondary pain variables:
    - Change from baseline in pain intensity score
    - Pain Relief
    - Time to Recue Medication

The Global Assessment of Investigational Product as a Sleep-Aid was rated using a 5-point categorical scale for which the potential response was poor (0), fair, (1), good (2), very good (3), or excellent (4).

The Karolinska Sleep Diary included the following questions and potential responses:
- How was your sleep? very poor (1); rather poor (2); neither poor nor good (3); rather good (4); very good (5)

- How calm was your sleep? very restless (1); rather restless (2); neither restless nor calm (3); rather calm (4); very calm (5)
- How easy was it to fall asleep? very difficult (1); rather difficult (2); neither difficult nor easy (3); rather easy (4); very easy (5)
- Premature awakening? woke up much too early (1); woke up somewhat too early (2); no (3) Ease of awakening? (1) very difficult; (2) rather difficult; (3) neither difficult nor easy; (4) rather easy; very easy (5)
- Well Rested? not rested at all (1); somewhat unrested (2); completely rested (3)
- Did you get enough (sufficient) sleep? no, definitely too little (1); no, much too little (2); no, somewhat too little (3); yes, almost enough (4); yes, definitely enough (5)

The Subjective Sleep Questionnaire included 4 items that requested subject responses to questions regarding the following for the previous night:

- Quality of sleep (10-point scale, where 1 was poor and 10 was excellent)
- Refreshing nature of sleep (10-point scale, where 1 was not refreshing and 10 was very refreshing)
- Estimate of how long it took to fall asleep (minutes)
- Estimate of the amount of time the subject was awake from the time he or she fell asleep until the time he or she got out of bed (hours and minutes)

Safety variables

- Adverse events: TEAEs, AEs, discontinuations, SAEs
- Vital signs: Vital signs included blood pressure (diastolic and systolic), pulse rate, and respiration rate. Vital signs were to have been measured while the subject was in a sitting position after the subject had been sitting for 5 minutes. These were measured at screening, Day 1 and Day 2.

Analysis Plan:

Plan for Primary Variables: In order to protect the overall Type 1 error at the 0.05 level, a hierarchical testing procedure was used separately for WASO and sleep latency for the treatment comparisons. Relevant treatment comparisons were tested sequentially, each at the 2-sided 0.05 level of significance, in the following order for the 2 primary efficacy variables:

- For WASO:
  - Naproxen sodium 440 mg/DPH 50 mg combination versus Naproxen sodium 440 mg
  - Naproxen sodium 220 mg/DHP 50 mg combination versus Naproxen sodium 440 mg
  - Naproxen sodium 440 mg/DPH 50 mg combination versus Naproxen sodium 220 mg/DPH 50 mg combination
- For sleep latency:
  - Naproxen sodium 440 mg/DPH 50 mg combination versus DPH 50 mg
  - Naproxen sodium 220 mg/DPH 50 mg combination versus DPH 50 mg
  - Naproxen sodium 440 mg/DPH 50 mg combination versus Naproxen sodium 220 mg/DPH 50 mg combination

Once a comparison was identified as statistically nonsignificant, subsequent comparisons technically were ineligible to be declared significant; however, all comparisons were presented.

Wake after sleep onset
Subjects were required to have a fixed in-bed time of 10 hours (600 minutes). Time zero was defined as time the study medication was taken and Hour 10 (600 minutes) was defined as the time when lights were turned on. Subjects who took rescue medication after sleep onset were treated as being awake from the time when the rescue medication was given to the end of the in-bed time. For subjects who took rescue medication before sleep onset, WASO was set to 600 minutes (the duration of the in-bed time). No formal imputation technique was used to replace missing data for withdrawn subjects.

For analysis of WASO, an analysis of covariance (ANCOVA) model was used and included treatment and center as fixed effects and baseline categorical pain score as the covariate. Least squares (LS) mean, standard error, and 95% confidence interval (CI) of LS means were calculated for each treatment group; LS mean differences were determined and associated P-values and 95% CI values were calculated.

According to the protocol, sensitivity analyses were to have been performed if a larger proportion of subjects required rescue medication in the naproxen sodium alone group.

- A sensitivity analysis was performed after imputing the values for all subjects who took rescue medication. The mean and standard deviation from those subjects who did not take rescue medication in the combined groups of comparison were used for the imputation. The random seed used was 256457239.
- A sensitivity analysis was also performed excluding subjects who took rescue medication.

Sleep latency
Sleep latency was defined as the time (in minutes) to sleep onset from the time of dosing by actigraphy. Subjects who took rescue medication before sleep onset were censored for sleep latency at 10 hours (600 minutes); sleep latency was not affected if rescue medication was taken after sleep onset. No formal imputation technique was used to replace missing data for withdrawn subjects.

Sleep latency was evaluated using the Kaplan-Meier method and logrank test. The treatment comparison of primary interest for sleep latency was naproxen sodium/DPH combinations versus DPH alone.

According to the protocol, sensitivity analyses were to have been performed if a larger proportion of subjects required rescue medication in the DPH alone group.

- A sensitivity analysis was performed on the ITT Population after imputing the values for all the subjects who took rescue medication before sleep onset. The mean and standard deviation from those subjects who did not take rescue medication before sleep onset in

the combined groups of comparison were used for the imputation. The random seed used was 145929879.

- A sensitivity analysis was also performed on the ITT Population excluding subjects who took rescue medication before sleep onset.

Plan for Secondary Variables

Objective sleep assessments

- Total sleep time was set to zero if rescue medication was taken before sleep onset; total sleep time was not to exceed 10 hours (600 minutes).
- Sleep efficiency was calculated as (total sleep time/total time in-bed time) × 100; total in-bed time was fixed at 10 hours.

Subjective sleep assessments

Global Assessment of Investigational Product as a Sleep-Aid, Subjective Sleep Questionnaire, and Karolinska Sleep Diary data were analyzed using the Cochran-Mantel-Haenszel (CMH) method controlling for center with a modified ridit score. Distribution of scores also was presented.

Sample size justification: It was planned that approximately 700 subjects would be randomized in a 2:2:2:1 ratio to 4 treatment groups, as follows:

- Naproxen sodium 440 mg/DPH 50 mg: 200 subjects
- Naproxen sodium 220 mg/DPH 50 mg: 200 subjects
- Naproxen sodium 440 mg: 200 subjects
- DPH 50 mg: 100 subjects

Assuming a WASO treatment difference of 52 minutes between naproxen sodium 440 mg/DPH 50 mg and naproxen sodium 440 mg and a standard deviation of 138 minutes, it was determined that approximately 200 subjects per treatment group would provide at least 90% power using a 2-sided 2-sample t-test at the significance level of 0.05. Assuming a treatment difference of 64 minutes and standard deviation of 200 minutes, this sample size would provide approximately 90% power to detect a treatment difference between naproxen sodium 220 mg/DPH 50 mg and naproxen sodium 440 mg. The 200 subjects in the naproxen sodium 440 mg/DPH 50 mg group and 100 subjects in the DPH 50 mg group (2:1 ratio) would provide at least 90% power to detect a treatment difference of at least 80 minutes in WASO and over 90% power to detect a treatment difference in sleep latency. In the power calculation for sleep latency, it was assumed that the percentage of subjects without experiencing sleep onset would be 15% for the naproxen sodium 440 mg/DPH 50 mg group and 35% for the DPH 50 mg group.

Trial Population, Enrollment and Patient Disposition**:** All, but three subjects in DPH group completed the study according to the protocol (Table 5).

Table 5: Reasons for not completing the study (Study 14837)

	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50[c] N=102	Total N=712
Subject (or legally acceptable representative) request [a]	0	0	0	2	2
Other [b]	0	0	0	1	2

[a] Subjects 14002-1032, 14002-1192
[b] Subject 14001-1480 (Protocol exclusion: participated in another protocol)
[c] N=99 completers

Reviewer Comment: It appears that 3 subjects from the DPH group were included in the analysis. But the sponsor mentions that these subjects were discontinued from the study.

Protocol deviations: A protocol deviation was identified for a total of 19 subjects (14 subjects at study site 14002 and 5 subjects at study site 14001): naproxen sodium 440 mg/DPH 50 mg (N=3), naproxen sodium 220 mg/DPH 50 mg (N=4), and naproxen sodium 440 mg groups (N=7) and DPH 50 mg (N=5) group. All of the protocol deviations for these subjects were considered minor. The sponsor did not exclude anyone from the ITT Population. The 2 highlighted below in Table 6 could affect the sleep parameters, but would not to impact the overall conclusion. Therefore, I agree with the sponsor to not exclude any from the ITT population.

Table 6: Protocol Deviations (ITT population) (Study 14837)

Treatment Group	Subject	Visit	Type	Description of Deviation
NP 440 mg/ DPH 50 mg	1043	Day 2	8	Subject discharged with clinically significant elevated blood pressure on (b) (6) not noted until Principal Investigator assessment on 23 November 2010. Subject was contacted and returned to clinic on 30 November 2010.
	1246	Follow-up call	10	Follow up call was 12 days out of window. Site made multiple attempts to contact subject, who indicated their cell phone was stolen.
	1307	Follow-up call	10	Follow up call was one day out of window due to subject not returning call within timeframe.
NP 220 mg/ DPH 50 mg	1030	Day 1	6	Actigraph event marker pressed 9 minutes early at rescue.
	1151	Day 1	1	Subject took Tylenol and ibuprofen 5 days before surgery (violation of Inclusion 4)
	1169	Day 2	8	Subject was discharged with clinically significant elevated blood pressure on (b) (6) which was not noted until Principal Investigator assessment later that same day. Subject was contacted and is scheduled to return to the clinic.
	1608	Informed Consent	10	Minor subject only signed first name and last initial on informed consent form; parent signed appropriately.
NP 440 mg	1002	Dosing Period	6	Subject given Benadryl 25 mg for adverse event of urticaria. Benadryl is one of the study medications and cannot be used.
	1141	Discharge	6	Subject did not arrange for a ride home (per protocol, page 19). Subject drove himself home.
	1224	Screening	6	Subject not using a double barrier method of contraception (condom + oral contraceptive < 3 months)
	1052	Screening	6	Study coordinator inadvertently did not print name or sign pages 14 and 17 of the informed consent form until 8 November 2010. The informed consent form was reviewed with the subject and the subject signed it on 3 November 2010.
	1089	Day 1	1	Subject's teeth did not meet inclusion criteria # 2, mandibular molar was only partially impacted
	1235	Day 1	1	Subject took Tylenol XS 5 days before surgery (violation of Inclusion #4)
	1522	Screening	1	Subject is allergic to Phenergan, an antihistamine. Violation of inclusion #1
DPH 50 mg	1441	Screening	6	Subject not using double barrier method of contraception (condom + oral contraceptive less than 3 months)
	1480	Screening	6	Subject participated in PPD study within 30 days of this study. Violation of protocol exclusion criterion 27.
DPH 50 mg	1007	Dosing Period	6	Physical examination was not done.
	1032	Day 1	10	Subject left research facility against medical advice after taking rescue medication
	1335	Day 1	6	Subject given 2 carpules Lidocaine on 18 December 2010. Site ran out of nitrous oxide. Subject returned on 20 December 2010 and was randomized. Per protocol, must have 5 day washout of prior meds, this was only 2.

Demographics: Demographic characteristics generally were comparable among treatment groups (Table 7).

Table 7: Demographics: age (Safety and Intent-to-Treat Populations) (Study 14837)

	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50 N=102	Total N=712
Age [mean (SD)]	21.4 (4.87)	21.0 (4.25)	21 (4.5)	21.5 (5.59)	21.2 (4.7)
Range	16-48	16-40	16-38	16-42	16-48
Gender [n (%)]					
Male	95 (46.8)	80 (39.2)	86 (42.4)	48 (47.1)	309 (43.4)
Female	108 (53.2)	124 (60.8)	117 (57.6)	54 (52.9)	403 (56.6)
Ethnicity [n (%)]					
Hispanic/Latino	40 (19.7)	39 (19.1)	49 (24.1)	25 (24.5)	153 (21.5)
Not Hispanic	163 (80.3)	165 (80.9)	154 (75.9)	77 (75.5)	559 (78.5)
Race [n (%)]					
White	184 (90.6)	174 (85.3)	185 (91.1)	91 (89.2)	634 (89.0)
Black	5 (2.5)	15 (7.4)	5 (2.5)	2 (2.0)	27 (3.8)
Asian	7 (3.4)	3 (1.5)	6 (3.0)	4 (3.9)	20 (2.8)
Pacific Islander	0	2 (1.0)	1 (0.5)	1 (1.0)	4 (0.6)
American Indian	1 (0.5)	1 (0.5)	0	0	2 (0.3)
Other	4 (2.0)	7 (3.4)	3 (1.5)	3 (2.9)	17 (2.4)
Multiple	2 (1.0)	2 (1.0)	3 (1.5)	1 (1.0)	8 (1.1)

The baseline pain assessed by categorical rating scale and VAS is given in Table 8:

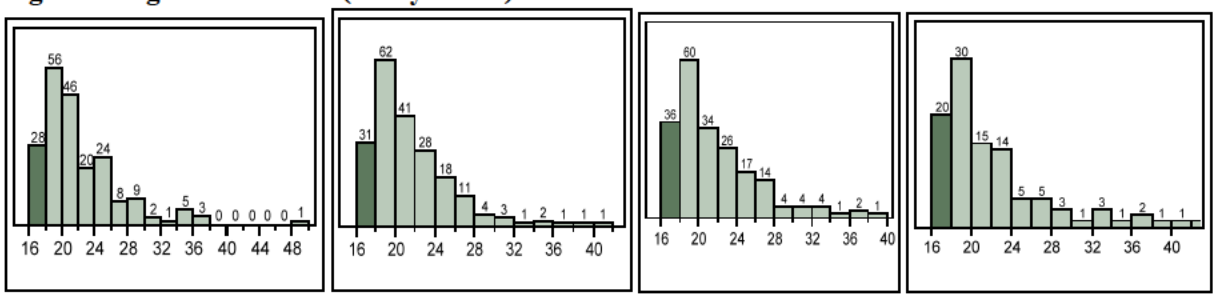
Table 8: Baseline Pain: Categorical Pain Rating Scale and Visual Analog Scale score (Safety Population) (Study 14837)

	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50 N=102	Total N=712
Baseline Categorical Pain Severity					
Moderate Pain	146 (71.9)	134 (65.7)	140 (69.0)	74 (72.5)	494 (69.4)
Severe Pain	57 (28.1)	70 (34.3)	63 (31.0)	28 (27.5)	218 (30.6)
Baseline Pain Severity					
Mean (SD)	71.8 (12.16)	73.0 (12.95)	72.6 (11.7)	72.3 (12.5)	72.4 (12.3)
Median	70.0	71.5	72	69.0	71
Range	51-100	50-100	51-100	51-99	50-100

Reviewer's Comment: The enrollment age criterion was 12, but no patients actually enrolled were less than 16 years.

Bayer is requesting an indication in >12 years of age. There were 115 children between the ages 16-17 in this study. About 90% of the subjects were less than 28 years across treatment arms The Distribution based on Treatment Groups is shown in Figure 3.

Figure 3: Age Distribution (Study 14837)



Outcome of Efficacy Analysis

Primary Efficacy Endpoints

Wake After Sleep Onset (WASO) by actigraphy:

Sponsor's analysis:
WASO comparison of NP440/DPH50 versus NP440 alone was the primary efficacy endpoint. According to the sponsor, the NP440/DPH50 combination showed benefit in improving sleep duration when compared to NP440 alone. WASO was shortest for the NP 440/DPH50 group (142 minutes) and followed by NP440 (214 minutes). **WASO was 70 minutes shorter for the NP 440/DPH50 group compared to the NP440 group and this difference was statistically significant (p=0.0002).** The difference in LS-mean WASO time between the NP440 mg/DPH 50 mg combination treatment group and the NP220 mg/DPH 50 mg combination treatment group was statistically significant ($P<0.0001$). The difference in WASO between the NP 220/DPH50 group and the NP440 group was not statistically significant (p=0.3627). WASO was the longest for the DPH50 group (429 minutes).

Sponsor's analysis of WASO in the ITT population is shown in Table 9 and 10.

Table 9: Analysis of wake after sleep onset: summary (Intent-to-Treat Population) (Study 14837)

Statistics	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50 N=102
No. of subjects in the analysis	**201***	**204**	**202***	**102**
Mean (SD)	**142.2 (164.500)**	**233.6 (208.50)**	**214.3 (188.47)**	**429.5 (194.48)**
Median	69.5	119.8	124.3	515.8
Range	17-600	8-600	22-600	18-600
ANCOVA Model				
LS mean (SE)	143.7 (13.17)	230.9 (13.08)	214.0 (13.13)	431.4 (18.49)

*Three subjects (14001-1459, 14001-1464, and 14001-1531) were excluded from the efficacy analyses because sleep parameters were not available due to malfunction of the Actigraph.

In addition a post-hoc analysis for the ITT Population of WASO and sleep latency was conducted by the sponsor in which data were excluded for 3 subjects (Subjects 14001-1259, 14001-1329, and 14002-1013) for whom sleep data had been rescored following database lock due to reconciliations between actigraphy and CRFs*.The p-values remained the same after excluding these subjects.

Reviewer's Comment: Subjects 14001-1459 and 14001-1464 were on NP440, yet the total number of subjects has changed to 202. Subject 14001-1459 has actigraphy data in the dataset, so it is not clear if malfunction of the actigraph affected the results. The conclusion did not change including this subject, obviously because the p-value is so small. 14001-1531 was on NP440/DPH50, but two subjects have been removed from this treatment arm. [No details of malfunction of the actigraph have been reported. This was not requested from the sponsor as the outcome is unlikely to change]. The 3 subjects that discontinued from DPH50 arm have been included in the analysis by the sponsor, which should not have been done. Excluding these subjects will not change the overall conclusion from this study.

**The Division of scientific investigation contacted the sponsor and learnt that the sponsor no longer has the Actigraphs. Hence the accuracy of other reconciliations between the actigraph and CFR cannot be verified by the Agency. The data does reflect inaccurate reporting in at least the subjects mentioned above.*

Table 10: Analysis of wake after sleep onset: treatment differences (Intent-to-Treat Population) (Study 14837)

Pairwise Comparisons	LS mean Difference	95% CI of LS mean Difference	p-value
NP 440 mg/DPH 50 mg versus NP 440 mg	**-70.3**	-106.8, -33.7	**0.0002**
NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg	-87.1	-123.6, -50.7	**<0.0001**
NP 440 mg/DPH 50 mg versus DPH 50 mg	-287.6	-332.2, -243.1	<0.0001
220 mg/DPH 50 mg versus NP 440 mg	16.9	-19.5, 53.3	**0.3627**
NP 220 mg/DPH 50 mg versus DPH 50 mg	-200.5	-245.0, -156.0	< 0.0001

Sensitivity Analysis: A sensitivity analysis was done if more subjects in the NP440 group (33.5%) took rescue medication than the NP440/DPH50 group (21.2%). See Sponsor's Table 11. Least number of subjects on NP440/DPH50 took rescue medication (21.2%), compared to other treatment groups.

Table 11: Cumulative proportion of subjects taking rescue medication (Study 14837)

Time After Dosing That Rescue Medication Was Taken	Treatment Group: NP 440 mg/ DPH 50 mg N = 203		NP 220 mg/ DPH 50 mg N = 204		NP 440 mg N = 203		DPH 50 mg N = 102	
	n	(%)	n	(%)	n	(%)	n	(%)
≤ 60 minutes	0		1	(0.5)	0		0	
≤ 120 minutes	18	(8.9)	36	(17.6)	27	(13.3)	53	(52.0)
≤ 180 minutes	23	(11.3)	50	(24.5)	41	(20.2)	66	(64.7)
≤ 240 minutes	25	(12.3)	57	(27.9)	47	(23.2)	70	(68.6)
≤ 300 minutes	29	(14.3)	65	(31.9)	50	(24.6)	74	(72.5)
≤ 360 minutes	34	(16.7)	69	(33.8)	55	(27.1)	76	(74.5)
≤ 420 minutes	36	(17.7)	78	(38.2)	62	(30.5)	77	(75.5)
≤ 480 minutes	39	(19.2)	83	(40.7)	63	(31.0)	78	(76.5)
≤ 540 minutes	42	(20.7)	87	(42.6)	67	(33.0)	78	(76.5)
≤ 600 minutes	43	(21.2)	89	(43.6)	68	(33.5)	78	(76.5)

Excluding subjects that took rescue medication, showed a treatment difference of 30 minutes (p=<0.0001). See Table 12. Statistical review agrees with the analysis.

Table 12: Sensitivity Analysis for WASO (Study 14837)

Sensitivity Analysis		NP 440 DPH 50 versus NP440
	N	N=158 vs 134
Excluding subjects who took rescue medication		treatment difference: -30 minutes p=<0.0001
	N	N=201 vs 202
Subjects with imputed values*		treatment difference: -19.7 minutes p=<0.0001

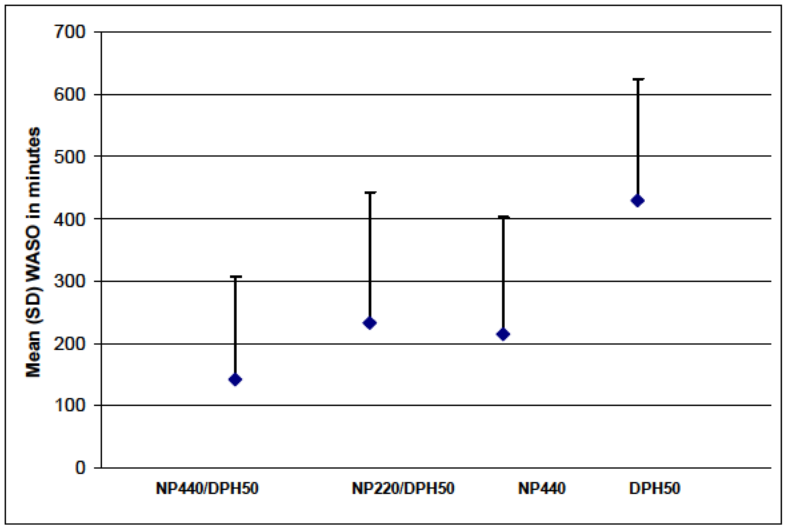
*The mean and standard deviation from those subjects who did not take rescue medication before sleep onset in the combined groups of comparison were used for the imputation. The random seed used was 145929879.

Reviewer's Analysis and Discussion:

The same LS mean differences were obtained between treatment comparisons, confirming that the WASO is 70.3 minutes shorter with the combination NP440/DPH50 compared to DPH50 alone (with a p-value of 0.0002 in JMP). The Statistical Review also confirms these analyses.

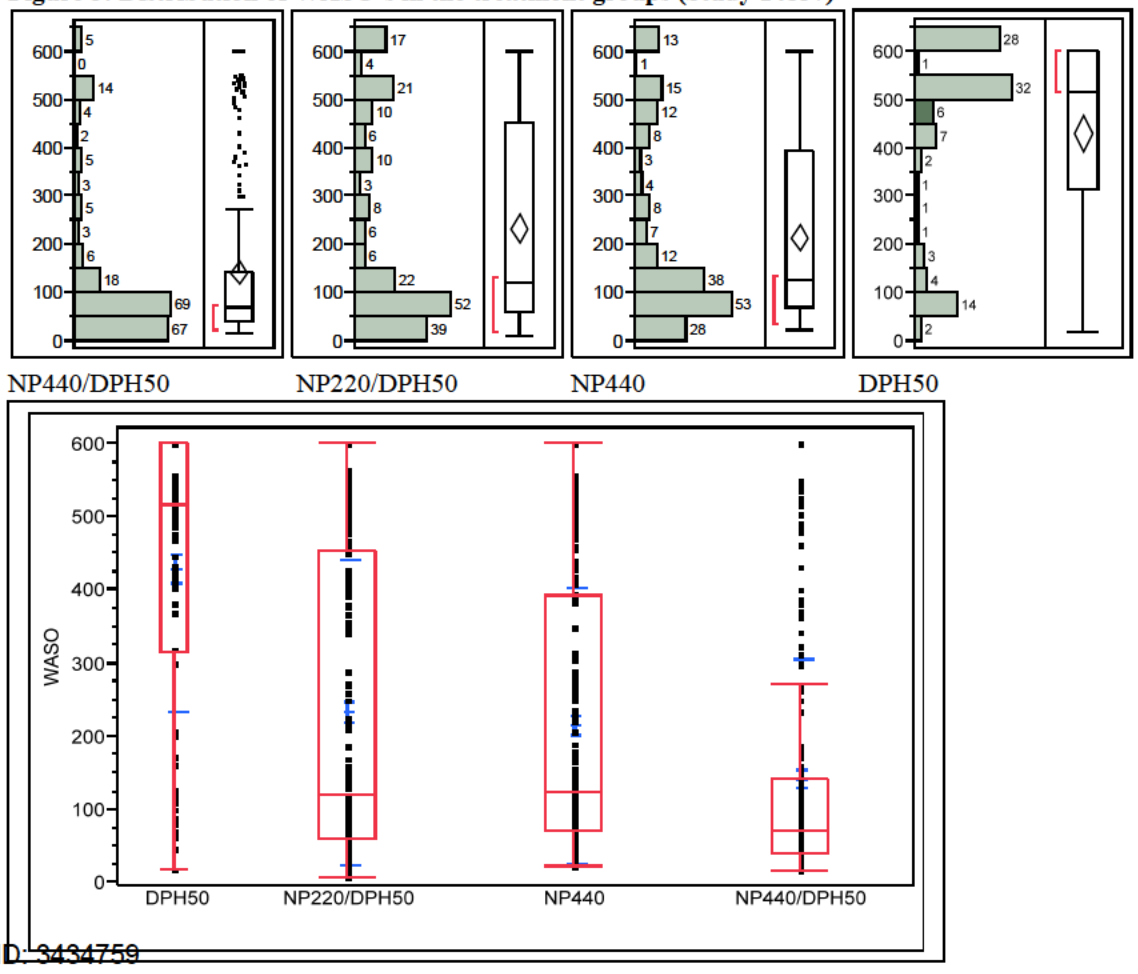
The treatment arm-response curve for WASO is shown in Figure 4 below:

Figure 4: Mean (SD) WASO for the treatment groups (Study 14837)



The distribution of WASO is shown in the following Figure 5 suggesting that there are some outliers in the NP440/DPH50 group that have long WASO's similar to the other treatment groups. It also shows that the number of subjects with a WASO of 600 (counts given in the Figure) was the highest in the DPH50 group (28 in the DPH50 group and 5 in the NP440/DPH50 group).

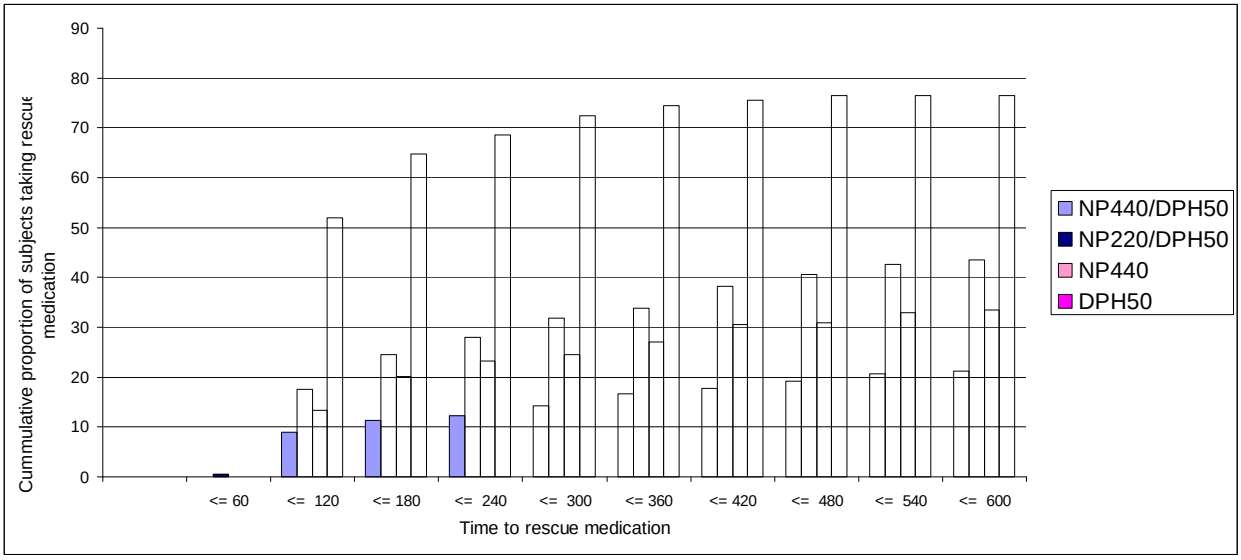
Figure 5: Distribution of WASO's in the treatment groups (Study 14837)



Subjects were allowed to take a rescue pain medication which affected the calculations of the WASO. Subjects who took rescue medication after sleep onset were treated as being awake from the time when the rescue medication was given to the remainder of the in-bed time. For subjects who took rescue medication before sleep onset, WASO was set to 10 hours (duration of the in-bed time). The highest number of subjects in the DPH group took rescue medication that lead to large WASO in this group.

Figure 6 shows the cumulative proportion of subjects taking recue medication in each treatment arm. More subjects in the NP440 group took rescue medication than that in the NP440/DPH50 group at all time points.

Figure 6: Cumulative proportion of subjects on rescue medication (Study 14837)



This could also suggest that DPH50 is helping with sleep maintenance; hence fewer subjects need rescue medication with the combination product. But there was also an increased effectiveness on pain with the combination NP440/DPH50. In addition, the intake of rescue medication may be directly correlated to the degree of pain after teeth extraction. The number of subjects with severe pain was slightly lower in the NP440/DPH50 group (28.1%) compared to NP440 (31.0 %) and NP2200/DPH50 group (34.3%). It is not clear if these differences in pain severity are likely to affect the outcome, but more patients with severe pain took rescue medication which would affect their WASO. Therefore, it is not totally clear if the superiority of NP440/DPH50 to NP440 for WASO is due to the contribution of DPH50 towards sleep maintenance or the difference in these subjects in pain severity that led to the least number of subjects taking rescue medication in the NP440/DPH50 group. Although, a conclusion that DPH50 is helping with sleep maintenance may not be unreasonable for this study.

A higher percentage of subjects had moderate pain at baseline (~70% across treatment arms) compared to the percentage of subjects with severe pain at baseline (~30% subjects across

treatment arms. See WASO difference in moderate and severe pain groups in each treatment arm in Table 13.

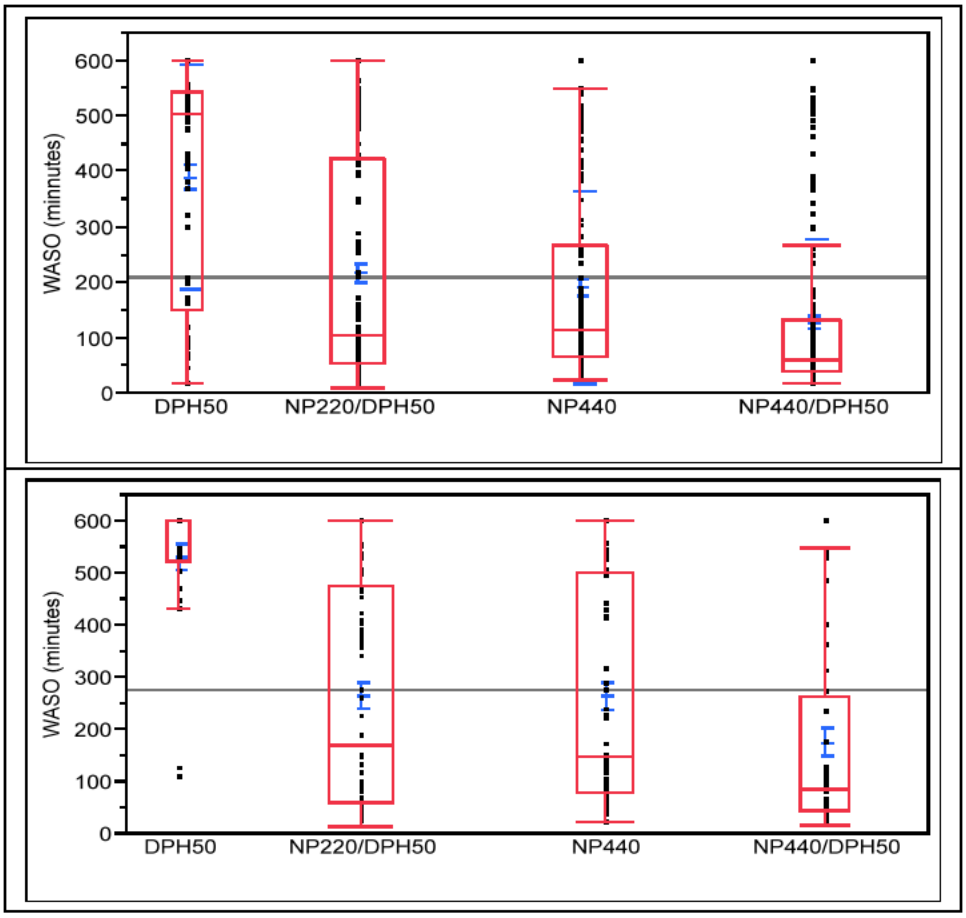
The WASO was still the shortest for the combination NP440/DPH50 followed by NP440 alone for subjects with moderate pain. For subjects with severe pain, the WASO was shortest with NP440/DPH50, but the same for the NP440 and the NP220/DPH50 group. The WASO always remained the highest with the DPH50 group. This also shows that the WASO is longer for subjects with severe pain (129 vs. 176 minutes).

Table 13: LS mean (SE) WASO by baseline pain severity (Study 14837)

Statistics	NP440/DHP50	NP220/DHP50	NP440	DHP50
Moderate Pain	128.9 (15.01) N=145	217.0 (15.61) N=134	191.9 (15.27) N=140	391.5 (21.01) N=74
Severe Pain	176.1 (26.60) N=56	264.7 (23.79) N=70	265.2 (25.30) N=62	532.8 (37.73) N=28

The box plot showing the quartiles in the subjects with moderate and severe pain is shown in Figure 5.

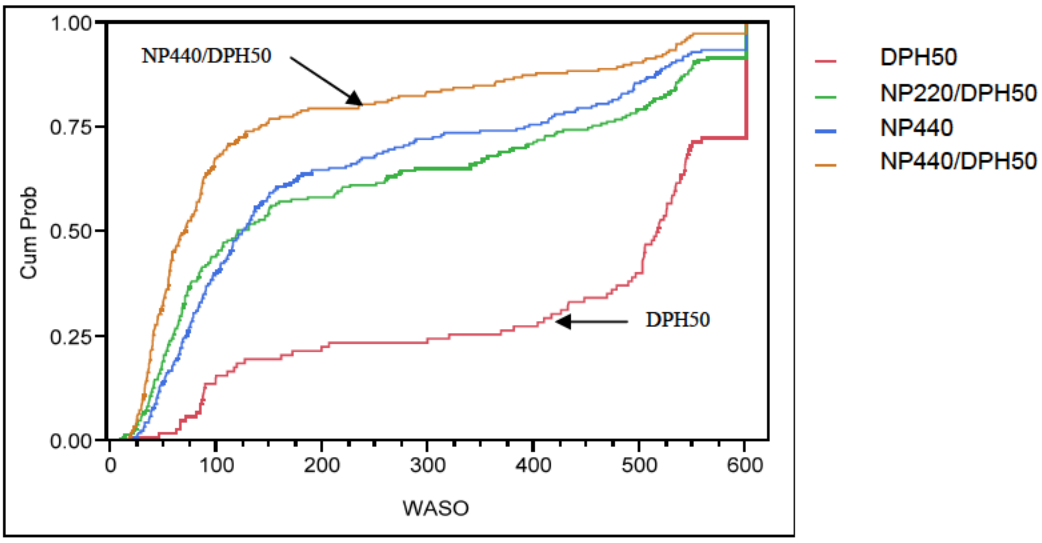
Figure 7: Box plot for WASO based on severity of pain (Study 14837)



The WASO analysis based on pain severity is not powered to look at differences due to pain severity (hence, p-values are not provided), but suggests that pain severity may impact the outcome. WASO is larger in subjects with severe pain.

The following cumulative probability plot (Figure 8) suggests that the percentage of subjects likely to have a WASO of <100 minutes is ~70-75% with NP440/DPH50, ~50-55% with NP220/DPH50, ~35% with NP440. It should be noted that this probability plot is based on the WASO data obtained in the study, which is highly impacted by the time to rescue medication.

Figure 8: Cumulative probability plot for WASO (Study 14837)



Sleep Latency by actigraphy:

Sleep Latency by actigraphy was another primary efficacy parameter for comparison of combination of NP/DHP compared to DPH alone. **According to the protocol specified efficacy comparisons, both NP440/DPH50 and NP220/DPH50 had significantly shorter time to sleep onset compared to DPH50 alone (p <0.0001).**

Sponsor's analysis:
The sponsor concludes that NP440/DPH50 had significantly shorter time to sleep onset compared to DPH50 alone (25.5 vs. 41.5 minutes; p <0.0001). The naproxen sodium 440 mg/DPH 50 mg and naproxen sodium 440 mg groups had similar times to sleep onset (median of 25.50 minutes and 25.75 minutes, respectively). In the naproxen sodium 220 mg/DPH 50 mg group, subjects had a longer time to sleep onset (median of 30.25 minutes). The DPH 50 mg group had the longest time to sleep onset (median of 41.5 minutes) (see Table 14).

Table 14: Kaplan-Meier analysis of sleep latency: summary (Intent-to-Treat Population) (Study 14837)

Statistics	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50 N=102
No. of subjects in the analysis	201*	204	202*	102
Number of subjects censored	5	17	13	28
Median time (mins)	**25.50**	**30.25**	**25.75**	**41.40**
95% CI	(22.50, 30.00)	(25.00, 33.50)	(22.50, 29.50)	(26.50, 54.50)

*Three subjects (14001-1459, 14001-1464, and 14001-1531) were excluded from the efficacy analyses because sleep parameters were not available due to malfunction of the Actigraph.

The Kaplan-Meier Analysis of sleep latency is given in Table 15. According to the protocol specified comparison, NP440/DPH50 was significantly better than DPH50 alone (p=0.0001)

Table 15: Kaplan-Meier analysis of sleep latency: *P*-values (Study 14837)

Pairwise Comparisons	p-value[a]
NP 440 mg/DPH 50 mg versus DPH 50 mg	<0.0001
NP 440 mg/DPH 50 mg versus NP 440 mg	**0.4164**
Protocol Specified NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg	0.0096
220 mg/DPH 50 mg versus NP 440 mg	0.1150
NP 220 mg/DPH 50 mg versus DPH 50 mg	0.0003

[a] *P*-value from log rank test.

← Protocol Specified

← Logical Comparison (see Reviewer's Discussion on page 40)

Sensitivity Analysis: According to the protocol, sensitivity analyses were to have been performed if a larger proportion of subjects required rescue medication in the DPH alone group.

The majority of subjects in the naproxen sodium 440 mg/DPH 50 mg group (78.8%), the naproxen sodium 220 mg/DPH 50 mg group (56.4%), and the naproxen sodium 440 mg group (66.5%) never took rescue medication, compared with only 23.5% of subjects in the DPH 50 mg group. The proportion of subjects taking rescue medication by sleep onset is shown in Table 16.

Table 16: The proportion of subjects taking rescue medication by sleep onset (Study 14837)

Rescue Medication	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50 N=102
Didn't take rescue medication	160 (78.8)	115 (56.4)	135 (66.5)	24 (23.5)
Took it before sleep onset	5 (2.5)	17 (8.3)	13 (6.4)	28 (27.5)

Took it after sleep onset	38 (18.7)	72 (35.3)	55 (27.1)	50 (49.0)

There is no statistical significant difference in Sleep onset between NP440/DPH50 and DPH50 arms excluding subjects that took rescue medication before sleep onset, as their sleep latency was set to 10 hours (p=0.2397) as shown in Table 17. The statistical review agrees with the sponsor's analysis.

Table 17: Sensitivity analysis of Kaplan-Meier analysis of sleep latency (Study 14837)

		NP 440 DPH 50 versus DPH 50	NP 440 /DPH 50 versus NP 220 /DPH 50	NP 220 /DPH 50 versus DPH 50
	N	N=196 vs 74	N=196 vs. 187	N=187 vs. 74
Excluding subjects who took rescue medication before sleep onset		**0.2397**	0.2224	0.7184
	N	N=201 vs 102	N=201 vs 204	N=204 vs 102
Subjects with imputed values		0.0016	0.0498	0.0491

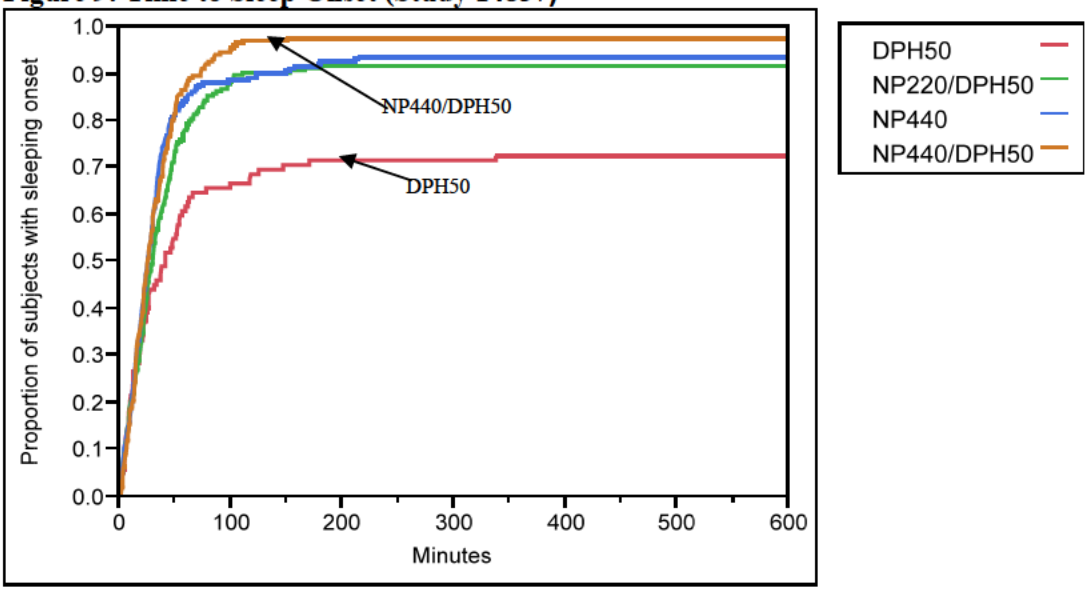
*these sensitivity analyses did not take rescue medication information into consideration when assessing efficacy results.

Reviewer's Analysis and conclusions:

The sponsor's results could be reproduced in JMP with the same p-value and my findings are confirmed by the Statistical Review. For sleep latency, the protocol specified comparison was between NP440/DPH50 versus DPH alone. According to the protocol specified efficacy comparison both NP440/DPH50 and NP220/DPH50 had significantly shorter time to sleep onset compared to DPH50 alone ($p < 0.0001$). This suggests DPH50 does not contribute to sleep latency in this model. Since the study population had pain following tooth extraction, it might not have been possible to detect a contribution of DPH50 to sleep latency without pain relief from an analgesic. According to the protocol specified criteria to establish efficacy, Study 14837 would be considered a positive study, but in reality an analgesic is driving the sleep latency effect in a population that has sleeplessness associated with pain. Unless the pain is abated, the subject will have difficulty to fall asleep. As seen in Table 15, the comparison between NP440/DPH50 versus NP440 gave a p-value of 0.4164 suggesting that when pain is abated to some extent, sleep latency is not different between the combination groups compared to NP440 alone. [Note: The Study conducted Advil PM had used the analgesic (ibuprofen) as the comparator for sleep latency].

The Time to sleep onset for the treatment groups is shown in the following Figure 9, suggesting time to sleep onset is shortest with NP440/DPH50

Figure 9: Time to Sleep Onset (Study 14837)



SubGroup Analysis:

There was no difference in objective WASO or Sleep latency based on age or gender. Distribution of ages was not wide enough to look at age based differences.

Pain severity did not affect the time taken to fall asleep in the NP440/DPH50 group, but did increase in all other treatment groups with severe pain**Error! Reference source not found.**.

Table 18: Pain Severity: Analysis of Sleep Latency (Median Time in minutes) (Study 14837)

Statistics	NP440/DHP50	NP220/DHP50	NP440	DHP50
Moderate Pain	25.5 N=145	27.5 N=134	24.0 N=140	29.0 N=74
Severe Pain	25.75 N=56	31.5 N=70	30.0 N=62	NE N=28

NE=non estimable

I looked at the subgroup analysis in the pediatrics as the sponsor is proposing the use of this product in >12 years of age. There were only 16-17 year-olds enrolled in this study. There were no children younger than 16 years in this study. The subgroup analysis for WASO and Sleep Latency in pediatrics is given in the following Tables Table 19 and Table 20. The p-value was statistically significantly superior for both WASO and Sleep Latency.

Table 19: WASO Analysis in pediatrics (Study 14837)

Statistics	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50 N=102
No. of subjects in the analysis	**28**	**31**	**36**	**20**
Mean (SD)	**114.41 (134.84)**	**270.8 (224.93)**	**229.0 (198.89)**	**507.9 (123.23)**
Median	71.00	149.5	122.5	542.5
Range	23.5-539.00	12-600	36-600	81-600
ANCOVA Model				
LS mean	114.59	275.68	226.91	503.93

Pairwise Comparisons	LS mean Difference	p-value
NP 440 mg/DPH 50 mg versus NP 440 mg	**-112.3**	**0.0144**
NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg	-161.09	0.0008
NP 440 mg/DPH 50 mg versus DPH 50 mg	-389.34	<0.0001
220 mg/DPH 50 mg versus NP 440 mg	48.76	0.2706
NP 220 mg/DPH 50 mg versus DPH 50 mg	-228.25	< 0.0001

Table 20: Kaplan Meier Analysis for Sleep Latency in the pediatrics (Study 14837)

Statistics	NP440/DHP50 N=203	NP220/DHP50 N=204	NP440 N=203	DHP50 N=102
No. of subjects in the analysis	28	31	36	20
Number of subjects censored	0	4	3	7
Median time (mins)	**22.50**	**30.5**	**32.5**	**39.75**
95% CI	(14.50, 31.5)	(18-39)	(25.50, 55)	(26.50, 54.50)

Pairwise Comparisons	p-value
NP 440 mg/DPH 50 mg DPH 50 mg	**0.0008**
NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg	0.1393
NP 440 mg/DPH 50 mg versus NP 440 mg	0.1055
220 mg/DPH 50 mg versus NP 440 mg	0.8326
NP 220 mg/DPH 50 mg versus DPH 50 mg	0.1062

Secondary Efficacy Endpoints:

The secondary analysis included both objective and subjective sleep assessments.

Total Sleep Time and Sleep Efficiency:

Both objective Total sleep time and objective Sleep Efficiency were statistically better in the combination NP440/DPH50 group compared to NP440 alone (P=0.0001 and 0.0007, respectively) as shown in Table 21.

Table 21: Secondary objective sleep parameters (Study 14837)

Parameter LS-Mean (SE)	NP440/DHP50 N=201	NP220/DHP50 N=204	NP440 N=202	DHP50 N=102	LS mean Treatment Difference P-value	
					NP440/DHP50 versus NP440	NP440/DHP50 versus NP220/DPH50
Total Sleep Time	426.2 (12.85)	337.7 (12.76)	355.8 (12.81)	141.4 (18.03)	70.4 p=0.0001	88.5 p=<0.0001
Sleep Efficiency	71.0 (2.14)	56.3 (2.13)	59.3 (2.14)	23.6 (3.01)	11.7 p=0.0007	14.7 p=<0.0001

*Three subjects (14001-1459, 14001-1464, and 14001-1531) were excluded from the efficacy analyses

Global Assessment of Investigational Product as a Sleep Aid:

Sponsor's analysis of Global Assessment of Investigational Product as Sleep Aid is summarized in Table 22 and 21. More subjects gave a rating of "good" and "very good" in the NP440/DPH50 group compared to other groups. NP440/DPH50 was statistically significantly superior to NP440 (P=<0.0001), suggesting the same trend as that of the primary endpoints. But the global assessment also indicated that NP220/DPH50 was also statistically superior to NP440 alone.

Table 22: Analysis of Global Assessment of Investigational Product as Sleep Aid; summary (Intent-to-Treat Population) (Study 14837)

	Treatment Group			
Statistic	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
Number of subjects included in the analysis	166	125	141	25
0 = Poor	8 (3.9)	10 (4.9)	29 (14.3)	3 (2.9)
1 = Fair	39 (19.2)	29 (14.2)	51 (25.1)	9 (8.8)
2 = Good	58 (28.6)	47 (23.0)	37 (18.2)	6 (5.9)
3 = Very good	49 (24.1)	26 (12.7)	17 (8.4)	7 (6.9)
4 = Excellent	12 (5.9)	13 (6.4)	7 (3.4)	0
Mean	2.1	2.0	1.4	1.7
Standard deviation	1.00	1.09	1.10	1.03
Median	2.0	2.0	1.0	2.0
Minimum	0	0	0	0
Maximum	4	4	4	3

Table 23: Analysis of Global Assessment of Investigational Product as Sleep Aid: P-values (Intent-to-Treat Population) (Study 14837)

Cochran-Mantel-Haenszel test [a] comparison	P-value
NP 440 mg/DPH 50 mg versus NP 440 mg	< 0.0001
NP 220 mg/DPH 50 mg versus NP 440 mg	< 0.0001
NP 440 mg/DPH 50 mg versus DPH 50 mg	0.0494
NP 220 mg/DPH 50 mg versus DPH 50 mg	0.1088
NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg	0.3997

[a] Cochran-Mantel-Haenszel test controlling for center with modified ridit scores.

Karolinska Sleep Dairy:

In most subjects NP440/DPH50 did statistically better than NP440 and DHP50 alone for the questions in the Karolinska sleep diary, except "Ease of awakening?" Ease of awakening was not different across treatment groups. Most Questions were scored on a scale of 1-5, with 5 being best. "Premature awakening" and "Well rested" were scored on a scale of 1-3 with 3 being a good outcome. These were analyzed using Cochran-Mantel-Haenszel test controlling for center with modified ridit scores. See Sponsor's Table 24.

Table 24: Comparison of secondary subjective sleep assessments from Study 14837 (Intent−to-Treat Population) (Study 14837)

	Study 14837			
	Treatment Groups			
Subjective assessments	**NS 440 mg/ DPH 50 mg**	**NS 220 mg/ DPH 50 mg**	**NS 440 mg**	**DPH 50 mg**
Karolinska sleep diary [a]				
How was your sleep?	3.6 (0.97)[d, e, f]	3.4 (0.98)[d]	3.2 (0.94)	3.1 (1.02)
How calm was your sleep?	3.5 (1.11)[d, e]	3.4 (1.09)[e]	3.2 (1.10)	2.8 (1.14)
How easy was it to fall asleep	3.2 (1.05)[d, e, f]	3.0 (1.06)[e]	2.9 (1.05)	2.6 (1.18)
Premature awakening?	2.2 (0.75)[d, e]	2.0 (0.81)[d, e]	1.8 (0.73)	1.6 (0.71)
Ease of awakening?	4.1 (0.77)	4.1 (0.72)	4.1 (0.76)	4.2 (0.85)
Well Rested?	2.4 (0.58)[d, e, f]	2.2 (0.64)[e]	2.2 (0.57)	2.0 (0.58)
Did you get enough (sufficient) sleep?	3.8 (1.02)[d, e, f]	3.3 (1.28)[e]	3.3 (1.16)	2.8 (1.29)
Sleep questionnaire[b]				
How would you rate the quality of your sleep?	6.4 (1.96)[d, e, f]	5.9 (2.13)[d, e]	5.4 (1.99)	4.9 (2.36)
How would you rate the refreshing nature of your sleep?	6.2 (2.03)[d, e]	5.8 (2.26)[e]	5.5 (2.14)	4.4 (2.45)
Estimate how long it took you to fall asleep?	40.0 (31.52)	40.7 (29.39)	53.4 (67.78)	42.4 (42.02)
Estimate the number of minutes you were awake?	73.8 (79.06)[d]	75.3 (81.55)[d]	103.5 (89.50)	81.7 (86.72)
IP as sleep aid [c]	2.1 (1.00)[d, e]	2.0 (1.09) [d]	1.4 (1.10)	1.7 (1.03)

a Karolinska Sleep Diary as mean (standard deviation) by treatment group (Cochran-Mantel-Haenszel test controlling for center with modified ridit score)
b Subjective Sleep Questionnaire as mean (standard deviation) by treatment group (Cochran-Mantel-Haenszel test controlling for center with modified ridit score)
c Global Assessment of Investigational Product as a Sleep Aid as mean (standard deviation) by treatment group (Cochran-Mantel-Haenszel test controlling for center with modified ridit score)
d Statistically significant ($P<0.05$) versus NS 440 mg
e Statistically significant ($P<0.05$) versus DPH 50 mg
f Statistically significant ($P<0.05$) versus NS 220 mg/DPH 50 mg

Subjective Sleep Questionnaire:

The subjective sleep questionnaires were scored on a scale of 1-10, with score 1 being poor and 10 being excellent. The following observations can be made from the subjective sleep questionnaire:

- For the questions "How will you rate the quality of your sleep last night?" and "How will you rate the refreshing nature of your sleep last night?" NP440/DPH50 was better than NP440 and DPH50 alone.
- "Once you took the medication estimate how long it took you to fall asleep?," a subjective measure of sleep latency was not different across NP440/DPH50, NP220/DPH50 and DPH50 groups.

Reviewer's Comment: The subjective measure of sleep onset was longer than the objective measure of sleep onset (~40 minutes vs. ~25 minutes), indicating a difference in objective and subjective sleep latency outcomes. This has commonly been seen with subjective assessments of sleep drugs.

- Estimate the number of minutes you think that you were awake from the time you fell asleep until the time you got out of bed, a subjective measure of WASO, showed NP440/DPH50 and NP220/DPH both better than NP440, but there was no difference between NP440/DPH50 and NP220/DPH.

Reviewer's Comment: This indicates no dose-response for subjective WASO. The subjective measure of WASO was shorter than the objective measure (~70 minutes vs. 142 minutes for the NP440/DPH50 treatment group). This is true for other treatment groups as well. The objective sleep assessments were more driven by the rescue medication taken.

The p-values for the comparisons are given in the following Table 25:

Table 25: Analysis of Subjective Sleep Questionnaire (Study 14837)

Subjective Sleep Questionaire	P-values			
	NP440/DPH50 versus NP440	NP220/DPH50 versus NP440	NP440/DPH50 versus NP220/DPH50	NP440/DPH50 versus DPH50
How will you rate the quality of your sleep last night?	<0.0001	0.0080	0.0232	<0.0001
How will you rate the refreshing nature of your sleep last night?	0.0016	0.1511	0.1256	<0.0001
Once you took the medication estimate how long it took you to fall asleep?	0.8252	0.9636	0.6922	0.6246
Estimate the number of minutes you think that you were awake from the time you fell asleep until the time you got out of bed	<0.0001	0.0001	0.9241	0.9100

The subjective sleep questionnaire suggests no difference in subjective measure of sleep onset between any treatment groups. It also suggests that both the combination doses are better than Naproxen alone for subjective assessment of WASO, although there is no dose response between the two combination doses. This suggests that diphenhydramine does not contribute to sleep onset in this model, but does help with staying asleep

Efficacy conclusions:

- The primary efficacy results based on the pre-specified statistical analysis plan demonstrated that the naproxen sodium 440 mg/DPH 50 mg combination was the only dose shown to be significantly more effective than either single ingredient alone for both efficacy endpoints, WASO and sleep latency based on pre-specified comparisons.
- Naproxen sodium 220 mg/DPH 50 mg failed to show added clinical benefit for prolonging sleep duration (as measured by WASO) compared to the analgesic alone (naproxen sodium 440 mg); however, naproxen sodium 220 mg/DPH 50 mg was associated with significantly better sleep latency versus DPH 50 mg.
- A nominally statistically significant dose-response was established for selection of naproxen sodium 440 mg/DPH 50 mg over naproxen sodium 220 mg/DPH 50 mg for both WASO and sleep latency, but this was not an eligible pre-specified comparison.
- The conclusions from the primary efficacy analysis were supported by the sensitivity analysis.
- Amongst the secondary efficacy parameters, Global Assessment and Karolinska Sleep Dairy results support the primary efficacy results that NP440/DPH50 was superior to either ingredient alone, but not all questions on the Subjective Sleep Questionaire support the primary efficacy results. The subjective assessment of sleep latency was longer than the objective assessment. The subjective assessment of WASO was shorter than the objective assessment. The subjective assessment of WASO does suggest that DPH helps with sleep maintenance, but not with sleep onset in the study population.

Safety Analysis:

The sponsor presented only treatment emergent AEs (TEAEs) for this study. Overall summary of TEAEs is given in the following Table 26. There were no deaths, discontinuations or serious adverse events in any treatment groups.

Table 26: Overall summary of subjects with treatment-emergent adverse events (Study 14837)

	Treatment Group							
	NP 440 mg/ DPH 50 mg N = 203		NP 220 mg/ DPH 50 mg N = 204		NP 440 mg N = 203		DPH 50 mg N = 102	
Subjects	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
With at least 1 TEAE	37	(18.2)	37	(18.1)	40	(19.7)	25	(24.5)
With at least 1 drug-related TEAE	2	(1.0)	4	(2.0)	2	(1.0)	4	(3.9)
With at least 1 severe TEAE	1	(0.5)	1	(0.5)	1	(0.5)	0	
Taking medication to treat the TEAE	5	(2.5)	5	(2.5)	3	(1.5)	2	(2.0)
With at least 1 serious TEAE	0		0		0		0	
With a TEAE leading to discontinuation	0		0		0		0	
Who died due to a TEAE	0		0		0		0	

Severe TEAEs: There were 3 severe TEAEs (1 subject in each of the naproxen sodium 440 mg/DPH 50 mg, naproxen sodium 220 mg/DPH 50 mg, and naproxen sodium 440 mg groups). These severe TEAEs were presyncope, vomiting and headache, respectively and were resolved upon follow up; no case reports or narratives were provided for these subjects.

There were no appreciable differences in the rates of TEAEs in the combination treatment group compared to naproxen sodium or diphenydramine alone.

The number of subjects with TEAEs of ≥1% is given in Table 27. The most common events were nausea, headache, dizziness and vomiting.

Table 27: Incidence of TEAEs (Study 14837)

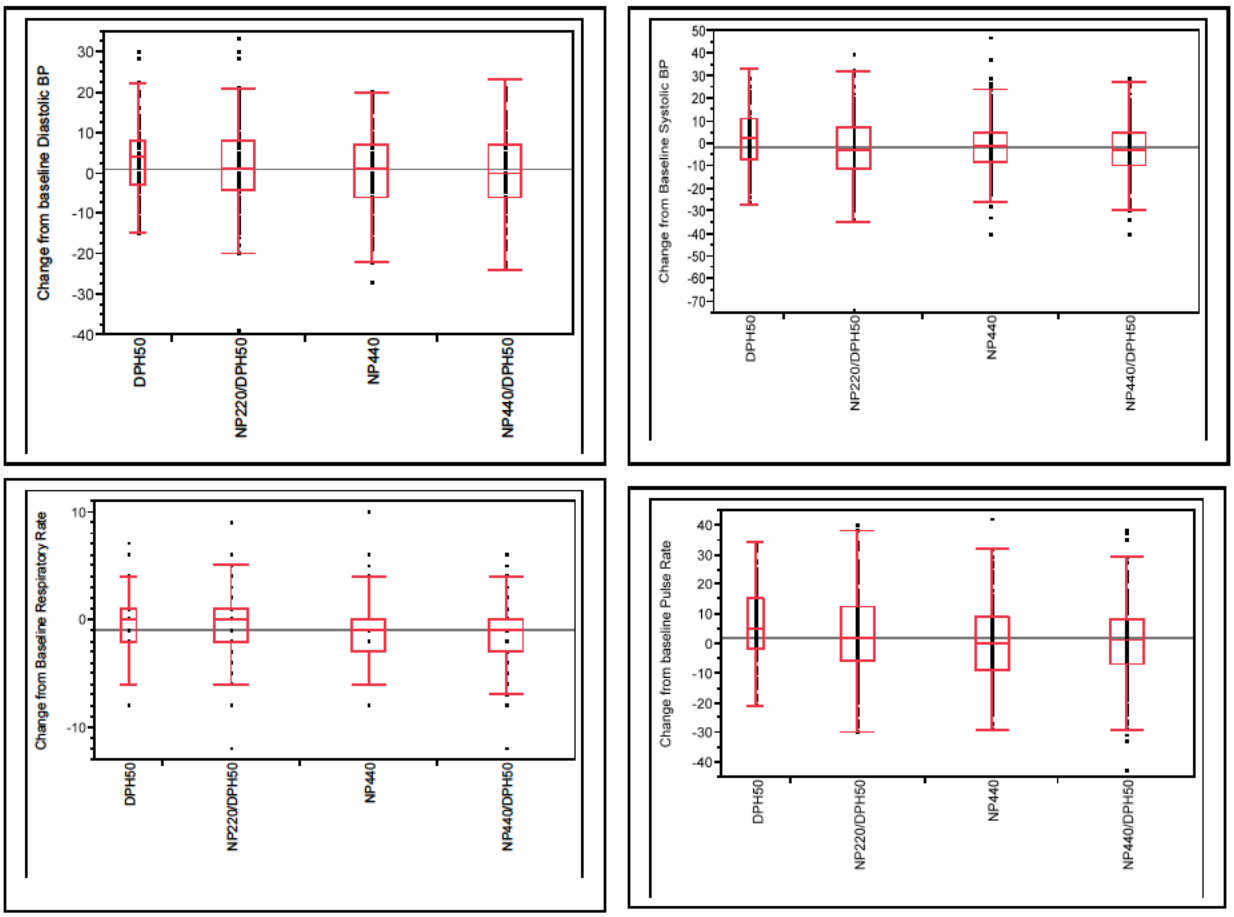
Preferred Term	NP440/DPH50 N=203	NP220/DPH50 N=204	NP440 N=203	DPH50 N=102
	N (%)			
Nausea	15 (7.4)	12 (5.9)	14 (6.9)	10 (9.8)
Headache	12 (5.9)	13 (6.4)	16 (7.9)	8 (7.8)
Dizziness	9 (4.4)	8 (3.9)	6 (3.0)	4 (3.9)
Vomiting	2 (1.0)	5 (2.5)	6 (3.0)	4 (3.9)
Presyncope	3 (1.5)	3 (1.5)	2 (1.0)	1 (1.0)
Paresthesia	3 (1.5)	0	1 (0.5)	2 (2.0)
Syncope	2 (1.0)	0	2 (1.0)	1 (1.0)
Feeling Hot				1 (1.0)
Tremor				1 (1.0)
Muscle Tightness				1 (1.0)
Ear Pain				1 (1.0)
Hiccups				1 (1.0)

Most events were resolved by Day 2. There were 4 cases of paresthesia and 1 case of dizziness that were not resolved by Day 2.

Reveiwer's Comment:
According to the protocol, the sponsor should have followed patients with adverse events for 2-5 (±2) days. No data from these patients have been given beyond 2 days. The paresthesia would likely be from the dental surgery.

Vital Signs:
Changes from baseline in systolic and diastolic blood pressure, pulse rate, and respiration rate (at Day 1 and Day 2) were evaluated using outlier plots generated by me using JMP. No appreciable differences were found across treatment groups. (see Figure 10 below)

Figure 10: Box plots for change from baseline for vital signs (Study 14837)



Reviewer's Comment: Patients' verbatim terms were not available and were requested from the sponsor. The sponsor provided these from the progress notes. The patient name was redacted from the progress notes, which was sent to the data management group for double data entry.

The verbatim terms were then linked to the reported term using the subject number. Upon review it appears that the progress notes were most likely written by the physicians and did not capture the patients' verbatim complaints. In the progress notes there were terms like paresthesia, epistaxis, presyncope, emesis, aleveolitis/dry socket that are likely recorded by the physicians. Since the pivotal studies were single-dose in-patient studies, it appears the AEs were assessed and recorded by the physician at study site. The sponsor was unable to provide more information as the AEs were entered onto the CRFs by the coordinators after the physician reviewed the source documents and signed off on the AE.

Based on the submitted information, I looked at adequate coding for all AEs. I did not find any discrepancies in coding of most AEs, except presyncope. One case each in the DPH, NP440 and the NP220/DPH50 group were written as lightheadedness in the progress note, but were coded as presyncope. It is unclear why these cases of lightheadedness were not coded as dizziness.

Safety Conclusions: There were no new safety concerns from the combination product compared to NP440 or DPH50.

5.3.2 Study 15881:

Title: A Multicenter, Randomized, Double-Blind, Parallel-Group Trial Assessing the Efficacy and Safety of Naproxen Sodium and Diphenhydramine Combination in Postsurgical Dental Pain with Phase Advanced Sleep

Study Dates: 19 Dec 2011 to 22 Feb 2012

This study was conducted by the sponsor after the Agency request to the sponsor evaluate a lower dose of diphenhydramine. The sponsor chose only to study NP440/DPH25. Their rationale to not study a lower dose of the analgesic along with the DPH25 was that the NP440/DPH50 dose was not effective in Study 14837.

This study was identical to Study 14837 in terms of in design, primary and secondary endpoints and sensitivity analyses, except that the treatment groups were different. A total of 267 subjects were randomized to a single oral dose of 1 of the 3 treatment groups.

Treatments administered: Single dose of:

- Naproxen sodium 440 mg/DPH 25 mg combination treatment group (n = 107)
- Naproxen sodium 440 mg treatment group (n = 106)
- DPH 50 mg treatment group (n = 54)

Investigators:
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Subject Disposition**:** All subjects in each treatment group completed the study.

Demographics: Demographic characteristics generally were comparable among treatment groups (Table 28).

Table 28: Demographics: age (Safety and Intent-to-Treat Populations) (Study 15881)

	NP440/DHP25 N=107	NP440 N=106	DHP50 N=54	Total N=267
Age [mean (SD)]	21.4(5.5)	21.3 (5.27)	20.8 (4.64)	21.2 (5.25)
Range	13-38	12-49	12-35	12-49
Gender [n (%)]				
Male	35 (32.7)	42 (39.6)	17 (31.5)	94 (35.2)
Female	72 (67.3)	64 (60.4)	37 (68.5)	173 (64.8)
Ethnicity [n (%)]				
Hispanic/Latino	24 (22.4)	20 (18.9)	11 (20.4)	55 (20.6)
Not Hispanic	83 (77.6)	86 (81.1)	43 (79.6)	212 (79.4)
Race [n (%)]				
White	93 (86.9)	93 (87.7)	48 (88.9)	234 (87.6)
Black	8 (7.5)	6 (5.7)	3 (5.6)	17 (6.4)
Asian	4 (3.7)	5 (4.7)	1 (1.9)	10 (3.7)
Pacific Islander	0	0	1 (1.9)	1 (0.4)
American Indian	0	0	0	0
Other	1 (0.9)	0	1 (1.9)	2 (0.7)
Multiple	1 (0.9)	2 (1.9)	0	3 (1.1)

The baseline pain assessed by categorical rating scale and VAS is given in Table 29:

There were 49 children in this study: 2 subjects 12 years old, 9 subjects 13-14 years old and 38 subjects 16-17 years old.

Table 29: Baseline Pain: Categorical Pain Rating Scale and Visual Analog Scale score (Safety Population) (Study 15881)

	NP440/DHP25 N=107	NP440 N=106	DHP50 N=54	Total N=267
	Categorical Pain rating Scale			
Moderate Pain	69 (64.5)	63 (59.4)	28 (51.9)	160 (59.9)
Severe Pain	38 (35.5)	43 (40.6)	26 (48.1)	107 (40.1)
	Visual Analog Score			
Mean (SD)	75.2 (10.01)	75.2 (11.01)	77.1 (9.2)	75.6 (10.26)
Median	75.0	76	80.0	76
Range	51-98	50-100	55-97	50-100

Reviewer's Comment: The percentage of subjects with severe pain is not balanced among treatment groups, being the lowest in the NP440/DPH25 group (35.5%). This could affect the number of patients taking rescue medication in this group.

Protocol Deviations:
A protocol deviation was identified for a total of 23 subjects (12 subjects at study site 14001 and 11 subjects at study site 14002) including 8, 6, and 9 subjects in the NP 440 mg/DPH 25 mg, NP 440 mg, and DPH 50 mg treatment group, respectively. All of the protocol deviations for these subjects were considered minor by the sponsor, and none were excluded from the ITT Population. I agree with the sponsor that these are minor protocol deviations. Across all treatment groups there were 10 subjects who completed global assessments and subjective sleep assessment even though they took rescue medication before sleep onset. In one subject, the dose time varied between the actigraphy and that noted at the source.

Outcome of Efficacy Analysis

Primary Efficacy Endpoint

The following treatment comparisons were made for the 2 primary efficacy endpoints (each at 0.05 level of significance):

- For WASO: NP 440 mg/DPH 25 mg versus NP 440 mg
- For sleep latency: NP 440 mg/DPH 25 mg versus DPH 50 mg

Both tests had to be statistically significant in order to claim NP 440 mg/DPH 25 mg to be efficacious.

Reviewer's Comment: In the previous pivotal study 14837, the sample size was calculated assuming a WASO treatment difference of 52 minutes and a standard deviation of 138 minutes. A sample size of 200 subjects was considered to provide adequate power for the study. In this study with a lower dose the sponsor assumed a WASO treatment difference of 56 minutes and a standard deviation of 14 minutes. A sample size of 100 subjects was considered to provide adequate power. A standard deviation of 14 was not realistic based on the results of the previous pivotal study, especially since the final report of Study 14837 was completed 2 months prior to the start of this study.

Wake After Sleep Onset (WASO) by actigraphy:

Sponsor's analysis:
WASO comparison of NP440/DPH25 versus NP440 alone was the primary efficacy endpoint. The NP440/DPH25 combination did not show statistically significant benefit in improving sleep duration when compared to NP440 alone. **WASO was 25 minutes shorter for the NP 440/DPH25 group compared to the NP440 group but this difference was not statistically significant (p=0.3047).** WASO was the longest for the DPH50 group (364 minutes).

Sponsor's analysis of WASO in the ITT population is shown in Table 30.

Table 30: Analysis of wake after sleep onset: summary (Intent-to-Treat Population) (Study 15881)

Statistics	NP440/DHP25 N=107	NP440 N=106	DHP50 N=54
Mean (SD)	**152.13 (165.44)**	**180.12 (173.62)**	**369.54 (207.64)**
Median	72.5	96.5	490.5
Range	18-600	11-600	20-600
ANCOVA Model			
LS mean (SE)	**155.25**	**180.08**	**364.83**
Treatment Difference NP440/DHP25 vs. NP440	-24.83		
95% CI of LS-Mean Treatment Difference	-72.38, 22.72		
P-value	**0.3047**		

[a]*P*-value from ANCOVA model including treatment and center as fixed effects and baseline categorical pain score as the covariate.
[b]Pairwise comparison NS 440 mg/DPH 25 mg versus NS 440 mg

Sensitivity Analysis: A sensitivity analysis was done if more subjects in the NP440 group (28.3%) took rescue medication than the NP440/DPH25 group (22.4%). The highest proportion of subjects taking rescue medication was in the DPH50 group (65%). The cumulative proportion of subjects taking rescue medication is shown in Table 31.

Table 31: Cumulative Proportion of Subjects Taking Rescue Medication

Time After Dosing That Rescue Medication Was Taken	Treatment Group: NP 440 mg/ DPH 25 mg N = 107 n	(%)	NP 440 mg N = 106 n	(%)	DPH 50 mg N = 54 n	(%)
≤ 60 minutes	0		1	(0.9)	0	
≤ 120 minutes	9	(8.4)	12	(11.3)	21	(38.9)
≤ 180 minutes	14	(13.1)	13	(12.3)	29	(53.7)
≤ 240 minutes	15	(14.0)	17	(16.0)	32	(59.3)
≤ 300 minutes	16	(15.0)	23	(21.7)	33	(61.1)
≤ 360 minutes	17	(15.9)	25	(23.6)	34	(63.0)
≤ 420 minutes	21	(19.6)	26	(24.5)	35	(64.8)
≤ 480 minutes	22	(20.6)	28	(26.4)	35	(64.8)
≤ 540 minutes	24	(22.4)	30	(28.3)	35	(64.8)
≤ 600 minutes	24	(22.4)	30	(28.3)	35	(64.8)

The majority of the subjects in the NP 440 mg/DPH 25 mg group (77.6%) and the NP 440 mg group (71.7%) never took rescue medication, compared with only 35.2% of subjects in the DPH 50 mg group.

Reviewer's Comment: The fact that a lower percentage of subjects took rescue medication in the NP440/DPH 25 group compared to NP440 alone group suggests that DPH25 may be contributing towards subjects staying asleep and hence not needing a rescue medication. On, the other hand, the percent of patients with severe pain in the NP440/DPH25 group was lower (35%) than the other groups (~40%), which could also be contributing to the difference in the percentage of subjects taking rescue medication in each treatment group.

See Table 32 for the sensitivity analyses conducted. These also show no treatment difference between NP440/25 and NP440. The Statistical review confirms these analyses.

Table 32: Sensitivity analysis of WASO (Study 15881)

Sensitivity Analysis		NP 440 DPH 25 versus NP440
	N	N = 83 vs 76
Excluding subjects who took rescue medication		treatment difference: - 8.82 minutes p=<0.1914
	N	N=107 vs 106
Subjects with imputed values		treatment difference: -4.49 minutes p=<0.4414
	N	N=107 vs 106
Subjects taken rescue medication are considered as not have taken rescue medication		treatment difference: - 12.20 minutes p=<0.0090

Reviewer's Analysis: The reviewer was able to reproduce the primary analysis in JMP. The fact that no treatment difference is seen between NP440/DPH25 and NP440 may be due to the study being underpowered. It had half the number of subjects that were evaluated in the pivotal study 14837 with the NP440/DPH50 dose.

WASO analysis was done based on baseline pain severity. It can be seen in Table 33, that subjects with severe pain have larger WASO.

Table 33: LS mean (SE) WASO by baseline pain severity

Statistics	NP440/DHP25	NP440	DHP50
Moderate Pain	139.5 (19.2) N=69	148.7 (20.8) N=63	339 (31.2) N=28
Severe Pain	188.8 (32.9) N=56	236.4 (30.3) N=62	409.7 (38.09) N=28

Sleep Latency:

Sponsor's Analysis:
The NP440 mg/DPH 25 mg, NP440 mg, and DPH 50 mg groups had median sleep onset times of 23.50 minutes, 16.75 minutes, and 27.50 minutes, respectively (Table 34). **The difference**

between the NP 440 mg/DPH 25 mg group and the DPH 50 mg group was not statistically significant (P = 0.1677).

Table 34: Kaplan-Meier analysis of sleep latency: summary (Intent-to-Treat Population)

Statistics	NP440/DHP25 N=107	NP440 N=106	DPH50 N=54
No. of subjects censored	4	2	5
Median time (mins)	**23.5**	**16.75**	**27.50**
95% CI	(18.00, 28.00)	(13.50, 25.00)	(16.00, 36.50)
P-value NP440/DPH25 vs. DPH50	0.1677		

P=value from long rank test

Reviewer's Comment: If analgesic was driving sleep latency, the effect on sleep latency should have been positive. The negative results may be due to the study being underpowered. With DPH25 added to NP440, the sleep latency is, seemingly unexpectedly, numerically longer, but the shortest with NP440 alone (16.75 minutes), and the longest with the higher diphenhydramine dose, DPH50 (27.5minutes).

Sensitivity Analysis: A sensitivity analysis was done if more subjects in the DPH group. Of the subjects who did take rescue medication, the majority took rescue medication after sleep onset: 83.3% (20/24) in the naproxen sodium 440 mg/DPH 25 mg group, 93.3% (28/30) in the NP 440 mg group, and 85.7% (30/35) in the DPH 50 mg group.

The results of the sensitivity analyses as confirmed by the Statistical Review are given in Table 35.

Table 35: Sensitivity analysis of Kaplan-Meier analysis of sleep latency (Study 15881)

Sensitivity Analysis		NP 440 DPH 25 versus DPH50
Excluding subjects who have taken rescue medication before sleep onset	N = 103 vs 49	p=<0.4605
Subjects with imputed values	N = 107 vs 54	p=<0.5100
Subjects taken rescue medication are considered as not have taken rescue medication	N = 107 vs 54	p=<0.0708

Reviewer's Analysis:
I was able to reproduce the sponsor's primary analysis in JMP. Looking at Sleep Latency based on pain severity, the role of DPH towards latency is unclear. In the moderate pain group, subjects on DPH50 alone had shorter latency than the combination. This also shows that subjects with

severe pain have longer Sleep Latency's. This study is generally underpowered to look for any treatment differences and any meaningful trends could not be obtained.

Sleep Latency based on pain severity is given in Table 36.

Table 36: Pain Severity: Analysis of Sleep Latency (Median Time in minutes) (Study 15881)

Statistics	NP440/DHP25	NP440	DHP50
Moderate Pain	18 N=69	19.5 N=63	15 N=28
Severe Pain	31.5 N=38	14.0 N=43	37.5 N=26

Secondary Efficacy Endpoints:

The secondary analysis included both objective and subjective sleep assessments.

Total Sleep Time and Sleep Efficiency:

Neither Total sleep time nor Sleep Efficiency were statistically different in the combination NP440/DPH25 group compared to NP440 alone (P=0.2764 for both). See Table 37.

Table 37: Secondary objective sleep parameters

Parameter LS-Mean (SE)	NP440/DHP50 N=107	NP440 N=106	DHP50 N=54	LS mean Treatment Difference P-value
				NP440/DHP25 versus NP440
Total Sleep Time	418.66 (17.07)	392.38 (17.09)	206.61 (23.98)	26.29 p=0.2764
Sleep Efficiency	69.77 (2.84)	65.39 (2.84)	34.43 (3.99)	4.31 p=0.2764

Global Assessment of Investigational Product as a Sleep Aid

According to the sponsor, the naproxen 440 mg/DPH 25 mg group had a significantly ($P < 0.0001$) better Global Assessment of Investigational Product as a Sleep Aid score than the NP 440 mg group. No statistically significant difference was observed between the naproxen 440 mg/DPH 25 mg group and the DPH 50 mg group. Results for the Global Assessment of Investigational Product as a Sleep Aid are summarized in Table 38.

Table 38: Analysis of Global Assessment of Investigational Product as a Sleep Aid: Summary (Intent-to-Treat Population) (Study 15881)

	Treatment Group					
	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54	
Statistic	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Number of subjects included in the analysis	85		79		19	
0 = Poor	2	(1.9)	13	(12.3)	1	(1.9)
1 = Fair	12	(11.2)	24	(22.6)	7	(13.0)
2 = Good	37	(34.6)	24	(22.6)	2	(3.7)
3 = Very good	23	(21.5)	13	(12.3)	8	(14.8)
4 = Excellent	11	(10.3)	5	(4.7)	1	(1.9)
Mean	2.3		1.7		2.1	
Standard deviation	0.96		1.13		1.13	
Median	2.0		2.0		2.0	
Minimum	0		0		0	
Maximum	4		4		4	

Cochran-Mantel-Haenszel Test[a] comparison	**P-value**
NP 440 mg/DPH 25 mg versus NP 440 mg	<0.0001
NP 440 mg/DPH 25 mg versus DPH 50 mg	0.3632

Reviewer's Comment: Ideally 4 subjects (14001-1013, 14002-1031, 14002-1067, 14002-1192) from the NP440/DPH25 group), 1 subject (14002-1111) from the NP440 group and 5 subjects (14001-1059, 1129, 14002-1070, 1080, 1153) from the DPH50 group should have been excluded in the global assessment analysis as these subjects took rescue medication before sleep onset and should not have undergone global assessments and subjective sleep questionnaires according to the protocol, thereby limiting the positive findings from this assessment. The data shows that the ratings by these subjects are biased due to the rescue medication taken.

It was intriguing to see the data on these subjects, for example;
Subject 14002-1031 on NP440/DPH25: took rescue medication before sleep onset (at 1 hour 6 minutes), was awake for 1 hour 10 minutes after asleep, rated the quality of sleep as 10 and refreshing nature as a score of 7. The imputed sleep onset and WASO were both 600 minutes. This subject obviously slept well after the rescue medication was taken, suggesting relief of pain was the key factor in being able to sleep well.

Subject 14002-1070 on DPH50: Ratings on
"How easy was it to fall asleep": very difficult.
Once Study medication taken time to fall asleep: 10 minutes.
The time subject was awake from time to fall asleep to out of bed was 20 minutes.
The quality of sleep and refreshing nature of sleep were rated as 1.

Since this subject took rescue medication before sleep onset, the imputed sleep latency was 600 minutes. The subjective onset seems to be in conflict with the timing of rescue medication (1 hour 27 minutes) or the subject may have interpreted the time to fall asleep from the time the rescue medication was taken.

These examples suggest the difficulty in comparing the objective data obtained from actigraphy due to the data handling conventions after taking a rescue medication to that with the subjective questionnaires and assessments. It suggests that the subjective outcomes likely combine effect of both study drug and rescue drug in rating the quality of sleep.

Karolinska Sleep Diary

Sponsor's Table of subjective sleep assessments [mean (SD)] based on the Karolinski sleep dairy is given in the Table 39 below. The Table shows that combination was rated better than NP440 alone on some questions and better than DPH50 on others.

Table 39: Comparison of secondary subjective sleep assessments (Intent−to-Treat Population) (Study 15881)

	Study 15881		
	Treatment Groups		
Subjective assessments	**NS 440 mg/ DPH 25 mg**	**NS 440 mg**	**DPH 50 mg**
Karolinska sleep diary [a]			
How was your sleep?	3.5 (0.85) [d, e]	3.3 (1.01)	2.8 (1.26)
How calm was your sleep?	3.4 (0.99) [e]	3.1 (0.98)	2.9 (1.23)
How easy was it to fall asleep	3.2 (1.08)	3.0 (1.14)	2.9 (1.23)
Premature awakening?	2.1 (0.75) [e]	1.9 (0.69)	1.8 (0.85)
Ease of awakening?	4.1 (0.69) [e]	4.0 (0.85)	4.3 (0.86)
Well Rested?	2.3 (0.61) [e]	2.3 (0.62)	2.0 (0.79)
Did you get enough (sufficient) sleep?	3.8 (0.93) [d, e]	3.5 (1.21)	2.8 (1.46)
Sleep questionnaire [b]			
How would you rate the quality of your sleep?	6.5 (1.95) [d, e]	5.8 (2.11)	4.9 (3.04)
How would you rate the refreshing nature of your sleep?	6.6 (2.15) [d, e]	5.7 (2.20)	4.6 (2.85)
Estimate how long it took you to fall asleep?	39.5 (36.63)	40.2 (38.10)	40.0 (42.66)
Estimate the number of minutes you were awake?	111.1 (121.86) [d]	144.8 (125.58)	98.4 (89.71)
IP as sleep aid [c]	2.3 (0.96) [d]	1.7 (1.13)	2.1 (1.13)

a Karolinska Sleep Diary as mean (standard deviation) by treatment group (Cochran-Mantel-Haenszel test controlling for center with modified ridit score); *P*-values are provided
b Subjective Sleep Questionnaire as mean (standard deviation) by treatment group (Cochran-Mantel-Haenszel test controlling for center with modified ridit score); *P*-values are provided
c Global Assessment of Investigational Product as a Sleep Aid as mean (standard deviation) by treatment group (Cochran-Mantel-Haenszel test controlling for center with modified ridit score); *P*-values are provided
d Statistically significant ($P<0.05$) versus NS 440 mg
e Statistically significant ($P<0.05$) versus DPH 50 mg
f Statistically significant ($P<0.05$) versus NS 220 mg/DPH 50 mg

Sub-Group Analysis:

There was no difference in objective WASO or Sleep latency based on age or gender. The age range was not wide enough to detect age related differences.

Reviewer's efficacy conclusions

- Based on pre-specified statistical analysis plan, NP440/DPH25 was not superior to NP440 alone for WASO.

- NP440/DPH25 was not superior to DPH50 alone for Sleep Latency.
- This study was underpowered. It had half the number of subjects per treatment group as compared to Study 14837 that evaluated a higher dose of DPH (50 mg) in the combination product.

Safety Analysis:

The sponsor overall summary of TEAEs is given in the following Table 40. There were no deaths, discontinuations, serious or severe adverse events in any treatment groups.

Table 40: Overall summary of subjects with treatment-emergent adverse events (Study 15881)

	Treatment Group							
	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54		Total	
Subjects	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
With at least 1 TEAE	21	(19.6)	14	(13.2)	17	(31.5)	52	(19.5)
With at least 1 serious TEAE	0		0		0		0	
With at least 1 severe TEAE	0		0		0		0	
With at least 1 drug-related TEAE	3	(2.8)	1	(0.9)	6	(11.1)	10	(3.7)
With a TEAE leading to discontinuation	0		0		0		0	
Taking medication to treat the TEAE	1	(0.9)	1	(0.9)	0		2	(0.7)
Subjects who died due to a TEAE	0		0		0		0	

There were no appreciable differences in the rates of TEAEs in the combination treatment group compared to naproxen sodium or diphenydramine alone. All TEAEs were mild in severity.

The number of subjects with TEAEs of ≥1% is given in Table 41.

Table 41: Incidence of TEAEs (Study 15881)

Preferred Term	NP440/DPH25 N=107	NP440 N=106	DPH50 N=54
	N (%)		
Dizziness	9 (8.4)	9 (8.5)	2 (3.7)
Headache	6 (5.6)	3 (2.8)	10 (18.5)
Nausea	6 (5.6)	4 (3.8)	2 (3.7)
Vomiting	0	0	1 (1.9)
Cold Sweat	3 (2.8)	0	1 (1.9)
Feeling Jittery	0	0	1 (1.9)
Vision Blurred	0	0	1 (1.9)
Polyalkiuria	0	0	1 (1.9)
Flushing	0	0	1 (1.9)
Blood Pressure increased	0	0	1 (1.9)

Like the previous study, the most common AEs were nausea, headache and dizziness.

Most events were resolved by Day 2. There were 2 cases of hypoesthesia and 1 case of cardiac murmur (NP440/DPH25 group) that were not resolved by Day 2.

Reviewer's Comment: According to the protocol, the sponsor should have followed subjects for 2-5 (±2) days. No data from these patients have been given beyond 2 days. The AE comparison provides little to no interpretable data about the NP/DPH combination, since so many DPH patients took rescue that it's not representative of DPH50 AE's. It is unclear how the investigator has assigned some AEs as treatment related. In addition, the AEs are probably not generalizable from this population (post-surgical) to the usual outpatient population

Vital Signs:
Changes from baseline in systolic and diastolic blood pressure, pulse rate, and respiration rate (at Day 1 and Day 2) were evaluated using outlier plots using JMP. No appreciable differences were found across treatment groups.

Safety Conclusions: There were no remarkable differences in treatment groups.

5.3.3 Study 13053:

Title: A Double-Blind, Randomized, Pilot Study Assessing the Analgesic and Hypnotic Effect of Naproxen Sodium and Diphenhydramine Combination in Dental Pain

This pilot study was similar in design to the pivotal studies, but used Aleve® and Benadryl® separately. The dental pain model with phase-advanced sleep was used in this study as well, but subjects were required to go to bed at least 3 hours earlier than usual as opposed to 5 hours in the pivotal studies. In this study Aleve® and Benadryl® were the control arms, in addition Advil® PM was also used as the active comparator.

Study Population:
The treatment arms used were:

- Aleve 440 Combination treatment group:
  2 - Aleve (naproxen sodium 220 mg tablets) + 2 Benadryl (diphenhydramine 25 mg tablets)
- Aleve 220 Combination treatment group:
  1 – Aleve (naproxen sodium 220 mg tablet) + 2 Benadryl (diphenhydramine 25 mg tablets) + 1 Placebo tablet
- Aleve 440 treatment group:
  2 - Aleve (naproxen sodium 220 mg tablet) + 2 Placebo tablets
- Aleve 220 treatment group:
  1 - Aleve (naproxen sodium 220 mg tablet) + 3 Placebo tablets
- Diphenhydramine treatment group

2 – Benadryl (diphenhydramine 25 mg tablets) + 2 Placebo tablets

- Advil PM treatment group
  2- Advil PM (ibuprofen 200 mg and diphenhydramine citrate 38 mg) caplets +
- 2 Placebo tablets

Efficacy Variables:

Primary: Total Sleep Time by actigraphy
Secondary:

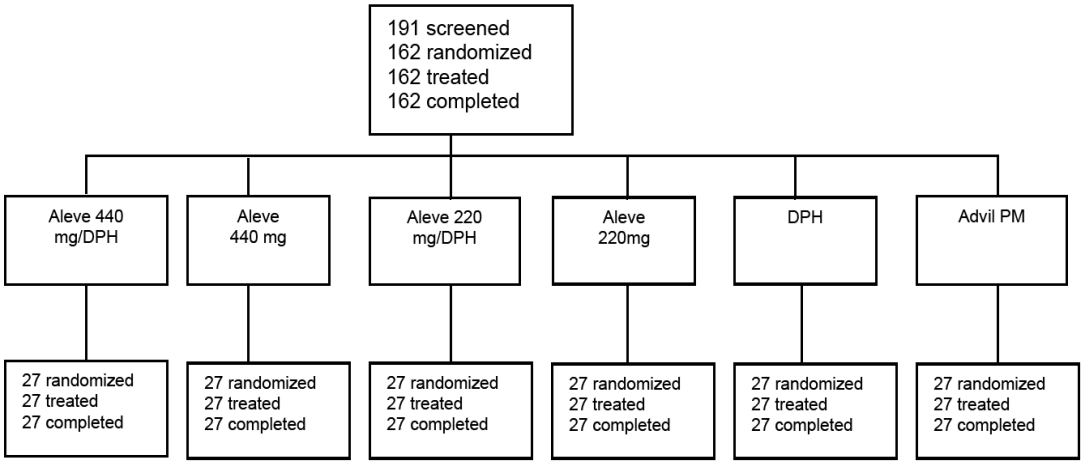
- Sleep Variables
  - WASO- Actigraph
  - Sleep latency- Actigraph
- Subjective Sleep Variables
  - Global assessment of study product as a sleep-aid
  - Karolinska Sleep Diary
  - Total Sleep Time by subject assessment
  - Sleep Quality Index – the mean score of the items 'sleep quality', 'calm sleep',
  - 'ease falling sleep', and 'slept throughout' in Karolinska Sleep Diary.
- Pain Variables (not part of this review)
  - Pain intensity score (both on 4-point Categorical Scale and VAS scale)
  - Pain Relief (Categorical Scales)
  - Time to rescue medication and the cumulative proportion of subjects taking
  - rescue medication by hour
  - Global assessment of study medication as a pain reliever

Safety Variables: Safety was evaluated by the incidence of TEAES. AE's were to be recorded throughout the Dosing Period through 5 days post dose. All SAEs were to be collected approximately 30 days after the last dose of study drug.

Analysis Plan: All hypotheses were to be tested at a 2-sided significance level of 0.05. Since this was a pilot study with small sample size, no p-value adjustments for multiple comparisons were made. Primary comparisons of interest were (Note: Sponsor refers to DPH50 as only DPH in their Tables):

- Aleve 440 mg /DPH50 combination versus Aleve 440 mg
- Aleve 440 mg/DPH50 combination versus DPH50
- Aleve 220 mg /DPH50 combination versus Aleve 220 mg
- Aleve 220 mg/DPH50 combination versus DPH50
- Aleve 440 mg /DPH50 combination versus Ibuprofen/DPH50 combination
- Aleve 220 mg/DPH50 combination versus Ibuprofen/DPH50 combination

Subject Disposition: Subject disposition is shown in the following Figure:



Protocol Deviations: A total of 15 (9%) subjects had 16 protocol violations (Subject 0126 treated with Aleve 440 mg/DPH had two minor violations). Of these, 11 (7%) subjects had major violations and four (2%) had minor ones. Among the 11 subjects with major protocol violations, 10 had 4 teeth pulled in violation of the maximum allowed limit of 3 by the protocol and one (Aleve 220 mg group, Subject 0051) had an upper respiratory tract infection on the day of surgery. Of the 10 subjects who had 4 teeth pulled, three were treated with Aleve 440 mg/DPH (Subjects 0093, 0097, 0104); three were treated with Aleve 440 mg (Subjects 0040, 0046, 0145); two were treated with Aleve 220 mg/DPH (Subjects 0004, 0128); one was treated with DPH (Subject 045), and one was treated with Advil PM (Subject 0058). These violations would not affect the study results.

Demographics and Baseline Characteristics: The subject demographics and baseline characteristics are given in Table 42.

Reviewer's Comment: The within-arm baseline categorical pain is more balanced in this study in most cohorts except DPH and Advil PM.

Table 42: Demographic and Baseline Characteristics (Study 13053)

	Aleve 440 mg/DPH	Aleve 440 mg	Aleve 220 mg/DPH	Aleve 220 mg	DPH	Advil PM	All
N	27	27	27	27	27	27	162
Age							
Mean (SD)	19 (2.8)	20 (2.6)	20 (2.8)	19 (2.0)	19 (3.0)	19 (2.5)	19 (2.6)
Range	17 - 30	17 - 28	17 - 28	17 - 25	16 - 30	17 - 27	16 - 30
Gender							
Female	16 (59.3%)	12 (44.4%)	15 (55.6%)	10 (37.0%)	19 (70.4%)	12 (44.4%)	84 (51.9%)
Male	11 (40.7%)	15 (55.6%)	12 (44.4%)	17 (63.0%)	8 (29.6%)	15 (55.6%)	78 (48.1%)
Race							
White	25 (92.6%)	27 (100.0%)	24 (88.9%)	27 (100.0%)	27 (100.0%)	27(100.0%)	157(96.9%)
Black/African American	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Asian	1 (3.7%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.9%)
Other	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Ethnicity							
Hispanic/Latino	3 (11.1%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	8 (4.9%)
Non-Hispanic/Latino	24 (88.9%)	26 (96.3%)	26 (96.3%)	26 (96.3%)	26 (96.3%)	26 (96.3%)	154 (95.1%)
Baseline Categorical Pain rating score							
Moderate pain	15 (55.6%)	14 (51.9%)	14 (51.9%)	14 (51.9%)	17 (63.0%)	21 (77.8%)	95 (58.6%)
Severe pain	12 (44.4%)	13 (48.1%)	13 (48.1%)	13 (48.1%)	10 (37.0%)	6 (22.2%)	67 (41.4%)
Baseline VAS Score							
Mean (SD)	76 (11.6)	77 (13.1)	78 (13.4)	74 (12.3)	79 (9.8)	73 (10.5)	76 (11.9)
Range	55 - 98	53 -100	53 -100	50 - 94	58 - 95	52 - 96	50 -100

Total Sleep Time (TST):

Total Sleep Time was to be derived from the time of lights out until the time the actigraphy was marked for wakening (lights on) or rescue medication, whichever came first. Total Sleep Time for subjects who asked for rescue medication before sleep onset will be set to zero. Subjects who took rescue medication were treated as awake from the time the rescue medication was given. This variable was analyzed via an ANCOVA model with the treatment effect and baseline pain score as the covariate.

Sponsor's Analysis: The ANCOVA analysis results are given in Table 43.

The longest TST was for the combination Aleve 220/DPH50 (414 minutes). The TST difference between Aleve440/DPH50 and Aleve440 was 35 minutes and that between Aleve220/DPH50 and Aleve440 was 105 minutes, but these differences were not statistically significant.

Table 43: Analysis Results for Total Sleep Time per Actigraph (Study 13053)

Total Sleep Time (minutes)	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
N	**27**	**27**	**27**	**27**	**27**	**27**
LSM	340	305	414	309	76	336
(SE)	(40.7)	(40.7)	(40.7)	(40.7)	(40.7)	(41.2)
95% CI	259 - 420	224 - 385	333 - 494	228 - 389	-4 – 157	254 - 417

Aleve 440 mg/ DPH vs.	Aleve 440mg	DPH	Advil PM
Difference	35	263	4
95% CI	(-78, 149)	(150, 377)	(-110, 119)
P-value	0.5412	<0.0001*	0.9435

Aleve 220 mg/ DPH vs.	Aleve 220mg	DPH	Advil PM
Difference	105	338	78
95% CI	(-9, 219)	(224, 451)	(-37, 193)
P-value	0.0697	<0.0001*	0.1807

* $p<0.05$

The cumulative proportion of subjects taking rescue medication by hour is presented in Table 44. The majority of the subjects took it in the first couple hours; hence the impact on TST was large due to imputations of TST in subjects taking rescue medication).

Table 44: Cumulative Proportion of Subjects Taking Rescue Medication by Hour (Study 13053)

	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
Hour	**N=27 n (%)**	**N=27 n (%)**	**N=27 n (%)**	**N=27 n (%)**	**N=27 n (%)**	**N=27 n (%)**
1	2 (7.4)	3 (11.1)	0 (0.0)	1 (3.7)	4 (14.8)	0 (0.0)
2	6 (22.2)	9 (33.3)	5 (18.5)	9 (33.3)	17 (63.0)	7 (25.9)
3	8 (29.6)	11 (40.7)	5 (18.5)	9 (33.3)	20 (74.1)	7 (25.9)
4	10 (37.0)	11 (40.7)	5 (18.5)	10 (37.0)	21 (77.8)	7 (25.9)
5	11 (40.7)	11 (40.7)	5 (18.5)	11 (40.7)	24 (88.9)	7 (25.9)
6	11 (40.7)	11 (40.7)	6 (22.2)	12 (44.4)	25 (92.6)	9 (33.3)
7	11 (40.7)	12 (44.4)	7 (25.9)	13 (48.1)	25 (92.6)	10 (37.0)
8	11 (40.7)	12 (44.4)	7 (25.9)	13 (48.1)	25 (92.6)	10 (37.0)
9	11 (40.7)	12 (44.4)	8 (29.6)	13 (48.1)	25 (92.6)	11 (40.7)
10	12 (44.4)	12 (44.4)	8 (29.6)	13 (48.1)	25 (92.6)	11 (40.7)

All subjects who received rescue medication took it once only with the exception that 3 (11.1%) subjects in the DPH group took rescue medication twice.

Reviewer's Comment: The cumulative proportion of subjects taking rescue medication by each hour is similar across most treatment groups with the exception of DPH and Aleve220/DPH group. The reason for lower proportion of subjects taking rescue medication in the Aleve220/DPH group is unclear, but that appears to be the main reason why this group had the largest TST. The data imputation procedure upon rescue medication makes the interpretation of the efficacy data difficult and less meaningful. Sponsor's sensitivity analysis given below shows that when subjects that took rescue medication were excluded from the analysis the treatment difference remained similar for the Aleve440/DPH group compared to Aleve 440 alone (35 and 37 minutes), but the treatment difference between the Aleve220/DPH and Aleve 220 reduced (105 and 5 minutes). This makes it clear that sleep parameters are driven by the imputations in patients that take rescue medication, making the clinical significance of these assessments questionable.

Another point to note is that the percentage of subjects taking rescue medication in this pilot study in the combination and analgesic group is higher than the two pivotal studies. One important difference is that the baseline pain distribution is different between these studies. There are more subjects with moderate pain in the pivotal studies, whereas there are equal numbers of subjects with moderate and severe pain in the pilot studies. It may be that the more severe the pain, the more likely the subjects will be to take rescue medication that will result in imputation as awake the rest of the night.

Sensitivity Analysis:

A sensitivity analysis was conducted by the sponsor excluding the subjects that took rescue medication (Table 45). As seen in Table 43, 29 % took rescue medication in the Aleve 220/DPH group compared to 48% in the Aleve 220 group. This led to the treatment difference between these groups to be only 5 minutes as compared to 105 minutes in the primary analysis. In pain severity these groups were similar; hence this cannot be attributed as a reason for the difference in percentage of subject on rescue medication.

Table 45: Analysis Results for Total Sleep Time, Patients Who Did Not Take Rescue Medication (Study 13053)

Total Sleep Time (minutes)	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
N	**15**	**15**	**19**	**14**	**2**	**16**
LSM	526.48	489.46	526.23	521.37	284.96	508.72
(SE)	(18.3)	(18.3)	(16.4)	(18.9)	(50.3)	(18.0)
95% CI	490 - 563	453 - 526	494 - 559	484 - 559	185 - 385	473 - 545

Aleve 440 mg/ DPH vs.	Aleve 440mg	DPH	Advil PM
Difference	37	242	18
95% CI	(-15, 89)	(135, 348)	(-34, 69)
P-value	0.1570	<0.0001*	0.4940

Aleve 220 mg/ DPH vs.	Aleve 220mg	DPH	Advil PM
Difference	5	241	18
95% CI	(45, 54)	(135, 347)	(32, 67)
P-value	0.8457	<0.0001*	0.4810

* $p < 0.05$

A second sensitivity analysis was done excluding those subjects that took rescue medication before sleep onset. The results are shown in Table 46. The mean treatment differences in TST between the combination to the analgesic control were large (50 and 69 minutes), but these were not statistically significant. This may be due to the small sample size. The absolute minutes of treatment difference appears clinically meaningful, although not statistically different.

Table 46: Analysis Results for Total Sleep Time, Excluding Subjects Who Took Rescue Medication Before Sleep Onset (Study 13053)

Total Sleep Time (minutes)	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
N	22	22	23	20	18	22
LSM	417.48	367.10	482.29	413.11	115.85	424.45
(SE)	(35.7)	(35.6)	(34.9)	(37.5)	(39.5)	(35.9)
95% CI	347 - 488	297 - 438	413 - 551	339 - 487	38 - 194	353 - 496

Aleve 440 mg/ DPH vs.	Aleve 440mg	DPH	Advil PM
Difference	50	302	-7
95% CI	(-50, 150)	(196, 407)	(-108, 94)
P-value	0.3202	<0.0001*	0.8914

Aleve 220 mg/ DPH vs.	Aleve 220mg	DPH	Advil PM
Difference	69	366	58
95% CI	(-32, 170)	(262, 471)	(-42, 157)
P-value	0.1783	<0.0001*	0.2520

Sleep Latency:

Sponsor's analysis for sleep latency per actigraphy is presented in Table 47. The least squares mean estimate of Sleep Latency was shortest for Aleve 440 mg/DPH (29 minutes) and longest for Aleve 220 mg/DPH (47 minutes). No statistically significant differences were observed between any of the treatment groups.

Table 47: Analysis Results for Sleep Latency (Study 13053)

Sleep Latency (minutes)	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
N	27	27	27	27	27	27
LSM (SE)	29 (10.4)	33 (10.4)	47 (10.2)	32 (10.9)	41 (11.5)	36 (10.5)
95% CI	9 - 50	12 - 53	27 - 67	10 - 53	18 - 64	16 - 57

Aleve 440 mg/ DPH vs.	Aleve 440mg	DPH	Advil PM
Difference	-4	-12	-7
95% CI	(-33, 25)	(-43, 19)	(-37, 22)
P-value	0.8045	0.4464	0.6277

Aleve 220 mg/ DPH vs.	Aleve 220mg	DPH	Advil PM
Difference	15	6	10
95% CI	(-14, 45)	(-25, 36)	(-19, 39)
P-value	0.3096	0.7108	0.4791

Wake After Sleep Onset (WASO):

The analysis of WASO is presented in Table 48. In this case too, in spite of the treatment difference of 51 minutes between the combination and analgesic arm, no statistically significant difference was seen. A negative result is inconclusive with an underpowered study.

Table 48: Analysis Results for Wake after Sleep Onset (WASO) (Study 13053)

WASO (minutes)	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
N	27	27	27	27	27	27
LSM (SE)	140 (35.4)	191 (35.3)	76 (34.6)	146 (37.1)	428 (39.1)	129 (35.6)
95% CI	70 - 210	121 - 261	7 - 144	72 - 219	351 - 506	59 - 199

Aleve 440 mg/ DPH vs.	Aleve 440mg	DPH	Advil PM
Difference	-51	-288	11
95% CI	(-150, 48)	(-393, -184)	(-89, 111)
P-value	0.3099	<0.0001*	0.8284

Aleve 220 mg/ DPH vs.	Aleve 220mg	DPH	Advil PM
Difference	-70	-353	-53
95% CI	(-170, 30)	(-456, -249)	(-152, 45)
P-value	0.169	<0.0001*	0.2857

Global assessment of study medication as a sleep-aid

Analysis results of global assessment of study medication as a sleep-aid are presented in Table 49. Both combination doses were rated better than the analgesic alone arm.

Table 49: Analysis Results for Global Assessment of Study Medication as a Sleep-Aid (Study 13053)

	Aleve 440mg /DPH	Aleve 440mg	Aleve 220mg /DPH	Aleve 220mg	DPH	Advil PM
N	**22**	**22**	**23**	**20**	**18**	**22**
Good	8 (36.4%)	7 (31.8%)	7 (30.4%)	6 (30.0%)	3 (16.7%)	9 (40.9%)
Very good	5 (22.7%)	4 (18.2%)	8 (34.8%)	3 (15.0%)	2 (11.1%)	7 (31.8%)
Excellent	4 (18.2%)	1 (4.5%)	3 (13.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Total	17 (77.3%)	12 (54.5%)	20 (78.2%)	10 (50.0%)	5 (27.8%)	16 (72.7%)

Aleve 440 mg/ DPH vs.	**Aleve 440mg**	**DPH**	**Advil PM**
P-value	0.0472*	0.0012*	0.3959

Aleve 220 mg/ DPH vs.	**Aleve 220mg**	**DPH**	**Advil PM**
P-value	0.0342*	0.0013*	0.3005

Karolinska Sleep Diary

Based on sponsor reported results both combination groups did better for subjective sleep parameter (TST) and both were rated the same as a sleep aid. Both combinations also did better for Question 6 and 7, but this was not the case for the other questions (See Table 50).

Table 50: Summary of secondary subjective sleep parameters in Study 13053 (Intent-to-Treat Population) (Study 13053)

	Treatment Groups					
	NS 440 mg/ DPH 50 mg	NS 440 mg	NS 220 mg/ DPH 50 mg	NS 220 mg	DPH 50 mg	Advil PM
	N = 27	N = 27	N = 27	N = 27	N = 27	N = 27
Subjective Sleep Parameters						
Total sleep time [a] (minutes)	306∞ (38.0)	310 (38.1)	339∞ (38.1)	309 (38.1)	160 (38.0)	300 (38.5)
95% CI	231 – 381	235 – 385	264 – 414	234 – 384	85 – 236	223 – 376
Sleep quality [a] (index)	3.5* (0.18)	2.9 (0.18)	3.4 (0.18)	3.1 (0.19)	3.0 (0.20)	3.4 (0.18)
95% CI	3.1 – 3.9	2.5 – 3.3	3.0 – 3.8	2.7 – 3.5	2.6 – 3.4	3.0 – 3.7
Sleep aid [b] (score)	2.3*∞ (1.13)	1.5 (1.22)	2.3±∞ (1.15)	1.6 (1.15)	1.1 (1.00)	2.0 (0.79)
95% CI	Na	na	Na	na	na	Na
Sleep diary [b](score)						
Question 1 How was your sleep?	3.5 (0.96)	3.0 (1.17)	3.7 (0.97)	3.4 (0.93)	3.1 (1.02)	3.5 (0.74)
Question 2 How calm was your sleep?	3.7∞ (0.57)	3.0 (1.25)	3.3 (1.05)	3.1 (1.00)	2.9 (1.11)	3.2 (1.02)
Question 3 How easy was it to fall asleep?	3.3* (0.78)	2.6 (1.10)	3.3 (0.86)	3.0 (1.30)	2.8 (0.88)	3.3 (0.88)
Question 4 Premature awakenings?	2.2 (0.80)	2.0 (0.76)	2.3∞ (0.63)	2.1 (0.83)	1.8 (0.81)	2.0 (0.65)
Question 5 Ease of awakening?	4.1 (0.68)	3.8 (1.01)	4.0 (0.98)	3.8 (0.89)	4.0 (0.84)	4.0 (0.62)
Question 6 Well rested?	2.3∞ (0.57)	2.0 (0.62)	2.4∞ (0.50)	2.4 (0.50)	1.9 (0.47)	2.1 (0.47)
Question 7 Did you get enough sleep?	3.5∞ (1.10)	3.1 (1.36)	3.9∞ (0.81)	3.8 (1.02)	2.8 (0.94)	3.6 (0.91)

[a] LS mean (SE)
[b] Mean (SD)
[c] Karolinska sleep diary:
* = $P<0.05$ versus NS 440 mg; ± = $P<0.05$ versus NS 220 mg; ∞ = $P<0.05$ versus DPH 50 mg

Reviewer's Efficacy Conclusions: The absolute differences in minutes appear potentially clinically meaningful, but were not statistically significant. The point estimate for Aleve220/DPH was better than for Aleve440/DPH, seemingly due to fewer subjects taking rescue medication in the lower dose Aleve combination arm (30% in Aleve220/DPH and 45% in Aleve440/DPH arm). The reason for this difference in rescue medication is unclear. A higher

proportion of subjects took rescue medication in the Aleve220 arm (48%), which has the same dose of analgesic as Aleve220/DPH. It may be related to the pain severity in these groups, but based on mean values these are exactly the same in the two groups.

Safety Analysis:

A total of 19 AEs were reported by 14 subjects. There were no severe, serious AEs, deaths or drop-outs due to AEs in this study. Nausea and vomiting were the only AEs reported by more than 1 subject. Nausea was reported by two subjects (7.4%) in Aleve 220 mg/DPH group and two (7.4%) in DPH group. Vomiting was reported by two subjects (7.4%) in DPH group (See Table 51).

Table 51: Adverse Events (Study 13033)

	Aleve440/DPH	Aleve440	Aleve220/DPH	Aleve220	DPH	Advil PM
Any AE	2 (7.4%)	2 (7.4%)	3(11.1%)	1 (3.7%)	5(18.5%)	1 (3.7%)
Any drug related AE	0	0	1 (3.7%)	0	1 (3.7%)	0

Clinical Labs and Vital Signs: were not performed.

5.3.3 Study 15506:

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Safety and Tolerability Trial of Naproxen Sodium/ Diphenhydramine Combination in an OTC Population

Objectives: The objective of the trial was to evaluate the safety and tolerability of naproxen sodium 440 mg/diphenhydramine hydrochloride (DPH) 50 mg compared to placebo when used for 10 consecutive days in a population representative of over-the-counter (OTC) users of analgesic/nighttime sleep-aid combination products.

Study Design: This was a maximum-use safety and tolerability trial. It was a multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and tolerability trial of naproxen sodium/DPH combination in an OTC population with a history of occasional sleeplessness associated with minor aches and pains (at least 2 times, but not continually for more than 14 days per month, in at least 2 of the past 3 months).The trial consisted of a Screening Visit, a 10-day Treatment Period, and an End of Trial (EOT) Visit. Subjects were randomized to NP440/DPH50 or placebo (2:1) and were instructed to take the drug 30 minutes before bedtime for 10 consecutive days in an outpatient setting. Over-encapsulation of the investigational products was used for blinding purpose. Subjects were permitted to take acetaminophen 1000 mg every 4 to 6 hours as rescue medication only as needed for additional pain relief if pain relief was inadequate, but no more than a total of 4000 mg per day. A self reported daily diary was provided for subjects to record each dose of investigational product taken, AEs that occurred during the 10-day Treatment Period, and concomitant medications

taken, if any. Severity, duration, outcome, and relationship to the investigational product of each AE and use of concomitant medications were assessed by the investigator. Vital signs and clinical laboratory tests were also done at end of treatment visit (10+2 days).
Study Population: Healthy male and female volunteers, ages 12 years and older who had a history of occasional sleeplessness associated with minor aches and pains. 25% of subjects were >65 years of age.

Key Exclusion Criteria:

- Subjects with a history of a chronic or severe sleep problem which did not respond to OTC medication and/or required a prescription hypnotic or sedative
- Subjects with chronic pain were excluded from the trial
- Chronic use of DPH containing products, including topical products

Prior and Concomitant therapy: Prohibited treatments were:

- Use of any NSAIDs or analgesics other than the investigational product or rescue medication (acetaminophen)
- Chronic use of antihistamines including topical products, defined as using 5 or more times a week for 2 or more consecutive weeks during the past 3 months

All other medications taken during study were recorded in subject's diary.

Safety Measurements: Safety was evaluated by summarizing the incidence of AEs by system organ class (SOC) and preferred term (PT) and the proportion of subjects who discontinued due to an AE for those subjects who were randomized and took at least 1 dose of investigational product. Safety was also evaluated by clinical laboratory tests and vital sign parameters. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0 and concomitant medications were coded using the World Health Organization (WHO) Drug Dictionary (March 2011).

An AE was any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Treatment emergent AEs (TEAE) are AEs that begin or worsen after the first dose of investigational product during the trial.

Analyses: Continuous data were summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Categorical data were summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data were summarized using shift tables where appropriate.
The Safety Population included all randomized subjects who took at least 1 dose of the investigational product. Safety measures were analyzed for all subjects in the Safety Population. Subgroup analyses of treatment-emergent adverse events (TEAEs) were performed for gender and age group (12-59 and ≥60 years).

Where dates were missing or partially missing, AEs were assumed to be treatment-emergent, unless there was clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of investigational product or more than 30 days after the last dose. If severity or causality was missing, the worst case was assumed.

Subject Disposition: The trial was conducted at 18 sites in the US from 25 May 2011 to 06 July 2011. A total of 326 subjects were screened and randomized into this trial. The Subject Disposition is summarized in Table 52.

Table 52: Subject Disposition (Study 15560)

	NS 440 mg/ DPH 50 mg (N=217)	Placebo (N=109)	Total (N=326)
Subjects screened	-	-	326
Randomized subjects	217 (100)	109 (100)	326 (100)
Received at least 1 dose of investigational product	217 (100)	109 (100)	326 (100)
Received incorrect study medication[a]	0	0	0
Completed study according to protocol			-
Yes	213 (98.2)	105 (96.3)	318 (97.5)
No	4 (1.8)	4 (3.7)	8 (2.5)
Reasons for early discontinuation			
Did not meet inclusion criteria	0	0	0
Fulfillment of exclusion criteria	0	0	0
AE/ SAE	4 (1.8)	4 (3.7)	8 (2.5)
Protocol violation	0	0	0

Protocol Deviations: No violations of inclusion or exclusion criteria were noted on the CRFs at screening and, therefore, no such violations were listed or summarized in the statistical output. However, subsequent review of the data by the clinical monitor after subjects completed the trial identified violations of inclusion/exclusion criteria and other protocol deviations. According to the sponsor no major deviations were identified to exclude any subject from the safety analysis. One subject (140021023) was excluded from the extent of exposure and treatment compliance analysis as he did not return his diary, which documented extent of exposure. No other subject data were excluded from analysis based on review of the protocol deviations.

The most commonly reported protocol deviations were related to administration of study treatment, such as missed or additional doses (55 subjects). Other protocol deviations were related to inclusion/exclusion criteria (10 subjects); disallowed medications (7 subjects); and other deviations (17 subjects).

Demographics: Baseline demographics are given in Table 53.

Table 53: Baseline Demographics (Study 15560)

Demographic Variable	NS 440 mg/ DPH 50 mg (N=217)	Placebo (N=109)	Total (N=326)
Age (years)[a]			
n	217	109	326
Mean (SD)	46.9 (18.14)	47.1 (19.26)	47.0 (18.49)
Median	44.0	49.0	46.0
Min, Max	15, 89	12, 82	12, 89
Age subgroup, n (%)			
n	217	109	326
<60 years	152 (70.0)	72 (66.1)	224 (68.7)
≥60 years	65 (30.0)	37 (33.9)	102 (31.3)
>65 years	46 (21.2)	28 (25.7)	74 (22.7)
Gender, n (%)[b]			
n	217	109	326
Male	84 (38.7)	44 (40.4)	128 (39.3)
Female	133 (61.3)	65 (59.6)	198 (60.7)
Race, n (%)[b]			
n	209	105	314
American Indian or Alaskan Native	2 (1.0)	1 (1.0)	3 (1.0)
Asian	4 (1.9)	4 (3.8)	8 (2.5)
Black or African American	26 (12.4)	17 (16.2)	43 (13.7)
Hispanic	45 (21.5)	19 (18.1)	64 (20.4)
Native Hawaiian or Other Pacific Islander	0	0	0
White	127 (60.8)	61 (58.1)	188 (59.9)
Other	5 (2.4)	3 (2.9)	8 (2.5)

Most subjects (325/326, 99.7%) had an active history of insomnia at screening, and 142/326 (43.6%) subjects had active back pain.

Extent of Exposure: The mean duration of exposure for all subjects was 9.9 days. Most subjects (301/325, 92.6%) had exposure duration of 10 days, including 93.1% (201/216) of subjects treated with naproxen sodium 440 mg/DPH 50 mg and 91.7% (100/109) of subjects treated with placebo. Nine (2.8%) of 325 subjects had an exposure duration longer than 10 days (maximum of 12 days): 5/216 (2.3%) naproxen sodium 440 mg/DPH 50 mg and 4/109 (3.7%) placebo subjects.

Extent of exposure is summarized by treatment group in Table 54.

Table 54: Extent of Exposure (Study 15560)

	NS 440 mg/DPH 50 mg (N=217)	Placebo (N=109)	Total (N=326)
Exposure duration summary (days)			
n	216[a]	109	325[a]
Mean (SD)	9.9 (0.76)	9.8 (1.37)	9.9 (1.00)
Median	10.0	10.0	10.0
Min, Max	3, 12	2, 11	2, 12

Adverse Events:

Deaths and Serious AEs: none

Treatment Emergent AEs:

Overall summary of TEAE is presented in Table 55. Most AEs were mild and moderate. There were 3 severe AEs in the Treatment Group and 1 in the Placebo Group.

Table 55: Summary of Treatment-emergent Adverse Events (Safety Population)

	NS 440 mg/ DPH 50 mg (N=217) n (%)	Placebo (N=109) n (%)
Number of TEAEs	196	90
Number of subjects with:		
Any TEAE	86 (39.6)	49 (45.0)
Any severe TEAE	3 (1.4)	1 (0.9)
Any TEAE related to investigational product	30 (13.8)	18 (16.5)
Any TEAE leading to death	0	0
Any serious TEAE	0	0
Any TEAE leading to discontinuation	4 (1.8)	4 (3.7)

The only TEAE reported by ≥5% of subjects in either treatment group was headache, which occurred in a lower percentage of naproxen sodium 440 mg/DPH 50 mg subjects (23/217, 10.6%) than placebo subjects (21/109, 19.3%).

Treatment-emergent AEs that occurred in ≥2% of naproxen sodium 440 mg/DPH 50 mg subjects and which occurred at a higher incidence than in the placebo group were somnolence (4.6% vs 3.7%, respectively), dizziness (4.1% vs 0%), nausea (4.1% vs 0.9%), back pain (3.7% vs. 2.8%), diarrhoea (3.2% vs 1.8%), abdominal discomfort (2.3% vs. 1.8%), and dyspepsia (2.3% vs. 0.9%).

Commonly reported TEAEs (≥2% of subjects in either treatment group) are summarized by treatment group in Sponsor's Table 56. Majority of the events were related to Nervous System Disorders and Gastrointestinal Disorders. The percentages of these events were verified by the reviewer.

Table 56: Common Treatment-emergent Adverse Events (≥2% of Subjects) (Study 15560)

System Organ Class Preferred Term	NS 440 mg/ DPH 50 mg (N=217) n (%)	Placebo (N=109) n (%)
Number of TEAEs reported	196	90
Subjects with at least 1 TEAE	86 (39.6)	49 (45.0)
Nervous system disorders		
Headache	23 (10.6)	21 (19.3)
Somnolence	10 (4.6)	4 (3.7)
Dizziness	9 (4.1)	0
Gastrointestinal disorders		
Nausea	9 (4.1)	1 (0.9)
Diarrhoea	7 (3.2)	2 (1.8)
Abdominal discomfort	5 (2.3)	2 (1.8)
Dyspepsia	5 (2.3)	1 (0.9)
Abdominal pain upper	3 (1.4)	3 (2.8)
Musculoskeletal and connective tissue disorders		
Back pain	8 (3.7)	3 (2.8)
Pain in extremity	0	4 (3.7)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	4 (1.8)	3 (2.8)

I further looked into the cases of somnolence to see the duration of somnolence during the study. The incidence rate was higher in the NP440/DPH50 group (4.6%), although not much higher than the placebo group (3.7%). Most somnolence events were mild to moderate. It lasted for the entire study duration in 30% of the subjects in the treatment group and 50% of the subjects in the placebo group (See Table 57 below).

Table 57: Somnolence and related terms (Study 15560)

Treatment	Age	AETERM	AESEV	AESTDY (AE start day)	AEENDDY (AE end day)
Placebo	38	DROWSY	MILD	2	2
Placebo	38*	DROWSY	MILD	11	11
Placebo	24	DROWSINESS	MODERATE	1	6
Placebo	63	EXCESSIVE SLEEPINESS	MILD	2	ongoing
Placebo	40	DROWSY	MILD	2	2
NP 440mg/ DPH 50 mg	57	DROWSINESS	MODERATE	3	4
NP 440mg/ DPH 50 mg	58	SLEEPINESS	MODERATE	4	4
NP 440mg/ DPH 50 mg	60	DROWSINESS	MILD	3	6
NP 440mg/ DPH 50 mg	32	GROGGY	MILD	2	3
NP 440mg/ DPH 50 mg	46	DROWSINESS	MILD	7	10
NP 440mg/ DPH 50 mg	41	DROWSINESS	MILD	1	11
NP 440mg/ DPH 50 mg	34	SOMNOLENCE	MILD	2	11

		EARLY MORNING			
NP 440mg/ DPH 50 mg	15	SOMNOLENCE EARLY MORNING	MILD	2	11
NP 440mg/ DPH 50 mg	28	DROWSINESS	MILD	4	4
NP 440mg/ DPH 50 mg	44	DROWSY	MILD	2	2
NP 440mg/ DPH 50 mg	44*	DROWSY	MILD	10	10

*same subject with somnolence on different study days

In addition to these, there were 3 subjects with lethargy and fatigue in the NP 440mg/ DPH 50 mg group and 1 in the placebo group, which could be terms related to somnolence.

All GI events in both groups lasted only one day.

Treatment-emergent Adverse Events by Severity:
Most TEAEs were mild in nature. There were 3 severe TEAEs in the NP440/DPH50 group and 1 one the placebo group. See Table 58 for these AEs.

Table 58: Treatment Emergent AEs by Severity (Study 15660)

	NS 440 mg/ DPH 50 mg (N=217) n (%)	Placebo (N=109) n (%)
Mild	56 (25.8)	35 (32.1)
Moderate	27 (12.4)	13 (11.9)
Severe	3 (1.4)	1 (0.9)
Back Pain	1 (0.5)	0
ALT increase	1 (0.5)*	0
AST increase	1 (0.5)*	0
Restlessness	1 (0.5)	0
Type 2 Diabetes Mellitus	0	1 (0.9)

* same subject

All TEAEs were resolved by the end of the trial.

Treatment-emergent Adverse Event by Age:
In the naproxen sodium 440 mg/DPH 50 mg group, the most commonly reported TEAEs (≥5% of subjects) in subjects aged 12-59 years were headache (19/152, 12.5%), somnolence (9/152, 5.9%), and back pain (8/152, 5.3%). The most frequently reported TEAEs in naproxen sodium 440 mg/DPH 50 mg subjects ≥60 years were dizziness (5/65, 7.7%) and headache (4/65, 6.2%). In the placebo group, headache was the only TEAE reported in ≥5% of subjects aged 12-59 years (19/72, 26.4%) and subjects ≥60 years (2/37, 5.4%). All severe events were reported in the younger age group. Sponsor's Table for TEAE by age, verified by the reviewer is given in Table 59. The red circles show adverse events that occur in >5% of the subjects in each treatment group by age.

Table 59: Common Treatment-emergent Adverse Events (≥2% of Subjects in Any Subgroup) by Age Group

System Organ Class Preferred Term	NS 440 mg/ DPH 50 mg (N=217) n (%)		Placebo (N=109) n (%)	
	12-59 years (n=152)	≥60 years (n=65)	12-59 years (n=72)	≥60 years (n=37)
Number of TEAEs	145	51	73	17
Subjects with at least 1 TEAE	61 (40.1)	25 (38.5)	38 (52.8)	11 (29.7)
Nervous system disorders				
Headache	19 (12.5)	4 (6.2)	19 (26.4)	2 (5.4)
Somnolence	9 (5.9)	1 (1.5)	3 (4.2)	1 (2.7)
Dizziness	4 (2.6)	5 (7.7)	0	0
Lethargy	0	1 (1.5)	0	1 (2.7)
Gastrointestinal disorders				
Nausea	7 (4.6)	2 (3.1)	1 (1.4)	0
Diarrhoea	4 (2.6)	3 (4.6)	1 (1.4)	1 (2.7)
Abdominal discomfort	2 (1.3)	3 (4.6)	2 (2.8)	0
Dyspepsia	2 (1.3)	3 (4.6)	1 (1.4)	0
Abdominal pain upper	2 (1.3)	1 (1.5)	2 (2.8)	1 (2.7)
Toothache	3 (2.0)	0	2 (2.8)	0
Musculoskeletal and connective tissue disorders				
Back pain	8 (5.3)	0	2 (2.8)	1 (2.7)
Arthralgia	1 (0.7)	0	0	1 (2.7)
Musculoskeletal pain	1 (0.7)	0	0	1 (2.7)
Pain in extremity	0	0	3 (4.2)	1 (2.7)
General disorders and administration site conditions				
Asthenia	2 (1.3)	0	0	1 (2.7)
Investigations				
Blood urine present	2 (1.3)	0	0	1 (2.7)
Urinary sediment present	1 (0.7)	0	1 (1.4)	1 (2.7)
Red blood cell count increased	0	0	0	1 (2.7)
Psychiatric disorders				
Insomnia	2 (1.3)	1 (1.5)	0	1 (2.7)
Restlessness	2 (1.3)	1 (1.5)	0	1 (2.7)
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	3 (2.0)	1 (1.5)	3 (4.2)	0
Rhonchi	0	0	0	1 (2.7)

Reviewer's Comment: The timing of dizziness was not recorded by the patient. Only the dates were entered.

Treatment-emergent Adverse Event by Gender:
Common TEAE were more in the females in both NP440/DPH50 and placebo groups. Somnolence, headache and dizziness were more common in females. TEAEs by gender are given in the following Table 60. All severe events were in females. Treatment-emergent AEs

considered to be related to investigational product were reported for 6/84 (7.1%) male subjects in the naproxen sodium 440 mg/DPH 50 mg group compared with 24/133 (18.0%) female subjects; and 8/44 (18.2%) male subjects in the placebo group compared with 10/65 (15.4%) female subjects.

Table 60: Common Treatment-emergent Adverse Events (≥2% of Subjects in Any Subgroup) by Gender

System Organ Class Preferred Term	NS 440 mg/ DPH 50 mg (N=217) n (%)		Placebo (N=109) n (%)	
	Male (n=84)	Female (n=133)	Male (n=44)	Female (n=65)
Number of TEAEs	51	145	30	60
Subjects with at least 1 TEAE	22 (26.2)	64 (48.1)	17 (38.6)	32 (49.2)
Nervous system disorders				
Headache	3 (3.6)	20 (15.0)	9 (20.5)	12 (18.5)
Somnolence	2 (2.4)	8 (6.0)	1 (2.3)	3 (4.6)
Dizziness	1 (1.2)	8 (6.0)	0	0
Lethargy	1 (1.2)	0	1 (2.3)	0
Gastrointestinal disorders				
Nausea	0	9 (6.8)	0	1 (1.5)
Diarrhoea	2 (2.4)	5 (3.8)	1 (2.3)	1 (1.5)
Abdominal discomfort	1 (1.2)	4 (3.0)	2 (4.5)	0
Dyspepsia	1 (1.2)	4 (3.0)	1 (2.3)	0
Abdominal pain upper	1 (1.2)	2 (1.5)	1 (2.3)	2 (3.1)
Toothache	1 (1.2)	2 (1.5)	0	2 (3.1)
Dry mouth	1 (1.2)	0	1 (2.3)	0
Musculoskeletal and connective tissue disorders				
Back pain	5 (6.0)	3 (2.3)	0	3 (4.6)
Arthralgia	1 (1.2)	0	1 (2.3)	0
Musculoskeletal pain	0	1 (0.8)	1 (2.3)	0
Pain in extremity	0	0	0	4 (6.2)
General disorders and administration site conditions				
Asthenia	0	2 (1.5)	1 (2.3)	0
Pain	0	2 (1.5)	1 (2.3)	0
Investigations				
Urinary sediment present	0	1 (0.8)	0	2 (3.1)
Psychiatric disorders				
Insomnia	0	3 (2.3)	0	1 (1.5)
Restlessness	0	3 (2.3)	0	1 (1.5)
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	3 (3.6)	1 (0.8)	2 (4.5)	1 (1.5)
Infections and infestations				
Nasopharyngitis	0	0	1 (2.3)	0
Metabolism and nutrition disorders				
Gout	1 (1.2)	0	1 (2.3)	0

Narratives of subjects that discontinued due to an AE:

Treatment Group:

Subject 140041020 (Dizziness): This 65-year-old white female had a medical history of removal of precancerous cell, tubal ligation, low back pain, occasional sleeplessness, and tooth infection. The subject was randomized to naproxen sodium 440 mg/DPH 50 mg on 21-Jun-2011. No concomitant medication was used by the subject. The subject reported dizziness (verbatim terms: dizziness and lightheaded) with date of onset as 24-Jun-2011 and severity reported as moderate. Dizziness led to discontinuation of the investigational product. The last dose of the investigational product was taken on 28-Jun-2011 and the subject was discontinued from the trial on 01-Jul-2011. No treatment medication was given for these TEAEs. Dizziness was reported as ongoing at the end of the trial. The systolic blood pressure was 159 mmHg and Diastolic blood pressure was 99 mmHg, pulse was 84 beats/min at screening visit. At EOT visit, these were 154 and 109 mmHg with a pulse of 91 beats/min. The subjects took 500 mg amoxicillin 5 days prior to the study and stopped two days into the study due to a tooth infection.

The investigator did not relate this to the study drug. The onset of dizziness was during the trial, but continued till 3 days after the last dose. The cause of dizziness is unclear.

Subject 140131003 (Alanine aminotransferase increased, Aspartate aminotransferase increased): This 45-year-old Hispanic female had a history of anemia, bilateral eye pterygium, tubal ligation, menstrual cramps, general aches, occasional sleeplessness secondary to general aches and pains, bilateral knee pain, intermittent headaches, and heart murmur 2/6. The subject was randomized to naproxen sodium 440 mg/DPH 50 mg on 09-Jun-2011. Concomitant medications included: women's one a day (vitamins) for anemia. Increased ALT (verbatim term: elevated ALT) and increased AST (verbatim term: elevated AST) were reported with date of onset as 09-Jun-2011 and severity reported as severe. These TEAEs led to discontinuation of the investigational product on 14-Jun-2011 and the subject was discontinued from the trial the same day. No rescue acetaminophen was taken by the subject.

Parameter	Screening	EOT	Normal range
ALT	274 U/L (09-Jun-2011)	313 U/L (14-Jun-2011)	0-67 U/L
AST	146 U/L (09-Jun-2011)	222 U/L (14-Jun-2011)	0-50 U/L

No treatment medication was reported. The events were reported as resolved on 25-Jul-2011. The subject also reported mild dizziness (10-Jun-2011 to 13-Jun-2011) and mild thirst.

Since ALT and AST were high at screening, I agree that it is not from the study drug.

Subject 140171001 (Oesophageal pain, Oesophageal oedema, Oesophageal discomfort, Dyspepsia, Muscle strain): This 31-year-old white female had a history of intermittent

insomnia, intermittent headaches, alcohol use, intermittent quadricep tendonitis, and gluten allergy. The subject was randomized to naproxen sodium 440 mg/DPH 50 mg on 27-May-2011. Concomitant medications included: Sprintec (ethinyl estradiol and norgestimate) for oral contraception and multi-vitamins as a nutritional supplement. The subject reported oesophageal pain (verbatim term: esophageal pain) and oesophageal oedema (verbatim term: esophageal swelling) with a date of onset as 31-May-2011, oesophageal discomfort (verbatim term: esophageal pressure) and dyspepsia (verbatim term: heartburn) with date of onset as 01-Jun-2011, and muscle strain (verbatim term: neck sprain) with a date of onset as 06-Jun-2011. The severity of each event was reported as mild. These TEAEs led to discontinuation of the investigational product. The last dose was taken on 04-Jun-2011 and the subject was discontinued from the trial on 08-Jun-2011. Treatment medications included: Tums antacid (calcium carbonate) and Pepcid AC (famotidine) for pain, swelling and pressure of esophagus, and heartburn. Oesophageal pain, oesophageal oedema, oesophageal discomfort, and dyspepsia were reported as resolved on 06-Jun-2011 and muscle strain on 10-Jun-2011. All events except muscle strain were deemed related to the investigational product. The subject also reported mild dysphagia (31-May-2011 to 31-May-2011) that was considered to be related to the investigational product.

Reviewer's Comment: More information on this subject was requested from the sponsor to find out if the problem could have been due to a retained pill in the esophagus, but the sponsor did not have any additional information on this patient.

Subject 140171013 (Blood urea increased, Blood creatinine increased, Blood potassium increased): This 17-year-old white male had a history of facial eczema, seasonal allergies, attention deficit disorder, intermittent headaches, intermittent back pain, and intermittent insomnia. The subject was randomized to naproxen sodium 440 mg/DPH 50 mg on 31-May-2011. No concomitant medications were used. The subject developed blood urea increased (verbatim term: elevated BUN), blood creatinine increased (verbatim term: elevated creatinine), and blood potassium increased (verbatim term: elevated potassium) with date of onset as 31-May-2011 and severity reported as mild. These TEAE led to discontinuation of the investigational product. The last dose was taken on 03-Jun-2011 and the subject was discontinued from the trial on 06-Jun-2011. No treatment medication was reported. The events were reported as resolved on 06-Jun-2011. The TEAEs were deemed not related to the investigational product. I agree since they were reported at screening as well. The subject also reported mild back pain (02-Jun-2011 to 02-Jun-2011 and 04-Jun-2011 to 05-Jun-2011) that was considered to be not related to the investigational product.

Parameter	Screening	EOT	Normal range
Blood urea	29 mg/dL (31-May-2011)	16 mg/dL (06-Jun-2011)	7-18 mg/dL
Blood creatinine	2.80 mg/dL (31-May-2011)	0.85 mg/dL (06-Jun-2011)	0.5-1.00 mg/dL
Blood potassium	5.3 mmol/L (31-May-2011)	4.2 mmol/L (06-Jun-2011)	3.4-4.7 mmol/L

EOT=end of trial.

Placebo Group: 4 subjects discontinued due to:
Subject 140031013: Type 2 diabetes mellitus
Subject 140131007: Anisocytosis, Basophil count increased, Lymphocyte count increased, Neutrophil count increased, White blood cell count increased, Hypochromasia, Haematocrit decreased, Haemoglobin decreased, Microcytosis
Subject 140141006: Diarrhea, Dyspepsia, Oropharyngeal pain, Abdominal pain upper
Subject 140151006: Insomnia

Laboratory Parameters:
The treatment-emergent abnormal values reported for ≥2% of naproxen sodium 440 mg/DPH 50 mg subjects and at a higher incidence than placebo were absolute eosinophil count (2.8% vs. 0%, respectively), random glucose (5.5% vs. 2.8%), potassium (3.7% vs. 1.8%), total protein (2.3% vs. 1.8%), and uric acid (2.3% vs. 0.9%).

Vital Signs:
One (0.5%) of 217 naproxen sodium 440 mg/DPH 50 mg subjects had a treatment-emergent abnormal vital sign parameter of heart rate (101 beats/min).

Safety Conclusions:

The most commonly reported TEAEs (≥2% of subjects) in subjects treated with naproxen sodium 440 mg/DPH 50 mg that occurred at a higher incidence than in placebo subjects were somnolence (4.6% vs. 3.7%, respectively), dizziness (4.1% vs. 0%), nausea (4.1% vs. 0.9%), back pain (3.7% vs. 2.8%), diarrhea (3.2% vs. 1.8%), abdominal discomfort (2.3% vs. 1.8%), and dyspepsia (2.3% vs. 0.9%).

Severity: Mild or moderate TEAEs were reported for 38.2% of naproxen sodium 440 mg/DPH 50 mg subjects and 44.0% of placebo subjects compared with severe TEAEs in 1.4% of naproxen sodium 440 mg/DPH 50 mg subjects and 0.9% of placebo subjects.

Discontinuations: 3/4 discontinuation in the naproxen sodium 440 mg/DPH 50 mg group was not related to the drug. One discontinuation in the treatment group was due to esophageal pain and edema, but mild in nature.

Age: No age-related effect on the incidence of most TEAEs was noted in subjects treated with naproxen sodium 440 mg/DPH 50 mg when comparing subjects ≥ 60 years of age with subjects 12 to 59 years of age (38.5% vs. 40.1%). Only dizziness was higher in subjects ≥ 60 years of age (7.7%), compared to placebo (2.8%).

Gender: Female subjects treated with naproxen sodium 440 mg/DPH 50 mg had a higher incidence of TEAEs than male subjects (48.1% vs. 26.2%); however, this effect was also noted in the placebo group (49.2% vs. 38.6%).

5.3.5 Study 16135: PK Food Interaction study

In this 4 way crossover study the treatment arms were:
A: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fasted conditions
B: 2 x Aleve® (naproxen sodium 220 mg tablet) under fasted conditions
C: 2 x Allergy Relief® (DPH HCl 25 mg tablet) under fasted conditions
D: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fed conditions
All AEs were considered mild in intensity. No subject discontinued study treatment because of an AE. No SAEs were reported. The overall summary of adverse events is given in Table 61.

Table 61: Overall summary of adverse events - Safety population

Category	Treatment A (N=29) n (%)	Treatment B (N=30) n (%)	Treatment C (N=29) n (%)	Treatment D (N=28) n (%)	Overall (N=32) n (%)
Subjects with at least one AE	15 (51.7)	5 (16.7)	16 (55.2)	14 (50.0)	29 (90.6)
Subjects with TEAEs	15 (51.7)	5 (16.7)	16 (55.2)	14 (50.0)	29 (90.6)
Subjects with SAEs	0	0	0	0	0
Subjects who discontinued due to an AE	0	0	0	0	0

The most common AE was somnolence that occurred in the combination treatment groups (fed and fasted and the DPH group, clearly indicating increased somnolence with DPH. The N(%) of subjects in each group having somnolence is given below:

A: NP440/DPH50 fasted (A): 11 (37.9%)
B: NP440 (B): 2 (6.7%)
C: DPH (C): 14 (48.3%)
D: NP440/DPH fed (D): 11 (39.3%)

Somnolence onset occurred within 3 hours post-dose for all 23 subjects. Median plasma DPH tmax for all subjects in the PK full population ranged from 1.75-2.50 hours, coinciding with the period of somnolence onset.

I further looked at the duration of somnolence. The percentage of subjects with the duration of somnolence for 1-3 hours, 4-6 hours and 6-8 and 8-10 hours in each treatment group is given in Table 62.

Table 62: Duration of Somnolence: N (%) of subjects

Treatment Group	Duration of Somnolence				
	1-3 hours	3-6 hours	6-8 hours	8-10 hours	14 hours
NP440/DPH50	5/11 (45%)	3/11 (27%)	1/11 (9%)	2/11 (18%)	

fasted					
NP440	1/2 (50%)		1/2 (50%)		
DPH	5/14 (36%)	3/14 (21%)	3/14 (21%)	3/14 (21%)	
NP440/DPH fed	2/11 (18%)	3/11 (27%)	3/11 (27%)	2/11 (18%)	1/11 (9%)

One subject in the NP440/DPH fed group had somnolence for almost 14 hours. The sponsor states that this subjects reported drowsiness for 9.5 hours then had dinner and reported sleepiness after that. This subject was not questioned further till the following morning. The DPH plasma concentration, starting from the time the subject reported sleepiness, was 20.94 ng/mL and decreased to 3.26 ng/mL by the time of AE resolution.

At 8 hours post-dose, which coincides with the expected wake time of general consumer population who took the combination product as a sleep-aid, the mean DPH plasma concentrations had declined (Cmax ranged from 67.49-78.17 ng/mL for the full PK population) by more than 50% to concentrations ranging from 23.42-28.81 ng/mL, but some individual concentrations were much higher. Please see section 4.4.3 for further discussion of blood levels related to DPH observed from this study and that thought to cause drowsiness/mental impairment. There were some subjects that had concentrations in the range believed to cause drowsiness in this study. It is noteworthy that not all subjects that had high DPH concentrations reported somnolence that lasted >8 hours. Some subjects reported somnolence for 8-10 hours had low DPH concentration at 8 hours post dose.

Laboratory values:
There were 5 total cases of anemia. These were considered mild and resolved at follow up visits according to the sponsor. In all cases hemoglobin and hematocrit decreased after screening. Anemia can occur in patients using NSAIDs due to fluid retention or GI blood loss. All subjects followed the same pattern of decline as shown below.

Patient	Laboratory Test	Screening	Discharge	10 day follow up	2 week follow up	1 month follow up	Reference Range
140011016	Hgb(g/dL)	11.6	10.3	10.3	9.9	11.0	
	HCT (%)	38.6	32.5	34.0	32.6	36.6	
140011017	Hgb(g/dL)	11.4	10.1	10.1	10.0	-	
	HCT (%)	35.8	30.5	31.4	31.2	-	
							11.5-15.6
140011023	Hgb(g/dL)	11.1	10.2	10.1	9.7	9.5	34.5-46.5
	HCT (%)	33.1	31.0	30.	29.2	28.8	
							for
140011028	Hgb(g/dL)	12.1	10.2	10.2	10.7	-	females
	HCT (%)	37.4	30.7	31.4	33.8		

140011032	Hgb(g/dL)	13.2	11.0	10.5	11.2	-	
	HCT (%)	40.4	33.3	32.6	34.7		
140011009	ALT (U/L)	38	54	35	-	-	<41 for males
140011015	ALT (U/L)	30	66	28	-	-	<41 for males
140011017	ALT (U/L)	14	52	22	-	-	<33 for females

Three subjects had ALT increase. All these cases were considered mild and resolved at follow up visits and were possibly related to product.

Vital Signs: no abnormalities were noted.

Safety Conclusions:

- Food did not alter the incidence of AEs.
- The most commonly reported AE was somnolence in the combination group and DPH alone group. The duration of somnolence ranged from 1-10 hours, with one subject reporting somnolence for 14 hours.
- No abnormalities in vital signs were noted.

6 Review of Efficacy

Efficacy Summary

The proposed label for Aleve® PM states "helps you fall asleep and stay asleep". Therefore, the clinical results must support both sleep onset and sleep maintenance labeling claims. In addition a combination product should meet the requirements of the OTC combination policy specified in 21CFR 330.10(a)(4)(iv). The combination product should show superiority of the combination over each of its components. Given this, to confirm the contribution of each component to the overall efficacy of the combination, co-primary endpoints of Wake After Sleep Onset (WASO) (measure of sleep maintenance) and sleep latency (measure of sleep onset) were defined on FDA's request during the pre-Investigational New Drug (IND) application meeting. These endpoints formed the basis of the primary efficacy analysis in the pivotal studies. For WASO the combination was compared to NP440 alone showing the added benefit of DPH for sleep maintenance. For Sleep Latency, the combination was compared to DPH50 alone, showing the added benefit of naproxen for latency.

Based on the pre-specified analyses, Study 14837 demonstrates the superiority of NP440/DPH50 to its individual components, thereby satisfying the combination rule, and providing adequate evidence of efficacy to support the marketing of NP440/DPH50 (given as two tablets of NP220/DPH25). The following results demonstrate the superiority findings from the pivotal clinical trials:

- NP440/DPH50 was superior to NP440 alone (Δ=-70 minutes, p=0.0002) for sleep maintenance as shown by WASO, suggesting that DPH50 contributes to sleep maintenance.
- NP440/DPH50 was superior to DPH50 alone (25.5 minutes versus 41.4 minutes, p<0.001) for sleep onset, suggesting that NP440 contributes to sleep onset in patients with pain post tooth extraction.
- NP220/DPH50 failed to show the contribution of both NP440 and DPH50 for efficacy. It was not superior to NP440 alone for sleep maintenance (p=0.3627), but was superior to DPH50 alone for sleep onset (p=0.0003). This suggests that pain relief is driving both sleep maintenance and sleep onset in a study population with sleeplessness associated with dental pain following tooth extraction. More subjects took rescue medication in the NP220/DPH50 group compared to NP440. The imputation method in subjects taking rescue medication could have driven the efficacy results.
- A lower DPH dose, 25 mg, in combination with NP440 failed to meet both co-primary end points (p=0.3047 for WASO and p=0.1677 for sleep latency). The study evaluating the lower dose was clearly under powered; it had half the number of subjects per treatment arm compared to the study with NP440/DPH50. The sponsor's power calculation used an unrealistic standard deviation of 14 minutes in WASO, when the previous study completed before the start of this study had a WASO standard deviation of 165-208 minutes. Another limitation of Study 15881 is that it did not include the higher DPH dose (NP440/DPH50) in the study which could have been more informative in evaluating assay sensitivity: A positive NP440/DPH50 arm could have been informative in interpreting the negative finding for NP440/DPH25.

The interpretation of the dental pain phase advance sleep studies is confounded by several factors. This sleep model may not be representative of the actual OTC population that would be using this product. However, this model has been historically used for the approval of other analgesic/nighttime sleep aids. Rescue pain treatment was allowed for all patients that needed additional pain relief. About 21% of patients in the NP440/DPH group, 33% in NP440 alone group and 76% in the DPH50 group took rescue medication. The WASO and sleep latency were imputed in patients that took rescue medication. If rescue medication was taken before sleep onset, WASO was set to 600 minutes. If rescue medication was taken after sleep onset, patients were treated as awake from the time the rescue medication was taken to the total time in bed. Similarly for sleep latency imputation, if rescue was taken before sleep onset, sleep onset was set to 600 minutes. Sleep Latency was not affected if rescue medication was taken after sleep onset.

A lower percentage of subjects requiring rescue medication in the NP440/DPH group versus NP440 could suggest increased sleepiness due to DPH's effect on sleep maintenance. It could

also suggest increased effectiveness of the combination both for pain relief and increased sleepiness, consistent with the objective of the combination. Overall, the efficacy results are driven largely by imputed values and not observed data making the interpretation problematic.

Another limitation of the clinical program is that elderly were not enrolled in the efficacy trials. Most of the patients were between the ages of 20-28 years.

Given the unusual conditions of the trial, post-surgical phase-advance patients, actigraphy may not be a reliable tool to assess if patients are sleeping or only laying still. Each actigraph was set to capture activity every 30 seconds, but it is unclear if it can distinguish between inactivity and sleep in this setting.

6.1 Indication

- For the relief of occasional sleeplessness associated with minor aches and pains.
- Helps you fall asleep and stay asleep

6.1.1 Methods

The efficacy of Aleve® PM for the treatment of occasional sleeplessness associated with pain was evaluated in a dental pain with phase-advance sleep model. The dental pain model, following removal of impacted third molars has been used in the evaluation of analgesics. To evaluate the treatment of sleeplessness associated with pain, the sleep phase was advanced by 5 hours. Subjects went to bed between 4 and 6 pm. According to Bayer, a phase shift of 5 hours was selected in order to produce a high magnitude of sleep disturbance to increase the sensitivity of the model. This model had been used and accepted by FDA for the evaluation/approval of analgesic/nighttime sleep-aid combination products such as Advil® PM and Tylenol® PM.

Phase-advanced sleep involves a shift of the circadian bedtime which is thought to result in disruption of normal sleep patterns. In several studies in the literature, phase advance has been known to cause transient insomnia, but several literature articles also discuss its limitation. Some criticism of the phase advance model has been that habitual bedtime may influence the results of a study in some individuals.[6] Phase advance manipulation does not produce consistent transient insomnia in all young normal sleepers, it can disrupt sleep in some individuals and can have no effect on others.[7] In addition, the duration of phase advance could have an impact too. The two pivotal studies (Study 14837 and 15881) were conducted with a 5 hours phase advance. The pilot study was conducted with a 3 hour phase advance. It has been shown that greater the phase advance, the greater the sleep disturbance in subjects.[8] In addition, an enforced time in bed is likely to affect sleep latency and may not be the best model for assessing sleep latency. Also, younger subjects have been shown to sleep relatively well compared to the middle aged subjects

[6] Walsh et. al., Sleep 11:251-64, 1988
[7] Walsh et. al., J Clin Psychopharmacology, vol 10(3): 184-189, 1990
[8] Bonnet et. al. Situational insomnia: Consistency, predictors, and outcomes. Sleep 2003;26(8):1029-1036

when going to bed at atypical times as shown in some shiftwork studies.[9] The two efficacy studies enrolled very young subjects (80-90% <24 years).

More importantly, this model does not represent all the population in which this OTC product will be used and may not be generalizable to sleeplessness associated with different types of pain, such as pain due to arthritis, muscle pain etc.

The subjects were required to stay in bed for 10 hours, which does not represent realistic OTC use. Most patients would want the drug to work for only 7-8 hours and then for the effect to be gone so they can get out of bed and be active for the day. Another important confounding factor affecting the sleep parameters was allowing the subjects to take rescue medication. The intake of rescue medication affected the calculations of WASO and Sleep Latency. Subjects who took rescue medication after sleep onset were treated as being awake from the time when the rescue medication was given to the end of the in-bed time. For subjects who took rescue medication before sleep onset, WASO was set to 600 minutes (the duration of the in-bed time). Hence, subjects taking rescue medication had unrealistically long WASOs. Similarly, subjects who took rescue medication before sleep onset were censored for sleep latency at 10 hours (600 minutes); sleep latency was not affected if rescue medication was taken after sleep onset. Since the need for rescue medication was dependent on the pain in these subjects, the DPH group had the highest numbers of subjects on rescue medication. Any imbalance in pain severity could affect the results too.

6.1.2 Demographics

Of the 1556 subjects enrolled in the 5 clinical studies supporting this NDA, a total of 477 subjects were exposed to at least 1 day of single doses of the naproxen sodium 440 mg/DPH 50 mg combination dose, of which 217 subjects were exposed to between 1 and 12 days of single doses of this proposed combination (See Table 63).

Table 63: Extent of Exposure

	Number of Subjects					
Study Medication	**Study 13053**	**Study 14837**	**Study 15881**	**Study 15660**	**Study 16135**	**Total**
NS 440 mg/DPH 50 mg[a,b]	27	203	0	217	30	477
NS 220 mg/DPH 50 mg	27	204	0	0	0	231
NS 440 mg/DPH 25 mg	0	0	107	0	0	107
NS 440 mg alone	27	203	106	0	30	366
NS 220 mg alone	27	0	0	0	0	27
DPH 50 mg	27	102	54	0	29	212
Advil PM	27	0	0	0	0	27
Placebo	0	0	0	109	0	109
Total	**162**	**712**	**267**	**326**	**89**	**1556**

Note: Study 16135 is a PK study

[9] Walsh et. al., J Clin Psychopharmacology, vol 10(3): 184-189, 1990

The overall demographics for the two pivotal efficacy studies are given in Table 64.

Table 64: Demographics for the pivotal efficacy studies

	Study14837 N=712	**Study15881** N=267
Age [mean (SD)]	21.2 (4.7)	21.2 (5.27)
Range	16-48	12-48
Gender [n (%)]		
Male	309 (43.4)	94 (35.2)
Female	403 (56.6)	173 (64.8)
Ethnicity [n (%)]		
Hispanic/Latino	153 (21.5)	55 (20.6)
Not Hispanic	559 (78.5)	212 (79.4)
Race [n (%)]		
White	634 (89.0)	234 (87.6)
Black	27 (3.8)	17 (6.4)
Asian	20 (2.8)	10 (3.7)
Other	23 (3.3)	3 (1.1)
Multiple	8 (1.1)	3 (1.1)

The mean age in Study 14837 and Study 15881 was 21 years (range 12-48 years). The efficacy has only been evaluated in the young population, which is not representative of the typical OTC population, although safety has been evaluated in a wider age range including subjects >65 years (see section 7).

The number of pediatric patients in the clinical studies is given in the Table 65. In study 14837, there were 115 children between the ages 16-17 years. In study 15881, there were 49 children between the ages 12-17 years.

Table 65: Number of pediatric subjects by age in the Clinical Studies

Age (years)	Number of Pediatric Subjects Enrolled				
	Study 13053	Study 14837	Study 15881	Study 15560	Total
17	37	56	19	2	114
16	35	59	13	0	107
15	0	0	6	2	8
14	0	0	5	1	6
13	0	0	4	1	5
12	0	0	2	1	3
Total	72	115	49	7	243

Baseline pain intensity as seen in Table 66 was rated moderate by more subjects in both efficacy studies, with a similar mean pain intensity on the VAS of ~ 70 mm.

Table 66: Baseline Pain for the pivotal efficacy studies

Baseline Pain	**Study14837** N=712	**Study15881** N=267
Baseline Pain Intensity (categorical Scale) n (%)		
Moderate	494 (69.4)	160 (59.5)

Severe	218 (30.6)	107 (40.1)
Baseline Pain Intensity(categorical Scale) Mean (SD)	72.4 (12.31)	75.6 (10.26)

6.1.3 Subject Disposition

In general, all randomized subjects in Study 14837 and Study 15881 completed the study according to the protocol, except for 3 subjects in Study 14837 (Table 67).

Table 67: Subject disposition for the pivotal efficacy studies

Subject disposition	**Study14837 (N=712)**	**Study15881 (N=267)**
Number of subjects randomized	712	267
Number of subjects completing the study	709	267
Number of subjects discontinuing	3	0
Adverse event	0	0
Voluntary withdrawal	2[a]	0
Protocol violation	0	0
Lost to follow up	0	0
Other	1[b]	0

[a] Two subjects voluntarily withdrew after randomization.
[b] One subject participated in another trial within 30 days prior to the screening visit

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints were Wake After Sleep Onset (WASO) and Sleep Latency determined by Actigraphy for both pivotal studies 14837 and 15881 to confirm the contribution of each component to the overall efficacy of the combination. The primary endpoint in the pilot study was Total Sleep Time (TST). The treatment comparisons were based on the treatment arms studied. The treatment arms for the two pivotal studies were:

Pivotal Study 14837:
Naproxen sodium 440/DPH 50
Naproxen sodium 220/DPH 50
Naproxen sodium 440
DPH 50

Pivotal Study 15881:
Naproxen sodium 440/DPH 25
Naproxen sodium 440
DPH 50

Pilot Study 13053:

Naproxen sodium 440/DPH 50
Naproxen sodium 220/DPH 50
Naproxen sodium 440
Naproxen sodium 220
DPH 50
Advil PM

To protect the overall Type 1 error at the 0.05 level, a hierarchical testing procedure was used separately for WASO and sleep latency. Relevant treatment comparisons were tested sequentially, each at the 2-sided 0.05 level of significance (see page 26). Once a comparison was identified as statistically non-significant, subsequent comparisons technically were ineligible to be declared significant; however, all comparisons were presented.

Wake after sleep onset

Table 68 shows the treatment difference for WASO from the two pivotal studies. The WASO for NP440/DPH50 was significantly shorter (Δ= -70 minutes) than NP440 alone (p=0.0002). The sensitivity analyses also showed significant difference between these two treatments.

Table 68: WASO Analysis

Analysis	Treatment Difference		
	Study 14837		Study 15881
	NP 440/DPH 50 vs. NP440	NP220/DPH 50 vs. NP440	NP 440/DPH 25 vs. NP440
Primary	-70 minutes (P=0.0002) (N=203 vs. 203)	16.9 minutes (p=0.3627) (N=204 vs. 203)	-25 minutes (p=0.3047) (N=107 vs. 106)
Sensitivity 1. Excluding Subjects on Rescue	-30 minutes (p<0.0001) (N=158 vs. 134)	-	-8.82 minutes (p=0.1914) (N=83 vs. 76)
2. With imputed values for subjects that took rescue medication	-19.7 minutes (p<0.0001) (N=201 vs. 202)	-	-4.49 minutes (p=0.4414) (N=107 vs. 106)

Dose-response was seen between the high and low analgesic combination dose with a treatment difference of -87 minutes (P <0.0001), although based on hierarchical comparison, this was ineligible for direct comparison of efficacy.

The results of study 14837 demonstrate the contribution of DPH50 in the combination 440/DPH 50 to improve sleep duration.

The results of study 15881 are inconclusive that the lower DPH dose (25 mg) in the combination is not effective. Assuming a WASO treatment difference of 52 minutes between naproxen sodium 440 mg/DPH 50 mg and naproxen sodium 440 mg and a standard deviation of 138 minutes, Bayer determined that approximately 200 subjects per treatment group would provide adequate power for Study 14837. For Study15881, Bayer assumed a WASO treatment difference of 56 minutes and a standard deviation of 14 minutes and concluded that a sample size of 100 subjects would give adequate power. Bayer's rationale for this is unclear, when the results of the previous completed study had shown a larger standard deviation.

Another limitation of study 15881 is that both lower and higher DPH doses were not evaluated in the same study.

Sleep Latency

Table 69 shows the p-values for the Kaplan Meier Analysis of sleep latency from the two pivotal studies. Sleep Latency was significantly shorter (Δ= -15.9 minutes) for NP440/DPH50 than DPH50 alone (P=<0.0001).

Table 69: Sleep Latency: Kaplan Meier Analysis (Median Time in minutes)

Analysis	Treatment Difference		
	Study 14837		**Study 15881**
	NP 440/DPH 50 vs. DPH50	NP 220/DPH 50 vs. DPH50	NP 440/DPH 25 vs. DPH50
Primary	25.5 vs. 41.4 mins (p<0.0001) (N=201 vs. 102)	30.25 vs. 41.4 mins (p=0.0003) (N=204 vs. 102)	23.5 vs. 27.5 mins (p=0.1677) (N=107 vs. 54)
Sensitivity 1. Excluding Subjects on Rescue before sleep onset	25 vs. 22.5 mins p=0.2397 (N=196 vs. 74)	-	21.5 vs 24.5 mins p=0.4605 (N=103 vs. 49) 23.5 vs. 26.25 mins p=0.5100 (N=107 vs. 54)
2. With imputed values for subjects that took rescue medication	25.5 vs. 33.5 mins p=0.0016 (N=201 vs. 102)	-	

The results of these studies do not support the contribution of DPH for sleep latency in this model. Since the study population was associated with pain following tooth extraction, one

would not expect a DPH50 to contribute to sleep latency without pain relief from an analgesic. According to the protocol specified criteria to establish efficacy, Study 14837 would be considered a positive study, but in reality an analgesic is driving the sleep latency effect in a population that has sleeplessness associated with pain. Unless the pain is abated, the subject will not be able to fall asleep as fast. A sleep-onset comparison of NP440/DPH50 with NP440 gave a p-value of 0.4164 suggesting that when pain is treated, sleep latency is not different between the combination groups compared to NP440 alone.

Sensitivity analysis excluding subjects that took rescue medication suggested that NP440/DPH50 was not superior to DPH50. Sensitivity analysis with imputed values showed that NP440/DPH50 was statistically different than DPH50.

Total Sleep Time

This was the primary endpoint for the pilot study.
Study 13053
Mean TST increased by 105 minutes in the NP220/DPH50 group compared to NP220.
Mean TST increased by 35 minutes in the NP440/DPH50 group compared to NP440.
These differences were not statistically different from each other, potentially due to the small sample size (26 per arm).

The least number of subjects in theNP220/DPH50 group took rescue medication. (Note: The subjective assessment of pain relief with this combination dose was rated better than other treatment groups)

Sensitivity Analysis of subjects who did not take rescue medication, showed that:
- Mean TST increased by 4 minutes in the NP220/DPH50 group compared to NP220.
- Mean TST increased by 37 minutes in the NP440/DPH50 group compared to NP440.

Sensitivity Analysis excluding subjects that took rescue before sleep onset, showed that:
- Mean TST increased by 69 minutes in the NP220/DPH50 group compared to NP220.
- Mean TST increased by 50 minutes in the NP440/DPH50 group compared to NP440.

- Mean TST increased by 78 minutes in the NP220/DPH50 group compared to active comparator Advil PM.
- Mean TST increased by 4 minutes in the NP440/DPH50 group compared to active comparator Advil PM.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints and analysis plan were the same for both Study 14837 and Study 15881. The treatment comparisons were based on the treatment arms studied.

Objective sleep assessments

The secondary objective sleep assessments (Total Sleep Time and Sleep Efficiency) followed the same trends as the primary endpoints for both pivotal studies. The combination NP440/DPH50 was the only dose that showed statistically significant superiority for both Total Sleep Time and Sleep Efficiency. The lower dose combination NP220/DPH50 failed to demonstrate superiority in comparison to NP440 alone. A statistically significant dose-response was established, but this was ineligible for direct comparison of efficacy. The combination NP440/DPH25 failed to demonstrate added benefit of this dose in comparison to NP440 alone.

- **Total sleep time**
  - For Study 14837 the mean treatment difference between NP440/DPH 50 and NP440 was 70.4 minutes (P=0.0001)
  - For Study 15881 the mean treatment difference NP440/DPH 25 and NP440 was 26.29 minutes (P=0.2764)
- **Sleep efficiency**
  - For Study 14837 the mean treatment between NP440/DPH 50 and NP440 difference was 11.7 minutes (P=0.0007)
  - For Study 15881 the mean treatment difference NP440/DPH 25 and NP440 was 4.31 minutes (P=0.2764)

Subjective sleep assessments
The subjective sleep assessments were:

- Global Assessment of Investigational Product as a Sleep-Aid
- Karolinska Sleep Diary data
- Subjective Sleep Questionnaire

These were analyzed using the Cochran-Mantel-Haenszel (CMH) method.

Study 14837: For both Global assessment of drug as sleep aid and Karolinska Sleep Diary, the combination NP440/DPH50 had better ratings (statistically) than the both NP440 and DPH50 alone treatment group, confirming the objective primary analysis. The combination NP220/DPH50 was rated statistically better than DPH50 for most questions, and better than NP440 only for only two questions "How was your sleep" and "Premature awakening". NP440/DPH50 was rated better than NP220/DPH50.

The subjective assessment of Sleep Onset based on Sleep Questionaire (Estimate how long it took you to fall asleep?) was not statistically different between any treatment groups. The estimated time to fall asleep was larger than objective assessment of sleep onset (~24-26 minutes vs. ~40 minutes). Subjective sleep assessment of WASO (Estimate the number of minutes you were awake?) was statistically better for both combination treatment groups compared to individual NP440 alone. Subjective WASO was shorter than the objective WASO assessment (~73 minutes vs. ~142 minutes). There was no statistical difference between NP440/DPH50 and NP220/DPH50. Difference in the objective and subjective assessments are commonly seen with sleep drugs.

Study 15881: For both Global assessment of drug as sleep aid and Karolinska Sleep Diary, the combination NP440/DPH25 had better ratings (statistically) than the both NP440 and DPH50 alone treatment group.

6.1.6 Other Endpoints

Pain Variables: see review by the Division of Anesthesia, Analgesia, and Addiction Products.

6.1.7 Subpopulations

There were no differences in objective WASO or Sleep Latency based on gender and age, although in these studies the age range was very narrow. About 90% of the subjects were between the ages of 18-28 years. The age distribution is not representative of the OTC population that would use this product. A subgroup analysis in pediatrics ages 16-17 only showed similar findings for both WASO and Sleep Latency were observed as those seen in adults. There were no children younger than 16 years in the pivotal study.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See section 6.1.4

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The pivotal efficacy studies were single dose studies. No persistence of efficacy or tolerance effects can be evaluated. The combination product is to be used to short term therapy (no more than 10 days).

6.1.10 Additional Efficacy Issues/Analyses

See section 6.1.4-9

7 Review of Safety

Safety Summary

- Safety has been evaluated in a total of 1556 subjects including placebo subjects. 477 subjects were on NP440/DPH50 combination, out of which 217 have been on NP440/DPH for 10 days.
- There was no evidence that the combination, NP440/DPH50, was associated with a higher incidence of adverse effects compared to NP 440 or DPH50 alone.
- The safety of NP440/DPH25 was not examined in a multiple dose study.
- Common Adverse events seen after single dose were nausea, headache, dizziness and vomiting. Somnolence was not observed in the efficacy studies, but 38% of subjects on NP440/DPH50 in the PK study had somnolence, compared to 6.7% in the NP440 group

and 48% in the DPH alone group. 27-45% of the subjects in combination or DPH alone group had somnolence that lasted 6-10 hours. In addition, one subject in the NP440/DPH50 fed group had somnolence that lasted up to 14 hours.

- Subjects ≥ 60 years (7.7%) had higher rate of dizziness than younger subjects (2.6%) compared to non in both placebo groups.

7.1 Methods

The sources of the safety data that I reviewed were from the controlled clinical trials conducted by the sponsor. Safety in the clinical trials was assessed by collection of adverse events (AEs), treatment emergent adverse events (TEAEs), vital parameters (blood pressure, pulse, respiratory rate), laboratory tests (hematology and chemistry). The safety analysis population consisted of all subjects exposed to at least one dose of study treatment. Adverse events, vital parameters and laboratory tests were summarized using descriptive statistics.

I reviewed the appropriateness of coding to assess whether related adverse events combined appropriately to assess the true incidence of an event. Patient verbatim terms were not available and were requested from the sponsor. The sponsor provided the terms entered in the progress notes. The patient name was redacted from the progress notes, which was sent to the data management group for double data entry. The verbatim terms were then linked to the reported term using the subject number. Upon review of these it appears that the progress notes were most likely written by the physicians and did not capture the patients' verbatim complaints. In the progress notes there were terms like paresthesia, epistaxis, presyncope, emesis, aleveolitis/dry socket that are likely recorded by the physicians. Since the pivotal studies were single dose in-patient studies, it appears the AEs were assessed and recorded by the physician at study site. According to the sponsor, the AEs were entered onto the CRFs by the coordinators after the physician reviewed the source documents and signed off on the AE.
The adverse events were mild and moderate in nature and the pivotal studies were single dose studies. Most events were resolved by Day 2. The adequacy of the preferred term was assessed for the multiple dose study and was appropriate.

Individual case reports of severe adverse events were reviewed for the 10-day safety study. Case report forms were not provided for the single dose studies.

Relative rates of TEAES were compiled by analyses of datasets in MAED and JReview to verify sponsor incidence table. Any event occurring at 1% or greater in any treatment arm was included in the table in the relevant sections of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review discusses the safety data from the controlled studies. Please see section 5.1 for the list of controlled studies.
For these studies all subjects that took at least 1 dose of the investigational product were included in the safety analysis.

The post marketing safety for naproxen and diphenhydramine is evaluated by OSE.

7.1.2 Categorization of Adverse Events

The sponsor defined an adverse event as any untoward medical occurrence in a subject administered with an investigational pharmaceutical product, which did not necessarily have a causal relationship with the investigational product. Thus, an adverse event was any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product, whether or not it was considered to be study drug related.

For the single dose studies the adverse events were reported through out the dosing period and the end of the trial. Only TEAEs were included for the safety analysis in these trials. TEAE was an AE that begins or worsens after the first dose of the study drug in the period. The number and percentage of subjects who experience any AEs, by System Organ Class (SOC), by preferred term and by rescue medication were given by treatment group. AEs were presented by seriousness, severity (mild, moderate, severe), relationship to drug, duration and outcome.

Adverse events were linked to system organ class and preferred term in MedDRA version 13.0. AETERM were provided for these studies. Verbatim terms were not provided, but were requested from the sponsor during the review. Events like paresthesia, epistaxis, presyncope were presented under AETERM. For example, there were 9 cases of presyncope or signs and symptoms of presyncope in the AETERM. The AETERM of lightheadedness were coded as Dizziness. Without knowing the verbatim term, it was unclear why signs and symptoms of presyncopy were not termed lightheadedness. Based on the progress notes information provided by the sponsor, one case each in the DPH, NP440 and the NP220/DPH50 group were written as lightheadedness, but was coded as presyncope. It is unclear why these cases of lightheadedness were not coded as dizziness. Most other AEs were adequately coded.

I reviewed the coding into the System Organ Class (SOC), which were accurate for these single dose studies. According to the protocol the follow-up from single dose studies, was 2-5 days (±2 days), where adverse events and concomitant medications had to be followed.

For the multiple dose study, AEs that occurred after informed consent, the TEAEs that occurred during and after the 10-day (±2 days) course of investigational product or the EOT visit were reported.

Categorization of AEs was based on MedRA Version 14. The categorization of AEs appeared adequate for the most part.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The sponsor presented the safety assessments separately for each controlled study and I reviewed them separately as well. Pooling these studies is not critical for this application as the efficacy study was single-dose and there was only one multiple-dose safety study.

7.2 Adequacy of Safety Assessments

The overall number of subjects at the proposed dose and the duration of safety assessments were agreed upon in the IND period. About 23% of the subjects were >65 year, with only 3% of the subjects being older than 75 years.

The post marketing safety assessments of naproxen and diphenhydramine are not part of this review. Please see review by OSE.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure:
In the development program, a total of 450 subjects were exposed to ≥1 day of single doses of the naproxen sodium 440 mg/DPH 50 mg combination product, of which 217 subjects were exposed to >1 to 12 days of single doses and 233 subjects were exposed to a single dose.
The extent of exposure of the combination product, active controls or placebo is given in the following Table 70.

Table 70: Extent of exposure to naproxen sodium/diphenhydramine combination product, active controls, or placebo (Safety Populations)

Study Medication	Duration	Number of Subjects	Study Number
NS 440 mg/DPH 50 mg NS 440 mg/DPH 50 mg NS 440 mg/DPH 50 mg	≥1 day >1 to 12 days 1 day	450 217[b] 233	14837, 16135, 15560 15560 14837, 16135
NS 440 mg + DPH 50 mg[a]	1 day	27	13053
NS 220 mg/DPH 50 mg	1 day	204	14837
NS 220 mg + DPH 50 mg[a]	1 day	27	13053
NS 440 mg/DPH 25 mg	1 day	107	15881
NS 440 mg alone	1 day	366	13053, 14837, 15881, 16135
NS 220 mg alone	1 day	27	13053
DPH 50 mg	1 day	212	13053, 14837, 15881, 16135
Advil PM	1 day	27	13053
Placebo	≥1 to 11 days	109	15560

[a]Commercially available products administered together
[b]One subject had missing Diary and was excluded from the extent of exposure analysis

The extent of exposure from the 10-day multiple dose study 15560 is given in the following Table 71. Nine subjects had exposure longer than 10 days, but not more than 12 days.

Table 71: Extent of Exposure from Safety Study 15560

	Treatment Groups		
Exposure Duration (days)	**NS 440 mg/ DPH 50 mg (N = 217)**	**Placebo (N = 109)**	**Total (N = 326)**
N	216 [a]	109	325 [a]
Mean (SD)	9.9 (0.76)	9.8 (1.37)	9.9 (1.00)
Median	10.0	10.0	10.0
Min, Max	3, 12	2, 11	2, 12
Days on study (n, %)			
10+	5 (2.3)	4 (3.7)	9 (2.8)
10	201 (93.1)	100 (91.7)	301 (92.6)

[a] One subject had missing diary data and was excluded from the analysis.

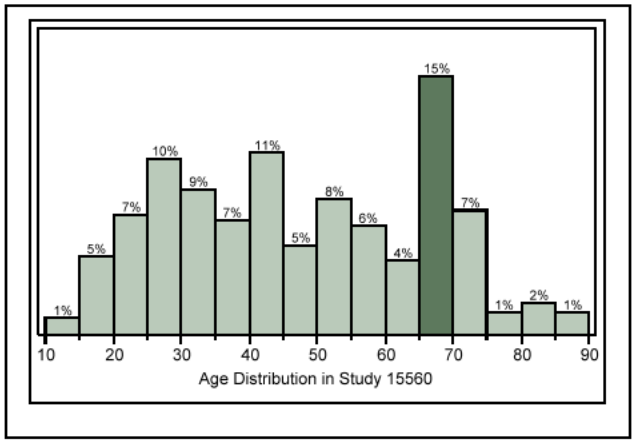
Demographics:
The single dose studies enrolled younger subjects than the multiple dose study. The enrollment criteria were 12-48 years in these studies. There were 59 adolescents (16 years of age) in Study 14837 and 24 (2 of 12 years, 4 of 13 years, 5 of 14 years and 13 of 16 years of age) in Study 15881. The multiple dose study had the requirement to enroll 25% of subjects who were >65 years of age to represent the population of OTC nighttime analgesic/sleep aid users in USA. There were 74 subjects >65 years in this study. The multiple dose study had a total of 7 children with 3 being on active treatment and 4 on placebo. The mean age in the multiple dose study was 47 years and that in the single dose studies was 21 years. The demographics of the studies evaluated by me are given in the following Table 72:

Table 72: Demographics for all studies

Study Number	Study Type	Age	Gender	Race [a]
		years (SD)	M/F n, %	n, %
13053	Pilot	19 (2.6)	M 78 (48.1) F 84 (51.9)	157 (96.9)
14837	Pivotal	21.2 (4.70)	M 309 (43.4) F 403 (56.6)	634 (89.0)
15881	Pivotal	21.2 (5.25)	M 94 (35.2) F 173 (64.8)	234 (87.6)
16135	PK	36.8 (9.14)	M 15 (46.9) F 17 (53.1)	17 (53.1)
15560	Safety	47.0 (18.49)	M 128 (39.3) F 198 (60.7)	188 (59.9)

[a] Results for White race unless further specified

Figure 11: Age Distribution in Study 15560



The age distribution of subjects in the multiple dose study is shown in Figure 11. Further details of the demographics of 326 subjects in the multiple dose study are given in Table 73.

Table 73: Distribution of subjects in multiple dose Study (Study 15660)

Demographic	Treatment Groups: NS 440 mg/ DPH 50 mg (N = 217)	Treatment Groups: Placebo (N = 109)	Total (N = 326)
Age (years) [a]			
N	217	109	326
Mean (SD)	46.9 (18.14)	47.1 (19.26)	47.0 (18.49
Median	44.0	49.0	46.0
Min, Max	15, 89	12, 82	12, 89
Age subgroup, n (%)			
N	217	109	326
<60 years	152 (70.0)	72 (66.1)	224 (68.7)
≥60 years	65 (30.0)	37 (33.9)	102 (31.3)
>65 years	46 (21.2)	28 (25.7)	74 (22.7)
Gender, n (%) [b]			
N	217	109	326
Male	84 (38.7)	44 (40.4)	128 (39.3)
Female	133 (61.3)	65 (59.6)	198 (60.7)
Race, n (%) [b]			
N	209	105	314
American Indian or Alaskan Native	2 (1.0)	1 (1.0)	3 (1.0)
Asian	4 (1.9)	4 (3.8)	8 (2.5)
Black or African American	26 (12.4)	17 (16.2)	43 (13.7)
Hispanic	45 (21.5)	19 (18.1)	64 (20.4)
Native Hawaiian or Other Pacific Islander	0	0	0
White	127 (60.8)	61 (58.1)	188 (59.9)
Other	5 (2.4)	3 (2.9)	8 (2.5)

7.2.2 Explorations for Dose Response

There was not enough data to evaluate dose-response. The different doses used were mainly across different studies so reliable comparison was not possible. No serious AEs were observed with either dose of naproxen (440 and 220 mg) or diphenhydramine (50 and 25 mg) when looking across studies after a single dose. The multiple dose study only had one dose (NP440/DPH50).

7.2.3 Special Animal and/or In Vitro Testing

No animal and/or in vitro testing was conducted.

7.2.4 Routine Clinical Testing

The collection of safety data in the controlled trials was adequate. AEs, vital signs and Laboratory tests were conducted at screening and End of Treatment in the multiple dose study. Laboratory tests were not done for the single dose studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

A PK study was conducted to evaluate the interaction between Naproxen Sodium 440 mg and DPH 50 mg in the combination product. No interaction was observed.

When the combination formulation was taken with food, there was no effect on the overall exposure (AUC) of naproxen or DPH in the combination product. With food, there is a delay in the rate (Tmax) of absorption by 1.75 hours and a 19% reduction in mean Cmax of naproxen. For DPH, the Tmax was similar with food, but the Cmax was higher (13%).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Gastrointestinal, cardiovascular, renal, hepatic and nervous system risks are common with analgesic and sleep aid combination products.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths any controlled clinical trials evaluated by this reviewer.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious in the studies evaluated by this reviewer.

7.3.3 Dropouts and/or Discontinuations

There were no dropouts or discontinuation in the single dose studies evaluated by this reviewer. Four subjects discontinued in the 10 day safety study, but 3 of these were not drug related. One discontinuation in the treatment group was due to esophageal pain and edema, but mild in nature. Concomitant medications for this subject included: Sprintec (ethinyl estradiol and norgestimate) for oral contraception and multi-vitamins as a nutritional supplement. The event was resolved 6 days after onset. Due to the concern of a retained pill, additional information was requested on this subject, but the sponsor did not have additional details on this subject.

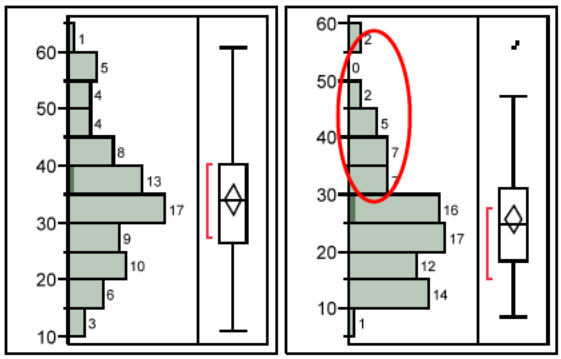
7.3.4 Significant Adverse Events

The adverse events observed with the combination NP440DHP50 were known events about NP440 and DPH. In the single dose Study 14837, there were 3 severe TEAEs (presyncope, vomiting and headache) that were resolved upon follow up. In the single dose Study 15881 there were no severe TEAEs. Most AEs were resolved by end of study or follow up period. The efficacy trials allowed rescue medication for pain relief, hence, it is difficult to attribute the drug relatedness of the AEs from these studies. In the PK study there were 5 cases of anemia and 3 cases (<2-fold) of ALT increase, which were resolved after a month of follow up. These side effects are observed with the use of naproxen.

7.3.5 Submission Specific Primary Safety Concerns

Safety concerns regarding naproxen would GI bleeding, ulceration, increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, especially in the elderly. Renal toxicity, anaphylactoid reactions, skin reactions, anemia, elevation in liver function tests are also known to occur with the use of naproxen.

Some of the safety concerns related to DPH50 mg in the combination product would be somnolence and next day residual sedative effects. Diphenhydramine is not recommended in the elderly due to anticholinergic effects in multiple references (America Association of sleep medicine, Goodman Gilman, Principles of Pharmacology). The variable pharmacokinetics of diphenhydramine is a concern in assessing the safety of DPH. A high incidence of somnolence was observed in the PK study with daytime dosing. Keeping this in mind I looked at the DPH concentration post doing in the PK study. Gengo et.al[10] have shown that DPH concentrations that produce drowsiness are 30.4 to 41.5 ng/ml and those producing mental impairment are higher (58.2 to 74.4 ng/ml). The mean Cmax of DPH was 67.64 ng/ml under fasted conditions and 78.17 under fed conditions (range 29.3-184.2 ng/ml). The distribution of blood levels in the PK study as shown in the following Figure suggest that some subjects on DPH may have concentrations that can cause drowsiness even 8 hours post dosing. In addition to the inter-individual variability, there is a fair degree of intra-individual variability as well. It is also worth pointing out that not all subjects that had high concentration at 8 hours post dose reported somnolence that lasted for > 8 hours. For additional discussion see pages 17-19.



6 hours post dosing 8 hours post dosing

The numbers in this figure represent the plasma samples, not the number of subjects.

[10] Genco FM et al. Clin Pharmacol Ther, 1989. 45(1):p 15-21

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A majority of the adverse events were related to Nervous System Disorders and Gastrointestinal Disorders.
Common events in the single dose efficacy studies were nausea, headache, dizziness and vomiting. The incidences of these were similar across all treatments (combination and individual components) with the exception of dizziness which was higher in the NP440/DPH50 treatment group compared to the other treatments (4.4 vs. 3.9%). Somnolence was not observed in the single dose efficacy study, but was observed in the PK study: 38% of the subjects in NP440/DPH50 (fasted) group, 39% in the NP440/DPH50 (fed) group, 48.3% in the DPH 50 group and 6.7% in the NP440 group. The PK study was a daytime dosing study.

Common events (treatment vs. placebo) in the multiple dose safety study were headache (10.6% vs. 19.3%), somnolence (4.6% vs. 3.7%, respectively), dizziness (4.1% vs. 0%), nausea (4.1% vs. 0.9%), back pain (3.7% vs. 2.8%), diarrhea (3.2% vs. 1.8%), abdominal discomfort (2.3% vs. 1.8%), and dyspepsia (2.3% vs. 0.9%).

7.4.2 Laboratory Findings

Laboratory assessments were not done for the single dose efficacy studies. Laboratory assessments were conducted for the PK study. 5 cases of anemia and 3 cases of ALT increase were observed that could be drug related. NSAIDS are known to cause these events. The treatment-emergent abnormal values reported for ≥2% of naproxen sodium 440 mg/DPH 50 mg subjects in the multiple dose safety study and also at a higher incidence than placebo were absolute eosinophil count (2.8% vs. 0%, respectively), random glucose (5.5% vs. 2.8%), potassium (3.7% vs. 1.8%), total protein (2.3% vs. 1.8%), and uric acid (2.3% vs. 0.9%).

7.4.3 Vital Signs

Changes from baseline in systolic and diastolic blood pressure, pulse rate, and respiration rate did not show any difference in any single dose study. Vital signs were not performed for the pilot study. 0.5% (N=1) of NP440/DPH50 subjects had an abnormal vital sign parameter heart rate (101 beats/min) in the multiple dose safety study.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected in these studies.

7.4.5 Special Safety Studies/Clinical Trials

See section 7.4.1-7.4.4

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency of AEs could not be adequately established. Only one dose (NP440/DPH50) was evaluated in a multiple dose setting.

7.5.2 Time Dependency for Adverse Events

None of the AEs in the multiple dose safety study appeared time dependent.

7.5.3 Drug-Demographic Interactions

Subjects ≥60 years had higher incidence of dizziness (7.7% vs. 0% for placebo) after multiple doses of NP440/DPH compared to the younger subjects (2.6% vs. 0% for placebo).

Most subjects in the clinical trials were White and Non Hispanics, hence racial or ethnic differences in safety cannot be assessed.

7.5.4 Drug-Disease Interactions

No significant Drug-Disease interactions were observed in the studies conducted, but naproxen could cause gatstrointestinal effects (Stomach bleeding), cardiovascular and cerebrovascular effects, blood pressure effects, renal effects (fluid and electrolyte disturbances, acute renal failure). Hence any underlying disease that causes stress to these conditions can be a concern. Warning has been included in the proposed Aleve PM label.

Diphenhydramine can cause anticholinergic effects. Subjects with somnolence due to other conditions/drugs could experience enhanced somnolence with the use of DPH products.

7.5.5 Drug-Drug Interactions

The AUC and Cmax of naproxen and DPH did not change when Naproxen and DPH were taken together in the combination. The Tmax of both were increased by about 30 minutes in the combination product. No other drug interaction study has been conducted with the combination product and other drugs. Since the combination product was bioequivalent to the single components, no new drug interactions would be expected with the combination product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information for the combination product for naproxen or diphenhydramine.

7.6.2 Human Reproduction and Pregnancy Data

Naproxen is known to have possible effect on the fetal cardiovascular system. It is also in the milk of lactating mothers. Diphenhydramine has been assigned Pregnancy Category B: Animal studies have not demonstrated fetal risk. Diphenhydramine hydrochloride has been found in the milk of lactating women.

There were no reports of pregnancy in subjects in the studies conducted in support of this application for an OTC naproxen sodium 440mg/DPH 50 mg combination product. Females who reported at Screening that they were breast-feeding were excluded from the study.

Warnings similar to that of the individual products had been proposed for the combination product.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were 115 pediatrics (only 16 and 17 year olds) enrolled in the pivotal study 14837 at the proposed dose NP440/DPH50. The multiple dose safety study included 7 children ages 12-17. The efficacies in these children were not different from the adults.

Naproxen is used for juvenile arthritis in children ≥2 years and diphenhydramine is used as sleep aid in children ≥12 years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses of the combination product were reported in the multiple-dose safety study.

The sponsor provides reference to the Aleve NDA# 20-204 where non-clinical data did not indicate any abuse potential of naproxen sodium. Naproxen has no known potential of withdrawal or rebound effects. Diphenhydramine hydrochloride, possessing anticholinergic properties, has been known to be abused due to its hallucinogenic, stimulating, and euphoric effects and may also produce withdrawal syndrome characteristics after abrupt cessation of high doses.

No abuse or dependence, withdrawal or rebound on the combination product was reported during the clinical program.

7.7 Additional Submissions / Safety Issues

Additional safety issues may be discussed in the OTC review.

8 Postmarket Experience

This will be evaluated by OSE.

9 Appendices

9.1 Literature Review/References

Discussion of literature included in the review where application.

9.2 Labeling Recommendations

Consider including “Can cause Dizziness” under “when using this product” section of the labeling.

9.3 Advisory Committee Meeting

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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01/10/2014

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