

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205352Orig1s000

MEDICAL REVIEW(S)

DNP CLINICAL REVIEW

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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 rescue 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 ($\Delta = -70$ minutes) for NP440/DPH50 than for NP440 alone ($p=0.0002$). The co-primary endpoint, Sleep Latency, was significantly shorter ($\Delta = -15.9$ 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 diphenhydramine 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 al¹ (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., 2008²) but remained as high as 45% even after 12 h (Zhang et al., 2010³). 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 diphenhydramine 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 diphenhydramine 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). Diphenhydramine is also the only ingredient in many OTC sleep aid products. [See OSE review for post marketing safety of diphenhydramine 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 olopatadine and 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, methapyrilone 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 diphenhydramine. 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 ethanamine 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

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Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

	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 H₁ receptor. By blocking histamine in the capillaries, DPH reduces the intensity of allergic symptoms. It also crosses the blood-brain barrier and antagonizes the H₁ 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.

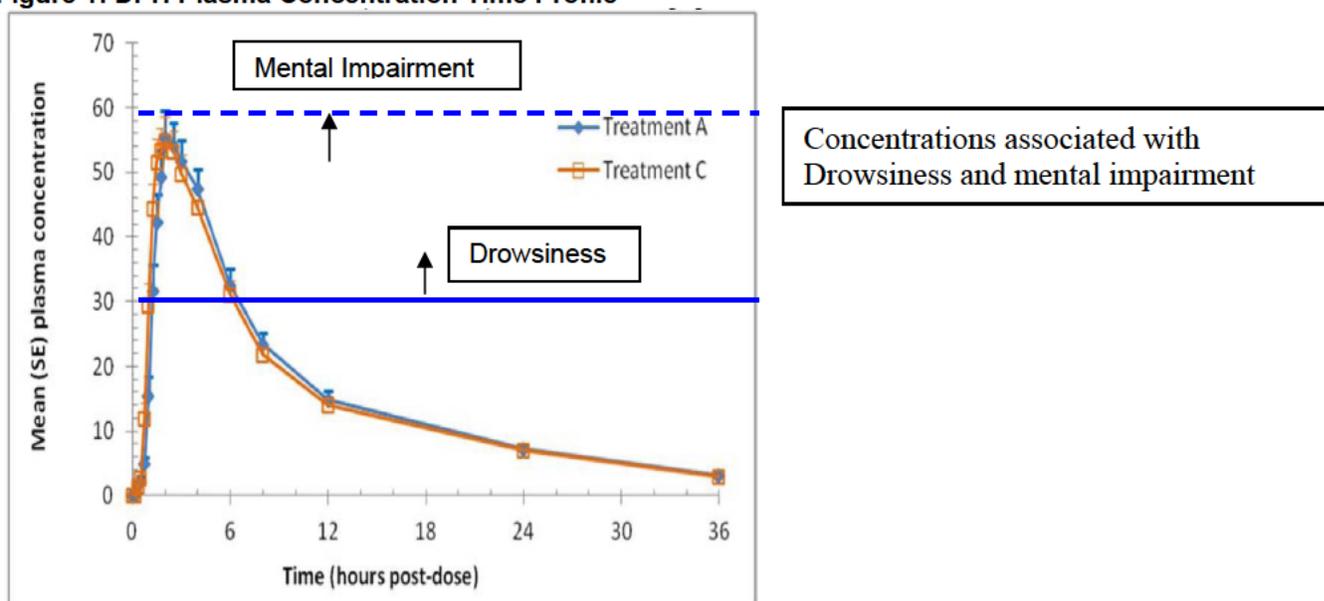
The probability of pharmacodynamic interaction between naproxen sodium and DPH is likely to be low based on their modes of action.

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 T_{max} is around 2-3 hours. Similar t_{max} was obtained for DPH in the combination in the PK study conducted by the sponsor [mean T_{max} 2.5 hours (range 1-6 hours)]. The $t_{1/2}$ of DPH reported in the literature is 9 hours in the young subjects. The mean $t_{1/2}$ 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 $t_{1/2}$ 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 diphenhydramine 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 C_{max} 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

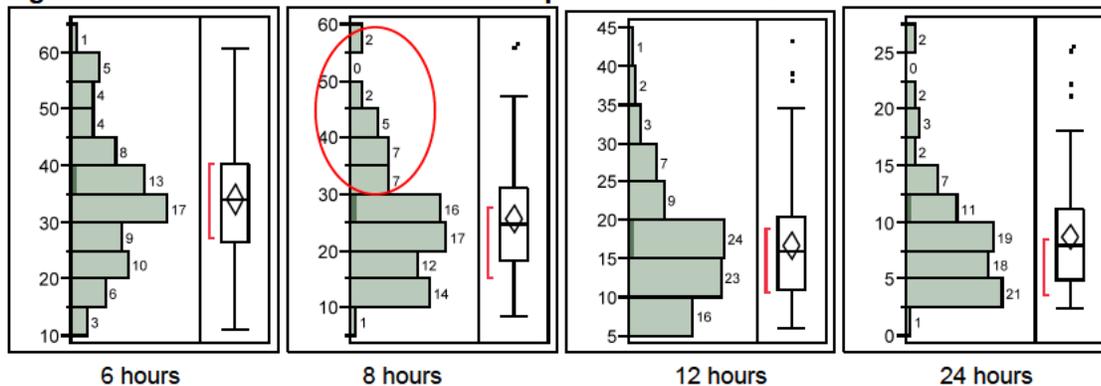


A: 2 x naproxen sodium 220 mg/DPH HCl 25 mg combination product tablets under fasted conditions

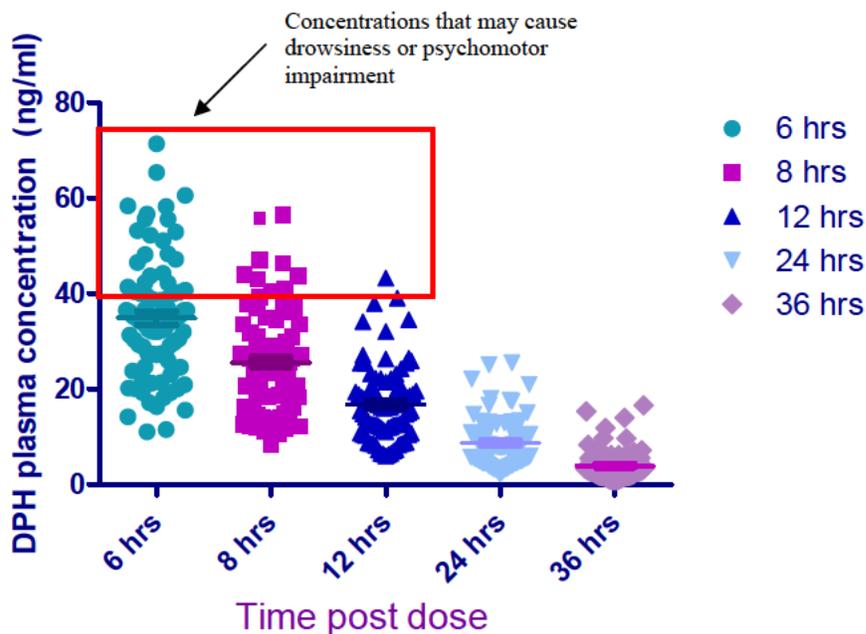
C: 2 x Allergy Relief® (DPH HCl 25 mg tablet) under fasted conditions

Genco 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 C_{max}. 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%) C_{max} and prolonged T_{max} [median (range): 3.0 (0.75 – 6.0) vs. 1.25 (0.33 – 3.0) hrs] in the presence of food. The T_{max} of DPH was similar [2.5 (1.25 – 6.0) vs. 2.5 (1.0 – 4.0) hrs]. The C_{max} 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	27	Healthy subjects, ages 16 to 45 years, with moderate to severe postoperative dental pain
			NS 220 mg + DPH 50 mg; single dose	27	
			NS 440 mg; single dose	27	
			NS 220 mg; single dose	27	
			DPH 50 mg; single dose	27	
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	203	Healthy subjects, ≥12 years of age, with moderate to severe postoperative dental pain
			NS 220 mg/DPH 50 mg; single dose	204	
			NS 440 mg; single dose	203	
			DPH 50 mg; single dose	102	
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	107	Healthy subjects, ≥12 years of age, with moderate to severe postoperative dental pain
			NS 440 mg; single dose	106	
			DPH 50 mg; single dose	54	

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.

Clinical Review

Veneeta Tandon

N205-352

Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

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/m ² 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 <i>Inpatient</i>		End of Trial
		Day 1	Day 2	within 2-5 (± 2) days
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)

Clinical Review
Veneeta Tandon
N205-352
Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

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.	
NP 440 mg	1608	Informed Consent	10	Minor subject only signed first name and last initial on informed consent form; parent signed appropriately.	
	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).

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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:

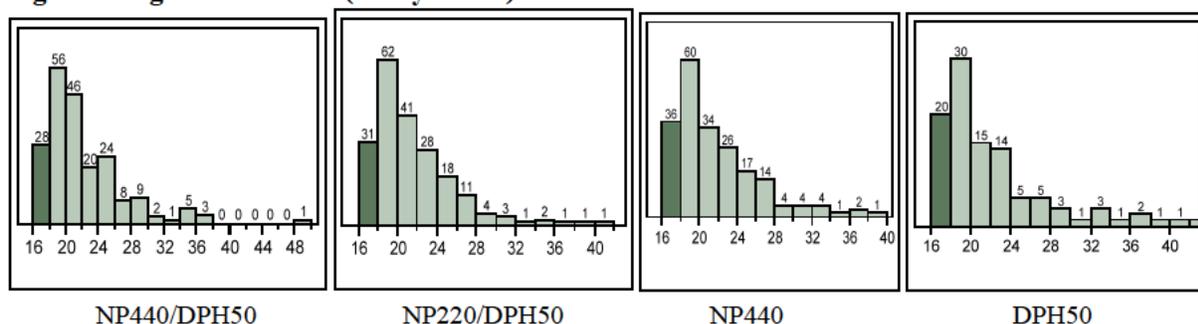
Table 8: Baseline Pain: Categorical Pain Rating Scale and Visual Analog Scale score (Safety Population) (Study 14837)

	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.

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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:

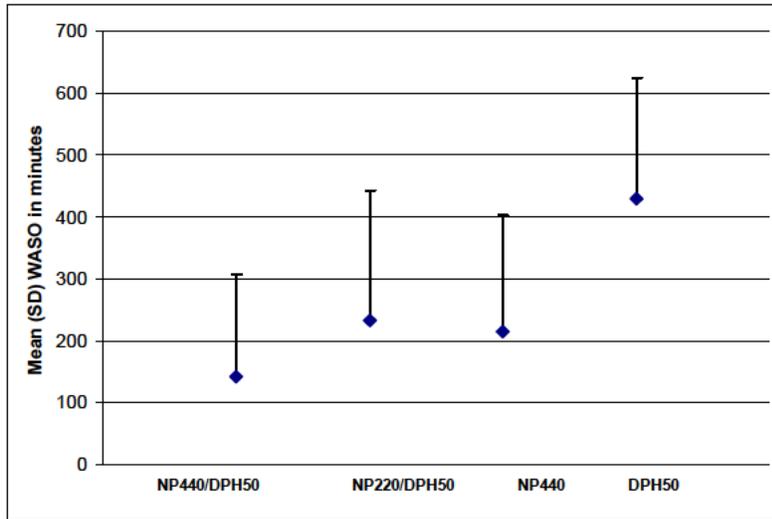
Figure 4: Mean (SD) WASO for the treatment groups (Study 14837)

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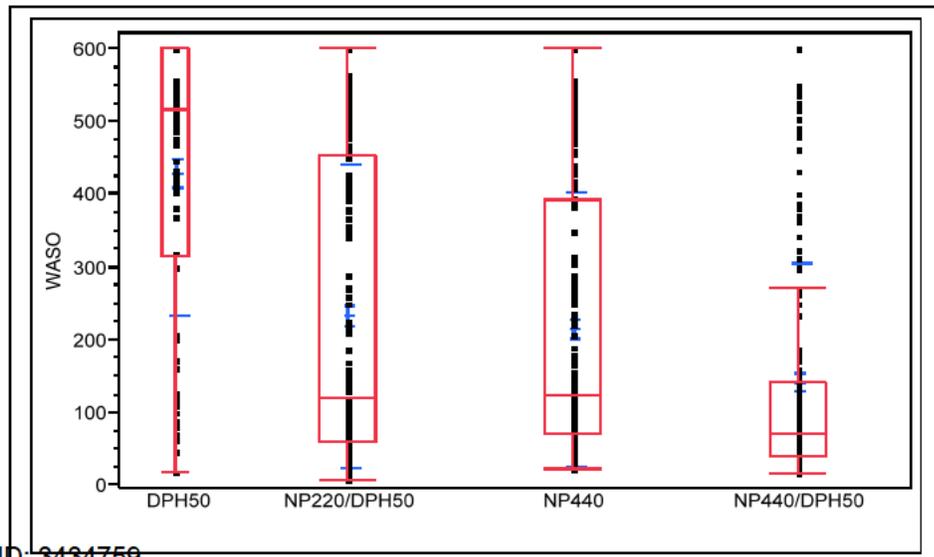
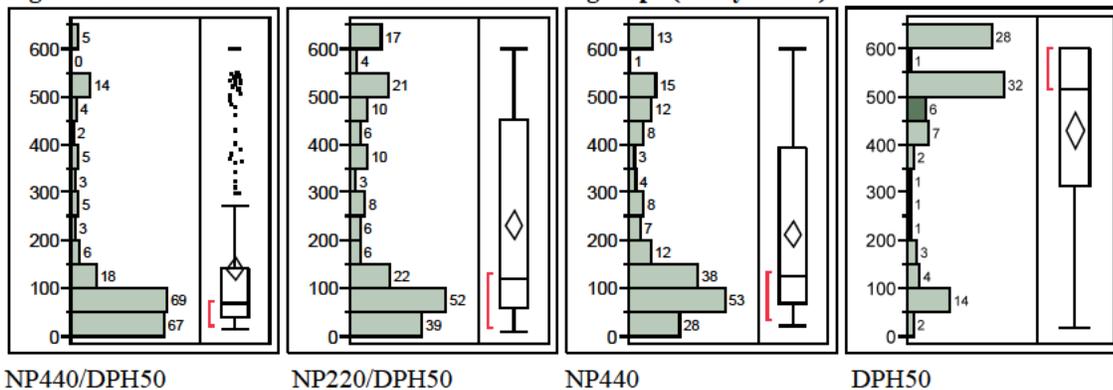
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The distribution of WASO is shown in the following Figure 5 suggesting that there are some outliers in the NP440/DPH50 group that have long WASO's similar to the other treatment groups. It also shows that the number of subjects with a WASO of 600 (counts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

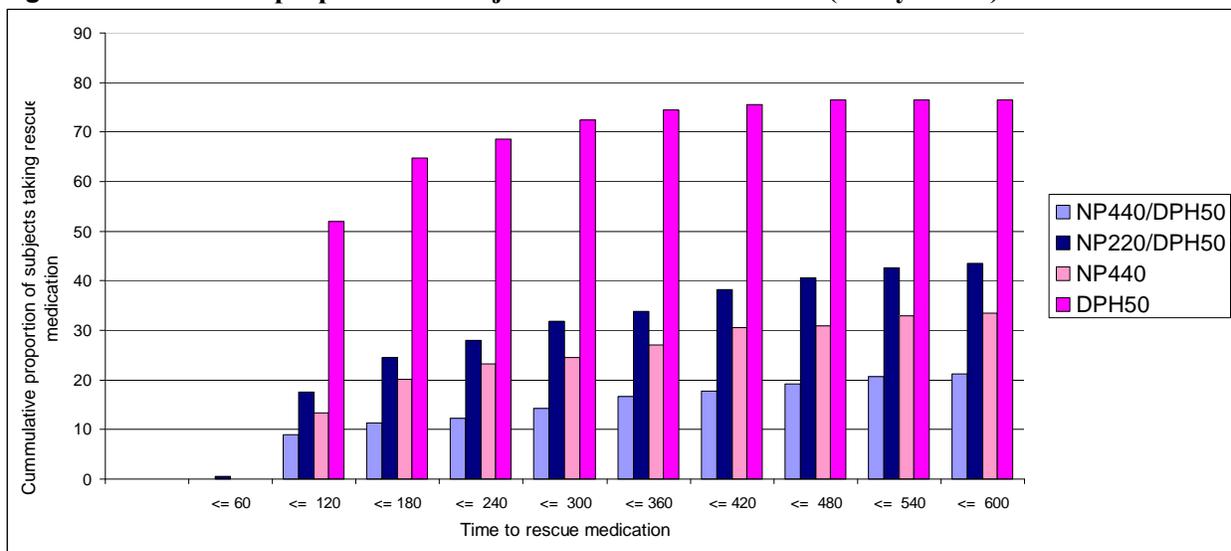
Figure 5: Distribution of WASO's in the treatment groups (Study 14837)



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 rescue 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.

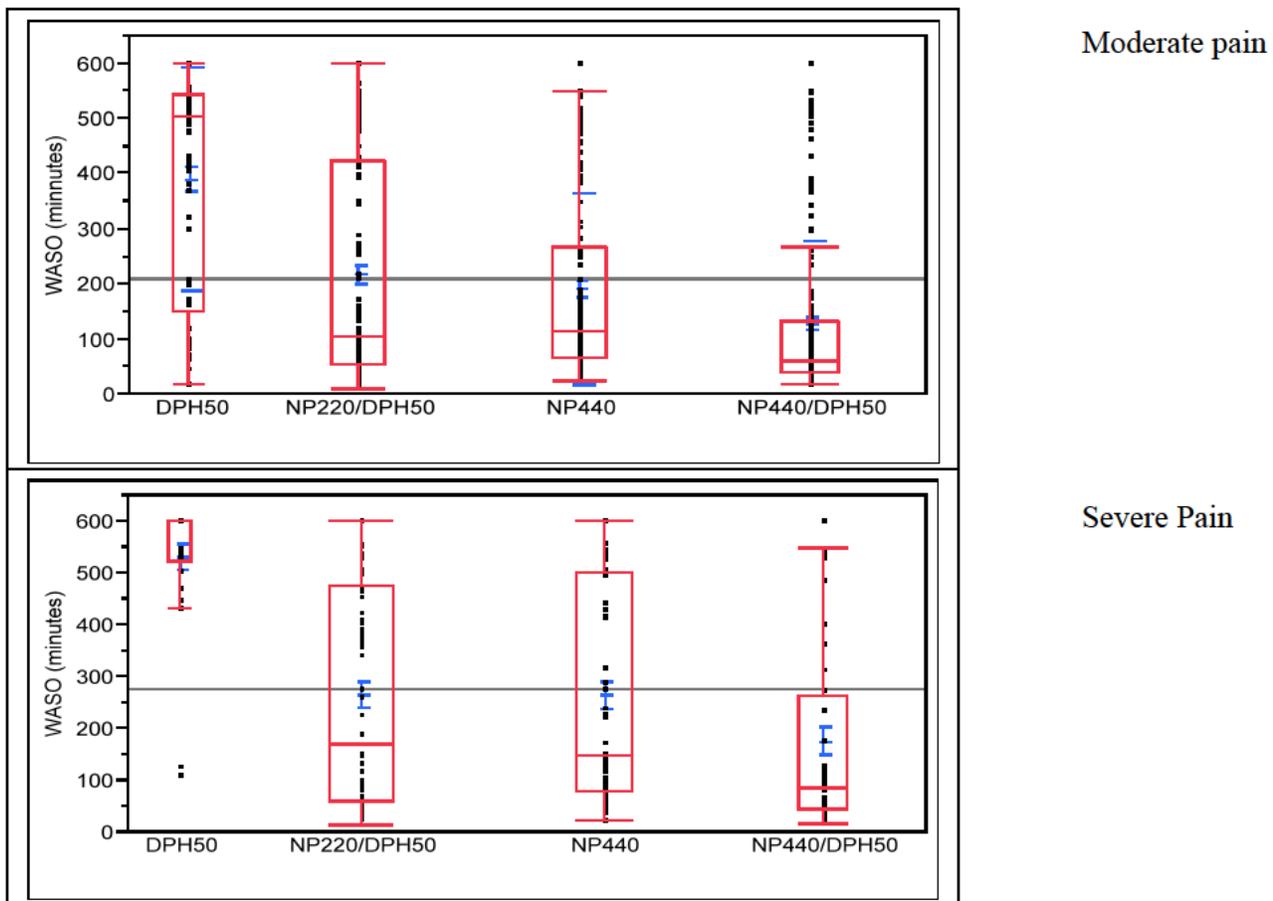
The WASO was still the shortest for the combination NP440/DPH50 followed by NP440 alone for subjects with moderate pain. For subjects with severe pain, the WASO was shortest with NP440/DPH50, but the same for the NP440 and the NP220/DPH50 group. The WASO always remained the highest with the DPH50 group. 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.

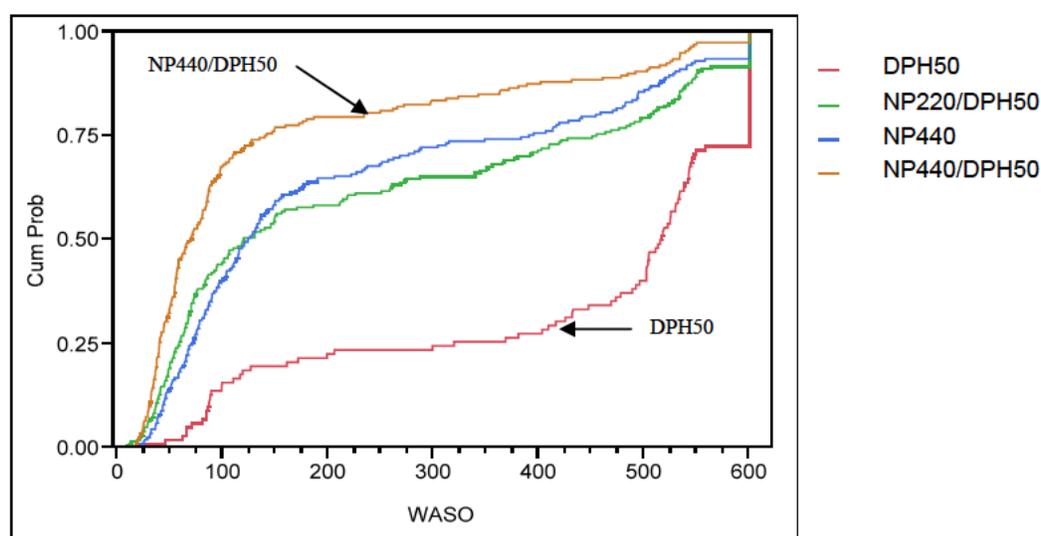
Figure 7: Box plot for WASO based on severity of pain (Study 14837)



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/DHP50 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	← Protocol Specified
NP 440 mg/DPH 50 mg versus NP 440 mg	0.4164	← Logical Comparison (see Reviewer's Discussion on page 40)
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	

^aP-value from log rank test.

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)

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

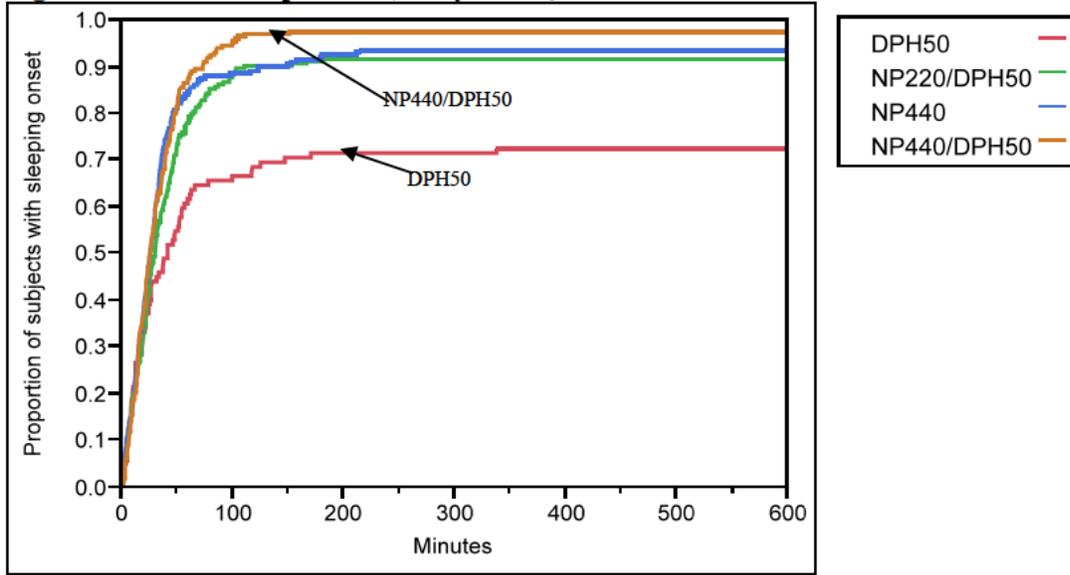
*these sensitivity analyses did not take rescue medication information into consideration when assessing efficacy results.

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.

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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 versus 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/DPH50 N=201	NP220/DPH50 N=204	NP440 N=202	DHP50 N=102	LS mean Treatment Difference P-value	
					NP440/DPH50 versus NP440	NP440/DPH50 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)

Statistic	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
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)

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

Subjects	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	(%)
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 diphenhydramine alone.

The number of subjects with TEAEs of $\geq 1\%$ 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.

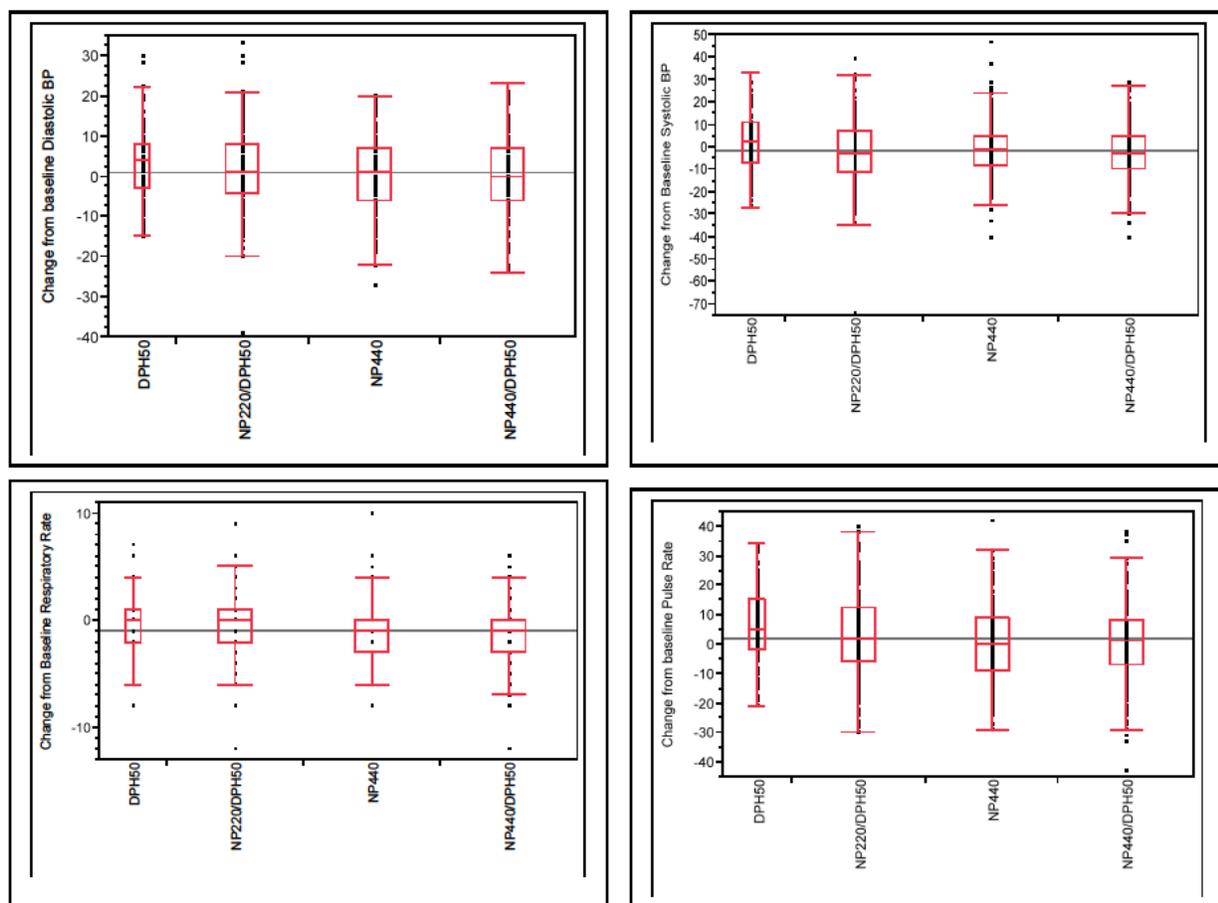
Reviewer's Comment:

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, alveolitis/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:

William L. Buchanan, MD, DDS
PPD Development, LP (PPD Dental Pain Research Clinic) (Study Site 14001)
7551 Metro Center Drive, Suite 200, Austin, TX 78744

Lynn R. Webster, MD
Lifetree Clinical Research (Study Site 14002)
3838 South 700 East, Suite 202, Salt Lake City, UT 84106

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		
<i>P-value</i>	0.3047		

^aP-value from ANCOVA model including treatment and center as fixed effects and baseline categorical pain score as the covariate.

^bPairwise 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		NP 440 mg N = 106		DPH 50 mg N = 54	
	n	(%)	n	(%)	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.

Clinical Review

Veneeta Tandon

N205-352

Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

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)

Statistic	Treatment Group					
	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54	
	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 diary 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			
<i>How was your sleep?</i>	3.5 (0.85) ^{d, e}	3.3 (1.01)	2.8 (1.26)
<i>How calm was your sleep?</i>	3.4 (0.99) ^e	3.1 (0.98)	2.9 (1.23)
<i>How easy was it to fall asleep?</i>	3.2 (1.08)	3.0 (1.14)	2.9 (1.23)
<i>Premature awakening?</i>	2.1 (0.75) ^e	1.9 (0.69)	1.8 (0.85)
<i>Ease of awakening?</i>	4.1 (0.69) ^e	4.0 (0.85)	4.3 (0.86)
<i>Well Rested?</i>	2.3 (0.61) ^e	2.3 (0.62)	2.0 (0.79)
<i>Did you get enough (sufficient) sleep?</i>	3.8 (0.93) ^{d, e}	3.5 (1.21)	2.8 (1.46)
Sleep questionnaire ^b			
<i>How would you rate the quality of your sleep?</i>	6.5 (1.95) ^{d, e}	5.8 (2.11)	4.9 (3.04)
<i>How would you rate the refreshing nature of your sleep?</i>	6.6 (2.15) ^{d, e}	5.7 (2.20)	4.6 (2.85)
<i>Estimate how long it took you to fall asleep?</i>	39.5 (36.63)	40.2 (38.10)	40.0 (42.66)
<i>Estimate the number of minutes you were awake?</i>	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 rdit score); <i>P</i> -values are provided		
^b	Subjective Sleep Questionnaire as mean (standard deviation) by treatment group (Cochran-Mantel-Haenszel test controlling for center with modified rdit score); <i>P</i> -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 rdit score); <i>P</i> -values are provided		
^d	Statistically significant (<i>P</i> <0.05) versus NS 440 mg		
^e	Statistically significant (<i>P</i> <0.05) versus DPH 50 mg		
^f	Statistically significant (<i>P</i> <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		NP 440 mg		DPH 50 mg		Total	
	N = 107		N = 106		N = 54			
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 diphenhydramine alone. All TEAEs were mild in severity.

The number of subjects with TEAEs of $\geq 1\%$ is given in Table 41.

Table 41: Incidence of TEAEs (Study 15881)

Preferred Term	NP440/DPH25	NP440	DPH50
	N=107	N=106	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 (\pm) 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

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Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

- 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

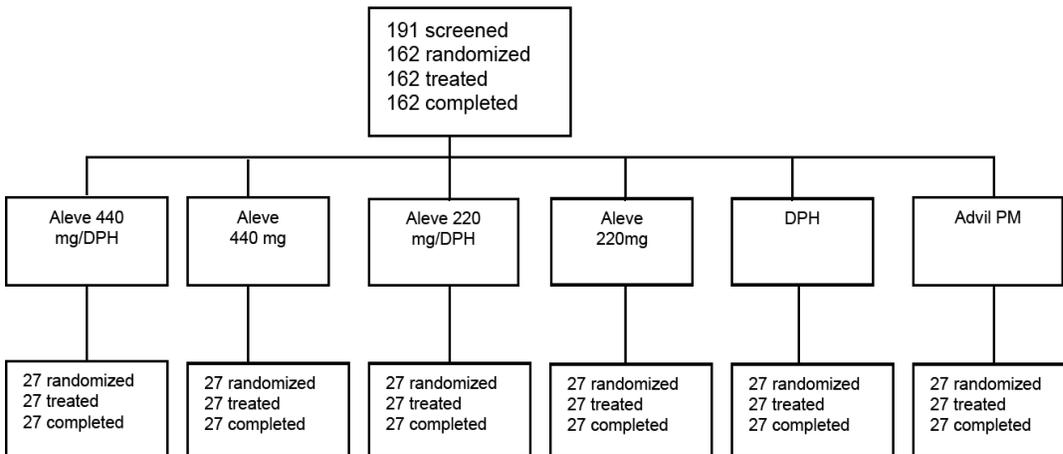
Subject Disposition: Subject disposition is shown in the following Figure:

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Aleve PM (naproxen sodium+diphenhydramine hydrochloride)



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 waking (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)

Hour	Aleve 440mg /DPH N=27 n (%)	Aleve 440mg N=27 n (%)	Aleve 220mg /DPH N=27 n (%)	Aleve 220mg N=27 n (%)	DPH N=27 n (%)	Advil PM 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 N = 27	NS 440 mg N = 27	NS 220 mg/ DPH 50 mg N = 27	NS 220 mg N = 27	DPH 50 mg N = 27	Advil PM 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)

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	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 $\geq 5\%$ 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 $\geq 2\%$ 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 ($\geq 2\%$ 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

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		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 ($\geq 5\%$ 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 $\geq 5\%$ 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

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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 quadriceps 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.

Clinical Review

Veneeta Tandon

N205-352

Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

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 $\geq 2\%$ 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 ($\geq 2\%$ 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	Treatment B	Treatment C	Treatment D	Overall
	(N=29)	(N=30)	(N=29)	(N=28)	(N=32)
	n (%)	n (%)	n (%)	n (%)	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%)	

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Veneeta Tandon

N205-352

Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

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	11.5-15.6 34.5-46.5 for females
	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	-	
140011023	Hgb(g/dL)	11.1	10.2	10.1	9.7	9.5	
	HCT (%)	33.1	31.0	30.	29.2	28.8	
140011028	Hgb(g/dL)	12.1	10.2	10.2	10.7	-	
	HCT (%)	37.4	30.7	31.4	33.8		

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Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

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 ($\Delta=-70$ 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

Study Medication	Number of Subjects					Total
	Study 13053	Study 14837	Study 15881	Study 15660	Study 16135	
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				Total
	Study 13053	Study 14837	Study 15881	Study 15560	
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	Study15881
	(N=712)	(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:

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Veneeta Tandon

N205-352

Aleve PM (naproxen sodium+diphenhydramine hydrochloride)

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 ($\Delta = -70$ 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		
	<u>Study 14837</u>		<u>Study 15881</u>
	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 Study 15881, 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 ($\Delta = -15.9$ 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)
2. With imputed values for subjects that took rescue medication	25.5 vs. 33.5 mins p=0.0016 (N=201 vs. 102)	-	23.5 vs. 26.25 mins p=0.5100 (N=107 vs. 54)

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 the NP220/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 Questionnaire (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 \geq 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 presyncope 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	≥ 1 day	450	14837, 16135, 15560
NS 440 mg/DPH 50 mg	>1 to 12 days	217 ^b	15560
NS 440 mg/DPH 50 mg	1 day	233	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

^aCommercially available products administered together

^bOne 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		
	NS 440 mg/ DPH 50 mg (N = 217)	Placebo (N = 109)	Total (N = 326)
Exposure Duration (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
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:

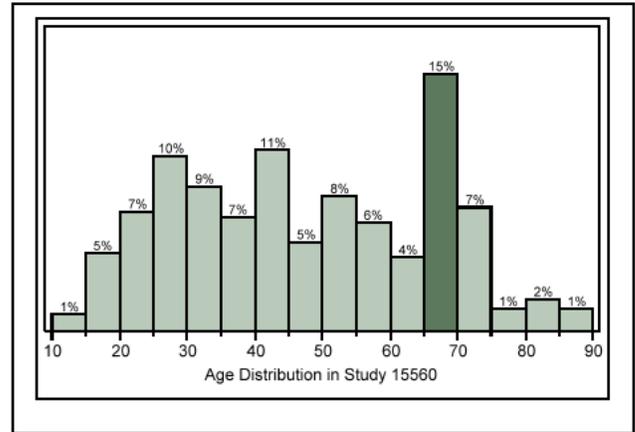
The single dose studies enrolled younger subjects than the multiple dose study. The enrollment criteria were 12-48 years in these studies. There were 59 adolescents (16 years of age) in Study 14837 and 24 (2 of 12 years, 4 of 13 years, 5 of 14 years and 13 of 16 years of age) in Study 15881. The multiple 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 years (SD)	Gender	Race ^a
			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		Total (N = 326)
	NS 440 mg/ DPH 50 mg (N = 217)	Placebo (N = 109)	
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.

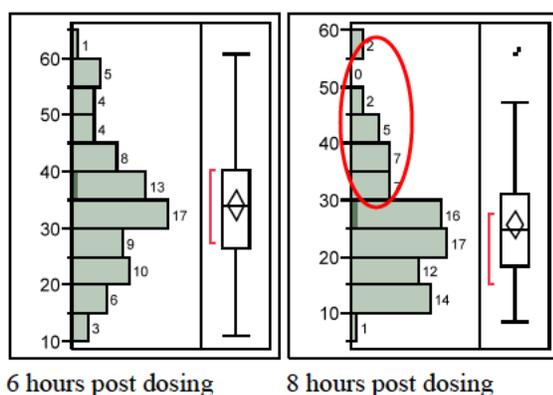
7.3.4 Significant Adverse Events

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 dosing in the PK study. Genco et.al¹⁰ 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 C_{max} 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.



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 $\geq 2\%$ 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 gastrointestinal 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/

VENEETA TANDON
01/10/2014

RONALD H FARKAS
01/10/2014

ERIC P BASTINGS
01/12/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205352
Priority or Standard	Standard
Submit Date(s)	March 20, 2013
Received Date(s)	March 21, 2013
PDUFA Goal Date	January 17, 2014
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Linda Hu
Review Completion Date	December 14, 2013
Established Name	Naproxen Sodium 220 mg/ Diphenhydramine HCl 25 mg
(Proposed) Trade Name	Aleve PM
Therapeutic Class	analgesic / sleep aid
Applicant	Bayer HealthCare
Formulation(s)	Caplets
Dosing Regimen	2 caplets at bedtime
Indication(s)	--Relief of occasional sleeplessness when associated with minor aches and pains --Helps you fall asleep and stay asleep
Intended Population(s)	12 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The review of the safety data submitted for Aleve PM, a fixed combination consisting of naproxen sodium (NS) 220 mg/diphenhydramine (DPH) 25 mg tablets, did not find safety issues that would preclude OTC approval. Safety information was reviewed covering both active drug ingredients, over various time periods depending on the database, but extending to 1969 for DPH from FAERS and to 2003 for NS from DAWN. This safety review included postmarket data from the Bayer Global Pharmacovigilance Database, the FDA FAERS database, the WHO Vigibase system, the Drug Abuse Warning Network (DAWN) database of hospital emergency department (ED) visits, the American Association of Poison Control Centers (AAPCC) database, and the published literature. The safety and efficacy results from the clinical trials including the pivotal trial (Study 14837: 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) are reviewed separately by Dr Tandon.

Naproxen, as an NSAID, is one of the most widely used drugs. In an average week of 2006, in the US, ~ 43 million adults took acetaminophen, 41 million took aspirin, 39 million took ibuprofen and 11 million took naproxen. Likewise DPH, a sedating antihistamine, is also among the most widely used drugs with over 70 million bottles/packages (single or combination products) sold OTC in 2007. DPH is allowed under the final monograph for sleep-aid products and for antihistamine (cough, cold, allergy) drug products.

Given the extremely widespread use of naproxen and diphenhydramine, even uncommon adverse events can yield detectable signals in postmarket databases. The postmarketing drug safety databases FAERS and WHO, and the DAWN and AAPCC databases from emergency departments and poison control centers, respectively, show that DPH poisonings are common, but that DPH is relatively non-toxic except in large overdoses. The serious or fatal cases of DPH toxicity are predominantly intentional overdoses or suicides.

The safety review shows that DPH-containing products are associated with accidents, misuse/abuse, suicide attempts, and both intentional and unintentional overdoses; however, the frequencies of these events are within proportion to the sales of these products. The association of DPH with suicides, misuse/abuse, and overdoses is not disproportionate to the sales of DPH products, when compared to other OTC drugs for the same indications. The rates of misuse and abuse ED visits relative to sales are higher for chlorpheniramine + acetaminophen combination products than for DPH-

containing products, but lower for DPH + ibuprofen combinations than for all DPH-containing products.

Independent analyses, using different methodologies, of the FAERS database performed by the Sponsor and by FDA OSE, additionally revealed an association between DPH used as a sleep aid and accidents. There were, however, relatively few cases considering the extent of use of DPH, and there was not an association with road traffic accidents.

The safety review also re-affirmed known risks of NSAIDs including naproxen. An expert opinion panel report in the literature stated that use of NSAIDs (including OTC doses) is associated with bronchospasm in aspirin-sensitive asthmatics. NSAID use at OTC doses is further associated with: elevated BP in hypertensive patients (moderate evidence for IBU and naproxen) and peptic ulcer disease. Data were inadequate to favor acceptance or rejection of a causal relation between naproxen and MI.

Available observational studies of stroke risk from NSAIDs suggest that stroke risks vary for different NSAIDs. Rofecoxib and diclofenac are associated with increased stroke risk versus non-use of NSAIDs, but not naproxen or ibuprofen.

In conclusion, while DPH is generally considered to have a wide safety profile, the use of DPH is also associated with misuse/abuse, suicide attempts, and both intentional and unintentional overdoses, but the frequencies of these events are not large compared to the sales of DPH products. DPH use as a sleep aid is associated with occurrence of accidents, but again the numbers of such events are not large considering the widespread use of DPH. There are known risks associated with use of NSAIDs including naproxen, but the safety review did not find new or unexpected events. This review did not find safety issues for either DPH or NS that would preclude approval of this NDA.

1.2 Risk Benefit Assessment

The applicant, Bayer HealthCare Consumer Care (Bayer), is filing this New Drug Applicant for Aleve PM, an analgesic/sleep-aid, fixed-combination of naproxen sodium (NS) 220 mg and diphenhydramine hydrochloride (DPH) 25 mg per tablet. This product is for relief of occasional sleeplessness when associated with minor aches and pains. The OTC dose for adults and children 12 years of age and over is two tablets before bedtime for no more than 10 consecutive days. Aleve PM would be the first OTC nighttime analgesic/sleep-aid available in the US to combine naproxen sodium with DPH for the relief of occasional sleeplessness associated with minor aches and pains.

Combining naproxen sodium and DPH into a single OTC product provides added benefit over the individual ingredients taken alone: it provides the convenience of taking a single medication for the relief of occasional sleeplessness associated with minor aches and pains.

DAWN data suggest that 1.4% of all misuse and abuse ED visits (2004 through 2011) were associated with DPH, and 7.6% of all suicide attempt ED visits were associated with DPH. DAWN reported 15143 ED visits involving DPH over the 4 yr period 2006-9, averaging 3786 visits per yr and steadily increasing over that time. In the DAWN database there were 1098 reportable deaths associated with DPH between 2004 and 2011 from 13 states.

AAPCC reported 277322 exposures to DPH over the 8 yr period 2004-2011, an average of 34665 cases per year, of which there were 346 deaths (average 43 deaths per year). WHO reported 5969 cases over the 9.16 year period 1/2004 to 2/2013, for an average of 652 DPH reports per yr, including 2355 deaths (average 257 deaths per yr). The Bayer database returned 425 fatal reports involving DPH, of which 411 reports (97%) were suicides, drug overdoses, or abuse/misuse reports. Suicides and intentional overdoses combined accounted for 71% of Bayer death reports. DPH was the most common substance detected in lethal amounts among 397 completed suicide overdose cases in Toronto, CA, present in ~14% of all overdose suicides between 1998 and 2007.

Although DPH-containing products are associated with misuse/abuse, suicide attempts, and both intentional and unintentional overdoses, the frequencies of these events are not disproportionate to the sales of DPH products, when compared to other OTC drugs for some of the same indications. Per 10000 bottles/packages sold in 2010, there were 6.18 ED misuse and abuse visits for DPH single ingredient and 9.95 for DPH + acetaminophen combination products; these rates are comparable to each other. The rates of these ED visits relative to sales are higher for chlorpheniramine + acetaminophen (12.59 ED visits per 10000 bottles/packages sold) compared to DPH products, but lower for DPH + ibuprofen (2.23 ED visits per 10000 bottles/packages sold) compared to all DPH products.

The FAERS database additionally reveals an association between DPH used as a sleep aid and accidents. Independent analyses were performed by the Sponsor and by FDA OSE to search for evidence of accidents after use of DPH as a sleep aid. OSE found that, based on data mining analyses, DPH is associated with accidents (EB05=4.8) but not with road traffic accidents. The FAERS search for accident cases found only 37 reports January 1, 1969 – July 10, 2013. The Sponsor performed a search of FAERS over a different period 1 Jan 2004 through 31 Dec 2011, using the Accidents and Injuries Standard Medical Query (AI SMQ), and finding 54 cases with DPH used as a sleep aid and with events in the AI SMQ. There were increased reporting rates for falls and head injuries among those using DPH as a sleep aid versus those using DPH for other indications, although the numbers are small. There was not an increased reporting rate for road accidents.

Hence the FDA and Sponsor analyses agree that use of DPH as a sleep aid is associated with accidents, but the numbers of events are small. The Federal Aviation Administration Office of Aerospace Medicine toxicology database, for pilots who died in aviation accidents from 2004-2008, found that DPH is the most commonly found drug in 1353 pilots who died in aviation accidents. DPH is found in 6.1% of pilot fatalities from 2004-2008, a percentage which has increased from 1.7% for 1989-1993. The FAA is re-evaluating guidelines to determine when it is safe for pilots to return to duty after taking DPH, because reliance on half-life dosing recommendations “may be inadequate when considering the potential duration of medication levels that may compromise aviation performance”.

There are many literature reports on objective psychometric and neurophysiologic tests after day-time dosing of DPH which generally show performance impairment for time periods up to 2-4 hrs after dosing. The objective measures do not necessarily correlate with the subjective drowsiness measurements, and test methods have not been standardized. Most studies report an increase of subjective drowsiness with DPH. Results of objective performance testing after DPH are inconsistent. Some studies did not find significant impairment beyond 4 hours after dosing by one or more objective measures, but other studies (for instance Katayose et al. 2012) found impairment on objective tests beyond 9 hours for DPH but not zolpidem. Subjective drowsiness is generally reported up to 8 hours post-dose.

For naproxen sodium, the DAWN database showed that ED visits in 2010 mainly involved single ingredient NS (85% of ED visits), with the NS-lansoprazole (PPI) combination accounting for 13.4% of visits. For NS, DAWN gives almost six times more visits involving adverse reactions (65.6%) than suicide attempt (11.8%), contrasting with DPH which is more often involved with suicide attempt.

The safety literature update included a published expert opinion (Lavonas et al. 2012) on comparative risks of non-prescription analgesics. This report was a consensus opinion issued after review of 1111 literature citations, but not a formal meta-analysis which was not attempted because of the large heterogeneity of the NSAIDs safety literature. There were eight topic areas of adverse events considered: pulmonary, renal, cardiovascular I (death + myocardial infarction (MI)), cardiovascular II (congestive heart failure, hypertension, stroke), hepatic, gastrointestinal, pregnancy outcomes and malignancy.

The expert opinion panel reached consensus on 8 adverse effects from non-prescription NSAID use: bronchospasm in asthmatics (high quality data); acute kidney injury (very low quality for non-prescription doses, high quality at greater doses); MI for IBU only (low quality); elevated BP in hypertensive patients (moderate quality for IBU and naproxen); peptic ulcer disease (moderate quality); miscarriage, congenital anomalies, and preterm birth (all low quality). The panel stated that data are inadequate to favor acceptance or rejection of a causal relation between naproxen and MI (low quality

evidence). In addition, the expert opinion panel reached consensus on three more risks from NSAIDs at prescription dosing levels: chronic kidney disease, new onset hypertension, and CHF, all at moderate quality of evidence.

Varas-Lorenzo¹ et al. 2010 reported on a meta-analysis of observational studies on the risk of stroke associated with the use of individual NSAIDs. Observational cohort or case-control studies were selected that reported on the risk of cardiovascular events associated with use of individual NSAIDs versus nonuse of NSAIDs. There were a total of 6 studies selected that reported relative risk (RR) of stroke, in study populations that totaled over 1.2 million people in the US and Europe. The observational studies were all completed prior to withdrawal of rofecoxib (reducing bias by contraindication to cardiovascular high risk subjects). It was concluded that the evidence on stroke risk from individual NSAIDs is still limited. Rofecoxib and diclofenac are associated with increased stroke risk versus non-use of NSAIDs, but not naproxen or ibuprofen. Stroke risks differ across individual NSAIDs.

Hernandez² et al. 2012 performed a case-control surveillance study using the National Birth Defects Prevention Study (NBDPS) to search for an association between use of NSAIDs in the first trimester of pregnancy with a range of structural birth defects. The NBDPS enrolled 14915 birth defect cases (live or still births with eligible birth defects) and 5546 controls (with no major defects, selected from the same population of women in 10 states). Of the pregnant women enrolled in the study (cases + controls), there were 22.6% who reported use of an NSAID in the first trimester (most often ibuprofen, aspirin or NS). The analysis focused on oral, single component NSAID use.

The NBDPS study found a small to moderate association between NSAID use and specific birth defects. Association was observed for anophthalmia/microphthalmia with adjusted ORs of 3.0 (95% CI 1.3-7.3) for aspirin, 1.9 (95% CI 1.1-3.3) for ibuprofen, and 2.8 (95% CI 1.1-7.3) for naproxen. Small to moderate association with naproxen exposure was also observed for cleft lip+/- cleft palate and transverse limb deficiency. The use of NSAIDs in early pregnancy does not appear to be a major risk factor for birth defects. Naproxen is moderately associated with specific defects including cleft lip. Existing NSAID warnings adequately inform consumers about use.

Combining naproxen sodium and DPH into a single OTC product provides the convenience of taking a single medication for the relief of occasional sleeplessness associated with minor aches and pains. While DPH is generally considered to have a wide safety profile, the use of DPH is also associated with misuse/abuse, suicide attempts, and both intentional and unintentional overdoses, but the frequencies of these events are not large compared to the sales of DPH products. DPH use as a sleep aid is

¹ Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidem Drug Saf.* 2011. 20:1225-36

² Hernandez RK, Werler MM, Romitti P, et al. Nonsteroidal anti-inflammatory drug use among women and the risk of birth defects. *Am J Obstet Gynecol.* 2012. 206:228.e1-8

associated with occurrence of accidents, but again the numbers of such events are not large considering the widespread use of DPH. There are known risks associated with use of NSAIDs including naproxen, but the safety review did not find new or unexpected events. This review did not find safety issues for either DPH or NS that would preclude approval of this NDA.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

none

1.4 Recommendations for Postmarket Requirements and Commitments

none

2 Introduction and Regulatory Background

2.1 Product Information

The product Aleve PM is a fixed-combination night time analgesic/sleep-aid in tablet form, where each tablet contains naproxen sodium (NS) 220 mg and diphenhydramine hydrochloride (DPH) 25 mg. This OTC drug product will be indicated for the relief of occasional sleeplessness when associated with minor aches and pains. The label directions, for adults and children 12 years of age and over, are to take 2-tablets before bedtime for no more than 10 consecutive days.

Naproxen sodium is a proprionic acid derivative of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Approved under NDA 20-204 on January 11, 1994 as an OTC analgesic/antipyretic, each naproxen sodium 220 mg tablet contains 200 mg of naproxen. It is dosed as 1 tablet every 8 to 12 hrs while symptoms last. For the first dose, 2 tablets may be taken within the 1st hour. Do not exceed 2 tablets in any 8-12 hr period, or 3 tablets in 24 hrs. Diphenhydramine is a first-generation ethanolamine antihistamine. Diphenhydramine hydrochloride is available OTC for allergic rhinitis at a dose of 25 to 50 mg every 4-6 hours, not to exceed 300 mg in 24 hours, or as directed by a doctor. The OTC Monograph allows 50 mg diphenhydramine hydrochloride and 76 mg diphenhydramine citrate as a nighttime sleep-aid. The OTC marketplace has available similar combination products that contain an analgesic and diphenhydramine. Examples of these are listed in section 2.2 in Table 1 below.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently available OTC analgesic/sleep-aid combination products marketed in the US include Tylenol® PM, Excedrin® PM, Advil® PM, Motrin PM®, and Bayer® PM, all of which contain diphenhydramine as the sleep-aid component combined with acetaminophen, ibuprofen, or aspirin as the analgesic component.

Table 1 Available OTC Analgesic and Diphenhydramine Combination Products

Product	Analgesic	Diphenhydramine	Dosing for ≥ 12 years of age
Tylenol PM caplet & geltab	Acetaminophen 500 mg	DPH* HCl 25 mg	2 caplets or geltabs at bedtime
Excedrin PM caplet & gelcap	Acetaminophen 500 mg	DPH citrate 38 mg	2 caplets or geltabs at bedtime
Advil PM liquigel	Ibuprofen 200 mg	DPH HCl 25 mg	2 liquigels at bedtime
Advil PM caplet	Ibuprofen 200 mg	DPH citrate 38 mg	2 caplets at bedtime
Bayer PM caplet	Aspirin 500 mg	DPH citrate 38 mg	2 caplets at bedtime

*DPH: diphenhydramine

2.3 Availability of Proposed Active Ingredient in the United States

DPH is marketed for OTC use as a Nighttime Sleep-Aid under the monograph (21 CFR 338.10). The OTC Monograph labels 50 mg diphenhydramine hydrochloride and 76 mg diphenhydramine citrate as a sleep-aid. DPH is also marketed under the Cold, Cough, and Allergy Final Monograph for OTC Antihistamine Drug Products. The oral dosage for diphenhydramine hydrochloride when used as an antihistamine is 25 to 50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours, or as directed by a doctor in adults and children 12 yrs of age and over; the oral dosage for diphenhydramine citrate is 38-76 mg every 4 to 6 hours, not to exceed 456 mg in 24 hours.

Dimenhydrinate is the chlorotheophylline salt of DPH, containing about 55% DPH and about 45% 8-chlorotheophylline. The active moiety of dimenhydrinate is DPH. Dimenhydrinate is also covered by the monograph as an antiemetic and is used for motion sickness.

NS is approved for OTC marketing as a single ingredient and in combination with pseudoephedrine.

2.4 Important Safety Issues With Consideration to Related Drugs

First-generation antihistamines more readily cross the blood brain barrier than second generation antihistamines, and are known to have sedating effects, which underlie the use of DPH as an OTC sleep-aid. However, published literature has suggested that such effects may impair the performance of complex, multifaceted tasks. The evidence primarily comes from studies conducted in subjects with allergic rhinitis, for which first-generation antihistamines can be taken around the clock by adults and children 12 years and older (e.g., DPH 25 to 50 mg every four to six hours).

Naproxen is a nonselective NSAID, a non-selective inhibitor of cyclooxygenase (COX), affecting both COX-1 and COX-2 isoenzymes. The most common adverse reactions involve the upper gastrointestinal tract. The risk of more severe gastrointestinal events such as ulceration, perforation or GI hemorrhage increases with increased duration of therapy and higher doses. The NSAIDs are also associated with renal adverse drug reactions. These agents may cause renal impairment, particularly when combined with other potentially nephrotoxic agents such as diuretics or ACE inhibitors. NSAIDs may increase the risk of cardiovascular events, stroke and congestive heart failure. COX-2 selective and nonselective NSAIDs have been linked to increases in the number of serious and potentially fatal cardiovascular events, such as myocardial infarctions and strokes. An advisory committee meeting in February 2014 will discuss whether naproxen may be associated with a lesser risk of cardiovascular events than the other NSAIDs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Interactions between FDA and Bayer regarding the development program for this combination product include the following discussion points:

Pre-IND meeting on February 10, 2009:

- A study to compare the naproxen 220 mg/ DPH 50 mg combination dose to 220 mg naproxen alone and to 50 mg DPH alone would be acceptable. If Bayer decided to continue development of naproxen 440 mg/DPH 50 mg, a study that included two combinations, naproxen 220 mg/DPH 50 mg and naproxen 440 mg/DPH 50 mg (with appropriate controls), would be acceptable.
- Two confirmatory phase 3 clinical trials are needed to support efficacy for the indication sought.
- Two co-primary endpoints were agreed upon:
 - WASO (wake after sleep onset) by actigraphy (NS/DPH vs. NS)
 - Sleep latency by actigraphy (NS/DPH vs. DPH)
- Pharmacokinetic data will be needed to assess food effect of this novel combination.

The two co-primary endpoints would be assessed using phase-advanced sleep testing: sleep latency and wake onset after sleep (WASO) in subjects who have undergone dental surgery and report at least moderate pain intensity. The sponsor expects naproxen sodium in the combination primarily to help consumers with pain fall asleep (affecting latency), and DPH would primarily work to keep consumers with pain stay asleep (affecting WASO).

Advice Letter sent on June 10, 2009:

- Amended the discussion as reflected in the meeting minutes for the 2009 Pre-IND meeting to indicate that actigraphy would be acceptable for evaluating sleep in the proposed dental pain/sleep phase advance study.

IND submission on November 25, 2009:

- Phase 3 protocol# 14837 submitted for special protocol assessment (SPA)
- Bayer's proposed analysis for dose selection:
 - NS 440 mg/DPH 50 mg would need to trend better than NS 220 mg/DPH 50 mg for either sleep latency or WASO to be the chosen dose.
 - NS 220 mg/DPH 50 mg would be chosen if it is equal to NS 440 mg/DPH 50 mg for either sleep latency or WASO.

SPA non-agreement letter sent on January 8, 2010:

- FDA recommended that Bayer include a treatment arm to assess NS 220 mg/DPH 25 mg to the four proposed treatment arms (NS 440 mg/DPH 50 mg, NS 220 mg/DPH 50 mg, NS 440 mg, DPH 50 mg).

Type A meeting on September 7, 2010:

- FDA did not agree with Bayer's rationale not to assess NS 220 mg/DPH 25 mg in study #14837. Bayer agreed to consider another trial in the clinical program to assess the lower-dose combination.
- Given that the pivotal efficacy trials will predominately enroll adolescents and young adults, the subjects enrolled in the multiple dose safety study should include older adults with reasonable representation from the expected target population of the product.
- A driving study will not be required to assess next-day residual effect of DPH.

Advice Letter dated December 27, 2010 in response to Bayer's request for clarification sent on October 28, 2010:

- FDA continued to recommend that Bayer study two doses of NS (440 mg and 220 mg) as well as two doses of DPH (50 mg and 25 mg).

Letter to deny Bayer's request for a Type B meeting, dated July 22, 2011:

- FDA cannot retract a recommendation to study DPH 25 mg in the clinical program without an in depth review of safety and efficacy data. That said, the proposed combination product can ultimately be approved if Bayer's data support that it is safe and effective for OTC use.

Advice letter dated July 25, 2011 in response to a submission containing protocol for proposed multiple-dose safety study (study #15560):

- Revise eligibility criteria so that only consumers with contraindications for taking the product are excluded.

- Final product labeling with respect to older adults (> 60 years of age) will include the same restriction as the current OTC naproxen labeling (i.e., to ask a doctor before use).

Advice letter dated December 23, 2011 in response to a submission containing protocol of the second pivotal efficacy trial (study #15581):

- Amend the protocol to include measurements of plasma diphenhydramine concentration on the morning after dosing.
- The proposed trial does not include a NS 220 mg/DPH 25 mg arm as recommended previously.
- The proposed trial will not address the relative efficacy of NS 440 mg/DPH 50 mg vs. NS 440 mg/DPH 25 mg.

Advice letter dated February 15, 2012 in response to the November 18, 2011 submission of amended clinical study protocol #15581:

- Randomization should be stratified by study center, gender, and age group.
- FDA recommended an additional sensitivity analysis for both co-primary variables to treat subjects who take rescue medication as if they have not taken rescue medication.

According to Bayer, a teleconference took place between Dr. Andrea Leonard (DNCE) and Bayer's Leonard Baum on April 11, 2012:

- In view of seeming discrepancies between advice conveyed on July 22, 2011 and December 23, 2011, Bayer was advised to follow the advice provided on July 22, 2011.

2.6 Other Relevant Background Information

- On April 7, 2005, FDA requested labeling changes for all COX-2 selective and non-selective prescription NSAIDs and OTC NSAIDs, to include more specific information about the potential CV and GI risks, stronger reminders about limiting dose and duration of treatment, and a warning for potential skin reactions.
- In December 2006, FDA required labeling changes for OTC Internal Analgesic drug products to include safety information regarding the potential for stomach bleeding and liver damage and when to consult a physician.
- The European Medicines Agency (EMA) scientific committee, the Committee for Medicinal Products for Human Use (CHMP), concluded in October 2005 that there are no new safety concerns regarding cardiovascular and gastrointestinal safety and serious skin reactions with nonselective NSAIDs, and that NSAIDs remain important treatments for arthritis and other painful conditions. The

Committee recommended the product information be consistent across the EU. No distinction in recommendations between low dose and high dose or long-term versus short-term (i.e. OTC versus prescription) NSAIDs was made by the EMEA.

- In September 2006, the French National Medicines Agency asked CHMP to give an opinion on the cardiovascular safety of the NSAIDs. CHMP concluded:
 - Non-selective NSAIDs are important treatments for arthritis and other painful conditions
 - It cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events, especially when used at high doses for long-term treatment
 - The overall benefit-risk balance for non-selective NSAIDs remains favorable when used in accordance with the product information
 - With regard specifically to naproxen, they concluded: Clinical trial and epidemiological data suggest that naproxen (1000 mg/day) may be associated with a lower risk for arterial thrombotic events than COX-2 inhibitors, but a small risk cannot be excluded. Overall, the data do not support a cardio-protective effect.
- The German regulatory authority (BfArM) conducted a benefit-risk evaluation of naproxen in OTC dosages in Germany in 2005. The prescription committee decided that there was no evidence or reason for returning naproxen sodium back to prescription only status, and no need to limit use or add further warnings.
- In September 2006, FDA released a Health Advisory and Science paper describing this potential pharmacodynamic interaction between OTC doses of ibuprofen and low dose aspirin. At the time, there was limited published information available about a potential interaction between prescription (Rx) doses of naproxen (250 to 500 mg) and low dose aspirin, and no information available about OTC doses of naproxen (220 mg) and low dose aspirin. Since September 2006, additional information about the potential for an interaction between Rx and OTC doses of naproxen has become available. The potential interaction is relevant because low dose aspirin may be used for cardioprotection and concomitant use with naproxen could lead to attenuation or loss of cardioprotection. In 2007, Bayer submitted a study (#12611, entitled, “A Randomized, Open Label, Parallel Group, Single Center Study to Investigate the Effects on Serum Thromboxane by the Addition of Naproxen Sodium or Acetaminophen to Aspirin Therapy versus Aspirin Therapy Alone”). These data were reviewed by FDA’s DCRP and do not rule out the possibility of a drug interaction between aspirin and naproxen. In a letter sent in March 2010 under the Aleve NDA (# 20-204), DNCE advised Bayer of the need for additional study to evaluate immediate release aspirin and OTC doses of naproxen.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission was adequate.

3.2 Compliance with Good Clinical Practices

Two clinical investigator sites were inspected in support of this application. The inspection of the two clinical investigators listed above revealed minor regulatory violations at Dr. Webster's site. The pending classification for Dr. Webster's site is Voluntary Action Indicated (VAI) and the pending classification for Dr. Buchanan's inspection is no action indicated (NAI). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these two sites are considered acceptable in support of the pending application. Refer to Dr. El-Hage's review for further details.

3.3 Financial Disclosures

Form FDA 3454 was completed and certified that the sponsor has not entered into any financial arrangement with the clinical investigators such that the value of the compensation to the investigator could be affected by the outcome of the study and that the clinical investigators did not have a proprietary interest in the product or significant equity in the sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

See specific discipline reviews.

4.1 Chemistry Manufacturing and Controls

4.3 Preclinical Pharmacology/Toxicology

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Diphenhydramine

Diphenhydramine hydrochloride is an inverse agonist of the histamine H1 receptor. By blocking histamine in the capillaries, DPH reduces the intensity of allergic symptoms. It also crosses the blood-brain barrier and antagonizes the H1 receptors centrally, causing drowsiness.

Naproxen

The mechanism of action of naproxen sodium includes inhibition of COX and lipoxygenase enzymes involved in the synthesis of prostaglandins and leukotrienes. It is a nonselective COX inhibitor, affecting both the COX-1 and COX-2 isoenzymes. 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. Pharmacology and toxicology information for naproxen sodium are provided in NDA# 20-204 for Aleve tablets (naproxen sodium, 220 mg).

4.4.2 Pharmacodynamics

4.4.3 Pharmacokinetics

Diphenhydramine

Diphenhydramine is a sedating antihistamines used to treat allergic conditions and motion sickness, and it is used as a sleep aid. It is a competitive antagonist of histamine at the H1 receptor. Anticholinergic (primarily antimuscarinic) effects develop in overdose.

The time to peak concentration after an oral dose is 2 to 4 hours. The C_{max} after a 100 mg oral dose ranges from 66 to 159 ng/mL. The elimination half-life is 4 to 8 hours and is prolonged with age. (Diphenhydramine Micromedex, June 20, 2013)

The prescription therapeutic dose for diphenhydramine hydrochloride in adults is 25 to 100 mg orally every 6 hours; the maximum parenteral dose is 400 mg per day. Mild sedation, dizziness, impaired coordination, and mild anticholinergic effects are common, paradoxical excitation develops in some patients.

Severe toxicity (ie, delirium, seizures, coma) generally develops only after ingestion of one gram or more in adults. The potentially fatal blood concentration of DPH is 0.5 mg/100 mL (= 5 mcg/mL = 5 mg/L). (Diphenhydramine Poisindex) In young children, ingestions of less than 7.5 mg/kg are not expected to cause significant toxicity. Children, in particular infants, tend to be more sensitive to the toxic effects of diphenhydramine than adults. Excessive topical application of dermal products may produce toxicity.

Poisoning is common but rarely severe. Adverse effects with mild to moderate poisoning are somnolence, anticholinergic effects (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds), tachycardia, mild hypertension, nausea and vomiting and are common after overdose., Agitation, confusion and hallucinations may develop with moderate poisoning. With severe poisoning, adverse effects may include delirium, psychosis, seizures, coma, hypotension, QRS widening, and

ventricular dysrhythmias, including torsades de pointe, but are generally only reported in adults after ingestions of one gram or more of DPH. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma or seizures.
(Diphenhydramine Poisindex)

Naproxen

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) and a nonselective inhibitor of cyclooxygenases (COX-1 and COX-2), leading to decreased synthesis of prostanoids. Naproxen, like other NSAIDs, has anti-inflammatory, analgesic, and antipyretic properties. Prostaglandin inhibition is responsible for the gastrointestinal irritant effects and nephrotoxicity. Gastrointestinal effects (eg, dyspepsia, ulceration, bleeding) are as common as with other NSAIDs.

The time to peak concentration after an oral dose for naproxen sodium is 1 to 2 hours and for regular release naproxen is 2 to 4 hours. The elimination half-life is 12 to 15 hours.

Poisoning with NSAIDs is not uncommon but rarely severe. With mild to moderate poisoning, gastrointestinal effects (eg, dyspepsia, ulceration, bleeding) are most commonly encountered. Renal dysfunction, most often in elderly patients, may occur. Mild CNS effects include altered cognition, drowsiness, headache, and mood changes, especially in the elderly population.

With severe poisoning, adverse effects include CNS depression, hallucinations, seizures, renal failure, gastrointestinal bleeding, and metabolic acidosis.

See Clinical Pharmacology for review of PK study 16135.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical program conducted by Bayer consists of efficacy trials # 14837 and 15881, as well as trial # 15560 to support safety over a 10-day period. In addition, the program includes a pharmacokinetic study (#16135) to assess food effect of this combination. The development program also includes the proof-of-concept study #13053. Table 2 shows the clinical trials submitted for this application.

Table 2 Table of Clinical Studies

Type of Study; Clinical Phase	Study No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients
PK; Phase 1	16135	To determine and compare the PK profile (specifically AUC and Cmax) of a single oral dose of NapSo 440 mg/DPH 50 mg combination relative to the currently marketed single ingredient products containing NapSo or DPH under fasting conditions. To determine and compare the PK profile (specifically AUC and Cmax) of a single oral dose of NapSo 440 mg/DPH 50 mg combination under fasting and fed conditions. To assess the safety and tolerability of NapSo 440 mg/DPH 50 mg combination.	Randomized, open label, 4-way crossover, single center study.	NapSo 440 mg/DPH 50 mg, single dose, oral under fasting conditions NapSo 440 mg, single dose, oral under fasting conditions DPH 50 mg, single dose, oral under fasting conditions NapSo 440 mg/DPH 50 mg, single dose, oral under fed conditions	32 (27 completed all 4 treatments)	Healthy subjects between 18 and 55 years of age with a BMI of approximately 18 to 30 kg/m ² , and a total body weight > 50 kg (110 lb).

Type of Study; Clinical Phase	Study No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients
Efficacy; Phase 3 (Pilot)	13053	To evaluate the efficacy and safety of a single oral dose of NapSo 440 mg/DPH 50 mg combination relative to NapSo 440 mg, DPH 50 mg, and Advil PM alone (active controls), and a single dose of NapSo 220 mg/DPH 50 mg combination relative to NapSo 220 mg, DPH 50 mg, and Advil PM alone (active controls) in subjects with post-surgical dental pain and phase-advanced sleep.	Randomized, double-blind, parallel group, single center, pilot efficacy study.	†NapSo 440 mg/DPH 50 mg, single dose, oral. †NapSo 220 mg/DPH 50 mg, single dose, oral. NapSo 440 mg, single dose, oral. NapSo 220 mg, single dose, oral DPH 50 mg, single dose, oral Advil PM (ibuprofen 400 mg and diphenhydramine citrate 76 mg), single dose, oral	27 27 27 27 27	Healthy subjects between 16 - 45 years of age with moderate to severe postoperative dental pain.
Efficacy; Phase 3	14837	To evaluate the efficacy and safety of a single oral dose of 2 dose combinations of NapSo 440 mg/DPH 50 mg and NapSo 220 mg/DPH 50 mg relative to NapSo 440 mg and DPH 50 mg alone (active controls) in subjects with post-surgical dental pain and phase-advanced sleep.	Randomized, double-blind, parallel group, multicenter, efficacy study.	NapSo 440 mg/DPH 50, single dose, oral. NapSo 220 mg/DPH 50 mg, single dose, oral. NapSo 440 mg, single dose, oral. DPH 50 mg, single dose, oral.	203 204 203 102	Healthy subjects at least 12 years of age with moderate to severe postoperative dental pain.

Type of Study; Clinical Phase	Study No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients
Efficacy; Phase 3	15881	To evaluate the efficacy and safety of a single oral dose of NapSo 440 mg/DPH 25 mg combination relative to NapSo 440 mg and DPH 50 mg alone (active controls) in subjects with post-surgical dental pain and phase-advanced sleep.	Randomized, double-blind, parallel group, multicenter, efficacy study.	NapSo 440 mg/DPH 25 mg, single dose, oral.	107	Healthy subjects at least 12 years of age with moderate to severe postoperative dental pain.
				NapSo 440 mg, single dose, oral.	106	
				DPH 50 mg, single dose, oral.	54	
Safety; Phase 3	15560	To evaluate the safety and tolerability of NapSo 440 mg/DPH 50 mg compared to placebo when used for 10 consecutive days in a population representative of OTC users of analgesic/nighttime sleep-aid combination products.	Randomized, double-blind, placebo-controlled, parallel group, multicenter, safety and tolerability study.	NapSo 440 mg/DPH 50 mg, once daily at bedtime for 10 consecutive days, oral.	217	Subjects at least 12 years of age 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).
Placebo, once daily at bedtime for 10 consecutive days, oral.	109					

† Commercial products Aleve® (naproxen sodium 220 mg tablets) and Benadryl® (DPH 25 mg tablets) administered concomitantly.

PK = pharmacokinetic
 AUC = area under the curve
 Cmax = maximum plasma concentration
 NapSo = naproxen sodium
 DPH = diphenhydramine hydrochloride
 OTC = over-the-counter
 BMI = body mass index

Source: Module 5, Section 5.2 Tabular Listing of Clinical Studies

5.2 Review Strategy

Dr. Veneeta Tandon from DNP reviewed the Aleve PM clinical trials and Dr. Ellen Fields from DAAAP evaluated the efficacy assessments for pain. This review will cover the literature and post-marketing data for DPH. Naproxen sodium post-marketing data and literature have been reviewed recently by Dr. Callahan Lyon and Dr. Osborne for NDA 200364. This review will include information from a safety update for NS.

5.3 Discussion of Individual Studies/Clinical Trials

Brief descriptions of the individual study designs are presented below. The reader is referred to the clinical pharmacology, ONP, and DAAAP reviews.

The Phase 1 PK trial 16135 compared the AUC and Cmax from single oral doses of the combination NS 440 mg/DPH 50 mg with the currently marketed single ingredient products under fasted and fed conditions. It enrolled 32 healthy subjects in an open label, crossover study. This study is being reviewed by Dr. Xinning Yang.

The pilot efficacy trial 13053 and the two additional Phase 3 efficacy trials 14837 and 15881 are being reviewed by Dr. Veneeta Tandon from the Division of Neurology Products (DNP). These were randomized, double blind parallel group studies. All three

studies assessed efficacy of single oral doses in patients with dental pain from third molar extractions using phase-advanced sleep. Primary endpoints for the phase 3 studies were wake after sleep onset (WASO, NS/DPH vs NS alone) and sleep latency (NS/DPH vs DPH alone). Combinations with reduced NS or DPH were also assessed (NS 220/DPH 50 in 13053 and 14837, and NS 440/DPH 25 in 15881). The efficacy assessments for pain are reviewed by Dr. Fields.

The safety trial 15560 tested NS 440/DPH 50 once daily over ten days dosing vs. placebo. This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group safety and tolerability trial. Three hundred twenty-six subjects were screened and randomized: 217 subjects to naproxen sodium/DPH and 109 subjects to placebo.

The pivotal trial Study 14837 was a multicenter, randomized, double-blind, parallel-group trial assessing the efficacy and safety of the NS/DPH combination in postsurgical dental pain with phase advanced sleep. This was a multicenter, randomized, double-blind, parallel group, pivotal efficacy study. The study included a Screening Visit, a Dosing Period, and an End of Trial (EOT) assessment. Subjects who had undergone surgical extraction of impacted third molars were housed and observed at a clinical research unit overnight and were required to go to bed approximately 5 hours earlier than usual. After surgery (scheduled between 1330 h and 1530 h), subjects who experienced postsurgical pain of at least moderate severity (between 1600 h and 1830 h) were randomized to 1 of the 4 treatment groups. The effects of a single dose administration of investigational product on sleep during the Dosing Period were evaluated objectively using actigraphy. Subjective sleep questionnaires, categorical pain scales, and global assessments were also used to evaluate the efficacy of the investigational products.

It was planned that approximately 700 subjects would be randomized into the study, with 200 subjects in each of 3 naproxen sodium treatment groups (2 combination [naproxen sodium/DPH] groups and 1 naproxen sodium alone group) and 100 subjects in the DPH alone treatment group. The duration of each subject's participation in the study from Screening to the EOT assessment was up to approximately 4 weeks, including a Screening Period of up to 28 days, a Dosing Period of 2 days, and a Follow-up Period of 2-5 days. See Dr. Tandon's review for the assessment.

The other Phase 3 efficacy trial Study 15881 was a randomized, double-blind, parallel group trial assessing the efficacy and safety of NS/DPH combination in postsurgical dental pain with phase- advanced sleep. This trial studied a single dose of NS 440 mg + DPH 25 mg in addition to NS 440mg and DPH 50mg doses of single ingredient products. Aside from testing the different dose of NS/DPH, the procedure was the same as in the pivotal trial 14837.

6 Review of Efficacy

Efficacy Summary

The objective of the efficacy studies was to demonstrate the added benefit of the combination product over each of the single ingredients. The postsurgical dental pain model with phase advance sleep was used to evaluate efficacy of the combination compared to the single ingredients in the pilot and pivotal efficacy studies. In their SPA response letter dated 08 January 2010, FDA agreed that this model was adequate to demonstrate the efficacy of the new naproxen sodium/DPH combination product in the target population of patients with sleeplessness associated with pain. Additionally, the Agency also agreed that the primary efficacy parameters of WASO and sleep latency as measured by actigraphy were appropriate to support the proposed label indication “for occasional sleeplessness when associated with minor aches and pains; helps you fall asleep and stay asleep”.

See Dr. Tandon’s review for results and Dr. Field’s review for an analysis of the analgesia-related endpoints.

7 Review of Safety

Safety Summary

See Dr. Tandon’s review of the clinical trial safety data.

7.6.2 Human Reproduction and Pregnancy Data

Diphenhydramine: Diphenhydramine is classified as FDA pregnancy risk category B.

Naproxen: Though use should be avoided in late pregnancy, naproxen is classified as FDA pregnancy risk category C drug throughout most of gestation. Use only if the potential therapeutic benefits justify its use during pregnancy. Naproxen use near term may result in prostaglandin synthetase inhibitor-induced *in utero* constriction of the fetal ductus arteriosus.

7.6.3 Pediatrics and Assessment of Effects on Growth

NA

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The use of DPH is associated with misuse/abuse, suicide attempts, and both intentional and unintentional overdoses (see Section 8 and OSE review of FAERS). Poisoning by

DPH is common but rarely severe and leads to anticholinergic (primarily antimuscarinic) effects in overdose which may occur via oral, parenteral or dermal route. With therapeutic use, common adverse effects include mild sedation, dizziness, impaired coordination, and mild anticholinergic effects; paradoxical excitation develops in some patients. With mild to moderate overdose adverse effects include: somnolence, anticholinergic effects (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds), tachycardia, mild hypertension, nausea and vomiting. Agitation, confusion and hallucinations may develop with moderate poisoning.

With severe poisoning, adverse effects may include delirium, psychosis, seizures, coma, hypotension, QRS widening, and ventricular dysrhythmias, including torsades de pointe, but are generally only reported in adults after ingestions of one gram or more of DPH. An adult male ingested 25 g of diphenhydramine and developed torsades de pointes, but made a complete recovery. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma or seizures. (Diphenhydramine Poisindex)

Poisoning with NS is not uncommon but rarely severe. With mild to moderate poisoning, gastrointestinal effects (eg, dyspepsia, ulceration, bleeding) are most commonly encountered. Renal dysfunction, most often in elderly patients, may occur. Mild CNS effects include altered cognition, drowsiness, headache, and mood changes, especially in the elderly population. Severe poisoning is rare but can include CNS depression, hallucinations, seizures, renal failure, gastrointestinal bleeding, and metabolic acidosis.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

8.1 Bayer Post-marketing Diphenhydramine

The Bayer Global Pharmacovigilance Database was queried on 17-Jun-2013 for all fatal and all non-fatal serious cases received between 01-Jan-1994 and 20-Mar-2013 in which diphenhydramine was classified as a suspect drug. The query returned 425 fatal and 168 non-fatal serious reports for this 19-year period, as of the actual query date of 17-Jun-2013.

Deaths

The Bayer database returned 425 reports of deaths with DPH as a suspect drug. The actual total number of deaths in these reports is 427.

MO Comment: *The reviewer determined from the CIOMS reports that one report was obtained from the literature and described 64 non fatal cases, while one report was for 4 fatal cases. Also, three of the 425 reports actually did not involve DPH at all, leaving a total of 421 deaths with DPH as a suspect drug. In this review, the Bayer database is considered to contain 425 death reports with a slightly different number of actual deaths.*

Of the 425 death reports from Bayer, 402 reports (95%) were derived from literature, of which 344 reports were derived from the annual reports of the American Association of Poison Control Centers (AAPCC). AAPCC reports typically do not include case details and are reviewed separately in Section 8.4. A vast majority of the AAPCC reported cases involved intentional multiple drug overdoses taken in suicide attempts. Of the 344 AAPCC reports, 320 (93%) reported overdoses of at least one drug or substance in addition to DPH. Overall, 360 (85%) of the 425 fatal reports involved ingestion of at least one other suspected agent in addition to DPH, and commonly included ethanol, acetaminophen, NSAIDs, opioids, antipsychotics, antidepressants, and benzodiazepines, and drugs of abuse.

MO Comment: *The AAPCC reports comprise the large majority of DPH reports in the Bayer Pharmacovigilance Database, and they also comprise a large proportion of the reports in the FAERS database. FAERS is in turn the largest source of reports in the WHO database. Although FAERS includes cases not reported to Bayer, and WHO includes cases reported from outside the US but not to the FDA, these databases are not independent, because the same cases, from the annual reports of the AAPCC, comprise major portions of the data in all of them.*

The route of administration in almost all cases was either oral or not reported. Also in most cases, product indication for DPH was either not provided or was unknown. Products classified as concomitant were reported in 22 (5%) of the 425 reports, and consisted chiefly of ethanol, antipsychotics and benzodiazepines. The Preferred Term

(PT) "Toxicity to various agents" accounted for the majority (390 or 55%) of the 704 total PTs contained in the 425 fatal reports. After Toxicity to various agents, the most frequently reported PTs ($n \geq 10$) among the fatal cases were Intentional overdose (42), Cardiac arrest, Drug abuse, and Pulmonary oedema (18), Overdose (14), Respiratory arrest (12) and Convulsion (10).

Of the 425 fatal reports, a total of 411 reports (97%) could be classified after review of the CIOMS reports as either suicide, some form of overdose (intentional, accidental, or intent unknown), or some form of abuse/misuse. Only 14/425 reports were not classifiable, typically because of lack of information; these cases could also have been overdoses. The large majority of the 425 fatal reports, a total of 301 reports (71%), were suicides and/or intentional overdoses; these categories were combined because suicidal intent is not assessable in some cases. There were 62 reports of abuse or misuse, including 7 reports of child abuse of which 2 reports were homicides of children. There were 21 reports of accidental overdose, of which 10 accidental overdose reports were in children. Of the 21 accidental overdose reports, there were cardiac arrests in 5 reports (2 in children). Finally the 425 fatal reports included an additional 27 overdoses where intention was not assessable.

In the 425 CIOMS reports of deaths, there were 362 reports of multi-drug ingestions, including reports of DPH plus ethanol ingestion only. There were 60 fatal reports of DPH mono-ingestions. In the 60 fatal reports with DPH only, there were 11 cardiac arrests, all of which were suicide or abuse cases.

MO Comment: *Of the 425 fatal reports involving DPH, 411 reports (97%) were suicides, drug overdoses, or abuse/misuse reports. Suicides and intentional overdoses combined accounted for 71% of death reports. Cardiac arrest was one of the 5 most frequent Preferred Terms, but was reported in connection with overdoses. In the 14 reports that were not classifiable as suicide, overdose, or misuse/abuse cases, two did not involve DPH at all, and all were multi-drug intoxications. Seven of these 14 cases were in children.*

Non-Fatal Serious Reports

Of the 168 non-fatal serious reports, 78 (46%) were received spontaneously, 72 (43%) were derived from literature and 18 (11%) were derived from published study reports

Examination of the 78 spontaneous reports revealed that a large majority reported DPH in cold-flu combination products, including paracetamol (49), pseudoephedrine (36), dextromethorphan (35) and aspirin (30), thereby confounding the assessment of diphenhydramine in up to 75 (96%) of these reports. In most cases, the reported adverse events could be attributed to drugs other than DPH or to pre-existing medical conditions, or were reported in consumers with identifiable risk-factors. Several other cases described hypersensitivity reactions that could be attributed to DPH or another

suspect medication. In other cases, adverse events were consistent with known anticholinergic effects of DPH.

There were 263 adverse event terms listed in the 78 spontaneous reports. The most frequently reported PTs ($n \geq 5$) were: Dizziness (10), Hallucination auditory (8), Somnolence, Vomiting (7), Nausea (6), Muscular weakness (6), and Syncope, Dysarthria, Asthenia, Dyspnoea, Tinnitus, Urticaria (5). While this PT distribution is largely consistent with the adverse event profile of DPH, it is also consistent with other co-suspect drugs as well (e.g., dextromethorphan).

The most frequently reported product indications (as MedDRA PTs) among the non-fatal serious spontaneous cases were: Product use for unknown indication (38), Nasopharyngitis (18), Sleep disorder (10) and Influenza (8). Overdose was cited in 13 (17%) of the 78 reports. Concomitant medications were reported in 29 (37%) of the 78 cases and commonly included analgesics, anti-hypertensives, anti-depressants, anti-diabetic agents and anti-hyperlipidemia agents.

Patient age was reported in 68 (87%) of the 78 spontaneous reports. Overall, adults 18 to 65 years of age accounted for 48 (71%) of the 78 reports, while the elderly (15) and adolescents (5) accounted for the remainder. Females accounted for 43 or 55% of the 78 reports while males accounted for 28 (36%) reports. In the 7 remaining reports gender was not reported.

Literature reports (72) and published reports from studies (18) together accounted for 90 (54%) of the 168 non-fatal serious reports. Most of these cases (59 or 66%) were overdoses, and most involved more than one suspect drug in addition to DPH. Of the 90 published reports, 51 reported either a combination product or a separate co-suspect drug, and 39 reported diphenhydramine as the sole-suspect drug. In nearly every case, the route of administration for DPH and other suspected drugs was oral or not specified. Most of these cases were intentional overdoses.

Of the 72 literature reports, 35 (49%) reported diphenhydramine as the only suspect agent. In these 35 reports, the most frequently reported Product indications were (where an indication was reported): Product use for unknown indication (18), and Suicide attempt (4). Among the 72 literature reports, 320 PTs were reported. The most frequently reported PTs ($n \geq 5$) were: Convulsion, Tachycardia (8), Mydriasis, Sinus tachycardia, (7), Confusional state, Delirium, Status epilepticus, Toxicity to various agents (6), Electrocardiogram QT prolonged, and Nausea (5).

See Section 9.1 for additional DPH safety literature discussion, and Section 9.4 summarizing 74 literature articles in the submission.

Naproxen

Postmarketing data for NS from Bayer has been previously reviewed by Dr. Callahan Lyons (May 17, 2010) and Osborne (May 7, 2013) where no unexpected findings were found for NDA 200364.

The Sponsor submitted an update analysis of naproxen adverse event (AE) reports in Bayer's Global Pharmacovigilance Database, covering the period from 16 November 2011 through 20 March 2013. The update covers cases reported for the 220 mg naproxen sodium product as well as other naproxen products marketed globally by Bayer. All cases in which naproxen was a suspect medication were included regardless of route of administration, and only those events linked to naproxen have been included.

There were a total of 11504 cases involving 15598 AE terms. Of these reports, 90.5% (10412/11504) were Non-serious; 9.0% (1039/11504) were Serious; and 0.5% (53/11504) were Death reports. Overall, 62.5% (7185/11504) of the reports had no reported patient gender. The gender ratio, for cases with known gender, was 2.55 female:male (3101 female and 1218 male).

A total of 20.9% (2401/11504) of the reports provided explicit age data and the mean age of the patients with age data was 58.8 years. The age distribution revealed that the largest fraction of cases was in the ≥ 65 year age range (10.5%, 1205/11504). The large majority of cases (79.0%, 9088/11504) did not have an explicit age reported.

Overall, 16 MedDRA adverse event terms had relative reporting rates of 1% or more. Together they accounted for 57.9% (9024/15598) of all reported terms. The 6 most commonly reported terms were Drug ineffective (16.2%, 2526/15598), No adverse event (11.8%, 1846/15598), Headache (7.4%, 1161/15598), Pain (4.6%, 723/15598), Back pain (2.1%, 321/15598) and Dysmenorrhoea (2.0%, 309/15598). These were predominantly in non-serious reports.

There were a total of 1039 Serious reports, not including deaths, with 2735 associated AE terms. Of the 1039 reports, 41.4% (430/1039) were in the adult age ranges and 1.5% (16/1039) were in the age ranges < 18 years. Overall, 5 SOCs accounted for 60.1% (1644/2735) of the AE terms for Serious reports. They were: Gastrointestinal disorders (17.8%, 488/2735), General disorders and administration site conditions (13.7%, 374/2735), Nervous system disorders (11.2%, 307/2735), Skin and subcutaneous tissue disorders (9.0%, 246/2735) and Psychiatric disorders (8.4%, 229/2735).

Among the serious non-death reports for naproxen, there were 19 adverse event terms which had relative reporting rates of 1% or more. Together they accounted for 27.7% (757/2735) of all reported terms. Of these 19 terms, 2 involved gastrointestinal disorders and 6 involved possible allergic phenomena. The 4 most commonly reported terms

were Drug dependence (3.5%, 95/2735), Hypersensitivity (2.3%, 62/2735), Dyspnoea (2.2%, 61/2735) and Loss of consciousness (2.0%, 54/2735).

There were 53 Death reports with 139 associated AE terms. Of the 53 reports, none was in the age range < 2 years and 3 were in the age ranges from 2 to < 18 years. A total of 47.2% (25/53) were in the adult age range (18 years to < 65 years) and 13.2% (7/53) were in the elderly age range (> 65 years old). A total of 34.0% (18/53) of the cases had no age data. Overall, 6 SOCs had relative reporting rates \geq 7% of all reported terms for the cases of death. Together they accounted for 78.4% (109/139) of the total terms. They were: Injury, poisoning and procedural complications (23.7%, 33/139), General disorders and administration site conditions (17.3%, 24/139), Gastrointestinal disorders (11.5%, 16/139), Nervous system disorders (10.1%, 14/139) Psychiatric disorders (8.6%, 12/139) and Musculoskeletal and connective tissue disorders (7.2%, 10/139). The most frequently reported AE term was Toxicity to various agents in the 18 to 65 year age range, with 21 instances (24.7%, 21/85). Most of the death reports were suicides as indicated by the verbatim reports.

MO Comment: *No unexpected findings or new safety signals resulted from this updated analysis of the AEs for naproxen from the Bayer drug safety database.*

8.2 FAERS FDA Post-marketing Database

The Sponsor performed an analysis of DPH Adverse Events in the FAERS database covering the period from 1 January 2004 through 31 December 2011. There were a total of 5644 cases involving 20581 AE terms. Of these reports, 45.9% (2590/5644) were serious and 43.9% (2476/5644) involved reports of a death.

OSE was consulted to analyze the FAERS postmarketing database for DPH and searched the entire database since Jan 1, 1969. The FAERS database contains 12,538 total reports for all adverse events, with 4637 death cases (36%).

MO Comment: *The analyses of FAERS submitted by sponsor and reviewed by OSE covered different time periods. The Sponsor reviewed only the publicly available data since approximately the approval of Advil PM and retrieved fewer serious and death reports. This review will summarize the OSE findings.*

OSE Consult

OSE performed analyses of the FAERS database for accidents associated with DPH use; reviewed literature regarding association between DPH products and abuse or suicide; analyzed the DAWN database to assess the rates of ED visits related to misuse and abuse of DPH; and reported on data mining analyses of accidents and of intentional and unintentional overdoses of DPH.



Figure 1 Estimated Sales of DPH Products, US Retail Outlets 2007-2012





Figure 2 Retail Sales of DPH Products by Market Category in 2011

The FAERS search retrieved 12,538 total reports for all adverse events reported with DPH and DPH combination products over the time period January 1, 1969 to July 10, 2013. The top 5 preferred terms reported with DPH-containing products are: completed suicide, toxicity to various agents, overdose, intentional overdose, and drug ineffective. Of the 12,538 cases, 4637 cases (36%) reported an outcome of death. The top 5 preferred terms reported with an outcome of death are: completed suicide, toxicity to various agents, cardiac arrest, death, and cardio-respiratory arrest.

Accidents. FAERS search was performed for accident reports with oral DPH as the only suspect medication and with a temporal association to DPH or a laboratory test showing a detectable level of DPH. Reports were excluded if multiple medications were reported as suspect medications, recreational drugs or alcohol were reportedly used, if accidents or injuries resulted from a non-drug cause, or if the injuries resulted from organ damage (e.g., liver injury), or if the case contained insufficient details. The period searched was January 1, 1969 - July 10, 2013. Only serious reports were included.

After accounting for duplicate reports, 37 cases were included in the case series of accidents reported with DPH use. All the accident reports were received from 2001-2013.

Of the 37 accident cases, there were 20 falls and 16 motor vehicle accidents. Two of the motor vehicle accident reports were fatalities. Most cases (n=23) reported using DPH consistent with DPH labeling. More than half of the cases (n=17) reported using between 25 to 50 mg DPH (38 -76 mg for DPH citrate) once daily prior to the accident or injury. Five cases reported using between 75 to 300 mg in divided doses daily prior to the accident. One case reported using 6.25 mg DPH once. Three of the 37 cases reported using doses greater than the labeled DPH dosing. One patient reported using 750 mg daily for months (case #3970755), and was involved in a minor motor vehicle accident. The second patient (case#4172909) reportedly took between 40 to 120 capsules of 50 mg Unisom SleepGels at one time, fell down the stairs, and sustained a head injury. The third patient (case#6908772) reportedly used 4 tablets of acetaminophen + DPH nightly at bedtime for 2 years. One day he fell asleep driving and caused a motor vehicle accident.

The data mining scores (EBGM values) and confidence limits for the accident-related MedDRA preferred terms reached EB05 = 4.8 for the PT "Accident" but not for "Road traffic accident" or "Fall".

Misuse and abuse. OSE also analyzed the DAWN database on drug-related ED visits from Jan 2004 through Dec 2011, using the SAMHSA definition of cases related to misuse and abuse, which are called All Misuse/Abuse (AllMA) cases, which are:

- suicide attempts only if illicit drugs were involved
- overmedication
- patient took a medication not prescribed for them
- detoxification seeking only if illicit drugs were involved
- malicious poisoning
- illicit drug or alcohol-related ED visits
- substance abuse

In addition to the AllMA cases, the search included suicide attempts involving DPH, completed suicides and deaths other than suicides involving DPH from 13 states through 2010 (Delaware, Massachusetts, Maryland, Maine, New Hampshire, New Mexico, Oklahoma, Oregon, Rhode Island, Utah, Virginia, Vermont, and West Virginia).. Fig 3 shows the temporal trend in the national estimates of All Misuse/Abuse (AllMA) ED visits associated with DPH between 2004 and 2011. The total number of DAWN misuse and abuse ED visits associated with single-ingredient DPH increased from 12,962 in 2004 to 22,966 in 2011. Misuse and abuse visits associated with DPH in combination with an analgesic remained relatively stable during that time period. Overall, more misuse and abuse ED visits are associated with single-ingredient DPH

than DPH in combination with an analgesic. For comparison, the numbers of misuse and abuse ED visits are also provided for hydrocodone (HC) and for chlorpheniramine (CPH) + acetaminophen. HC products with a known abuse liability ranged from 46,536 to 115,739 visits, while CPH + acetaminophen ranged from 3,376 to 4,478 visits (estimates could only be provided for 2005-2011).

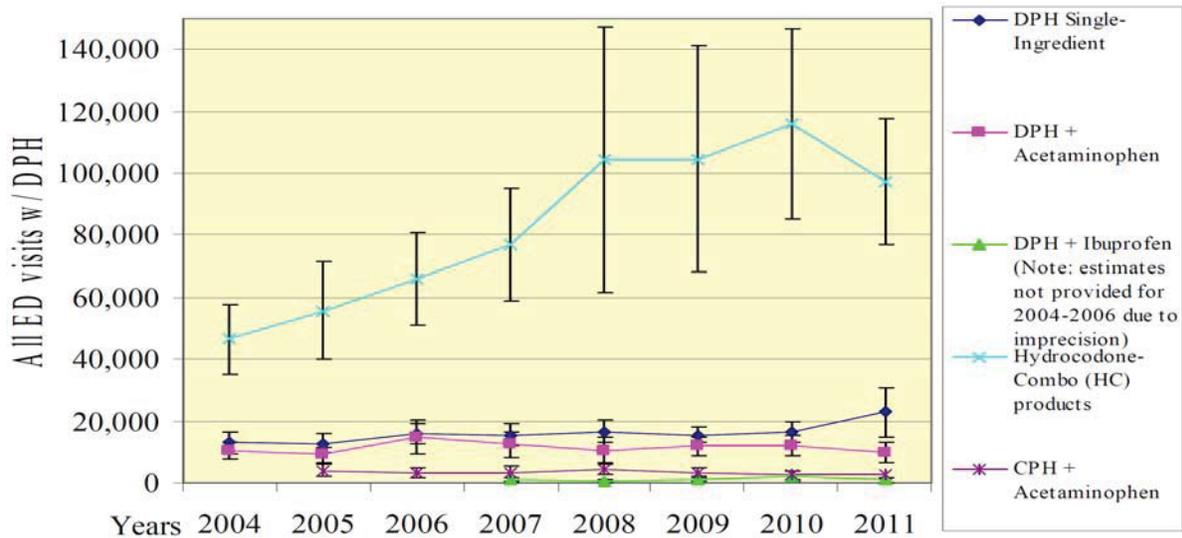


Figure 3 DPH Misuse and Abuse ED Visits, 2004-2011

Fig 4 shows the number of suicide attempt (SA) ED visits associated with DPH. Between 2004 and 2011, single ingredient DPH SA visits increased from 7,461 in 2004 to 9,301 in 2011. Visits for DPH combined with acetaminophen increased from 4,581 visits in 2004 to 5,863 visits in 2011. However, visits for DPH with acetaminophen peaked at 8,755 in 2007.

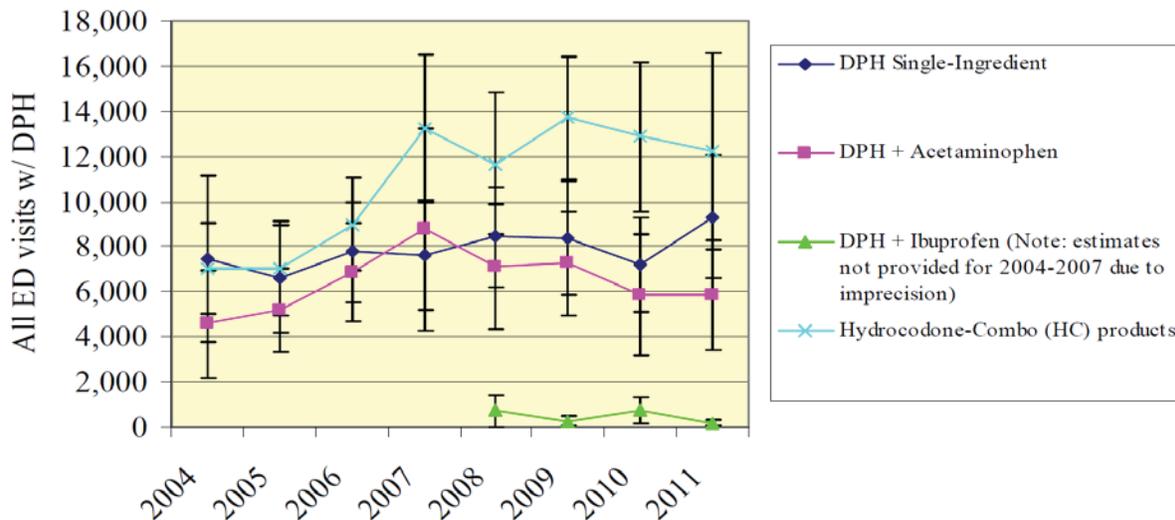


Figure 4 DPH Suicide Attempt ED Visits, 2004-2011

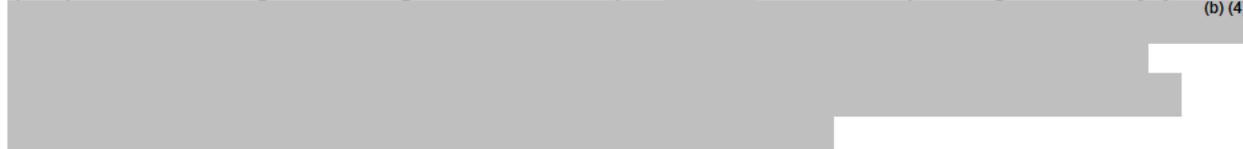
Aside from 2007, single-ingredient DPH is associated with more SA ED visits than DPH with acetaminophen. For comparison, visits for HC products ranged from 7,034 to 13,701. CPH + acetaminophen had only one reportable estimate in 2007, with 684 visits.

DPH had markedly fewer ED visits associated with it than HC, but more than CPH + acetaminophen. DAWN ED visit estimates related to suicide attempts (SAs), showed increasing trends for both single-ingredient DPH and DPH + acetaminophen.

DAWN data suggest that 1.4% of all AllMA ED visit estimates were associated with DPH, and 7.6% of all suicide attempt ED visits were associated with DPH.

There were 1,098 reportable deaths associated with DPH in the 13 states covered by DAWN reported by coroners and medical examiners between 2004 and 2011 (death reports are suppressed if the total count from a state is four or fewer in any year or if the subject is under 5 years old). This total is not directly comparable to the total number (4637 cases) of death reports in FAERS, from all 50 states since 1969.

The AllMA estimates for DPH single-ingredient and DPH +acetaminophen combination ED visits for 2007-2011 are normalized to sales during that time period by AllMA Ratio (AR), shown in Fig 5 which gives ED visits per ^{(b) (4)} bottles or packages sold by year.



Overall, during 2007-2011, the ARs for DPH + acetaminophen appears to account for about as many AllMA ED visits as single-ingredient DPH relative to sales. For comparison, CPH + acetaminophen ARs are also provided. Despite fewer ED visits, ARs for CPH + acetaminophen are noticeably higher than for DPH + acetaminophen and for DPH single-ingredient from 2007 through 2010, but not in 2011.



Figure 5 Misuse and Abuse ED Visits per ^{(b) (4)} Bottle/Package Sales

Similarly, the rates of ED visits for suicide attempts, relative to sales, are a little higher for DPH + acetaminophen than for DPH single-ingredient, except for 2011 where again there was an increase in SA visits per ^{(b) (4)} bottles/packages sold, possibly affected by the J&J product recall. Comparisons can be made to CPH+acetaminophen, whose SA ratio (for 2007 only) was similar to that for DPH +acetaminophen.

The SA ratio for DPH+ibuprofen is several times lower than that for DPH+acetaminophen.



Figure 6 ED Visits for Suicide Attempts per (b) (4) Bottles/Packages Sold

Intentional Overdose. FAERS search retrieved 4467 cases coded with the preferred terms drug abuse, intentional drug misuse, intentional overdose, overdose, completed suicide, or toxicity to various agents. These were assessed as 4401 cases of intentional overdose and 66 cases of accidental overdose. In the 4401 cases, DPH was the primary suspect drug in 2231 cases, of which 1338 were single ingredient DPH, and 785 were DPH+acetaminophen. Of the 4401 cases, 69% (3047/4401) appeared in published literature, and 59% (2595/4401) were published in a single source, the Annual Reports of the AAPCC.

Three-fourths of the intentional overdose cases reported an outcome of death (3315/4401). Nearly all of these cases, 95.5% (4204/4401), were reported between the 2000 and 2013, and 71% (3133/4401) were reported between December 22, 2007 and July 10, 2013. Public Law 109-462 became effective on December 22, 2007, requiring expedited 15 day reports for monograph products.

FAERS data mining analyses. OSE determined data mining scores (EBGM values) and confidence limits for MedDRA preferred terms (PT) associated with intentional overdoses with DPH. Scores are sorted by EB05 value, i.e., the lower confidence limit of the EBGM value. This data mining analysis includes all years of AERS data (1969 through August 10, 2013).

Table 3 FAERS Data Mining Scores for Intentional Overdoses with DPH

PT	N	EB05	EBGM	EB95
Toxicity to various agents	1295	11.5	12.1	12.6
Drug abuse	311	8.7	9.6	10.5
Completed suicide	1548	6.9	7.2	7.5
Intentional overdose	741	6.0	6.4	6.8
Intentional drug misuse	336	4.5	4.9	5.4
Overdose	845	4.0	4.3	4.5

Data Mining Scores for Unintentional Overdoses with DPH

PT	N	EB05	EBGM	EB95
Accidental overdose	245	5.3	5.9	6.5

The data mining scores show that DPH is associated with overdoses (intentional and unintentional), suicides, misuse and abuse. An EBO5 level ≥ 2 is the empiric threshold described by Szarfman³ et al.

CONCLUSION. OSE’s review shows that DPH-containing products are associated with accidents, misuse/abuse, suicide attempts, and both intentional and unintentional overdoses; however, the frequencies of these events are within proportion to the sales of these products. Per (b) (4) bottles/packages sold in 2010, there were 6.18 ED misuse and abuse visits for DPH single ingredient and 9.95 for DPH+acetaminophen, which are comparable to each other. The rates of these ED visits relative to sales are higher for CPH+acetaminophen (12.59 ED visits per (b) (4) bottles/packages) but lower for DPH+ibuprofen (2.23). There were 1,098 reportable deaths associated with DPH in the 13 states covered by DAWN reported by coroners and medical examiners between 2004 and 2011, and there were a total of 4637 death reports in FAERS. DAWN data suggest that 1.4% of all AIIIMA ED visit estimates were associated with DPH, and 7.6% of all suicide attempt ED visits were associated with DPH. These numbers should be considered in light of the total sales of over (b) (4) bottles/packages per year (2007-2010). The association of DPH with suicides, misuse/abuse, and overdoses is not disproportionate to the sales of DPH products, when compared to other OTC drugs for similar indications—see Figures 5 and 6. Finally based on the data mining analyses, DPH is associated with accidents (EB05=4.8) but not with road traffic accidents. The FAERS search for accident cases found only 37 cases January 1, 1969 – July 10, 2013.

³ Szarfman A, Machado SG, O’Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than expected combinations of drugs and events in the US FDA’s spontaneous reports database. *Drug Saf* 2002; 25 (6): 381-92

DPH AI SMQ analysis on FAERS data by Bayer

The Sponsor performed a supplemental analysis of DPH Adverse Events in the FAERS database covering the period from 1 January 2004 through 31 December 2011, where the cases of interest were those with at least one AE in the MedDRA Accidents and Injuries Standard Medical Query (AISMQ). The purpose of the supplemental analysis was to search for evidence in postmarketing data for AEs that may be associated with use of DPH as a sleep aid. Reports in the published literature were also surveyed for studies of performance impairment and next day sedation effects from DPH (see Section 9.1).

The supplemental analysis adopted the following methodology to identify case reports involving DPH as a suspect drug where DPH was used as a sleep aid and where at least one AE within the AI SMQ was reported. Any use of DPH with trade name including "Sleep", "Nighttime" or "PM" was assumed to involve use of DPH as a sleep aid. The supplemental analysis compared the reporting rates for DPH AEs in the AI SMQ for cases using DPH as a sleep aid versus cases using DPH not as a sleep aid. The ratio of the reporting rates for the respective populations gives an estimate of the relative reporting rate for the AEs after nighttime use as a sleep aid versus daytime uses of DPH.

The supplemental analysis identified 54 cases in which DPH was used as a sleep aid and was associated with an AE reported in the AI SMQ (the S.A group). These cases represented 1.0% (54/5644) of all reports and 6.1% (54/887) of the cases in which DPH was used as a sleep aid. There were 248 cases in which DPH was not used as a sleep aid but did report an AE in the AI SMQ (the NS.A group). These cases represented 4.4% (248/5644) of all reports and 5.2% (248/4757) of the cases in which DPH was not used as a sleep aid.

Relative reporting rates for these groups were computed as the ratio of the number of cases with an AE in the SMQ over the total number of cases. there was a 17% increase (6.1%/5.2%) in the reporting rate for cases with AEs in the AI SMQ for the group using DPH as a sleep aid with at least 1 event in the AI SMQ (the S.A group), compared to the reporting rate for the group that did not use DPH as a sleep aid but had at least 1 AE in the AI SMQ (the NS.A group).

There were three specific AEs in the AI SMQ with notably increased reporting rates in the group using DPH as a sleep aid. Falls had a reporting rate ratio of 3.06, with 32 and 56 events in the S.A group (those who took DPH as a sleep aid and reported an accident or injury) and NS.A group (those who did not take DPH as a sleep aid and reported an accident or injury), respectively. Head injury had a reporting rate ratio of 6.44, with 6 and 5 events in the S.A and NS.A groups respectively, and Laceration had a reporting rate ratio of 2.23, with 5 and 12 events in the S.A and NS.A groups, respectively. These were the only AEs in the AI SMQ with notably increased reporting rate ratios and sufficient numbers of events to make the ratios plausible. However, the

reporting ratio of Road traffic accidents was not substantially increased (1.29 with 6 events in the S.A group and 25 events in the NS.A group).

MO Comment: *The sponsor's supplemental analysis of FAERS data revealed a significant increase in the rate of accidents and injuries following nighttime use of DPH as a sleep aid versus other daytime uses of DPH ($p < 0.03$). These were falls, head injuries and lacerations, although the numbers of head injuries and head lacerations is small. The analysis did not find evidence of a significant increase in road accidents.*

8.3 WHO Post-marketing Diphenhydramine

The Sponsor submitted an analysis of the AEs reported for oral DPH as suspect or interacting drug in the WHO drug safety database covering reports from 1 January 2004 to 1 June 2012. The WHO analysis revealed 5198 cases involving 17891 MedDRA Preferred Terms. Of these reports, 1087 cases involving 2860 terms were reported from outside the United States and were a primary focus of this update (because the US cases are also reported to FDA AERS, and so they are analyzed separately). Five countries accounted for 85% of the ex-US reports: Germany (28.2%), Canada (22.9%), Cuba (19.4%), Singapore (6.5%) and the UK (3.7%).

For the 1087 ex-US reports, 57 were Not Serious (5.2%), 406 were Serious (37.4%) and there were 104 deaths (9.6%). A large fraction (47.8%, 520/1087) of the ex-US cases had no data for seriousness. A higher proportion of reports from the US are Serious or death reports: 47.3% (1945/4111) of the reports of US origin were categorized as serious and 44.9% (1846/4111) were deaths. The difference in proportions of death may reflect a change in FDA policy, whereby only expedited reports from manufacturers (serious or unexpected events or deaths) are currently entered in AERS for drugs with a 3 year marketing history.

Four SOCs accounted for 55.4% (9904/17891) of the terms in the overall total. They were: Psychiatric disorders 16.9% (3021/17891), Nervous system disorders 13.3% (2372/17891), Injury, poisoning and procedural complications 13.0%, (2318/17891) and General disorders and administration site conditions 12.3% (2193/17891).

For the exUS reports, the same four SOCs had the highest frequencies of reports and together represented 64.6% (1848/2860) of the terms in the overall total. They were: Psychiatric disorders 26.8% (766/2860), Nervous system disorders 18.4% (525/2860), Injury, poisoning and procedural complications 10.2%, (292/2860) and General disorders and administration site conditions 9.3% (265/2860).

Among exUS reports, females accounted for 57.3% (623/1087) of the reports and 59.2% (1694/2860) of the associated AE terms. Males accounted for 37.7% (410/1087) of the reports and 37.7% (1078/2860) of the reported AE terms. A total of 5.0% (54/1087) of the cases had no gender data.

There were no important differences in SOC relative reporting rates between the genders. However, females had moderately higher relative reporting rates for terms in the Eye disorders SOC compared to males (2.4%, 40/1694 versus 1.8%, 19/1078) and in the Vascular disorders SOC (2.9%, 49/1694 versus 2.1%, 23/1078).

The 15 most frequently reported terms with an overall total of $\geq 1\%$ of all reported terms accounted for 25.2% (4515/17891) of reported terms. The most frequent term overall was Completed suicide (4.0%, 724/17891, Table 4). A total of 699 of these 724 reports were from the US. Of the 15 most frequently reported terms, the sponsor notes that 14 terms are plausibly related to misuse or overdose of the drug.

Among ex-US cases, a similar picture arises. Of the 24 terms with relative reporting rates $\geq 1\%$, 19 involved drug misuse, overdose or symptoms associated with DPH overdose. Overall, the 3 most commonly reported terms were Suicide attempt (7.4%, 213/2860), Somnolence (5.7%, 164/2860) and Intentional drug misuse (4.6%, 131/2860). These same 3 terms were the most commonly reported for the serious reports and accounted for 27.4% (403/1469) of the reports in that category. Among the 104 fatal cases, the 5 most frequently reported terms accounted for 58.4% (139/238) of the terms reported for the category. They were: Toxicity to various agents (27.3%, 65/238), Substance abuse (13.0%, 31/238), Completed suicide (9.7%, 23/238), Overdose (4.6%, 11/238) and Drug abuse (3.8%, 9/238).

Table 4 WHO Most Frequently Reported Terms (>0.5%) DPH 2004-2012

MedDRA SOC Abbr.	MedDRA Preferred term	exUS	US	Overall Total
Psych	Completed suicide	25 (0.9)	699 (4.7)	724 (4.0)
Inj&P	Toxicity to various agents	95 (3.3)	481 (3.2)	576 (3.2)
Nerv	Somnolence	164 (5.7)	196 (1.3)	360 (2.0)
Genrl	Death	5 (0.2)	330 (2.2)	335 (1.9)
Psych	Suicide attempt	213 (7.4)	101 (0.7)	314 (1.8)
Psych	Intentional drug misuse	131 (4.6)	139 (0.9)	270 (1.5)
Card	Cardiac arrest	3 (0.1)	253 (1.7)	256 (1.4)
Inj&P	Overdose	30 (1.0)	222 (1.5)	252 (1.4)
Card	Cardio-respiratory arrest	2 (0.07)	239 (1.6)	241 (1.3)
Resp	Respiratory arrest	4 (0.1)	225 (1.5)	229 (1.3)
Inj&P	Intentional overdose	76 (2.7)	146 (1.0)	222 (1.2)
Nerv	Dizziness	56 (2.0)	136 (0.9)	192 (1.1)
Resp	Dyspnoea	32 (1.1)	154 (1.0)	186 (1.0)
Skin	Rash	69 (2.4)	117 (0.8)	186 (1.0)
Gastr	Vomiting	36 (1.3)	136 (0.9)	172 (1.0)
Skin	Urticaria	44 (1.5)	125 (0.8)	169 (0.9)
Inj&P	Multiple drug overdose	6 (0.2)	161 (1.1)	167 (0.9)
Gastr	Nausea	29 (1.0)	132 (0.9)	161 (0.9)
Immun	Hypersensitivity	16 (0.6)	145 (1.0)	161 (0.9)
Nerv	Convulsion	19 (0.7)	134 (0.9)	153 (0.9)
Skin	Pruritus	17 (0.6)	135 (0.9)	152 (0.8)
Psych	Insomnia	28 (1.0)	121 (0.8)	149 (0.8)

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Nerv	Loss of consciousness	16 (0.6)	131 (0.9)	147 (0.8)
Psych	Drug abuse	71 (2.5)	74 (0.5)	145 (0.8)
Genrl	Drug ineffective	15 (0.5)	128 (0.9)	143 (0.8)
Genrl	Product quality issue	2 (0.07)	141 (0.9)	143 (0.8)
Card	Tachycardia	81 (2.8)	56 (0.4)	137 (0.8)
Genrl	Fatigue	30 (1.0)	94 (0.6)	124 (0.7)
Nerv	Tremor	40 (1.4)	82 (0.5)	122 (0.7)
Psych	Agitation	47 (1.6)	73 (0.5)	120 (0.7)
Psych	Hallucination	34 (1.2)	85 (0.6)	119 (0.7)
Nerv	Headache	22 (0.8)	93 (0.6)	115 (0.6)
Inj&P	Accidental overdose	10 (0.3)	102 (0.7)	112 (0.6)
Nerv	Coma	18 (0.6)	94 (0.6)	112 (0.6)
Psych	Confusional state	32 (1.1)	80 (0.5)	112 (0.6)
Inj&P	Medication error	12 (0.4)	96 (0.6)	108 (0.6)
Inv	Heart rate increased	2 (0.07)	97 (0.6)	99 (0.6)
Genrl	Drug interaction	7 (0.2)	88 (0.6)	95 (0.5)
Genrl	Feeling abnormal	4 (0.1)	91 (0.6)	95 (0.5)
Surg	Off label use	3 (0.1)	91 (0.6)	94 (0.5)
Vasc	Hypotension	22 (0.8)	72 (0.5)	94 (0.5)
Psych	Anxiety	8 (0.3)	75 (0.5)	83 (0.5)
	Total AE terms^b (col %)	2860 (100)	15031 (100)	17891 (100)
	Total AE terms^b (row %)	2860 (16.0)	15031 (84.0)	17891 (100)
	Total cases (row %)	1087 (20.9)	4111 (79.1)	5198 (100)

^a Unless otherwise indicated, all percents are calculated based on the total number of terms for each geographic area group. Cells with 10 or more reports and relative reporting rates at least 25% higher than the relative reporting rate for the corresponding cell in the other geographic area are highlighted in bold type.

^b Total of all terms not just those in the table.

Source: Module 5, Section m 5-3-6-4, WHO DPH Table 4, p17/427

The Sponsor submitted an update covering the period 01 June 2012 through 26 February 2013 for DPH adverse event reports in the WHO drug safety database. All cases involving oral DPH as a suspect or interacting medication were extracted from the WHO database, omitting cases for which DPH was reported only as a concomitant medication. The route of administration acceptance criteria also included cases with “unknown”, “null” and transplacental administration. The latter is presumed to be fetal exposure from a maternal dose of oral drug.

The WHO database included 590 cases originating in the US which were provided to the WHO by the FDA and which were already included in FAERS, separately reported by the Sponsor. The Sponsor excluded the US cases from the report of cases in the WHO database. Cases of exUS origin comprised 23.5% (181/771) of all WHO cases, whereas reports from the US accounted for the remaining 76.5% (590/771). Among the exUS reports, 58.6% (106/181) were for females and 34.8% (63/181) were for males and 6.6% (12/181) had no reported gender.

Using data from both the Outcome and Seriousness fields, 405 deaths were identified (27 exUS, 378 US). Outcome data were not reported (Unknown or No outcome data) for 60.8% (110/181) of the exUS reports. Based on criteria employed by the WHO, 66.3% (120/181) of the reports of exUS origin were categorized as serious. In addition, 14.9% (27/181) were deaths.

For the exUS reports, 6 SOCs accounted for 76.6% (479/625) of the total AE terms. They were: Psychiatric disorders (29.3%, 183/625), Nervous system disorders (13.3%, 83/625), Injury, poisoning and procedural complications (13.0%, 81/625), General disorders and administration site conditions (7.7%, 48/625), Cardiac disorders (6.7%, 42/625) and Gastrointestinal disorders (6.7%, 42/625).

For the US reports, the four SOCs with the highest frequencies of reports together represented 59.7% (1027/1720) of the total terms for US cases. They were: Psychiatric disorders (19.3%, 332/1720), Injury, poisoning and procedural complications (15.8%, 271/1720), General disorders and administration site conditions (12.4%, 213/1720) and Cardiac disorders (12.3%, 211/1720).

Table 5 presents the most frequently reported MedDRA Preferred Terms in descending order of overall frequency for the exUS and US reports in the WHO drug safety database. The highest frequency terms pertain to completed suicides, suicide attempts, drug abuse, intentional overdoses and misuse, and toxic effects known to be associated with DPH overdoses.

MO Comment: *The WHO drug safety database for DPH over the period from Jan 1, 2004 through Feb 26, 2013 received 5198+771=5969 reports including 1950+405=2355 deaths. These reports were predominantly suicides, suicide attempts, drug abuse, intentional overdoses and misuse, or reports of AEs known to be associated with DPH overdoses.*

Table 5 WHO Most Frequently Reported ($\geq 0.05\%$) MedDRA Terms in Descending Order of Overall Frequency N (%) June 2012 to 26 Feb 2013

MedDRA SOC Abbr.	MedDRA Preferred term	exUS	US	Overall Total
Inj&P	Toxicity to various agents	12 (1.9)	150 (8.7)	162 (6.9)
Psych	Completed suicide	5 (0.8)	152 (8.8)	157 (6.7)
Card	Cardio-respiratory arrest		95 (5.5)	95 (4.1)
Card	Cardiac arrest	1 (0.2)	79 (4.6)	80 (3.4)
Psych	Suicide attempt	70 (11.2)	10 (0.6)	80 (3.4)
Resp	Respiratory arrest		74 (4.3)	74 (3.2)
Psych	Intentional drug misuse	40 (6.4)	22 (1.3)	62 (2.6)
Psych	Drug abuse	15 (2.4)	45 (2.6)	60 (2.6)
Inj&P	Intentional overdose	42 (6.7)	12 (0.7)	54 (2.3)
Genrl	Death	1 (0.2)	41 (2.4)	42 (1.8)
Card	Tachycardia	32 (5.1)	5 (0.3)	37 (1.6)
Inj&P	Overdose	7 (1.1)	30 (1.7)	37 (1.6)
Nerv	Somnolence	21 (3.4)	11 (0.6)	32 (1.4)
Surg	Off label use	1 (0.2)	30 (1.7)	31 (1.3)
Gastr	Nausea	8 (1.3)	21 (1.2)	29 (1.2)
Genrl	Fatigue	18 (2.9)	9 (0.5)	27 (1.2)
Inj&P	Poisoning		27 (1.6)	27 (1.2)
Gastr	Vomiting	13 (2.1)	13 (0.8)	26 (1.1)
Skin	Rash	10 (1.6)	13 (0.8)	23 (1.0)
Psych	Hallucination	6 (1.0)	14 (0.8)	20 (0.9)
Genrl	Drug ineffective		19 (1.1)	19 (0.8)
Genrl	Drug interaction		18 (1.0)	18 (0.8)
Immun	Hypersensitivity	2 (0.3)	16 (0.9)	18 (0.8)
Skin	Urticaria	2 (0.3)	16 (0.9)	18 (0.8)
Nerv	Coma	9 (1.4)	7 (0.4)	16 (0.7)
Nerv	Dizziness	7 (1.1)	8 (0.5)	15 (0.6)
Psych	Agitation	8 (1.3)	7 (0.4)	15 (0.6)
Psych	Insomnia	1 (0.2)	14 (0.8)	15 (0.6)
Skin	Pruritus	5 (0.8)	10 (0.6)	15 (0.6)
Immun	Drug hypersensitivity		14 (0.8)	14 (0.6)
Nerv	Convulsion	5 (0.8)	9 (0.5)	14 (0.6)
Resp	Dyspnoea	2 (0.3)	12 (0.7)	14 (0.6)
Skin	Angioedema	6 (1.0)	8 (0.5)	14 (0.6)
Inv	Drug level increased	11 (1.8)	2 (0.1)	13 (0.6)
Nerv	Loss of consciousness	4 (0.6)	9 (0.5)	13 (0.6)
Genrl	Chest pain	2 (0.3)	9 (0.5)	11 (0.5)
Nerv	Dysarthria	8 (1.3)	3 (0.2)	11 (0.5)
Vasc	Hypotension	2 (0.3)	9 (0.5)	11 (0.5)
Vasc	Systolic hypertension	11 (1.8)		11 (0.5)
	Total AE terms^b (col %)	625 (100)	1720 (100)	2345 (100)
	Total AE terms^b (row %)	625 (26.7)	1720 (73.3)	2345 (100)
	Total cases (row %)	181 (23.5)	590 (76.5)	771 (100)

^a Unless otherwise indicated, all percents are calculated based on the total number of terms for each geographic area group. Cells with 10 or more reports and relative reporting rates at least 25% higher than the relative reporting rate for the corresponding cell in the other geographic area are highlighted in bold type.

^b Total of all terms not just those in the table.

Source: Module 5, Section m 5-3-6-4, WHO DPH Update Table 4, p17/155

Naproxen WHO Update

The Sponsor submitted an analysis of the AEs reported for oral naproxen as suspect or interacting drug in the WHO drug safety database covering the period from 4 December 2011 to 26 February 2013. The WHO analysis revealed 13750 cases involving 19714 MedDRA Preferred Terms. Of these reports, 2361 cases involving 3576 terms were reported from outside the United States and were a primary focus of this update (because the US cases are also reported to FDA AERS, and so they are analyzed separately). Three countries accounted for 72.3% (1706/2361) of the exUS reports. These were: Singapore 52.0% (1227/2361), Peru 12.3% (290/2361) and Thailand 8.0%, (189/2361).

Overall, there was no reported gender for 40.1% (5517/13750) of cases. The gender ratio for cases with reported gender was 2.56 female:male (5918 female and 2315 male). Among the exUS reports, the gender ratio was 1.65 female:male (1411 female and 853 male) with only a small fraction of cases, 4.1% (97/2361) that reported no gender.

There were 199 naproxen death reports identified by WHO (11 exUS, 188 US). Based on WHO criteria, 13.6% (320/2361) of the reports of exUS origin were categorized as serious and 0.5% (11/2361) were deaths. A total of 10.0% (1135/11389) of the reports of US origin were categorized as serious and 1.7% (188/11389) were deaths.

A minority of exUS reports (31.9%, 753/2361) had valid daily dose data and 5.4% (127/2361) were in the daily dose group of interest, \leq 440 mg.

Four SOCs accounted for 68.3% (13461/19714) of the terms in the overall total. They were: General disorders and administration site conditions (33.3%, 6560/19714), Gastrointestinal disorders (13.5%, 2660/19714), Nervous system disorders 12.3% (2430/19714) and Skin and subcutaneous tissue disorders (9.2% (1811/19714).

For the exUS reports, the four SOCs with the highest frequencies of reports together represented 78.4% (2802/3576) of the terms in the overall total. They were: Skin and subcutaneous tissue disorders (31.4%, 1124/3576), Gastrointestinal disorders (19.1%, 683/3576), Eye disorders (19.0%, 678/3576) and General disorders and administration site conditions (8.9%, 317/3576).

In general, compared to the relative reporting rates for US reports, the rates for the exUS reports were higher in the Skin and subcutaneous tissue disorders SOC (31.4%, 1124/3576 versus 4.3%, 687/16138) and in the Eye disorders SOC (19.0%, 678/3576 versus 1.0%, 160/16138).

The 19 AE terms with an Overall (US and exUS) frequency \geq 1% of all reported terms accounted for 53.0% (10452/19714) of reported terms. The 5 most frequent terms overall were: No adverse event (15.4%, 3040/19714), Headache (6.3%, 1246/19714),

Drug ineffective (5.8%, 1137/19714), Pain (3.4%, 668/19714) and Periorbital oedema (2.8%, 544/19714). For the 4 most frequently reported terms, nearly all the reports were from the US (6062/6091), and only 29/6091 reports were exUS. However, for the overall 5th most frequently reported term, all 544 reports of Periorbital oedema were exUS reports.

Eight of the 10 most frequently reported terms for exUS reports were related to allergy. These were: Periorbital oedema, Angioedema, Rash, Urticaria, Pruritus, Face oedema, Dyspnoea and Eyelid oedema. Together these 8 terms accounted for 48.4% (1731/3576) of all reported terms for the exUS cases. Hypersensitivity was reported more frequently in cases from the US than from exUS (1.1%, 177/16138 versus 0.4%, 16/3576).

There were 320 serious cases (total 753 terms) and 11 deaths (total 93 terms) among the exUS reports. Among the 10 most frequently reported terms for serious reports, 5 involved gastrointestinal events. The five terms were: Gastrointestinal haemorrhage (3.9%, 29/753), Melaena (2.3%, 17/753), Upper gastrointestinal haemorrhage (2.1%, 16/753), Haematemesis (1.6%, 12/753) and Gastric ulcer (1.6%, 12/753). Among the 93 reported terms for deaths, gastrointestinal haemorrhage (3.2%, 3/93) was the term most frequently reported. All but three AE terms (Gastrointestinal haemorrhage [3 instances], Renal failure [2 instances] and Death [2 instances]) were single occurrences.

8.4 American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) formerly known as the Toxic Exposure Surveillance System (TESS)

Diphenhydramine

Data on cases reported to a participating poison control center (PCC) in the United States involving a human exposure to diphenhydramine are maintained in the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS), formerly known as the Toxic Exposure Surveillance System (TESS). The Sponsor reported data on DPH cases from NPDS covering the period from January 2004 to December 2011.

Background

The TESS system was developed in 1983 to identify toxic hazards and to help prevent poisoning. The database, now known as NPDS, accumulates approximately 2.4 million cases per year and has recorded over **50 million human exposure cases, not all of which are poisonings or overdoses**. The NPDS database records information on the demographic characteristics of the patients reported and on the circumstances, management and outcome of the exposure. In general, the information is provided by a telephone call made to a PCC by a patient or someone acting on behalf of a patient. Commonly, follow-up calls to the reporter are made for additional information. Information recorded in the database includes clinical effects (CE), therapies (TH) and

exposure scenarios (SC). Narrative case reports are not part of the standard NPDS database.

Case selection

Data from the NPDS system were requested for all cases of diphenhydramine drug exposure from January 2004 to December 2011, excluding requests for information from the PCCs. After removal of duplicate data, the dataset comprised 277322 reports of exposure to DPH.

Demographics of DPH reports to AAPCC

More than half of all DPH exposures (52+34717+113331, 53.4%) occurred in children under the age of 13. Only 36.4% of DPH exposures occurred in adults aged 18-60 yo. In the pediatric age ranges up to 13 years, there was an approximately equal distribution of females and males, whereas in all older age ranges females outnumbered males in approximately the ratio 1.7:1 (63% female, 37% male).

The route of exposure was oral ingestion in 98.9% of reports. The majority of cases involved exposure to a single substance (71.6%, 198583/277322), whereas 17.8% (49357/277322) involved 2 substances and 10.6% (29382/277322) involved 3 or more substances. Single substance exposures predominated in all age ranges and in both genders.

Nature of Exposure

Unintentional exposures accounted for 39.5% of reports (109481/277322) and were the largest category, followed by Intentional – Suspected suicide (25.7%, 71202/277322) and Unintentional – therapeutic error (22.8%, 63103/277322). Lesser fractions were reported for Intentional misuse (3.8%, 10617/277322) and Adverse reaction – drug (2.3%, 6345/277322). No other reason for exposure accounted for more than 2.7% of overall reports.

The reasons for exposure depended on age, where unintentional exposures were more frequent for infants and children, while intentional and suspected suicide reports accounted for the majority of reports for adolescents and adults. In the two age ranges from 1 month to < 13 years, more than two thirds of reports (67.9%, 23583/34717 among the infants and 67.3%, 76307/113331 among the children) were of Unintentional – General exposure. In the adolescent and adult age ranges, Intentional – Suspected suicide accounted for 51.0% (10807/21175) and 57.6% (58096/100825) of the reports, respectively. Among infants, children and elderly, Unintentional – Therapeutic error accounted for 30.1% (10465/34717), 28.7% (32506/113331) and 38.9% (2334/6005) of the reports, respectively. Adverse reaction – drug was reported in 8.0% (478/6005) of the cases among the elderly. Intentional – Misuse was reported predominantly in the adolescent, adult and elderly age ranges with a mean relative reporting rate for these age ranges of 7.6% (9783/128005).

There were notable gender-dependent differences in the relative reporting rates of the two most frequently reported reasons for exposure. Among females, Unintentional – General (35.9%, 54306/151376), was the most commonly reported reason for exposure, followed by Intentional – Suspected suicide (30.1%, 45633/151376). For males, the most commonly reported reason for exposure was Unintentional – General (44.0%, 55002/125006) and Intentional – Suspected suicide (20.1%, 25137/125006) was second.

There were 346 reported deaths, including 1 in the neonate <1 mo, 8 in the 1 mo ≤ age <2 yr, 6 in the 2 ≤ age <13 yr range and 7 in the 13 ≤ age <18 yr range. A total of 284 of the 346 deaths were adults 18 yr to <60 yr, and there were 37 death reports in the ≥ 60 yr age range. Overall, major effects (that were life-threatening or resulted in significant residual disability or disfigurement) were reported in 1.6% (4323/277322) of cases and were more frequent in the adolescent, adult and elderly age ranges (3.2%, 4155/128005) than in the pediatric age ranges (0.1%, 163/148100). The majority of cases, 56.9% (157770/277322), did not have the patient seen at a health care facility. There is Level of care data for only 43.1% (119552/277322) of the reports. Among the adolescents, 24.8% (5250/21175) were treated and released whereas for adults the proportion was 17.7% (17811/100825). Similar proportions of adolescents and adults were admitted to critical care units (14.6%, 3083/21175 versus 20.2%, 20417/100825), psychiatric facilities (12.0%, 2540/21175 versus 12.7%, 12773/100825) and non-critical care units (8.9%, 1879/21175 versus 8.0%, 8059/100825).

Table 6 provides a listing of the most commonly reported CEs which were judged to be related to DPH exposure. The 14 most frequently reported CEs together accounted for 81.1% (191876/236646) of the total reported effects. These included: Drowsiness/lethargy, Tachycardia, Agitated/irritable, Confusion, Hypertension, Hallucinations, Mydriasis, Vomiting, Slurred speech, Dizziness, Nausea, Tremor, and Coma. Also noteworthy CEs are ataxia, seizure, and conduction disturbance.

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Table 6 Most Frequently Reported Clinical Effect Terms Judged to be Related to DPH Exposure by Age Group

Organ System	Clinical effect term	< 1 mo	1 mo to < 2 yr	2 yr to < 13 yr	13 yr to < 18 yr	18 yr to < 60 yr	≥ 60 yr	No age group data	Overall Total
Neuro	Drowsiness/lethargy	11 (21.2)	3470 (10.0)	15329 (13.5)	5715 (27.0)	31974 (31.7)	1281 (21.3)	136 (11.2)	57916 (20.9)
Cardio	Tachycardia	3 (5.8)	395 (1.1)	1646 (1.5)	6064 (28.6)	27891 (27.7)	520 (8.7)	52 (4.3)	36571 (13.2)
Neuro	Agitated/irritable	4 (7.7)	818 (2.4)	3253 (2.9)	2090 (9.9)	10466 (10.4)	367 (6.1)	38 (3.1)	17036 (6.1)
Misc	Other	2 (3.8)	420 (1.2)	1886 (1.7)	1440 (6.8)	8053 (8.0)	464 (7.7)	73 (6.0)	12338 (4.4)
Neuro	Confusion		35 (0.1)	543 (0.5)	2161 (10.2)	8852 (8.8)	443 (7.4)	15 (1.2)	12049 (4.3)
Cardio	Hypertension		51 (0.1)	242 (0.2)	1505 (7.1)	9413 (9.3)	358 (6.0)	12 (1.0)	11581 (4.2)
Neuro	Hallucinations/delusions		82 (0.2)	1088 (1.0)	1949 (9.2)	5272 (5.2)	145 (2.4)	20 (1.6)	8556 (3.1)
Ocular	Mydriasis		165 (0.5)	1077 (1.0)	1711 (8.1)	5169 (5.1)	95 (1.6)	10 (0.8)	8227 (3.0)
Gastro	Vomiting	1 (1.9)	337 (1.0)	979 (0.9)	1261 (6.0)	4942 (4.9)	118 (2.0)	30 (2.5)	7668 (2.8)
Neuro	Slurred speech		2 (0.01)	118 (0.1)	614 (2.9)	4323 (4.3)	187 (3.1)	13 (1.1)	5257 (1.9)
Neuro	Dizziness/vertigo		34 (0.10)	364 (0.3)	706 (3.3)	2868 (2.8)	181 (3.0)	19 (1.6)	4172 (1.5)
Gastro	Nausea		27 (0.08)	247 (0.2)	718 (3.4)	2723 (2.7)	93 (1.5)	12 (1.0)	3820 (1.4)
Neuro	Tremor	1 (1.9)	66 (0.2)	260 (0.2)	564 (2.7)	2649 (2.6)	118 (2.0)	12 (1.0)	3670 (1.3)
Neuro	Coma		9 (0.03)	28 (0.02)	191 (0.9)	2654 (2.6)	118 (2.0)	15 (1.2)	3015 (1.1)
Dermal	Erythema/flushed		133 (0.4)	536 (0.5)	334 (1.6)	1520 (1.5)	85 (1.4)	4 (0.3)	2612 (0.9)
Neuro	Ataxia		149 (0.4)	534 (0.5)	357 (1.7)	1439 (1.4)	81 (1.3)	10 (0.8)	2570 (0.9)
Cardio	Conduction disturbance		4 (0.01)	39 (0.03)	265 (1.3)	2023 (2.0)	91 (1.5)	1 (0.08)	2423 (0.9)
Misc	Electrolyte abnormality		3 (0.01)	17 (0.02)	211 (1.0)	1887 (1.9)	76 (1.3)	1 (0.08)	2195 (0.8)
Neuro	Seizure (single)		11 (0.03)	66 (0.06)	376 (1.8)	1528 (1.5)	17 (0.3)	4 (0.3)	2002 (0.7)
Cardio	Hypotension		10 (0.03)	41 (0.04)	181 (0.9)	1635 (1.6)	99 (1.6)	4 (0.3)	1970 (0.7)
Misc	Fever/hyperthermia		52 (0.1)	146 (0.1)	259 (1.2)	1277 (1.3)	44 (0.7)	6 (0.5)	1784 (0.6)
Resp	Respiratory depression		6 (0.02)	25 (0.02)	76 (0.4)	1243 (1.2)	74 (1.2)	4 (0.3)	1428 (0.5)
Resp	Hyperventilation/tachypnea	1 (1.9)	22 (0.06)	60 (0.05)	213 (1.0)	1054 (1.0)	40 (0.7)	1 (0.08)	1391 (0.5)
Gastro	Abdominal Pain		4 (0.01)	212 (0.2)	289 (1.4)	783 (0.8)	18 (0.3)	5 (0.4)	1311 (0.5)
Misc	CPK elevated		7 (0.02)	23 (0.02)	81 (0.4)	914 (0.9)	42 (0.7)	1 (0.08)	1068 (0.4)
Cardio	ECG change (other)		7 (0.02)	18 (0.02)	118 (0.6)	751 (0.7)	48 (0.8)		942 (0.3)
Ocular	Nystagmus		6 (0.02)	31 (0.03)	150 (0.7)	730 (0.7)	12 (0.2)		929 (0.3)
Misc	Acidosis		6 (0.02)	8 (0.01)	90 (0.4)	771 (0.8)	41 (0.7)	1 (0.08)	917 (0.3)
Misc	ADR to treatment		16 (0.05)	88 (0.08)	112 (0.5)	513 (0.5)	13 (0.2)	1 (0.08)	743 (0.3)
Heme Hep	AST, ALT>100<=1,000		1 (0.00)	5 (0.00)	43 (0.2)	657 (0.7)	28 (0.5)		734 (0.3)
Cardio	Bradycardia	1 (1.9)	6 (0.02)	25 (0.02)	83 (0.4)	544 (0.5)	61 (1.0)	1 (0.08)	721 (0.3)
Renal	Urinary retention		6 (0.02)	36 (0.03)	106 (0.5)	534 (0.5)	33 (0.5)	2 (0.2)	717 (0.3)
Neuro	Headache			78 (0.07)	128 (0.6)	473 (0.5)	23 (0.4)	10 (0.8)	712 (0.3)
Ocular	Miosis		11 (0.03)	30 (0.03)	75 (0.4)	536 (0.5)	38 (0.6)		690 (0.2)
Neuro	Seizures (multi/discrete)		11 (0.03)	22 (0.02)	119 (0.6)	483 (0.5)	10 (0.2)	1 (0.08)	646 (0.2)

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Organ System	Clinical effect term	< 1 mo	1 mo to < 2 yr	2 yr to < 13 yr	13 yr to < 18 yr	18 yr to < 60 yr	≥ 60 yr	No age group data	Overall Total
Dermal	Rash		54 (0.2)	180 (0.2)	43 (0.2)	308 (0.3)	44 (0.7)	2 (0.2)	631 (0.2)
Dermal	Pruritus		12 (0.03)	153 (0.1)	50 (0.2)	359 (0.4)	47 (0.8)	3 (0.2)	624 (0.2)
Resp	Dyspnea	2 (3.8)	7 (0.02)	33 (0.03)	39 (0.2)	455 (0.5)	32 (0.5)	9 (0.7)	577 (0.2)
Misc	Diaphoresis		4 (0.01)	33 (0.03)	51 (0.2)	455 (0.5)	30 (0.5)	2 (0.2)	575 (0.2)
Dermal	Edema		37 (0.1)	157 (0.1)	36 (0.2)	282 (0.3)	56 (0.9)	3 (0.2)	571 (0.2)
Ocular	Ocular - Irritation/pain		99 (0.3)	252 (0.2)	17 (0.08)	165 (0.2)	25 (0.4)	1 (0.08)	559 (0.2)
Ocular	Blurred vision			13 (0.01)	92 (0.4)	439 (0.4)	8 (0.1)		552 (0.2)
Cardio	Chest pain (incl noncardiac)			10 (0.01)	61 (0.3)	448 (0.4)	22 (0.4)	5 (0.4)	546 (0.2)
Dermal	Dermal - Irritation/pain		26 (0.07)	174 (0.2)	37 (0.2)	233 (0.2)	47 (0.8)	3 (0.2)	520 (0.2)
Neuro	Dystonia		18 (0.05)	124 (0.1)	48 (0.2)	277 (0.3)	22 (0.4)	3 (0.2)	492 (0.2)
Dermal	Hives/welts		29 (0.08)	139 (0.1)	28 (0.1)	238 (0.2)	28 (0.5)	3 (0.2)	465 (0.2)
Renal	Creatinine increased			1 (0.00)	17 (0.08)	378 (0.4)	35 (0.6)	2 (0.2)	433 (0.2)
Dermal	Puncture wound/sting		25 (0.07)	166 (0.1)	14 (0.07)	158 (0.2)	36 (0.6)		399 (0.1)
Gastro	Oral irritation		25 (0.07)	110 (0.10)	27 (0.1)	166 (0.2)	59 (1.0)		387 (0.1)
Neuro	Numbness		1 (0.00)	21 (0.02)	41 (0.2)	282 (0.3)	16 (0.3)	4 (0.3)	365 (0.1)
Cardio	Dysrhythmia (other)			7 (0.01)	39 (0.2)	292 (0.3)	21 (0.3)	2 (0.2)	361 (0.1)
Resp	Respiratory arrest	1 (1.9)	9 (0.03)	10 (0.01)	12 (0.06)	300 (0.3)	27 (0.4)	2 (0.2)	361 (0.1)
Misc	Hypoglycemia		2 (0.01)	7 (0.01)	17 (0.08)	309 (0.3)	5 (0.08)	1 (0.08)	341 (0.1)
Misc	Anion gap increased		2 (0.01)	2 (0.00)	33 (0.2)	287 (0.3)	13 (0.2)		337 (0.1)
Misc	Rhabdomyolysis			2 (0.00)	19 (0.09)	286 (0.3)	12 (0.2)		319 (0.1)
Cardio	Cardiac arrest	1 (1.9)	7 (0.02)	7 (0.01)	9 (0.04)	255 (0.3)	27 (0.4)	2 (0.2)	308 (0.1)
Resp	X-ray findings(+)			6 (0.01)	18 (0.09)	264 (0.3)	19 (0.3)	1 (0.08)	308 (0.1)
Gastro	Throat irritation		1 (0.00)	52 (0.05)	34 (0.2)	177 (0.2)	36 (0.6)	2 (0.2)	302 (0.1)
Neuro	Muscle weakness		3 (0.01)	17 (0.02)	29 (0.1)	219 (0.2)	23 (0.4)	3 (0.2)	294 (0.1)
Gastro	Diarrhea		16 (0.05)	65 (0.06)	27 (0.1)	171 (0.2)	12 (0.2)	2 (0.2)	293 (0.1)
Heme Hep	AST, ALT>1,000				14 (0.07)	251 (0.2)	9 (0.1)		274 (0.1)
Total related CE terms^b (row %)		28 (0.01)	6896 (2.9)	31269 (13.2)	31700 (13.4)	159714 (67.5)	6455 (2.7)	584 (0.2)	236646 (100)
Cases with related CE term(s) (row %)		19 (0.02)	5262 (4.8)	22551 (20.7)	12977 (11.9)	65110 (59.7)	2852 (2.6)	352 (0.3)	109123 (100)
Total cases (row %)		52 (0.02)	34717 (12.5)	113331 (40.9)	21175 (7.6)	100825 (36.4)	6005 (2.2)	1217 (0.4)	277322 (100)
% Total cases with CE term(s)		36.5	15.2	19.9	61.3	64.6	47.5	28.9	39.3

^a Unless otherwise indicated, all percentages are calculated based on the total number of case reports for each column, i.e., for each age group or for the Overall Total.

^b The total is for all the terms not just those displayed in this table.

Source: Module 5, Section m 5-3-6-5, AAPCC DPH Table 5, p19/74

Gender and Exposure

As noted above in the 13 yr to < 60 yr age group, the majority of reports involved females (13316+62650)/(21175+100825) about 62%. This is roughly consistent with the gender ratio of **intentional/suicides, 45633 in females and 25137 in males**. Likewise, in the pediatric age groups, the proportions of males and females are approximately equal, and the gender ratio for unintentional/therapeutic error is close to unity, 33154 female and 29866 male.

Table 7 Exposure Site and Reason for Patients Exposed to DPH (2004-2011) by Significant Medical Outcome

Category ^a	Moderate effects	Major effects	Death
Total case reports	33131	4323	346
Exposure site (N, %)			
Own residence	30488 (92.0)	3880 (89.8)	277 (80.1)
Unknown	1140 (3.4)	224 (5.2)	39 (11.3)
Other residence	552 (1.7)	69 (1.6)	14 (4.0)
Other	352 (1.1)	51 (1.2)	6 (1.7)
Public area	286 (0.9)	68 (1.6)	5 (1.4)
Health care facility	172 (0.5)	25 (0.6)	4 (1.2)
School	103 (0.3)	4 (0.09)	
Workplace	32 (0.10)	1 (0.02)	1 (0.3)
Restaurant / food service	6 (0.02)	1 (0.02)	
Exposure reason (N, %)			
Intentional - Suspected suicide	23849 (72.0)	3589 (83.0)	207 (59.8)
Unintentional - General	2604 (7.9)	199 (4.6)	7 (2.0)
Intentional - Abuse	1830 (5.5)	167 (3.9)	49 (14.2)
Intentional - Misuse	1420 (4.3)	67 (1.5)	3 (0.9)
Intentional - Unknown	1077 (3.3)	125 (2.9)	25 (7.2)
Adverse reaction - Drug	769 (2.3)	43 (1.0)	5 (1.4)
Unintentional - Therapeutic error	712 (2.1)	23 (0.5)	2 (0.6)
Unknown reason	452 (1.4)	81 (1.9)	42 (12.1)
Unintentional - Misuse	221 (0.7)	9 (0.2)	
Unintentional - Unknown	72 (0.2)	11 (0.3)	3 (0.9)
Unintentional - Bite / sting	37 (0.1)	1 (0.02)	
Other - Malicious	19 (0.06)	4 (0.09)	3 (0.9)
Adverse reaction - Food	25 (0.08)		
Adverse reaction - Other	14 (0.04)	2 (0.05)	
Other - Withdrawal	12 (0.04)	1 (0.02)	
Unintentional - Environmental	11 (0.03)		
Unintentional - Food poisoning	3 (0.01)		
Unintentional - Occupational	3 (0.01)		
Other - Contamination / tampering	1 (0.00)	1 (0.02)	

^a Unless otherwise indicated, all percentages are calculated based on the total number of case reports for each column, *i.e.*, for each medical outcome.

Source: Module 5, Section 5-3-6-5, Table 15, p39/74

The exposure reason for the majority of reports for each of the outcome groups was Intentional – Suspected suicide and this varied from moderate effects (72.0%, 23849/33131) to major effects (83.0%, 3589/4323) to deaths (59.8%, 207/346). Unintentional-general was reported for 7.9% (2604/33131) of the reports with moderate effects and for 4.6% (199/4323) of the reports with major effects. Among the deaths,

Intentional – abuse (14.2%, 49/346) and Unknown reason (12.1%, 42/346) were the second and third most frequently reported terms

8.5 DAWN

Diphenhydramine from DAWN

This section summarizes data on cases involving diphenhydramine reported to the Drug Abuse Warning Network (DAWN) which is supported by the Substance Abuse and Mental Health Services Administration (SAMHSA). The dataset covers the period from 01 January 2006 to 31 December 2009 and comprises information for all types of drug-related emergency department (ED) visits from a national sample of EDs, with an over-sampling of selected metropolitan areas. Days of operation are selected systematically within each hospital's ED. National estimates of ED visits are generated, after weighting and adjustments, from the aggregate data submitted by these hospitals.

DAWN gathers information on all types of drugs, including illegal drugs, prescription and non-prescription pharmaceuticals, nonpharmaceutical inhalants and alcohol in combination with a drug. Alcohol use alone as a reason for an emergency department visit is reported only if the patient is < 21 years old. Information is collected on visits related to drug use, drug misuse and drug abuse. The following categories are used to classify a case: Suicide attempt, Seeking detox, Adverse reaction, Overmedication, Malicious poisoning, Accidental ingestion and Other.

DAWN also captures information regarding deaths, including suicides, associated with drug substances for 13 States: Delaware (DE), Massachusetts (MA), Maryland (MD), Maine (ME), New Hampshire (NH), New Mexico (NM), Oklahoma (OK), Oregon (OR), Rhode Island (RI), Utah (UT), Virginia (VA), Vermont (VT), and West Virginia (WV). These data are not national estimates but are actual counts from medical examiner and coroner reports. DAWN death data exclude deaths at ages five and younger, and they are suppressed if the count is less than four. Death data were obtained through 2010.

MO Comment: *The DAWN death data were not available to the Sponsor. The submission notes a total of 5 deaths in the DAWN database, which is not correct. There were 1098 reportable deaths associated with DPH between 2004 and 2011 (from 13 states; age greater than 5; reports are suppressed from an entire state for a year if the count is less than 4).*

Over the 4 year period between 2006 and 2009, there were 15143 ED visits reported involving diphenhydramine. The numbers of ED visits increased steadily over the years: there were 3141 in 2006, 3485 in 2007, 4185 in 2008, and 4332 in 2009. The gender distribution was consistently female-dominated in a ratio 1.8:1 (64% female, 35.9% male).

MO Comment: *This is the same gender ratio as reported by AAPCC for DPH.*

The proportions of case types were similar across the years. The three case types with the largest proportions of reports for diphenhydramine were: Overmedication (34.4%, 5212/15143), Suicide attempt (26.7%, 4041/15143) and Adverse reaction (23.6%, 3577/15143). Route of administration data was not documented for 67.5% (10214/15143) of the reports and was recorded as oral for 33.4% (5052/15143). Seven other route of administration categories accounted for < 1.7% of reports. These percentages sum to more than 100% since some visits recorded more than one form of diphenhydramine.

Table 8 Characteristics and Case Report Data for Reports Associated with DPH Stratified by Year of Reporting N(%)

	2006	2007	2008	2009	Overall
Type of case					
Overmedication	1074 (34.2)	1147 (32.9)	1460 (34.9)	1531 (35.3)	5212 (34.4)
Suicide attempt	844 (26.9)	994 (28.5)	1134 (27.1)	1069 (24.7)	4041 (26.7)
Adverse reaction	722 (23.0)	823 (23.6)	927 (22.2)	1105 (25.5)	3577 (23.6)
Other	365 (11.6)	335 (9.6)	468 (11.2)	406 (9.4)	1574 (10.4)
Accidental ingestion	112 (3.6)	165 (4.7)	175 (4.2)	205 (4.7)	657 (4.3)
Seeking detox	18 (0.6)	19 (0.5)	17 (0.4)	13 (0.3)	67 (0.4)
Malicious poisoning	6 (0.2)	2 (0.06)	4 (0.10)	3 (0.07)	15 (0.10)
Route of administration					
Oral	1427 (45.4)	1277 (36.6)	1287 (30.8)	1061 (24.5)	5052 (33.4)
Injected	22 (0.7)	26 (0.7)	28 (0.7)	35 (0.8)	111 (0.7)
Missing	23 (0.7)	10 (0.3)	26 (0.6)	25 (0.6)	84 (0.6)
Other	6 (0.2)	6 (0.2)	15 (0.4)	12 (0.3)	39 (0.3)
Multiple routes for this drug	3 (0.10)	3 (0.09)	2 (0.05)	1 (0.02)	9 (0.06)
Inhaled, sniffed, snorted	1 (0.03)	2 (0.06)	2 (0.05)	3 (0.07)	8 (0.05)
Smoked	1 (0.03)	2 (0.06)	1 (0.02)		4 (0.03)
Transdermal				2 (0.05)	2 (0.01)
Not documented	1729 (55.0)	2241 (64.3)	2928 (70.0)	3316 (76.5)	10214 (67.5)

MO Comment: *The ED visits from DAWN were predominantly from oral ingestion, in cases where route of administration is known, also reported by AAPCC. However, DAWN gives AE as similar to suicide attempt, whereas AAPCC reports far more intentional/suicide in comparison to AE.*

Over the years, the number of drugs reported for a case was relatively stable. The median number of reported drugs was 2.

Three formulations of diphenhydramine accounted for 98.8% (15330/15523) of the reports for diphenhydramine. These were: Diphenhydramine (65.0%, 10093/15523), Acetaminophen/Diphenhydramine (31.7%, 4916/15523) and Diphenhydramine/Ibuprofen (2.1%, 321/15523).

Overall, a minority of cases (8.0%, 1208/15143) involved illicit drugs but slightly less than half of all cases (44.9%, 6801/15143) involved the misuse or abuse of diphenhydramine.

Patient disposition was similar across the years. Overall, almost half of the cases (47.7%, 7224/15143) were discharged home. The fraction of cases admitted to an ICU or critical care unit was 9.4% (1431/15143) of the overall total.

The profile of demographic and case characteristics for diphenhydramine as reflected in the Dawn data covering the years from 2006 to 2009 was, in general, similar across the years of reporting. Adult patients (18-29 years old) appear to have had the highest rates of reporting for ED visits associated with diphenhydramine and these visits appeared to be primarily the result of overmedication, suicide attempts and adverse drug reactions.

MO Comment: *The vast majority of ED visits 2006-2009 were associated with single ingredient DPH and DPH/Acetaminophen (together, over 97% of ED visits). About half of the cases involved misuse or abuse of DPH. The DPH update showed similar results.*

MO Summary Comment: *The postmarketing drug safety databases AERS and WHO, and the DAWN and AAPCC databases from emergency departments and poison control centers, respectively, show that DPH poisonings are common, but that DPH is relatively non-toxic except in large overdoses. The serious or fatal cases of DPH toxicity are predominantly intentional overdoses or suicides. DAWN reported 15143 ED visits over the 4 yr period 2006-9, averaging 3786 visits per yr and steadily increasing over that time. The DAWN death data were not available to the Sponsor. The submission notes a total of 5 deaths in the DAWN database, which is not correct. There were 1098 reportable deaths associated with DPH between 2004 and 2011 from 13 states. AAPCC reported 277322 exposures to DPH over the 8 yr period 2004-2011, an average of 34665 cases per year, of which there were 346 deaths (average 43 deaths per year). WHO reported 5969 cases over the 9.16 year period 1/2004 to 2/2013, for an average of 652 DPH reports per yr, including 2355 deaths (average 257 deaths per yr).*

Naproxen DAWN Update

This section summarizes data on cases involving NAP reported to the Drug Abuse Warning Network (DAWN) which is supported by the Substance Abuse and Mental Health Services Administration (SAMHSA). The dataset covers the period from 01 January 2010 to 31 December 2010 and comprises information for all types of drug-related emergency department (ED) visits from a sample of the nation's emergency departments, with an over-sampling of selected metropolitan areas.

DAWN gathers information on all types of drugs, including illegal drugs, prescription and non-prescription pharmaceuticals, nonpharmaceutical inhalants and alcohol in combination with a drug. Alcohol use alone as a reason for an emergency department visit is reported only if the patient is < 21 years old. Information is collected on visits

related to drug use, drug misuse and drug abuse. The following categories are used to classify a case: Suicide attempt, Seeking detox, Adverse reaction, Overmedication, Malicious poisoning, Accidental ingestion and Other.

In 2010, there were 1901 ED visits reported involving NS. The gender distribution of ED visits was female-dominated in a ratio 1.7:1 (62.8% female, 37% male).

Table 9 DAWN NS Update 2010

Category	2010
Total reports N (row %)	1901 (100)
Total drugs^b N (row %)	5084 (100)
Type of case	
Adverse reaction	1247 (65.6)
Overmedication	315 (16.6)
Suicide attempt	224 (11.8)
Other	79 (4.2)
Accidental ingestion	32 (1.7)
Seeking detox.	4 (0.2)
Route of administration	
Oral	416 (21.9)
Missing	22 (1.2)
Other	6 (0.3)
Not documented	1462 (76.9)

MO Comment: *NS ED visits are female-dominated as is the case for DPH visits*

The three case types with the largest proportions of reports for naproxen were: Adverse reaction (65.6%, 1247/1901), Overmedication (16.6%, 315/1901) and Suicide attempt (11.8%, 224/1901). Route of administration data was not documented for 76.9% (1462/1901) of the reports and was recorded as oral for 21.9% (416/1901). The route of administration categories "Missing" and "Other" accounted for 1.5% (28/1901) of reports.

Two naproxen formulations accounted for 98.8% (1883/1906) of the naproxen reports. These were: Naproxen (85.4%, 1627/1906) and Lansoprazole-Naproxen (13.4%, 256/1906).

Overall, almost two thirds of the cases (65.9%, 1253/1901) were discharged home. A total of 31.6% (601/1901) were admitted for treatment or referred to a treatment unit. The fraction of cases admitted to an ICU or critical care unit was 4.1% (78/1901) of the overall total. There were no reported deaths.

MO Comment: *For NS, ED visits mainly involved single ingredient NS (85% of ED visits), with the NS-lansoprazole (PPI) combination accounting for 13.4% of visits. For NS, DAWN gives almost six times more visits involving AE (65.6%) than suicide attempt (11.8%), contrasting with DPH which is more often involved with suicide attempt. There were no reported deaths for NS during this update.*

9 Appendices

9.1 Literature Review/References

The original submission of Aleve PM provided a review of the safety literature for diphenhydramine covering the period from January 2005 through March 2012. A total of 74 references were provided on DPH in the original submission, and updates through March 2013 were provided on DPH and on naproxen in separate updates. The sponsor concluded that the literature reviewed is consistent with the established safety profile of diphenhydramine and posed no new safety concerns. (See Table 15 in Section 9.4, 74 DPH references in original submission). Naproxen literature reviews covering the time period January 2006 to November 2011 were referenced to NDA 200364 which was reviewed by Dr. Callahan Lyons and Dr. Steven Osborne. They concluded that there were no new safety concerns raised by the literature reviews.

Notable literature reports for DPH include the following. In cases of acetaminophen overdoses with co-ingestion of DPH, the standard protocol of iv N-acetylcysteine may not provide adequate hepatic protection because of delayed absorption, leading to maximum acetaminophen concentration beyond 4 hr after ingestion or an atypical, delayed, bimodal peak in the serum acetaminophen concentration observed. . Patients in whom delayed absorption might be anticipated (e.g., co-ingested anticholinergics/ opioids or massive overdoses) should have acetaminophen concentrations measured before the acetylcysteine infusion is terminated and may require further acetylcysteine therapy.

Schwartz EA, Hayes BD, Sarmiento KF "Development of hepatic failure despite use of intravenous acetylcysteine after a massive ingestion of acetaminophen and diphenhydramine" *Annals of Emergency Medicine*, 54 (3), 421-423, 2009

Doyon S, Klein-Schwartz W Hepatotoxicity despite early administration of intravenous N-acetylcysteine for acute acetaminophen overdose. *Academic Emergency Medicine* 16:34-39, 2009

There are case reports in the literature of DPH overdoses which describe one or more of the following: Brugada syndrome, QT prolongation, Renal failure, Rhabdomyolysis, Seizures, Tachycardia, Torsade de pointes. Similar to tricyclic antidepressants overdoses, diphenhydramine can cause blockade of the voltage-gated sodium channel and lead to a cardiac depolarization abnormality. This is represented by widening of the

QRS interval on the ECG and can lead to ventricular tachycardia and cardiovascular collapse.

- López-Barbeito B, Lluís M, Delgado V, Jiménez S, Díaz-Infante E, Nogué-Xarau S, Brugada J. Diphenhydramine overdose and Brugada Sign. *PACE* 28:730-732, 2005
- Levine M, LoVecchio F. Diphenhydramine-induced Brugada pattern. *Resuscitation* Year: 2010
- Ramachandran K, Sirop P. Rare Complications of Diphenhydramine Toxicity. *Connecticut Medicine*, 72:79-82, 2008
- McKeown NJ, West PL, Hendrickson RG, Horowitz BZ. Source: *Journal of Medical Toxicology*, Survival after Diphenhydramine Ingestion with Hemodialysis in a Toddler. *Pharm Line* Number: PL_2010, PUBM20865465, 2010
- Husain Z, Hussain K, Nair R, Steinman R. Diphenhydramine induced QT prolongation and torsade de pointes: An uncommon effect of a common drug. *Cardiol J* 17:509-511, 2010

The sponsor also submitted safety literature updates for NS covering the period 1 Dec 2011 through 20 Mar 2013 and for DPH covering the period April 2012 through 20 March 2013. Articles from these safety literature updates are included in the special topics discussions which follow. The NS literature update also included case reports of a NS-induced MI as a result of an allergic reaction (Kounis syndrome; patient recovered; Abuzetun et al.); a fatal drug-induced TEN and rhabdomyolysis from NS and atorvastatin (Noordally et al.); and two cases of photosensitivity induced by NS (Gutiérrez-González et al.). The DPH literature update included a report of APAP/DPH overdose in hypothermia (Rollstin and Seifert) and another report of urticaria from DMH (Paffumi et al.). The hypothermia case was noteworthy because the patient did not develop signs of liver injury despite significant ingestion of acetaminophen and delayed presentation. The patient's absorption or metabolism of acetaminophen was likely slowed by the hypothermia and possibly also the co-ingestion of DPH which has anticholinergic activity..

- Abuzetun JY, Satpathy R, Suker M, Elder M, Mooss A. Naproxen-induced ST elevation myocardial infarction in a 33-year-old man. *J Cardiovasc Med (Hagerstown)*. 2012 Jul;13(7):471-3.
- Noordally SO, Sohawon S, Vanderhulst J, Duttmann R, Corazza F, Devriendt J. A fatal case of cutaneous adverse drug-induced toxic epidermal necrolysis associated with severe rhabdomyolysis. *Ann Saudi Med*. 2012 May-Jun;32(3):309-11.
- Gutiérrez-González E, Rodríguez-Pazos L, Rodríguez-Granados MT, Toribio J. Photosensitivity induced by naproxen. *Photodermatol Photoimmunol Photomed*. 2011 Dec;27(6):338-40
- Rollstin AD, Seifert SA. Acetaminophen/diphenhydramine overdose in profound hypothermia. *Clin Toxicol*. 2013; 51: 50-53
- Paffumi I, Saitta S, Isola S, Gangemi S. Urticaria caused by dimenhydrinate. *Allergol Immunopathol (Madr)*. 2012 Jul-Aug;40(4):253-4.

The Sponsor submission included an article which presented a case report of a fatality from DPH monointoxication and a review of the pediatric and adult literature case series involving deaths from DPH, one from the US (Nine and Rund 2006). Another case series (Shkrum et al. 1990).described deaths due to DPH from Ontario, Canada. These reports included literature reviews.

Nine and Rund reviewed a case series of 25 fatalities from DPH monoingestion reported in PubMed 1949-2004, together with another 50 cases from AAPCC annual reports from 1983-2002. Of these cases, there were 19/25 cases from the PubMed series and 16/50 cases from AAPCC which reported DPH blood levels. Of the 41 cases from the combined PubMed and AAPCC datasets (see Table 10), there were 20 adults, 13 pediatrics, and 8 infants. Corresponding average blood DPH levels were adult, 16.14 mg/L (range, 0.87–48.5); pediatric, 6.35 mg/L (0.69–13.7); and infant, 1.51 mg/L (1.1–2.2).

Table 10 Diphenhydramine (DPH) Monointoxication

Diphenhydramine (DPH) Monointoxication: Age and DPH Levels: Combined Case Reviews From the PubMed Database and the Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System			
	Adult Mean (Range) n = 20	Pediatric Mean (Range) n = 13	Infant Mean (Range) n = 8
Age	34.3 years (18–60)	6.5 years (1.25–17)	12.4 weeks (6–24)
DPH level*	16.14 mg/L (0.87–48.5)	6.35 mg/L (0.69–13.7)	1.51 mg/L (1.1–2.2)

*The blood DPH level represents 35 of the 75 reported cases (20 adult, 8 pediatric, 7 infant).

For the cases that were assigned a manner of death, all of the adult deaths were certified as suicide. Of the pediatric deaths, 4 were considered accident and 2 suicide. Of the infant deaths, 1 was an accident, 3 were homicides, and 1 was undetermined. The most common symptoms for all cases were cardiac dysrhythmias, seizure activity, and/or sympathetic pupil responses. The most common autopsy finding was pulmonary congestion.

The Pragst dataset which included 55 fatal poisonings with DPH alone or in combination at the University Hospital Charite between 1992 and 2004 also supports a threshold for the lethal DPH blood concentration level of 5 mg/L (or 0.5 mg/100 mL) for adults. Nine and Rund noted that lesser concentrations are fatal for children. There is individual variation in the tolerance of overdoses.

Shkrum et al. 1990 earlier reported a case series of 16 DPH deaths in Ontario from 1984-1987. All were suicides. There were additionally 8 DPH deaths in 1982-1983 of which 5 were DPH monoingestions with blood levels above the fatal threshold concentration of 0.5 mg/100 mL. From the 1984-1987 series of 16 cases, there were 4 DPH monoingestions, 8 cases of DPH with ethanol, and 4 cases of DPH with CNS depressant drugs. The average DPH blood concentration in fatal monoingestions was 1.44 mg/100 mL (minimum, 0.69 mg/100 mL), consistent with Nine and Rund. The blood concentration in fatal DPH + ethanol cases is lower, with average 0.90 mg/100 mL and minimum 0.33 mg/100 mL., suggesting that the fatal concentration of DPH is lower if co-ingested with ethanol.

There were 5 fatal cases with DPH blood levels <0.5 mg/100 mL. All were older, average age 57 yr, all had taken ethanol and/or CNS depressants with DPH, and all had evidence of significant heart disease. The fatal blood level of DPH may be reduced in the presence of these conditions.

Finally Shkrum et al. noted that sleep-aids dominated in the DPH deaths. In 12 of the 16 DPH suicide cases, the form of DPH was known: Nytol, Unisom and Benadryl were involved in six, three and two deaths respectively, and Compoz, Sleep-Eze-D, Sominex, Sedicin and Dormiphen accounted for one case each. Some of the cases were multiple ingestions. In at least 10 of the cases, the DPH was in an OTC sleep-aid.

Sinyor et al., 2012, studied coroner data for 397 documented overdose suicides in Toronto, Canada, between the years 1998 and 2007. During this period, opioid analgesics, sedative hypnotic or anxiolytic medications, OTC medications, and tricyclic antidepressants represented the most frequently detected classes of drugs in lethal amounts (28.2%, 26.4%, 21.4%, and 20.4% of cases, respectively). Diphenhydramine (14.4%), amitriptyline (12.3%), and alcohol (9.8%) were the most common specific substances detected in lethal amounts of all overdose suicides during that time period. There were also 53 cases where an SSRI, DNRI and/or another newer antidepressant drug was present in lethal amounts. There was a low proportion of suicides involving illegal drugs (approximately 4%), which may relate to coroner misclassification of an overdose death involving illegal drugs as unintentional instead of intentional, if investigators felt that illegal drugs were taken for intoxication and not deliberate harm. The gender ratio of suicides was about one to one, female:male.

MO Comment: *The case series reported by Nine and Rund and by Shkrum et al. are consistent with the postmarketing data from AERS, WHO, DAWN and AAPCC, which find that DPH poisonings are common and that the serious or fatal cases are predominantly intentional overdoses or suicides. In the Shkrum et al. series, the form of DPH in the fatal cases was predominantly OTC sleep-aids, but in the larger post-market databases this information is often not reported. In the Sinyor et al. series of completed suicides, DPH was the most common substance detected in lethal amounts.*

Nine JS and Rund CR. Fatality from Diphenhydramine Monointoxication A Case Report and Review of the Infant, Pediatric, and Adult Literature. 2006. Am J Forensic Med Pathol, 27: 36- 41.

Shkrum MJ, Hall AE, Tallon SG. Deaths due to diphenhydramine. 1990. Can. Soc. Forens. Sci. J. Vol. 23:1-8)

Pragst F et al, Poisonings with diphenhydramine-A survey of 68 clinical and 55 death cases. 2006. Forensic Science International. 161: 189-197

Sinyor, M., Howlett, A., Cheung, A. H., and Schaffer, A (2012) Substances used in completed suicide by overdose in Toronto: an observational study of coroner's data, Canadian Journal of Psychiatry - Revue canadienne de psychiatrie; 57: 184-191.

Special topic: Next Day Safety

Since DPH is a first generation antihistamine with known sedative and hypnotic effects, and DPH 50 mg is used as a non-prescription sleep aid, the FDA recommended the Sponsor conduct a review of published literature on psychomotor effects of DPH on driving performance the day after nighttime administration. Although sedation, drowsiness and cognitive/psychomotor impairment are associated with DPH use, the sponsor notes that there is no established standard method for evaluating driving ability. Commonly used methods include neuropsychological tests, simulator vehicle tests, and behind-the-wheel driving tests.

The Sponsor also notes that the majority of the published literature described studies where DPH was administered and testing performed during regular waking hours, as opposed to administered prior to start of a sleep period with testing following a sleep period. Studies involving daytime dosing of DPH are not representative of the psychomotor performance effects on driving that might be seen the day after nighttime dosing of DPH. The data on psychomotor performance effects on driving after night time doses are limited. Nevertheless, they generally seem to show that patients who report experiencing residual effects the morning after taking DPH 50 mg at bedtime, predominantly report drowsiness and sleepiness. The studies reveal that impairment with DPH generally occur within 3 hours post-dose and by about 8 hours after dosing these effects seem to become minimal or indistinguishable from placebo. The overall findings suggest that following the nighttime dosing with DPH 50 mg and a usual sleep period, some residual drowsiness may exist but impairment in performance is not evident.

MO Comment: *The reviewer generally agrees with the sponsor summary and with the caution that the studies of psychomotor effects after daytime dosing may not apply to performance impairment after nighttime dosing as a sleep aid. Discussion of selected studies follows below.*

Weiler et al. 2000 performed a four-way crossover, double-blind study using the Iowa Driving Simulator to evaluate driving performance in 40 licensed drivers with allergic rhinitis. The subjects drove in the driving simulator for one hour after taking a single dose of DPH (50 mg), fexofenadine (60 mg), alcohol (at estimated 0.1% blood alcohol concentration), or placebo. The drive took place 2.5 hours after administration of study drugs to coincide with expected peak plasma concentrations of the antihistamines. The investigators found that lane keeping ability (steering instability and crossing the center line) and speed matching was poorer after diphenhydramine and alcohol use compared with fexofenadine use. The impairment observed with diphenhydramine was greater than that seen with a blood alcohol concentration of 0.1%. Self-reported drowsiness was weakly associated with these skills.

Additionally, the performance of on-the-road driving in normal traffic following DPH (50 mg) was assessed by Ramaekers and O'Hanlon 1994, who performed driving tests on 18 drivers in a double-blind, crossover study. The driving test measured lane-keeping ability (standard deviation of lateral position) and reaction time (to movements of the leading vehicle in a car-following test) after a single dose of DPH. The mean reaction time increased from 1.3 s for placebo to 1.8 s on DPH ($p < 0.05$), for testing 2.5 to 2.75 hr post dosing. The reaction times were not significantly different between placebo and DPH for testing 4.25 to 4.5 hours post dosing.

Verster et al. 2003 also reported significant impairment of driving ability following DPH (50 mg) use with respect to standard deviation of lateral position (SDLP). They performed a standardized driving test enrolling 48 drivers in a double-blind, crossover study. Treatments were administered on 4 successive days, and driving was tested on Days 1 and 4, with the drug given 1.5 hr before the driving test. On Day 1, the SDLP was significantly increased for DPH ($20.5 \text{ cm} \pm 5 \text{ cm}$) relative to placebo ($17.7 \text{ cm} \pm 3.6 \text{ cm}$). SDLP was also increased significantly for DPH on Day 4, but by a lesser amount, suggesting development of tolerance.

Gengo et al. 1990 used a driving simulator and additional psychometric tests on 15 subjects in a double blind, crossover study. Two hours after dosing, the reaction time was increased significantly by DPH ($2.01 \text{ s} \pm 0.84 \text{ s}$) versus placebo ($0.86 \text{ s} \pm 0.43 \text{ s}$). However, by 4 hours after dosing, the reaction times were not significantly different.

All four of these studies used DPH as a positive control, in order to demonstrate the relative lack of driving impairment with use of other antihistamines.

Weiler JM, Bloomfield JR, Woodworth GG, Grant AR, Layton TA, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa Driving Simulator. *Ann Intern Med* 2000; 132: 354-363.

Ramaekers JG and O' Hanlon JF. Acrivastine, terfenadine, and diphenhydramine effects on driving performance as a function of dose and time after dosing. *Eur J Clin Pharmacol* 1994; 47: 261-6.

Verster JC, de Weert AM, Bijtjes SIR, Aarab M, van Oosterwijk AWAA, et al. Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology* 2003; 1669: 84-90.

Gengo FM, Gabos C, Mechtler L. Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. *Ann Allergy* 64:520-6

MO Comment: *Single doses of DPH 50 mg consistently produce objective impairment of driving ability as measured by simulated and real-road driving tests, within 2 to 3 hours after dosing. By 4-5 hours after dosing, the impairment is generally not significant relative to placebo.*

Studies of psychomotor performance in aviation personnel are also pertinent to the issue of performance impairment. Bower et al. studied 42 naval aviators in a double blind, crossover study of subjective drowsiness, cognitive performance, and vigilance. The cognition and vigilance tests were selected for relevance to aviator skills and performance. Testing began 1.5 hr after dosing. DPH 50 mg significantly increased hit reaction time versus placebo in the vigilance testing, but the cognitive testing (six specific measures) did not find significant differences between DPH and placebo. Subjective drowsiness was significantly increased for DPH versus placebo.

Paul et al. tested 21 subjects in a double blind crossover study. Psychomotor testing was performed before and once every hour for 7 hour after dosing. Dimenhydrinate 50 mg (equiv to 28 mg DPH) impaired psychomotor speed (SRT) from 1.25 hr to 3.25 hr after dosing, but did not affect higher order cognition (LRT), mental arithmetic and short-term memory (SST) or tracking and piloting performance (MT). DMH produced subjective impairment and subject sleepiness. The authors suggested that DMH caused subjective sleepiness that impaired the speed-related SRT task but not the higher order cognitive tasks.

Valk and Simons performed a double blind crossover study in 23 subjects under simulated cabin pressure environment. Testing performed at baseline and every hour from 1 to 6 hr after dosing. DPH impaired vigilance and tracking up to 3 hr and 5 hr, respectively, versus placebo. Subjective sleepiness was increased by DPH versus placebo up to 5 hours post dosing.

- Bower EA, Moore JL, Moss M, Selby KA, Austin m, Meeves S. The effects of single dose fexofenadine, diphenhydramine and placebo on cognitive performance in flight personnel. *Aviation, Space and Environ Medicine*. 2003. 74:145-52.
- Paul, M.A., M. MacLellan, and G. Gray, Motion-sickness medications for aircrew: Impact on psychomotor performance. *Aviation, Space, and Environ Medicine*, 2005. 76(6): p. 560-5.
- Valk P.J.L. and Simons M., Effects of loratadine/montelukast on vigilance and alertness task performance in a simulated cabin environment. *Adv Ther*, 2009. 26(1): p. 89-98.
- O' Hanlon JF and Ramaecker JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy*, 1995. 50: 234-42.

MO Comment: *Single doses of DPH 50 mg consistently produce objective impairment of psychomotor ability as measured by some, but not all, tests of cognitive tasks relevant to flying an airplane. Subjective drowsiness does not consistently correlate with objective measures of psychomotor performance as was found with tests of driving performance.*

The Sponsor submitted more than 20 additional literature reports on psychometric and neurophysiologic measurements after day-time dosing of DPH, in most cases comparing DPH to other antihistamines. These studies used diverse subjective and objective laboratory measures. The Sponsor concludes that most studies show the

results for impairment in the DPH treatment groups to be comparable to and not significantly different from placebo by 6-8 hours post-dose.

MO Comment: *Results of objective psychometric and neurophysiologic tests after day-time dosing of DPH generally show performance impairment for time periods up to 2-4 hrs after dosing. The objective measures do not necessarily correlate with the subjective drowsiness measurements, and test methods have not been standardized. Most studies report an increase of subjective drowsiness with DPH. Results of objective performance testing after DPH are inconsistent. Some studies (e.g. Gengo et al. 1989) did not find significant impairment after four hours by one or more objective measures, but other studies (for instance Katayose et al. 2012) found impairment on objective tests beyond 9 hours for DPH but not zolpidem. Subjective drowsiness is generally reported up to 8 hours post-dose.*

Several literature reports studied next-day effects of 50 mg DPH after nighttime dosing. These results may be more directly relevant to the present product which is indicated as a sleep-aid for those with minor pain. In a randomized, double blind crossover study, Zhang *et al.* evaluated the residual sedative effect of DPH given at bedtime by measuring brain histamine H1 receptor occupancy (H1RO) the next day using the radioactive tracer ¹¹C-doxepin (which competitively binds to these H1 receptors) and positron emission tomography. The occupancy of H1 receptors in the brain by antihistamines is an objective measure of sedation. Results showed that, 12 hours following the bedtime administration of DPH at 2300 hour, H1RO in the cortical regions assessed in the brain was 44.7% for DPH compared to 16.6% for the second-generation antihistamine bepotastine (p<0.01). This result means that the antihistamine inhibited ¹¹C-doxepin uptake so as to reduce the distribution volume to 44.7% of its value for placebo in the case of DPH, 12 hours after dosing. The study also measured plasma concentrations of DPH and bepotastine as well as subjective measures of sleepiness. Despite the significant differences in H1RO, the study did not demonstrate statistically significant differences in sleepiness between treatment groups or correlation between plasma concentration and subjective sleepiness. However, the study sample size was small (eight adult males).

The Katayose *et al.* study studied next-day sleepiness and psychomotor performance following nighttime administration of antihistamines in 22 healthy adult males. The study evaluated four drugs (zolpidem 10 mg, DPH 50 mg, ketotifen 1 mg, and placebo) with a double blind, crossover design. Each treatment session included a one-day lead-in period with baseline polysomnography recorded on the first night in the study center. The subjects received one dose of study drug at 23:45 pm on day 2, and were awakened at 0800 am on day 3. Objective and subjective sleepiness as well as psychomotor performance were evaluated during the morning (9 to 11 hours post-dose) and afternoon (13-15 hours postdose). When compared with placebo, the results for DPH and ketotifen demonstrated carryover effects in objective sleepiness (level of wakefulness as measured by Alpha Attenuation Test, AAC) and in psychomotor

performance. In the psychomotor performance tests, sedative– hypnotic effects were more pronounced during more difficult tasks requiring working memory, as in the n-back task, than during relatively easy and simple tasks such as the Simple Reaction Time. No significant carryover effect was observed with zolpidem. Furthermore, the investigators stated that the strength of the DPH carryover effects appeared to surpass pharmacokinetic predictions. Since the half life of DPH ranged between 5-8 hours in healthy Japanese adults, the carryover sedative effects of DPH observed in this study continued longer than would have been expected based from pharmacokinetics alone.

The submission included additional sleep studies of effects after nighttime dosing of DPH. Most of the studies used only subjective assessments of next-day sedation effects, except the study of Meuleman et al. in 14 nursing home residents with sleep problems. treated for 5 consecutive nights with DPH 50 mg, temazepam 15 mg, and placebo in a randomized, double-blind, crossover study. Compared to placebo, there was no difference in perceived morning drowsiness or feeling of rest with DPH. Eight tests of neurologic function were performed after the first, third, and fifth nights of each medication. There was no significant difference found in any of the tests with DPH compared to placebo. However, 5 instances of daytime hypersomnolence were observed after nighttime DPH, and 4 instances with temazepam, versus none with placebo.

MO Comment: *The Zhang et al. demonstration of continued high H1RO the next day after nighttime administration of DPH may provide an explanation for the objective measurements of next-day performance impairment by Katayose et al. A high proportion of brain H1 receptors is still occupied by DPH nine or more hours after dosing, even after plasma levels have cleared, leading to continued potential for sedation. Nevertheless, it appears to be difficult to establish next day hypnotic or sedative effects of DPH in elderly subjects, as Meuleman et al. did not find any such effects by subjective or objective measures, although daytime hypersomnolence was observed after DPH.*

- Zhang D, Tashiro M, Shibuya K et al. Next day residual effect after nighttime administration of an over the counter antihistamine sleep aid, diphenhydramine... J Clin Psychopharm 2010. 30:694-01
- Katayose Y, Aritake S, Kitamura S, et al. Carryover effect on next-day sleepiness and psychomotor performance of nighttime administered antihistamine... Human Psychopharm. 2012. 27:428-36
- Meuleman, J.R., R.C. Nelson, and R.L. Clark, Jr., Evaluation of temazepam and diphenhydramine as hypnotics in a nursing-home population. Drug Intell Clin Pharm, 1987. 21(9): p. 716-20

Two additional approaches were taken to search for objective evidence of performance impairment from DPH use. The first is an examination of civil aviation accident pilot fatality data, discussed below. The second was the supplemental analysis performed by

the Sponsor of postmarketing data for DPH, using the accidents and injuries Standard Medical Query (AI SMQ) in the FAERS database, discussed in Section 8.

The Federal Aviation Administration Office of Aerospace Medicine recently published a report (Canfield et al. 2012) on the toxicology database for pilots who died in aviation accidents from 2004-2008. Toxicology testing is performed to determine if the pilot was impaired by any drugs. The study found that **DPH is the most commonly found drug in 1353 pilots who died** in aviation accidents. DPH is found in 6.1% of pilot fatalities from 2004-2008, a percentage which has increased from 1.7% for 1989-1993.

MO Comment: *According to the Canfield et al. FAA report, the Office of Aerospace Medicine is re-evaluating the algorithm to determine when it is safe to return to duty after taking DPH, because reliance on half-life dosing recommendations “may be duration of medication levels that may compromise aviation performance”. The Zhang et al. and Katayose et al. studies provide a physiologic basis and objective evidence supporting next day performance impairment more than one half life after nighttime dosing of DPH.*

Canfield DV, Dubowski KM, Chaturvedi AK, Whinnery JE. Drugs and alcohol found in civil aviation accident pilot fatalities from 2004-2008. Av Space Environ Med. 2012. 83:764-70

MO Comment: *The proposed label states “Do not use unless you have time for a full night’s sleep” and “When using this product do not drive a motor vehicle or operate machinery. These warnings instruct consumers to allow for a full night’s sleep and not to drive once this drug is taken as a sleep aid. The drowsiness warnings on the proposed label are consistent with those in the labels for the currently approved NDA ibuprofen-DPH combination products for the same indications.*

NSAIDs and Birth Defects (from safety literature update)

Hernandez et al. 2012 performed a case-control surveillance study using the National Birth Defects Prevention Study (NBDPS) to search for an association between use of NSAIDs in the first trimester of pregnancy with a range of structural birth defects. The NBDPS enrolled women in 10 states with expected due dates from Oct 1, 1997 through December 2004. The study enrolled 14915 cases (live or still births with eligible birth defects) and 5546 controls (with no major defects, selected from the same population). Of the pregnant women enrolled in the study (cases+controls), there were 22.6% who reported use of an NSAID in the first trimester (most often ibuprofen, aspirin or NS). The analysis focused on oral, single component NSAID use.

The study found a small to moderate association between NSAID use and specific birth defects. Association was observed for anophthalmia/microphthalmia with adjusted ORs of 3.0 (95% CI 1.3-7.3) for aspirin, 1.9 (95% CI 1.1-3.3) for ibu, and 2.8 (95% CI 1.1-7.3) for NAP. Small to moderate association with NAP exposure was also observed for cleft lip+/- cleft palate and transverse limb deficiency. In the present study, there were 7

cases observed with anophthalmia/microphthalmia and maternal NAP exposure, and there were 45 cases of cleft lip with maternal NAP exposure. An association between NAP and cleft lip with or without cleft palate was reported by a previous study which used prospectively reported registry data (Ericson and Kellen). Similar conclusions were reached by Burdan et al. who reviewed studies of prenatal use of NSAIDs including naproxen: NSAIDs may induce congenital malformations, intrauterine growth retardation and preterm delivery, and should be avoided if possible, and used at minimum therapeutic dose if required.

MO Comment: *Agree with authors' conclusion that "use of NSAIDs in early pregnancy does not appear to be a major risk factor for birth defects, although there [are] moderate associations between NSAIDs and specific birth defects." NS is moderately associated with specific defects including cleft lip. Label does warn if pregnant or breast-feeding to ask a health professional before use, that it is especially important not to use naproxen sodium during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.*

Table 11. Association of Birth Defects and NSAIDs in NBDPS 1997-2004

Birth defect	Adjusted odds ratio (95% CI) ^b		
	Aspirin	Ibuprofen	Naproxen
Non-heart			
Anencephaly/craniorachischisis			
Total	2.0 (1.0–3.9)	1.3 (0.85–2.0)	0.84 (0.30–2.3)
Isolated	2.2 (1.1–4.3)	1.3 (0.84–2.0)	0.69 (0.22–2.2)
Spina bifida			
Total	1.6 (0.93–2.7)	1.6 (1.2–2.1)	0.77 (0.35–1.7)
Isolated	1.6 (0.94–2.9)	1.6 (1.2–2.1)	0.48 (0.18–1.3)
Encephalocele			
Total	2.1 (0.75–6.1)	1.2 (0.58–2.5)	2.5 (0.89–7.3)
Isolated	2.8 (0.99–8.1)	1.0 (0.42–2.4)	3.5 (1.2–10)
Anophthalmia/micropthalmia			
Total	3.0 (1.3–7.3)	1.9 (1.1–3.3)	2.8 (1.1–7.3)
Isolated	0.94 (0.13–7.0)	1.0 (0.40–2.6)	c
Cleft lip ± cleft palate			
Total	1.1 (0.72–1.7)	1.3 (1.1–1.6)	1.7 (1.1–2.5)
Isolated	1.2 (0.76–1.8)	1.4 (1.1–1.7)	1.8 (1.2–2.7)
Cleft palate			
Total	1.8 (1.1–2.9)	1.3 (0.99–1.7)	1.4 (0.84–2.5)
Isolated	1.7 (1.0–2.9)	1.3 (0.99–1.8)	1.6 (0.90–2.8)
Transverse limb deficiency			
Total	1.2 (0.58–2.5)	1.3 (0.88–1.9)	2.0 (1.0–3.8)
Isolated	1.3 (0.62–2.7)	1.2 (0.84–1.8)	1.9 (0.95–3.7)
Amniotic bands/limb body wall			
Total	2.5 (1.1–5.6)	2.2 (1.4–3.5)	1.6 (0.55–4.4)
Isolated	2.5 (1.1–5.7)	2.2 (1.4–3.5)	1.6 (0.56–4.5)
Heart			
Isolated pulmonary valve stenosis ^d	1.1 (0.47–2.6)	1.3 (0.91–1.9)	2.4 (1.3–4.5)
CI, confidence interval.			
^a Exposed vs unexposed (as needed excluded);			
^b Adjusted for site, race/ethnicity, folic acid, smoking, binge drinking, and fever in the first trimester;			
^c Too few cases to estimate adjusted odds ratios;			
^d Analysis limited to term births only.			

Hernandez RK, Werler MM, Romitti P, et al. Nonsteroidal anti-inflammatory drug use among women and the risk of birth defects. *Am J Obstet Gynecol.* 2012. 206:228.e1-8
 Ericson A, Kellen B. Nonsteroidal Antiinflammatory drugs in early pregnancy. *Reprod Toxicol* 2001. 15:371-5
 Burdan F, Staroslawska E, Szumilo J. Prenatal tolerability of acetaminophen and other over-the-counter nonselective cyclooxygenase inhibitors. *Pharmacol Rep.* 2012;64(3):521-7.

NSAIDs and Stroke Risk (from safety literature update)

Varas-Lorenzo et al. performed a meta-analysis of observational studies on the risk of stroke associated with the use of individual NSAIDs. Observational cohort or case-control studies were selected that reported on the risk of cardiovascular events

associated with use of individual NSAIDs versus nonuse of NSAIDs. There were a total of 6 studies selected that reported relative risk (RR) of stroke, in study populations that totaled over 1.2 million people in the US and Europe. The observational studies were all completed prior to withdrawal of rofecoxib (reducing bias by contraindication to cardiovascular high risk subjects).

The risks of incident stroke and of ischemic stroke were significantly increased with current use of rofecoxib and diclofenac, but not with current use of NAP, IBU or celecoxib. The pooled RR of all subtypes of incident stroke, from the random effects model, was increased with the current use of rofecoxib (RR = 1.64, 95% CI = 1.15–2.33) and diclofenac (RR = 1.27, 95% CI = 1.08–1.48). The pooled estimates for naproxen, ibuprofen, and celecoxib were close to unity for incident stroke, all subtypes. See Table 12. Data were inadequate to estimate the pooled RR by dose and duration, or for other individual NSAIDs.

Table 12 Relative Risks for Incident Stroke and for All Types of Stroke

Author (no. studies)	Cases (N)	Naproxen RR (95% CI)	Ibuprofen RR (95% CI)	Diclofenac RR (95% CI)	Celecoxib RR (95% CI)	Rofecoxib RR (95% CI)
All types of stroke (n = 6)*						
Abraham <i>et al.</i> ¹²	NR	2.00 (1.49–2.70)	1.70 (1.24–2.32)	NA	1.70 (1.14–2.54)	3.00 (2.04–4.42)
Andersohn <i>et al.</i> ^{13†}	684	1.16 (0.80–1.70)	1.12 (0.91–1.37)	1.32 (1.10–1.57)	1.07 (0.79–1.44)	1.71 (1.33–2.18)
Bak <i>et al.</i> ^{14†}	158	0.70 (0.44–1.13)	1.30 (1.03–1.64)	1.10 (0.70–1.70)	NA	NA
Haag <i>et al.</i> ^{15†}	52	2.63 (1.47–4.72)	1.47 (0.73–3.00)	1.60 (1.00–2.57)	NA	3.38 (1.48–7.74)
Roumie <i>et al.</i> ^{18†}	574	0.94 (0.80–1.11)	0.88 (0.73–1.06)	0.94 (0.59–1.49)	1.04 (0.87–1.23)	1.28 (1.06–1.53)
Solomon <i>et al.</i> ¹⁹	1904	0.83 (0.67–1.04)	0.95 (0.78–1.16)	0.98 (0.75–1.29)	1.00 (0.92–1.09)	1.15 (1.04–1.26)
				Pooled RR (95% CI)		
Random effects		1.19 (0.85–1.65)	1.15 (0.95–1.39)	1.17 (0.98–1.40)	1.08 (0.93–1.25)	1.70 (1.25–2.31)
Fixed effects		1.05 (0.94–1.17)	1.08 (0.98–1.19)	1.20 (1.05–1.36)	1.03 (0.96–1.10)	1.27 (1.18–1.38)
Heterogeneity (P)		<0.00001	0.004	0.21	0.09	<0.00001
Incident stroke (n = 4)†						
				Pooled RR (95% CI)		
Random effects		1.14 (0.76–1.69)	1.10 (0.89–1.36)	1.27 (1.08–1.48)	1.04 (0.90–1.21)	1.64 (1.15–2.33)
Fixed effects		1.00 (0.87–1.15)	1.06 (0.95–1.20)	1.27 (1.10–1.47)	1.04 (0.90,1.21)	1.45 (1.26–1.68)
Heterogeneity (P)		0.003	0.05	0.37	0.85	0.02

Results from published studies and pooled estimates, overall analysis, and studies of incident stroke.

NR, not reported; NA, not applicable.

*All types of stroke, incident plus prevalent cases of all subtypes of stroke.

†Denotes studies restricted to incident events.

The risk of ischemic stroke was likewise increased with rofecoxib (RR = 1.82, 95% CI = 1.09–3.04) and diclofenac (RR = 1.20, 95% CI = 0.99–1.45), but not with NAP or with IBU (see Figure 7). For NAP, the pooled result for relative risk of ischemic stroke, was RR = 1.05, 95% CI = 0.71–1.55). These were pooled estimates from random effects models, using the Solomon, Haag, Andersohn, and Bak studies (see Table 13) of a combined population totaling over 600,000 subjects.

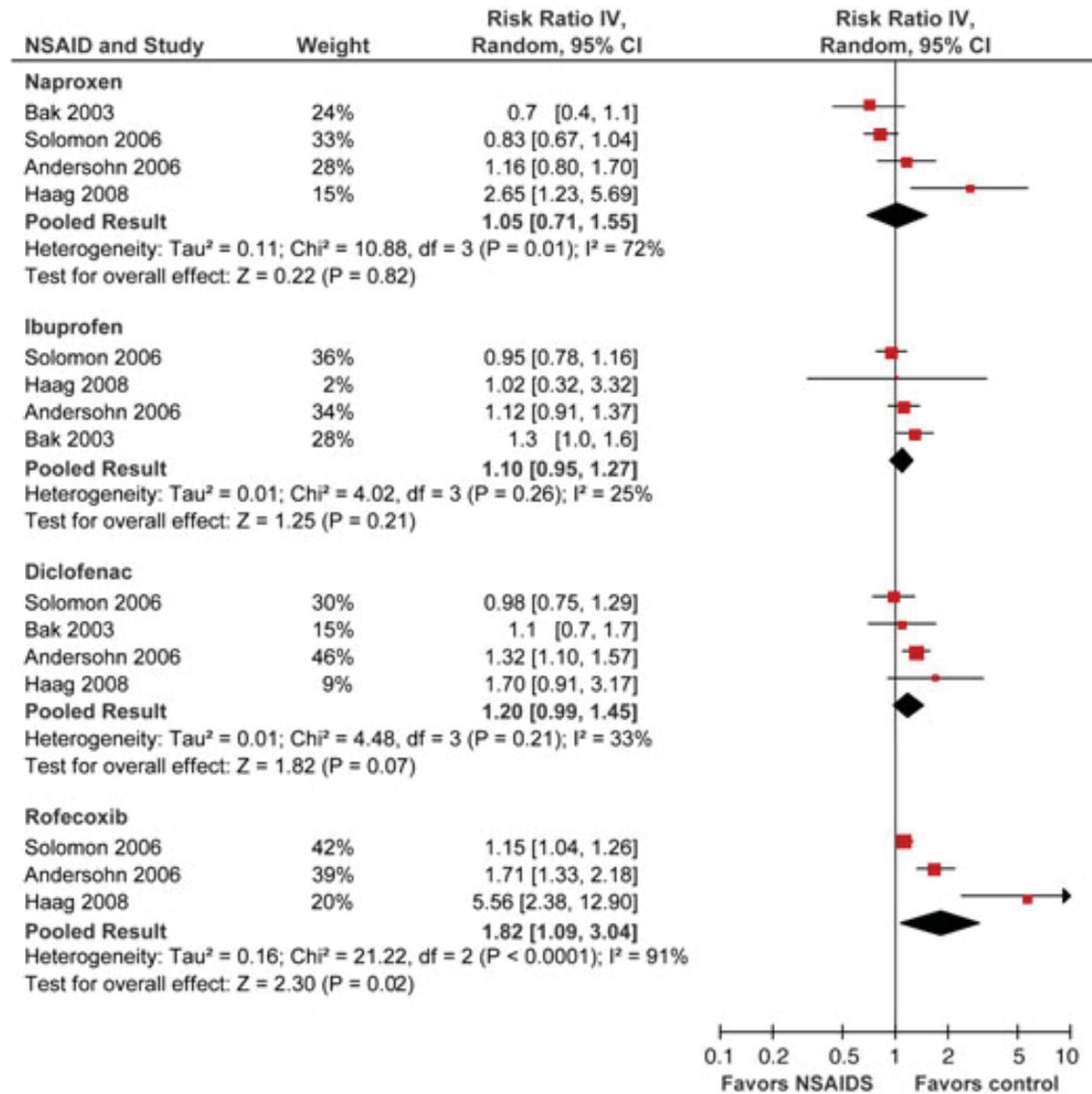


Figure 7 Forest Plots of the Risk Of Ischemic Stroke Associated With Current Use of Naproxen, Ibuprofen, Diclofenac and Rofecoxib Relative to Nonuse; Results From Published Studies (See Table 13) and Pooled Estimates by Random Effects.

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Table 13 NSAIDs and Stroke Risk, Studies Included for Meta-Analysis

Author	Source population	Study population (N)	Study design and time period	End point definition	Case validation	Assessment of NSAID dose and duration; concomitant ASA use	Exposure assessment	Exposure definition
USA								
Roumie <i>et al.</i> ¹⁸	Medicaid, TN, USA	N = 336,906, men and women, aged 50–84 years	Cohort, 1999–2004	First ever hospitalization for ischemic, thrombotic, or hemorrhagic stroke (included SAH)	Internal partial validation of a sample of 250 identified cases, PPV 97%	Yes Yes No	Ever and new use, filled prescriptions	Current, use at index day
Abraham <i>et al.</i> ¹²	VA, USA	N = 384,322, men, aged 65–99 years	Cohort, 2000–2002	Hospitalization for cerebrovascular accidents (excluded SAH)	External, PPV 91%	No No No	Ever use, electronic prescriptions	Current, use in the last 180 days
Solomon <i>et al.</i> ¹⁹	Medicare, USA	N = 98,370, men and women, aged ≥65 years	Cohort, 1999–2003	Hospitalization for ischemic stroke	External, PPV 94%	Yes No No	New users, filled prescriptions	Current, use at index day
Europe								
Haag <i>et al.</i> ¹⁵	Rotterdam study, The Netherlands	N = 7,636, men and women, aged ≥55 years	Cohort, 1990–2004	First ever diagnosis for ischemic or hemorrhagic stroke (excluded SAH)	Internal complete validation blinded to exposure status	No No No	Ever use, filled prescription	Current, use at index day
Andersohn <i>et al.</i> ¹³	GPRD, UK	N = 469,674, men and women, aged ≥40 years	Nested case-control, 2000–2004	First ever recorded diagnosis of ischemic stroke or cerebrovascular accident	External. 90% of confirmed cases, review of electronic PP blinded to exposure status	Yes Yes No	Ever use and new use, electronic prescriptions	Current, use in the last 14 days
Bak <i>et al.</i> ¹⁴	Funen County, Denmark	N = 44,765, men and women, aged ≥20 years	Nested case-control, 1994–1999	First ever hospitalization for ischemic or hemorrhagic stroke (included SAH)	Internal complete validation blinded to exposure status	No No Yes	Ever use, filled prescription	Current, use in the last 30 days

ASA, acetylsalicylic acid (aspirin); GPRD, General Practice Research Database (UK); PP, patient profile; PPV, positive predictive value; SAH, subarachnoid hemorrhage; TN, Tennessee; UK, United Kingdom; VA, Veterans Administration.

MO Comment: *Evidence on stroke risk from individual NSAIDs is still limited. Rofecoxib and diclofenac are associated with increased stroke risk versus non-use of NSAIDs, but not NAP or IBU. Stroke risks differ across individual NSAIDs. Existing warnings are adequate to inform consumers.*

Varas-Lorenzo C, Riera-Guardia N, Calingaert B, et al. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidem Drug Saf.* 2011. 20:1225-36

Expert Opinion on Comparative Risks of Nonprescription NSAIDs

The safety literature update included a published expert opinion (Lavonas et al.) on comparative risks of OTC analgesics. This report was a consensus opinion issued after review of 1111 literature citations, but not a formal meta-analysis which was not attempted because of the large heterogeneity of the NSAIDs safety literature. There were eight topic areas of adverse events considered: pulmonary, renal, cardiovascular I (death + myocardial infarction (MI)), cardiovascular II (congestive heart failure, hypertension, stroke), hepatic, gastrointestinal, pregnancy outcomes and malignancy.

The report listed pairs of medications and adverse events. The consensus panel consisted of 7 voting members and two non-voting members (chair and moderator), where panel members could vote to approve, object or strongly object to each summary statement. Consensus required at least six votes to approve a summary statement with no votes to strongly object. The panel determined that the data 'favor' or 'strongly favor' acceptance of a causal relationship with harm for 13 medication--AE pairs at non-prescription dosing levels, and for an additional 4 medication--AE pairs at dosing that exceeded non-prescription doses, as shown in Table 14.

Five of these associations were supported with high quality evidence (further research is very unlikely to change the confidence in the estimate): i) use of maximal therapeutic doses of acetaminophen is associated with hepatic transaminase elevations, though the clinical importance of this observation is unclear; ii) acetaminophen overdosage causes liver failure; iii) aspirin use is associated with bleeding and/or symptomatic peptic ulcer disease; iv) aspirin causes bronchospasm in aspirin-sensitive asthmatics; and v) use of NSAIDs is associated with bronchospasm in aspirin-sensitive asthmatics. In addition, the association between NSAID use and peptic ulcer disease is supported by moderate quality data (further research is likely to affect the confidence in the estimate and may change the estimate) for non-prescription dosing and high quality data for greater than non-prescription dosing.

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Table 14 Medications and AEs for Which Evidence Favors a Causal Relationship

Medication	Adverse effect	Summary statement	Quality of evidence
<i>Risks associated with medication use at non-prescription dosing levels</i>			
Acetaminophen	Chronic kidney disease	The available data favor acceptance of a causal relationship between the use of acetaminophen and chronic kidney disease in the setting of a relatively high cumulative intake	Low
	Hepatic transaminase elevations	The available data strongly favor acceptance of a causal relationship between the use of acetaminophen and elevation of hepatic transaminase levels in serum	High
Aspirin	Bronchospasm in asthmatics	The available data strongly favor acceptance of a causal relationship between the use of aspirin and triggered bronchospasm in aspirin-sensitive asthmatics	High
	Peptic ulcer disease	The available data strongly favor acceptance of a causal relationship between the use of aspirin and symptomatic or bleeding peptic ulcer disease	High
	Congenital anomalies	The available data favor acceptance of a causal relationship between the use of aspirin in the first trimester of pregnancy and congenital anomalies in the fetus	Low
NSAID	Bronchospasm in asthmatics	The available data strongly favor acceptance of a causal relationship between the use of NSAID medications and bronchospasm in aspirin-sensitive asthmatics. A substantial minority of asthmatics are aspirin-sensitive. NSAID medications are likely to produce bronchospasm in this subpopulation	High
	Acute kidney injury	The available data favor acceptance of a causal relationship between the use of NSAID medications and acute kidney injury	Very low (non-prescription doses) [*]
	MI	The available data favor acceptance of a causal relationship between the use of ibuprofen and MI [†]	Ibuprofen: low

^{*}For greater than non-prescription doses, the data strongly favor acceptance of a causal relationship (high quality evidence).

[†]The data are inadequate to favor acceptance or rejection of a causal relationship with regard to naproxen (low quality evidence), and no evidence exists with regard to ketoprofen (quality of evidence N/A).

[‡]Very few data are available about ketoprofen; the panel voted on this association based on a presumed class effect.

[§]High quality data for greater than non-prescription doses.

[¶]For this question, the panel considered all possible doses > 4000 mg/day. The panel did not establish a threshold dose for this effect.

CHF: Congestive heart failure; MI: Myocardial infarction; N/A: Not available.

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Medication	Adverse effect	Summary statement	Quality of evidence
	Elevated blood pressure in hypertensive patients	The available data favor acceptance of a causal relationship between the use of NSAID and elevation of blood pressure in patients with pre-existing hypertension [§]	Ibuprofen: moderate Naproxen: moderate Ketoprofen: very low
	Peptic ulcer disease	The available data strongly favor acceptance of a causal relationship between the use of NSAID medications and symptomatic or bleeding peptic ulcer disease	Moderate (non-prescription doses) [¶]
	Miscarriage	The available data favor acceptance of a causal relationship between the use of NSAID medications during pregnancy and miscarriage	Low
	Congenital anomalies	The available data favor acceptance of a causal relationship between the use of NSAID medications in the first trimester of pregnancy and congenital anomalies in the fetus	Low
	Preterm birth	The available data strongly favor acceptance of a causal relationship between the use of maximal non-prescription doses of NSAID medications and preterm birth, particularly when NSAID use occurs in the third trimester of pregnancy	Low
<i>Additional risks associated with medication use at greater than non-prescription dosing levels</i>			
Acetaminophen	Liver failure	The available data strongly favor acceptance of a causal relationship between the use of acetaminophen at doses > 4000 mg/day and acute liver failure [#]	High
NSAID	Chronic kidney disease	The available data strongly favor acceptance of a causal relationship between the use of NSAID medications at greater than non-prescription doses and chronic kidney disease	Moderate
	New-onset hypertension	The available data strongly favor acceptance of a causal relationship between the use of NSAID medications at greater than non-prescription doses and development of hypertension	Moderate
	CHF	The available data favor acceptance of a causal relationship between the use of NSAID medications at greater than non-prescription doses and hospital admission for CHF	Moderate

[§]For greater than non-prescription doses, the data strongly favor acceptance of a causal relationship (high quality evidence).

[†]The data are inadequate to favor acceptance or rejection of a causal relationship with regard to naproxen (low quality evidence), and no evidence exists with regard to ketoprofen (quality of evidence N/A).

[‡]Very few data are available about ketoprofen; the panel voted on this association based on a presumed class effect.

[¶]High quality data for greater than non-prescription doses.

[#]For this question, the panel considered all possible doses > 4000 mg/day. The panel did not establish a threshold dose for this effect.

CHF: Congestive heart failure; MI: Myocardial infarction; N/A: Not available.

The panel reached consensus about 8 adverse effects from non-prescription NSAID use: bronchospasm in asthmatics (high quality data); acute kidney injury (very low quality for non-prescription doses, high quality at greater doses); MI for IBU only (low quality); elevated BP in hypertensive patients (moderate for IBU and NAP); peptic ulcer disease (moderate quality); miscarriage, congenital anomalies, and preterm birth (all low quality). The panel stated that data are inadequate to favor acceptance or rejection of a causal relation between NAOP and MI (low quality evidence).

In addition, the panel reached consensus on three more risks from NSAIDs at prescription dosing levels: chronic kidney disease, new onset hypertension, and CHF, all at moderate quality of evidence.

MO Comment: *The consensus panel report reaffirmed the known risks of NSAID use: Drug facts labeling for NSAIDs covers these risks and directs consumers to ‘Ask a doctor before use’ if they are risk for stomach bleeding, have hypertension, heart disease, kidney disease or asthma. In addition, those who are pregnant or breast-feeding are warned to ask a health professional before use.*

Lavonas EJ, Fries J, Furst Dee et al. Comparative risks of non-prescription analgesics...Expert Opin Drug Saf. 2012. 11:33-44

9.2 Labeling Recommendations/Comments

The proposed labeling for this product has the same drowsiness warnings as the currently approved product Advil PM, which is an ibuprofen-DPH combination for the same indication as the present product. This labeling states:

Do not use :

- unless you have time for a full night’s sleep

Ask a doctor or pharmacist before use if you are

- taking sedatives or tranquilizers, or any other sleep-aid

When using this product:

- drowsiness will occur
- avoid alcoholic drink
- do not drive a motor vehicle or operate machinery

MO Comment: The drowsiness warning for DPH as a sleep aid, “do not drive a motor vehicle or operate machinery”, differs from the monograph warning language for the same dosage (25 to 50 mg) of DPH indicated for allergic rhinitis [21 CFR 341.72]

“May cause marked drowsiness; alcohol, sedatives and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery.”

Monograph labeling also does not include warnings about getting a full night’s sleep. These label inconsistencies could cause confusion in the marketplace.

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See the IDS review for further label comments.

9.3 Advisory Committee Meeting

NA

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9.4 Table of References

Table 15 Summary of DPH Literature Submitted in NDA 205352

	Reference	Title	Study	Result
1	Erdur B, Tura P, Aydin B, Ozen M, Ergin A, Parlak I, Kabay B. Am J Emerg Med. 2012 Jan;30(1):84-91	A trial of midazolam vs diphenhydramine in prophylaxis of metoclopramide-induced akathisia	RCT in 75 subjects; midazolam 1.5 mg, DPH 20 mg	Midazolam effective against metoclopramide-induced akathisia, but not DPH. Midazolam more sedating than DPH; DPH more sedating than placebo (Ramsey Sedation Scale).
2	Liao CC, Chang CS, Tseng CH, Sheen MJ, Tsai SC, Chang YL, Wong SY. Chang Gung Med J. 2011 Mar-Apr;34(2):172-8	Efficacy of intramuscular nalbuphine versus diphenhydramine for the prevention of epidural morphine-induced pruritus after cesarean delivery	RCT in 150 subjects; nalbuphine 10 mg, DPH 30 mg	Nalbuphine superior to DPH for pruritus. No difference in sedation (Ramsey Sedation Scale)
3	Hahn A, Novotný M, Shotekov PM, Cirek Z, Bogner-Steinberg I, Baumann W. Clin Drug Investig. 2011;31(6):371-83.	Comparison of cinnarizine/dimenhydrinate fixed combination with the respective monotherapies for vertigo of various origins: a randomized, double-blind, active-controlled, multicentre study	RCT in 182 subjects; cinnarizine 20 mg, DMH 40 mg	Fixed combination superior efficacy. 3/61 on DMH monotherapy reported AEs (somnolence, headache, tachycardia) and two discontinued from trial
4	Vanspauwen R, Weerts A, Hendrickx M, Buytaert KI, Blaivie C, Jorens PG, Van de Heyning PH, Wuyts FL Otol Neurotol. 2011 Apr;32(3):497-503.	No effects of anti-motion sickness drugs on vestibular evoked myogenic potentials outcome parameters	RCT in 24 and 20 subjects (two phases of trial)	for combination cinnarizine (20 mg) + dimenhydrinate (40 mg), no effect versus placebo, no safety issues
5	Zhang D, Tashiro M, Shibuya K, Okamura N, Funaki Y, Yoshikawa T, Kato M, Yanai K.. J Clin Psychopharmacol. 2010 Dec;30(6):694-701	Next-day residual sedative effect after nighttime administration of an over-the-counter antihistamine sleep aid, diphenhydramine, measured by positron emission tomography	RCT in 8 subjects; DPH 50 mg, bepotastine 10 mg, placebo (crossover study design)	PET scans showed significantly greater binding to brain H1 receptors for DPH than for bepotastine (2 nd gen antihist) or placebo. No significant differences in subjective sleepiness ratings. Should account for possible hangover effect of DPH.

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6	Lu CW, Jean WH, Wu CC, Shieh JS, Lin TY. Eur J Anaesthesiol. 2010 Dec;27(12):1052-7.	Antiemetic efficacy of metoclopramide and diphenhydramine added to patient-controlled morphine analgesia: a randomized controlled trial	RCT in 200 women; included DPH 0.6 mg/ml in patient-controlled analgesia	metoclopramide with diphenhydramine in patient-controlled morphine analgesia treated with dexamethasone at induction decreased postoperative nausea and vomiting compared to metoclopramide or diphenhydramine
7	Siddik-Sayyid SM, Yazbeck-Karam VG, Zahreddine BW, Adham AM, Dagher CM, Saasouh WA, Aouad MT. Acta Anaesthesiol Scand. 2010 Jul;54(6):764-9.	Ondansetron is as effective as diphenhydramine for treatment of morphine-induced pruritus after cesarean delivery	RCT in 113 women; ondansetron 4 mg iv versus DPH 25 mg iv	Success rate was comparable in the two groups as was side effect profile; both drugs were well tolerated
8	Valk PJ, Simons M. Adv Ther. 2009 Jan;26(1):89-98	Effects of loratadine/montelukast on vigilance and alertness task performance in a simulated cabin environment	RCT in 23 subjects; DPH 50 mg, L/M 10 mg/10mg, placebo (crossover study design)	L/M is similar to placebo in effects on daytime somnolence and psychomotor performance. L/M treatment resulted in significantly less sleepiness and impairment of vigilance and tracking than DPH. Significant increases in sleepiness occurred between 1-5 hours post treatment in diphenhydramine treated patients versus placebo-treated patients ($P \leq 0.05$). Fatigue and headache occurred in DPH group.
9	Wang H, Bolognese J, Calder N, Baxendale J, Kehler A, Cummings C, Connell J, Herman G. J Pain. 2008 Dec;9(12):1088-95	Effect of morphine and pregabalin compared with diphenhydramine hydrochloride and placebo on hyperalgesia and allodynia induced by intradermal capsaicin in healthy male subjects	RCT in 20 subjects; pregabalin 300 mg, morphine 10 mg iv, DPH 50 mg, placebo (crossover study design)	Pregabalin and morphine significantly reduced the area of secondary hyperalgesia over 15 to 240 minutes after capsaicin injection. DPH caused increased hyperalgesia compared to placebo

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10	Kennedy LD, Case LD, Hurd DD, Cruz JM, Pomper GJ. Transfusion. 2008 Nov;48(11):2285-91.	A prospective, randomized, double-blind controlled trial of acetaminophen and diphenhydramine pretransfusion medication versus placebo for the prevention of transfusion reactions	RCT in 315 subjects; Apap 500mg+DPH 25 mg versus placebo	No significant difference in the overall risk of transfusion reactions between groups.
11	Jones DH, Romero FA, Casale TB, Ann Allergy Asthma Immunol. 2008 May;100(5):452-6.	Time-dependent inhibition of histamine-induced cutaneous responses by oral and intramuscular diphenhydramine and oral fexofenadine	RCT in 18 subjects; fexofenadine 180 mg versus DPH 50 mg (crossover study design)	No significant differences were found in inhibition of histamine-induced flares
12	Tashiro M, Duan X, Kato M, Miyake M, Watanuki S, Ishikawa Y, Funaki Y, Iwata R, Itoh M, Yanai K. Br J Clin Pharmacol. 2008 Jun;65(6):811-21.	Brain histamine H1 receptor occupancy of orally administered antihistamines, bepotastine and diphenhydramine, measured by PET with 11C-doxepin.	RCT in 8 subjects; DPH 30 mg, bepotastine 10 mg, placebo (crossover study design)	Similar to reference 5
13	Willett J, Reader A, Drum M, Nusstein J, Beck M. J Endod. 2008 Dec;34(12):1446-50	The anesthetic efficacy of diphenhydramine and the combination diphenhydramine/ lidocaine for the inferior alveolar nerve block	RCT in 30 subjects	1% diphenhydramine solution was irritating and had low anesthetic effect. The combination lidocaine/ diphenhydramine solution was irritating postinjection and was not as effective as a lidocaine solution for dental anesthesia
14	Ho TW, Backonja M, Ma J, Le bensperger H, Froman S, Polydefkis M. Pain. 2009 Jan;141(1-2):19-24.	Efficient assessment of neuropathic pain drugs in patients with small fiber sensory neuropathies	RCT in 59 subjects gabapentin vs DPH 50 mg) and 48 subjects (tramadol vs DPH 50 mg)	Gabapentin and tramadol were both effective in the treatment of painful small fiber neuropathy. Tramadol and DPH not different for sleep interference. Nausea for 24% of DPH subjects

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15	Feltner DE, Haig G. J Psychopharmacol. 2011 Jun;25(6):763-73.	Evaluation of the subjective and reinforcing effects of diphenhydramine, levetiracetam, and valproic acid	RCT in 24 subjects; DPH 400 mg, levetiracetam 4 g, valproic acid 1.5 g, diazepam 30 mg, placebo (single dose crossover)	Levetiracetam, diphenhydramine, and valproic acid all have increased ratings for abuse potential versus placebo, but less so than for diazepam. DPH is subject to little abuse. DPH produces stronger unpleasant somatic side effects than benzodiazepines (queasy, sick to stomach). A DPH subject experienced anticholinergic crisis.
16	Sharma A, Pibarot P, Pilote S, Dumesnil JG, Arsenault M, Bélanger PM, Me bohm B, Hamelin BA. J Clin Pharmacol. 2010 Feb;50(2):214-25.	Toward optimal treatment in women: the effect of sex on metoprolol diphenhydramine interaction	RCT in 16 men and 20 women	Diphenhydramine coadministration increased S-metoprolol AUC by 84% in extensive CYP2D6 metabolizer women and 45% in such men. Authors suggest metoprolol dose should be adjusted for body weight, particularly in women
17	Friedman BW, Bender B, Davitt M, Solorzano C, Paternoster J, Esses D, Bijur P, Gallagher EJ. Ann Emerg Med. 2009 Mar;53(3):379-85	A randomized trial of diphenhydramine as prophylaxis against metoclopramide-induced akathisia in nauseated emergency department patients	RCT in 289 subjects; metoclopramide 10 mg or 20 mg with DPH 25 mg or placebo (4 groups)	Routine prophylaxis with DPH to prevent akathisia is unwarranted when iv metoclopramide is given over 15 minutes. For patients given metoclopramide 20 mg, prophylactic DPH may decrease subjective restlessness
18	Otto V, Fischer B, Schwarz M, Baumann W, Preibisch-Effenberger R. Int Tinnitus J. 2008;14(1):57-67.	Treatment of vertebrobasilar insufficiency--associated vertigo with a fixed combination of cinnarizine and dimenhydrinate.	RCT in 37 subjects, betahistine 12 mg vs cinnarizine 20 mg/DMH 40 mg	Fixed combination superior efficacy. 2/11 in fixed combination group reported AEs, neither related to study drug per investigator

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19	Glass JR, Sproule BA, Herrmann N, Busto UE. J Clin Psychopharmacol. 2008 Apr;28(2):182-8.	Effects of 2-week treatment with temazepam and diphenhydramine in elderly insomniacs: a randomized, placebo-controlled trial.	RCT in 20 subjects; temazepam 15 mg, DPH 50 mg, and placebo (crossover study design)	Both active drugs improved sleep, although only for improvement on the number of awakenings for DPH. Dropouts were: 2 in the temazepam arm (dizziness and fall resulting in minor injury), 1 in the placebo arm (lack of efficacy), and 2 in the diphenhydramine arm (oversedation and nausea)
20	Hahn A, Sejna I, Stefflova B, Schwarz M, Baumann W. Clin Drug Investig. 2008;28(2):89-99.	A fixed combination of cinnarizine/dimenhydrinate for the treatment of patients with acute vertigo due to vestibular disorders: a randomized, reference-controlled clinical study	RCT in 66 subjects, betahistine 12 mg vs cinnarizine 20 mg/DMH 40 mg	Similar to reference 3
21	Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG. Arch Phys Med Rehabil. 2007 Dec;88(12):1547-60	Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury.	RCT in 38 subjects, gabapentin 1.2 g tid, amitriptyline 50 mg tid, DPH 25 mg tid (crossover)	Amitriptyline more effective than DPH. Withdrawal or early crossover for 4 subjects on amitriptyline, 5 on gabapentin, 2 on DPH (palpitations; drowsiness)
22	Pongrojapaw D, Somprasit C, Chanthasenanon A. J Med Assoc Thai. 2007 Sep;90(9):1703-9.	A randomized comparison of ginger and dimenhydrinate in the treatment of nausea and vomiting in pregnancy	RCT in 170 women, ginger 500 mg bid, DMH 50 mg bid	Ginger as effective as DMH for nausea and vomiting. More drowsiness for DMH (78%) than ginger (6%)
23	Kanamaru Y, Kikukawa A, Miyamoto Y, Hirafuji M. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Jan 1;32(1):107-15	Dimenhydrinate effect on cerebral oxygen status and salivary chromogranin-A during cognitive tasks.	RCT in 12 subjects, DMH 50 mg or placebo (crossover study design)	Poor cognitive performance was observed in the subjects taking DMH

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24	Parlak I, Erdur B, Parlak M, Ergin A, Ayrik C, Tomruk O, Turkcuier I, Ergin N. Acad Emerg Med. 2007 Aug;14(8):715-21.	Midazolam vs. diphenhydramine for the treatment of metoclopramide induced akathisia: a randomized controlled trial	RCT in 56 subjects; midazolam 2 mg, DPH 20 mg	Similar to reference 1
25	Carter JR, Ray CA. Clin Auton Res. 2007 Jun;17(3):186-92	Effect of dimenhydrinate on autonomic activity in humans	RCT in 16 subjects, DMH 100 mg and placebo	DMH induced heart rate increase
26	Pytel J, Nagy G, Tóth A, Spellenberg S, Schwarz M, Répassy G. Clin Ther. 2007 Jan;29(1):84-98.	Efficacy and tolerability of a fixed low-dose combination of cinnarizine and dimenhydrinate in the treatment of vertigo: a 4-week, randomized, double-blind, active- and placebo-controlled, parallel-group, outpatient study.	RCT in 246 subjects, cinnarizine 20 mg/ DMH 40 mg, cinnarizine 50 mg, DMH 100 mg, placebo	Fixed combination superior efficacy. Most frequent AEs somnolence, amnesia, headache
27	Apiliogullari S, Keles B, Apiliogullari B, Balasar M, Yilmaz H, Duman A. Eur J Anaesthesiol. 2007 Mar;24(3):235-8.	Comparison of diphenhydramine and lidocaine for prevention of pain after injection of propofol: a double-blind, placebo-controlled, randomized study	RCT in 180 subjects, placebo, DPH 2mL (20 mg) iv, lidocaine 2mL (40mg)	Pain significantly less for DPH than placebo, no difference between lidocaine and DPH. No local reactions or extrapyramidal reactions observed.
28	Hou RH, Langley RW, Szabadi E, Bradshaw CM. J Psychopharmacol. 2007 Aug;21(6):567-78	Comparison of diphenhydramine and modafinil on arousal and autonomic functions in healthy volunteers	RCT in 16 males, placebo, DPH 75 mg, modafinil 200 mg, DPH-modafinil combination (crossover)	DPH and modafinil evoked opposite effects on arousal and sympathetic functions
29	McEvoy LK, Smith ME, Fordyce M, Gevins A. Sleep. 2006 Jul;29(7):957-66.	Characterizing impaired functional alertness from diphenhydramine in the elderly with performance and neurophysiologic measures	RCT in 12 elderly subjects, placebo and DPH 50mg	EEG and ERP are sensitive to subtle impairments of functional alertness in elderly subjects. DPH led to decreased alertness, but psychometric task performance was relatively insensitive to that

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30	Friedman BW, Hochberg M, Esses D, Bijur PE, Corbo J, Paternoster J, Solorzano C, Toosi B, Lipton RB, Gallagher EJ. Headache. 2006 Jun;46(6):934-41.	A clinical trial of trimethobenzamide/diphenhydramine versus sumatriptan for acute migraines	RCT in 40 subjects, sumatriptan 6mg SQ, trimethobenzamide 200 mg/ DPH 25 mg im	Adverse effects were similar in the 2 groups. No serious AEs.
31	Hou RH, Scaife J, Freeman C, Langley RW, Szabadi E, Bradshaw CM. Br J Clin Pharmacol. 2006 Jun;61(6):752-60.	Relationship between sedation and pupillary function: comparison of diazepam and diphenhydramine.	RCT in 15 males, diazepam 10 mg, DPH 75 mg and placebo (crossover)	Single doses both drugs showed sedative effect. DPH reduced pupil diameter in darkness and at all three luminance levels studied; diazepam did not change pupil diameter
32	Raphael GD, Angello JT, Wu MM, Druce HM. Ann Allergy Asthma Immunol. 2006 Apr;96(4):606-14. Comment in Ann Allergy Asthma Immunol. 2006 Jul;97(1):121-2.	Efficacy of diphenhydramine vs desloratadine and placebo in patients with moderate-to-severe seasonal allergic rhinitis	RCT in 610 subjects, DPH 50 mg, desloratadine 5 mg, placebo	DPH 50 mg for 1 week superior for SAR but somnolence more frequent than for desloratadine or placebo
33	Weigert G, Zawinka C, Resch H, Schmetterer L, Garhöfer G. Invest Ophthalmol Vis Sci. 2006 Mar;47(3):1096-100	Intravenous administration of diphenhydramine reduces histamine induced vasodilator effects in the retina and choroid	RCT crossover in 18 males, DPH versus placebo	DPH reduced histamine-induced changes. In ocular circulation, histamine effects mediated in part by H1 receptors
34	Turner C, Handford AD, Nicholson AN. J Psychopharmacol. 2006 Jul;20(4):506-17	Sedation and memory: studies with a histamine H-1 receptor antagonist	RCT in 12 subjects, DPH (50, 75, 100 mg), lorazepam (0.5, 1.5 mg), crossover design	all doses of DPH caused sedation, reduced sleep latencies and reduced performance on the digit substitution, reaction time and sustained attention tasks. No such effects with 0.5 mg lorazepam. With 1.5 mg lorazepam, subjects had sedation, fewer digit substitutions, slowed reaction time, impaired attention and memory, but no effect on sleep latency. Peak effect of DPH ~2hrs after ingestion.

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35	Tu RH, Grewall P, Leung JW, Suryaprasad AG, Sheykhzadeh PI, Doan C, Garcia JC, Zhang N, Prindiville T, Mann S, Trudeau W. Gastrointest Endosc. 2006 Jan;63(1):87-94	Diphenhydramine as an adjunct to sedation for colonoscopy: a double blind, randomized, placebo-controlled study	RCT in 270 subjects, DPH 50 mg iv or placebo, before iv midazolam and meperidine	Intravenous DPH improved level of sedation and reduced amount of midazolam and meperidine used. 8 sedation related complications --2 in DPH group (transient hypoxia which responded to increased conc of O2, and bradycardia of 32 which responded to atropine) and 6 in placebo group (one hypoxia responding to O2 and hypotension responding to fluids). All complications were considered mild.
36	Morin CM, Koetter U, Bastien C, Ware JC, Wooten V. Sleep. 2005 Nov;28(11):1465-71.	Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial	RCT in 184 subjects, valerian-hops combination 28 days, DPH 50 mg 14 days and placebo 14 days, placebo 28 days	valerian-hops combination and DPH yield improvements in subjective sleep latency, sleep efficiency, total sleep time. No group differences in polysomnography. No significant residual effects and no rebound insomnia.
37	Scaife JC, Groves J, Langley RW, Bradshaw CM, Szabadi E. J Psychopharmacol. 2006 Jul;20(4):485-95.	Sensitivity of late-latency auditory and somatosensory evoked potentials to threat of electric shock and the sedative drugs diazepam and diphenhydramine in human volunteers	RCT in 12 males, diazepam 10 mg, DPH 75 mg, placebo (crossover)	Threat cues can modify late-latency components of auditory and somatosensory evoked potential. Diazepam, but not DPH, suppressed some components of the evoked potentials. DPH, diazepam equally sedating from visual analog scales

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38	Paul MA, MacLellan M, Gray G. Aviat Space Environ Med. 2005 Jun;76(6):560-5.	Motion-sickness medications for aircrew: impact on psychomotor performance	RCT 21 subjects, promethazine 25 mg, promethazine 25 mg+pseudo ephedrine 60 g, promethazine 25 mg+ d- amphetamine 10 mg, meclizine 50 mg, DMH 50 mg, placebo (crossover)	DMH induced subjective sleepiness and impaired performance on serial reaction time test but not the higher order cognitive tests of logical reasoning, serial subtraction or multitasking. DMH not as effective as promethazine for motion sickness
39	Lin TF, Yeh YC, Yen YH, Wang YP, Lin CJ, Sun WZ. Br J Anaesth. 2005 Jun;94(6):835-9.	Antiemetic and analgesic-sparing effects of diphenhydramine added to morphine intravenous patient-controlled analgesia	RCT 120 subjects, placebo+morphine, DPH 30 mg+DPH/ morphine (1.2:1 or 4.8:1 ratios)	DPH 30 mg IV at anesthetic induction and postop patient-controlled analgesia with 4.8:1, but not 1.2:1, DPH-morphine mixture provides effective antiemesis. Sedation and dry mouth similar among groups
40	Sharma A, Pibarot P, Pilote S, Dumesnil JG, Arsenault M, Bélanger PM, Me bohm B, Hamelin BA. J Pharmacol Exp Ther. 2005 Jun;313(3):1172-81..	Modulation of metoprolol pharmacokinetics and hemodynamics by diphenhydramine coadministration during exercise testing in healthy premenopausal women	RCT 20 women (crossover) of metoprolol and DPH 50 mg PK/PD interaction	DPH competitively inhibits metoprolol metabolism. DPH coadministration caused a 2.2- to 3.2-fold decrease in clearance of metoprolol enantiomers and a 21% increase in area-under-effect-curves (increases cardiac effects in extensive metabolizers of metoprolol). Somnolence reported by 10/20 subjects (see reference 16)

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41	Mitsias DI, Vovolis V. J Investig Allergol Clin Immunol. 2011;21(4):317-8	Anaphylaxis to dimenhydrinate caused by the theophylline component	case report	<p>COPYRIGHT MATERIAL WITHHELD</p>
42	Mur Gimeno P, Alfaya Arias T, Iglesias Aranzazu M, Lombardero Vega M, Sastre B. J Investig Allergol Clin Immunol. 2011;21(4):321-2	Anaphylactic shock caused by antihistamines.	case report	
43	Mota MS, Natera AH, Poussivert EN, Valero RS. Rev Clin Esp. 2008 Mar;208(3):170	Anticholinergic syndrome. A case report	case report	
44	Vearrier D, Curtis JA. J Med Toxicol. 2011 Sep;7(3):213-9.	Case files of the medical toxicology fellowship at Drexel University. Rhabdomyolysis and compartment syndrome following acute diphenhydramine overdose	case report	

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45	Pyle R, Scott M, Bartholomew J, McGrath S, Moffett B. Am J Med. 2011 Oct;124(10):e5-6.	Accidental polydipsia and hyponatremia from diphenhydramine urinary retention	case report	COPYRIGHT MATERIAL WITHHELD
46	Gitrakou S, Papadavid E, Kalogeromitros D, Theodoropoulos K, Toumbis-Ioannou E, Makris M, Stavrianeas NG. J Am Acad Dermatol. 2011 Mar;64(3):608-10	Fixed drug eruption caused by dimenhydrinate	case report	
47	Jang DH, Manini AF, Trueger NS, Duque D, Nestor NB, Nelson LS, Hoffman RS. Clin Toxicol (Phila). 2010 Nov;48(9):945-8.	Status epilepticus and wide-complex tachycardia secondary to diphenhydramine overdose	case report	
48	Husain Z, Hussain K, Nair R, Steinman R. Cardiol J. 2010;17(5):509-11.	Diphenhydramine induced QT prolongation and torsade de pointes: An uncommon effect of a common drug	case report	

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49	Lin KH, Chen YJ, Wei CF, Yen MH, Hsueh WC, Liao KC, Lu CL. Prog Neuropsychopharmacol Biol Psychiatry. 2010 May 30;34(4):705-6.	Prolonged withdrawal delirium in concomitant diphenhydramine and nefopam dependence: A case report	case report
50	Levine M, Lovecchio F. Resuscitation. 2010 Apr;81(4):503-4	Diphenhydramine-induced Brugada pattern.	case report
51	Carstairs SD, Schneir AB. N Engl J Med. 2010 Dec 30;363(27):e40	Images in clinical medicine. Opsoclonus due to diphenhydramine poisoning	case report

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52	Schwartz EA, Hayes BD, Sarmiento KF. Ann Emerg Med. 2009 Sep;54(3):421-3.	Development of hepatic failure despite use of intravenous acetylcysteine after a massive ingestion of acetaminophen and diphenhydramine	case report	COPYRIGHT MATERIAL WITHHELD
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53	Kamijo Y, Soma K, Sato C, Kurihara K. Clin Toxicol (Phila). 2008 Nov;46(9):864-8	Fatal diphenhydramine poisoning with increased vascular permeability including late pulmonary congestion refractory to percutaneous cardiovascular support.	case report
54	Rodríguez-Jiménez B, Domínguez-Ortega J, González-García JM, Kindelan-Recarte C J Investig Allergol Clin Immunol. 2009;19(4):334-5	Dimenhydrinate-induced fixed drug eruption in a patient who tolerated other antihistamines.	case report
55	Health Canada, Prescrire Int. 2008 Aug;17(96):161	Confusion and stroke due to an "umbrella brand" product	case report
56	Kimlin EJ, Easter JS, Ganetsky M. J Emerg Med. 2009 Jul;37(1):69-74.	A 46-year-old woman with altered mental status and garbled speech	case report

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57	Irioka T, Yamanami A, Uchida N, Iwase M, Yasuhara H, Mizusawa H. J Neuroophthalmol. 2009 Mar;29(1):72-3	Opsoclonus caused by diphenhydramine self-poisoning	case report
58	Jeffery AD, Lytle-Saddler T. J Emerg Nurs. 2008 Dec;34(6):543-4.	Diphenhydramine overdose in a 26-year-old woman	case report
59	Fernández-Jorge B, Goday Buján J, Fernández-Torres R, Rodríguez-Lojo R, Fonseca E. Contact Dermatitis. 2008 Aug;59(2):115-6.	Concomitant allergic contact dermatitis from diphenhydramine and metronidazole	case report
60	Charbonneau K, Landry P. J Clin Psychopharmacol. 2008 Dec;28(6):706-7	Leukopenia and neutropenia after intoxication with diphenhydramine (Nytol) during clozapine treatment	case report

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61	Thomas A, Nallur DG, Jones N, Deslandes PN. J Psychopharmacol. 2009 Jan;23(1):101-5.	Diphenhydramine abuse and detoxification: a brief review and case report	case report
62	Ramachandran K, Sirop P. Conn Med. 2008 Feb;72(2):79-82.	Rare complications of diphenhydramine toxicity	case report
63	de Leon J, N koloff DM. CNS Spectr. 2008 Feb;13(2):133-5.	Paradoxical excitation on diphenhydramine may be associated with being a CYP2D6 ultrarapid metabolizer: three case reports	case report
64	Evans CE, Sebastian J. Emerg Med J. 2007 Apr;24(4):e20	Serotonin syndrome	case report
65	Frick S, Roos M, Fattinger K. Hum Exp Toxicol. 2007 Feb;26(2):131-3.	How much is too much? Oligosymptomatic presentation after 11.5 g of diphenhydramine	case report

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66	López-Barbeito B, Lluís M, Delgado V, Jiménez S, Díaz-Infante E, Nogué-Xarau S, Brugada J. Pacing Clin Electrophysiol. 2005 Jul;28(7):730-2.	Diphenhydramine overdose and Brugada sign	case report
67	Sype JW, Khan IA. Int J Cardiol. 2005 Mar 18;99(2):333-5.	Prolonged QT interval with markedly abnormal ventricular repolarization in diphenhydramine overdose	case report
68	Hermann DM, Bassetti CL. Eur Neurol. 2005;53(1):46-7.	Reversible opsoclonus after diphenhydramine misuse	case report
69	Nakanishi T, Yasuda S, Kubota Y, Kajimoto A, Kamo R, Kobayashi H, Ishii M. Contact Dermatitis. 2005;52(1):52-3.	Allergic contact dermatitis presenting in the emergency department	case report
70	Thakur AC, Aslam AK, Aslam AF, Vasavada BC, Sacchi TJ, Khan IA. Int J Cardiol. 2005 Feb 15;98(2):341-3	QT interval prolongation in diphenhydramine toxicity	case report
71	Nine JS, Rund CR. Am J Forensic Med Pathol. 2006 Mar;27(1):36-41	Fatality from diphenhydramine monointoxication: a case report and review of the infant, pediatric, and adult literature	case report

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Aleve PM (naproxen sodium/diphenhydramine)

72	Benson BE, Farooqi MF, Klein-Schwartz W, Litovitz T, Webb AN, Borys DJ, Lung D, Rutherford Rose S, Aleguas A, Sollee DR, Seifert SA. Clin Toxicol (Phila). 2010 Oct;48(8):820-31	Diphenhydramine dose-response: a novel approach to determine triage thresholds	clinical investigation	Retrospectively analyzed APAP/DPH only exposures in patients 2–80 years of age using case data from 15 U.S. poison centers. Support referring patients to hospital for evaluation if more than 7.5 mg/kg of DPH.
73	Pragst F, Herre S, Bakdash A. Forensic Sci Int. 2006 Sep 12;161(2-3):189-97.	Poisonings with diphenhydramine--a survey of 68 clinical and 55 death cases	clinical investigation	68 clinical and 55 death cases at one hospital 1992-2004. Majority of fatal intoxications were suicides. Two cases involvement in homicides (one case 3 yo boy).
74	Czeizel AE, Vargha P. Arch Gynecol Obstet. 2005 Feb;271(2):113-8.	A case-control study of congenital abnormality and dimenhydrinate usage during pregnancy	case control study	In 38,151 newborns without congenital abnormalities (control group), 1,726 (4.5%) exposed to DMH during pregnancy, while in 22,843 cases with congenital abnormalities, there were 914 (4.0%; unadjusted odds ratio at 95% CI: 0.9, 0.8–1.0). No indication of teratogenicity.

Clinical Review
Dr. Linda Hu
NDA 205352
Aleve PM (naproxen sodium/diphenhydramine)

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/s/

LINDA S HU
12/16/2013

LUCIE L YANG
12/16/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205352 Applicant: Bayer HealthCare Stamp Date: March 20, 2013

Drug Name: Aleve PM NDA/BLA Type: Standard

Naproxen Sodium (NS) Diphenhydramine HCl (DPH)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic submission
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?				
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(2) references monograph for DPH—PMs looking into this further
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: 14837 {p25/51} Study 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 Sample Size: 203/204/203/102 Arms: NS 440/DPH50mg; NS 220/DPH50mg; NS 440;	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	DPH 50mg Location in submission: Module 5				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 14837 Indication: relief of occasional sleeplessness associated with minor aches and pains; helps you fall asleep and stay asleep Pivotal Study #2 Indication:	X			Efficacy of the proposed dose appears to be supported by one pivotal trial in the development program. The Agency noted that this may be acceptable provided the Sponsor has an acceptable rationale for why the data from this study alone should be considered adequate to demonstrate efficacy for this product.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	Not requested
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	DPH and NS have both been marketed separately as single ingredient products for many years.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Exception: For PK study, patient data has been submitted in pdf format only.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
38.	Has the applicant submitted the required Financial Disclosure information?	X			Form 3454
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Information Requests

Provide narrative summaries for subjects who:

--dropped out or withdrew from PK study 16135

--did not complete study 14837

For DPH

For the Bayer pharmacovigilance database, provide a tabular case by case summary for the serious case reports and deaths with the following column headings: Case ID Age, Gender, DPH dose, Route of Administration, Suspect Medications, Concomitant Medications, Reported Adverse Events In MedDRA Terms, Outcome, Narrative Summary, and Comments. Provide a discussion and analysis of these reports.

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/s/

LINDA S HU
05/17/2013

LESLEYANNE FURLONG
05/17/2013