U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	205-352
Drug Name:	Aleve PM (Naproxen Sodium and Diphenhydramine Combination)
Indication(s):	Postsurgical Dental Pain with Phase Advanced Sleep
Applicant:	Bayer Health Care
Date of Submission	3/21/2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
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Keywords: Hierarchical testing procedure, WASO, Sleep latency	

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1 EXECUTIVE SUMMARY

This NDA submission includes two pivotal efficacy studies, Study 14837 and Study 15881. The data of Study 14837 suggests that naproxen sodium 440 mg/diphenhydramine hydrochloride 50 mg (NP 440 mg/DPH 50 mg) was more effective than NP 440 mg on wake after sleep onset (WASO) and more effective than DPH 50 mg on sleep latency. For Study 15881, NP 440 mg/DPH 25 mg didn't achieve statistical significance in both the comparison of NP 440 mg/DPH 25 mg versus NP 440 mg on WASO and the comparison of NP 440 mg/DPH 25 mg versus DPH 50 mg. The designs of Study 14837 and Study 15881 were very similar. The major difference was the different combination dose used in the two studies, NP 440 mg/DPH 50 mg and NP 440 mg/DPH 25 mg for Study 14837 and 15881, respectively. The data shows that the treatment effect of NP 440 mg/DPH 50 mg in Study 14837 at least doubled the treatment effect of NP 440 mg/DPH 25 mg in Study 15881. However, the number of subjects per treatment group in Study 15881 was only half of the number of subjects per treatment group in Study 14837. The statistical insignificance of Study 15881 might be partially due to lack of power.

Study 14837 was a multicenter, randomized, double-blind, parallel group, pivotal efficacy study to evaluate the efficacy and safety of a single oral dose of 2 dose combinations of naproxen sodium and diphenhydramine hydrochloride (DPH) to demonstrate that the naproxen sodium/DPH combination provides added clinical benefit to sleep improvement than either single ingredient (naproxen sodium or DPH) alone in subjects with post-surgical dental pain and phase-advanced sleep. The study included a Screening Period of up to 28 days, a Dosing Period of 2 days, and a Follow-up Period of 2-5 days. A total of 712 subjects were randomized. There were 203, 204, and 203 subjects in the naproxen sodium 440 mg/DPH 50 mg, naproxen sodium 220 mg/DPH 50 mg, and naproxen sodium 440 mg groups, respectively, and 102 subjects in the DPH 50 mg group. A vast majority of subjects (99.6% overall) completed the study. This study was conducted in two sites in US.

The study objective and design of Study 15881 were similar to those of Study 14837. A total of 267 subjects were randomized. There were 107, 106, and 54 subjects in the NP 440 mg/DPH 25 mg, NP 440 mg, and DPH 50 mg groups, respectively. All subjects completed the study. This study was conducted in two sites in US.

For Study 14837, the p-value for the comparison of NP 440 mg/DPH 50 mg versus NP 440 mg on WASO was 0.0002 (LS mean treatment difference: -70.3 minutes) and the p-value for the comparison of NP 440 mg/DPH 50 mg versus DPH 50 mg on sleep latency was <0.0001 (median time to sleep onset: 25.5 and 41.5 minutes for NP 440 mg/DPH 50 mg and DPH 50 mg, respectively) according to the sponsor. Therefore, NP 440 mg/DPH 50 mg reached statistical significance for both WASO and sleep latency. No other doses achieved statistical significance on both WASO and sleep latency. For Study 15881, both WASO and sleep latency failed to demonstrate statistical significance for NP 440 mg/DPH 25 mg (p-value=0.30 for WASO and p-value=0.17 for sleep latency).

There are four treatment groups in Study 14837. In sponsor's analysis for sleep latency, each of the five pairwise comparisons was based on an individual model. However, in order to comply with the study design, this reviewer thinks the pairwise comparisons should be conducted within

one analysis model which takes all four treatment groups into consideration. Table 24 presents the results of sponsor's analysis and this reviewer's analysis. Even though there is slight difference in the p-values between sponsor's analysis and this reviewer's analysis, the interpretation of the study results remains same.

In the Statistical Analysis Plan (SAP) for Study 15881, it clearly states that "Both tests (for WASO and sleep latency) had to be statistically significant in order to claim NP 440 mg/DPH 25 mg to be efficacious." However, from the protocol and SAP for Study 14837, it is not clear if both WASO and sleep latency need to be statistically significant for an efficacy claim. Based on this reviewer's discussion with the Medical Reviewer, it seems that the Medical Division thinks both WASO and sleep latency need to be statistically significant in order for claiming a dose to be efficacious. This reviewer would like to point out that for Study 14837 the separate hierarchical testing procedure for WASO and sleep latency proposed by the sponsor in Section 3.2.1.4 doesn't control the studywise Type I error at 0.05 level (two-sided). For this study, it is sensible to test NP 440 mg/DPH 50 mg versus either single ingredient (naproxen sodium or DPH) alone first for both WASO and Sleep latency. The reviewer consider both WASO and sleep latency were statistically significant for NP 440 mg/DPH 50 mg.

This reviewer conducted subgroup analysis by sex, race, age group and site for WASO and sleep latency. It seems that the treatment effects of primary interest (NP440 mg/DPH 50 mg versus NP 440 mg for WASO; NP440 mg/DPH 50 mg versus DPH 50 mg for sleep latency) are all in the right direction for the subgroups investigated except that the point estimate of treatment effect isn't in the right direction for non-white patients for WASO. However, this doesn't raise concerns since there are only 11% (78/712) non-white patients in this study. Please refer to Section 4.1 for more details.

The "pain" part of this NDA is evaluated by Division of Anesthesia, Analgesia and Addiction products.

2 INTRODUCTION

2.1 Overview

A new nighttime analgesic/sleep-aid, fixed-combination over-the-counter (OTC) drug product containing naproxen sodium 220 mg and diphenhydramine hydrochloride (DPH HCl) 25 mg per tablet has been developed by Bayer Healthcare Consumer Care for the relief of occasional sleeplessness when associated with minor aches and pains. The proposed OTC product is indicated for adults and children 12 years of age and over, and is taken as a 2-tablet dose before bedtime for no more than 10 consecutive days.

Naproxen sodium is a nonselective cyclooxygenase (COX) inhibitor, which is in a class of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). Naproxen sodium inhibits prostaglandin synthesis through the reduction of the formation of its chemical precursors by decreasing the activity of the enzyme cyclooxygenase. Naproxen sodium has been marketed as a prescription

since 1976 under the brand name Naprosyn®. In 1994, the Food and Drug Administration (FDA) approved naproxen sodium tablets 220 mg for OTC marketing under the brand name Aleve®. Aleve is generally safe and well tolerated when taken as indicated for the temporary relief of minor aches and pains due to the minor pain of arthritis, muscular aches, backaches, menstrual cramps, headaches, toothaches, and the common cold. It also temporarily reduces fever. The safety profile of this product is well established.

Diphenhydramine hydrochloride (DPH) is indicated for use as an OTC antihistamine and a nighttime sleep aid. As a nonprescription nighttime sleep aid, DPH at a dose of 50 mg has been demonstrated with sufficient clinical evidence to be generally safe and effective under the FDA's Nighttime Sleep-Aid Drug Products for Over-The-Counter Human Use. Diphenhydramine hydrochloride and citrate salts have been used as one of the main ingredients in several marketed OTC analgesic/nighttime sleep aid combination products, such as Tylenol® PM, Bayer® PM, Excedrin® PM, Motrin® PM, and Advil® PM.

Currently, there is no OTC nighttime analgesic/sleep-aid combination product available in the United States (US) that combines the analgesic naproxen sodium with the sleep-aid DPH for the relief of occasional sleeplessness associated with minor aches and pains.

This submission includes two pivotal efficacy studies, Study 14837 and Study 15881. Both studies were similar in design and were conducted in subjects with postoperative pain and phase-advanced sleep allowing investigation of the efficacy of the combination product under the intended condition of occasional sleeplessness associated with pain. The efficacy parameters were WASO by actigraphy for the comparison of naproxen sodium/DPH versus naproxen sodium taken alone and sleep latency by actigraphy for the comparison of naproxen sodium/DPH versus DPH taken alone.

2.2 Data Sources

The sponsor's electronic submission was stored in the directory of \\Cdsesub1\evsprod\NDA205352 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality are generally acceptable. The analyses conducted by this reviewer were produced from raw data.

3.2 Evaluation of Efficacy

3.2.1 STUDY 14837

3.2.1.1 Study Objectives

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

3.2.1.2 Study Design

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 the three 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.

3.2.1.3 Efficacy Measures

The primary efficacy variables, which were derived from actigraphy data, were the following:

- WASO (naproxen sodium/DPH versus naproxen sodium alone)
- Sleep latency (naproxen sodium/DPH versus DPH alone)

Secondary efficacy variables included sleep and pain variables.

Objective secondary sleep variables, which were derived from actigraphy data, included the following:

- 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

Secondary pain variables included the following:

- Change from baseline in pain intensity score (4-point Categorical Pain Rating Scale)
- Pain relief (categorical Pain Relief Rating Scale)
- Time to rescue medication (if taken for pain), and the cumulative proportion of subjects taking rescue medication by hour
- Global Assessment of Investigational Product as a Pain Reliever

3.2.1.4 Statistical Analysis Plan

The ITT Population consisted of all subjects who were randomized and provided at least one observation of an efficacy parameter after the first dose of investigational product. The ITT Population was used for efficacy analyses.

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. 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.

Wake after sleep onset was defined as the total wake time (in minutes) after sleep onset during the in-bed time by actigraphy. 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. The primary treatment comparison of interest for WASO was naproxen sodium/DPH combinations versus naproxen sodium alone. Sensitivity analyses were performed to corroborate the primary analysis on the ITT population for WASO and to assess the robustness of the efficacy results. 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 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. Sensitivity analyses were performed to corroborate the primary analysis on the ITT Population for sleep latency and to provide a complete efficacy profile while preserving the efficacy with respect to the proportion of subjects who took rescue medication. 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.

Total sleep time and sleep efficiency were analyzed using the methodologies used for the primary analysis of WASO. 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.

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.

Pain severity data were analyzed using an ANCOVA model including treatment and center as fixed effects and baseline categorical pain rating score as the covariate. If a subject took rescue

medication, the worst score before rescue medication (including baseline) was carried forward to the morning score.

Pain relief data were analyzed using the CMH method with a modified ridit score. If a subject took rescue medication, a score of zero (no relief) was used for the morning rating of pain relief.

Global Assessment of Investigational Product as a Pain Reliever data was analyzed using the CMH method controlling for center with a modified ridit score.

Time to rescue medication was estimated using the Kaplan-Meier method and logrank test for pairwise comparisons. Subjects who did not take rescue medication were censored at 10 hours (600 minutes) for time to rescue medication. The cumulative proportion of subjects taking rescue medication was calculated as the number of subjects who had taken rescue medication at a given time divided by the number subjects treated.

3.2.1.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Subject disposition is summarized in Table 1. A total of 712 subjects were randomized, all of whom were included in both the Safety and ITT Populations. There were 203, 204, and 203 subjects in the naproxen sodium 440 mg/DPH 50 mg, naproxen sodium 220 mg/DPH 50 mg, and naproxen sodium 440 mg groups, respectively, and 102 subjects in the DPH 50 mg group. The vast majority of subjects (99.6% overall) completed the study according to the protocol, including all subjects (100%) in each of the naproxen sodium 440 mg/DPH 50 mg, naproxen sodium 220 mg/DPH 50 mg, and naproxen sodium 440 mg groups. The 3 subjects who did not complete the study according to the protocol were in the DPH 50 mg group. The reason for not completing the study was request of the subject (or legally acceptable representative) for 2 subjects and not meeting inclusion criteria for 1 subject.

Table 1: Subject Disposition (All 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		Total N = 712	
Numbers of subjects	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Randomized	203	(100)	204	(100)	203	(100)	102	(100)	712	(100)
Treated (Safety Population)	203	(100)	204	(100)	203	(100)	102	(100)	712	(100)
ITT Population	203	(100)	204	(100)	203	(100)	102	(100)	712	(100)
Completed study according to protocol	203	(100)	204	(100)	203	(100)	99	(97.1)	709	(99.6)
Did not complete the study according to protocol	0		0		0		3 [a]	(2.9)	3	(0.4)

DPH = diphenhydramine hydrochloride; ITT = Intent-to-Treat; NP = naproxen sodium

[a] Subjects 14002-1032, 14002-1192, and 14001-1480

Source: Table 14.1.1

Listing Reference: Listing 16.2.2.1

Source: Table 2 of sponsor's Clinical Study Report

Demographics

Demographic characteristics generally were comparable among treatment groups.

- Mean age overall was 21.2 years; age ranged from 16 to 48 years.
- Overall, 309 subjects (43.4%) were male and 403 subjects (56.6%) were female.
- Race for most subjects (89.0%) was white. Most subjects (78.5%) were not Hispanic or Latino.

Demographic data are summarized in Table 2 (age) and Table 3 (gender, ethnicity, and race).

Table 2: Demographics: Age (Safety and ITT Population)

	Treatment Group				
Age (Years)	**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**	**Total N = 712**
Mean	21.4	21.0	21.0	21.5	21.2
Standard deviation	4.87	4.25	4.50	5.59	4.70
Median	20.0	20.0	20.0	20.0	20.0
Minimum	16	16	16	16	16
Maximum	48	40	38	42	48

DPH = diphenhydramine hydrochloride; NP = naproxen sodium
Source: Table 14.1.2 and Table 14.1.3
Listing Reference: Listing 16.2.4.1

Source: Table 5 of sponsor's Clinical Study Report

Table 3: Demographics: Gender, Ethnicity and Race (Safety and ITT Population)

		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		Total N = 712	
Demo-graphic	Category	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender	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	Hispanic or Latino	40	(19.7)	39	(19.1)	49	(24.1)	25	(24.5)	153	(21.5)
	Not Hispanic or Latino	163	(80.3)	165	(80.9)	154	(75.9)	77	(75.5)	559	(78.5)
Race	White	184	(90.6)	174	(85.3)	185	(91.1)	91	(89.2)	634	(89.0)
	Black or African American	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)
	Native Hawaiian/ Other Pacific Islander	0		2	(1.0)	1	(0.5)	1	(1.0)	4	(0.6)
	American Indian/Alaska Native	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)

DPH = diphenhydramine hydrochloride; NP = naproxen sodium
Source: Table 14.1.2 and Table 14.1.3
Listing Reference: Listing 16.2.4.1

Source: Table 6 of sponsor's Clinical Study Report

Baseline Characteristics

Categorical Pain Rating Scale score was moderate for 494 subjects (69.4%) and was severe for 218 subjects (30.6%). Pain Severity VAS score mean score was 72.4 mm (standard deviation 12.31 mm), and was comparable among treatment groups. Baseline pain is summarized in Table 4 for categorical pain intensity and in Table 5 for pain severity VAS score.

Table 4: Baseline Categorical Pain Rating Scale (Safety Population)

	Treatment Group									
Baseline Categorical Pain Severity [a]	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		Total N = 712	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
No pain	0		0		0		0		0	
Mild pain	0		0		0		0		0	
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)

DPH = diphenhydramine hydrochloride; NP = naproxen sodium
[a] 0 = No Pain, 1 = Mild Pain, 2 = Moderate Pain and 3 = Severe Pain.
Source: Table 14.1.2 and Table 14.1.3
Listing Reference: Listing 16.2.4.1

Source: Table 7 of sponsor's Clinical Study Report

Table 5: Baseline Pain Severity Visual Analog Scale Score (Safety Population)

	Treatment Group				
Pain Severity VAS Score (mm) [a]	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	Total N = 712
Mean	71.8	73.0	72.6	72.3	72.4
Standard deviation	12.16	12.95	11.75	12.51	12.31
Median	70.0	71.5	72.0	69.0	71.0
Minimum	51	50	51	51	50
Maximum	100	100	100	99	100

DPH = diphenhydramine hydrochloride; NP = naproxen sodium; VAS = visual analog scale

[a] The pain severity score was measured on a 100-mm VAS.

Source: Table 14.1.2 and Table 14.1.3

Listing Reference: Listing 16.2.4.1

Source: Table 8 of sponsor's Clinical Study Report

3.2.1.6 Sponsor's Primary Efficacy Results

Wake After Sleep Onset (WASO) by Actigraphy

The naproxen sodium 440 mg/DPH 50 mg group had the shortest WASO time (LS mean 143.7 minutes) compared with the naproxen sodium 220 mg/DPH 50 mg group (LS mean 230.9 minutes) and the naproxen sodium 440 mg group (LS mean 214.0 minutes). The DPH 50 mg group had the longest WASO time (LS mean 431.4 minutes). The results were presented in Table 6 and Table 7. The difference between the naproxen sodium 440 mg/DPH 50 mg and the naproxen sodium 440 mg groups was statistically significant (P = 0.0002); however, the difference between the naproxen sodium 220 mg/DPH 50 mg group and the naproxen sodium 440 mg group was not (P = 0.36). Results of sensitivity analyses are consistent with the results from the primary efficacy analysis.

Table 6: Analysis of Wake After Sleep Onset: Summary (ITT Population)

	Treatment Group			
Statistic (minutes)	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	201	204	202	102
Mean	142.2	233.6	214.3	429.5
Standard deviation	164.50	208.54	188.47	194.48
Median	69.5	119.8	124.3	515.8
Minimum	17	8	22	18
Maximum	600	600	600	600
Model				
n*	201	204	202	102
LS-Mean	143.7	230.9	214.0	431.4
(Standard error)	(13.17)	(13.08)	(13.13)	(18.49)
95% CI of LS-Mean	117.9, 169.6	205.2, 256.5	188.2, 239.8	395.1, 467.6

CI = confidence interval; DPH = diphenhydramine hydrochloride; LS = least square; NP = naproxen sodium.

n* = Number of subjects included in the model.

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.

All measurements are in minutes.

Source: Table 14.2.1a

Listing Reference: Listing 16.2.6.1

Source: Table 9 of sponsor's Clinical Study Report

Table 7: Analysis of Wake After Sleep Onset: Treatment Difference (ITT Population)

	Treatment Group		
Statistic	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	P-value [a]
LS-Mean Treatment Difference	-70.3 [b] -87.1 [d] -287.6 [e]	 16.9 [c] -200.5 [f]	
95% CI of LS-Mean Treatment Difference	-106.8, -33.7 [b] -123.6, -50.7 [d] -332.2, -243.1 [e]	 -19.5, 53.3 [c] -245.0, -156.0 [f]	
P-value	0.0002 [b] < 0.0001 [d] < 0.0001 [e]	 0.3627 [c] < 0.0001 [f]	
Treatment Effect			< 0.0001

[a] P-value from ANCOVA model including treatment and center as fixed effects and baseline categorical pain score as the covariate.
[b] Pairwise comparison NP 440 mg/DPH 50 mg versus NP 440 mg
[c] Pairwise comparison NP 220 mg/DPH 50 mg versus NP 440 mg
[d] Pairwise comparison NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg
[e] Pairwise comparison NP 440 mg/DPH 50 mg versus DPH 50 mg
[f] Pairwise comparison NP 220 mg/DPH 50 mg versus DPH 50 mg
ANCOVA analysis of covariance; CI = confidence interval; DPH = diphenhydramine hydrochloride; LS = least square; NP = naproxen sodium.
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.
Measurements are in minutes.
Source: Table 14.2.1a
Listing Reference: Listing 16.2.6.1

Source: Table 10 of sponsor's Clinical Study Report

Reviewer's Comments:

According to the sequential testing procedure pre-specified by the sponsor (first, Naproxen sodium 440 mg/DPH 50 mg combination versus Naproxen sodium 440 mg; second, Naproxen sodium 220 mg/DHP 50 mg combination versus Naproxen sodium 440 mg; third, Naproxen sodium 440 mg/DPH 50 mg combination versus Naproxen sodium 220 mg/DPH 50 mg combination), since the difference between the naproxen sodium 220 mg/DPH 50 mg group and the naproxen sodium 440 mg group was not statistically significant (P = 0.36), the subsequent comparison (the comparison of Naproxen sodium 440 mg/DPH 50 mg combination versus Naproxen sodium 220 mg/DPH 50 mg combination) is ineligible to be declared significant. For additional comments regarding multiplicity, please refer to Section 3.2.3.2.

Sleep Latency by Actigraphy

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). Differences between both the naproxen sodium 440 mg/DPH 50 mg and naproxen sodium 220 mg/DPH 50 mg groups compared with the DPH 50 mg group were statistically significant (P < 0.0001 and P = 0.0003, respectively). The difference between the naproxen sodium 440 mg/DPH 50 mg group and the naproxen sodium 220 mg/DPH 50 mg group also was statistically significant (P = 0.0096). The results were summarized in Table 8 and Table 9. Results of sensitivity analyses are generally consistent with the results from the primary efficacy analysis. Time to sleep onset is presented graphically for ITT population in Figure 1.

Table 8: Kaplan-Meier Analysis of Sleep Latency: Summary (ITT Population)

	Treatment Group			
Statistic	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
Number of subjects in analysis	201	204	202	102
Number of subjects censored	5	17	13	28
Median time (minutes)	25.50	30.25	25.75	41.50
95% confidence interval (minutes)	(22.50, 30.00)	(25.00, 33.50)	(22.50, 29.50)	(26.50, 54.50)

DPH = diphenhydramine hydrochloride; NP = naproxen sodium.
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.
Measurements are in minutes.
Source: Table 14.2.2a
Listing Reference: Listing 16.2.6.1

Source: Table 11 of sponsor's Clinical Study Report

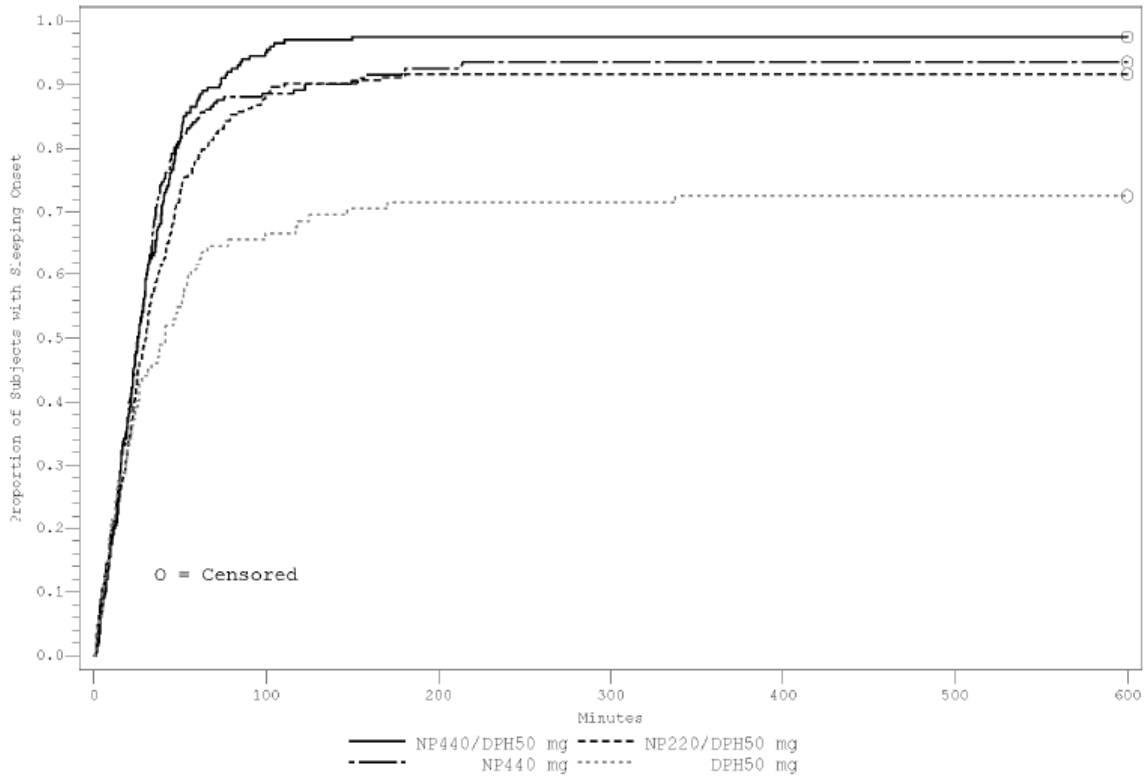
Table 9: Kaplan-Meier Analysis of Sleep Latency: P-values (ITT Population)

Comparison	P-value [a]
NP 440 mg/DPH 50 mg versus DPH 50 mg	< 0.0001
NP 220 mg/DPH 50 mg versus DPH 50 mg	0.0003
NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg	0.0096
NP 220 mg/DPH 50 mg versus NP 440 mg	0.1150
NP 440 mg/DPH 50 mg versus NP 440 mg	0.4164

[a] P-value from log rank test.
DPH = diphenhydramine hydrochloride; NP = naproxen sodium.
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.
All measurements are in minutes.
Source: Table 14.2.2a
Listing Reference: Listing 16.2.6.1

Source: Table 12 of sponsor's Clinical Study Report

Figure 1: Time to Sleep Onset (ITT Population)



Source: Figure 2 of sponsor's Clinical Study Report

Reviewer's Comments:

In sponsor's analysis for sleep latency, each p-value for a pairwise comparison is based on an individual log-rank test. However, since there are four treatment groups in this study, in order to comply with the study design, this reviewer thinks the p-values should be based on the pairwise comparisons under one integrated model. The p-values produced by this updated analysis are similar to those from sponsor's analysis, and the interpretation of the study results remains same. Please refer to Section 3.2.3.1 for more details.

3.2.1.7 Sponsor's Secondary Efficacy Results

Cumulative Proportion of Subjects Taking Rescue Medication

The cumulative proportion of subjects taking rescue medication after administration of investigational product is summarized in Table 10. During the first 60 minutes after dosing, only 1 (0.5%) subject requested rescue medication; this subject was in the naproxen sodium 220 mg/DPH 50 mg group. At all post-dose time points after the first 60 minutes, the naproxen sodium 440 mg/DPH 50 mg group had the lowest proportion of subjects taking rescue medication, ranging from 8.9% at ≤ 120 minutes after dose administration to 21.2% at ≤ 600 minutes after dose administration. The naproxen sodium 440 mg group followed, ranging from 13.3% at ≤ 120 minutes to 33.5% at ≤ 600 minutes after dose administration. In the naproxen sodium 220 mg/DPH 50 mg group, the proportions ranged from 17.6% at ≤ 120 minutes to

43.6% at ≤ 600 minutes after dose administration. At all post-dose time points after the first 60 minutes, the DPH 50 mg group had the highest proportion of subjects taking rescue medication, ranging from 52.0% at ≤ 120 minutes to 76.5% at ≤ 600 minutes after dose administration.

Table 10: Cumulative Proportion of Subjects Taking Rescue Medications (Safety Population)

Time After Dosing That Rescue Medication Was Taken	Treatment Group: NP 440 mg/ DPH 50 mg N = 203 n	(%)	NP 220 mg/ DPH 50 mg N = 204 n	(%)	NP 440 mg N = 203 n	(%)	DPH 50 mg N = 102 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)

The proportion of subjects taking rescue medication was calculated as the cumulative number of subjects who took rescue medication by a given hour divided by the number of subjects treated.

DPH = diphenhydramine hydrochloride; NP = naproxen sodium.

Source: Table 14.2.11

Listing Reference: Listing 16.2.4.9

Source: Table 13 of sponsor's Clinical Study Report

Total Sleep Time by Actigraphy

Table 11 summarizes total sleep time for the ITT Population. Among the 4 treatment groups, the naproxen sodium 440 mg/DPH 50 mg group had the longest total sleep time (LS mean of 426.2 minutes; approximately 7 hours). The naproxen sodium 220 mg/DPH 50 mg group and the naproxen sodium 440 mg group had similar total sleep time (LS means of 337.7 minutes and 355.8 minutes, respectively; approximately 5.5 to 6 hours). The DPH 50 mg group had the shortest total sleep time (LS mean of 141.4 minutes; approximately 2.5 hours).

Table 11: Analysis of Total Sleep Time (ITT Population)

	Treatment Group			
Statistic	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
n	201	204	202	102
Mean (minutes)	427.7	335.1	355.6	143.2
Standard deviation	165.01	202.10	186.36	178.27
Median	497.0	437.8	440.5	59.5
Minimum	0	0	0	0
Maximum	573	583	566	575

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.
All measurements are in minutes.
Source: Table 14.2.3
Listing Reference: Listing 16.2.6.1

Source: Excerpt from Table 14 of sponsor's Clinical Study Report

Sleep Efficiency by Actigraphy

For sleep efficiency, the naproxen sodium 440 mg/DPH 50 mg group had the best sleep efficiency (LS mean of 71.0%). The naproxen sodium 220 mg/DPH 50 mg group and the naproxen sodium 440 mg group had similar sleep efficiency (LS means of 56.3% and 59.3%, respectively). The DPH 50 mg group had the poorest sleep efficiency (LS mean of 23.6%). The results are presented in Table 12.

Table 12: Analysis of Sleep Efficiency (ITT Population)

	Treatment Group			
Statistic	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
n	201	204	202	102
Mean (minutes)	427.7	335.1	355.6	143.2
Standard deviation	165.01	202.10	186.36	178.27
Median	497.0	437.8	440.5	59.5
Minimum	0	0	0	0
Maximum	573	583	566	575

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.
All measurements are in minutes.
Source: Table 14.2.3
Listing Reference: Listing 16.2.6.1
Source: Table 15 of sponsor's Clinical Study Report

Global Assessment of Investigational Product as a Sleep Aid

In the analysis of the Global Assessment of Investigational Product as a Sleep Aid, the overall median response for the naproxen sodium 440 mg/DPH 50 mg group, the naproxen sodium 220 mg/DPH 50 mg group, and the DPH 50 mg group was 2.0, corresponding to a rating of "good" on the 0 to 4 scale (where 0 = poor and 4 = excellent). The naproxen sodium 440 mg group scored lowest on the scale (median of 1.0). These results were also supported by mean values that correlated to the median values, with mean responses of 2.1, 2.0, 1.7, and 1.4 for the naproxen sodium 440 mg/DPH 50 mg group, the naproxen sodium 220 mg/DPH 50 mg group, the DPH 50 mg group, and the naproxen sodium 440 mg group, respectively. Results are summarized in Table 13.

Table 13: Analysis of Global Assessment of Investigational Product as Sleep Aid (ITT Population)

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

DPH = diphenhydramine hydrochloride; NP = naproxen sodium.
Source: Table 14.2.5
Listing Reference: Listing 16.2.6.2
Source: Table 16 of sponsor's Clinical Study Report

Pain Intensity and Change from Baseline

Pain intensity was collected on a 4-point Categorical Pain Rating Scale, where 0 = no pain and 3 = severe pain. The naproxen sodium 440 mg/DPH 50 mg, naproxen sodium 220 mg/DPH 50 mg, and naproxen sodium 440 mg groups all reported reductions in pain intensity from baseline (median reduction of 1.0 point for each group). The DPH 50 mg group had no reduction in pain intensity from baseline. Mean change from baseline values correlated to the median values, with mean reductions of 1.2 points, 0.7 points, and 0.9 points in the naproxen sodium 440 mg/DPH 50 mg group, the naproxen sodium 220 mg/DPH 50 mg group, and the naproxen sodium 440 mg group, respectively and a mean increase of 0.1 points in the DPH 50 mg group. Table 14 summarized the results.

Table 14: Summary of Pain Intensity and Change from Baseline (ITT Population)

		Treatment Group			
Visit	Statistic	NP 440 mg/ DPH 50 mg N = 203	NP 220 mg/ DPH 50 mg N = 204	NP 440 mg N = 203	DPH 50 mg N = 102
Day 1 (Baseline)	Mean	2.3	2.3	2.3	2.3
	Standard deviation	0.45	0.48	0.46	0.45
	Median	2.0	2.0	2.0	2.0
	Minimum	2	2	2	2
	Maximum	3	3	3	3
Post-baseline	Mean	1.1	1.6	1.4	2.4
	Standard deviation	0.96	1.05	1.02	0.85
	Median	1.0	1.0	1.0	3.0
	Minimum	0	0	0	0
	Maximum	3	3	3	3
Change from Baseline	Mean	-1.2	-0.7	-0.9	0.1
	Standard deviation	1.01	1.05	0.99	0.82
	Median	-1.0	-1.0	-1.0	0.0
	Minimum	-3	-3	-3	-2
	Maximum	1	1	1	1

0 = No Pain, 1 = Mild Pain, 2 = Moderate Pain, and 3 = Severe Pain.
Negative changes from baseline imply a reduction in pain intensity from baseline.
If rescue medication was taken, the worst score prior to rescue including baseline was carried forward to the morning score and used for analysis.
DPH = diphenhydramine hydrochloride; NP = naproxen sodium.
Source: Table 14.2.8.1
Listing Reference: Listing 16.2.4.13

Source: Table 18 of sponsor's Clinical Study Report

3.2.2 STUDY 15881

3.2.2.1 Study Objectives

The objective of the study was to evaluate the efficacy and safety of a single oral dose of NP 440 mg in combination with DPH 25 mg in subjects with postsurgical dental pain and phase-advanced sleep.

3.2.2.2 Study Design

This was a multicenter, randomized, double-blind, parallel group, 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 hours and 1530 hours), subjects who experienced postsurgical pain of at least moderate severity (between 1600 hours and 1830 hours) were randomized to 1 of 3 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 300 subjects would be screened with the aim of having 250 subjects complete, 100 subjects in each of 2 NP treatment groups (NP/DPH combination group and NP alone group) and 50 subjects in the DPH alone treatment group. The duration of each subject's participation in the study from Screening Visit 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.

3.2.2.3 Efficacy Measures

The primary efficacy variables, which were derived from actigraphy data, were the following:

- WASO (naproxen sodium/DPH versus naproxen sodium alone)
- Sleep latency (naproxen sodium/DPH versus DPH alone)

Secondary efficacy variables included sleep and pain variables.

Objective secondary sleep variables, which were derived from actigraphy data, included the following:

- 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

Secondary pain variables included the following:

- Change from baseline in pain intensity score (4-point Categorical Pain Rating Scale)
- Pain relief (categorical Pain Relief Rating Scale)
- Time to rescue medication (if taken for pain), and the cumulative proportion of subjects taking rescue medication by hour
- Global Assessment of Investigational Product as a Pain Reliever

3.2.2.4 Statistical Analysis Plan

The ITT Population consisted of all subjects who were randomized and provided at least 1 postdose observation of an efficacy parameter. The ITT Population was used for efficacy analyses.

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.

The statistical analysis methods for the primary and secondary endpoints are the same as the methods for Study 14837. Please refer to Section 3.2.1.4 for details.

3.2.2.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 267 subjects were randomized, all of whom were included in both the Safety Population and ITT Populations. There were 107, 106, and 54 subjects in the NP 440 mg/DPH 25 mg, NP 440 mg, and DPH 50 mg groups, respectively. All subjects completed the study according to the protocol. Subject disposition is summarized in Table 15.

Table 15: Subject Disposition (All Randomized Subjects)

	Treatment Group							
	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54		Total N = 267	
Number of subjects	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Randomized	107	(100)	106	(100)	54	(100)	267	(100)
Treated (Safety Population)	107	(100)	106	(100)	54	(100)	267	(100)
ITT Population	107	(100)	106	(100)	54	(100)	267	(100)
Completed study according to protocol	107	(100)	106	(100)	54	(100)	267	(100)
Did not complete the study according to protocol	0		0		0		0	

DPH = diphenhydramine hydrochloride; ITT = Intent-to-Treat; N = number of subjects randomized; NP = naproxen sodium.
Source: Table 14.1.1
Listing Reference: Listing 16.2.1

Source: Table 2 of sponsor's Clinical Study Report

Demographics

Demographic characteristics generally were comparable among treatment groups.

- Mean age overall was 21.2 years; age ranged from 12 to 49 years.
- Overall, 94 subjects (35.2%) were male and 173 subjects (64.8%) were female.
- Race for most subjects (87.6%) was white. Most subjects (79.4%) were not Hispanic or Latino.

Demographic data are summarized in Table 16 (age) and Table 17 (gender, ethnicity, and race).

Table 16: Demographics: Age (Safety and ITT Population)

	Treatment Group			
	NP 440 mg/DPH 25 mg N = 107	NP 440 mg N = 106	DPH 50 mg N = 54	Total N = 267
Age (Years)				
Mean	21.4	21.3	20.8	21.2
Standard deviation	5.55	5.27	4.64	5.25
Median	20.0	20.0	20.0	20.0
Minimum	13	12	12	12
Maximum	38	49	35	49

DPH = diphenhydramine hydrochloride; N = number of subjects randomized; NP = naproxen sodium.
Source: Table 14.1.2 and Table 14.1.3
Listing Reference: Listing 16.2.4.1

Source: Table 4 of sponsor's Clinical Study Report

Table 17: Demographics: Gender, Ethnicity and Race (Safety and ITT Population)

		Treatment Group							
		NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54		Total N = 267	
Demographic	**Category**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Gender	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	Hispanic or Latino	24	(22.4)	20	(18.9)	11	(20.4)	55	(20.6)
	Not Hispanic or Latino	83	(77.6)	86	(81.1)	43	(79.6)	212	(79.4)
Race	White	93	(86.9)	93	(87.7)	48	(88.9)	234	(87.6)
	Black or African American	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)
	American Indian/Alaska Native	0		0		0		0	
	Native Hawaiian/ Other Pacific Islander	0		0		1	(1.9)	1	(0.4)
	Other	1	(0.9)	0		1	(1.9)	2	(0.7)
	Multiple	1	(0.9)	2	(1.9)	0		3	(1.1)

DPH = diphenhydramine hydrochloride; N = number of subjects in the Safety and Intent-to-Treat Populations; NP = naproxen sodium.
Source: Table 14.1.2 and Table 14.1.3
Listing Reference: Listing 16.2.4.1

Source: Table 5 of sponsor's Clinical Study Report

Baseline Characteristics

Categorical Pain Rating Scale score was moderate for 160 subjects (59.9%) and was severe for 107 subjects (40.1%). Pain Severity VAS score mean score was 75.6 mm (standard deviation 10.26 mm) and was comparable among treatment groups. Baseline pain is summarized in Table 18 for categorical pain intensity and in Table 19 for Pain Severity VAS score.

Table 18: Baseline Categorical Pain Rating Scale (Safety and ITT Population)

	Treatment Group							
Baseline Categorical Pain Severity [a]	NP 440 mg/ DPH 25 mg N = 107		NP 440 mg N = 106		DPH 50 mg N = 54		Total N = 267	
	n	(%)	n	(%)	n	(%)	n	(%)
No pain	0	0	0	0	0	0	0	0
Mild pain	0	0	0	0	0	0	0	0
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)

DPH = diphenhydramine hydrochloride; N= number of subjects in the Safety and Intent-to-Treat Populations; NP = naproxen sodium.
Source: Table 14.1.2 and Table 14.1.3
Listing Reference: Listing 16.2.4.1

Source: Table 6 of sponsor's Clinical Study Report

Table 19: Baseline Pain Severity Visual Analog Scale Score (Safety and ITT Population)

	Treatment Group			
Pain Severity VAS Score (mm) [a]	NP 440 mg/ DPH 25 mg N = 107	NP 440 mg N = 106	DPH 50 mg N = 54	Total N = 267
Mean	75.2	75.2	77.1	75.6
Standard deviation	10.01	11.01	9.22	10.26
Median	75.0	76.0	80.0	76.0
Minimum	51	50	55	50
Maximum	98	100	97	100

DPH = diphenhydramine hydrochloride; N = number of subjects in the Safety and Intent-to-Treat Populations; NP = naproxen sodium; VAS = visual analog scale.
Source: Table 14.1.2 and Table 14.1.3
Listing Reference: Listing 16.2.4.1

Source: Table 7 of sponsor's Clinical Study Report

3.2.2.6 Sponsor's Primary Efficacy Results

Wake After Sleep Onset

The NP 440 mg/DPH 25 mg, NP 440 mg, and DPH 50 mg groups had WASO times (LS mean) of 155.25 minutes, 180.08 minutes, and 364.83 minutes, respectively (Table 20). Although the P-value for overall treatment effect was statistically significant ($P < 0.0001$), the difference between the NP 440 mg/DPH 25 mg group and the NP 440 mg group was not statistically significant ($P = 0.30$, Table 21).

Table 20: Analysis of Wake After Sleep Onset: Summary (ITT Population)

	Treatment Group		
Statistic (minutes)	NP 440 mg/ DPH 25 mg N = 107	NP 440 mg N = 106	DPH 50 mg N = 54
Mean	152.13	180.12	369.54
Standard deviation	165.436	173.623	207.644
Median	72.50	96.50	490.50
Minimum	18.0	11.0	20.0
Maximum	600.0	600.0	600.0
Model			
LS-Mean	155.25	180.08	364.83
(Standard error)	(17.104)	(17.126)	(24.029)
95% CI of LS-Mean	121.57, 188.93	146.36, 213.80	317.52, 412.15

CI = confidence interval; DPH = diphenhydramine hydrochloride; LS = least square; N = number of subjects in the Intent-to-Treat Population; NP = naproxen sodium.
All measurements are in minutes.
Source: Table 14.2.1a
Listing Reference: Listing 16.2.6.1

Source: Table 8 of sponsor's Clinical Study Report

Table 21: Analysis of Wake After Sleep Onset: Treatment Differences (ITT Population)

	Treatment Group	
Statistic	NP 440 mg/ DPH 25 mg N = 107	P-value[a]
LS-Mean Treatment Difference	-24.83[b]	
95% CI of LS-Mean Treatment Difference	-72.38, 22.72[b]	
P-value	0.3047[b]	
Treatment Effect		<0.0001

[a] P-value from ANCOVA model including treatment and center as fixed effects and baseline categorical pain score as the covariate.
[b] Pairwise comparison of NP 440 mg/DPH 25 mg versus NP 440 mg.
ANCOVA = analysis of covariance; CI = confidence interval; DPH = diphenhydramine hydrochloride; LS = least square; N = number of subjects in the Intent-to-Treat Population; NP = naproxen sodium.
Measurements are in minutes.
Source: Table 14.2.1a
Listing Reference: Listing 16.2.6.1

Source: Table 9 of sponsor's Clinical Study Report

Sleep Latency by Actigraphy

The NP 440 mg/DPH 25 mg, NP 440 mg, and DPH 50 mg groups had median sleep onset times of 23.50 minutes, 16.75 minutes, and 27.50 minutes, respectively (Table 22). The difference between the NP 440 mg/DPH 25 mg group and the DPH 50 mg group was not statistically significant (P = 0.17, Table 23).

Table 22: Kaplan-Meier Analysis of Sleep Latency: Summary (ITT Population)

	Treatment Group		
Statistics	NP 440 mg/ DPH 25 mg N = 107	NP 440 mg N = 106	DPH 50 mg N = 54
Number of subjects censored	4	2	5
Median time (minutes)	23.50	16.75	27.50
95% confidence interval (minutes)	(18.00, 28.00)	(13.50, 25.00)	(16.00, 36.50)

DPH = diphenhydramine hydrochloride; N = number of subjects in the Intent-to-Treat Population; NP = naproxen sodium.
All measurements are in minutes.
Source: Table 14.2.2a
Listing Reference: Listing 16.2.6.1

Source: Table 11 of sponsor's Clinical Study Report

Table 23: Kaplan-Meier Analysis of Sleep Latency: P-values (ITT Population)

Comparison	P-value[a]
NP 440 mg/DPH 25 mg versus DPH 50 mg	0.1677

[a] P-value from logrank test.
DPH = diphenhydramine hydrochloride; NP = naproxen sodium.
All measurements are in minutes.
Source: Table 14.2.2a
Listing Reference: Listing 16.2.6.1

Source: Table 12 of sponsor's Clinical Study Report

3.2.2.7 Sponsor's Secondary Efficacy Results

Since both primary endpoints failed to show efficacy, the results of the secondary efficacy analysis aren't presented in this review.

3.2.3 REVIEWER'S ANALYSIS

This reviewer verified sponsor's efficacy analyses presented in this review. The analyses shown in this session were conducted by this reviewer for Study 14837. No additional analysis was performed for Study 15881 since both co-primary endpoints failed to show efficacy.

3.2.3.1 Log Rank Test for Sleep Latency for Study 14837

There are four treatment groups in Study 14837. In sponsor's analysis for sleep latency, each of the five pairwise comparisons was based on an individual model. However, in order to comply with the study design, this reviewer thinks the pairwise comparisons should be conducted within one analysis model which takes all four treatment groups into consideration. Table 24 presents the results of sponsor's analysis and this reviewer's analysis. Even though there is slight difference in the p-values between sponsor's analysis and this reviewer's analysis, the interpretation of the study results remains same.

Table 24: Log Rank Test of Sleep Latency–Sponsor's and Reviewer's Analysis (ITT)

Comparison	Sponsor's P-value	Reviewer's P-value
NP 440 mg/DPH 50 mg versus DPH 50 mg	<0.0001	<0.0001
NP 220 mg/DPH 50 mg versus DPH 50 mg	0.0003	0.0099
NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg	0.0096	0.025
NP 220 mg/DPH 50 mg versus NP 440 mg	0.12	0.13
NP 440 mg/DPH 50 mg versus NP 440 mg	0.42	0.47

Source: Reviewer's Analysis

3.2.3.2 Multiplicity

In the Statistical Analysis Plan (SAP) for Study 15881, it clearly states that "*Both tests (for WASO and sleep latency) had to be statistically significant in order to claim NP 440 mg/DPH 25 mg to be efficacious.*" However, from the protocol and SAP for Study 14837, it is not clear if both WASO and sleep latency need to be statistically significant for an efficacy claim. Based on this reviewer's discussion with the Medical Reviewer, it seems that the Medical Division thinks both WASO and sleep latency need to be statistically significant in order for claiming a dose to be efficacious.

For Study 14837, the p-value for the comparison of NP 440 mg/DPH 50 mg versus NP 440 mg on WASO was 0.0002 and the p-value for the comparison of NP 440 mg/DPH 50 mg versus DPH 50 mg on sleep latency was <0.0001 according to the sponsor and 0.0099 according to this reviewer. Therefore, both WASO and sleep latency were statistically significant for NP 440 mg/DPH 50 mg. No other doses achieved statistical significance on both WASO and sleep latency.

This reviewer would like to point out that for Study 14837 the separate hierarchical testing procedure for WASO and sleep latency proposed by the sponsor in Section 3.2.1.4 doesn't control the studywise Type I error at 0.05 level (two-sided). For this study, it is sensible to test NP 440 mg/DPH 50 mg versus either single ingredient (naproxen sodium or DPH) alone first for both WASO and Sleep latency. For example, this hierarchical testing procedure could be illustrated as follows:

- Step 1: Test both NP 440 mg/DPH 50 mg versus NP 440 mg on WASO and NP 440 mg/DPH 50 mg versus DPH 50 mg on sleep latency at 0.05 level (two-sided). If either test isn't statistically significant, stop. If both tests are statistically significant, then go to Step 2.
- Step 2: Test both NP 220 mg/DPH 50 mg versus NP 440 mg on WASO and NP 220 mg/DPH 50 mg versus DPH 50 mg on sleep latency at 0.05 level (two-sided). If either test isn't significant, stop. If both tests are significant, then go to Step 3.
- Step 3: Test NP 440 mg/DPH 50 mg versus NP 220 mg/DPH 50 mg on both WASO and sleep latency at 0.05 level (two-sided).

Based on the results of Study 14837, the reviewer consider both WASO and sleep latency were statistically significant for NP 440 mg/DPH 50 mg.

3.2.3.3 Subgroup Analysis for Study 14837

This reviewer conducted subgroup analysis by sex, race, age group and site for WASO and sleep latency. It seems that the treatment effects of primary interest (NP440 mg/DPH 50 mg versus NP 440 mg for WASO; NP440 mg/DPH 50 mg versus DPH 50 mg for sleep latency) are all in the right direction for the subgroups investigated except that the point estimate of treatment effect isn't in the right direction for non-white patients for WASO. However, this doesn't raise concerns since there are only 11% (78/712) non-white patients in this study. Please refer to Section 4.1 for more details.

3.3 Evaluation of Safety

Please read Dr. Tandon's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region

4.1.1 STUDY 14837

4.1.1.1 Subgroup Analysis for Wake After Sleep Onset (WASO)

Table 25 presents the results of subgroup analysis by sex, race, age group (<=20 and >20) and site (14001 and 14002) for WASO. It seems that the point estimates of treatment effects of primary interest (NP440 mg/DPH 50 mg versus NP 440 mg) are all in the right direction for sex, age, and site. For race, the point estimate of treatment effect isn't in the right direction for non-white patients. However, this doesn't raise concerns since there are only 11% (78/712) non-white patients in this study.

Table 25: Subgroup Analysis by Sex, Race, Age and Site for WASO (ITT Population)

Subgroup	Treatment Group	N	Mean	Median	Std Dev	Std Error
F	DPH50	54	443.9	518.3	181.6	24.7
	NP220/DPH50	124	221.4	108.0	206.0	18.5
	NP440	117	222.2	132.5	191.1	17.7
	NP440/DPH50	108	150.2	64.0	172.7	16.6
M	DPH50	48	413.2	503.0	208.8	30.1
	NP220/DPH50	80	252.5	150.5	212.4	23.7
	NP440	85	203.3	115.0	185.3	20.1
	NP440/DPH50	93	132.9	76.0	154.8	16.1
Non-white	DPH50	11	388.3	525.0	215.1	64.8
	NP220/DPH50	30	209.5	110.5	200.7	36.6
	NP440	18	128.6	99.8	123.4	29.1
	NP440/DPH50	18	180.0	79.8	200.9	47.4
White	DPH50	91	434.5	515.0	192.5	20.2
	NP220/DPH50	174	237.7	125.3	210.1	15.9
	NP440	184	222.6	128.8	191.9	14.1
	NP440/DPH50	183	138.4	67.0	160.7	11.9
<=20	DPH50	56	470.7	535.8	167.3	22.4
	NP220/DPH50	112	245.0	140.8	210.1	19.9
	NP440	117	208.1	118.5	189.4	17.5
	NP440/DPH50	108	137.8	67.3	159.2	15.3
>20	DPH50	46	379.3	498.8	214.4	31.6
	NP220/DPH50	92	219.6	108.0	206.9	21.6
	NP440	85	222.7	131.5	188.0	20.4
	NP440/DPH50	93	147.2	70.5	171.1	17.7
14001	DPH50	50	359.1	470.8	213.6	30.2
	NP220/DPH50	100	206.4	108.0	192.9	19.3
	NP440	99	230.3	136.5	184.7	18.6
	NP440/DPH50	98	160.9	76.0	176.8	17.9
14002	DPH50	52	497.1	539.8	146.8	20.4
	NP220/DPH50	104	259.7	183.5	220.3	21.6
	NP440	103	198.9	107.0	191.7	18.9
	NP440/DPH50	103	124.3	64.5	150.6	14.8

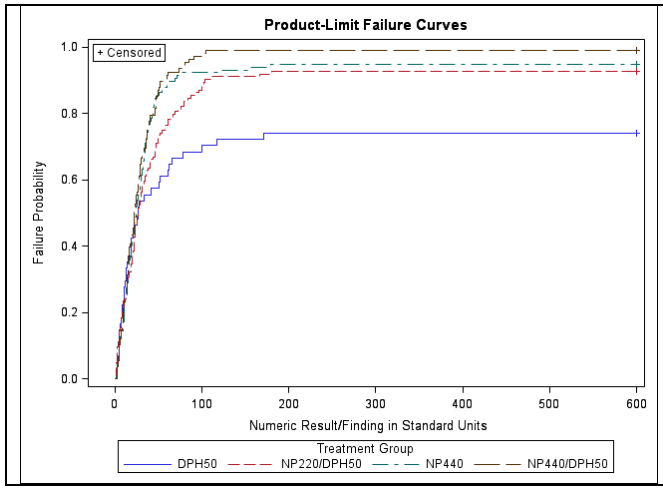
Source: Reviewer's Analysis

4.1.1.2 Subgroup Analysis for Sleep Latency

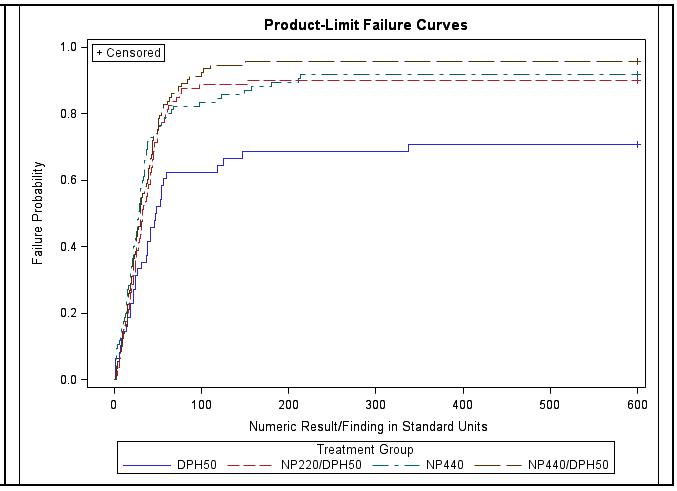
Figure 2, Figure 3, Figure 4, and Figure 5 present time to sleep onset by sex, race, age group (<=20 and >20) and site (14001 and 14002) for sleep latency. It appears that the treatment effects of primary interest (NP440 mg/DPH 50 mg versus DPH 50 mg) are all in the right direction for sex, race, age, and site.

Figure 2: Subgroup Analysis by Sex for Sleep Latency (ITT Population)

Females



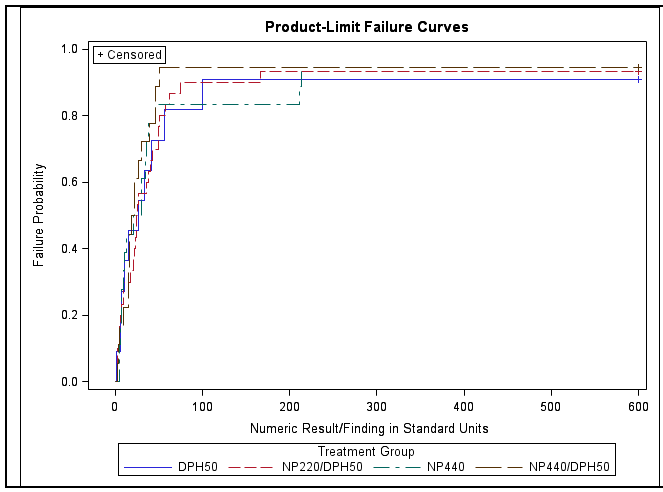
Males



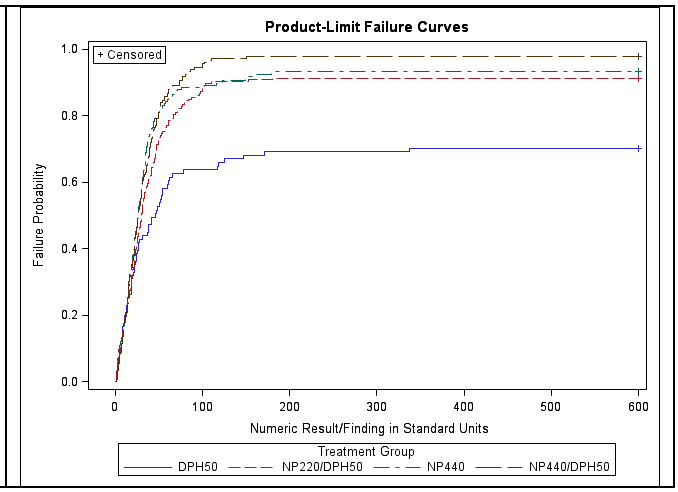
Source: Reviewer's Analysis

Figure 3: Subgroup Analysis by Race for Sleep Latency (ITT Population)

Non-white



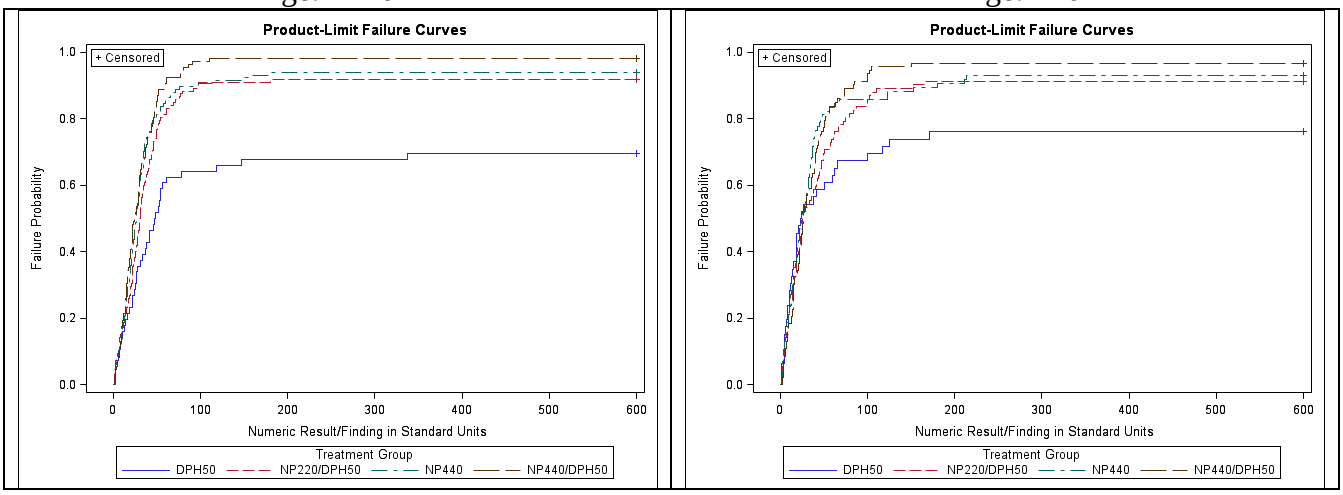
White



Source: Reviewer's Analysis

Figure 4: Subgroup Analysis by Age Group for Sleep Latency (ITT Population)

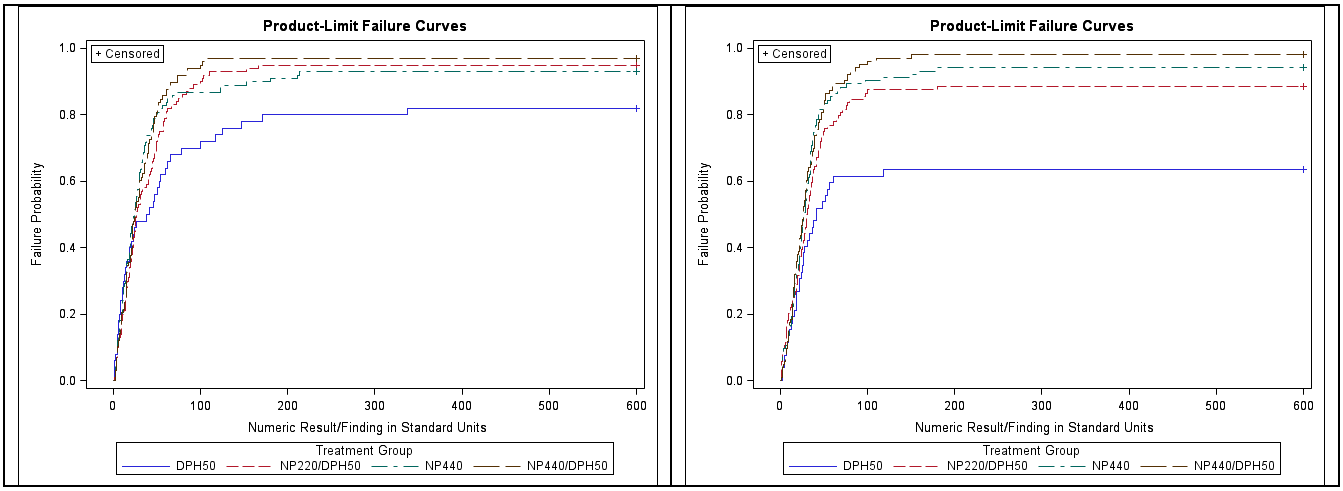
Age: <=20 | Age: >20



Source: Reviewer's Analysis

Figure 5: Subgroup Analysis by Site for Sleep Latency (ITT Population)

Site: 14001 | Site: 14002



Source: Reviewer's Analysis

4.1.2 STUDY 15881

Since for this study both primary endpoints failed to show efficacy, the results of subgroup analysis aren't presented in this review.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This NDA submission includes two pivotal efficacy studies, Study 14837 and Study 15881.

Study 14837 was a multicenter, randomized, double-blind, parallel group, pivotal efficacy study to evaluate the efficacy and safety of a single oral dose of 2 dose combinations of naproxen sodium and diphenhydramine hydrochloride (DPH) to demonstrate that the naproxen sodium/DPH combination provides added clinical benefit to sleep improvement than either single ingredient (naproxen sodium or DPH) alone in subjects with post-surgical dental pain and phase-advanced sleep. A total of 712 subjects were randomized. A vast majority of subjects (99.6% overall) completed the study. This study was conducted in two sites in US.

The study objective and design of Study 15881 were similar to those of Study 14837. A total of 267 subjects were randomized. All subjects completed the study. This study was conducted in two sites in US.

For Study 14837, the p-value for the comparison of NP 440 mg/DPH 50 mg versus NP 440 mg on WASO was 0.0002 and the p-value for the comparison of NP 440 mg/DPH 50 mg versus DPH 50 mg on sleep latency was <0.0001 according to the sponsor. Therefore, NP 440 mg/DPH 50 mg reached statistical significance for both WASO and sleep latency. No other doses achieved statistical significance on both WASO and sleep latency. For Study 15881, both WASO and sleep latency failed to demonstrate statistical significance for NP 440 mg/DPH 25 mg (p-value=0.30 for WASO and p-value=0.17 for sleep latency).

There are four treatment groups in Study 14837. In sponsor's analysis for sleep latency, each of the five pairwise comparisons was based on an individual model. However, in order to comply with the study design, this reviewer thinks the pairwise comparisons should be conducted within one analysis model which takes all four treatment groups into consideration. Table 24 presents the results of sponsor's analysis and this reviewer's analysis. Even though there is slight difference in the p-values between sponsor's analysis and this reviewer's analysis, the interpretation of the study results remains same.

In the Statistical Analysis Plan (SAP) for Study 15881, it clearly states that "Both tests (for WASO and sleep latency) had to be statistically significant in order to claim NP 440 mg/DPH 25 mg to be efficacious." However, from the protocol and SAP for Study 14837, it is not clear if both WASO and sleep latency need to be statistically significant for an efficacy claim. Based on this reviewer's discussion with the Medical Reviewer, it seems that the Medical Division thinks both WASO and sleep latency need to be statistically significant for claiming a dose to be

efficacious. This reviewer would like to point out that for Study 14837 the separate hierarchical testing procedure for WASO and sleep latency proposed by the sponsor in Section 3.2.1.4 doesn't control the studywise Type I error at 0.05 level (two-sided). For this study, it is sensible to test NP 440 mg/DPH 50 mg versus either single ingredient (naproxen sodium or DPH) alone first for both WASO and Sleep latency. The reviewer consider both WASO and sleep latency were statistically significant for NP 440 mg/DPH 50 mg.

This reviewer conducted subgroup analysis by sex, race, age group and site for WASO and sleep latency. It seems that the treatment effects of primary interest (NP440 mg/DPH 50 mg versus NP 440 mg for WASO; NP440 mg/DPH 50 mg versus DPH 50 mg for sleep latency) are all in the right direction for the subgroups investigated except that the point estimate of treatment effect isn't in the right direction for non-white patients for WASO. However, this doesn't raise concerns since there are only 11% (78/712) non-white patients in this study. Please refer to Section 4.1 for more details.

The "pain" part of this NDA is evaluated by Division of Anesthesia, Analgesia and Addiction products.

5.2 Conclusions and Recommendations

This NDA submission includes two pivotal efficacy studies, Study 14837 and Study 15881. The data of Study 14837 suggests that NP 440 mg/DPH 50 mg was more effective than NP 440 mg on wake after sleep onset (WASO) and more effective than DPH 50 mg on sleep latency. For Study 15881, NP 440 mg/DPH 25 mg didn't achieve statistical significance in both the comparison of NP 440 mg/DPH 25 mg versus NP 440 mg on WASO and the comparison of NP 440 mg/DPH 25 mg versus DPH 50 mg. The designs of Study 14837 and Study 15881 were very similar. The major difference was the different combination dose used in the two studies, NP 440 mg/DPH 50 mg and NP 440 mg/DPH 25 mg for Study 14837 and 15881, respectively. The data shows that the treatment effect of NP 440 mg/DPH 50 mg in Study 14837 at least doubled the treatment effect of NP 440 mg/DPH 25 mg in Study 15881. However, the number of subjects per treatment group in Study 15881 was only half of the number of subjects per treatment group in Study 14837. The statistical insignificance of Study 15881 might be partially due to lack of power.

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

/s/

JINGYU J LUAN
12/19/2013

KUN JIN
12/19/2013
I concur with the review.

HSIEN MING J HUNG
12/19/2013