

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205352Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

**Cross-Discipline Team Leader (CDTL) Review**

|                                               |                                                                                                                                                                                    |
|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Date</b>                                   | See electronic stamp                                                                                                                                                               |
| <b>From</b>                                   | Lucie Yang, MD, PhD                                                                                                                                                                |
| <b>Subject</b>                                | Cross-Discipline Team Leader Review                                                                                                                                                |
| <b>NDA/BLA #</b>                              | NDA 205352, Supplement # 1                                                                                                                                                         |
| <b>Supplement#</b>                            |                                                                                                                                                                                    |
| <b>Applicant</b>                              | Bayer Healthcare – Consumer Care                                                                                                                                                   |
| <b>Date of Submission</b>                     | 03/20/ 2013 (received same day)                                                                                                                                                    |
| <b>PDUFA Goal Date</b>                        | 01/20/2014                                                                                                                                                                         |
| <b>Proprietary Name (Established Name(s))</b> | Aleve PM (naproxen sodium 440 mg / diphenhydramine hydrochloride 50 mg)                                                                                                            |
| <b>Dosage forms / Strength</b>                | Naproxen sodium 220 mg / diphenhydramine hydrochloride 25 mg per tablet                                                                                                            |
| <b>Proposed Indication(s)</b>                 | <ul style="list-style-type: none"> <li>• Relief of occasional sleeplessness when associated with minor aches and pains</li> <li>• Helps you fall asleep and stay asleep</li> </ul> |
| <b>Recommended:</b>                           | <i>Approval, pending acceptable manufacturing facility inspection</i>                                                                                                              |

| <b>Material reviewed, including:</b>                                                    | <b>Names of discipline reviewers</b>                                                                                                        |
|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| DNP Medical Officer Review, draft                                                       | Veneeta Tandon, Ronald Farkas                                                                                                               |
| DNCE Medical Officer Review, 12/16/2013                                                 | Linda Hu, Lucie Yang                                                                                                                        |
| DAAAP Medical Officer Consult Response, 10/18/2013                                      | Ellen Fields, Sharon Hertz, Bob Rappaport                                                                                                   |
| Office of Scientific Investigations Clinical Inspection Reviews and Summary, 09/13/2013 | Antoine El Hage, Susan Leibenhaut, Kassa Ayalew                                                                                             |
| DNCE Pharmacology Toxicology Review, 12/17/2013                                         | Xinguang (Cindy) Li, Paul Brown                                                                                                             |
| CMC Review, 11/08/2013                                                                  | Olen Stephens, Danae Christodoulou                                                                                                          |
| OSE Pharmacovigilance and Drug Use Review, 10/29/2013                                   | Carolyn Volpe, Joseph Tanning, Alex Secora, Tracy Pham, Peter Dik, Allen Brinker, Cynthia Kornegay, Hina Mehta, Judy Staffa, Scott Proestel |
| DMEPA Proprietary Name, 06/21/2013; Label Review, 09/26/2013, 11/12/2013                | Chi-ming (Alice) Tu, Todd Bridges, Carol Holquist, Jo Wyeth                                                                                 |
| DNCE Promotional Review, 07/01/2013                                                     | Barbara Cohen, Lesleyanne Furlong                                                                                                           |
| Clinical Pharmacology Review, 12/20/2013                                                | Xinning Yang, Bilal Abu Asal, Yuxin (Angela) Men                                                                                            |
| Biometrics Review, 12/19/2013                                                           | Jingyu Luan, Kun Jin, Hsien Ming Hung                                                                                                       |
| Environmental Assessment, 05/03/2013                                                    | Raanan Bloom, Nakissa Sadrieh                                                                                                               |
| Biopharmaceutics Review, 12/06/2013                                                     | Minerva Hughes, Angelica Dorantes                                                                                                           |
| Office of Generic Drugs Consult Response,                                               |                                                                                                                                             |
| DNRD Labeling Review, 11/20/2013, 12/11/2013                                            | Kathleen (Kate) Phelan, Ayana Rowley, Steven Adah                                                                                           |
| PerC meeting minutes, 11/06/2013                                                        | George Greeley                                                                                                                              |

CMC = Chemistry, Manufacturing, and Controls  
DAAAP = Division of Anesthesia, Analgesia, and Addiction Products  
DMEPA = Division of Medication Error and Prevention  
DNCE = Division of NoNprescription Clinical Evaluation

DNP = Division of Neurology Products  
DNRD = Division of NoNprescription Regulation Development  
OSE = Office of Surveillance and Epidemiology

## EXECUTIVE SUMMARY

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) marketed as an over-the-counter product for symptomatic treatment of pain and inflammation in variety of disease states. Diphenhydramine is an antihistamine marketed as an over-the-counter product for various uses including sleep-aid and allergic rhinitis.

The applicant of NDA 205352, Bayer Healthcare – Consumer Care, has requested approval of a naproxen sodium 440 mg and diphenhydramine 50 mg combination product to help one fall asleep and stay asleep when experiencing minor aches and pains. There are several analgesic / sleep-aid combination products on the OTC market which include 50 mg diphenhydramine. Although there are NSAID / diphenhydramine combination products currently available as OTC products, the proposed product would be the first to combine naproxen with diphenhydramine for the proposed indication.

The primary reviewers of this application support the approval of this application (pending acceptable manufacturing facility inspection). This memo documents my concurrence with these recommendations.

Finally, I recommend a full waiver for pediatric studies in order to be consistent with prescription products for insomnia and previously approved analgesic / sleep-aid combination products.

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## 1. Introduction

Bayer Healthcare – Consumer Care (Bayer) submitted a new drug application for over-the-counter (OTC) use of a new nighttime analgesic / sleep-aid, fixed dose combination of naproxen sodium (NP) and diphenhydramine HCl (DPH) tablets (proposed trade name Aleve PM) to relieve occasional sleeplessness when associated with minor aches and pains, and to help one fall asleep and stay asleep. The proposed dose is 440 mg NP (400 mg naproxen) and 50 mg DPH at bedtime in adults and adolescents 12 years of age and older. Each caplet contains 220 mg NP and 25 DPH, so two caplets are taken at bedtime. If approved, Aleve PM would be the first OTC nighttime analgesic/sleep-aid available in the US combining NP with DPH.

To reduce confusion, the following abbreviations will be used in this document:

**NP 440 / DPH 50:** naproxen sodium 440 mg / diphenhydramine hydrochloride 50 mg

**NP 440:** naproxen sodium 440 mg alone

**DPH 50:** diphenhydramine hydrochloride 50 mg alone

**NP 220 / DPH 50:** naproxen sodium 220 mg / diphenhydramine hydrochloride 50 mg

**NP 440 / DPH 25:** naproxen sodium 440 mg / diphenhydramine hydrochloride 25 mg

The application is based primarily on two pivotal efficacy and safety studies, only one of which assesses efficacy of the proposed product, NP 440 / DPH 50. A pilot efficacy study, 10-day multiple dose safety study, and bioavailability study were also submitted to support the application. This document provides an overview of the application, with a focus on the two pivotal studies and next-day effects of DPH.

## 2. Background

Both naproxen and diphenhydramine are approved products. Naproxen sodium was approved as a prescription product in 1976 as Naprosyn. Approval of naproxen sodium 200mg tablets (Aleve) for OTC marketing was granted in 1994. Uses include temporary relief of minor aches and pains due to minor pain of arthritis, muscular aches, backaches, menstrual cramps, headaches, toothaches, and the common cold, in addition to temporary reduction of fever.

Diphenhydramine hydrochloride is an OTC antihistamine and a nighttime sleep aid. The OTC final monograph (21 CFR 338) Nighttime Sleep-Aid Drug Products for Over-The-Counter Human Use allows DPH 50 mg and diphenhydramine citrate 76mg to be active ingredients for use as nighttime sleep aids.

Combination products that contain an analgesic and diphenhydramine are available as OTC products (Table 1). Advil PM is an approved NDA. The applicant's proposed indication is consistent with that of other marketed OTC analgesic / nighttime sleep aids.

Table 1. Currently available OTC analgesic / diphenhydramine combination products for pain relief / sleep aid

| Product Name                 | Generic Name (dose per tablet / caplet)                             | Directions                                                |
|------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------|
| Advil PM                     | IBUPROFEN (200 mg),<br>DIPHENHYDRAMINE CITRATE (38 mg)              | 2 caplets at bedtime, not to exceed 2 caplets in 24 hrs   |
| Advil PM                     | IBUPROFEN (200 mg),<br>DIPHENHYDRAMINE HCL (25 mg)                  | 2 capsules at bedtime, not to exceed 2 capsules in 24 hrs |
| Motrin PM                    | IBUPROFEN (200 mg),<br>DIPHENHYDRAMINE CITRATE (38 mg)              | 2 caplets at bedtime, not to exceed 2 caplets in 24 hours |
| Tylenol PM<br>Extra Strength | ACETAMINOPHEN (500 mg),<br>DIPHENHYDRAMINE<br>HYDROCHLORIDE (25 mg) | 2 geltabs at bedtime, not to exceed 2 geltabs in 24 hrs   |
| Excedrin PM                  | ACETAMINOPHEN (500 mg),<br>DIPHENHYDRAMINE CITRATE (38 mg)          | 2 tablets at bedtime                                      |

### ***Biological Basis of Efficacy for Sleep Initiation and Maintenance***

The time to maximum plasma concentration ( $t_{max}$ ) and half-life ( $t_{1/2}$ ) are important pharmacokinetic parameters for determining whether a drug is effective for sleep initiation, maintenance, or both (Table 2).<sup>1</sup>

Table 2. Effect of pharmacokinetic parameters on efficacy regarding sleep initiation and maintenance

| $t_{max}$             | $t_{1/2}$           | Efficacy Characteristic Regarding Sleep             |
|-----------------------|---------------------|-----------------------------------------------------|
| Rapid (~0.5 – 1.5 h)  | Short (~1 to few h) | Effective for sleep initiation only                 |
| Rapid                 | Longer              | Effective for both sleep initiation and maintenance |
| Delayed ( $\geq 1$ h) | Intermediate        | Effective for sleep maintenance only                |

h=hours

The  $t_{max}$  and  $t_{1/2}$  of DPH 50 are 1.75 h and 10.85 h, respectively (see section 4. Clinical Pharmacology below).

The relationship between pharmacokinetic parameters and efficacy for sleep initiation / maintenance may not necessarily apply when the major effect of a drug is for pain rather than for sleep. That being said, the  $t_{max}$  and  $t_{1/2}$  of NP 440 are 0.75 h and 16.52 h, respectively (see section 4. Clinical Pharmacology below).

<sup>1</sup> DNP Clinical Team Leader review for Tylenol PM by Ronald Farkas, 2011, p14

## Regulatory History

Regulatory history highlights are presented by topic in Table 3. Please see Dr. Hu's review for additional details.

Table 3. Regulatory History

| Topic                          | Date             | Interaction Type and Discussion Points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Design of confirmatory studies | 2009 February 10 | <p><u>pre-IND 103407 meeting</u></p> <p><i>Primary endpoint:</i> FDA recommended sleep latency and wake after sleep onset (WASO) for co-primary endpoints in order to support the proposed indication “helps you fall asleep and stay asleep.”</p> <p><i>Combination product:</i> FDA stated the proposed product “will need to meet the requirements of the OTC<sup>2</sup> combination policy specified in 21 CFR 330.10 (a)(4)(iv)” and that the applicant would “need a DPH arm, a naproxen arm, and a combination arm in order to show superiority of the combination over each of its components.” Furthermore, “one possible approach would be to show that the combination was superior to naproxen alone for sleep duration and to DPH alone for sleep latency.”</p> |
|                                | 2009 June 10     | <p><u>Advice Letter</u></p> <p><i>Actigraphy:</i> In the context of a question asking about the use of actigraphy to measure total sleep time as the primary efficacy parameter and another question asking about the use of actigraphy for secondary endpoints, FDA clarified, “actigraphy would be acceptable for evaluating sleep in the proposed dental pain/ sleep phase advance study.”</p>                                                                                                                                                                                                                                                                                                                                                                             |
|                                | 2010 January 08  | <p><u>SPA<sup>3</sup> No Agreement letter</u></p> <p><i>Treatment arms:</i> FDA recommended adding a NP 220 / DPH 25 arm to the proposed arms (NP 440 / DPH 50, NP 220 / DPH 50, NP 440, DPH 50).</p> <p><i>Imputation:</i> FDA indicated that the imputation scheme for subjects taking rescue medication proposed by the applicant<sup>4</sup> is “biased in favor of NP 440 / DPH 50” and that</p>                                                                                                                                                                                                                                                                                                                                                                         |

<sup>2</sup> Over-the-counter

<sup>3</sup> Special Protocol Assessment

<sup>4</sup> The scheme proposed in the SPA is the one used in the pivotal studies. For WASO, subjects who take rescue medication before sleep onset, WASO is set to the duration of the in-bed time (10 hours); subjects who take rescue

| Topic                          | Date              | Interaction Type and Discussion Points                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                |                   | the applicant would “need to propose another method that will not benefit NP 440 / DPH 50 or NP 220 / DPH 50.”                                                                                                                                                                                                                                                                                                                                      |
|                                | 2010 December 27  | <u>Advice letter – response to Bayer’s request for clarification</u><br><i>Imputation</i> : FDA reiterated the recommendation to develop statistical algorithms that “allow for an unbiased evaluation of the combinations by not favoring one combination to win over another.”                                                                                                                                                                    |
|                                | 2012 February 15  | <u>Advice letter – response to 2011 November 18 submission of amended protocol for Study 15881</u><br><i>Imputation / sensitivity analyses</i> : FDA again indicated that the proposed imputation scheme <sup>5</sup> biases in favor of the combination. FDA requested addition of another sensitivity analysis for both co-primary variables that treats subjects who take the rescue medication as if they have not taken the rescue medication. |
| Number of confirmatory studies | 2009 February 10  | <u>pre-IND meeting</u><br>Although FDA expressed a preference for two adequate and well-controlled studies, FDA stated that “a single, well-designed, robust study may be sufficient to support the proposed product, but this would be a review issue.”                                                                                                                                                                                            |
| Next-day effects               | 2010 September 07 | <u>Type A meeting</u><br>FDA clarified that “a next-day driving study is not a requirement for approval.”                                                                                                                                                                                                                                                                                                                                           |
|                                | 2012 October 09   | <u>Type B pre-NDA meeting</u><br>FDA advised the applicant to provide a comprehensive, up-to-date literature review regarding DPH and next-day effects, as well as a targeted analysis of postmarketing safety information for DPH, focusing on adverse events pertinent to next-day residual effects as related to nighttime administration of DPH for sleep.                                                                                      |
| Dose selection                 | 2009 February 10  | <u>pre-IND meeting</u>                                                                                                                                                                                                                                                                                                                                                                                                                              |

medication after sleep onset would be treated as being awake from the time when the rescue medication is given to the remainder of the in-bed time. For sleep latency, subjects who take the rescue medication before sleep onset would be assigned a latency of 10 hours.

<sup>5</sup> Subjects who take rescue medication will be assigned maximum penalty in the proposed primary analysis.

| Topic | Date              | Interaction Type and Discussion Points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|       |                   | <p>FDA asked for rationale for selecting the 440 mg naproxen (NP) sodium dose and stated the data thus far did not support that the NP 440 mg / DPH 50 mg dose offered any therapeutic advantage over NP 220 mg / DPH 50.</p> <p>FDA would accept a study that compared NP 220 / DPH 50 to NP 220 and to DPH 50. If the applicant pursued development of NP 440 / DPH 50, then a study that included NP 220 / DPH 50 and NP 440 / DPH 50 (with appropriate controls) would be acceptable.</p>                                                                                                                                                                            |
|       | 2010 September 07 | <p><u>Type A meeting</u></p> <p>FDA invoked a quote from the ICH E4 Guidance on dose response studies: “the highest tolerated dose or the dose with the largest effect... will not always be the optimal dose.” FDA again<sup>6</sup> recommended inclusion of a NP 220 / DPH 25 treatment arm because “a lower dose combination product may be more appropriate due to safety considerations such as residual next-day effects on driving and acceptable safety profile in elderly consumers.” Bayer considers a separate trial to assess a lower-dose combination (NP 220 / DPH 25).</p>                                                                               |
|       | 2010 December 27  | <p><u>Advice letter – response to applicant’s request for clarification</u></p> <p>FDA reiterates recommendation to study two doses of NP (220 and 440 mg) and two doses of DPH (25 and 50 mg) in order to optimize safety by finding the lowest effective dose of each component of the proposed combination.</p>                                                                                                                                                                                                                                                                                                                                                       |
|       | 2011 July 22      | <p><u>Meeting Denied letter</u></p> <p>The applicant requested a Type B meeting to discuss its rationale for not needing to perform a second study to evaluate a lower dose of DPH (25 mg). FDA denied the meeting, stating: “We cannot make a recommendation that the evaluation of a 25 mg diphenhydramine arm is not needed without an in depth review of your safety and efficacy data.”</p> <p>FDA advised the applicant that “if you decide not to evaluate the 25 mg dose of diphenhydramine as the potential dose for the diphenhydramine component of your planned combination drug product, please submit your rationale and justification for your chosen</p> |

<sup>6</sup> See above in same table: Design of Confirmatory Studies, 2010 January 08

| Topic | Date             | Interaction Type and Discussion Points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|       |                  | development program in your future NDA.”                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|       | 2011 December 23 | <p><u>Advice letter – response to submission of protocol for second pivotal efficacy trial (Study 15881)</u></p> <p>FDA recommended amending the protocol to determine plasma DPH concentration on the morning after dosing to aid evaluation of next-day impairment</p> <p>FDA indicated that the protocol did not adequately address optimal dose selection for the proposed product because:</p> <ul style="list-style-type: none"> <li>• The study did not include a NP 220 / DPH 25 arm (potential lowest effective combination dose)</li> <li>• The study did not address the relative efficacy of NP 440 / DPH 50 vs NP 440 / DPH 25</li> </ul> |
|       | 2012 April 05    | <p><u>Meeting Denied letter</u></p> <p>The applicant requested a Type B meeting to discuss its rationale for not needing to evaluate NP 220 / DPH 25 or evaluate NP 440 / DPH 50 vs NP 440 / DPH 25, as well as its plan for addressing FDA’s recommendation to determine plasma DPH concentration. FDA indicated that it recognized “there are alternative ways to evaluate dose selection and next-day plasma diphenhydramine concentrations” and recommended that the applicant “submit your reasoning and data” in the NDA.</p>                                                                                                                    |

### ***Issues Raised by the Tylenol PM Development Program***

That an analgesic improving sleep through pain relief could be used to support a claim for improvement of sleep was questioned during the development of Tylenol PM:<sup>7</sup>

“even if it could be concluded that APAP<sup>8</sup> improved sleep through pain relief, FDA has generally concluded that this is not adequate to support a claim for improvement of sleep. For example, during the monograph process FDA stated that ‘The promotion of sleep through the relief of pain is not a therapeutic effect properly associated with a “nighttime sleep-aid”; a nighttime sleep-aid exerts its

<sup>7</sup> DNP Clinical Team Leader review for Tylenol PM by Ronald Farkas, 2011, p18

<sup>8</sup> acetaminophen

therapeutic effect through a pharmacologic action that brings about or maintains drowsiness, not through the elimination of distractions that inhibit or interrupt sleep’ (pg 25550, Tentative Final Monograph, 6/13/1978, 43FR25544).”

### ***Approval Basis for Advil PM (NDA 021393, 021394)***

Advil PM (ibuprofen 400 mg / DPH 50 mg) was approved based on three efficacy studies.<sup>9</sup>

Two partial-factorial studies (AE-98-01 and AE-98-02) were performed first using an oral surgery model with phase advanced sleep. These studies compared (1) the analgesic efficacy and (2) the sleep efficacy of Advil PM to that of placebo. Advil PM was statistically superior to ibuprofen for sleep duration. The combination product improved sleep latency compared to placebo but ibuprofen alone was numerically superior to Advil PM for sleep latency in AE-98-02. Thus, ibuprofen was the primary contributor to sleep latency. Importantly, the studies failed to demonstrate the contribution of the DPH component of the combination, and there were design issues<sup>10</sup> that raised concern about the validity of the studies.

When asked to conduct another study to validate the results using objective measures, the sponsor disputed the request. Dr. Jenkins agreed with the primary review divisions,<sup>11</sup> and the sponsor conducted a third study, AE-04-14.

Study AE-04-14 was a randomized, double blind, parallel, single center study in subjects who underwent oral surgery. Advil PM was compared to ibuprofen 400 mg alone for sleep parameters including sleep latency, wake after sleep onset (WASO) using actigraphy, total sleep time by actigraphy, and time to rescue medication.

Sleep latency was not different between the groups, consistent with previous studies suggesting that time to sleep onset in this population is primarily driven by pain relief. WASO was significantly reduced by 1.35 hours in the Advil PM group (n=165) vs ibuprofen alone (n=164). Total sleep time was significantly longer by 1.2 hours in Advil PM group vs ibuprofen group alone: 9.29 hours vs 8.09 hours. It was concluded that this study demonstrated that DPH contributes to the combination to improve the quality of sleep (WASO) and sleep duration, justifying approval of Advil PM.

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<sup>9</sup> DNP clinical review for NDA 021393 and 021394 by Dawn McNeil, finalized 10/28/2005; summary review for same NDAs by Charles Ganley, finalized 12/19/2005

<sup>10</sup> Protocol-specified forced patient awakenings at 90 and 120 minutes post-dose to assess analgesic efficacy, which may have biased the sleep duration assessment.

<sup>11</sup> Review by John Jenkins addressing Formal Dispute Resolution Request for NDA 021393 and 021394, finalized 2/26/2003

### 3. CMC/ Biopharmaceutics

#### CMC

Dr. Stephens (CMC) recommends approval from the CMC perspective, pending an acceptable recommendation from the Office of Compliance regarding the facility inspection. I agree.

A 24-month shelf-life was granted for Aleve PM tablets, with storage conditions of (b) (4).

During review of this application, the applicant was asked to report all related impurities that exceed the (b) (4) % ICH Q3B reporting limit as an additional measure to assure quality. To address the Agency's request, the applicant amended the analytical methods section to report all impurities above the (b) (4) % limit of detection.

#### Biopharmaceutics

Dr. Hughes (biopharmaceutics) recommends approval from the biopharmaceutics perspective. I agree.

Regarding stability, the applicant collected and submitted incomplete dissolution data. During the review of this application, the Agency requested dissolution profile data on stability. The applicant subsequently clarified that data from registration stability lots after twelve months of storage were provided in the method development report and committed to collecting complete dissolution profiles on the remaining stability pulls. When informed that the proposed acceptance criterion of  $Q = \frac{(b) (4)}{(4)}\%$  at  $\frac{(b) (4)}{(4)}$  minutes was (b) (4), the applicant agreed to the Agency's recommendation of an acceptance criterion of  $Q = \frac{(b) (4)}{(4)}\%$  at 30 minutes.

### 4. Nonclinical Pharmacology/Toxicology

Dr. Li recommends approval from the pharmacology / toxicology perspective. I agree.

Rather than submit new nonclinical studies, the applicant refers to data and information supporting NDA 20204 for naproxen sodium 220 mg and the Final Monograph 21CFR338 for diphenhydramine hydrochloride. Dr. Li notes that both naproxen and diphenhydramine are previously approved products with well-characterized mechanisms of action. Though the combination of naproxen and diphenhydramine was not evaluated in animals, it has been studied clinically. Dr. Li had no concerns regarding impurities / degradants and noted that there are no novel excipients in the proposed product.

Dr. Li concluded that "Based on the previous human use experience and the agency's previous findings of safety and efficacy of naproxen and diphenhydramine, as well as the lack of novel significant toxicity issues identified during the current review, this NDA can be approved from

the nonclinical perspective. Due to the clinical and nonclinical findings with NSAIDs, this product is not recommended for nursing mothers and not for women in late pregnancy, in labor and delivery.”

Of note, the proposed label addresses the concern regarding pregnant and breast-feeding women with the following text:

“If pregnant or breast-feeding, ask a health professional before use. 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.”

## 5. Clinical Pharmacology

Please see reviews by Dr. Tandon, Dr. X. Yang, and Dr. Hu for general clinical pharmacology information regarding naproxen and diphenhydramine.

DPH plasma concentration and histamine receptor occupancy as potential predictors of somnolence and mental performance will be briefly discussed. This information will be used to further discuss potential safety risks of a sleep aid containing DPH 50 the day after nighttime administration (see the Next-day Effects subsection of section 8. Safety).

Additionally, results of a trial (Study 16135) assessing drug-drug interactions between NP 440 and DPH 50 in a combination product, as well as potential effects of food on the pharmacokinetic parameters for NP 440 / DPH 50 will be discussed.

### ***DPH Plasma Concentration, Histamine Receptor Occupancy, Drowsiness, and Cognitive Performance***

Although some publications suggest there may be predictors of mental function and drowsiness after DPH dosing, other studies appear to cast doubt on this relationship.

A 1989 study assessing the time course of DPH plasma concentrations, objective effects on mental performance, and subjective feelings of drowsiness in fifteen male subjects suggested that 30 to 42 ng/mL of DPH is the threshold to produce drowsiness, and 58 to 74 ng/mL of DPH is the threshold to produce mental impairment (assessed with an automobile driving simulator and digit symbol substitution scores).<sup>12</sup> DPH produced drowsiness for up to 6 hours post-dosing, and mental impairment for up to 2 hours post-dosing. As pointed out by the clinical pharmacology reviewer, DPH 50 was given at 8am rather than just before bedtime, so whether the thresholds identified in this study would be similar to those for next-day residual effects of

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<sup>12</sup> Gengo F. et al. (1989) The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance. *Clin Pharmacol Ther* **45**: 15-21.

nighttime DPH dosing is not known. Since only male subjects were enrolled, whether the results of this study would be generalizable to females is also not known--particularly given that the DPH plasma concentration profile may be different between males and females (see Gender Effects subsection under Study 16135 below).

The plasma concentration below which drowsiness would not be a concern may be as high as 50 ng/mL.<sup>13</sup>

A study assessing the relation between DPH plasma levels and performance on driving-related tasks (visual search, tracking, and divided attention tasks) in eight males over 24 hours following oral administration concluded that plasma DPH levels may have limited value to predict performance decrements under certain circumstances.<sup>14</sup> While a close relation was observed between DPH levels and errors in signal detection, no simple relation was observed for DPH levels and tracking under divided attention.

The histamine neuron system promotes wakefulness and cognition through histamine H1 receptors. Blockage of the H1 receptors by antihistamines such as DPH induces sedation and mental impairment. By measuring H1 receptor occupancy using <sup>11</sup>C doxepin positron emission tomography, it was shown that DPH blocks a greater proportion of H1 receptors than placebo twelve hours after DPH 50 dosing.<sup>15</sup> The decline of H1 receptor occupancy level over time appeared to parallel the decline in DPH plasma concentration. However, neither H1 receptor occupancy nor DPH plasma concentration correlated with subjective sleepiness.

### ***Study 16135 – Bioavailability Trial of NP 440 / DPH 50 Under Fasting and Fed Conditions***

The objectives of this study were

- to determine the potential for drug-drug interactions between NP 440 and DPH 50 in the combination product under fasting conditions, and
- to compare the PK profile of a single dose of NP 440 / DPH 50 under fasting and fed conditions.

In this randomized, open-label, four-way cross-over, single-center study, healthy adults were randomized to one of four randomization sequences (ACBD, BADC, CDAB, DBAC) where:

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<sup>13</sup> Carruthers S.G. et al. (1978) Correlation between plasma diphenhydramine level and sedative and antihistamine effects. *Clin Pharmacol Ther* **23**: 375-382.

<sup>14</sup> Licko V. et al. (1986) Asynchronies of diphenhydramine plasma-performance relationships. *Pharmacol Biochem & Behav* **25**: 365-370.

<sup>15</sup> Zhang D. 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.

- Treatment A: NP 440 / DPH 50, fasting
- Treatment B: NP 440, fasting
- Treatment C: DPH 50, fasting
- Treatment D: NP 440 / DPH 50, fed

Twenty-seven of the 32 subjects exposed to at least one dose of investigational product within four single-dose periods completed the study as planned. Blood samples were collected at frequent intervals to 36 hours post-dose, and PK variables ( $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $t_{max}$ ,  $t_{1/2}$ ) were determined (Table 4).

Table 4. Study 16135 - PK parameters for NP and DPH by treatment<sup>16</sup>

| PK Parameters (units)                 | Treatment A<br>N=27 | Treatment B<br>N=27 | Treatment C<br>N=27 | Treatment D<br>N=27 |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|
| <b>NP</b>                             |                     |                     | Not applicable      |                     |
| $C_{max}$ (µg/mL) <sup>a</sup>        | 74.6 (10.4)         | 80.4 (11.5)         | ↓                   | 60.8 (11.1)         |
| $AUC_{0-t}$ (mg*hr/mL) <sup>a</sup>   | 913.2 (135.8)       | 909.1 (124.8)       |                     | 882.4 (119.2)       |
| $AUC_{0-inf}$ (mg*hr/mL) <sup>a</sup> | 1063 (156.9)        | 1060 (147.1)        |                     | 980.1 (138.8)       |
| $t_{1/2}$ (h) <sup>a</sup>            | 17.0 (3.8)          | 16.5 (2.6)          |                     | 16.4 (2.9)          |
| $t_{max}$ (h) <sup>b</sup>            | 1.25                | 0.75                |                     | 3.00                |
| <b>DPH</b>                            |                     | Not applicable      |                     |                     |
| $C_{max}$ (µg/mL) <sup>a</sup>        | 67.7 (27.1)         | ↓                   | 68.9 (22.4)         | 77.1 (35.0)         |
| $AUC_{0-t}$ (mg*hr/mL) <sup>a</sup>   | 613.9 (238.5)       |                     | 598.2 (233.5)       | 685.3 (263.5)       |
| $AUC_{0-inf}$ (mg*hr/mL) <sup>a</sup> | 646.5 (239.6)       |                     | 636.4 (257.6)       | 709.5 (267.0)       |
| $t_{1/2}$ (h) <sup>a</sup>            | 11.0 (2.7)          |                     | 10.9 (2.5)          | 10.8 (1.9)          |
| $t_{max}$ (h) <sup>b</sup>            | 2.50                |                     | 1.75                | 2.50                |

a: Mean (SD); b: Median

### Drug-drug Interaction

Regarding drug-drug interaction, the applicant pre-specified that no meaningful drug-drug interaction occurred if the 90% confidence intervals (CI) of the ratios for  $C_{max}$  and AUCs<sup>17</sup> for the combination product (Treatment A) vs the single ingredient products (Treatment B, Treatment C) were within 80% to 125% (bioequivalence criteria). Because the bioequivalence criteria were met for NP  $C_{max}$  and AUCs and for DPH  $C_{max}$  and AUCs, Dr. Yang agreed with the sponsor that “there is no drug-drug interaction” for the combination product.<sup>18</sup> This result is consistent with results presented in Toothaker et al (2000).<sup>19</sup>

<sup>16</sup> Adapted from Module 2.7.2, Table 2.1.1 in NDA 205352, Supporting Document 1

<sup>17</sup>  $C_{max}$ : Maximum concentration; AUC: area under the concentration vs time curve

<sup>18</sup> Clinical pharmacology review for NDA 205352 by Xinning Yang, finalized 12/20/2013, p10

<sup>19</sup> Toothaker R.D. et al. (2000) Absence of pharmacokinetic interaction between orally co-administered naproxen sodium and diphenhydramine hydrochloride. *Biopharm & Drug Dispo* **21**:229-233.

### Food Effects

Regarding food effects, the overall exposure of NP or DPH ( $AUC_{0-inf}$ ,  $AUC_{0-t}$ ) in the combination was not affected by a high-fat meal.  $C_{max}$  for DPH met bioequivalence criteria for fed vs fasting states.  $t_{max}$ <sup>20</sup> for DPH was somewhat delayed by food intake: median (range) being 2.5 (1.0-4.0) hours in the fasting state and 2.5 (1.25-6.0) hours in the fed state, with the 90% CIs for the Treatment D/A (fed / fasting) ratio being 86.6, 136.9.

For NP,  $C_{max}$  and  $t_{max}$  did not meet bioequivalence criteria for the fasting vs fed states:

- $C_{max}$  (mean (SD) ( $\mu$ g/mL): 74.6 (10.4) fasting, 60.8 (11.1) fed
- $t_{max}$  (median (hour): 1.25 fasting, 3.00 fed

For NP, the 90% CIs for the Treatment D/A (fed / fasting) ratio for  $C_{max}$  and  $t_{max}$  were as follows:

- $C_{max}$ : 76.1, 85.1
- $t_{max}$ : 167.3, 275.2

The clinical pharmacology reviewer concludes that “There was no food effect on the extent of absorption of naproxen or DPH in the combination product...however, there is a delay in the rate of absorption for naproxen under fed state with a lower peak plasma concentration. Food intake increased the peak plasma concentration of DPH slightly.”

The proposed Drug Facts Label states, “if taken with food, this product may take longer to work.” This proposal appears reasonable, considering the effect of food on the naproxen component of the combination product.

### Gender Effects

For DPH, the clinical pharmacology reviewer points out that “females appear to have 14-30% higher DPH plasma concentrations than males at 8 hours post-dose (based on geometric mean values). The clinical significance of such difference is unknown.”<sup>21</sup> See Figure 1 and Table 5.

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<sup>20</sup> Time to reach maximum plasma concentration

<sup>21</sup> Clinical Pharmacology review for NDA 205352 by Xinning Yang, finalized 12/20/2013, p9

Figure 1. Plasma concentrations of DPH at 8 hours post-dose (C8hr) grouped by gender for Treatments A, C, and D. Horizontal bars represent medians.<sup>22</sup>

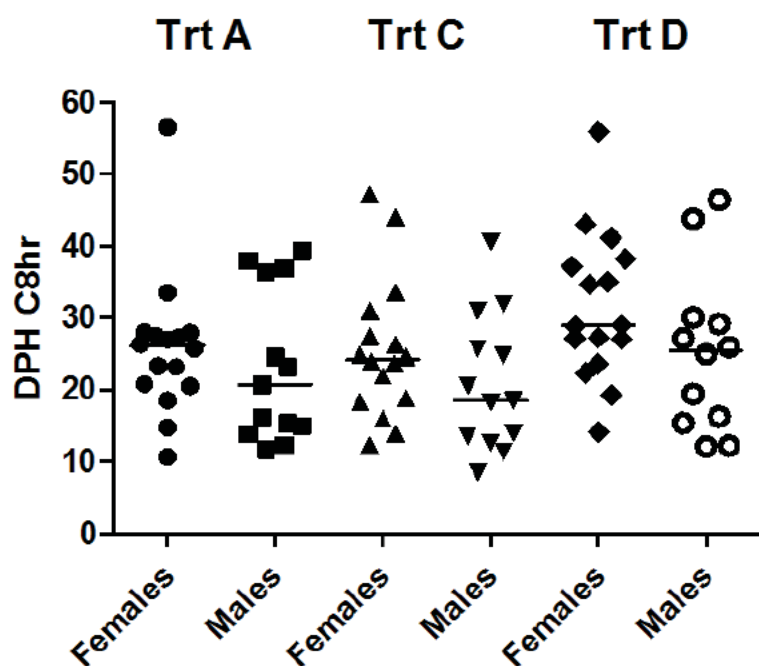


Table 5. Descriptive statistics of plasma concentrations of DPH at 8 hours post-dose (C8hr) grouped by gender for Treatments A, C, and D<sup>23</sup>

| C8hr           | Treatment A     |                  |      | Treatment C     |                 |      | Treatment D      |                  |      |
|----------------|-----------------|------------------|------|-----------------|-----------------|------|------------------|------------------|------|
|                | Females (F)     | Males (M)        | F/M  | F               | M               | F/M  | F                | M                | F/M  |
| N              | 16              | 13               |      | 16              | 13              |      | 16               | 12               |      |
| Mean (SD)      | 25.75<br>(9.96) | 23.31<br>(10.66) | 1.10 | 25.49<br>(9.75) | 20.87<br>(9.46) | 1.22 | 31.49<br>(10.28) | 25.24<br>(11.23) | 1.25 |
| Geometric mean | 24.21           | 21.17            | 1.14 | 23.88           | 18.97           | 1.26 | 29.92            | 23.06            | 1.30 |
| Median         | 26.08           | 20.73            | 1.26 | 24.22           | 18.54           | 1.31 | 28.96            | 25.46            | 1.14 |
| Range          | 10.69,<br>56.52 | 11.68,<br>39.30  |      | 12.28,<br>47.16 | 8.53,<br>40.60  |      | 14.15,<br>55.88  | 12.13,<br>46.44  |      |

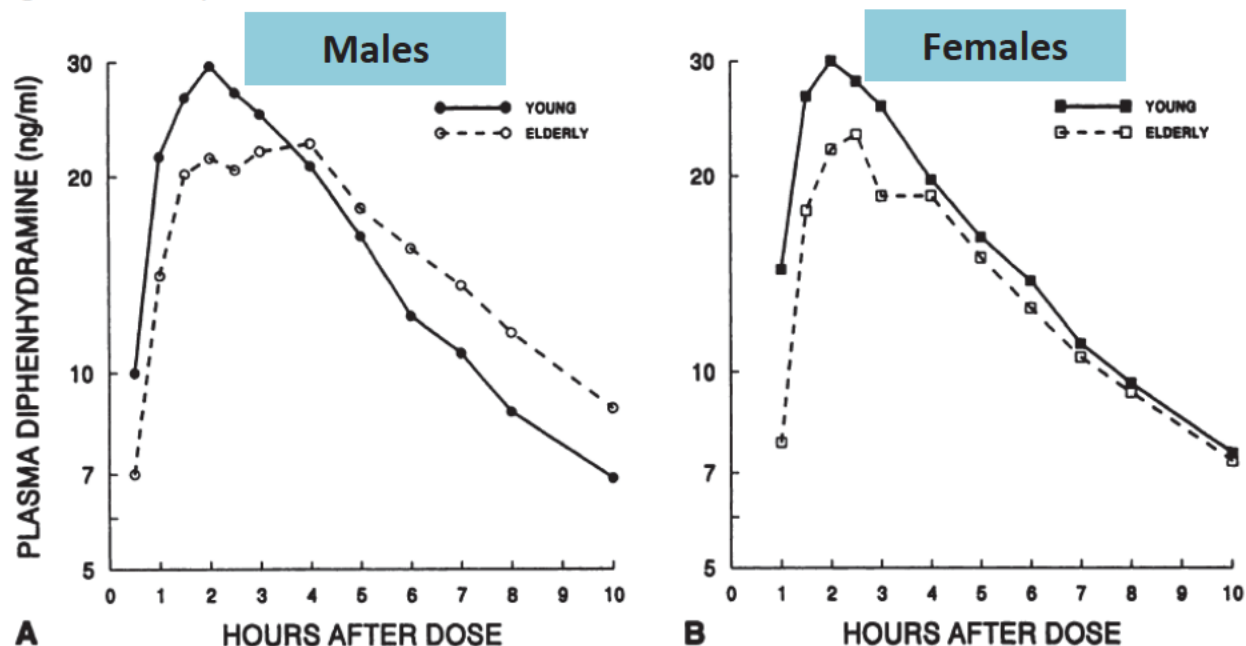
In contrast to the apparent gender difference observed for the DPH concentration in Study 16135, a previous study administering a lower dose of DPH (25 mg) demonstrated that young

<sup>22</sup> Caption and figure reproduced from Clinical Pharmacology review for NDA 205352 (Figure 5) by Xinning Yang, finalized 12/20/2013

<sup>23</sup> Adapted from Clinical Pharmacology review for NDA 205352 (Table 3) by Xinning Yang, finalized 12/20/2013

females (n=10) had similar concentrations of DPH at 8 hours post-dose (C8hr) as young males (n=10), and elderly females (n=10) had slightly lower C8hr than elderly males (n=7) (Figure 2).<sup>24</sup>

Figure 2. Mean plasma DPH concentrations<sup>25</sup>



## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

Efficacy highlights from the two pivotal studies are described below. Only one pivotal study tested the proposed dose combination (NP 440 / DPH 50). The pain-related endpoints (all secondary) will be briefly discussed in a separate subsection following the subsections describing the primary sleep endpoints in the pivotal studies (each study separately, then together). The final two subsections will discuss limitations of the pivotal studies and dose selection.

Regarding sleep-related efficacy, I agree with the following summary comments by the clinical reviewer from DNP, Dr. Tandon:<sup>26</sup>

<sup>24</sup> Scavone J.M. et al. (1998) Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. *J Clin Pharm* **38**: 603-609

<sup>25</sup> Reproduced from Scavone J.M. et al. (1998) Pharmacokinetics and pharmacodynamics of diphenhydramine 25 mg in young and elderly volunteers. *J Clin Pharm* **38**: 603-609

“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 that NP440/DPH50 is superior to the individual ingredients based on pre-specified comparisons on both WASO (vs NP 440,  $P=0.0002$ ) and Sleep Onset (vs DPH 50,  $P<0.0001$ ). 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.”

The discussion will focus on whether each active ingredient in the combination product makes a contribution to the claimed effects, and whether combining the two active ingredients decreases the effectiveness of either ingredient alone.

The proposed uses for Aleve PM are:

- for relief of occasional sleeplessness when associated with minor aches and pains
- helps you fall asleep and stay asleep

Two pivotal efficacy studies were conducted:

- Study 14837 (**Study 37**): Tested NP 440 mg / DPH 50 mg and NP 220 mg / DPH 50 mg
- Study 15881 (**Study 81**): Tested NP 440 mg / DPH 25 mg

Table 6. Endpoints used to support proposed claims

| Proposed claim                            | Endpoint tested               |
|-------------------------------------------|-------------------------------|
| Helps you fall asleep (sleep initiation)  | Sleep latency                 |
| Helps you stay asleep (sleep maintenance) | Wake After Sleep Onset (WASO) |

Definitions:

- Sleep latency is defined as the time to sleep onset from the time of dosing investigational product.
- WASO is defined as the total wake time after sleep onset during the ten-hour in-bed time.

Both pivotal studies were multicenter, randomized, double-blind, parallel-group studies. The studies were nearly identical in design (including primary and secondary endpoints and sensitivity analyses). Notable differences between the two pivotal studies were (a) the different treatment groups (see bullets above), and (b) whether both WASO and sleep latency endpoints need to be met to claim efficacy (Study 81, but not Study 37, specified both endpoints need to be met).

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<sup>26</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p10

See reviews by Dr. Tandon (DNP – sleep efficacy), Dr. Fields (DAAAP - pain efficacy), and Dr. Luan (biometrics – sleep efficacy) for detailed descriptions of the efficacy findings in the pivotal studies. The biometrics review supported the DNP conclusions regarding sleep efficacy.

The reviews cited above describe the sleep-related and pain-related secondary endpoints for the pivotal studies, as well as a pilot efficacy study (Study 13053). The sleep-related secondary endpoints for the pivotal studies and Study 13053 will not be discussed further in this document, beyond the following comments.

- The sleep-related secondary endpoint results for Study 37 support some advantage of the proposed product, NP 440 / DPH 50, over either single ingredient alone.
- Study 81 did not test the proposed product.
- Although the pilot efficacy study were designed somewhat differently from the pivotal studies (used total sleep time as the primary endpoint [sleep latency and WASO were secondary variables], advanced sleep by three hours rather than five hours as in the pivotal studies, and did not administer the to-be-marketed formulation), the results supported further development of developing the combination product.

### ***Study 37 – Primary Sleep Endpoints***

The objective of this study was to evaluate the efficacy and safety of a single oral dose of two dose combinations of NP and DPH. The applicant aimed to demonstrate that the NP / DPH combination provides added clinical benefit for sleep improvement over single ingredients alone in subjects with post-surgical dental pain and phase advanced sleep.

Healthy individuals 12 years and older who underwent surgical removal of at least two third molars (at least one mandibular) between 13:30 h and 15:30 h, had moderate to severe postoperative pain on the 4-point Categorical Pain Rating Scale (none, mild, moderate, severe), and had a score of  $\geq 50$  mm on the 100 mm Visual Analog Scale (VAS) for pain severity between 16:00 h and 18:30 h were eligible to participate. Subjects were randomized to one of four treatment groups:

- NP 440 / DPH 50
- NP 220 / DPH 50
- NP 440
- DPH 50

Subjects were dosed between 16:00 h and 18:30 h and instructed to go to bed for ten hours. Subjects were equipped with a wrist actigraph<sup>27</sup> which was used to collect sleep/wake activity

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<sup>27</sup> Module 2.5, section 4.1.5 in NDA 205352, Supporting Document 1. The Phillips Respironics Actiwatch is an actigraph worn on the non-dominant wrist that uses an individual's movements to derive the quantity and timing of sleep. Acceleration is sampled 32 times per second. Activity count is defined as the sum of the peak acceleration values within the epoch. Mobility was defined as any 30-second epoch having an activity count of two or higher. Activity counts of forty or more signified the awake state; counts below forty signified sleep. Sleep onset was

data. Rescue medication (hydrocodone 5 mg / acetaminophen 500 mg tablets) was available if adequate pain relief was not achieved after administration of the investigational product and on return of pain. Subjects were encouraged to wait 60 minutes for the study drug to take effect. For extreme pain, other appropriate analgesics were allowed at the discretion of the investigator. Subjects rated pain intensity and pain relief immediately prior to taking rescue medication and upon awakening the next morning.

Primary efficacy endpoints included sleep latency and WASO. Overall type 1 error at the 0.05 level was protected by using a hierarchical testing procedure applied separately to sleep latency and WASO. Treatment comparisons were tested sequentially (each at the 0.05 level of significance) in the order listed in Table 7 for the primary efficacy endpoints. If a particular comparison was not statistically significant, subsequent comparisons were not eligible to be deemed significant.

Table 7. Sequential comparisons for sleep latency and WASO

| Comparison order | Sleep latency --<br>Pairwise comparisons |                 | WASO --<br>Pairwise comparisons |                 |
|------------------|------------------------------------------|-----------------|---------------------------------|-----------------|
|                  | Drug 1                                   | Drug 2          | Drug 1                          | Drug 2          |
| 1                | NP 440 / DPH 50                          | DPH 50          | NP 440 / DPH 50                 | NP 440          |
| 2                | NP 220 / DPH 50                          | DPH 50          | NP 220 / DPH 50                 | NP 440          |
| 3                | NP 440 / DPH 50                          | NP 220 / DPH 50 | NP 440 / DPH 50                 | NP 220 / DPH 50 |

Sleep latency was estimated using the Kaplan-Meier method and analyzed using a log-rank test. If a larger proportion of subjects required rescue medication in the DPH only group, two pre-specified sensitivity analyses were performed to try to corroborate the primary analysis.

- Subject exclusion: An analysis excluding subjects who had taken rescue medication before sleep onset.
- Imputation: An analysis on the intent to treat population after imputing values for all subjects who took rescue medication before sleep onset. The imputation used the mean and standard deviation of sleep latency for subjects who did not take rescue medication before sleep onset in the combined groups of comparison. The random seed was 145929879.

For WASO, an ANCOVA model with treatment and center as fixed effects and VAS pain score as the covariate was used to analyze the data. If a larger proportion of subjects required rescue medication in the NP only group, two pre-specified sensitivity analyses were performed. The sensitivity analyses were similar to those for sleep latency except for imputation, the mean and standard deviation of the WASO for subjects who did not take rescue medication (before or

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defined as the first 10 minutes of immobility with no more than one epoch of mobility in ten minutes. WASO was calculated by counting the awake minutes after initiation of sleep onset during the in-bed interval.

after sleep onset) in the combined groups of comparison was used. Also, a different random seed was used (256457239).

Results for sleep latency and WASO are summarized in separate subsections below. I agree with the Dr. Luan's comment that in Study 37,

"NP 440 mg / DPH 50 mg reached statistical significance for both sleep latency and WASO. No other doses [in combination] achieved statistical significance on both sleep latency and WASO."<sup>28</sup>

### Sleep Latency

The median times to sleep onset after investigational drug dosing were similar for NP 440 / DPH 50 and NP 440 (Table 8). The median time was longer for NP 220 / DPH 50 and longest for DPH 50 alone.

Table 8. Study 37 -- sleep latency<sup>29</sup>

| Statistics                       | NP 440 / DPH 50<br>N=203 | NP 220 / DPH 50<br>N=204 | NP 440<br>N=203 | DPH 50<br>N=102 |
|----------------------------------|--------------------------|--------------------------|-----------------|-----------------|
| # subjects in analysis           | 201*                     | 204                      | 202*            | 102             |
| # subjects censored <sup>^</sup> | 5                        | 17                       | 13              | 28              |
| Median time (min)                | 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 were excluded from the efficacy analyses because sleep parameters were not available (actigraph malfunction).

<sup>^</sup>Rescue medication taken before sleep onset and assigned a sleep latency of 600 minutes

Adding an analgesic (NP 440 or NP 220) to DPH 50 significantly shortened sleep latency compared to DPH 50 alone (Table 9, blue rows 1 and 2). Thus, both NP 440 and NP 220 can contribute to the claimed effect of helping one fall asleep. Increasing the analgesic dose from 220 mg to 440 mg in the combination product further shortened sleep latency ( $p=0.096$ , blue row 3), suggesting a dose response.

Although not pre-specified in the set of sequential comparisons (Table 7), the difference in sleep latency between NP 440 / DPH 50 and NP 440 failed to achieve statistical significance (Table 9, yellow row). This result suggests that DPH 50 does not contribute to helping post-surgical dental pain subjects fall asleep (in phase advanced sleep) when the pain is somewhat relieved by an analgesic.

If the analgesic or diphenhydramine were to decrease the effectiveness of either ingredient alone, then one would expect the combination product to have a significantly longer time to sleep onset. The data do not suggest that this is happening.

<sup>28</sup> Biometrics review for NDA 205352 by Jingyu Luan, finalized 12/19/2013, p5; order of sleep latency and WASO switched to be consistent with remainder of review

<sup>29</sup> Adapted from draft DNP clinical review (Table 14) for NDA 205352 by Veneeta Tandon

Table 9: Study 37 -- sleep latency: log-rank test<sup>30</sup>

| Pairwise Comparisons |                 | p-value |
|----------------------|-----------------|---------|
| Drug 1               | Drug 2          |         |
| NP 440 / DPH 50      | DPH 50          | <0.0001 |
| NP 220 / DPH 50      | DPH 50          | 0.0003  |
| NP 440 / DPH 50      | NP 220 / DPH 50 | 0.0096  |
| NP 440 / DPH 50      | NP 440          | 0.4164  |
| NP 220 / DPH 50      | NP 440          | 0.1150  |

Fewer subjects required rescue medication in the NP 440 / DPH 50 arm compared to the NP 440 only arm (Table 10), suggesting that adding DPH 50 to NP 440 may have delayed or reduced the need for rescue pain medication. Increased sleepiness after sleep onset (consistent with DPH contributing to sleep maintenance, see below) is most plausible though other explanations such as synergistic effects of NP and DPH for analgesia cannot be entirely excluded.

That a greater proportion of subjects used rescue medication in the DPH 50 arm compared to the NP 440 / DPH 50 arm and the NP 220 / DPH 50 arm (Table 10) suggests that NP retains its analgesic properties when combined with DPH 50. Since a larger proportion of subjects required rescue medication in the DPH only group (Table 10), the two pre-specified sensitivity analyses were performed.

Table 10. Study 37 -- proportion of subjects taking rescue medication<sup>31</sup>

| Rescue Medication                             | NP 440 / DHP 50<br>N=203 | NP 220 / DHP 50<br>N=204 | NP 440<br>N=203 | DHP 50<br>N=102 |
|-----------------------------------------------|--------------------------|--------------------------|-----------------|-----------------|
| Took rescue medication<br>n (%)               | 43 (21.2)                | 89 (43.6)                | 68 (33.5)       | 78 (76.5)       |
| Took it <u>before</u><br>sleep onset<br>n (%) | 5 (2.5)                  | 17 (8.3)                 | 13 (6.4)        | 28 (27.5)       |
| Took it <u>after</u><br>sleep onset<br>n (%)  | 38 (18.7)                | 72 (35.3)                | 55 (27.1)       | 50 (49.0)       |

The sensitivity analyses excluding subjects who took rescue medication before sleep onset suggest that the difference in sleep latency between NP (440 or 220) / DPH products and DPH 50 lost statistical significance (Table 11, orange cells). The applicant caveats this finding with the large number of subjects excluded from analysis from the DPH alone group. Interestingly, the comparison between NP 440 / DPH 50 and NP 220 / DPH 50 also lost statistical significance when subjects who took rescue medication before sleep onset were excluded (Table 11, blue cell), suggesting the dose response seen in Table 9 may not be very robust. Fewer subjects were

<sup>30</sup> Adapted from draft DNP clinical review (Table 15) for NDA 205352 by Veneeta Tandon

<sup>31</sup> Adapted from clinical study report, Table 14.2.14

excluded from the NP 440 / DPH 50 and NP 220 / DPH 50 groups than from the DPH 50 alone group used in other comparisons in Table 11.

Table 11. Study 37 -- sensitivity analyses for sleep latency<sup>32</sup>

|                                                                  | NP 440 / DPH 50<br>vs<br>DPH 50 | NP 220 / DPH 50<br>vs<br>DPH 50 | NP 440 / DPH 50<br>vs<br>NP 220 / DPH 50 |
|------------------------------------------------------------------|---------------------------------|---------------------------------|------------------------------------------|
| Excluding subjects who took rescue medication before sleep onset | N=196 vs 74<br>p = 0.2397       | N=187 vs 74<br>p = 0.7184       | N=196 vs 187<br>p = 0.2224               |
| Subjects with imputed values*                                    | N=201 vs 102<br>p = 0.0016      | N=204 vs 102<br>p = 0.0491      | N=201 vs 204<br>p = 0.0948               |

\* used the mean and standard deviation of sleep latency for subjects who did not take rescue medication before sleep onset in the combined groups of comparison

### WASO

The LS Mean for WASO was shortest for NP 440 / DPH 50, longer for NP 440, even longer for NP 220 / DPH 50, and longest for DPH 50 (Table 12).

Table 12. Study 37 -- WASO<sup>33</sup>

| Statistics             | NP 440 / DPH 50<br>N=203 | NP 220 / DPH 50<br>N=204 | NP 440<br>N=203 | DPH 50<br>N=102 |
|------------------------|--------------------------|--------------------------|-----------------|-----------------|
| # subjects in analysis | 201*                     | 204                      | 202*            | 102             |
| Mean (SD)              | 142.2 (164.50)           | 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          |
| <b>ANCOVA Model</b>    |                          |                          |                 |                 |
| LS Mean (SE)           | 143.7 (13.17)            | 230.9 (13.08)            | 214.0 (13.13)   | 431.4 (18.49)   |

\*Three subjects were excluded from analyses because sleep parameters were not available (actigraph malfunction).

SD: standard deviation; SE: standard error

The difference in LS Mean WASO time between NP 440 / DPH 50 and NP 440 was statistically significant (Table 13, blue row), suggesting that DPH 50 makes a contribution to the claimed effect of helping one stay asleep. The statistical significance for the comparison with NP 440 disappears when the analgesic dose is lowered to 220 mg in combination with DPH 50 (Table 13, purple row), suggesting that pain relief may also drive sleep maintenance.

The comparison between NP 440 / DPH 50 and NP 220 / DPH 50 is statistically significant, suggesting a dose response (Table 13, white row). However, according to the protocol, this comparison (same as comparison 3 in Table 7 for WASO) is not eligible to be deemed

<sup>32</sup> Adapted from draft DNP clinical review (Table 17) for NDA 205352 by Veneeta Tandon; clinical study report for Study 37, Tables 14.2.2a, b, and c

<sup>33</sup> Adapted from draft DNP clinical review (Table 9) for NDA 205352 by Veneeta Tandon

statistically significant because comparison 2 in Table 7 (NP 220 / DPH 50 vs NP 440) was not statistically significant (Table 13, purple row).

The applicant focused on developing a combination product with NP 440 rather than NP 220, primarily based on the results in the blue, purple, and white rows in Table 13.

Based on the comparisons discussed thus far, pain relief appears to help one stay asleep after sleep onset. Even though the results of the comparisons between the combination product (using NP 440 or NP 220) and DPH 50 (yellow rows in Table 13, which not pre-specified in the set of sequential comparisons (Table 7)) are consistent with this notion, these results are not interpretable due to the large number of subjects in the DPH 50 group who took rescue medication (77%: 28% before and 49% after sleep onset) and the imputation scheme used (see Pivotal Study Limitations subsection below, bullet #4).

Table 13. Study 37 -- WASO: ANCOVA model<sup>34</sup>

| Pairwise Comparisons |                 | LS Mean Difference | 95% CI of LS Mean Difference | p-value  |
|----------------------|-----------------|--------------------|------------------------------|----------|
| Drug 1               | Drug 2          |                    |                              |          |
| NP 440 / DPH 50      | NP 440          | -70.3              | -106.8, -33.7                | 0.0002   |
| NP 220 / DPH 50      | NP 440          | 16.9               | -19.5, 53.3                  | 0.3627   |
| NP 440 / DPH 50      | NP 220 / DPH 50 | -87.1              | -123.6, -50.7                | <0.0001* |
| NP 440 / DPH 50      | DPH 50          | -287.6             | -332.2, -243.1               | <0.0001  |
| NP 220 / DPH 50      | DPH 50          | -200.5             | -245.0, -156.0               | <0.0001  |

LS: least square; CI: confidence interval; \* not eligible to be declared significant because the NP 220 / DPH 50 vs NP 440 comparison was not statistically significant (see Table 7 and associated text)

If the analgesic or diphenhydramine were to decrease the effectiveness of either ingredient alone, then one would expect the combination product to have a significantly longer WASO time. The data do not suggest that this is the case.

Since a larger proportion of subjects required rescue medication in the NP 440 only group compared to the NP 440 / DPH 50 group (Table 10), the two pre-specified sensitivity analyses were performed. Statistical significance was maintained in both sensitivity analyses (Table 14), suggesting that the result for NP 440 / DPH 50 vs NP 440 in the primary analysis was robust.

<sup>34</sup> Adapted from draft DNP clinical review (Table 10) for NDA 205352 by Veneeta Tandon

Table 14. Study 37 -- sensitivity analyses for WASO<sup>35</sup>

|                                               | NP 440 / DPH 50<br>vs<br>NP 440                               |
|-----------------------------------------------|---------------------------------------------------------------|
| Excluding subjects who took rescue medication | N=158 vs 134<br>treatment difference: -30 min<br>p < 0.0001   |
| Subjects with imputed values*                 | N=201 vs 202<br>treatment difference: -19.7 min<br>p < 0.0001 |

\* Used the mean and standard deviation of the WASO for subjects who did not take rescue medication (before or after sleep onset) in the combined groups of comparison

### ***Study 81 – Primary Sleep Endpoints***

The applicant conducted this study to respond to the Agency’s request to evaluate a lower dose of DPH. The objective of this study was to evaluate the efficacy and safety of a lower dose of DPH (25 mg) combined with the selected dose of naproxen sodium (440 mg) based on the results from Study 37.

The design of Study 81 mimicked that of Study 37. Key differences are listed below.

- the treatment groups were different:
  - o NP 440 / DPH 25
  - o NP 440
  - o DPH 50
- the primary efficacy endpoints were:
  - o Sleep latency: NP 440 / DPH 25 vs DPH 50 alone
  - o WASO: NP 440 / DPH 25 vs NP 440 alone
- the protocol for Study 81 specified that both the WASO and sleep latency tests had to be statistically significant in order to claim NP 440 / DPH 25 to be efficacious.

I agree with Dr. Tandon that Study 81 is likely underpowered and therefore no conclusions may be drawn regarding the efficacy of 25 mg DPH in combination with NP 440. Dr. Tandon comments:<sup>36</sup>

“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

<sup>35</sup> Adapted from draft DNP clinical review (Table 12) for NDA 205352 by Veneeta Tandon; clinical study report for Study 37, Tables 14.2.1a, b, and c

<sup>36</sup> Draft DNP clinical review (Table 12) for NDA 205352 by Veneeta Tandon

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."

On this issue, Dr. Luan is in agreement:<sup>37</sup>

"The statistical insignificance of Study 15881 might be partially due to lack of power."

Results for sleep latency and WASO are briefly summarized in separate subsections below.

### Sleep Latency

The median time was shorter for NP 440 / DPH 25 than for DPH 50 (Table 15), although the difference between the treatment groups was not statistically significant (Table 16).

I agree with Dr. Tandon's comments regarding the sleep latency results:<sup>38</sup>

"If analgesic were 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 (27.5 minutes)."

Although it may appear that addition of DPH 25 to NP 440 prolongs the time to initiate sleep compared to NP 440 alone (Table 15), it is noted that in Study 37, addition of DPH 50 to NP 440 did not prolong sleep latency (Table 8, yellow row in Table 9).

Table 15. Study 81 -- sleep latency<sup>39</sup>

| Statistics          | NP 440 / DPH 25<br>N=107 | NP 440<br>N=106 | DPH 50<br>N=54 |
|---------------------|--------------------------|-----------------|----------------|
| # 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) |

<sup>37</sup> Biometrics review for NDA 205352 by Jingyu Luan, finalized 12/19/2013, p35

<sup>38</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p55

<sup>39</sup> Adapted from draft DNP clinical review (Table 34) for NDA 205352 by Veneeta Tandon

Table 16: Study 81 -- sleep latency: log-rank test<sup>40</sup>

| Pairwise Comparison |        | p-value* |
|---------------------|--------|----------|
| Drug 1              | Drug 2 |          |
| NP 440 / DPH 25     | DPH 50 | 0.1677   |

Fewer subjects required rescue medication in the NP 440 / DPH 25 arm compared to the NP 440 only arm (Table 17), suggesting that adding DPH 25 to NP 440 may have delayed or reduced the need for rescue pain medication. Increased sleepiness after sleep onset (consistent with DPH contributing to sleep maintenance, see below) is most plausible though other explanations such as synergistic effects of NP and DPH for analgesia cannot be entirely excluded.

Since a larger proportion of subjects required rescue medication in the DPH only group (Table 17), the two pre-specified sensitivity analyses were performed.

Table 17. Study 81 -- proportion of subjects taking rescue medication<sup>41</sup>

| Rescue Medication                             | NP 440 / DHP 25<br>N=107 | NP 440<br>N=106 | DHP 50<br>N=54 |
|-----------------------------------------------|--------------------------|-----------------|----------------|
| Took rescue medication<br>n (%)               | 24 (22.4)                | 30 (28.3)       | 35 (64.8)      |
| Took it <u>before</u><br>sleep onset<br>n (%) | 4 (3.7)                  | 2 (1.9)         | 5 (9.3)        |
| Took it <u>after</u><br>sleep onset<br>n (%)  | 20 (18.7)                | 28 (26.4)       | 30 (55.6)      |

As expected, the difference between the treatment groups was not statistically significant for the sensitivity analyses (Table 18). Considering subjects who took rescue medication as having not taken rescue medication was a sensitivity analysis requested by FDA,<sup>42</sup> and this analysis was closest to achieving statistical significance.

<sup>40</sup> ibid<sup>41</sup> Adapted from clinical study report, Table 14.2.14<sup>42</sup> February 15, 2012 advice letter

Table 18. Study 81 -- sensitivity analyses for sleep latency<sup>43</sup>

|                                                                                      | NP 440 / DPH 25<br>vs<br>DPH 50 |
|--------------------------------------------------------------------------------------|---------------------------------|
| Excluding subjects who took rescue medication before sleep onset                     | N=103 vs 49<br>p = 0.4605       |
| Subjects with imputed values*                                                        | N=107 vs 54<br>p = 0.5100       |
| Subjects who took rescue medication considered as having not taken rescue medication | N=107 vs 54<br>p = 0.0708       |

\*Random seed 145929879. Used the mean and standard deviation of sleep latency for subjects who did not take rescue medication before sleep onset in the combined groups of comparison.

### WASO

The LS Mean for WASO was shortest for NP 440 / DPH 25, 25 minutes longer for NP 440, and longest for DPH 50 (Table 19).

Table 19. Study 81 -- WASO<sup>44</sup>

| Statistics   | NP 440 / DPH 25<br>N=107 | NP 440<br>N=106 | DPH 50<br>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          |

The difference in LS Mean WASO time between NP 440 / DPH 25 and NP 440 was not statistically significant (Table 20).

<sup>43</sup> Adapted from draft DNP clinical review (Table 35) for NDA 205352 by Veneeta Tandon; clinical study report for Study 81, Tables 14.2.2a, b, and c

<sup>44</sup> Adapted from draft DNP clinical review (Table 30) for NDA 205352 by Veneeta Tandon

Table 20. Study 81 -- WASO: ANCOVA model<sup>45</sup>

| Pairwise Comparisons |        | LS Mean Difference | 95% CI of LS Mean Difference | p-value |
|----------------------|--------|--------------------|------------------------------|---------|
| Drug 1               | Drug 2 |                    |                              |         |
| NP 440 / DPH 25      | NP 440 | -24.83             | -72.38, 22.72                | 0.3047  |

I agree with Dr. Tandon that the lack of a significant treatment difference “may be due to the study being underpowered.” Dr. Tandon also points out that a lower proportion of subjects in the NP 440 / DPH 25 group took rescue medication compared to the NP 440 group (particularly after sleep onset, Table 17), suggesting that “DPH 25 may be contributing towards subjects staying asleep and hence not needing a rescue medication.” However, Dr. Tandon also points out that the percent of patients with severe pain in the NP 440 / DPH 25 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.”

Since a larger proportion of subjects required rescue medication in the NP 440 only group compared to the NP 440 / DPH 25 group (Table 17), sensitivity analyses were performed. As expected, the treatment difference was not statistically significant for either of the two pre-specified sensitivity analysis (Table 21). Considering subjects who took rescue medication as having not taken rescue medication was a sensitivity analysis requested by FDA,<sup>46</sup> and this analysis achieved statistical significance.

Table 21. Study 81 -- sensitivity analyses for WASO<sup>47</sup>

|                                                                                      | NP 440 / DPH 25<br>vs<br>NP 440                                |
|--------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Excluding subjects who took rescue medication                                        | N=83 vs 76<br>treatment difference: -8.82 min<br>p = 0.1914    |
| Subjects with imputed values*                                                        | N=107 vs 106<br>treatment difference: -4.49 min<br>p = 0.4414  |
| Subjects who took rescue medication considered as having not taken rescue medication | N=107 vs 106<br>treatment difference: -12.20 min<br>p = 0.0090 |

\*Random seed 256457239. Used the mean and standard deviation of the WASO for subjects who did not take rescue medication (before or after sleep onset) in the combined groups of comparison.

<sup>45</sup> Adapted from draft DNP clinical review (Table 10) for NDA 205352 by Veneeta Tandon

<sup>46</sup> February 15, 2012 advice letter

<sup>47</sup> Adapted from draft DNP clinical review (Table 32) for NDA 205352 by Veneeta Tandon; clinical study report for Study 81, Tables 14.2.1a, b, and c

**Study 37 and Study 81 -- Primary Sleep Endpoints****NP 440 / DPH 50**

Each active ingredient in NP 440 / DPH 50 contributes to the claimed effect of helping one fall asleep and stay asleep in the post-surgical dental, phase advanced sleep model.

- Sleep latency: The difference between the median times for NP 440 / DPH 50 (25.5 min, shorter) and DPH 50 (41.4 min, longer) was statistically significant<sup>48</sup> ( $p < 0.0001$ , Table 22, purple outline), suggesting that adding NP 440 to DPH 50 provides an advantage over DPH 50 alone in helping post-surgical dental patients (with sleep phase advanced by five hours) fall asleep.
- WASO: The difference between the LS means for NP 440 / DPH 50 and NP 440 (-70.3 min) was statistically significant ( $p = 0.0002$ , Table 23, purple outline), suggesting that adding DPH 50 to NP 440 provides an advantage over NP 440 alone in helping post-surgical dental patients (with sleep phase advanced by five hours) stay asleep.

Table 22. Study 37 and 81 -- sleep latency<sup>49</sup>

|                                                                 | <b>Study 37</b>                                            |                                                     |                                                     | <b>Study 81</b>                             |
|-----------------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|---------------------------------------------|
|                                                                 | NP 440 / DPH 50<br>vs<br>DPH 50                            | NP 220 / DPH 50<br>vs<br>DPH 50                     | NP 440 / DPH 50<br>vs<br>NP 220 / DPH 50            | NP 440 / DPH 25<br>vs<br>DPH 50             |
| Primary                                                         | 25.5 vs 41.4 min*<br><b>p&lt;0.0001**</b><br>N=201 vs 102) | 30.2 vs 41.4 min<br><b>p=0.0003</b><br>N=204 vs 102 | 25.5 vs 30.2 min<br><b>p=0.0096</b><br>N=201 vs 204 | 23.5 vs 27.5 min<br>p=0.1677<br>N=107 vs 54 |
| Sensitivity                                                     |                                                            |                                                     |                                                     |                                             |
| 1. Excluding subjects on rescue                                 | 25.0 vs 22.3 min<br>p=0.2397<br>N=196 vs 74                | 26.5 vs 22.3 min<br>p=0.7184<br>N=187 vs 74         | 25.0 vs 26.5 min<br>p=0.2224<br>N=196 vs 187        | 21.5 vs 24.5 min<br>p=0.4605<br>N=103 vs 49 |
| 2. With imputed values for subjects that took rescue medication | 25.5 vs 33.5 min<br><b>p=0.0016</b><br>N=201 vs 102        | 29.0 vs 33.5 min<br><b>p=0.0491</b><br>N=204 vs 102 | 25.5 vs 28.5 min<br><b>p=0.0948</b><br>N=203 vs 204 | 23.5 vs 26.2 min<br>p=0.5100<br>N=107 vs 54 |

\*Median time

\*\*Kaplan-Meier analysis, log-rank test

<sup>48</sup> Statistical significance was maintained when the five pairwise comparisons were conducted within one analysis model taking all four treatment groups into consideration. See section 3.2.3.1 in biometrics review for NDA 205352 by Jingyu Luan, finalized 12/19/2013.

<sup>49</sup> Adapted from draft DNP clinical review (Table 69) for NDA 205352 by Veneeta Tandon; clinical study report for Study 37, Tables 14.2.2a, b, and c; clinical study report for Study 81, Tables 14.2.2a, b, and c

Table 23. Study 37 and 81 -- WASO<sup>50</sup>

|                                                                 | Study 37                                 |                                      |                                          | Study 81                              |
|-----------------------------------------------------------------|------------------------------------------|--------------------------------------|------------------------------------------|---------------------------------------|
|                                                                 | NP 440 / DPH 50<br>vs<br>NP 440          | NP 220 / DPH 50<br>vs<br>NP 440      | NP 440 / DPH 50<br>vs<br>NP 220 / DPH 50 | NP 440 / DPH 25<br>vs<br>NP 440       |
| Primary                                                         | -70.3 min*<br>p=0.0002**<br>N=203 vs 203 | 16.9 min<br>p=0.3627<br>N=204 vs 203 | -87.2 min<br>p<0.0001^<br>N=203 vs 204   | -24.8 min<br>p=0.3047<br>N=107 vs 106 |
| Sensitivity                                                     |                                          |                                      |                                          |                                       |
| 1. Excluding subjects on rescue                                 | -30.0 min<br>p<0.0001<br>N=158 vs 134    | —                                    | —                                        | -8.8 min<br>p=0.1914<br>N=83 vs 76    |
| 2. With imputed values for subjects that took rescue medication | -19.7 min<br>p<0.0001<br>N=201 vs 202    | —                                    | —                                        | -4.5 min<br>p=0.4414<br>N=107 vs 106  |

\*LS Mean treatment difference ; \*\*ANCOVA model ; ^as specified in the protocol, this comparison is ineligible to be declared significant because the comparison between NP 220 / DPH 50 and NP 440 was not statistically significant. See Table 7 and associated text.

### NP 220 / DPH 50

A lower dose of analgesic (220 mg) in combination with DPH 50 shortened the time to sleep onset compared to DPH 50 alone (p=0.0003, Table 22, orange outline). However, DPH 50 combined with NP 220 does not shorten WASO over NP 440 alone (p=0.3627, Table 23, orange shading). Since the addition of the same dose of DPH (50 mg) to the higher dose of analgesic (NP 440) improves maintenance of the sleeping state over NP 440 alone (p=0.0002, Table 23, purple outline), I agree with Dr. Tandon that pain relief appears to drive “both sleep onset and sleep maintenance in a study population with sleeplessness associated with dental pain following tooth extraction.”<sup>51</sup> Dr. Tandon also points out that more subjects in the NP 220 / DPH 50 group took rescue medication than in the NP 440 group (Table 10), and that “the imputation method in subjects taking rescue medication could have driven the efficacy results.” See Pivotal Study Limitations subsection below, bullet #4.

Increasing the analgesic dose from 220 mg to 440 mg in combination with DPH 50 shortened sleep latency (compared to DPH 50 alone, p=0.0096, Table 22, black outline) and appeared to shorten WASO time (compared to NP 440 alone, p<0.0001, Table 23, gray column), suggesting a dose response. However, the NP 440 / DPH 50 vs NP 220 / DPH 50 comparison is not eligible to be declared significant (see Table 7 and associated text).

<sup>50</sup> Adapted from draft DNP clinical review (Table 68) for NDA 205352 by Veneeta Tandon; clinical study report for Study 37, Tables 14.2.1a, b, and c; clinical study report for Study 81, Tables 14.2.1a, b, and c

<sup>51</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p87

### NP 440 / DPH 25

A lower dose of DPH (25 mg) in combination with NP 440 failed to shorten both (a) the time to sleep onset compared to DPH 50 alone ( $p=0.1677$ , Table 22, right column) and (b) WASO time compared to NP 440 alone ( $p=0.3047$ , Table 23, right column). However, no conclusions may be drawn based on these results because Study 81 was underpowered (see turquoise shading in Table 22 and Table 23; see also quote from Dr. Tandon in the Study 81 – Primary Sleep Endpoints section above). Inclusion of a NP 440 / DPH 50 arm would have helped to distinguish between a failed study and a negative study.

### ***Study 37 and Study 81 – Secondary Pain Endpoints***

There were no primary endpoints related to pain. DAAAP was consulted to review and evaluate the pain-related efficacy assessments in the studies provided.

Although the pain assessments in the pivotal studies were non-traditional,<sup>52</sup>

“Traditional pain assessments such as repeated assessments of pain intensity and pain relief over the treatment period were not used in the efficacy studies because the target population was subjects with sleeplessness associated with pain, and the primary purpose of the studies was to assess the impact of the treatment on sleep. It would have been inappropriate to wake subjects to assess their pain levels. Instead, the subjects’ pain levels were assessed after waking using validated categorical scales.”

Results from Study 37 for pain intensity and pain relief will be briefly summarized here. Please see review by Dr. Fields for details and additional pain endpoint analyses.

For both pain intensity and pain relief, the applicant provided p-values for various comparisons). Dr. Fields comments that there was no correction of the secondary endpoint analyses for multiple endpoints, so the p-values are merely descriptive. These p-values will not be presented here.

### ***Pain Intensity***

In both Study 37 and Study 81, pain intensity was rated by the subject upon awakening in the morning or when the subject requested rescue medication, whichever came first. Subjects were asked to complete the sentence “my pain at this time is” by selecting a number from 0 (no pain) to 3 (severe pain). If a subject took rescue medication, the worst score prior to rescue medication administration (baseline included) was carried forward and used for the analysis.

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<sup>52</sup> DAAAP clinical review for NDA 205352 by Ellen Fields, finalized 10/18/2013, p4

In Study 37, NP 440 / DPH 50, NP 220 / DPH 50 and NP 440 demonstrated a mean reduction in pain intensity from baseline of ~1 point (Table 24).

Table 24. Study 37 – pain intensity<sup>53</sup>

| Visit                | Statistics | NP 440 / DPH 50<br>N=203 | NP 220 / DPH 50<br>N=204 | NP 440<br>N=203 | DPH 50<br>N=102 |
|----------------------|------------|--------------------------|--------------------------|-----------------|-----------------|
| Baseline             | Mean (SD)  | 2.3 (0.45)               | 2.3 (0.48)               | 2.3 (0.46)      | 2.3 (0.45)      |
|                      | Median     | 2.0                      | 2.0                      | 2.0             | 2.0             |
|                      | Range      | 2-3                      | 2-3                      | 2-3             | 2-3             |
| Post-baseline        | Mean (SD)  | 1.1 (0.96)               | 1.6 (1.05)               | 1.4 (1.02)      | 2.4 (0.85)      |
|                      | Median     | 1.0                      | 1.0                      | 1.0             | 3.0             |
|                      | Range      | 0-3                      | 0-3                      | 0-3             | 0-3             |
| Change from baseline | Mean (SD)  | -1.2 (1.01)              | -0.7 (1.05)              | -0.9 (0.99)     | 0.1 (0.82)      |
|                      | Median     | -1.0                     | -1.0                     | -1.0            | 0.0             |
|                      | Range      | -3 to 1                  | -3 to 1                  | -3 to 1         | -2 to 1         |

0=no pain; 1=mild pain; 2=moderate pain; 3=severe pain

In Study 81, NP 440 / DPH 25 and NP 440 demonstrated a mean reduction in pain intensity from baseline of ~ 1 point (Table 25).

Table 25. Study 81 – pain intensity<sup>54</sup>

| Visit                | Statistics | NP 440 / DPH 25<br>N=107 | NP 440<br>N=106 | DPH 50<br>N=54 |
|----------------------|------------|--------------------------|-----------------|----------------|
| Baseline             | Mean (SD)  | 2.4 (0.48)               | 2.4 (0.49)      | 2.5 (0.50)     |
|                      | Median     | 2.0                      | 2.0             | 2.0            |
|                      | Range      | 2-3                      | 2-3             | 2-3            |
| Post-baseline        | Mean (SD)  | 1.2 (0.92)               | 1.3 (1.02)      | 2.0 (0.89)     |
|                      | Median     | 1.0                      | 1.0             | 2.0            |
|                      | Range      | 0-3                      | 0-3             | 0-3            |
| Change from baseline | Mean (SD)  | -1.2 (0.87)              | -1.1 (0.90)     | -0.5 (0.79)    |
|                      | Median     | -1.0                     | -1.0            | 0.0            |
|                      | Range      | -3 to 0                  | -3 to 0         | -2 to 0        |

0=no pain; 1=mild pain; 2=moderate pain; 3=severe pain

### Pain Relief

In both Study 37 and Study 81, pain relief was rated by the subject upon awakening in the morning. Subjects were asked to complete the sentence “overall, the relief from my starting

<sup>53</sup> Adapted from clinical study report for Study 37, Table 18

<sup>54</sup> Adapted from clinical study report for Study 81, Table 18

pain is” by selecting a number from 0 (no relief) to 4 (complete relief). If a subject took rescue medication, a score of “0” was assigned.

In Study 37, mean and median responses suggest a trend of relief by NP 440 and NP 440 / DPH 50 greater than that for NP 220 / DPH 50, with DPH 50 providing the least relief (Table 26).

Table 26. Study 37 – pain relief<sup>55</sup>

| Statistics | NP 440 / DPH 50<br>N=203 | NP 220 / DPH 50<br>N=204 | NP 440<br>N=203 | DPH 50<br>N=102 |
|------------|--------------------------|--------------------------|-----------------|-----------------|
| Mean (SD)  | 2.4 (1.47)               | 1.7 (1.58)               | 2.0 (1.58)      | 0.6 (1.14)      |
| Median     | 3.0                      | 2.0                      | 3.0             | 0.0             |
| Range      | 0-4                      | 0-4                      | 0-4             | 0-4             |

0=no relief; 1=a little relief; 2=some relief; 3=a lot of relief; 4 complete relief

In Study 81, mean and median suggest NP 440 / DPH 25 and NP 440 provide greater relief than DPH 50 (Table 27).

Table 27. Study 81 – pain relief<sup>56</sup>

| Statistics | NP 440 / DPH 25<br>N=107 | NP 440<br>N=106 | DPH 50<br>N=54 |
|------------|--------------------------|-----------------|----------------|
| Mean (SD)  | 2.3 (1.44)               | 2.2 (1.52)      | 0.9 (1.29)     |
| Median     | 3.0                      | 3.0             | 0.0            |
| Range      | 0-4                      | 0-4             | 0-4            |

0=no relief; 1=a little relief; 2=some relief; 3=a lot of relief; 4 complete relief

### Pain Efficacy Conclusions

Dr. Fields concludes that:<sup>57</sup>

“Secondary assessments for pain included categorical scales for pain intensity and pain relief, a patient global impression of the combination as a pain reliever, and rescue use (both amount and proportion of subjects requiring rescue).

The secondary analgesia-related endpoints consistently demonstrated that naproxen behaved as an analgesic in combination with DPH, and a dose response was demonstrated between naproxen 440 mg and naproxen 220 mg. DPH alone did not appear to have analgesic properties.

The analgesic-related variables and timing of assessments were acceptable.

<sup>55</sup> Adapted from clinical study report for Study 37, Table 21

<sup>56</sup> Adapted from clinical study report for Study 81, Table 21

<sup>57</sup> DAAAP clinical review for NDA 205352 by Ellen Fields, finalized 10/18/2013, p2, 26

The results were consistent among the three studies [two pivotal, one pilot] and showed that naproxen in combination with DPH acts as an analgesic, and in general, a dose response in terms of analgesia was shown for naproxen 440 mg compared to naproxen 220 mg when administered in combination with DPH. In all studies, naproxen at doses of 440 mg and 220 mg, in combination with DPH (25 mg or 50 mg), demonstrated numerically similar or slightly superior analgesia compared to naproxen alone at the same doses. DPH alone demonstrated little to no analgesic efficacy.”

I agree with Dr. Fields’s assessment and add that as with sleep latency and WASO, the imbalanced use of rescue medication between groups coupled with the imputation scheme may have increased the apparent difference seen between NP 220 / DPH 50 and NP 440 and the apparent difference seen between NP 440 / DPH 50 and NP 220 / DPH 50 for pain endpoints.

### ***Pivotal Study Limitations***

Dr. Tandon’s review points out several design limitations in these pivotal studies. The key design limitations are summarized below.

- Imputation scheme that biases in favor of NP 440 / DPH 50, coupled with differential use of rescue medication for pain among groups and differential pain severity among groups:<sup>58</sup>

The use of rescue medication for pain likely affected the calculations of WASO and sleep latency in light of the imputation scheme used. For the primary analyses in Study 37 and 81, unrealistically long WASOs and sleep latencies were assigned to subjects taking rescue medication. For both studies, subjects who took rescue medication before sleep onset were assigned a WASO of 600 minutes (duration of ten-hour in-bed time). 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 sleep latency, subjects who took rescue medication before sleep onset were assigned a latency of 600 minutes; sleep latency was not affected if rescue medication was taken after sleep onset.

The imputation method used biases in favor of finding superiority for sleep in study arm(s) administered a test drug that primarily acts to relieve pain (NP 440 and NP 440 / DPH 50 in Study 37) due to a higher rate of rescue treatment in the DPH arm.

In Study 37, a high percentage of subjects used rescue medication (Table 10). The high rate of rescue medication use, more so in certain groups than others, may have driven the results given the imputation scheme described above. This notion is somewhat

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<sup>58</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p9, 36, 46, 87, 89

supported by a protocol-specified sensitivity analysis for sleep latency: when subjects who took rescue medication before sleep onset were excluded, the statistically significant difference in sleep latency between NP 440 / DPH 50 and DPH 50 disappeared (Table 11,  $p = 0.2397$ ). A caveat which the sponsor points out is that the number of subjects who were excluded from analysis (took rescue medications before sleep onset) was much higher in the DPH 50 alone group.

A second sensitivity analysis for sleep latency imputing values for all subjects who took rescue medication<sup>59</sup> before sleep onset retained statistical significance for the NP 440 / DPH 50 vs DPH 50 comparison (Table 11,  $p=0.0016$ ). For WASO, sensitivity analyses for the NP 440 / DPH 50 comparison with NP 440 maintained statistical significance (Table 14,  $p \leq 0.0001$  when either method [exclusion or imputation<sup>60</sup>] was used).

In Study 37, more subjects in the NP 220 / DPH 50 group took rescue medication than in the NP 440 group (Table 10). That an imbalance (in the long WASOs assigned to subjects who took rescue medication) between the two groups drove the lack of significance in WASO for the NP 220 / DPH 50 vs NP 440 comparison (Table 13) is plausible. Likewise, the imbalance in the use of rescue medication between the NP 440 / DPH 50 and the NP 220 / DPH 50 groups, as well as the subsequent assignment of long WASO values to more subjects in the NP 220 / DPH 50 group may have driven the appearance of a dose response.

The need for rescue medication depended on the pain experienced, resulting in the DPH alone group having the highest percentage of subjects taking rescue medication (Table 10). An imbalance in pain severity among treatment groups may have contributed to an imbalance in the percentage of subjects taking rescue medication in each group.

In Study 37, there were slightly more subjects with severe pain in the NP 220 / DPH 50 and NP 440 groups (34.3% and 31.0%, respectively) compared to the NP 440 / DPH 50 group (28.1%). WASO for NP 440 / DPH 50 was shorter than that for NP 440 alone whereas WASO for NP 220 / DPH 50 was not shorter than that for NP 440 alone; WASO for NP 440 / DPH 50 was shorter than that for NP 220 / DPH 50 (Table 12, Table 13). Given that more subjects with severe pain took rescue medication, the difference in pain severity between treatment groups may have contributed to the WASO superiority of NP 440 / DPH 50 over other treatments due to the imputation scheme used.

Dr. Tandon questions whether the superiority of NP 440 / DPH 50 over NP 440 for WASO is due to the contribution of DPH 50 towards sleep maintenance or to the difference in pain severity among treatment groups (the group with the lowest number and proportion of subjects taking rescue medication was the NP 440 / DPH 50 group

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<sup>59</sup> Used the mean and standard deviation of sleep latency for subjects who did not take rescue medication before sleep onset in the combined groups of comparison.

<sup>60</sup> Used the mean and standard deviation of the WASO for subjects who did not take rescue medication (before or after sleep onset) in the combined groups of comparison.

[Table 10]). She follows this discussion with an acknowledgement that it may not be unreasonable to conclude that DPH 50 helps with sleep maintenance in Study 37. I agree.

While imputation confounds the WASO results, the difference in the use of rescue medication between the NP 440 / DPH 50 and NP 440 arms would seemingly be due to an effect of DPH. While not necessarily an effect on sleep, such a conclusion would not be unreasonable. Less extreme values could be chosen for imputation. However, the study results would still be largely determined by imputed rather than actual, observed data.

- Underpowered pivotal study:<sup>61</sup> Study 81 was underpowered. Therefore, no conclusions may be drawn regarding the efficacy of 25 mg DPH in combination with NP 440 even though there was lack of statistical superiority of NP 440 / DPH 25 over NP 440 alone or DPH 50 alone.
- Lack of a positive control in a pivotal study:<sup>62</sup> Study 81 lacked a NP 440 / DPH 50 arm which may have helped with differentiating a failed study from a negative study.
- Pain / sleep model:<sup>63</sup> The pivotal studies do not test the proposed product in a population of patients who would be expected to take the combination product. Rather, the pivotal studies used the dental pain with phase advanced sleep model. Post-surgical pain after molar extraction is likely more severe than the “minor aches and pains” that the target population may have. Phase advanced sleep was used in the pivotal studies: subjects were asked to go to sleep five hours earlier than their normal bedtime, between 16:00 h and 18:30 h. Although phase advanced sleep may have disrupted “normal” sleep patterns as intended, Dr. Tandon’s review (p 88) describes several limitations of the phase advanced model. Another aspect of the model used in the pivotal studies is that subjects were required to remain in bed for ten hours -- a duration that is not realistic for typical OTC users of such products.

Considering the above, results from studies using the dental pain with phase advanced sleep model may not be generalizable to the population which may take Aleve PM (those with minor muscle aches, headache, joint pain, etc who may go to bed at their normal time for a duration less than ten hours), if marketed. The submitted studies do not provide evidence that NP improves sleep in the context of pain typically encountered in the OTC setting: post-surgical pain interferes with sleep and NP likely improves sleep secondary to more severe pain such as that following surgery, but not necessarily for “minor aches and pains” proposed in the label. It is noted, however, that

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<sup>61</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p9, 52, 60, 93

<sup>62</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p87

<sup>63</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p87-88

the dental pain with phase advance sleep model was used in studies to support approval of other analgesic / nighttime sleep aids (e.g., Advil PM and Tylenol PM).

Additional limitations regarding the pivotal studies from Dr. Tandon's review include:

- Ages of enrolled subjects likely not representative of anticipated users:<sup>64</sup> elderly subjects were not enrolled in the pivotal trials. No subjects younger than 16 years were enrolled in Study 37, the only pivotal study administering the proposed drug (NP 440 / DPH 50); the protocol allowed subjects 12 years and older and the proposed label provides directions for children 12 years and over. The age distribution of the enrolled subjects is most likely not representative of the distribution of eventual users of Aleve PM.
- Uncertain actigraph sensitivity:<sup>65</sup> Whether the actigraph is capable of distinguishing between inactivity and sleep in post-surgical, sleep phase advanced subjects is not clear.
- Inability to validate information on case report forms:<sup>66</sup> A computer algorithm was used to calculate sleep parameters from the actigraphs, and the sleep data was transferred electronically to a spreadsheet. The applicant returned the actigraphs used for the studies to the actigraph owner after the study. Thus, it was not possible to validate the sleep / wake information in case report forms.

## ***Dose Selection***

### ***Applicant's Dose Selection Method***<sup>67</sup>

The applicant maintains that NP 440 / DPH 50 is the only dose demonstrated to be safe and effective.

#### ***Selection of NP 440 as the Appropriate Analgesic Dose***

The applicant's perspective is that Study 37 "established that the dose of naproxen sodium 440 mg/DPH 50mg combination statistically significantly improved sleep duration and onset (measured by WASO and sleep latency) compared to the single ingredients while the safety profile remained similar. Naproxen sodium 220 mg/DPH 50 gm failed to improve WASO compared to naproxen 440 mg, and therefore, did not meet the combination rule."

#### ***Selection of DPH 50 as the Appropriate Antihistamine Dose***

The applicant's perspective is that Study 81 "failed to meet both primary efficacy endpoints of WASO and sleep latency for naproxen sodium 440 mg/DPH 25 mg combination and confirmed

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<sup>64</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p88, Table 7, Table 28

<sup>65</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p88

<sup>66</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p14, 33

<sup>67</sup> Module 2.7.3, section 4 in NDA 205352, Supporting Document 1.

that the lower dose of DPH 25 mg in combination with naproxen sodium did not provide any additional benefits over the single ingredients alone.”

#### Support for the NP 440 / DPH 50 Dose from a Safety Perspective

The applicant’s perspective is that Study 37 did not demonstrate increased safety risk with NP 440 / DPH 50 compared to NP 220 / DPH 50 or the single ingredients alone. The applicant also invokes the results of a multiple dose safety study (Study 15560), claiming that NP 440 / DPH 50 was “well tolerated compared to placebo when used for 10 consecutive days. There was no increased rate of adverse event seen in the elderly compared to the younger population.”

#### Critique of the Applicant’s Dose Selection Method

Minutes from the pre-IND meeting from February 10, 2009 state that FDA informed the applicant that “a clinical trial would have to demonstrate the superiority of the proposed combination over its individual components for the sleep latency and sleep duration endpoints...each drug would have to show a contribution to either one or both of the primary endpoints (sleep latency, and sleep duration).” The supplied data do not convincingly show that a combination that includes a lower dose of NP or a lower dose of DPH than in NP 440 / DPH 50 would not meet the criterion set forth in 2009.

According to the ICH E4 Guidance on dose response studies, “the highest tolerated dose or the dose with the largest effect... will not always be the optimal dose.”

#### Selection of NP 440 as the Appropriate Analgesic Dose

In discussions with the applicant during product development, FDA had recommended that the applicant evaluate the efficacy of NP 220 / DPH 25 in addition to the combinations already being evaluated (see Regulatory History above). The applicant’s rationale for not evaluating NP 220 / DPH 25 for efficacy was as follows:<sup>68</sup>

Because NP 220 / DPH 50 “failed to show a significant difference compared with naproxen sodium 440 mg alone for the primary efficacy endpoint of WASO in the first efficacy study (Study 14837), it was expected that decreasing the dose of DPH by 50% to 25 mg in the combination product would have minimal, if any, contribution to the overall efficacy and was not likely to meet the criteria for the combination rule (i.e., significantly better than naproxen sodium 440 mg alone).” The applicant concluded that NP 220 / DPH 25 was not a viable candidate for further development.

On the face of it, the applicant’s rationale appears reasonable. However, as described above, use of an imputation method which biases in favor of NP440 / DPH 50 somewhat confounds the results of Study 37: a greater proportion of subjects in the NP 220 / DPH 50 group took rescue medication than in the NP 440 and the NP 440 / DPH 50 groups (Table 10), so an imbalance in

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<sup>68</sup> Module 2.5, section 1.4 in NDA 205352, Supporting Document 1

the assignment of long WASO times between groups may have driven the apparent lack of significance for the NP 220 / DPH 50 vs NP 440 comparison and the apparent dose response. Thus, the applicant's rationale for selecting NP 440 rather than NP 220 as the appropriate analgesic dose is not convincing.

#### Selection of DPH 50 as the Appropriate Antihistamine Dose

Even if the applicant were to show that NP 220 / DPH 25 does not meet efficacy standards, the possibility that NP 440 / DPH 25 has a level of efficacy such that its risk-benefit profile would be comparable to or be better than that for NP 440 / DPH 50 has not been excluded. Study 81 was designed without a NP 440 / DPH 50 arm and underpowered. Thus, the apparent statistical insignificance for the primary endpoints does not allow one to conclude that NP 440 / DPH 25 lacks efficacy regarding sleep.

Regarding pain, I agree with the applicant that in Study 37, NP 440 / DPH 50 "had the lowest proportion of patients taking rescue medication compared with the other treatment groups." Although cross-study comparisons have limitations, it is interesting to note that similar proportions of subjects took rescue medication in the NP 440 / DPH 25 group (22.4%) in Study 81 and the NP 440 / DPH 50 group (21.2%) in Study 37.

The sponsor maintains that NP 440 / DPH 50 "consistently surpassed the analgesia seen with naproxen sodium 440 alone," demonstrating "a synergistic effect on analgesia when combining naproxen sodium and DPH."<sup>69</sup> In making this statement, the applicant takes into account the pilot efficacy study together with the pivotal studies (see review by Dr. Fields for pain-related results in the pilot study). However, with only one pivotal study for which multiple comparisons were not taken into account in the analysis of secondary pain endpoints, it would be more convincing to demonstrate the synergistic effect of combining NP 440 with DPH 50 on analgesia if the results were replicated in another pivotal study. Assuming the claimed synergistic effect between NP 440 and DPH 50 exists, Study 81 data are not convincing regarding the absence of synergy between NP 440 and DPH 25 for analgesia: an adequately powered study comparing NP 440 / DPH 25 and NP 440 / DPH 50 would be needed to evaluate whether a synergistic effect between DPH 25 and NP 440 exists for analgesia. While the applicant's proposal regarding synergy cannot be entirely excluded, a more plausible explanation is that DPH increased sleepiness after sleep onset (consistent with the effect of DPH on sleep maintenance), reducing the need to request rescue pain medication.

## 8. Safety

Regarding safety, the submission included clinical trial data, post-marketing data, information from various safety databases, and literature.

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<sup>69</sup> Module 2.5 in NDA 205352, Supporting Document 1, p42

OSE was consulted to (a) review post-marketing databases and published literature for an association between accidents, abuse and misuse with OTC DPH, and (b) analyze drug utilization patterns of oral OTC DPH-containing products from 2007 to 2012.

Summary information for clinical trials, from various safety-related databases, and the OSE review will be presented first, followed by a discussion regarding next-day effects in a separate subsection.

### ***Clinical Trials***

Clinical trial data related to safety were reviewed by Dr. Tandon (DNP) and Dr. Yang (Clinical Pharmacology). Please see their reviews for details as only safety highlights are presented below.

Of the 1556 subjects (including placebo subjects) in the clinical trials conducted by the sponsor in support of this application, 477 subjects were administered NP 440 / DPH 50; 217 subjects were administered NP 440 / DPH 50 for ten days. Regarding clinical trial data, I agree with the following summary comments by Dr. Tandon:<sup>70</sup>

- “There was no evidence that the combination, NP 440 / DPH 50, was associated with a higher incidence of adverse effects compared to NP 440 or DPH 50 alone.
- The safety of NP 440 / DPH 25 was not examined in a multiple dose study.”

In the single dose study comparing NP 440 / DPH 25 with NP 440 and DPH 50 (Study 81), Dr. Tandon’s safety conclusion was that “There were no remarkable differences in treatment groups.”<sup>71</sup>

The most commonly reported adverse events in the single dose efficacy studies administering investigational drug just before going to bed (Study 37, 81, and 15560) were nausea, headache, dizziness, and vomiting. Somnolence was the most commonly reported adverse event in the bioavailability study (Study 16135) which dosed subjects at approximately 8am. The applicant postulates that daytime administration of the investigational product rather than dosing just before going to bed likely explains the somnolence reported since somnolence typically began during the one-to-three-hour post-dose period which overlapped with the median  $t_{max}$  for DPH (Table 4).

### ***Study 15560 – Multi-dose Ten-day Safety and Tolerability Trial of NP 440 / DPH 50***

The applicant conducted a multi-dose ten-day trial to evaluate the safety and tolerability of NP 440 / DPH 50 compared to placebo in a population representative of OTC users of analgesic /

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<sup>70</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p96

<sup>71</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p61

nighttime sleep-aid combination products. Healthy adults age twelve and above with a history of occasional sleeplessness associated with minor aches and pains were enrolled. As requested by FDA, approximately 25% of subjects were > 65 years of age. The 326 subjects were randomized to NP 440 / DPH 50 (n=217) or placebo (n=109).

Investigational drugs were taken orally with a full glass of water approximately thirty minutes prior to bedtime for ten consecutive days. Subjects recorded adverse events and concomitant medications in a diary.

The frequency and severity of adverse events were consistent with known effects of NP 440 and DPH 50. Dr. Tandon points out that “No age-related effect on the incidence of most TEAEs<sup>72</sup> was noted in subjects treated with naproxen sodium 440 mg / DPN 50 mg when comparing subjects  $\geq$  60 years of age with subjects 12 to 59 years of age (38.5% vs. 40.1%). Only dizziness was higher in subjects  $\geq$  60 years of age (7.7%), compared to placebo (2.8%).”<sup>73</sup>

Regarding dizziness, it is noted that of the 78 spontaneously reported non-fatal serious reports in the applicant’s post-marketing pharmacovigilance database, dizziness was the most frequently reported preferred term (n=10).

### ***Databases for Post-market Safety, Emergency Departments, and Poison Control Centers***

The DNCE clinical reviewer (Dr. Hu) and OSE reviewed safety information from various sources other than clinical trials, including post-market adverse event, emergency department drug abuse, and poison control databases. Please refer to her review for details. I agree with Dr. Hu’s conclusions:<sup>74</sup>

“The safety review also re-affirmed known risks of NSAIDs including naproxen” and  
“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.”

### ***OSE’s Conclusions Regarding DPH***

OSE came to a similar conclusion as Dr. Hu regarding DPH-containing products:<sup>75</sup>

“DPH-containing products are associated with accidents, misuse/abuse, suicide attempts, and unintentional overdoses; however, the frequencies of these

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<sup>72</sup> Treatment emergent adverse events

<sup>73</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p83

<sup>74</sup> DNCE clinical review for NDA 205352 by Linda Hu, finalized 12/16/2013, p6

<sup>75</sup> OSE review for NDA 205352, finalized 10/29/2013, p3

events are relatively modest given its wide OTC utilization. There is potential for abuse/misuse and suicide attempts with DPH, but the data suggest a lower risk of these events compared to drugs with a known high potential for abuse/misuse (e.g., hydrocodone-combination products). Furthermore, the data do not show that the risk is disproportionate, given its widespread availability.”

Accidents will be discussed in greater detail in the next section.

### ***Next-day Effects of DPH***

Certain drugs that treat insomnia have posed a risk for morning driving impairment. For zolpidem, this degree of risk was dependent on several factors including formulation, dose, and gender.<sup>76</sup> Analyses of relationships among drug dose, blood levels, and driving impairment informed regulatory decisions.

For a drug to be taken at bedtime such as Aleve PM, residual effects the next day (around eight hours after dosing) could affect one’s ability to drive a vehicle or operate heavy machinery. This subsection will focus on next-day effects of DPH.

Safety concerns regarding DPH for sleep and other indications have been raised.<sup>77</sup> For example, the NIH consensus statement on insomnia drugs concluded that there were “significant concerns” about the risks antihistamines.<sup>78</sup> The pharmacology text by Goodman and Gilman comments, “with an elimination half-life of about 9 hours, the nighttime use of diphenhydramine can be associated with prominent residual daytime sleepiness.”<sup>79</sup> Sleepiness and impaired psychomotor performance have been documented more than eight hours after administration of DPH 50.<sup>80</sup>

Highlights from published articles, post-marketing adverse event analyses, and clinical trials relevant to next-day effects of DPH are described below.

### **Literature**

See Dr. Hu’s review for descriptions of select literature articles describing effects of DPH after day-time dosing (p58) and also next-day effects after nighttime dosing (p61).

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<sup>76</sup> Farkas R.H. et al. (2013) Zolpidem and Driving Impairment – Identifying Persons at Risk. *NEJM* **369**:689-691.

<sup>77</sup> DNP Clinical Team Leader review for Tylenol PM by Ronald Farkas, 2011, p20

<sup>78</sup> <http://consensus.nih.gov/2005/insomniastatement.htm>, accessed December 29, 2013

<sup>79</sup> Goodman and Gilman (2008). Manual of Pharmacology and Therapeutics, p275.

<sup>80</sup> Gengo F.M. et al. (1990) Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. *Ann Allergy* **64**:520-526.

Katayose Y. et al. (2012) Carryover effect on next-day sleepiness and psychomotor performance of nighttime administered antihistaminic drugs: a randomized controlled trial. *Hum. Psychopharmacol Clin Exp* **27**: 428-436.

The applicant comments that published studies on the effect of DPH following daytime dosing “are not representative of the psychomotor performance effects on driving that might be seen the day after nighttime dosing of DPH.”<sup>81</sup> The applicant found the literature on DPH effects on psychomotor performance the day after nighttime dosing of DPH to be limited.

Based on an analysis of the literature, the applicant’s perspective is that nighttime dosing of DPH 50 may result in residual drowsiness the following morning, but not mental impairment. One recent article,<sup>82</sup> however, demonstrated that DPH 50 administered at 11:45pm resulted in sleepiness (subjective and objective assessment) and psychomotor performance decline (n-back, simple reaction time, choice reaction time, and go/no go tests) beyond nine hours after dosing. Reduced mental performance (simulated driving reaction time) more than eight hours following daytime (8am) administration of DPH 50.<sup>83</sup>

Finally, a study performed to determine the extent of drug use in pilots who died in aviation accidents from 2004 to 2008 found that DPH was the most commonly found drug in pilots who died in an aviation accident.<sup>84</sup>

### Postmarketing Adverse Event Analysis Focused on Next-day Effects

To address the Agency’s request to conduct an analysis of DPH postmarketing data focusing on events suggesting next-day functional impairment such as motor vehicle accidents, falls, or hypersomnolence, the applicant analyzed adverse event reporting rates in FDA’s Adverse Event Reporting System (FAERS) for such cases using DPH as a sleep aid from January 1, 2004 to December 31, 2011.<sup>85</sup> The adverse events of interest were those in the Medical Dictionary for Regulatory Activities Accidents and Injuries Standard Medical Query (AI SMQ).

Of the 5644 total reports for DPH,

- 887 cases: DPH was used as a sleep aid
- 4757 cases: DPH was not used as a sleep aid
- 54 cases: DPH was used as a sleep aid and at least 1 adverse event in the AI SMQ was reported (SA group)
- 248 cases: DPH was not used as a sleep aid but at least 1 adverse event in the AI SMQ was reported (NSA group)

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<sup>81</sup> Module 2.7.4, section 5.8 in NDA 205352, Supporting Document 1

<sup>82</sup> Katayose, Y. et al. (2012) Carryover effect on next-day sleepiness and psychomotor performance of nighttime administered antihistaminic drugs: a randomized controlled trial. *Hum. Psychopharmacol Clin Exp* **27**: 428-436.

<sup>83</sup> Gengo F. et al. (1990) Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. *Ann Allergy* **64**: 520-526.

<sup>84</sup> Canfield D.V. et al. (2012) Drugs and alcohol found in civil aviation accident pilot fatalities from 2004 – 2008. *Aviat Space Environ Med* **83**:764-770.

<sup>85</sup> Module 5.3.6.8 in NDA 205352, Supporting Document 1

Relative reporting rates were calculated as the ratio of the number of cases with an adverse event in the AI SMQ over the total number of cases using DPH as a sleep aid (887) or not using DPH as a sleep aid (4757).

The applicant reports that falls, head injury, and laceration were the only adverse events in the AI SMQ with absolute numbers of events that made the ratios plausible and “notably” increased relative reporting rates. According to the applicant, “the ratio of road traffic accidents was *not* substantially increased.”

Table 28. Relative reporting rates for certain adverse events in AI SMQ

| Adverse Event in AI SMQ | # events (SA group) | # events (NSA group) | Relative reporting rate |
|-------------------------|---------------------|----------------------|-------------------------|
| Falls                   | 32                  | 56                   | 3.06*                   |
| Head injury             | 6                   | 5                    | 6.44                    |
| Laceration              | 5                   | 12                   | 2.23                    |
| Road traffic accidents  | 6                   | 25                   | 1.29                    |

\*(32/887) / (56/4757) = 3.06

OSE’s FAERS analysis of accidents revealed 295 reports, of which 37 met the case definition of accident<sup>86</sup> after duplicate reports were accounted for.<sup>87</sup> Of the 23 accident cases reporting use of a single ingredient DPH product, ~1/4 (n=6) reported using the DPH product as a sleep aid and more than ½ (n=17) reported using labeled doses (between 25 to 50 mg DPH HCl, 38-76 mg DPH citrate) once daily prior to the accident or injury.

Of the 37 accident cases, fifteen reported injuries ranging from non-serious (e.g., “sore ribs and nose”) to serious (e.g., bone fractures, head injuries, ruptured vertebrae). There were two accident cases resulting in death. One had a blood DPH level of 73 ng/mL (therapeutic range not reported) and the other had a blood DPH level of 637 ng/mL (therapeutic range 30-300 ng/mL). See p14 of the OSE review for details.

OSE also performed data mining for accidents. None of the preferred terms in the “Accidents” query had an EB05 score  $\geq 2$ , the threshold for higher-than-expected combinations of drugs and events.<sup>88</sup> There were no reports for the preferred term “Accident at home.”

<sup>86</sup> Inclusion criteria: Oral DPH as the only suspect medication, domestic case, temporal association to DPH or a laboratory test showing a detectable level of DPH; Exclusion criteria: multiple medications reported as suspect medications, recreational drugs or alcohol reportedly used, accidents or injuries resulted from a non-drug cause, injuries resulted from organ damage (e.g. liver injury), no accident or injury reported; OSE review for NDA 205352, finalized 10/29/2013, p5

<sup>87</sup> OSE review for NDA 205352, finalized 10/29/2013, p12

<sup>88</sup> Szarfman A. et al. (2002) 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* 25:381-392.

Table 29. Data mining scores for accidents query preferred terms reported for DPH products as of August 10, 2013.<sup>89</sup>

| Preferred Term           | N   | EB05 | EBGM | EB95 |
|--------------------------|-----|------|------|------|
| Accident                 | 61  | 4.8  | 5.9  | 7.3  |
| Road traffic accident    | 43  | 1.1  | 1.5  | 1.9  |
| Fall                     | 111 | 0.7  | 0.8  | 0.9  |
| Impaired driving ability | 5   | 0.3  | 0.6  | 1.1  |
| Injury                   | 24  | 0.3  | 0.4  | 0.5  |
| Accident at work         | 1   | 0.1  | 0.7  | 2.1  |

EBGM: empirical Bayes geometric mean; EB05 – EB95: 95% confidence interval

Regarding postmarketing analyses of DPH as it relates to next-day effects, I agree with the conclusions of Dr. Hu and OSE.

Dr. Hu concludes:<sup>90</sup>

“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.”  
and

“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.”

OSE concludes:<sup>91</sup>

“The review did not identify any new issues with diphenhydramine hydrochloride. OSE agrees with the proposed labeling for CNS effects and effects on driving submitted with NDA 205352...”

### Study 15560 – Incidence of Somnolence in Multidose Ten-day Safety and Tolerability Trial of NP 440 / DPH 50

Regarding somnolence, Dr. Tandon comments, “The incidence rate was higher in the NP 440 / DPH 50 group (4.6%), although not much higher than the placebo group (3.7%). Most somnolence events were mild to moderate.”<sup>92</sup> Of the five placebo subjects with somnolence at

<sup>89</sup> Adapted from OSE review (Table 6) for NDA 205352, finalized 10/29/2013, p3

<sup>90</sup> DNCE clinical review for NDA 205352 by Linda Hu, finalized 12/16/2013, p6

<sup>91</sup> OSE review for NDA 205352, finalized 10/29/2013, p3

<sup>92</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p77

any time during the study, one subject experienced excessive sleepiness for the entire study duration and another subject experienced drowsiness for six days. Of the eleven NP 440 / DPH 50 subject with somnolence at any time during the study, three subjects experienced drowsiness or somnolence for the entire study duration.

### Study 16135 – DPH Plasma Concentration at Eight Hours Post-dosing

The bioavailability trial of NDP 440 / DPH 50 under fasting and fed conditions described in section 5. Clinical Pharmacology / Biopharmaceutics provided DPH plasma concentration data that Dr. Tandon and Dr. Yang examined in the context of DPH threshold concentrations identified by Gengo et al (1989)<sup>93</sup> for drowsiness (30 to 42 ng/mL) and mental impairment (58 to 74 ng/mL).

The mean DPH concentration eight hours after dosing was 23.4-28.8 ng/mL after a single dose of DPH 50 either alone or in combination with NP 440.<sup>94</sup> Five of the twenty-seven subjects who completed the trial as planned had a DPH plasma concentration that was above 40 ng/mL eight hours after dosing (Table 30, blue). For one subject (1026), the DPH plasma concentration nearly reached the threshold for mental impairment as identified by Gengo et al (1989), after NP 440 / DPH 50 in the fasting and fed states. For graphical representation of DPH plasma concentration for all subjects eight hours after dosing, see Figure 1.

Table 30. Study 16135 – DPH plasma concentrations (ng/mL)<sup>95</sup>

| Subject #           | Treatment A<br>NP 440 / DPH 50<br>fasting | Treatment C<br>DPH 50<br>fasting | Treatment D<br>NP 440 / DPH 50<br>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                                    |

F: female; M: male; Am: American

### Cross-study Comparisons of DPH Plasma Levels 8-12 Hours After Administration

The clinical pharmacology reviewer compared DPH plasma concentrations at eight and twelve hours after drug administration between Aleve PM and other DPH-containing products in the fasting (Table 31) and fed (Table 32) states. The plasma concentrations for the different products were extracted from different studies submitted to various NDAs and ANDAs.<sup>96</sup> Taking into consideration the limitations of cross-study comparisons, it appears that the DPH plasma

<sup>93</sup> Gengo F. et al. (1989) The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance. *Clin Pharmacol Ther* **45**: 15-21.

<sup>94</sup> Clinical Pharmacology review for NDA 205352 by Xinning Yang, finalized 12/20/2013, p2

<sup>95</sup> Adapted from draft DNP clinical review (Table 2) for NDA 205352 by Veneeta Tandon

<sup>96</sup> Clinical Pharmacology review for NDA 205352 by Xinning Yang, finalized 12/20/2013, p11 and 12

concentrations at eight and twelve hours post-dose for Aleve PM are comparable to those for currently marketed nighttime analgesic / sleep-aid fixed combination OTC drugs.

Table 31. Fasting state plasma DPH concentrations at 8 and 12 hours post-dose

| Product name       | DPH Dose             | Concentration at 8 hr<br>(ng/mL) | Concentration at 12 hr<br>(ng/mL) |
|--------------------|----------------------|----------------------------------|-----------------------------------|
| Aleve PM           | 2x25 mg DPH HCl      | 24.7 ± 10.2**<br>(10.7 – 56.5)   | 15.7 ± 7.3<br>(6.3 – 39.1)        |
| Advil PM Liqui-gel | 2x25 mg DPH HCl      | 37.4 ± 12.9<br>(17.8 - 67.5)     | 24.8 ± 11.0<br>(12.0 - 61.6)      |
| Advil PM Caplets   | 2x38 mg DPH Citrate* | 37.9 ± 16.5<br>(16.4 - 99.3)     | 23.3 ± 9.4<br>(11.1 - 55.4)       |
| Advil PM Caplets   | 1x38 mg DPH Citrate  | 15.2 ± 6.1<br>(6.1 - 31.4)       | 8.7 ± 4.0<br>(2.6 - 20.7)         |
| Motrin PM          | 1x38 mg DPH Citrate  | 15.0 ± 6.3<br>(4.9 - 30.4)       | 8.7 ± 4.1<br>(2.3 - 18.5)         |

\* 38 mg DPH citrate contains the same amount of free base DPH as 25 mg DPH HCl

\*\*Mean ± SD (range)

Table 32. Fed state plasma DPH concentrations at 8 and 12 hours post-dose

| Product name     | DPH Dose             | Concentration at 8 hr<br>(ng/mL) | Concentration at 12 hr<br>(ng/mL) |
|------------------|----------------------|----------------------------------|-----------------------------------|
| Aleve PM         | 2x25 mg DPH HCl      | 28.8 ± 11.0**<br>(12.1 - 55.9)   | 19.5 ± 8.7<br>(7.4 - 43.3)        |
| Advil PM Caplets | 1x38 mg DPH Citrate* | 16.9 ± 6.7<br>(6.7 - 39.1)       | 9.5 ± 4.7<br>(3.0 - 26.6)         |
| Motrin PM        | 1x38 mg DPH Citrate  | 15.7 ± 6.8<br>(6.4 - 43.9)       | 9.0 ± 4.8<br>(2.6 - 28.9)         |

\* 38 mg DPH citrate contains the same amount of free base DPH as 25 mg DPH HCl

\*\*Mean ± SD (range)

## 9. Advisory Committee Meeting

No advisory committee meeting was held on this application.

## 10. Pediatrics

### *Clinical Trials*

The completed trials enrolled 243 subjects who were 12-17 years of age. None were younger than 12 years (Table 33, Table 34).

Table 33. Number of pediatric subjects by age in the clinical studies

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

Table 34. Number of pediatric subjects by study treatment in the clinical studies

| Study Treatment | Number of Subjects |             |             |             |       |
|-----------------|--------------------|-------------|-------------|-------------|-------|
|                 | Study 13053        | Study 14837 | Study 15881 | Study 15560 | Total |
| NP 440 / DPH 50 | 13                 | 28          | -           | 3           | 44    |
| NP 440 / DPH 25 | -                  | -           | 22          | -           | 22    |
| NP 220 / DPH 50 | 12                 | 31          | -           | -           | 43    |
| NP 440 alone    | 10                 | 36          | 16          | -           | 62    |
| DPH 220 alone   | 8                  | -           | -           | -           | 8     |
| DPH 50 alone    | 13                 | 20          | 11          | -           | 44    |
| Advil PM        | 16                 | -           | -           | -           | 16    |
| Placebo         | 0                  | -           | -           | 4           | 4     |
| Total           | 72                 | 115         | 49          | 7           | 243   |

The pivotal study that assessed efficacy of NP 440 / DPH 50 (Study 37) demonstrated efficacy in adolescents. For sleep latency, the p-value for the NP 440 / DPH 50 vs DPH 50 comparison was 0.0008. For WASO, the p-value for the NP 440 / DPH 50 vs NP 440 comparison was 0.0144, with a LS mean difference of -112.3.<sup>97</sup>

### ***Pediatric Studies***

The application triggers the Pediatric Research Equity Act because there is a new active ingredient (new combination). (b) (4)

(b) (4)

<sup>97</sup> Draft DNP clinical review (Tables 19 and 20) for NDA 205352 by Veneeta Tandon

The Pediatric Review Committee (PeRC) recommended that a partial waiver be granted in patients ages birth to < 12 years because the product would be ineffective and/or unsafe, noting that this would be consistent with labeling for other OTC products for this indication.

For patients 12 to <17 years, the PeRC suggested that a waiver is not necessary. The rationale provided was that pediatric assessment could be provided because the sponsor provided data in the application for patients down to 12 years of age.

(b) (4)

(b) (4)

### ***Pediatric Labeling***

The Aleve PM Drug Facts Label (DFL) proposes directions for use in children 12 years and above:  
“Uses

- for relief of occasional sleeplessness when associated with minor aches and pains
- helps you fall asleep and stay asleep”

“Do not use

- in children under 12 years of age”

“Directions

- adults and children 12 years and over: take 2 caplets at bedtime”

The proposed pediatric language is acceptable.

Comparison with other analgesic / nighttime sleep aid is provided below.

**Aleve PM** is naproxen 220mg / diphenhydramine HCl 25mg per caplet. Two caplets is the recommended dose for adults and children 12 years and over.

**Advil PM** (ibuprofen 200mg / diphenhydramine HCl 25mg) is an NDA product (NDA 21393) approved for the same indication that Aleve PM is seeking and with the same pediatric text in the DFL as what Aleve PM’s sponsor is proposing (except with capsules instead of caplets). The labeling down to 12 years was likely based on the diphenhydramine monograph (see below).

(b) (4)

<sup>98</sup> DNCE clinical review for NDA 021393, 021394, finalized 11/4/2005, p46

There is a final monograph for nighttime sleep-aid products for OTC use that specifies labeling for diphenhydramine (HCl and citrate) (54FR6814, specifically 6827):

“Warnings

(1) Do not give to children under 12 years of age.”

For diphenhydramine HCl, “Adults and children 12 years of age and over: Oral dosage is 50 milligrams at bedtime if needed, or as directed by a doctor.”

**Tylenol PM Extra Strength** (acetaminophen 500mg, diphenhydramine HCl 25mg—not an NDA product) is marketed for

“temporary relief of occasional headaches and minor aches and pains with accompanying sleeplessness”

Tylenol PM has the following pediatric text in the DFL:

“Do not use

- in children under 12 years of age”

“Directions

|                                       |                                                                                                                                                           |
|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| adults and children 12 years and over | <ul style="list-style-type: none"><li>▪ take 2 gelcaps at bedtime</li><li>▪ do not take more than 2 gelcaps of this product in 24 hours</li></ul>         |
| children under 12 years               | do not use this adult product in children under 12 years of age; this will provide more than the recommended dose (overdose) and may cause liver damage ” |

**Excedrin PM** (acetaminophen 500mg/ diphenhydramine citrate 38mg—not an NDA product) is marketed for the same indication as Tylenol PM.

Excedrin PM has the following pediatric text in the DFL:

“Do not use

- in children under 12 years of age”

“Directions

- do not use in children under 12 years of age
- adults and children 12 years of age and over: take 2 tablets at bedtime, if needed, or as directed by a doctor”

## 11. Other Relevant Regulatory Issues

Because Aleve PM was determined to not be expected to have a significant impact on the environment, an environmental impact statement was not prepared.

Two clinical investigator sites were inspected. According to the review from the Office of Scientific Investigations finalized 09/13/2013, the pending classification is Voluntary Action Indicated for one site (minor protocol deviations which were discussed with the investigator) and No Action Indicated for the other site. No Form 483s were issued. Of note, the raw data from the actigraphs were not available so the data on case report forms were not validated.

The proprietary name, Aleve PM, was determined to be acceptable from a promotional and safety perspective by DMEPA in a review finalized 06/21/2013.

## 12. Labeling

See Appendix A – E for proposed labels submitted December 6, 2014.

The DNRD labeling review focused primarily on regulatory compliance. I concur with their recommendations which were communicated to the applicant on November 22, 2013. One request sent to the sponsor was to revise (b) (4) on the principal display panel so that (b) (4) would not be perceived as a different category of pain relief (vs daytime). This request was sent after discussion with DAAAP clinical reviewers who agreed with the concern. The applicant addressed each comment and DNRD recommended approval in their 12/11/2013 review which requested that sponsor submit final printed labeling identical to the labels submitted on December 6, 2013..

Subsequent to the December 6, 2013 submission, the applicant was asked to revise the background color to one that would allow consumers to easily distinguish Aleve PM from currently marketed Aleve and Aleve-D products based on a DMEPA recommendation. The concern was that consumers would fail to recognize the differences between Aleve PM and Aleve or Aleve-D, leading to medication errors and adverse events. Aleve PM includes DPH which, if taken according to the Aleve or Aleve-D dosing regimen (up to 3 tablets in a 24-hour period for Aleve), could lead to undesired sleepiness and/or mental impairment due to increased exposure to DPH -- among other adverse events.

The applicant indicated that it would submit revised labeling on January 9, 2014 to address the above request: the background colors for Aleve PM, Aleve, and Aleve-D would be (b) (4), blue, and turquoise, respectively. The revised label would also change the “+” symbol (could be mistaken for the number “4”) to “plus.”

The Drug Facts Label is nearly identical to the Advil PM label. As mentioned in section 5. Clinical Pharmacology, the label adds “if taken with food, this product may take longer to work” due to the longer  $t_{max}$  for naproxen in the combination product in the fed state. This proposal appears

reasonable. The proposed label also adds “drink a full glass of water with each dose,” which is reasonable given that this was how subjects in the trials were instructed to take the investigational product. It is not known whether the subject who experienced esophageal pain / edema / discomfort in Study 15560<sup>99</sup> followed directions regarding the full glass of water.

One aspect of the label that is not very clear is that one should not take this combination product for more than ten days. The label states, “Stop use and ask a doctor if pain gets worse or lasts more than 10 days.” However, the directions section does not include any comment regarding the duration of use. Since the proposed label is based on the Advil PM label, this suggestion may be one to keep in mind for the future if a safety issue were to arise that would prompt a label change for both products.

### 13. Recommendations/Risk Benefit Assessment

The risk-benefit profile of NP 440 alone and DPH 50 mg alone has been determined to be acceptable in the OTC setting. The issue for this application is whether the risk-benefit profile of the NP 440 / DPH 50 combination is acceptable for use in the OTC setting to help one fall asleep and stay asleep when experiencing minor aches and pains.

Many aspects of the submitted data weaken the application. For example, the primary support for the application is a single study with (a) design flaws that raise questions regarding the applicability of the data to the intended population and (b) a statistical plan that biases in favor of the proposed drug. A second pivotal study which tested a lower dose of DPH for efficacy was underpowered and lacked a positive control so that it was not possible to differentiate a failed study from a negative study.

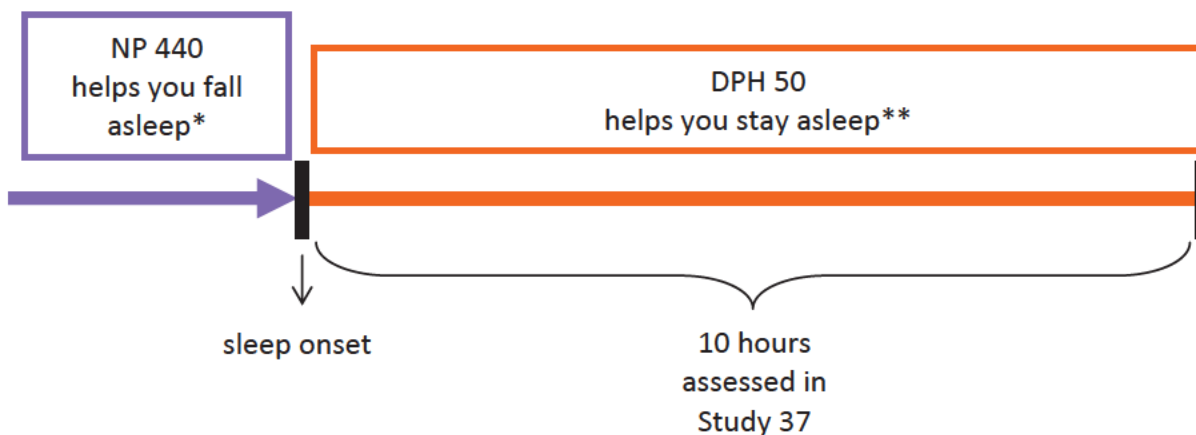
The two pivotal studies used a dental pain with phase advanced sleep model and an imputation scheme which penalized use of rescue medication. Only Study 37 administered the proposed product. The results of Study 37 suggest that the two active ingredients in the combination product make specific contributions to the two parts of the proposed indication (Figure 3) based on the following observations:

- NP 440 / DPH 50 is superior to DPH 50 alone for sleep latency
- NP 440 / DPH 50 is superior to NP 440 alone for sleep maintenance

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<sup>99</sup> Draft DNP clinical review for NDA 205352 by Veneeta Tandon, p81

Figure 3. Contributions of the active ingredients in the proposed product to the two aspects of the proposed indication.<sup>^</sup>



<sup>^</sup> Based on the dental pain / phase advanced sleep model and a specific imputation scheme.

\* Adding NP 440 to DPH 50 shortens the time to sleep onset compared to DPH 50 alone. When pain is abated by NP 440, DPH 50 does not further shorten the time to sleep onset. See Table 22 and Table 9.

\*\* Adding DPH 50 to NP 440 shortens the amount of time spent awake after sleep onset compared to NP 440 alone (Table 23 and Table 13). The effect of adding NP 440 to DPH 50 on the amount of time spent awake after sleep onset is not interpretable due to imputation scheme used and the large proportion of subjects who took rescue medication, particularly in the DPH 50 group (Table 23, Table 13, Table 10).

Although the manner in which the dose for the combination product was selected has many shortcomings, the totality of the data regarding NP 440 or DPH 50 does not suggest any new safety signals for these products which have extensive human exposure already as single ingredients. Additionally, literature, postmarketing, and clinical trial data do not suggest that the NP 440 / DPH 50 combination would lead to any more road traffic accidents than any other analgesic / sleep-aid combination products currently marketed. Some subjects may be drowsy the next day, but the vast majority of consumers who take the proposed product according to label will not likely experience mental impairment the next day.

Although it would be ideal to gather more data regarding the efficacy of NP 440 combined with a lower dose of DPH (25 mg), the data do not suggest that the NP 440 / DPH 50 combination would put consumers at greater risk than those taking currently marketed OTC products that contain DPH. In addition to a sleep indication, DPH is available to treat allergic rhinitis at a dose of 25 to 50 mg every 4 to 6 hours, not to exceed 300 mg in 24 hours, or as directed by a doctor. The proposed combination would expose subjects to 50 mg DPH once per day, which is a much lower dose than the 300 mg DPH per day currently allowed to treat allergic rhinitis.

In addition, although the pivotal study designs are suboptimal, for the most part, Study 37 was performed in accordance with the advice provided by the Agency. Furthermore, combining NP 440 with DPH does not reduce the pain relieving capability of NP 440.

Considering the totality of the data, the benefits of NP 440 / DPH 50 outweigh the risks for OTC marketing.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LUCIE L YANG  
01/09/2014