

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-875**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**



**Letter, the Sponsor's responses, including the OCP's follow-up comments and the Sponsor's response are summarized in Section 1.2.**

## **1.2. SPONSOR'S RESPONSES TO OCP COMMENTS:**

### **CLINICAL PHARMACOLOGY**

You have communicated that the evaluation of the drug-drug interaction potential between armodafinil and substrates of P-glycoprotein has been completed. As communicated in our April 28, 2006 action letter, this evaluation may be submitted as a post-marketing commitment. Alternatively, these evaluations may be submitted as a part of your response to this letter. Submission of these evaluations will not affect the review period for a future action date, if a complete response is submitted.

#### **Sponsor response:**

Cephalon has conducted an in vitro study to evaluate armodafinil as an inhibitor and substrate of P-glycoprotein (P-gp). The study report (Report DP-2006-055) is provided as a part of this submission.

Preliminary feasibility work has been performed to conduct a study to assess induction of P-gp activity. This remains an ongoing project. As a postmarketing commitment, Cephalon will conduct an assessment of armodafinil as a P-gp inducer.

Please see the Clinical Pharmacology response located within item 20 [Response to Clinical Pharmacology Request].

#### **OCP comments:**

1. **As part of the Sponsor's responses** (June 30, 2006) to the Phase IV Commitment recommended by OCP, the Sponsor had agreed to assess the capacity of armodafinil to function as a substrate for or an inhibitor of human P-glycoprotein (hP-gp) in vitro via functional assays. For induction potential for P-glycoprotein, the Sponsor planned a collaborative project for the assessment using in vitro cell line. In response, the OCP made following comments:
  - (1) **The Sponsor's response and proposal** to evaluate whether armodafinil is a P-gp substrate or inhibitor is reasonable.
  - (2) The in vitro and in vivo results have indicated that armodafinil is a CYP3A4 inducer. Because of the shared mechanism of regulation, co-induction of P-gp and CYP3A is likely, and that formed the basis for our previous recommendation for the evaluation for the P-gp inducibility. However, based on current understanding, methods for in vitro evaluation for P-gp induction are not well understood and P-gp induction potential of an investigational drug can only be more reliably evaluated in vivo. Therefore, our original intent was for the Sponsor to conduct a literature search for any available information on the induction potential. In our view, the in-vitro investigation for the potential P-gp induction is not necessary at this point. However, a thorough literature search should be undertaken to see if there is any information on the P-gp induction

potential of modafinil in vivo. This can form the basis for discussion and to see if any future in vivo P-gp induction study is necessary.

- The above Comment #2 was conveyed to the Sponsor on May 01, 2007. Our current thinking in terms of the P-gp induction assessment is that the in vitro investigation is not necessary. However, a thorough literature search by the Sponsor is still necessary for any pertinent information on the P-gp induction potential of armodafinil (or modafinil) and should remain as a Phase IV commitment.

**Sponsor response (dated May 09, 2007):**

Cephalon agrees to provide as a post-marketing commitment a thorough literature search to determine whether there is any information on the P-gp induction potential of modafinil in vivo. This information will serve as the basis for discussion with the Agency regarding the need for further evaluation of in vivo P-gp induction of modafinil.

**1.2.1. Study 6CEPHP1 (Report DP-2006-055)**

**Title:** The Assessment of Armodafinil as a Pgp Substrate and a Pgp Inhibitor in MDR1-MDCK Cells

**Objective:** Assessment of Armodafinil as P-gp Substrate or P-gp Inhibitor

**Permeability Assay:**

MDR1-MDCK cell monolayers were grown to confluence ~~in~~ plates. Cell batch certification results are shown in the table below.

b(4)

Plate:	TW12		TW12		
Seed Date:	9/18/06		9/25/06		
Passage #:	27		28		
Age at QC (days):	7		7		
	No CSA	10 $\mu$ M CSA	No CSA	10 $\mu$ M CSA	Acceptance Criteria
TEER Value ( $\Omega \cdot \text{cm}^2$ ):	1511.19	1590.66	2714.64	2673.96	>1400
Lucifer Yellow $P_{app}$ x $10^{-6}$ cm/s:	0.21	0.21	0.28	0.23	<0.4
Atenolol $P_{app}$ x $10^{-6}$ cm/s:	0.18	0.21	0.34	0.18	<0.50
Propranolol $P_{app}$ x $10^{-6}$ cm/s:	14.07	15.03	16.72	17.80	10-30
Digoxin (A-B) $P_{app}$ x $10^{-6}$ cm/s:	0.13	0.77	0.36	1.06	None
Digoxin (B-A) $P_{app}$ x $10^{-6}$ cm/s:	9.71	0.89	11.88	1.00	None
Digoxin (B-A $P_{app}$ ) / (A-B $P_{app}$ ):	77.38	1.16	33.08	0.95	>3

Bi-directional permeability of armodafinil (at 3  $\mu$ M, 30  $\mu$ M, and 300  $\mu$ M) and digoxin (at 10  $\mu$ M), a marker P-gp substrate, was tested in the absence or in the presence of P-gp inhibitors, CsA (10  $\mu$ M) and verapamil (100  $\mu$ M), in HBSSg pH 7.4 buffer at 37°C. For assessing the potential of armodafinil to inhibit P-gp, bi-directional permeability of digoxin (10  $\mu$ M) in the absence and in the presence of 300  $\mu$ M armodafinil was tested. The bi-directional permeation of pindolol was tested as a control for passive transport.

All experiments were performed in triplicate and the apparent permeability (Papp) and recovery were calculated as follows:

$$P_{app} = (dCr/dt) \times V_r / (A \times CD)$$

$$\text{Percent Recovery} = 100 \cdot ((V_r \cdot Cr^{final}) + (V_d \cdot Cd^{final})) / (V_d \cdot CD)$$

where,

dCr/dt: the slope of cumulative concentration in the receiver compartment over time  
in  $\mu\text{M s}^{-1}$

V<sub>r</sub>: the volume of the receiver compartment

V<sub>d</sub>: the volume of the donor compartment

A: the diffusional area of the cell monolayer

Cr<sup>final</sup>: the cumulative receiver concentration in  $\mu\text{M}$  at the end of the incubation period

Cd<sup>final</sup>: the concentration of the donor in  $\mu\text{M}$  at the end of the incubation period

CD: the initial (0 minutes) donor chamber concentration in  $\mu\text{M}$

Results of the permeability studies and statistical analysis are presented in the following table:

Treatment	A-to-B Papp (x 10 <sup>-6</sup> cm/s)	B-to-A Papp (x 10 <sup>-6</sup> cm/s)	B-A/A-B Ratio
	Mean ± SD	Mean ± SD	
Armodafinil 3 $\mu\text{M}$	6.87 ± 0.09	29.99 ± 3.27	4.73
Armodafinil 3 $\mu\text{M}$ + CsA	12.04 ± 0.50	10.29 ± 0.64	0.85
Armodafinil 3 $\mu\text{M}$ + Verapamil	11.00 ± 0.59	9.45 ± 1.29	0.86
Armodafinil 30 $\mu\text{M}$	6.16 ± 0.45	30.92 ± 0.39	5.02
Armodafinil 30 $\mu\text{M}$ + CsA	12.09 ± 0.25	10.92 ± 0.33	0.90
Armodafinil 30 $\mu\text{M}$ + Verapamil	13.01 ± 0.55	11.09 ± 0.47	0.85
Armodafinil 300 $\mu\text{M}$	6.38 ± 0.29	28.44 ± 0.85	4.46
Armodafinil 300 $\mu\text{M}$ + CsA	10.83 ± 0.91	8.51 ± 0.55	0.79
Armodafinil 300 $\mu\text{M}$ + Verapamil	10.37 ± 0.50	9.94 ± 0.62	0.96
Pindolol 10 $\mu\text{M}$	3.87 ± 1.29	7.86 ± 0.89	2.03
Digoxin 10 $\mu\text{M}$	0.23 <sup>+</sup> ± 0.09	8.37 <sup>++</sup> ± 0.41	35.67
Digoxin 10 $\mu\text{M}$ + CsA	0.47 ± 0.02	0.59 ± 0.02	1.25
Digoxin 10 $\mu\text{M}$ + Verapamil	0.47 ± 0.04	1.60 ± 0.10	3.41
Digoxin 10 $\mu\text{M}$ + Armodafinil 300 $\mu\text{M}$	0.19 <sup>+</sup> ± 0.06	10.67 <sup>++</sup> ± 0.24	56.03
Pindolol 10 $\mu\text{M}$	4.18 ± 0.20	9.40 ± 1.02	2.25

+ No statistically significant difference between A-B Papp of digoxin when tested alone or in the presence of armodafinil (p = 0.1181, paired t-test with 99 % confidence interval).

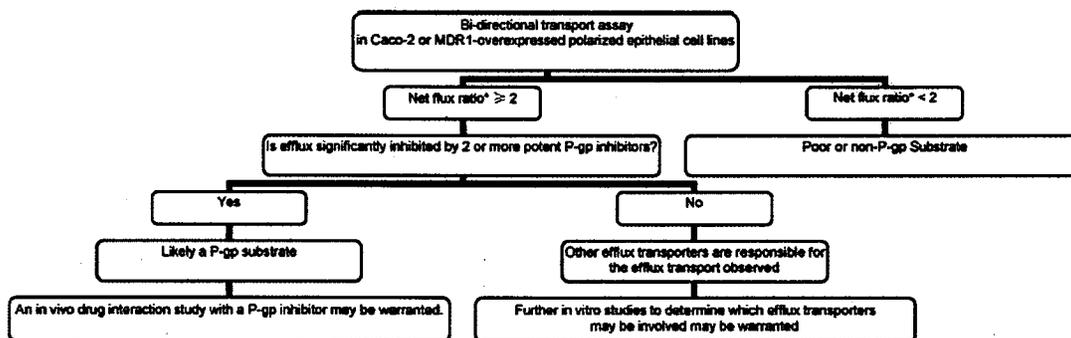
++ In the presence of armodafinil, the digoxin B-A Papp was significantly higher from the corresponding value when digoxin was assayed alone ( $p = 0.0105$ , paired t-test with 99 % confidence interval).

**Permeability Results:**

1. Armodafinil was subject to activity of efflux transporter at all the concentrations tested with no saturation observed. The B-A Papp/A-B Papp ratios at 3  $\mu\text{M}$ , 30  $\mu\text{M}$ , and 300  $\mu\text{M}$  tested were 4.37, 5.02, and 4.46, respectively.
2. The efflux phenomenon was abolished by inhibitors of P-gp (CsA and verapamil), as reflected by reduction of armodafinil B-A Papp/A-B Papp ratios to less than unity, which indicates that armodafinil is a P-gp substrate.
3. In the presence of armodafinil, the B-A Papp/A-B Papp ratio of digoxin was increased from 35.67 to 56.03, indicating that armodafinil is not a P-gp inhibitor. While digoxin A-B Papp values were not statistically different, the B-A Papp was significantly increased in the presence of armodafinil with reason remaining unclear.

**Reviewer's Comments:**

1. The possible model for decision-making for P-gp-based drug-drug interaction studies, as outlined in the Agency's Guidance, is presented as follows:



The Agency recommends that the net flux ratio when using MDR1-overexpressed cell lines be calculated as ratio of (B-A Papp/A-B Papp) MDR1 to (B-A Papp/A-B Papp) wild-type. The sponsor did not include MDCK-WT in studies as negative control to allow more accurate assessment for net flux ratios using recommended method.

2. This reviewer, however, agrees with the sponsor's conclusion that the armodafinil is a P-gp substrate based on (a) polarized bi-directional transport in MDR1-overexpressed cell lines, and (b) significant reductions (near 3~5-times) in B-A Papp values or net flux ratios and near 2-fold increases in A-B Papp (representing the net absorptive transport) in the presence of two P-gp inhibitors in MDCK-MDR1 monolayers which express other efflux transporters at very low levels

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3. Considering that the Provigil has been approved and on the market for some time, instead of conducting an in vivo study with P-gp inhibitor, the Sponsor should conduct a comprehensive literature search at this point as part of the Phase IV commitment for any in-vivo drug-drug interaction information via this mechanism.

### 1.3. RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the current submission and finds the **Sponsor's response to OCP's Comments** acceptable. Additional labeling recommendations for both NUVIGIL and PROVIGIL are provided in Section 2 of this review starting page 8. **Regarding the Sponsor's** in vitro findings that armodafinil is a P-gp substrate, we recommend that the Sponsor conduct a comprehensive literature search at this point for any in-vivo drug-drug interaction information via this mechanism. Please see the detailed OCP comment to the Sponsor's response #2 below.

#### OCP comments:

- 1) Considering that armodafinil is a P-gp substrate, the Sponsor should conduct a comprehensive literature search at this point for any in-vivo drug-drug interaction information via this mechanism, as a Phase IV commitment.
- 2) In addition, as provided previously as a Phase IV commitment, the Sponsor should conduct a thorough literature search to determine whether there is any information on the P-gp induction potential of modafinil in vivo.

These (1 and 2) should be submitted within 1 year from the date of approval of Nuvigil.

Ta-Chen Wu, Ph.D.  
Reviewer, Neurology Drug Products, DCP-1, OCP

Ramana S. Uppoor, Ph.D.  
Deputy Director (and Team Leader), Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 NDA 21-875  
CSO/J.H. Ware  
/TL Clin Pharm/R. Uppoor  
HFD-860 /DD DCP-1/M. Mehta

## **2. LABELING RECOMMENDATIONS**

The Sponsor accepts the NUVIGIL package insert as proposed by the Division in the March 28, 2007 approvable letter, and additional text concerning rash has been added to the patient package insert as requested by the Agency. For the language consistency between NUVIGIL and PROVIGIL, a side-by-side label comparison based on NUVIGIL label (dated 4/16/07) and PROVIGIL label (dated 4/24/07) submitted by the Sponsor, is compiled by the Agency for revision. The Office of Clinical Pharmacology has reviewed the current proposed labeling and finds it generally acceptable from a clinical pharmacology and biopharmaceutics perspective, with some revisions.

### **2.1. Proposed Package Inserts**

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\_\_\_\_\_ Trade Secret / Confidential (b4)

\_\_\_\_\_ Draft Labeling (b4)

\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

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Ramana S. Uppoor  
5/31/2007 07:18:09 PM  
BIOPHARMACEUTICS

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from the Agency, the Sponsor has decided not to market the 100-mg strength tablet at this time and will utilize the 50-mg strength instead for dosage adjustment based on patient status and/or tolerability.

Upon reviewing the original NDA submission, OCP made recommendations pertaining to change of dissolution specifications and investigation for potential drug-drug interaction involving P-glycoprotein. The investigation for interaction potential involving P-gp was recommended as a Phase IV Commitment as stated in the AE Letter conveyed to the Sponsor. The sponsor agrees to the recommendation for tightening dissolution specification and to the Phase IV commitment with additional studies. The OCP comments in AE Letter and the Sponsor's responses are summarized as follows:

## 1.2. SPONSOR'S RESPONSES TO OCP COMMENTS:

### OCP Comment #1:

*We note that a tighter dissolution specification for Nuvigil was conveyed to you in our December 27, 2005 communication, and that you agreed, in your January 25, 2006 submission, to the revised specification. Accordingly, the agreed upon dissolution method and specifications for NUVIGIL tablets are as follows:*

*Apparatus: USP apparatus 2 (Paddle)*

*Stirring Speed: 50 rpm*

*Dissolution Medium: 0.1N HCl*

*Volume of Medium: 900 mL*

*Temperature: 37.0 °C*

*Specification:  $Q = \dots$  in 30 minutes*

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### Sponsor response:

Cephalon confirms that the agreed upon dissolution specification and method, as described in the approvable letter of April 28, 2006, will be used for the dissolution testing of all finished drug product.

### OCP Comment #2 (Phase IV Commitment):

*We ask that you provide information pertaining to the drug-drug interaction potential between armodafinil and substrates (e.g., digoxin) of P-glycoprotein through literature ~~as~~ as a post-marketing commitment. This evaluation should address whether armodafinil is a substrate or inhibitor (or inducer) of P-glycoprotein.*

b(4)

### Sponsor response:

A validated, commercially-available MDCK-MDR1 test system will be used to assess the capacity of armodafinil to function as a substrate for or an inhibitor of human P-glycoprotein (hP-gp) in vitro. Both assessments will be via functional assays. The laboratory work for this study is planned for initiation in early 3Q2006, with completion and reporting prior to the end of 2006.

Determination of the capability of armodafinil to induce hP-gp is less straightforward than that for transport or inhibition due to the lack of a validated and commercially available test system for induction. Hence, a collaborative arrangement has been proposed with a contract research organization for the purpose of evaluation of a group of cell lines (eg, LS180V) for which there are literature reports of utility in assessment of hP-gp induction in vitro. The assessments of hP-gp induction are not functional assays, however, but rather are measurements of the levels of hP-gp mRNA with and without pretreatment of the cells with a test substance. This collaborative project is planned for initiation in 3Q2006, with a feasibility evaluation expected in 4Q2006. We will then update the agency with the results of that feasibility evaluation and the subsequent plan and timeline for completion of the induction assessment.

OCP comments:

1. **The Sponsor's response and proposal** to evaluate whether armodafinil is a P-gp substrate or inhibitor is reasonable.
2. The in vitro and in vivo results have indicated that armodafinil is a CYP3A4 inducer. Because of the shared mechanism of regulation, co-induction of P-gp and CYP3A is likely, and that formed the basis for our previous recommendation for the evaluation for the P-gp inducibility. However, based on current understanding, methods for in vitro evaluation for P-gp induction are not well understood and P-gp induction potential of an investigational drug can only be more reliably evaluated in vivo. Therefore, our original intent was for the Sponsor to conduct a literature search for any available information on the induction potential. In our view, the in-vitro investigation for the potential P-gp induction is not necessary at this point. However, a thorough literature search should be undertaken to see if there is any information on the P-gp induction potential of modafinil in vivo. This can form the basis for discussion and to see if any future in vivo P-gp induction study is necessary.

### 1.3. PROPOSED LABELING CHANGES AND RATIONALE

Proposed changes are denoted by text in red with underline or single strikethrough.

b(4) b(5)

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Justification: The effect of food has been studied only after single-dose administration of armodafinil. However, analysis utilizing the principle of superimposition allowed a prediction of the effect of food on the pharmacokinetics of armodafinil following multiple-dose administration. These

data indicate an approximate 2-hour delay in the time to maximum concentration (t<sub>max</sub>) in the fed state compared to the fasted state (t<sub>max</sub> of 4.1 versus 1.9 hours, respectively).

The instructions for the Phase 3 clinical studies were as follows: For study C10953/3020/NA/MN (narcolepsy), study C10953/3021/AP/MN (obstructive sleep apnea/hypopnea syndrome [OSAHS]), and C10953/3025/AP/MN (OSAHS), participating patients were to take study drug about 30 minutes before breakfast. There were no food restrictions before administration of study drug. The instructions for study C10953/3022/CM/US (shift work sleep disorder [SWSD]) were to take study drug 30 minutes to 1 hour before the start of the night shift, but no later than 2300. It was recommended that patients refrain from eating/drinking at least 2 hours before taking study drug. There were no specific instructions for eating/drinking after taking study drug. For Phase 3 open-label study C10953/3023/ES/MN (narcolepsy, OSAHS, SWSD), there were no instructions in regard to taking the study drug relative to food consumption. For Phase 3 open-label study C10953/3024/ES/MN (narcolepsy, OSAHS, SWSD) patients with narcolepsy or OSAHS were instructed to take study drug before a meal (no specific time before) and there were no restrictions for food consumption after taking study drug. Patients with SWSD were to take study drug 30 minutes to 1 hour, but no later than 2300, before the start of the night shift and they were instructed to refrain from eating/drinking for at least 2 hours before study drug administration.

In general, a fasted state is considered one in which no food/drink was consumed for a several hours before and after taking a drug. Because in the Phase 3 clinical studies these conditions were not met, the systemic exposure expected in these studies is likely most consistent with those in the fed state. On this basis, Cephalon requests that the package insert not include any restrictions regarding food intake relative to taking NUVIGIL.

b(4)  
b(5)

Justification: On the basis of in vitro data, drug interaction studies were performed to fully evaluate the potential for NUVIGIL to alter the metabolism of other medications by induction or inhibition. The conclusions from these studies were in line with conclusions from comparable drug interaction studies (using

different probes) for PROVIGIL®. Probes utilized in all NUVIGIL and/or PROVIGIL studies along with other clinically relevant substrates have been included, as appropriate. For drug interactions not specifically assessed with armodafinil (eg, CNS active drugs and warfarin), data from studies with PROVIGIL are considered appropriate for inclusion. However, in these cases, Cephalon requests that the package insert include the conclusions without the description of study design to be consistent with the NUVIGIL data presented under this section (PRECAUTIONS). This will also avoid the potential to conclude that the studies were performed with NUVIGIL.

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b(4) b(5)

Justification: See above CLINICAL PHARMACOLOGY, Pharmacokinetics, *Absorption*.

#### 1.4. RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the current submission and finds the **Sponsor's response to OCP's Comment #1 acceptable. In addition, the Sponsor's rationale and justification for the proposed labeling change pertaining to guideline for drug administration with respect to food and to the drug-drug interactions appear to be reasonable.** Additional labeling recommendations are provided in Section 2 of this review starting page 7. Regarding the **Sponsor's response to OCP's Comment #2** ~~we recommend that~~ we recommend that the Sponsor first conduct literature search for any pertinent information to form basis for future proceedings. Please see the detailed **OCP comment to the Sponsor's response #2** below.

b(4)

#### OCP comments on the sponsor's response #2:

1. **The Sponsor's response and proposal to evaluate whether armodafinil is a P-gp substrate or inhibitor is reasonable.**
2. The in vitro and in vivo results have indicated that armodafinil is a CYP3A4 inducer. Because of the shared mechanism of regulation, co-induction of P-gp and CYP3A is likely, and that formed the basis for our previous recommendation for the evaluation for the P-gp inducibility. However, based on current understanding, methods for in vitro evaluation for P-gp induction are not well understood and P-gp induction potential of an investigational drug can only be more reliably evaluated in vivo. Therefore, our original intent was for the Sponsor to conduct a literature search for any available information on the induction potential. In our view, the in-vitro investigation for the potential P-gp induction is not necessary at this point. However, a thorough literature search should be undertaken to see if there is any information on

the P-gp induction potential of modafinil in vivo. This can form the basis for discussion and to see if any future in vivo P-gp induction study is necessary.

Ta-Chen Wu, Ph.D.  
Reviewer, Neurology Drug Products, DCP-1, OCP

Concurrence: Ramana S. Uppoor, Ph.D.  
Team Leader, Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 NDA 21-875  
CSO/J.H. Ware  
/TL Clin Pharm/R. Uppoor  
HFD-860 /DD DCP-1/M. Mehta

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## 2. LABELING RECOMMENDATIONS

The Sponsor has provided responses to FDA labeling recommendation in AE Letter dated April 28, 2006, and provided justification for proposed revisions to the following sections of the package insert: Clinical Pharmacology (Mechanism of Action and Pharmacology, and Pharmacokinetics), Precautions (Drug Interactions), and Dosage and Administration.

The Office of Clinical Pharmacology has reviewed the current proposed labeling for **NUVIGIL™ Tablets** and found it **generally acceptable** from a clinical pharmacology and biopharmaceutics perspective, provided that revision is made to the labeling languages.

### Labeling recommendation to be sent to the Sponsor:

The proposed changes made by the Sponsor are in **RED text** with underline or single ~~striketrough~~. The proposed changes made by the OCP to the label language are in **RED text** with yellow-highlight: the underlined text is the proposed change and the ~~striketrough~~ text is recommendation for deletion from an OCP perspective.

### 2.1. Proposed Package Insert

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       Draft Labeling (b5)

       Deliberative Process (b5)

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11/9/2006 02:26:59 PM  
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**OFFICE OF CLINICAL PHARMACOLOGY  
REVIEW**

<b>NDA:</b>	21-875	
<b>Brand Name:</b>	NUVIGIL™	
<b>Generic Name:</b>	Armodafinil (CEP-10953)	
<b>Sponsor:</b>	Cephalon, Inc.	
<b>Type of Dosage Form:</b>	Immediate-Release Oral Tablets	
<b>Strengths:</b>	50 mg, 100 mg, 150 mg, 250 mg	
<b>Indications:</b>		
<b>OCP Reviewer:</b>	Ta-Chen Wu, Ph.D.	
<b>OCP Team Leader:</b>	Ramana S. Upoor, Ph.D.	
<b>OCP Division:</b>	DCPB-I HFD-860	
<b>OND Division:</b>	Division of Neurology Drug Products HFD-120	
<b>Submission Date:</b>	March 31, 2005	August 12, 2005
	June 10, 2005	September 27, 2005
	June 13, 2005	September 29, 2005
	June 24, 2005	
<b>Type of Submission:</b>	New, Standard NDA	

b(4)

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## *1. EXECUTIVE SUMMARY*

Cephalon, Inc. is seeking approval for NUVIGIL™ oral tablets of 50, 100, 150, and 250 mg strengths for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). The NDA for this application was originally submitted on March 31, 2005. Armodafinil (NUVIGIL™) is the R-enantiomer of commercially available racemic modafinil (PROVIGIL®). PROVIGIL® was previously reviewed under NDA 20-717 and approved for the same indications.

Since the Sponsor referenced the PROVIGIL® NDA and the language in approved Provigil label, it is important to bridge the pharmacokinetics and the exposure-response relationships between the two. In support of the application the Sponsor has included in the original submission seven Phase 1 studies, population pharmacokinetics and pharmacokinetics/pharmacodynamics modeling and simulation, six Phase 3 clinical trials, and the supportive in vitro dissolution studies.

### *1.1. Recommendations*

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology and Biopharmaceutics I (OCP/DCPB-I) has reviewed the submission and finds NDA 21-875 acceptable from an OCP perspective provided that the Sponsor responds to OCP comments adequately. In addition, agreement on the labeling language should be reached between the Sponsor and the Agency.

#### Comments to be conveyed to the Sponsor:

- (1) The dissolution of all test formulations occurred rapidly and exceeded ~~\_\_\_\_\_~~ of the label claim amount in ~~\_\_\_\_\_~~, while near completion occurred in ~~\_\_\_\_\_~~. We believe that the regulatory specifications of armodafinil tablets could be tightened. We notice that this dissolution specification has been communicated by the Chemistry reviewer and you have agreed to tighten the specification at the **Agency's request. The recommended dissolution method and specifications for NUVIGIL tablets are as follows:**

Apparatus: USP apparatus 2 (Paddle)  
Stirring Speed: 50 rpm  
Dissolution Medium: 0.1N HCl  
Volume of Medium: 900 mL  
Temperature: 37.0 °C  
Specification: Q = ~~\_\_\_\_\_~~ in 30 minutes

- (2) In the future, the sponsor should follow the FDA Guidance for food effect studies when designing food effect study for a new product.

b(4)

b(4)

- (3) The Sponsor is recommended to provide information pertaining to the drug-drug interaction potential between armodafinil and substrates (e.g., digoxin) of P-glycoprotein through literature or in vitro study as a Phase IV commitment. This evaluation should address whether armodafinil is a substrate or inhibitor (or inducer) of P-glycoprotein.

### *1.2. Phase IV Commitments*

The Sponsor is recommended to provide information pertaining to the drug-drug interaction potential between armodafinil and substrates (e.g., digoxin) of P-glycoprotein through literature or in vitro study. This evaluation should address whether armodafinil is a substrate or inhibitor (or inducer) of P-glycoprotein.

### *1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings*

The original NDA 21-875 was submitted for the **approval of the NUVIGIL™ oral tablets** of 50, 100, 150, and 250 mg strengths for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD). NUVIGIL tablets are formulated as immediate release uncoated tablets for oral **administration**. **Armodafinil (NUVIGIL™)** is the R-enantiomer of commercially available racemic modafinil (PROVIGIL®). PROVIGIL® was previously reviewed under NDA 20-717 and approved for the same indications.

Armodafinil and the racemic modafinil exhibit essentially similar pharmacological properties, but the precise mechanism(s) through which armodafinil (or modafinil) promotes wakefulness is unknown. The **recommended dose of NUVIGIL™ is 150 or 250 mg once daily (QD)** administered in the morning for patients with OSAHS or narcolepsy, and 150 mg QD for SWSD patients administered approximately 1 hour prior to start of work shift. Similar to the PROVIGIL tablets, dose adjustment should be made based on potential drug-drug interactions, severe hepatic function \_\_\_\_\_ and age (lower dose for elderly).

b(4) b(5)

Since the Sponsor referenced the PROVIGIL® NDA and the language in approved Provigil label, it is important to bridge the pharmacokinetics and the exposure-response relationships between the two. In support of the application the Sponsor has included seven clinical pharmacology and biopharmaceutic studies and six Phase 3 clinical efficacy studies:

- C10953a/101/PK/UK: Single ascending dose PK and food effect
- C10953a/102/PK/UK: Multiple ascending dose PK
- C10953a/103/PK/MN: PD profile and PK/PD relationship
- C10953/1023/BE/US: Dosage form bioequivalence
- C10953/1021/PK/US: Drug-drug interaction (CYP2C19)
- C10953/1022/PK/US: Drug-drug interaction (CYP3A4)
- C10953/1025/PK/US: Drug-drug interaction (CYP1A2)

- C10953/3020/NA/MN: Controlled efficacy trial (narcolepsy)
- C10953/3021/AP/MN: Controlled efficacy trial (OSAHS)
- C10953/3022/CM/MN: Controlled efficacy trial (Chronic SWSD)
- C10953/3025/AP/MN: Controlled efficacy trial (OSAHS)
- C10953/3023/ES/MN: Uncontrolled, ongoing efficacy trial
- C10953/3024/ES/MN: Uncontrolled, ongoing efficacy trial

Additional data were pooled from the Phase 1 and Phase 3 studies of PROVIGIL for the population PK and PK/PD modeling and simulation for dose and dose regimen selection.

### **Pharmacokinetic properties:**

The pharmacokinetic properties of armodafinil following administration of modafinil have been characterized and described in the approved PROVIGIL<sup>®</sup> label. On the basis of the distinct pharmacokinetic profiles of the R- and S-enantiomers following modafinil administration (NDA 20-717), the Sponsor expects the R-enantiomer or armodafinil to provide better tolerance (due to the lower  $C_{max}$ ) and a prolonged effect at the later time due to the 3-fold lower clearance. The half-lives of R- and S-enantiomers were 15 hours and 4 hours, respectively.

Following oral administration of NUVIGIL, the armodafinil exhibited dose-proportionality across the dose range of 50-400 mg in mean exposure measures ( $C_{max}$  and  $AUC_{0-inf}$ ). The time to reach peak concentration ( $T_{max}$ ) was approximately 2 hours in fasted state. Armodafinil exhibits an apparent monoexponential decline after reaching its peak concentrations, with a mean terminal  $t_{1/2}$  of approximately 15 hours. The mean terminal  $t_{1/2}$  of its major circulating metabolites, R-modafinil acid and modafinil sulfone, are approximately 16 and 38 hours, respectively.

Following multiple daily doses, the steady-state was achieved after 7 days and the steady-state levels of same dose remain similar between Day 7 and Day 14. The steady-state accumulation ratios of different doses remain consistent at approximately 1.4-1.9, suggesting the time-invariant linear PK properties across the dose range studied and with the proposed doses. The CL/F of armodafinil following multiple oral doses is approximately 33 mL/min. The V/F of armodafinil is approximately 42 L. Following multiple doses, contributions of R-modafinil acid remained similar (7%), while contribution of modafinil sulfone increased from 33% to 56%, suggesting the accumulation of this metabolite. No significant changes in mean trough concentrations of armodafinil, obtained from Phase 3 clinical trials in patients, with time were observed following chronic dosing.

### **Exposure-response relationship:**

(1) Comparison of armodafinil exposure following Nuvigil or Provigil administration: The PK profiles of R-modafinil and S-modafinil have been assessed with PROVIGIL at doses of 50 to 800 mg (NDA 20-717). Data were pooled from those studies for the comparison. The PK parameters were similar and dose-normalized (to 50 mg) mean

concentration profiles of armodafinil were approximately superimposable following single 50-mg doses of armodafinil or 100-mg doses of PROVIGIL. Mean concentration-time profiles and exposures ( $C_{max}$  and AUC) were generally comparable following daily doses of 150 mg and 250 mg of NUVIGIL with that following daily doses of 200 mg and 400 mg of PROVIGIL, respectively. Results support the dose and dose regimen used in efficacy studies and the proposed doses, and also support the potential dosage adjustments for armodafinil in reference to the PROVIGIL label.

(2) Time course of effect across the indications:

The primary objective measure in the trials was change from baseline to endpoint in average sleep latency, which was obtained from MWT for narcolepsy and OSAHS and from MSLT for the SWSD study. The analysis was performed with effect-time plots on the time course of effect over different weeks compared with placebo. It was concluded by the Pharmacometrics reviewer (based on the analysis on the time course of effect over different weeks compared with placebo) that treatment with Nuvigil increases the mean change in latency of sleep (MWT/MSLT) from baseline compared to placebo for all the three indications, the effect of Nuvigil was maintained over a period of 8 hours compared to placebo, and no consistent increase in effect was observed between various doses tested in the trials. Since there was no additional safety concern for the higher 250 mg/day dosing regimen, the proposed doses and the once daily dosing regimen for Nuvigil are justified.

(3) Relationship between effect and headache:

Headache was the most common adverse event reported in Nuvigil-treated patients in narcolepsy, OSAHS and SWSD patient populations. The relationship between wake promotion effect and headache (as a safety endpoint) was explored. Results show that no systematic relationship was seen across different treatment and placebo arms; however, a trend of increase in MWT seems to associate with increased proportion of patients in the treatment groups with headache.

**Drug-drug interactions:**

(1) CYP2C19:

Effect of armodafinil on activity of CYP2C19, using omeprazole as a probe substrate, was investigated in an open-label, 2-way crossover study in healthy subjects. Coadministration of armodafinil moderately inhibited CYP2C19 activity and increased omeprazole systemic exposure (i.e.,  $AUC_{0-\infty}$ ,  $AUC_{0-t}$ , and  $C_{max}$ ) by approximately 40%. Results of this study also suggest that co-medications that are substrates for CYP2C19 may require dosage reduction.

(2) CYP3A4:

Effect of armodafinil on CYP3A activity, using midazolam as a probe substrate, was investigated in an open-label, nonrandomized PK and safety study in healthy subjects. Pharmacokinetic profiles of midazolam following single-dose intravenous (2 mg) and oral (5 mg) alone and after approximately 4 weeks of repeated armodafinil doses starting 100 mg/day, then titrated up to 250 mg/day by day 11 were determined.

Coadministration of armodafinil resulted in approximate 17% and 32% reduction in systemic exposure for intravenous and oral midazolam, respectively, with corresponding **increases in exposure of 1'-hydroxymidazolam** metabolite. The 90% CI of the geometric mean ratios difference for ln-transformed exposure between two treatments fell outside the boundary of 80~125%, suggesting an interaction between armodafinil and midazolam. Armodafinil moderately induced both hepatic and intestinal CYP3A4 activity, which may result in reduced efficacy of drugs that are substrates for CYP3A4.

### (3) CYP1A2:

Effects of armodafinil on CYP1A2 activity was evaluated in an open-label, nonrandomized pharmacokinetics and safety study in healthy, non-smoking subjects. Pharmacokinetic profiles of caffeine following a single dose of 200-mg oral caffeine alone and after approximately 4 weeks of repeated armodafinil doses starting 100 mg/day, then titrated up to 250 mg/day by day 9 were determined. The results of this study show that armodafinil did not affect the systemic exposure (AUC or the  $C_{max}$ ) of caffeine and appears not to affect CYP1A2 activity.

### **BE of clinical vs. TBM formulation:**

The relative bioavailability of armodafinil was evaluated in a single-dose, randomized, open-label, 2-way crossover study designed to compare the 5 x 50-mg film-coated tablets employed in the Phase 3 clinical trials with 1 x 250-mg uncoated TBM tablet in healthy subjects under fasting conditions. Bioavailability and the pharmacokinetic profiles of a single oral dose of 5 x 50-mg coated tablets (clinical formulation) were similar to 1 x 250-mg uncoated tablet (proposed commercial formulation). The 90% CI of  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  based on the active parent moiety falls within acceptance criteria for BE, i.e., 80-125% CI. Therefore, statistical analysis demonstrated the bioequivalence between clinical formulations used in pivotal trials and the to-be-marketed formulation.

### **Effects of food:**

Food effects on relative bioavailability of armodafinil were evaluated with a prototype 50-mg capsule formulation (the lowest dosage strength) as part of a Phase 1, randomized, double-blind, placebo-controlled, parallel-group, single oral rising dose PK study in healthy young adult male subjects. Potential food effect was evaluated in 100 mg dose cohort in a parallel study design in 6 subjects. High-fat food had minimal effect on the  $C_{max}$  and AUC of armodafinil. However,  $t_{max}$  was prolonged from 2.3 hours to 6 hours. Statistical analysis of exposure measurements,  $AUC_{0-\infty}$  and  $C_{max}$ , estimated by this reviewer did not conform to the acceptance criteria for BE and could be attributed to the deficiencies in study design (parallel design and small number of subjects).

This food effect study was conducted on the prototype capsule formulations, instead of either clinical formulations or the TBM formulations. The capsules are qualitatively similar in composition to the clinical formulations which are of identical composition to the TBM formulations. In view of the similarity in formulation composition and in in-vitro dissolution profiles between the prototype and clinical formulations, plus the BE

results with TBM formulations, the similar food effect could be anticipated on the armodafinil absorption from NUVIGIL tablets. Even though no major food effect was noted on  $C_{max}$  and AUC, the effect on  $T_{max}$  (delay) could be a concern with a potential for delayed onset of action and higher armodafinil levels later in the day (with a concern for insomnia) when given with food. \_\_\_\_\_

b(5)

**Dissolution Specifications:**

The proposed dissolution method and specification for NUVIGIL tablet was based on the previously approved method and specification for the PROVIGIL tablet. The dissolution of all test armodafinil formulations occurred rapidly and exceeded \_\_\_\_\_ of the label claim amount in \_\_\_\_\_ while near completion occurred in \_\_\_\_\_. We believe that the regulatory specifications of armodafinil tablets could be tightened. The recommended dissolution method and specifications for NUVIGIL tablets are as follows:

b(4)

Apparatus: USP apparatus 2 (Paddle)

Stirring Speed: 50 rpm

Dissolution Medium: 0.1N HCl

Volume of Medium: 900 mL

Temperature: 37.0 °C

Specification:  $Q =$  \_\_\_\_\_ in 30 minutes

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Office of Clinical Pharmacology

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## ***2. QUESTION-BASED REVIEW (QBR)***

### ***2.1 General Attributes of the Drug***

#### ***2.1.1 What pertinent regulatory background or history contributes to the current assessments of this drug?***

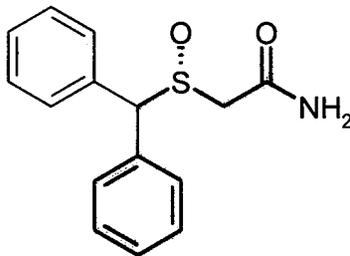
Cephalon, Inc. submitted an original NDA on March 31, 2005, for NUVIGIL™ oral tablets of 50, 100, 150, and 250 mg strengths to seek approval for the treatment of adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS), and shift work sleep disorder (SWSD).

Armodafinil (NUVIGIL™) is the R-enantiomer of commercially available racemic modafinil (PROVIGIL®). PROVIGIL® was previously reviewed under NDA 20-717 and approved for the same indications, with recommended dose at 200 mg given once a day. In support of the application, the sponsor has conducted one BE study for 5 x 50 mg coated tablets (clinical formulation) vs. 1 x 250 mg uncoated tablets (TBM formulation), two Phase 1 studies to evaluate single- and multiple-dose PK, tolerability, and food effects, three Phase 1 studies to evaluate the potential drug-drug interactions, one pharmacokinetic/pharmacodynamic study and population pharmacokinetic analysis to determine the dosing regimen, and six Phase 3 clinical trials (4 controlled, 2 uncontrolled and ongoing) to evaluate the efficacy and safety of the armodafinil treatment in patients with OSAHS, SWSD, and narcolepsy. In vitro dissolution profiles of TBM uncoated formulation of all four strengths were constructed in 5 media of different pH values, including deionized water. Comparative in vitro dissolution was also evaluated between 50 mg (clinical formulation) and 250 mg (TBM formulation) strengths, and between 50 mg prototype capsule and 50 mg clinical formulation.

#### ***2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?***

NUVIGIL™ (armodafinil) is a wakefulness-promoting agent for oral administration. Armodafinil is the R-enantiomer of modafinil which is a racemic mixture of the R- and S-enantiomers in 1:1 ratio. Provigil label states that there is no interconversion between the R- and S-enantiomers. The chemical name for armodafinil is 2-[(R)-(diphenylmethyl)sulfinyl]acetamide. The molecular formula is C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>S and the molecular weight is 273.35.

Figure 1. Chemical structure of armodafinil



Armodafinil is a white to off-white, crystalline powder that is very slightly soluble in water, sparingly soluble in acetone and soluble in methanol. NUVIGIL tablets contain 50, 100, 150 or 250 mg of armodafinil and inactive ingredients, including lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, and magnesium stearate.

Four dose strengths (50 mg, 100 mg, 150 mg, and 250 mg) are proposed for the to-be-marketed NUVIGIL™ (armodafinil) uncoated tablets to cover the therapeutic dose range, with appearance described in Section 2.5.1. The composition of the proposed commercially available armodafinil tablets are shown in Table 13. The clinical formulations are film-coated tablets. The armodafinil used in pharmacokinetic profiling in Phase 1 studies was formulated as prototype capsules.

### *2.1.3 What are the proposed mechanism of action and therapeutic indication?*

Similar to PROVIGIL, the proposed indication of NUVIGIL™ (armodafinil) tablet formulation is for the treatment of excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome (OSAHS), shift work sleep disorder (SWSD), or narcolepsy. In OSAHS, NUVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction.

According to the PROVIGIL label, nonclinical animal and in vitro studies demonstrated essentially similar pharmacological properties for both armodafinil and modafinil. In addition to its wake-promoting effects in nonclinical animal models, armodafinil enhanced cognitive ability in aged rats. The precise mechanism(s) through which armodafinil (or modafinil) promotes wakefulness is unknown. At pharmacologically relevant concentrations, armodafinil does not bind to receptors potentially relevant for sleep/wake regulation, nor does armodafinil inhibit the enzymes relevant to sleep/wake regulation. It is not a direct- or indirect-acting dopamine receptor agonist. However, armodafinil increased activation in wake-associated brain regions in the rat, including the tuberomammillary nucleus and cortex. The pharmacological profiles of armodafinil and modafinil are distinct from that of sympathomimetic agents, while both armodafinil and modafinil produced similar levels of wake enhancement in animals. Additional information is available in the approved PROVIGIL label.

### *2.1.4 What are the proposed dosages and route of administration?*



Table 1. Clinical pharmacology programs and clinical trials for this NDA submission

Study Protocol	Dose regimen Duration of treatment	Study population Variables	No. treated
<b>C10953a/101/PK/UK: (Study 101)</b>  A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Pharmacokinetics, Safety, and Tolerability of Single Oral Rising Doses of CEP-10953 in Healthy Young Men	Armodafinil: <b>fasting (d1)</b> – 50, 100, 200, 300, or 400 mg and <b>nonfasting (d12)</b> – 100 mg (only subjects who received 100-mg dose on d1)  matching placebo	Healthy male subjects  Pharmacokinetics  Safety	N=40
<b>C10953a/102/PK/UK: (Study 102)</b>  A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Pharmacokinetics, Safety, and Tolerability of Multiple Ascending Oral Doses of CEP-10953 in Healthy Young Men	Armodafinil: once daily (AM) 50, 100, 200, 250, 300 or 400 mg  matching placebo: once daily (AM)  14 days	Healthy male subjects  Pharmacokinetics  Safety	N=49
<b>C10953a/103/PK/MN: (Study 103)</b>  A Double-Blind, Randomized, Placebo-Controlled and Active-Controlled (PROVIGIL®), Parallel-Group Study to Evaluate the Pharmacodynamic Profile and the Pharmacokinetic/ Pharmacodynamic Relationship of Single Doses of CEP-10953 (100, 150, 200, and 300 mg) in Subjects Undergoing Acute Sleep Deprivation	Armodafinil: 100, 150, 200, or 300 mg  PROVIGIL: 200 mg  matching placebos: (6 capsules and 2 tablets)  single dose	Healthy young men  Pharmacokinetics  Pharmacodynamics  Safety	N=107
<b>C10953/1023/BE/US: (Study 1023)</b>  A Randomized, Open-Label Crossover Study to Evaluate the Bioequivalence of CEP 10953 Tablets (Five 50-mg Tablets Versus One 250 mg Tablet) in Healthy Subjects	Armodafinil: 5 x 50-mg tablets and 1 x 250-mg tablet in randomized sequence with a 7-day washout period  2 single doses	Healthy subjects  Pharmacokinetics  Safety	N=30

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<p><b>C10953/1021/PK/US: (Study 1021)</b></p> <p>An Open-Label, Crossover Pharmacokinetics and Safety Study to Evaluate the Effect of CEP-10953 on CYP2C19 Activity in Healthy Subjects Using Omeprazole as a Probe Substrate</p>	<p>Omeprazole: 1 x 40-mg capsule (Treatment A) and armodafinil: 8 x 50-mg tablets followed in 2 hr by 40 mg omeprazole (Treatment B)</p> <p>Treatment A and Treatment B were administered in randomized sequence and separated by a 7-day washout period.</p> <p>2 single doses</p>	<p>Healthy subjects</p> <p>Pharmacokinetics</p> <p>Safety</p>	<p>N=24</p>
<p><b>C10953/1022/PK/US: (Study 1022)</b></p> <p>An Open-Label Pharmacokinetics and Safety Study to Evaluate the Effect of Repeated Administration of CEP-10953 on CYP3A4 Activity in Healthy Subjects Using Midazolam (Intravenous and Oral) as the Probe Substrate</p>	<p>Armodafinil: once daily d5-6: 100 mg d7-8: 150 mg d9-10: 200 mg d11-36: 250 mg</p> <p>IV midazolam: 2 mg d1 and d33 oral midazolam: 5 mg d4 and d36</p> <p>36 days</p>	<p>Healthy subjects</p> <p>Pharmacokinetics</p> <p>Safety</p>	<p>N=24</p>
<p><b>C10953/1025/PK/US: (Study 1025)</b></p> <p>An Open-Label Pharmacokinetic and Safety Study to Evaluate the Effect of Repeated Administration of CEP-10953 on CYP1A2 Activity in Healthy Subjects Using Caffeine as the Probe Substrate</p>	<p>Armodafinil: once daily d3-4: 100 mg d5-6: 150 mg d7-8: 200 mg d9-32: 250 mg</p> <p>oral caffeine: 200 mg d1 and d31</p> <p>32 days</p>	<p>Healthy subjects</p> <p>Pharmacokinetics</p> <p>Safety</p>	<p>N=29</p>
<p><b>C10953/3020/NA/MN: (Study 3020)</b></p> <p>A 12-Week, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CEP-10953 (150 and 250 mg/day) as Treatment for Adults With Excessive Sleepiness Associated With Narcolepsy</p>	<p>Armodafinil: once daily (AM) 150 or 250 mg</p> <p>placebo: once daily (AM)</p> <p>12 weeks</p>	<p>Narcolepsy</p> <p>Pharmacodynamics</p> <p>Pharmacokinetics</p> <p>Safety</p>	<p>N=194</p>
<p><b>C10953/3021/AP/MN: (Study 3021)</b></p> <p>A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CEP-10953 (150 and 250 mg/day) as Treatment for Adults With Residual Excessive Sleepiness Associated With Obstructive Sleep Apnea/ Hypopnea Syndrome</p>	<p>Armodafinil: once daily (AM) 150 or 250 mg</p> <p>placebo: once daily (AM)</p> <p>12 weeks</p>	<p>OSAHS</p> <p>Pharmacodynamics</p> <p>Pharmacokinetics</p> <p>Safety</p>	<p>N=392</p>

<p><b>C10953/3022/CM/MN: (Study 3022)</b></p> <p>A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CEP-10953 (150 mg) as Treatment for Adults With Excessive Sleepiness Associated With Chronic Shift Work Sleep Disorder</p>	<p>Armodafinil: once daily 150 mg</p> <p>placebo: once daily</p> <p>12 weeks</p> <p>Study drug taken prior to night shift, but not later than 2300 only on nights worked.</p>	<p>Chronic SWSD</p> <p>Pharmacodynamics</p> <p>Safety</p>	<p>N=254</p>
<p><b>C10953/3025/AP/MN: (Study 3025)</b></p> <p>A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of CEP-10953 (150 mg/day) as Treatment for Adults With Residual Excessive Sleepiness Associated With Obstructive Sleep Apnea/ Hypopnea Syndrome</p>	<p>Armodafinil: once daily (AM) 150 mg</p> <p>placebo: once daily (AM)</p> <p>12 weeks</p>	<p>OSAHS</p> <p>Pharmacodynamics</p> <p>Pharmacokinetics</p> <p>Safety</p>	<p>N=259</p>
<p><b>C10953/3023/ES/MN: (Study 3023)</b></p> <p>A 12-Month, Open-Label, Flexible-Dosage (100 to 250 mg/day) Study of the Safety and Efficacy of CEP-10953 in the Treatment of Patients With Excessive Sleepiness Associated With Narcolepsy, Obstructive Sleep Apnea/ Hypopnea Syndrome, or Chronic Shift Work Sleep Disorder</p>	<p>Armodafinil: once daily 100 to 250 mg</p> <p>Up to 12 months</p> <p>Narcolepsy or OSAHS: AM</p> <p>Chronic SWSD: prior to night shift but no later than 2300, only on nights worked</p>	<p>Narcolepsy, OSAHS, or chronic SWSD (ongoing)</p> <p>Pharmacodynamics</p> <p>Safety</p>	<p>N=319</p>
<p><b>C10953/3024/ES/MN: (Study 3024)</b></p> <p>A 12-Month, Open-Label, Flexible-Dosage (100 to 250 mg/day) Extension Study of the Safety and Efficacy of CEP-10953 in the Treatment of Patients With Excessive Sleepiness Associated With Narcolepsy, Obstructive Sleep Apnea/ Hypopnea Syndrome, or Chronic Shift Work Sleep Disorder</p>	<p>Armodafinil: once daily 100 to 250 mg</p> <p>Up to 12 months</p> <p>Narcolepsy or OSAHS: AM</p> <p>Chronic SWSD: prior to night shift but no later than 2300, only on nights worked</p>	<p>Narcolepsy, OSAHS, or chronic SWSD (ongoing)</p> <p>Pharmacodynamics</p> <p>Safety</p>	<p>N=521</p>

Note: Related IND and NDA are IND 68,571 and NDA 20-717

The prototype formulation of lower strength (50 mg capsule) was used in three Phase 1 PK and PK/PD studies (101, 102, and 103). The food effect was evaluated as part of the Phase 1 study (101) using this lower 50 mg strength capsule formulation. The clinical formulation (film-coated tablets) was used in the remaining three Phase 1 drug-drug interactions studies (1021, 1022, and 1025) and was linked to the to-be-marketed formulation (TBM, uncoated tablets) through a bioequivalence study (1023).

***2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?***

The primary efficacy endpoint in the trials for OSAHS and narcolepsy was Maintenance of Wakefulness Test (MWT). The patient was instructed to stay awake in a darkened room, and four 20 minute-sessions performed at 2-hour intervals. The score for that visit is the average of the time it takes for the patient to fall asleep over the 4 sessions. It was assessed as the mean change from the baseline assessment in mean sleep latency from MWT (average of 4 naps at 0900, 1100, 1300, and 1500) at week 12 or last post-baseline observation.

The primary efficacy endpoint in the trials for SWSD was Multiple Sleep Latency Test (MSLT, average of 4 naps at 0200, 0400, 0600 and 0800 hours) at week 12 or last post-baseline observation. MSLT is a test similar to the MWT and scored the same way as MWT, except that subjects are instructed to not resist falling asleep.

These primary efficacy endpoints, along with the Clinical Global Impression of Change (CGI-C) ratings, are considered as standard measures commonly used in clinical studies of sleep disorders and have been used in clinical studies with PROVIGIL (NDA 20-717).

***2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?***

The plasma levels of R-modafinil (the active moiety) and its 2 major circulating metabolites, R-modafinil acid and modafinil sulfone, were identified and measured using validated methods employing ~~high-performance liquid chromatography~~ high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection. Detailed description of the analytical procedures is presented in the Analytical Section 2.6. Use of ~~assay~~ assay is acceptable because there is no interconversion between the R- and S-enantiomers (labeling statement). ~~assay~~ assay was used to measure R-enantiomer for relevant PROVIGIL studies where exposure comparison of armodafinil to PROVIGIL was made.

***2.2.4 Exposure-response relationships***

***2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy and safety, and are dose and dose regimen properly selected based on population PK and PK/PD analyses?***

The Sponsor performed population PK modeling using Phase 1 armodafinil studies and Phase 1 PROVIGIL studies to simulate plasma concentration-time profiles to be included in PK/PD modeling. The previously established PK/PD modeling and simulation for PROVIGIL were used to assist in the design and dosage regimen selection for the armodafinil Phase 3 studies. The Phase 1 study (103) with armodafinil provided the primary source of information for bridging PROVIGIL efficacy and the predicted

armodafinil efficacy. Details related to the following questions (2) and (3) are summarized in Pharmacometric review section.

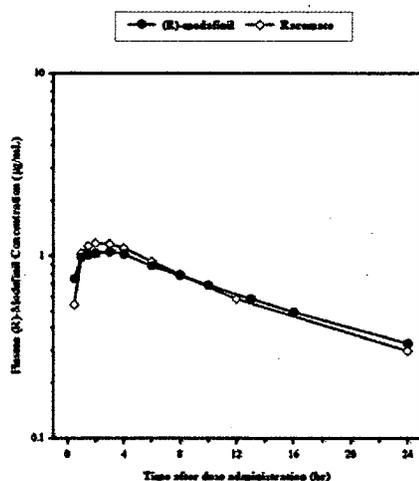
*(1) How does the exposure of armodafinil compare when administered as Nuvigil compared to Provigil?*

The pharmacokinetic characterization for armodafinil was conducted in 3 Phase 1 studies (studies 101, 102, and 103), a BE study (Study 1023), 3 Phase 1 drug-drug interaction studies (Studies 1021, 1022, and 1025), and three 12-weeks Phase 3 clinical trials (Studies 3020, 3021, and 3025). The single-dose and multiple-dose pharmacokinetic profiles of R-modafinil and S-modafinil have been assessed, using enantioselective HPLC-UV methods, in PROVIGIL Studies 103, 106, and 2101, following PROVIGIL administration at doses of 50 to 800 mg (NDA 20-717).

The Sponsor pooled data from PROVIGIL studies (referred to data in NDA 20-717) to support the present submission by comparing the PK profiles of R-enantiomer following administration of PROVIGIL (the racemate) and NUVIGIL (pure R-enantiomer) under fasting conditions. The data were dose-normalized to a 50 mg of armodafinil (representative of the R-modafinil fraction in the lowest dose of the racemic modafinil 100 mg in the PROVIGIL studies).

As shown in the following figure, pharmacokinetic properties of R-modafinil following single-dose of oral armodafinil 50 mg (armodafinil Studies 101, 102, and 103) or PROVIGIL 100 mg (PROVIGIL Study 103) were similar and mean R-modafinil concentration profiles were approximately superimposable.

Figure 2: Mean plasma concentration profiles of R-modafinil following a single dose of NUVIGIL 50 mg or PROVIGIL 100 mg



As shown in the following figure and table, the mean concentration-time profiles of R-modafinil and racemic modafinil were also compared following multiple doses of armodafinil (150 mg and 250 mg) and PROVIGIL (200 mg and 400 mg), respectively, at

their respective therapeutic doses. Of note, the slightly lower  $C_{max}$  of R-modafinil is offset by higher plasma levels at later time. The systemic exposure measures ( $C_{max}$  and AUC) were generally comparable.

Figure 3: Mean plasma concentration profiles of R-modafinil and modafinil following multiple daily doses of NUVIGIL or PROVIGIL

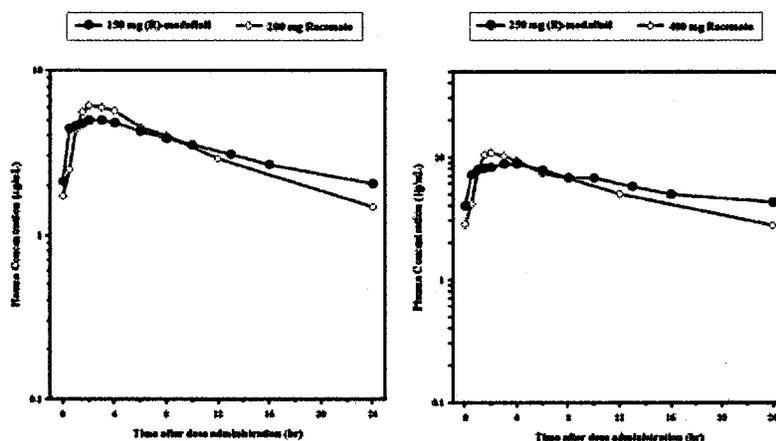


Table 2: Comparison of systemic exposure of R-modafinil and racemic modafinil following multiple daily doses of NUVIGIL or PROVIGIL

	$C_{max}$ ( $\mu\text{g/mL}$ )	AUC ( $\mu\text{g}\cdot\text{h/mL}$ )
150 mg R-modafinil	5	~80
200 mg modafinil	6	
250 mg R-modafinil	9	~140
400 mg modafinil	11	

The multiple daily doses of 150 mg and 250 mg of NUVIGIL are thus expected to result in the comparable systemic exposure with that following daily doses of 200 mg and 400 mg of PROVIGIL, respectively, and therefore supporting the dose and dose regimen for efficacy studies and for proposed doses. Results also support the potential dosage adjustments for armodafinil in reference to the PROVIGIL label.

*(2) What is the time course of effect across the indications?*

The primary objective measure in the trials was change from baseline to endpoint (last post-baseline observation) in average sleep latency, which was obtained from MWT (average of 4 tests at 0900, 1100, 1300 and 1500 hours) for narcolepsy and OSAHS and from MSLT (average of 4 naps at 0200, 0400, 0600 and 0800 hours) for the SWSD study.

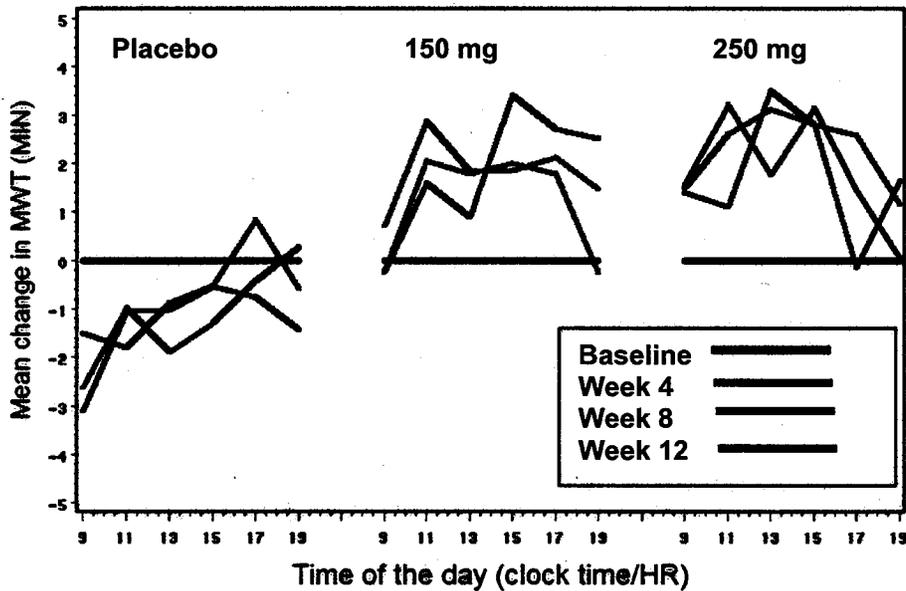
**The sponsor's effectiveness analysis involved** comparisons of the change in sleep latency from baseline averaged across clusters of time-points following dosing (early and late). Such an analysis will not be able to accurately describe wake promotion over the entire

day. Since the average change in the sleep latency does not provide insight into the time course of drug effect, the graphic presentation of effect-time plots were used to describe the time course of effect over different weeks compared with placebo.

Narcolepsy:

The time course of change in time matched mean sleep latency from baseline over the 6 naps at weeks 4, 8 and 12 for placebo and Nuvigil (150 and 250 mg/day) groups is shown in the figure (Figure 4) below. Either doses of Nuvigil consistently increase the sleep latency to a similar extent from baseline **and maintained till 15:00–17:00 hours at weeks 4, 8 and 12 respectively**. However, the intensity of the effect begins to decline by 15:00 hrs and is more pronounced with 250 mg/day dosing regimen. The loss of drug effect by 19:00 hours is more evident by 12th week compared to weeks 4 and 8.

Figure 4: Time course of effect in patients with Narcolepsy (Study 3020)



OSAHS:

The time course of baseline corrected change in time-matched mean sleep latency over 6 naps at weeks 4, 8 and 12 for placebo and Nuvigil (150 and 250 mg/day) groups is shown in the figures (Figures 5 & 6) below. It can be seen from the effect-time plots, Nuvigil increases the sleep latency compared to **placebo and maintains till 17:00–19:00 hours**. However, the effect of Nuvigil starts to decline by 15:00 hours with 150 mg/day and by 13:00 hours for 250 mg/day regimen. This decline is comparatively more pronounced at weeks 8 and 12.

Figure 5: Time course of effect in patients with OSAHS (Study 3021)

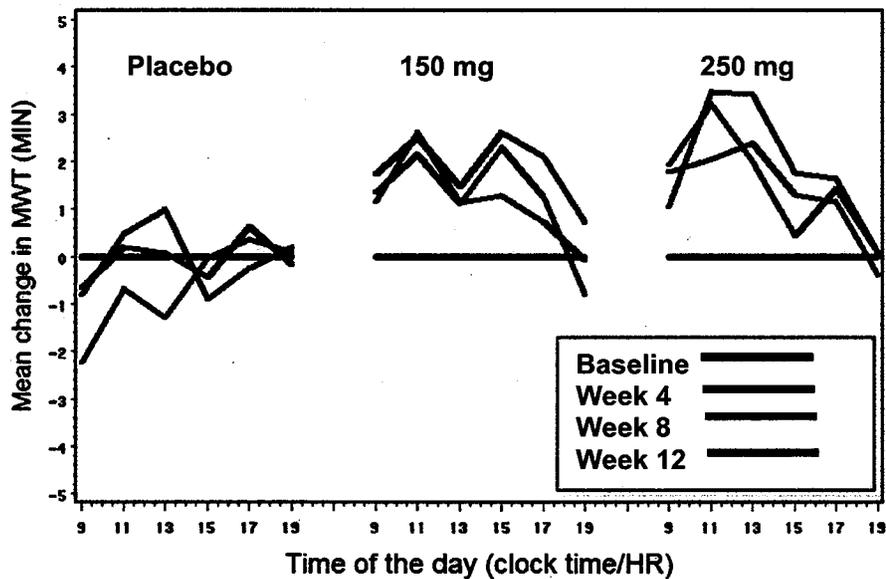
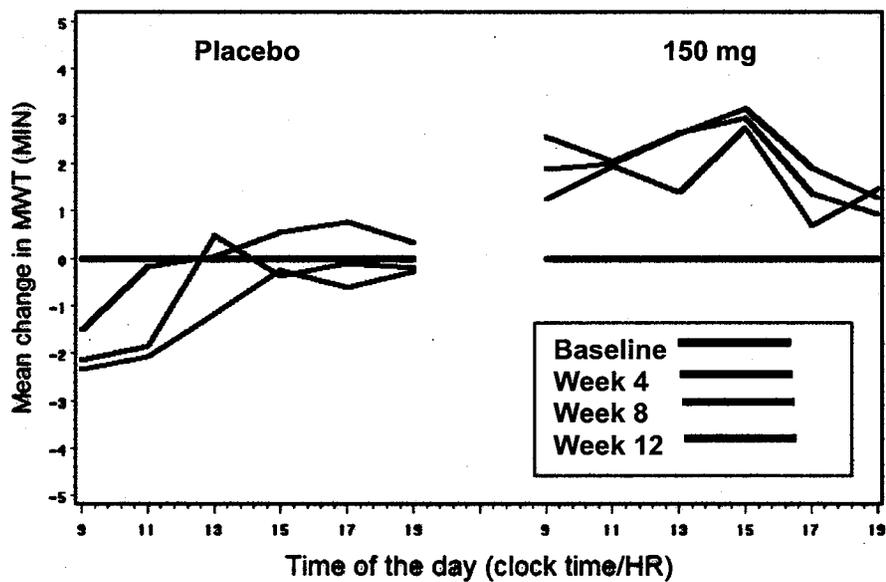


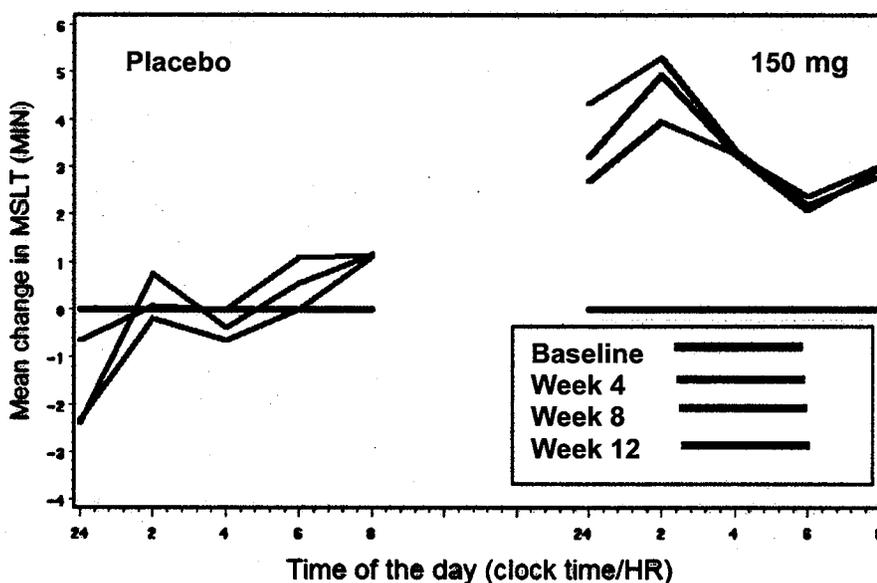
Figure 6: Time course of effect in patients with OSAHS (Study 3025)



**SWSD:**

The time course of change in sleep latency as assessed from MSLT from baseline over 5 naps at weeks 4, 8 and 12 for placebo and Nuvigil (150 mg/day) groups is shown in the figure (Figure 7) below. Nuvigil increases the sleep latency by 24:00 hours and maintains wakefulness consistently above the baseline levels till 08:00 hours. The maximum increase from baseline was seen at 02:00 hours which increased with every visit.

Figure 7: Time course of effect in patients with SWSD (Study 3022)



Therefore, on the basis of the present analysis, it can be concluded that:

1. Treatment with Nuvigil increases the mean change in latency of sleep (MWT/MSLT) from baseline compared to placebo for all the three indications.
2. The effect of Nuvigil was maintained over a period of 8 hrs compared to placebo. Hence once a day dosing regimen for Nuvigil is justified.
3. No consistent increase in effect was observed between various doses tested in the trials.

***(3) Is there a relationship between effect and headache?***

The Sponsor did not conduct formal analysis for the safety endpoints. As reported, headache was the most common adverse event reported for 22%, 17% and 12% of the Nuvigil treated patients in narcolepsy, OSAHS and SWSD patient populations, respectively, compared to 8-11% range of incidence among the placebo-treated patients across the target populations.

Attempt was made by the Pharmacometrics reviewer to explore the relationship between headache and the wake promotion effect of Nuvigil. Patients treated with 150 mg/day Nuvigil had lesser percent of patients with headache compared with those receiving 250 mg/day (16% vs. 28% for Narcolepsy, 15% vs. 21% for OSAHS). Similarly the change in mean latency from baseline increases with increase in the dose from 150 mg/day to 250 mg/day (1.3 min vs. 2.6 min for Narcolepsy, 1.7 min vs. 2.2 min for OSAHS). Plots of change in MWT and the corresponding proportion of patients experiencing headache were generated to explore the relationship between effect and headache. Effect versus headache rate for various treatment arms are shown in the figure (Figure 8-10) below.

Narcolepsy:

No systematic relationship was seen across different treatment and placebo arms. However, in the treatment arms, an increase in MWT from baseline corresponding to the 4th quartile was associated with high proportion of patients with headache.

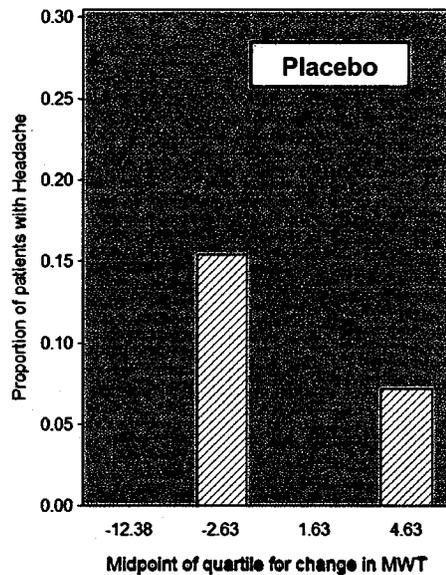
OSAHS:

Trends toward increase in the proportion of patients experiencing headache with the increase in MWT from baseline could be observed in the Nuvigil arms. Moreover, the change in MWT corresponding to 3rd and 4th quartiles were associated with the highest proportion of the patients reporting headaches for the arms in the trial

SWSD:

No relationship was found between the change in MSLT and proportion of patients experiencing headache for the placebo and Nuvigil groups. However, in the treatment arm, increase in MWT was associated with increased proportion of patients with headache.

Figure 8: Relationship between proportion of patients with headache and MWT in Narcolepsy study



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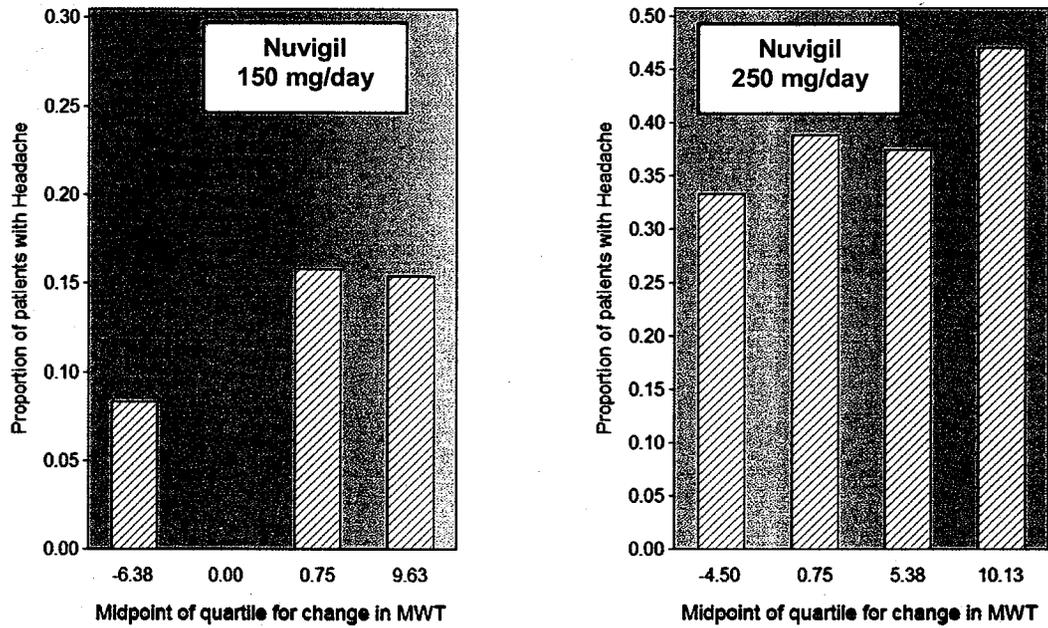
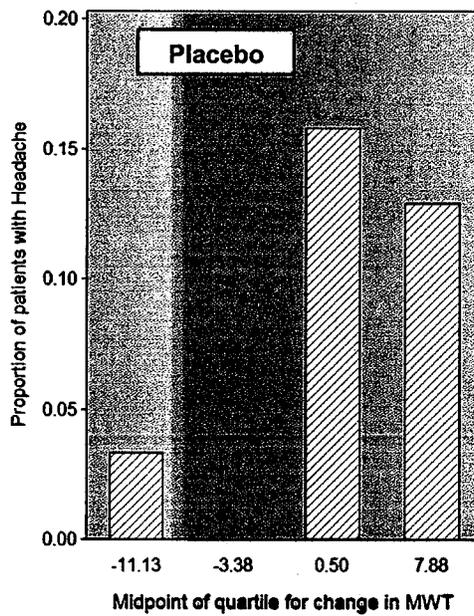


Figure 9: Relationship between proportion of patients with headache and MWT in OSAHS study.



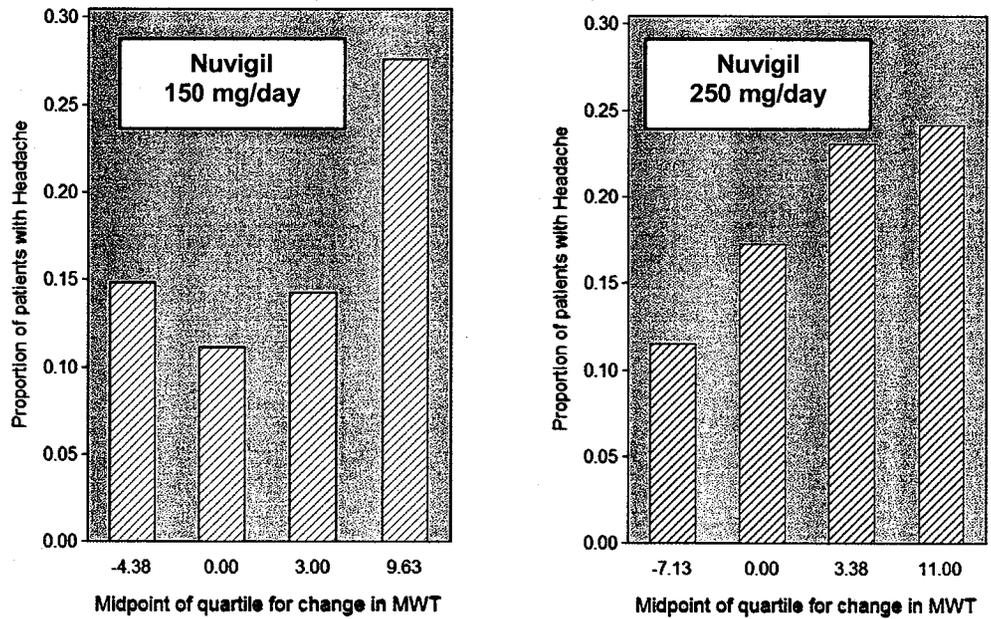
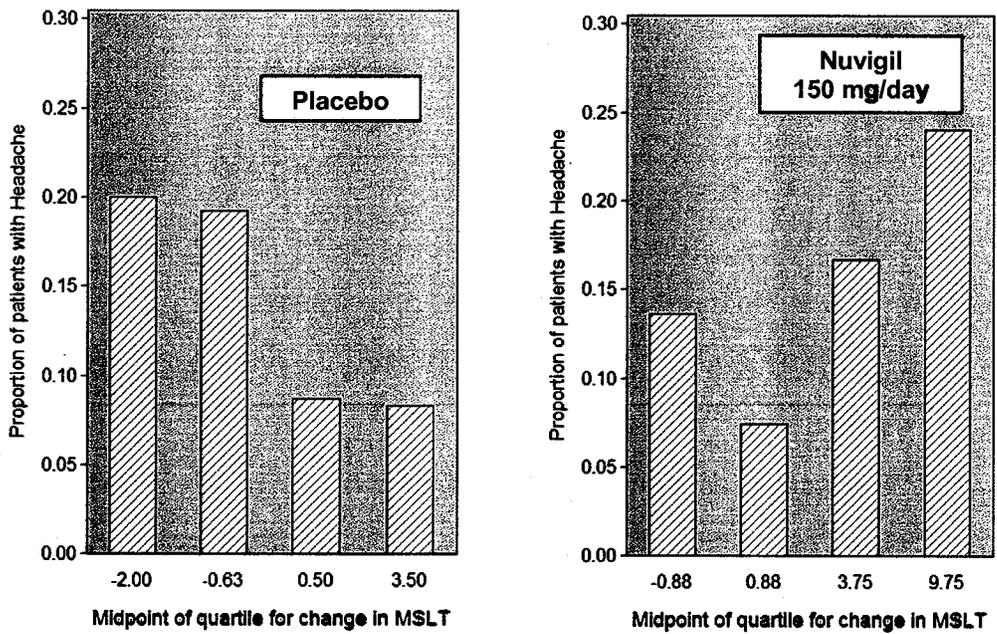


Figure 10: Relationship between proportion of patients with headache and MWT in SWSD study.



Thus on the basis of the present analysis, it can be concluded that in the treatment arms, the 4th quartiles corresponding to the increase in MWT from baseline were associated with a higher proportion of patients experiencing headaches.

**Reviewer's comment:**

- The above questions (2) and (3) were summarized based on review of population PK and PK/PD analyses by the pharmacometric reviewer, Dr. Rajanikanth Madabushi. It was concluded that the dose and dose regimen used in the pivotal Phase 3 clinical trials were properly selected by the Sponsor.
- Since there was no safety concern for the higher 250 mg/day dose and dose regimen, this proposed dose and dose regimen is deemed acceptable. More details are available in Pharmacometric review in the Appendix section.

***2.2.4.3 Does this drug prolong the QT or QTc interval?***

There was no formal QT study conducted by the sponsor. In Phase 1 PK studies, the 12-lead ECG was carried out at baseline, during and at the completion of the study and no treatment-emergent ECG abnormalities were found. According to the safety report for the double-blind, placebo-controlled clinical studies for up to 12 weeks, there were no clinically meaningful changes with respect to relevant QT/QTc or other ECG interval values from baseline to endpoint between the active armodafinil treatment and placebo treatment groups across the sleep disorder populations.

***2.2.4.4 Are the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? (In some cases, it may be possible to combine this with 2.2.4.2 and 2.2.4.3.)***

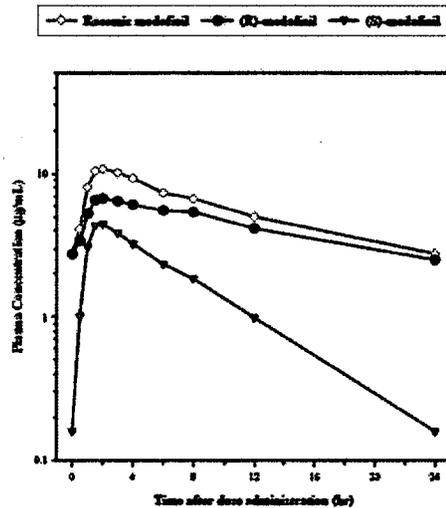
Reanalysis of the population PK and PK/PD relationships by Pharmacometric reviewer confirms that the dose and dosing regimen (i.e., 150 and 250 mg/day for OSAHS and narcolepsy, and 150 mg/day for SWSD) selected by the sponsor for pivotal clinical trials and for labeling are appropriate. (Referred to Section 2.2.4.1.)

***2.2.5. What are the pharmacokinetic characteristics of the drug and its major metabolite?***

***2.2.5.1 What are the single dose and multiple dose PK parameters?***

Comparison of the typical pharmacokinetic profiles between R- and S-enantiomers is shown in the following figure (NDA 20-717). The terminal  $t_{1/2}$  of R- and S-modafinil are approximately 15 hours and 4 hours, respectively. The ratio of AUCs for R-modafinil to S-modafinil is approximately 3:1, where R-modafinil represents approximately 75% of the exposure following multiple-dose administration of the racemate. Therefore, R-modafinil is the predominant enantiomer following administration of the racemic modafinil.

Figure 11. Mean steady-state plasma concentration profiles of R-modafinil and S-modafinil compared with modafinil (racemate) after multiple-dose administration of PROVIGIL 400 mg/day (NDA 20-717)



In the current submission, pharmacokinetic profiling of R-modafinil was carried out in armodafinil Study 101 and 102. Additional PK information was available from the BE study 1023.

**Study 101:** This was a randomized, double-blind, placebo-controlled, parallel-group study of single oral rising doses (50, 100, 200, 300, and 400 mg) of CEP-10953 in 40 healthy young adult male subjects under fasting condition. Food effect on PK profile of the single 100-mg dose was also evaluated.

**Study 102:** This was a randomized, double-blind, placebo-controlled, parallel-group study of multiple rising oral doses (50, 100, 200, 300, and 400 mg QD) of CEP-10953 in 49 healthy young adult male subjects under fasting condition.

**Study 1023:** This was a randomized, open-label, single-center, two-way crossover PK and safety study in 30 healthy subjects under fasting conditions. The PK profiles of single oral doses of 5 x 50-mg and 1 x 250 mg tablets were evaluated.

Representative plasma concentration-time profiles following single and multiple doses are shown in the following figures (Study 102). The mean pharmacokinetic parameters of armodafinil and its two major circulating metabolites, R-modafinil acid and modafinil sulfone, based on pooled results (Study 101, 102, and 1023) are summarized in the following tables. More details are available in the Individual Review section.

Figure 12. Mean plasma concentration-time profiles following multiple oral doses of NUVIGIL in healthy subjects on Day 1 (left) and Day 14 (right)

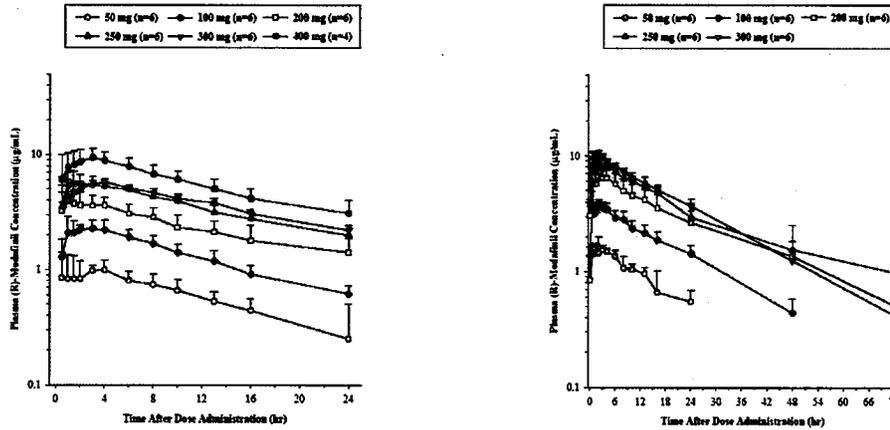


Table 3. Mean pharmacokinetic parameters of R-modafinil following single and multiple doses of NUVIGIL in healthy subjects (parameters normalized to a 50-mg dose)

Parameter (unit) Statistic	Single dose	Multiple dose	
	(N=93)	Day 7 (N=34)	Day 14 (N=30)
<b>AUC<sub>0-∞</sub> (µg·h/mL)</b>			
n	93	NA	NA
Mean±SD	24.1±6.89	NA	NA
<b>AUC<sub>0-t</sub> (µg·h/mL)</b>			
n	NA	34	30
Mean±SD	NA	27.1±5.75	26.1±4.03
<b>C<sub>max</sub> (µg/mL)</b>			
n	93	34	30
Mean±SD	1.3±0.36	1.8±0.36	1.9±0.37
<b>t<sub>max</sub> (h)</b>			
n	93	34	30
Median (range)	1.5 (0.5, 6.0)	2.0 (0.5, 6.0)	1.8 (0.0, 4.0)
<b>t<sub>1/2</sub> (h)</b>			
n	87	4	30
Mean±SD	13.8±3.31	15.3±3.04	16.9±3.13
<b>V/F (L)</b>			
n	93	4	30
Mean±SD	42.4±12.54	54.5±31.42	47.4±8.66
<b>CL/F (mL/min)</b>			
n	93	34	30
Mean±SD	38.6±9.86	32.4±8.72	32.7±5.16
<b>R<sub>ss</sub></b>			
n	NA	34	30
Mean±SD	NA	1.2±0.18	1.2±0.19
<b>R<sub>obs</sub></b>			
n	NA	34	30
Mean±SD	NA	1.8±0.27	1.7±0.20

Table 4. Mean pharmacokinetic parameters of R-modafinil acid following single and multiple doses of NUVIGIL in healthy subjects (parameters normalized to a 50-mg dose)

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Parameter (unit) Statistic	Single dose	Multiple dose	
	(N=57)	Day 7 (N=22)	Day 14 (N=18)
AUC <sub>0-∞</sub> (µg·h/mL)			
n	57	NA	NA
Mean±SD	2.7±0.89	NA	NA
AUC <sub>0-t</sub> (µg·h/mL)			
n	NA	22	18
Mean±SD	NA	2.1±0.65	1.9±0.67
C <sub>max</sub> (µg/mL)			
n	57	22	18
Mean±SD	0.1±0.04	0.1±0.04	0.1±0.04
t <sub>max</sub> (h)			
n	57	22	18
Median (range)	3.0 (1.0, 6.0)	2.0 (0.0, 24.0)	2.0 (0.0, 4.0)
t <sub>1/2</sub> (h)			
n	57	4	15
Mean±SD	15.3±4.34	17.4±5.47	20.7±9.13

Table 5. Mean pharmacokinetic parameters of modafinil sulfone following single and multiple doses of NUVIGIL in healthy subjects (parameters normalized to a 50-mg dose)

Parameter (unit) Statistic	Single dose	Multiple dose
	(N=39)	Day 14 (N=24)
AUC <sub>0-∞</sub> (µg·h/mL)		
n	39	NA
Mean±SD	8.0±2.29	NA
AUC <sub>0-t</sub> (µg·h/mL)		
n	NA	24
Mean±SD	NA	14.7±10.19
C <sub>max</sub> (µg/mL)		
n	39	24
Mean±SD	0.1±0.03	0.7±0.50
t <sub>max</sub> (h)		
n	39	24
Median (range)	24.0 (13.0, 42.0)	3.0 (0.0, 16.0)
t <sub>1/2</sub> (h)		
n	39	24
Mean±SD	37.6±12.78	39.2±17.27

**2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

The mean trough concentrations of armodafinil were compared between Day 14 in healthy subjects (Study 102) and in Phase 3 clinical trials for up to 12 weeks (Study 3020 as an example) following the same multiple daily doses. PK appears to be similar between patients and healthy volunteers. As shown in the following table, no significant changes in mean trough concentrations of armodafinil with time were observed following chronic dosing.

Table 6. Mean trough plasma concentrations of armodafinil in patients administered armodafinil at 250 mg/day (Study 102 and Study 3021)

	Mean ± SD (µg/mL)			
	Day 14	Week 4	Week 8	Week 12
250 mg/day (Study 102)	2.93 ± 1.36 (n=6)			

<b>250 mg/day (Study 3021)</b> (All Patients)		3.23 ± 1.36 (n=116)	2.83 ± 1.29 (n=108)	2.70 ± 1.27 (n=106)
<b>250 mg/day (Study 3021)</b> (Patients with All Visits, n=99)		3.26 ± 1.44	2.82 ± 1.33	2.72 ± 1.29

#### ***2.2.5.3 What are the characteristics of drug absorption?***

According to the Sponsor, R-modafinil is readily absorbed following oral administration of NUVIGIL. Time to reach peak concentration ( $T_{max}$ ) was approximately 2 hours in fasted state and was prolonged to approximately 6 hours with high-fat meal.

#### ***2.2.5.4 What are the characteristics of drug distribution?***

Following single oral doses the V/F of armodafinil is approximately 42 L or 0.6 L/kg (based on 70 kg body weight), suggesting that it is well distributed in the body. No formal study was conducted to evaluate the protein binding of armodafinil. Since the protein binding of racemic modafinil is moderate, approximately 60% (referred to PROVIGIL label), the sponsor anticipates a minimal drug interaction potential with other highly protein-bound drugs.

#### ***2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?***

No formal mass balance study was conducted specifically for armodafinil. However, according to the PROVIGIL label, results of mass balance and metabolism studies of racemic modafinil suggest that the compound is nearly exclusively metabolized in the liver. Less than 10% of the parent compound and majority of the metabolites were excreted in the urine.

#### ***2.2.5.6 What are the characteristics of drug metabolism?***

No formal study was conducted to characterize the metabolic pathways of armodafinil. In the present application, the reference is made to the information on the basic metabolism of R-modafinil available in the approved labeling for PROVIGIL.

In vitro and in vivo data show that R- and S-enantiomers of modafinil undergo qualitatively similar hydrolytic deamidation, S-oxidation, and aromatic ring hydroxylation, with subsequent glucuronide conjugation of the hydroxylated products. Amide hydrolysis is the most prominent metabolic pathway, with sulfone formation by CYP3A4/5 being next in importance. The other oxidative products are formed too slowly in vitro to enable identification of the enzyme(s) responsible.

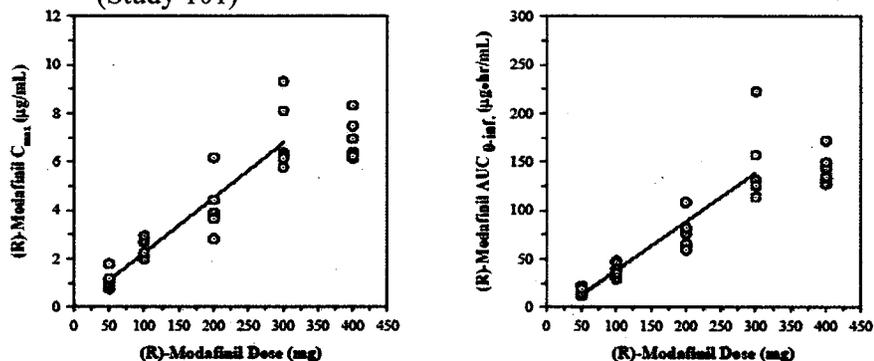
#### ***2.2.5.7 What are the characteristics of drug excretion?***

No formal mass balance study was conducted specifically for the armodafinil. As described above in Section 2.2.5.5 (referred to PROVIGIL label), less than 10% of the parent compound and majority of the metabolites were excreted in the urine. Results of the PK characterization in the present application indicated that after oral administration, armodafinil exhibits an apparent monoexponential decline after reaching its peak concentrations. Armodafinil is characterized by a relatively slow elimination with a mean terminal  $t_{1/2}$  of approximately 15 hours. The mean terminal  $t_{1/2}$  of its major circulating metabolites, R-modafinil acid and modafinil sulfone, are approximately 16 and 38 hours, respectively (details available in individual study review). The CL/F of armodafinil following multiple oral doses is approximately 33 mL/min.

**2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

R-modafinil exhibits dose-proportionality in mean exposure measures ( $C_{max}$  and  $AUC_{0-\infty}$ ) following single oral doses (50, 100, 200, and 300 mg) in Study 101 and following multiple oral doses (50, 100, 200, 250, 300, and 400 mg) for up to 14 days in Study 102. Similar results were obtained for  $C_{max}$  and initial  $AUC_{0-14hr}$  in Study 103 following single doses of 100, 150, 200, and 300 mg. The dose-proportionality was evaluated and demonstrated across the dose range studied using unweighted linear regression method by the Sponsor.

Figure 13. Individual  $C_{max}$  and  $AUC_{0-\infty}$  values of (R)-modafinil as a function of the dose (Study 101)



Note: The lines shown represent the best fit of the data and were obtained by unweighted linear regression analysis of the 50-300-mg dose data for  $C_{max}$  and  $AUC_{0-\infty}$ .

Figure 14. Individual  $C_{max}$  and  $AUC_{0-\infty}$  values of (R)-modafinil as a function of the dose (Study 102)

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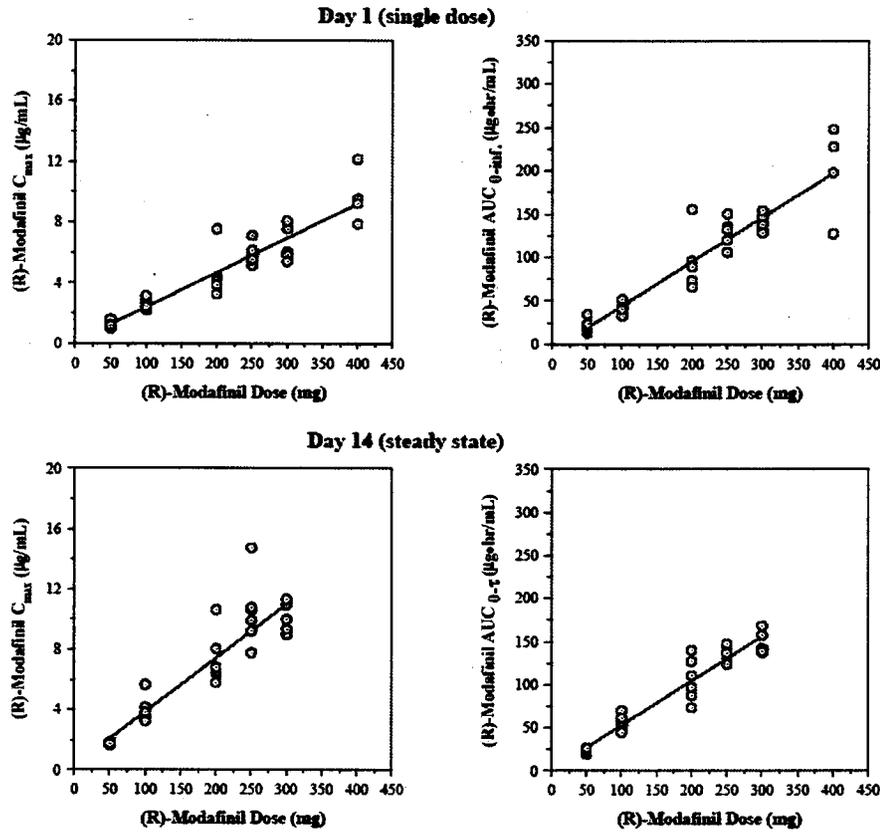
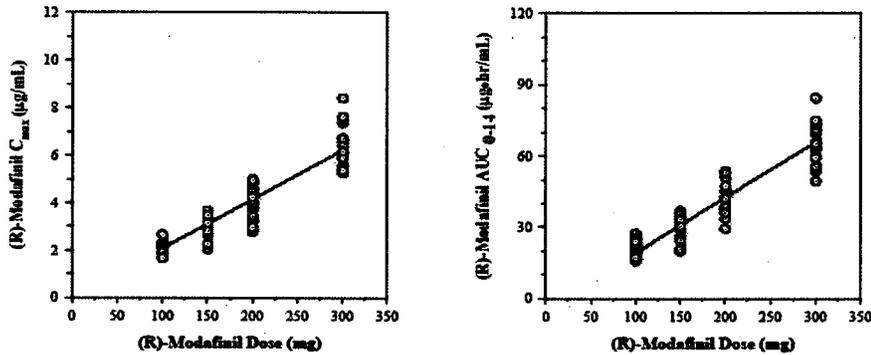


Figure 15. Individual  $C_{max}$  and  $AUC_{0-\infty}$  values of (R)-modafinil as a function of the dose (Study 103)



Note: The lines shown represent the best fit of the data and were obtained by unweighted linear regression analysis of the 100-300-mg dose data for  $C_{max}$  and  $AUC_{0-14}$ .

### 2.2.5.9 How do the PK parameters change with time following chronic dosing?

As seen in the single- and multiple-dose PK results presented above in Section 2.2.5.1, the CL/F values remain similar across dose ranges studied. Following multiple daily

doses, the steady-state was achieved after 7 days and the steady-state levels of same dose remain similar between Day 7 and Day 14. The steady-state accumulation ratios of different doses remain consistent at approximately 1.4-1.9 (slightly higher than predicted  $R_{ss}=1.2$  based on single-dose PK profile), suggesting time-invariant linear PK properties across the dose range studied and with the proposed doses.

Following single doses of armodafinil, R-modafinil acid and modafinil sulfone contributed to approximately 11% and 33%, respectively, of the parent drug concentrations. Following multiple doses of armodafinil, R-modafinil acid and modafinil sulfone contributed to approximately 7% and 56%, respectively, of the parent drug exposure, suggesting accumulation of modafinil sulfone.

The mean trough concentrations were obtained through sparse PK sampling in weeks 4, 8, and 12 in three controlled Phase 3 clinical trials (Study 3020, 3021, and 3025). No PK parameters were provided for each study. The trough levels of the armodafinil not only appeared to be dose-related between 150 mg/day and 250 mg/day dose groups, but also remained consistent between weeks 4 and 12. The slight fluctuations obtained overtime in two of the clinical trials remained within the overall variability in the means for different dose groups, suggesting the time-invariant linear PK properties across the dose range studied and with the proposed doses. The trough concentrations of both metabolites of each dose group also appeared to parallel the trend of the parent moiety. Additional information is seen in Section 2.2.5.2.

#### *2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?*

Based on the single- and multiple-dose PK results presented above in Section 2.2.5.1, the inter-subject variability (as expressed as %CV) was mostly less than 35% either following single doses or at steady state following multiple doses. The potential sources of the variability may include the body weight, metabolic rate and/or absorption. No intra-subject variability was evaluated.

### *2.3 Intrinsic Factors*

#### *2.3.1 What intrinsic factors influence the exposure and/or response?*

No formal studies were conducted to assess the effects of race, sex, age, or hepatic or renal impairment on the pharmacokinetics of armodafinil. According to the Sponsor, the impact of these covariates was assessed based on data from PROVIGIL studies alone. Therefore, the information and relevant dosage adjustments can be referenced to the approved PROVIGIL label (NDA 20-717) based on the known exposure-response relationships.

**2.3.2 What dosage regimen adjustments, if any, are recommended for each of these groups based on the known exposure-response relationships or alternative basis?**

**2.3.2.1 What is the effect of Age (elderly)?**

No formal clinical studies have been conducted to assess the effect of age on the pharmacokinetics of armodafinil. Studies with PROVIGIL in limited number of elderly **Alzheimer's disease patients suggested that the** clearance of modafinil may be reduced in the elderly (NDA 20-717).

**2.3.2.2 What is the effect of Gender?**

No formal studies have been conducted to assess the effect of sex on the pharmacokinetics of armodafinil. Population PK analysis indicated no effect of gender on the pharmacokinetic profiles of armodafinil. The pharmacokinetic profiles of PROVIGIL are not affected by gender (NDA 20-717).

**2.3.2.3 What is the effect of Race?**

The effect of race on the pharmacokinetic property of armodafinil has not been studied.

**2.3.2.4 What is the effect of Body Weight?**

The impact of intrinsic factors was explored in PK/PD modeling, clinical trial simulation, and population PK modeling of pooled data from NUVIGIL and PROVIGIL studies. Only bodyweight was found to have a linear relationship with volume of distribution (V/F). However, the analysis did not reveal any significant covariates which could potentially lead to dosing adjustment.

**2.3.2.5 What is the effect of Hepatic Impairment?**

Even though no armodafinil studies have been conducted in subjects with hepatic impairment, hepatic impairment is expected to have an impact on the pharmacokinetic profile mainly because of the dominant hepatic metabolism of this drug. According to the PROVIGIL label, modafinil was absorbed more slowly and was eliminated more slowly in adult patients with cirrhosis (Child-Pugh class B or C), compared with healthy subjects. The approximately 60% reduction in oral CL/F of modafinil and the doubling of the steady-state levels suggest that the dose of armodafinil should be reduced in patients with severe hepatic impairment.

b(5)

**2.3.2.6 What is the effect of Renal Impairment?**

No armodafinil studies have been conducted in subjects with renal impairment. According to the PROVIGIL label, severe chronic renal failure did not affect the single

dose PK profile of modafinil and hence no specific recommendation was made for dose adjustment. A 9-fold increase in modafinil acid exposure was noted.

## ***2.4. Extrinsic Factors***

### ***2.4.1 What extrinsic factors influence the exposure and/or response?***

Effects of smoking, herbal products, and alcohol use were not evaluated in armodafinil studies. The information and relevant dosage adjustments can be referenced to the approved PROVIGIL label (NDA 20-717) based on the known exposure-response relationships.

### ***2.4.2 Drug-drug interaction***

#### ***2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?***

According to the Sponsor, results of in vitro studies demonstrated that armodafinil weakly induced CYP1A2 and possibly CYP3A activities in a concentration-related manner, and reversibly inhibited the CYP2C19 activity.

The racemic modafinil (and modafinil sulfone) has been shown to inhibit CYP2C19 activity in vitro with a  $K_i$  value of 39  $\mu\text{M}$  ( $\sim C_{\text{max}}$  at steady state following 400 mg/day doses). The magnitude of the inhibitory effect in vivo on substrates for CYP2C19 is not yet quantified. In primary cultures of human hepatocytes in vitro, R-modafinil was shown to be a marginally more potent CYP inducer (though still considered weak) than S-enantiomer or the racemic modafinil. The induction appeared to be primarily intestinal in nature but was not well characterized. Other CYP isozymes were not affected by armodafinil.

#### ***2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?***

According to the PROVIGIL label, R-modafinil undergoes qualitatively similar metabolic transformations as its S-enantiomer. Multiple metabolic pathways are involved for its metabolism. Among them, the non-CYP-related pathway is the most prominent metabolic pathway and most rapid for armodafinil. The formation of the metabolite, sulfone, is by CYP3A4/5 and is next in importance. The impact of genetics has not been well characterized.

#### ***2.4.2.3 Are there major drug-drug interactions and are dosage adjustments required?***

The involvement of multiple metabolic pathways and non-CYP-related pathway as the most prominent and rapid among all, the effects of other drugs or co-medications on PK profiles armodafinil involving CYP enzymes are low.

Based on the in vitro results related to CYP1A2, 3A4, and 2C9, as discussed in Section 2.4.2.1 above, the Sponsor conducted three in vivo drug-drug interaction studies in healthy subjects to investigate the potential influence of armodafinil on these CYP isozymes.

*(1) What is the effect of armodafinil on CYP2C19?*

Effect of armodafinil on activity of CYP2C19, using omeprazole as a probe substrate, was investigated in an open-label, 2-way crossover study (Study 1021). Healthy subjects were randomized to receive one of the 2 treatment sequences (A→B or B→A), with a 7-day washout period between treatments. Single dose omeprazole or armodafinil was administered in the morning of days 1 and 8. This study evaluated the effect of the coadministration of a single dose of 400-mg armodafinil on the pharmacokinetic profile of 40-mg omeprazole and its 5'-hydroxy metabolite.

Results are summarized in the following table. Coadministration of armodafinil moderately inhibited CYP2C19 activity and increased omeprazole systemic exposure (i.e., AUC<sub>0-∞</sub>, AUC<sub>0-t<sub>1/2</sub></sub>, and C<sub>max</sub>) by approximately 40%, with a corresponding decrease in the V/F and CL/F values. The 90% confidence interval of the geometric mean ratios difference for ln-transformed exposure between two treatments fell outside the boundary of 80~125%, further supporting interaction between armodafinil and omeprazole. Results of this study also suggest that co-medications that are substrates for CYP2C19 may require dosage reduction.

Table 7. Primary pharmacokinetic parameters and statistical analysis

PK parameter	N	Omeprazole <sup>a</sup>	Omeprazole + CEP-10953 <sup>a</sup>	Geometric mean ratio (omeprazole + CEP-10953/omeprazole)	90% CI for geometric mean ratio
AUC <sub>0-∞</sub> (ng·hr/mL)	23 <sup>b</sup>	2401.1±1606.09	3268.4±2062.48	1.42	1.29, 1.57
AUC <sub>0-t<sub>1/2</sub></sub> (ng·hr/mL)	24	2420.8±1569.67	3263.2±2008.47	1.43	1.30, 1.57
C <sub>max</sub> (ng/mL)	24	800.6±354.50	1051.7±404.26	1.36	1.17, 1.59

**Reviewer's comment:**

- The accumulation of modafinil sulfone has been observed following multiple dosing. The inhibition potential on CYP2C19 by sulfone metabolite has been reported (according to the Provigil label). Therefore, the inhibitory effect of armodafinil on CYP2C19 following chronic doses may potentially be greater than what was observed in this single dose study.

*(2) What is the effect of armodafinil on CYP3A4?*

Effect of armodafinil on CYP3A activity, using midazolam as a probe substrate, was investigated in an open-label, nonrandomized pharmacokinetics and safety study in 24 healthy adults (male and female subjects) (Study 1022). Pharmacokinetic profiles of midazolam following single-dose intravenous (2 mg) and oral (5 mg) alone and after

approximately 4 weeks following repeated armodafinil doses up to 250 mg/day were determined.

Results are summarized in the following table. Coadministration of armodafinil resulted in approximate 17% and 32% reductions in systemic exposure for intravenous and oral midazolam, respectively, **with corresponding increases in exposure of 1'-hydroxymidazolam metabolite**. The moderate CYP3A4 inducing ability of armodafinil may result in reduced efficacy of drugs that are substrates for CYP3A4.

Table 8. Primary pharmacokinetic parameters of midazolam and statistical analysis by treatment group

PK parameter	N	Midazolam* (Geomean)	Midazolam + CEP-10953 <sup>a,b</sup> (Geomean)	Geometric mean ratio (with/without CEP-10953)	90% CI for mean ratio
<b>Intravenous</b>					
AUC <sub>0-∞</sub> (ng·hr/mL)	17	76.9±16.47 (75.3)	63.5±11.97 (62.5)	0.83	0.78, 0.89
AUC <sub>0-t</sub> (ng·hr/mL)	17	74.8±15.92 (73.3)	61.8±11.88 (60.7)	0.83	0.77, 0.89
C <sub>max</sub> (ng/mL)	17	NA	NA	NA	NA
<b>Oral</b>					
AUC <sub>0-∞</sub> (ng·hr/mL)	17	53.8±19.53 (51.0)	36.5±16.85 (33.6)	0.66	0.58, 0.74
AUC <sub>0-t</sub> (ng·hr/mL)	17	51.6±18.03 (49.0)	34.9±16.37 (32.1)	0.65	0.58, 0.74
C <sub>max</sub> (ng/mL)	17	18.7±6.29 (17.6)	15.2±7.22 (14.0)	0.79	0.68, 0.93

Attempt was made by the Sponsor to analyze the fractional bioavailability of midazolam, as seen in the following table. **Supplemented by the greater increase in 1'-hydroxymidazolam exposure after oral administration**, results suggest that armodafinil induced both hepatic and intestinal CYP3A4 activity. The overall oral bioavailability was approximately 28%, with a larger contribution to the first-pass effect from the intestine (F<sub>G</sub> ~0.45) than from the liver (F<sub>H</sub> ~0.62).

Table 9. Fractions of bioavailability of midazolam and statistical analysis

PK parameter	N	Midazolam* (Geomean)	Midazolam + CEP-10953 <sup>a,b</sup> (Geomean)	Geometric mean ratio (with/without CEP-10953)	90% CI for mean ratio
F <sub>int</sub>	17	0.28±0.063 (0.272)	0.23±0.079 (0.215)	0.791	0.697, 0.897
F <sub>G</sub>	17	0.45±0.100 (0.439)	0.42±0.134 (0.401)	0.915	0.788, 1.063
F <sub>H</sub>	17	0.62±0.073 (0.618)	0.54±0.089 (0.537)	0.868	0.822, 0.915

**Reviewer's comment:**

- Results of this study suggest that dosage adjustment may be needed for co-medications that are substrates for CYP3A4, such as cyclosporine. A stronger labeling language for drug interaction with cyclosporine (than what is currently in Provigil label) should be considered for inclusion upfront in the Precautions section.

*(3) What is the effect of armodafinil on CYP1A2?*

Effects of armodafinil on CYP1A2 activity was evaluated in a single-center, open-label, nonrandomized pharmacokinetics and safety study in 29 healthy, non-smoking, adults (male and female subjects) (Study 1025). Pharmacokinetic profiles of caffeine following single-dose of 200 mg oral caffeine alone and after approximately 4 weeks following repeated armodafinil doses up to 250 mg/day were determined.

Results are summarized in the following table. The results of PK parameters and 90% CIs of this study show that armodafinil did not affect the systemic exposure (AUC or the C<sub>max</sub>) of caffeine, and appears not to affect CYP1A2 activity.

Table 10. Primary pharmacokinetic parameters of caffeine and statistical analysis

Pharmacokinetic parameter	n	Caffeine* (Geomean) (N=24)	n	Caffeine + CEP-10953 <sup>a,b</sup> (Geomean) (N=24)	Geometric mean ratio (caffeine + CEP-10953)	90% CI for mean ratio
AUC <sub>0-∞</sub> (ng•hr/mL)	23	47338±20374.1 (43309)	24	44291±19302.7 (40148)	95.32	90.88, 99.97
AUC <sub>0-t</sub> (ng•hr/mL)	24	45307±19677.6 (41337.0)	24	43523±18769.3 (39479)	95.51	91.10, 100.12
C <sub>max</sub> (ng/mL)	24	5006±1160.7 (4878)	24	5193±1128.4 (5074)	104.03	100.47, 107.72

**Reviewer's comment:**

- Other drug interactions stated in Provigil label should also be included in Nuvigil label.

*2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

No pertinent information is provided by the Sponsor or available in previously approved PROVIGIL label. It appears that the Sponsor has not conducted in vitro screening or in vivo study to investigate whether armodafinil (or modafinil) is a substrate and/or an inhibitor of P-glycoprotein. This needs to be evaluated (see Phase IV commitment).

*2.5 General Biopharmaceutics*

The Biopharmaceutic program was designed to compare the performance of the film-coated tablet formulation used in the pivotal Phase 3 clinical trials and the proposed TBM uncoated tablet formulation via in vivo BE and in vitro dissolution studies. The potential

food effect was evaluated using a prototype capsule of lowest strength (2 x 50 mg) as part of Phase 1 study with single rising doses (Study 101).

**2.5.1 What is the proposed formulation of the drug product?**

The armodafinil drug substance is derived from \_\_\_\_\_  
 \_\_\_\_\_ The inactive excipients used in the formulation, the manufacturing process, and the formulation for all doses of armodafinil tablets are the same as those in the commercial product PROVIGIL.

Also same as the current PROVIGIL tablets, NUVIGIL tablets are formulated at a drug load of \_\_\_\_\_ as an uncoated immediate release oral tablet containing 50 mg, 100 mg, 150 mg or 250 mg of armodafinil. The higher strengths (100 mg, 150 mg or 250 mg) weigh 2, 3, and 5 times of that of the 50-mg strength. As described in the following table, the various strengths of the tablets are differentiated by tablet size and are \_\_\_\_\_

b(4)

Table 11. Descriptions of proposed commercial NUVIGIL tablets

Tablet strength	Description
50 mg	Round, white to off-white tablet, debossed with Cephalon "C" on one side and "205" on the other side
100 mg	_____
150 mg	Oval, white to off-white tablet, debossed with Cephalon "C" on one side and "215" on the other side
250 mg	Oval, white to off-white tablet, debossed with Cephalon "C" on one side and "225" on the other side

b(4)

The quantitative composition of the to-be-marketed NUVIGIL formulations is shown in the following table.

Table 12. Composition of the to-be-marketed NUVIGIL tablets

Component	Reference to standard	Function	Amount (mg)/ 50 mg tablet	Amount (mg)/ 100 mg tablet	Amount (mg)/ 150 mg tablet	Amount (mg)/ 250 mg tablet
Armodafinil drug substance	In-house standard	Drug substance	50.0	100.0	150.0	250.0
Lactose	NF					
Microcrystalline Cellulose	NF					
Pregelatinized Starch	NF					
Povidone	USP					
Croscarmellose	NF					
Sodium _____	USP					
Magnesium Stearate	NF					
Total tablet weight						

b(4)

Comment:

The active moiety, armodafinil, and the inactive excipients are quantitatively and compositionally proportional across different strengths. In vivo bioequivalence study is not necessary and demonstration of the similarity through in vitro dissolution profiles will be adequate to bridge different strengths.

*2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?*

The armodafinil 50-mg film-coated tablets were used throughout the Phase 3 clinical trials. The clinical formulation (film-coated tablets) contains 50 mg of armodafinil and inactive ingredients, including lactose, starch, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and povidone, and coating containing lactose and a. The proposed to-be-marketed formulations are uncoated tablets consisting of armodafinil of 50, 100, 150 and 250 mg. To bridge between these 2 different formulations, the sponsor conducted a BE study (Study 1023) to compare the relative bioavailability and to establish the dosage form equivalency between 5 x 50-mg film-coated tablets and the highest proposed commercial strength 250-mg uncoated tablet.

b(4)

Study C10953/1023/BE/US was a single-dose, randomized, open-label, 2-way crossover study designed to compare the 5 x 50-mg film-coated tablets employed in the Phase 3 clinical trials with 1 x 250-mg uncoated TBM tablet in 30 healthy male and female subjects under fasting conditions. All subjects were randomized to one of the two treatment sequences (A→B or B→A). Armodafinil concentration-time profiles, pharmacokinetic parameters and statistics are summarized in the following figure and table.

Figure 16. Armodafinil plasma concentration-time profiles following single oral doses of 5 x 50 mg test (Treatment A) and 1 x 250 mg reference (Treatment B) formulations (N = 21)

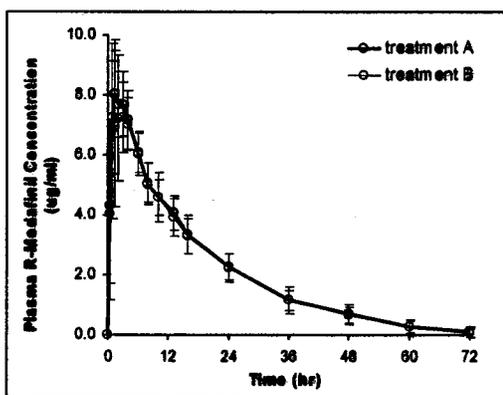


Table 13. Summary of pharmacokinetic results and statistical analysis

Pharmacokinetic parameters	Plasma Armodafinil		90% CI <sup>a</sup>	% Mean Ratio <sup>a</sup>
	Treatment B (N=21)	Treatment A (N=21)		
C <sub>max</sub> (µg/mL)	8.48±1.21	8.61±1.15	92.6-105.1	98.7
AUC <sub>0-t</sub> (µg·hr/mL)	139.9±1.189	144.3±1.155	94.2-99.3	96.7
AUC <sub>0-∞</sub> (µg·hr/mL)	146.4±1.188	151.0±1.157	94.2-99.4	96.7
T <sub>max</sub> (hr)	2.06±1.79	1.53±1.67	NA	NA
T <sub>1/2</sub> (hr)	12.6±1.23	12.8±1.23	NA	NA
λ <sub>z</sub> (hr <sup>-1</sup> )	0.0551±0.0123	0.0540±0.0123	NA	NA
CL/F (mL/min)	28.5±1.19	27.6±1.16	NA	NA
V <sub>z</sub> /F (L)	31.0±1.5	30.6±1.18	NA	NA

<sup>a</sup> Analysis based on ln-transformed data.

Treatment A=single oral dose of five 50-mg CEP-10953 tablets.

Treatment B=single oral dose of one 250-mg CEP-10953 tablet.

Bioavailability, as reflected by rate and extent of absorption, and the pharmacokinetic profiles of a single oral dose of 5 x 50-mg coated tablets (test) was similar to 1 x 250-mg tablet (reference). The 90% CI of AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> falls within acceptance criteria for BE, i.e., 80-125% CI. Therefore, statistical analysis of exposure measurements of the parent armodafinil, the active moiety, demonstrated the bioequivalence between clinical formulations used in pivotal trials and the TBM tablet formulation under single-dose fasting conditions.

Similar pharmacokinetic profiles were also observed for the metabolites, modafinil sulfone and (R)-modafinil acid, following oral administration of these two 250-mg armodafinil tablet formulations. (Results are shown in individual study report). Since both are inactive moieties and do not contribute to the pharmacological activity of armodafinil, no statistical analysis was performed as part of the BE evaluation.

**Reviewer's comment:**

- PK and BE results were reanalyzed by this reviewer based on DSI recommendation. In the DSI report issued on November 29, 2005, Dr. Sriram Subramaniam, recommended further exclusion of the CEP-10953 concentration data for Subjects 10, 11, 12, and 13 from the BE estimation, with reason being the lack of accuracy assurance in certain analytical runs. The same size (N=21) is still sufficient to provide >80% power at α=0.05 level for the statistical analysis. The above BE results **were obtained from reviewer's re-analysis** per DSI recommendation. No re-analysis is necessary for both metabolites since BE decision was made based on the active moiety only, i.e., the parent drug CEP-10953. BE is still shown even when these 4 subjects were excluded.

***2.5.3 What data support or do not support a waiver of in vivo BE study for the lower strengths of the TBM formulation?***

No in vivo study was conducted by the Sponsor to establish the dosage form equivalence for various strengths of the TBM tablet formulations. A biowaiver of in vivo BE data can be granted for the lower 50-mg, 100-mg, and 150-mg strengths of the TBM formulation on the following basis:

- Same uncoated tablet dosage form for all TBM strengths
- Active and inactive ingredients are in the same proportion between different strengths
- Bioequivalence was established via an in vivo BE study between 5 x 50-mg clinical trial formulation and 1 x 250-mg TBM formulation.
- Similar dissolution profiles of all strengths of TBM tablets in multiple pH media

**2.5.4** *What is the effect of food on the bioavailability (BA) of the drug from the NUVIGIL tablet and what dosing recommendation should be made, if any? Does food affect the bioavailability of NUVIGIL tablet formulation? [Is it appropriate to conduct food effect study on lower dosage strength and is there a food effect on the bioavailability of armodafinil?]*

The food effect was evaluated using a prototype 50-mg capsule formulation (the lowest dosage strength) as part of a Phase 1 study (Study 101). No food effect study was conducted on either clinical trial or TBM formulation.

Study C10953a/101/PK/UK was a randomized, double-blind, placebo-controlled, parallel-group study of single oral rising doses (50, 100, 200, 300, and 400 mg) of CEP-10953 in 40 healthy young adult male subjects under fasting condition. Subjects receiving 100 mg of CEP-10953 returned 1 week later to receive the same dose of CEP-10953 under the fed conditions (after a standard high-fat meal). Armodafinil concentration-time profiles, pharmacokinetic parameters and statistics are summarized in the following figure and table.

Figure 17. Mean plasma concentration-time profiles of (R)-modafinil following a 100-mg oral dose of armodafinil under fed and fasted conditions

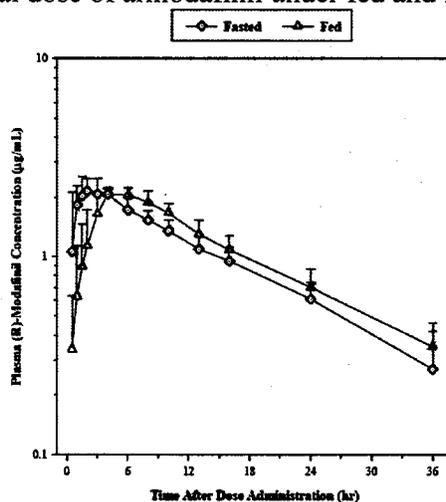


Table 14. Summary of PK results (mean ± SD) for armodafinil under fed and fasted conditions

Pharmacokinetic parameters	Plasma R-modafinil		90% CI <sup>a</sup>	% Mean Ratio <sup>a</sup>
	Fasted (N=6)	Fed (N=6)		
C <sub>max</sub> (µg/mL)	2.44 ± 0.38	2.17 ± 0.09	79.46 - 101.3	0.897
t <sub>max</sub> (hr)	2.3 [3.0-6.0]	6.0 [3.0-6.0]		
AUC <sub>0-∞</sub> (µg·hr/mL)	40.6 ± 7.4	43.8 ± 8.2	88.52 - 131.8	1.08
CL/F (mL/min)	42.4 ± 8.7	39.2 ± 7.2		
V/F (L)	42.0 ± 3.0	40.3 ± 3.7		
t <sub>1/2</sub> (hr)	11.5	11.9		

<sup>a</sup> Estimated by the reviewer

Similar pharmacokinetic profiles of armodafinil were observed following oral administration of 2 x 50-mg CEP-10953 capsules after high-fat food or without food. Food did not significantly affect the extent of armodafinil absorption from the prototype capsules, as indicated by slight decrease (by ~10%) in C<sub>max</sub> and increase (by ~8%) in AUC<sub>0-∞</sub>. High-fat food decreased the rate of absorption of armodafinil from capsule formulations, as indicated by the increase in t<sub>max</sub> from 2.3 hours to 6 hours. Statistical analysis of exposure measurements, AUC<sub>0-∞</sub> and C<sub>max</sub>, performed by this reviewer did not conform to the acceptance criteria for BE, i.e., 80-125% CI based on parent moiety.

**Reviewer's comments:**

- Per FDA's Guidance for Industry for conducting food effect bioavailability study, the highest strength, instead of a lowest strength, of a drug product intended to be marketed should be tested.
- Even though a pilot food effect study can be conducted with minimal number of subjects, a sufficient number of subjects (e.g., ≥N=12) should be included in a properly designed crossover study to achieve adequate power for a formal statistical assessment for food effects.
- This food effect study was conducted on the prototype capsule formulations, instead of either clinical formulations or the TBM formulations. The capsules are qualitatively similar in composition to the clinical formulations which are of identical composition to the TBM formulations. In view of the similarity in formulation composition and in in-vitro dissolution profiles between the prototype and clinical formulations, plus the BE results with TBM formulations, the similar food effect could be anticipated on the armodafinil absorption from NUVIGIL tablets. Even though no major food effect was noted on C<sub>max</sub> and AUC, the effect on T<sub>max</sub> (delay) could be a concern with a potential for delayed onset of action and higher armodafinil levels later in the day (with a concern for insomnia) when given with food.

b(5)

Table 15. Composition of armodafinil formulations



were collected at 7.5, 15.0, 22.5, 30.0, 37.5, 45.0, 52.5, and 60.0 minutes. Dissolution profiles of armodafinil tablets in 5 dissolution media for examining the effects of pH are shown as follows:

Figure 18. Dissolution profiles for 50 mg armodafinil tablets

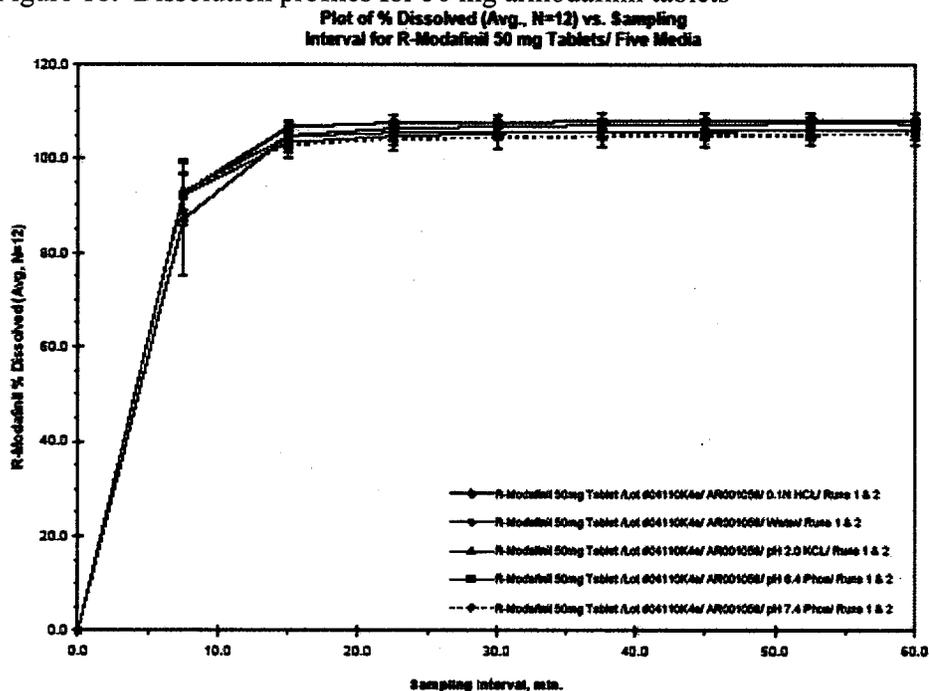


Figure 19. Dissolution profiles for 100 mg armodafinil tablets

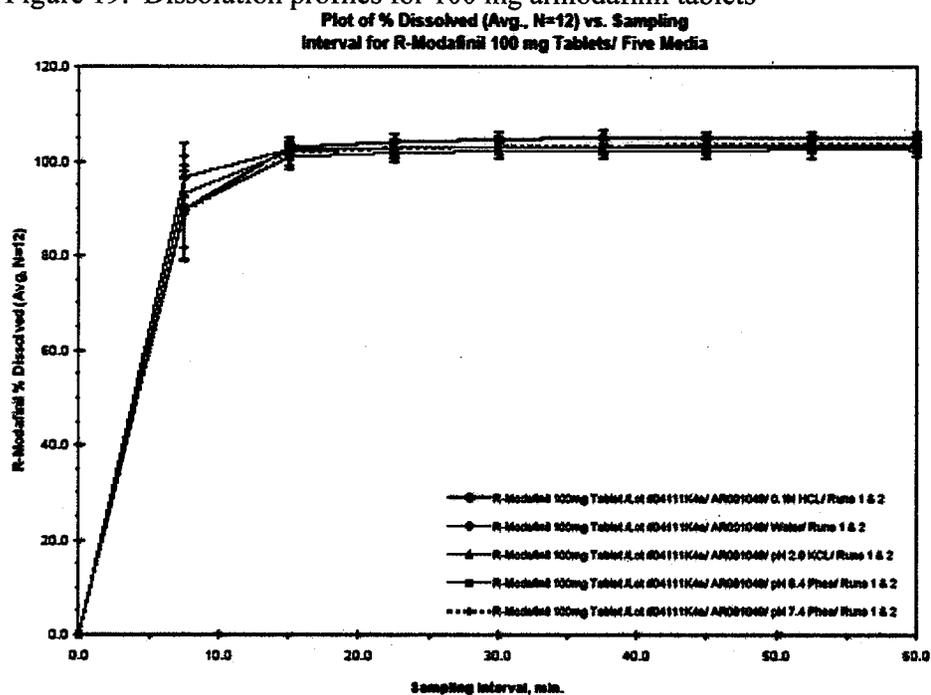


Figure 20. Dissolution profiles for 150 mg armodafinil tablets  
 Plot of % Dissolved (Avg. N=12) vs. Sampling Interval for R-Modafinil 150 mg Tablets/ Five Media

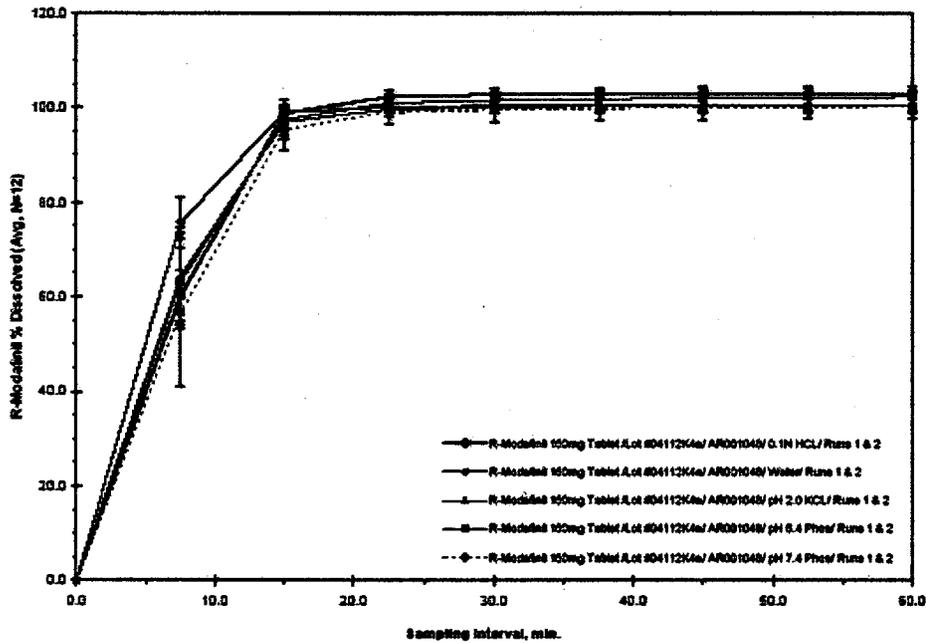
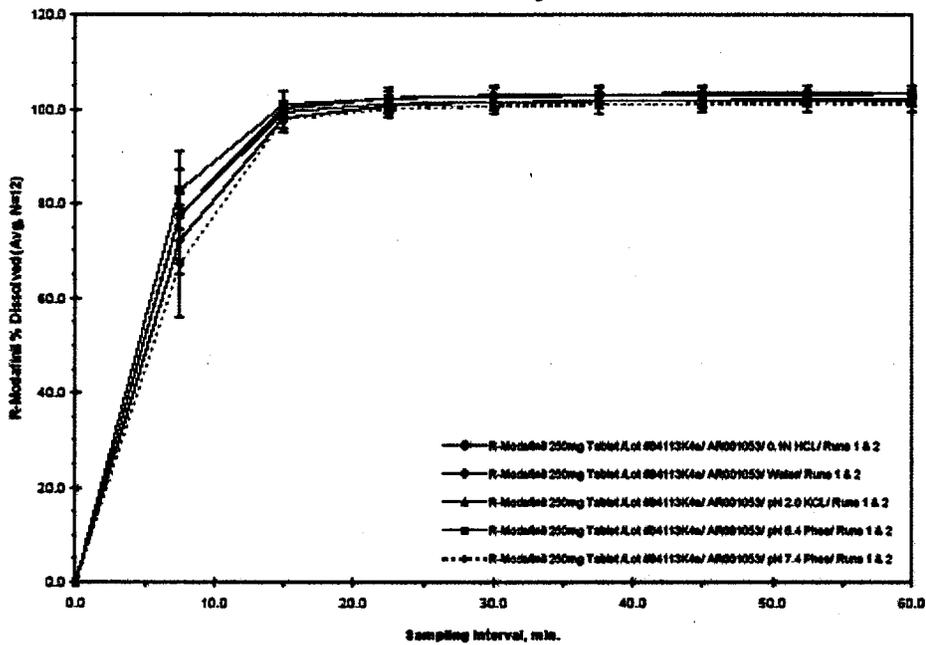


Figure 21. Dissolution profiles for 250 mg armodafinil tablets  
 Plot of % Dissolved (Avg. N=12) vs. Sampling Interval for R-Modafinil 250 mg Tablets/ Five Media

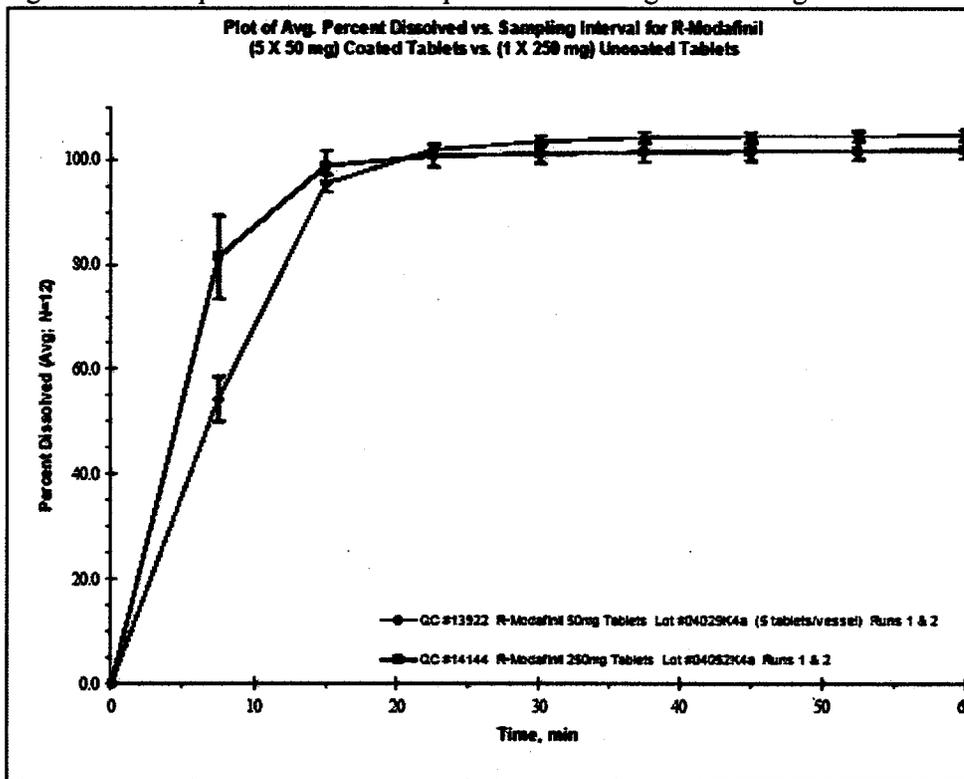


Greater than \_\_\_\_\_ (or near completion) of the label claim was dissolved in all media within \_\_\_\_\_ and the sponsor concluded that there were no discernable differences among different strengths in each medium of different pH values. The F2 comparison for dissolution profiles is unnecessary in these **conditions according to Agency's guidance** for SUPAC-IR.

b(4)

For bridging the clinical and TBM formulations, the sponsor conducted a comparative dissolution study in 0.1N HCl medium between 5 x 50 mg film-coated tablets (04053K5a) and 1 x 250 mg uncoated tablets (04092K5a) (both were used in the bioequivalence study) (Study 1023). The comparative mean dissolution profiles in 0.1N HCl medium are shown in the following figure:

Figure 22. Comparative dissolution profiles for 50 mg and 250 mg armodafinil tablets



Both formulations dissolved > \_\_\_\_\_ (i.e. \_\_\_\_\_ on average) of the label claim amount of drug within \_\_\_\_\_, and the complete dissolution occurred by \_\_\_\_\_. Even though the F2 comparison is unnecessary, the sponsor provided parameters for F1 difference and F2 similarity based on the first 3 points and the complete 8 points dissolution profiles, as shown in the following table. Even though results of both F1 (<15) and F2 (>50) comparisons show some difference between these two formulations, in vivo BE was shown.

b(4)

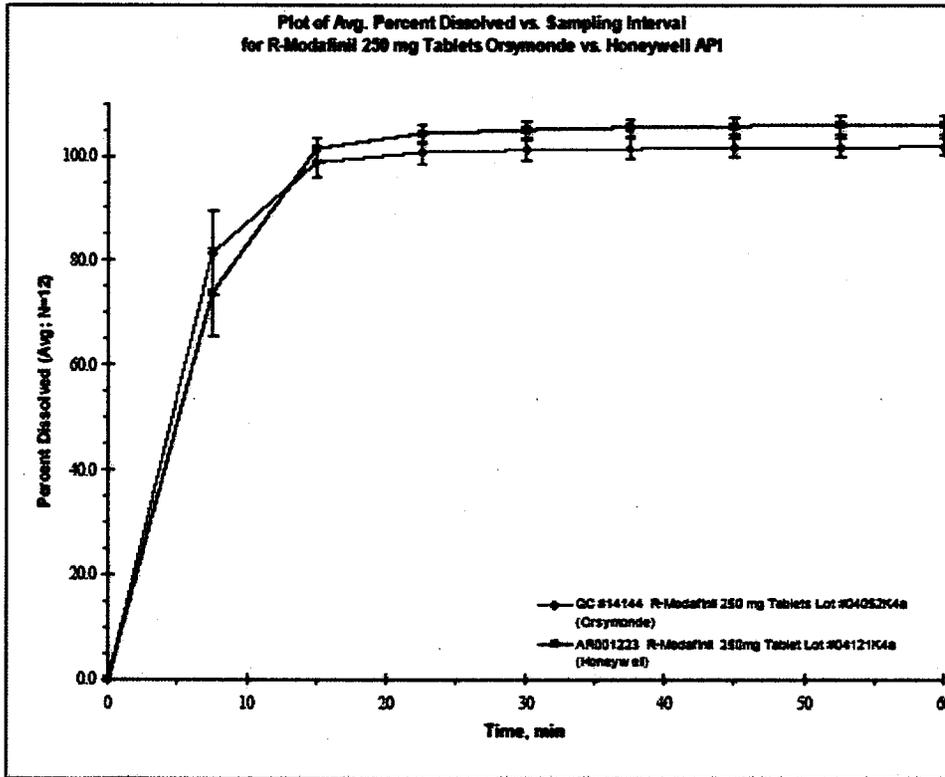
Table 17. Dissolution comparison with F1 and F2 parameters

Disolution medium	F1 parameter 3-point calculation	F2 parameter 3-point calculation	F1 parameter 8-point calculation	F2 parameter 8-point calculation
0.1N HCl	12.52	40.13	5.86	50.17
Target	<15	NA	<15	NA

Even though the drug products were manufactured at [redacted] part of the [redacted] biobatches used in BE and Phase 3 studies were manufactured from [redacted] drug substance [redacted]. The sponsor has conducted dissolution study in 0.1N HCl medium to compare the dissolution profiles of [redacted] tablets manufactured with [redacted] drug substance used in the biobatch and [redacted] drug substance from the commercial drug substance manufacturing site, the [redacted]. As shown in the following figure and table, both drug substances were found to be equivalent based on similar dissolution profiles with dissolution in [redacted].

b(4)

Figure 23. Comparative dissolution profiles of 250 mg armodafinil tablets



The sponsor has submitted the comparative dissolution data (N=6) for 50-mg capsule (03011K5a) vs. 50-mg tablet (04053K5a, clinical film-coated formulation). The dissolution studies were conducted in 900-mL 0.1N HCl medium, with USP Apparatus II at paddle speed of 50 rpm.

Of note, the prototype capsule formulation was used in pharmacokinetic profiling in Phase 1 studies and bridging the efficacy to PROVIGIL in PK/PD study for determining the dose and dose regimen for the pivotal Phase 3 efficacy trials. Therefore, it is important to bridge these two formulations using in vitro dissolution data since no additional in vivo BE study was conducted. As demonstrated in the following figures, the in vitro dissolution profiles for both formulations were found to be comparable, except the initial difference with ~~in~~ Nearly 95% or greater, on average, of both formulations dissolved at ~~the~~ timepoint. The %CV was <20% at first 7.5-minute timepoint and <10% at subsequent timepoints for both formulations.

Figure 24. Dissolution profiles of 50 mg capsule vs. 50 mg film-coated tablets (N=6)

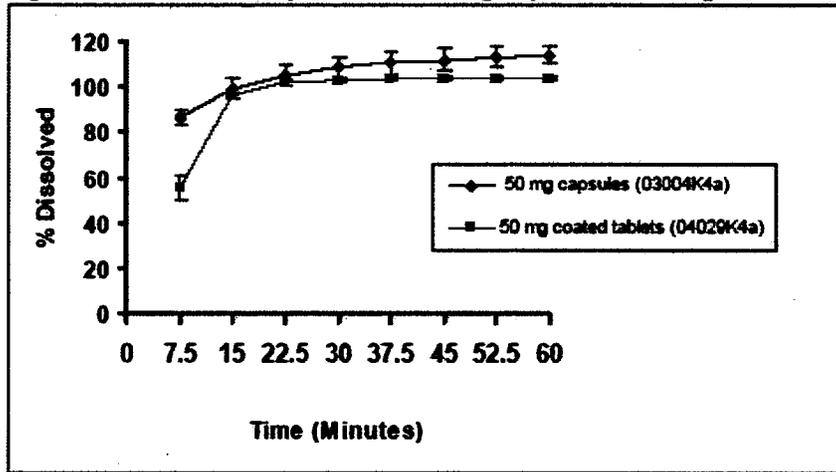
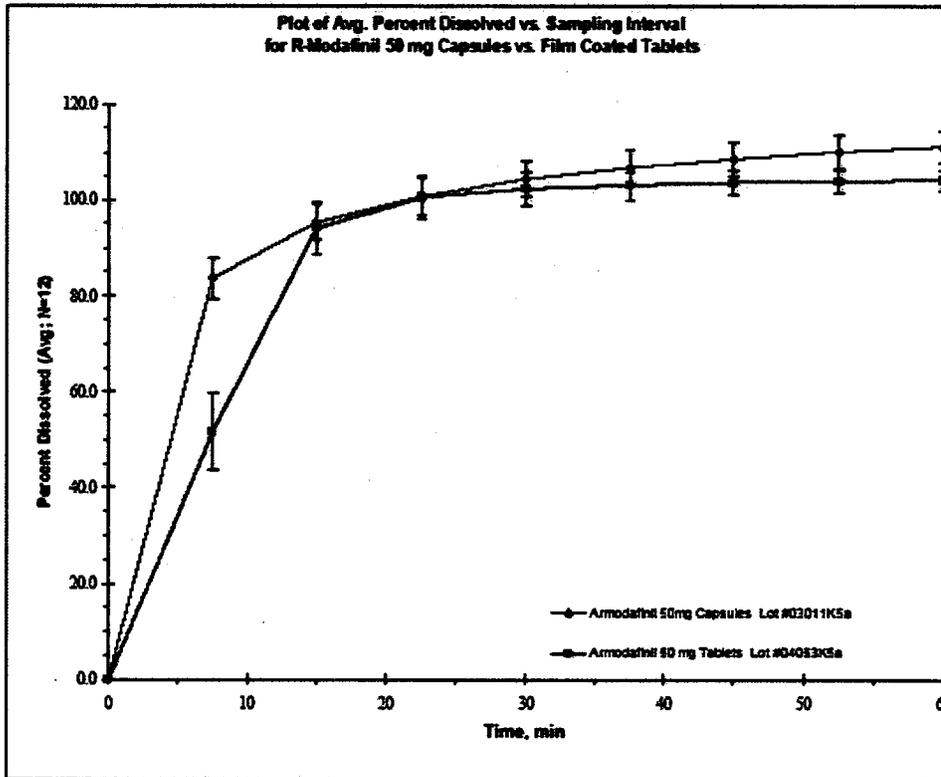


Figure 25. Dissolution profiles of 50 mg capsule vs. 50 mg film-coated tablets (N=12)

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**Reviewer's comments:**

1. The dissolution of all test formulations occurred rapidly and exceeded ~~100%~~ of the label claim amount in ~~15 minutes~~, while near completion occurred in ~~30 minutes~~. The results suggest that the regulatory specifications of armodafinil tablets could be tightened to Q ~~100%~~ at 30 minutes.
2. Chemistry reviewer has conveyed the same recommendation for the in vitro dissolution to the sponsor, and the Sponsor has agreed to tighten the specification at the Agency's request.

b(4)

**2.6. Analytical Section**

The OCP finds the bioanalytical methods adequate and justified.

**2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

Concentrations of CEP-10953 or (R)-Modafinil and its metabolites, modafinil sulfone, and (R)-Modafinil acid, in human plasma containing heparin were analyzed using a validated ~~method~~ HPLC-UV method. This method was validated by ~~the sponsor~~ at the request of Cephalon, Inc. The same method was used in all the Phase 1 BA, BE, drug-drug interaction, and PK/PD studies

b(4)

with CEP-10953 doses  $\leq 300$  mg and was performed by \_\_\_\_\_ and Cephalon, Inc. (West Chester, PA, USA).

b(4)

The standard solutions for the analytes were prepared using (R)-modafinil, modafinil sulfone, and (R)-modafinil acid. The analytes and the internal standard (\_\_\_\_\_) were first extracted from human plasma samples using liquid-liquid extraction. After the evaporation and reconstitution, aliquots of the final extracts were injected and analyzed using reversed-phase HPLC with UV absorbance detection. In all cases, the analytes in plasma matrix were free from interference with the presence of other analytes.

b(4)

This method is applicable to the quantitation of (R)-modafinil, modafinil sulfone, and (R)-modafinil acid within a nominal range of 0.200 through 50.0  $\mu\text{g/mL}$  and requires a 200  $\mu\text{L}$  human plasma aliquot containing sodium heparin. Samples are kept frozen at approximately  $-20^\circ\text{C}$  prior to analysis.

*2.6.2 Which metabolites have been selected for analysis and why?*

Both (R)-Modafinil acid and \_\_\_\_\_ modafinil sulfone were analyzed for plasma concentration mainly because they are major detectable circulating metabolites of the parent compound, either (R)-modafinil or (RS)-modafinil. These metabolites are present in human plasma but do not appear to contribute to the CNS-activating properties of CEP-10953.

b(4)

*2.6.3 Is free, bound, or total of the moieties measured?*

The fractions of plasma protein binding of the analytes are approximately 60%, thus total of the moieties were measure.

*2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

An eight-point calibration curve, excluding the blank sample, was constructed in human plasma in duplicate over the nominal concentration range between LLOQ and ULOQ (0.200, 0.500, 1.00, 2.00, 5.00, 10.0, 20.0, and 50.0  $\mu\text{g/mL}$ ) for (R)-modafinil, modafinil sulfone, and (R)-modafinil acid using a linear-weighted ( $1/\text{conc}$ ), least-squares regression algorithm to plot the peak height of the appropriate analyte to its internal standard vs. nominal concentration from extracted human plasma calibration standards. Linearity as indicated by correlation coefficients for each standard curve of the 3 analytes was  $\geq 0.990$ . The standard curve concentration range reasonably covers the concentrations seen in PK and clinical studies.

*2.6.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

Lower and upper limits of quantification (LLOQ and ULOQ) with respect to analysis of (R)-Modafinil, modafinil sulfone, and (R)-Modafinil acid are 0.200 µg/mL and 50.0 µg/mL, respectively.

*2.6.6 What are the accuracy, precision, and selectivity at these limits?*

Samples were found to be free of significant interfering peaks.

These assays were validated at 0.200 µg/mL (LLOQ), 0.600 µg/mL (QC Low), 20.0 µg/mL (QC Med), and 50.0 µg/mL (QC High) with the intra-assay and inter-assay precision and accuracy within ——— and are found acceptable.

b(4)

The intra-assay precision and accuracy based on six duplicates for these 3 analytes at LLOQ and at ULOQ were <10%. The inter-assay precision and accuracy based on six duplicates for these 3 analytes at LLOQ and at ULOQ were <10%. These values are found acceptable.

In addition, precision and accuracy was tested for the ability to dilute samples by analyzing 6 replicate, diluted QC Med samples. The assay precision and accuracy fall within ——— and are found acceptable.

b(4)

*2.6.7 What are the sample Recovery and stability under the conditions used in the study?*

The percent recovery was evaluated by comparing extracted samples to samples representing ——— recovery. The percent recovery for 3 analytes was tested by analyzing 0.500 µg/mL, 2.00 µg/mL, and 20.0 µg/mL (QC Med) based on peak heights. The mean recovery for (R)-modafinil, modafinil sulfone, and (R)-modafinil acid was 80.6~82.8%, 90.6~98.0%, and 90.5~94.8%, respectively.

b(4)

Three Freeze-thaw stability cycles for analytes in human plasma was tested at -20°C and room temperature controlled at QC Low (0.600 µg/mL) and QC High (50.0 µg/mL) levels, and was found acceptable. The precision and accuracy of R-modafinil based on six duplicates were <10% and were found acceptable. Analyte stability in thawed matrix was tested by analyzing QC Low and QC High at room temperature for 26.75 hours and was found to be stable.

Short-term stability in frozen matrix was tested by analyzing QC Low and QC High at -20°C for 13 days and was found to be stable. Long-term stability in frozen matrix was tested by analyzing QC Low and QC High at -20°C.

Post-preparative storage acceptability was tested by analyzing QC Low, QC med, QC High, and calibration curve, and was found to be stable for up to 85.3 hours for (R)-modafinil and 102 hours for the 2 metabolites.

*2.6.7. What is the QC sample plan?*

According to the Sponsor, the validation consists of at least ~~one~~ separate core validation runs (i.e., extraction batches). Each core run includes a reagent blank (RB), matrix blank (MB), matrix blank with internal standard (MB/IS), duplicate calibration standards, six replicate LLOQ, low-, medium-, and high-level QCs, and additional test samples as described in this section. If additional runs are required to complete the validation, they include low-, medium-, and high-level QCs at least in triplicate.

b(4)

For validation, duplicated QC samples for each analyte at four concentration levels, along with two calibration curves, were analyzed with each batch of the samples. Six replicates of 4 QC samples for all 3 analytes consisted of 0.200 µg/mL (LLOQ), 0.600 µg/mL (QC Low), 20.0 µg/mL (QC Med), and 50.0 µg/mL (QC High).

***3. DETAILED LABELING RECOMMENDATIONS***

Office of Clinical Pharmacology has reviewed the proposed labeling for NUVIGIL and found it acceptable provided that revision is made to the labeling language.

Labeling recommendation to be sent to the Sponsor:

The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~strike through~~ is recommendation for deletion from the perspective of OCP.

***4. APPENDICES***

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       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

## *4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews*

### **Study C10953a/101/PK/UK**

#### **A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Pharmacokinetics, Safety, and Tolerability of Single Oral Rising Doses of CEP-10953 in Healthy Young Men**

Principal Investigator: Stephen Freestone

Study Center: Inveresk Research, Tranent, EH33 2NE, Scotland, U.K.

Study Period: May 12, 2003 – June 22, 2003

#### **Objectives:**

##### **Primary:**

- To determine the single-dose pharmacokinetic profile of CEP-10953 in healthy young adult men

##### **Secondary:**

- To assess the safety and tolerability of single oral rising doses of CEP-10953.
- To assess the effect of food consumption on the pharmacokinetic profile of a single 100-mg oral dose of CEP-10953

#### **Drug Products:**

**Test formulation:** CEP-10953, 50-mg capsules, Lot #: 03011K5a (Cephalon, Inc.)

**Matching Placebo:** matching placebo capsules, Lot #: 03010K5a (Cephalon, Inc.)

#### **Study Design:**

This first study in humans was a randomized, double-blind, placebo-controlled, parallel-group design of single oral rising doses of CEP-10953 in 40 healthy young adult male subjects under fasting condition. To be enrolled, all subjects must be of any ethnic origin aged 21~40 years, a Body Mass Index (BMI)  $\leq 30$  kg/m<sup>2</sup>, who met the inclusion and exclusion criteria. Prescription or OTC medication (with the exception of paracetamol) was not allowed during the study. Alcohol, antiseptic mouthwash, or grapefruit juice were prohibited within 48 hours before dosing.

Duration of treatment was a total of 19 days, including a 3-days inpatient (dosing on second day), follow-up on an outpatient basis on days 4-5, and additional study 1 week later in the fed state with subjects who received 100 mg of study drug. The morning dose was given as 1~8 capsules with 180 mL of water on second day after an overnight fasting. Subjects (8 per panel) were randomized to receive 1 of 5 doses of CEP-10953 (50, 100, 200, 300, and 400 mg) or matching placebo capsules with 6:2 ratio in each panel. Each panel was initiated sequentially after a safety review, with approximately 7 days in between and an adjustment to the dose in 50-mg increments if necessary. Pharmacokinetics, safety, and tolerability assessments were performed over 5 days postdose. Subjects in panel receiving 100 mg of CEP-10953 returned 1 week later to

receive 100 mg of CEP-10953 under the fed state (after a high-fat meal). No efficacy assessment was performed in this study.

**Safety Assessments:**

Safety assessments were conducted at screening, baseline, and during the study, including physical examination, vital signs (blood pressure, pulse, and temperature), 12-lead electrocardiograms (ECG), and clinical laboratory test results (hematology, serum chemistry, and urinalysis) up to 96 hours postdose. Adverse events were continuously monitored throughout the study. The ECG monitoring was carried out prior to starting the study, throughout day 1 at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 16 h, and 24, 36, 48, and 96 hours post-treatment. Adverse events were monitored throughout the study.

**Pharmacokinetics Assessments:**

A total of 16 blood samples were collected from each subject for the determination of CEP-10953 and metabolites modafinil sulfone and R-modafinil acid at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 16, 24, 36, 48, 72, and 96 hours postdose. Plasma samples were stored frozen at -20°C until assayed.

Plasma concentrations of CEP-10953, modafinil sulfone, and R-modafinil acid were analyzed by a validated HPLC method performed at \_\_\_\_\_

**Table 1. Assay validation for Study C10953a/101/PK/UK**

		R-modafinil (CEP-10953)	R-modafinil acid	Modafinil sulfone
<b>Method:</b>		HPLC	HPLC	HPLC
<b>Standard curve</b>				
	Range:	0.20~50.00 µg/mL	0.20~50.00 µg/mL	0.20~50.00 µg/mL
	Precision:	0.0~5.0 %	0.0~5.2 %	0.0~5.6 %
	Accuracy:	92.2~102 %	92.6~102 %	93.1~102 %
	Linearity:	r <sup>2</sup> = 0.9977	r <sup>2</sup> = 0.9980	r <sup>2</sup> = 0.9979
<b>LOQ</b>	LLOQ:	0.20 µg/mL	0.20 µg/mL	0.20 µg/mL
<b>QC</b>	Low:	0.60 µg/mL	0.60 µg/mL	0.60 µg/mL
	Precision:	5.1 %	3.3 %	5.2 %
	Accuracy:	98.3 %	100 %	96.7 %
	Med:	20.00 µg/mL	20.00 µg/mL	20.00 µg/mL
	Precision:	5.6 %	5.7 %	5.9 %
	Accuracy:	96.3 %	96.4 %	95.2 %
	High:	50.00 µg/mL	50.00 µg/mL	50.00 µg/mL
	Precision:	4.9 %	5.0 %	4.9 %
	Accuracy:	94.0 %	93.9 %	93.1 %

b(4)

**Pharmacokinetic Analysis:**

The following pharmacokinetic parameters for CEP-10953 and its metabolites (when possible) were calculated by standard non-compartmental methods: C<sub>p</sub>, C<sub>max</sub>, T<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, K<sub>el</sub>, t<sub>1/2</sub>, CL/F, and V/F.

**Statistical Analysis:**

All pharmacokinetic data available from each time point were included in the pharmacokinetic analysis. Descriptive statistics, including mean, median, standard deviation (SD), and inter-subject coefficient of variation (CV), were employed for summarizing all pharmacokinetic parameters of CEP-10953, modafinil sulfone, and R-modafinil acid. All data listings, summaries, and statistical analyses were generated using Statistical Analysis Software (SAS<sup>®</sup>) Version 8.2.

## RESULTS

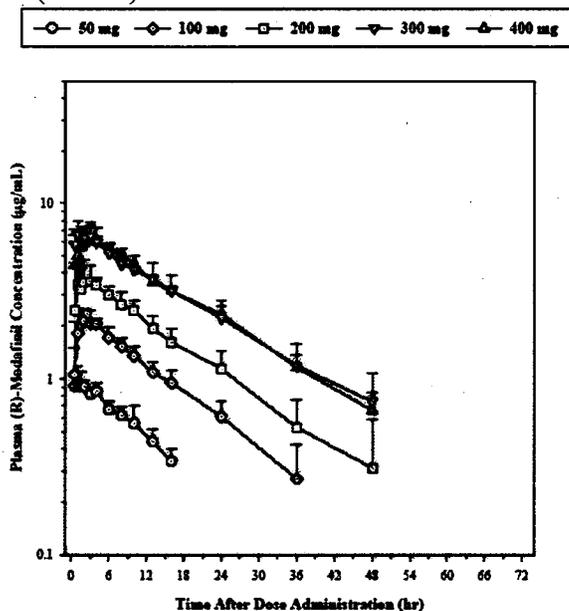
### Demographics of Subjects:

A total of 40 male subjects were enrolled in study, and all subjects received drug and completed the study. The subjects consisted of 92.5% Caucasians and 7.5% black. The mean age, weight, height and BMI were 28.5 years (22-39 years of age), 79.0 kg (61-103 kg), 178.8 cm (168-192 cm), and 24.7 kg/m<sup>2</sup> (19-30 kg/m<sup>2</sup>), respectively. Final Pharmacokinetics and safety analyses were performed on all 40 subjects and on all pharmacokinetic data available from each sampling time point.

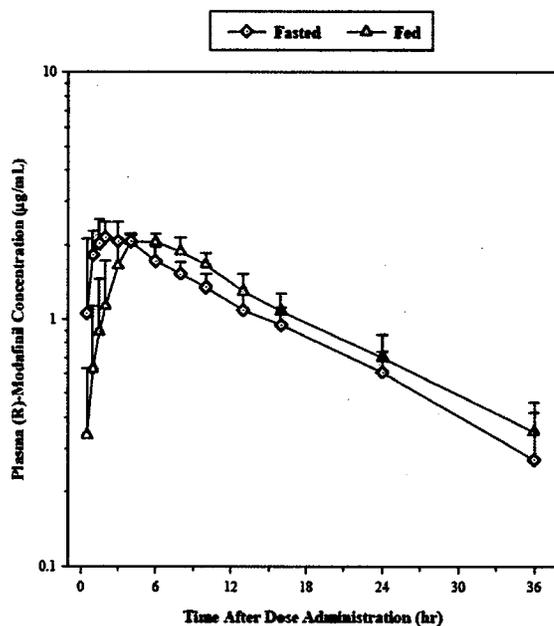
### Pharmacokinetic Summary:

The mean plasma concentration-profiles and pharmacokinetic parameters of CEP-10953, R-modafinil acid, and modafinil sulfone following single rising oral doses of 50, 100, 200, 300, and 400 mg are shown in Figures 1-4. The summary of pharmacokinetic parameters and statistics are shown in Tables 2-4.

**Figure 1.** Mean (R)-modafinil plasma concentration-time profiles following single oral doses of CEP-10953 (N = 40)



**Figure 2.** Mean plasma concentration-time profiles of (R)-modafinil following a 100-mg single oral dose of CEP-10953 under fed and fasted conditions



**Table 2.** Summary of PK results (mean ± SD) for R-modafinil following single oral doses of CEP-10953

Dose (mg)	n	C <sub>max</sub> (µg/mL)	t <sub>max</sub> <sup>a</sup> (hr)	AUC <sub>0-∞</sub> (µg·hr/mL)	CL/F (mL/min)	V/F (L)	t <sub>1/2</sub> <sup>b</sup> (hr)
50	6	1.12 ± 0.36	0.8 [0.5-2.0]	15.9 ± 3.7	54.7 ± 11.6	51.0 ± 7.9	10.6
100 (Fasted)	6	2.44 ± 0.38	2.3 [0.5-4.0]	40.6 ± 7.4	42.4 ± 8.7	42.0 ± 3.0	11.5
100 (Fed)	6	2.17 ± 0.09	6.0 [3.0-6.0]	43.8 ± 8.2	39.2 ± 7.2	40.3 ± 3.7	11.9
200	6	4.10 ± 1.13	2.5 [0.5-4.0]	75.9 ± 17.9	45.7 ± 9.2	51.2 ± 8.1	12.8
300	6	6.98 ± 1.40	1.5 [0.5-3.0]	146.0 ± 40.3	36.0 ± 7.7	45.6 ± 6.8	14.7
400	6	6.92 ± 0.85	3.0 [0.5-4.0]	142.9 ± 16.3	47.1 ± 5.0	55.3 ± 3.8	13.5

<sup>a</sup> Median [range]  
<sup>b</sup> Harmonic mean

**Table 3.** Summary of exposure results and statistical analysis for R-modafinil following a 100-mg single oral doses of CEP-109535 under fed and fasted conditions (provided by this reviewer)

Pharmacokinetic parameters	Plasma CEP-10953		90% CI <sup>a</sup>	% Mean Ratio <sup>a</sup>
	100 mg fasted (N=6)	100 mg fed (N=6)		
C <sub>max</sub> (µg/mL)	2.44±0.38	2.17±0.09	79.46-101.3	0.897
AUC <sub>0-∞</sub> (µg·hr/mL)	40.6±7.4	43.8±8.2	88.52-131.8	1.08

<sup>a</sup> Analysis based on ln-transformed data.

**Table 4.** Summary of pharmacokinetic results (mean  $\pm$  SD) for (R)-modafinil acid and modafinil sulfone in healthy male volunteers following multiple oral doses of CEP-10953

Compound	Dose (mg)	n	C <sub>max</sub> (µg/mL)	t <sub>max</sub> <sup>a</sup> (hr)	AUC <sub>0-∞</sub> (µg·hr/mL)	t <sub>1/2</sub> <sup>b</sup> (hr)
(R)-Modafinil Acid	200	6	0.28 $\pm$ 0.14	3.0 [1.0-4.0] <sup>c</sup>	8.4 $\pm$ 1.6 <sup>c</sup>	16.3 <sup>c</sup>
	300	6	0.64 $\pm$ 0.22	3.5 [1.0-6.0]	13.7 $\pm$ 3.3	15.5
	400	6	0.56 $\pm$ 0.07	3.0 [2.0-6.0]	13.8 $\pm$ 3.6	15.0
Modafinil Sulfone	200	6	0.23 $\pm$ 0.12	24.0 [16.0-24.0] <sup>e</sup>	9.0 $\pm$ 6.7 <sup>d</sup>	NC
	300	6	0.52 $\pm$ 0.15	24.0 [24.0-36.0]	45.7 $\pm$ 11.2	43.6
	400	6	0.68 $\pm$ 0.25	24.0 [24.0 for all]	52.7 $\pm$ 20.8	38.1

NC: Not Calculable

<sup>a</sup> Median [range]

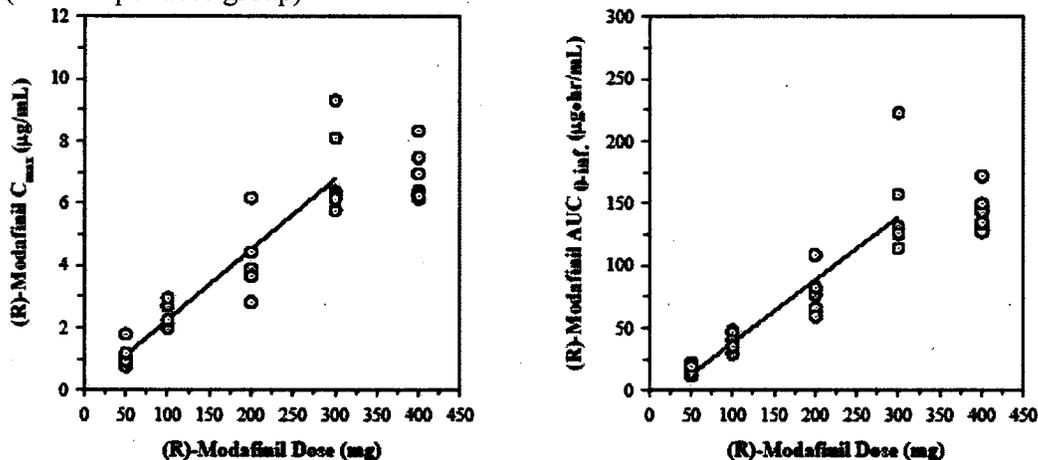
<sup>b</sup> Harmonic mean

<sup>c</sup> Parameter was calculable in only 5 of 6 subjects.

<sup>d</sup> AUC<sub>0-∞</sub> was not calculable; the value shown is for AUC<sub>0-t</sub>

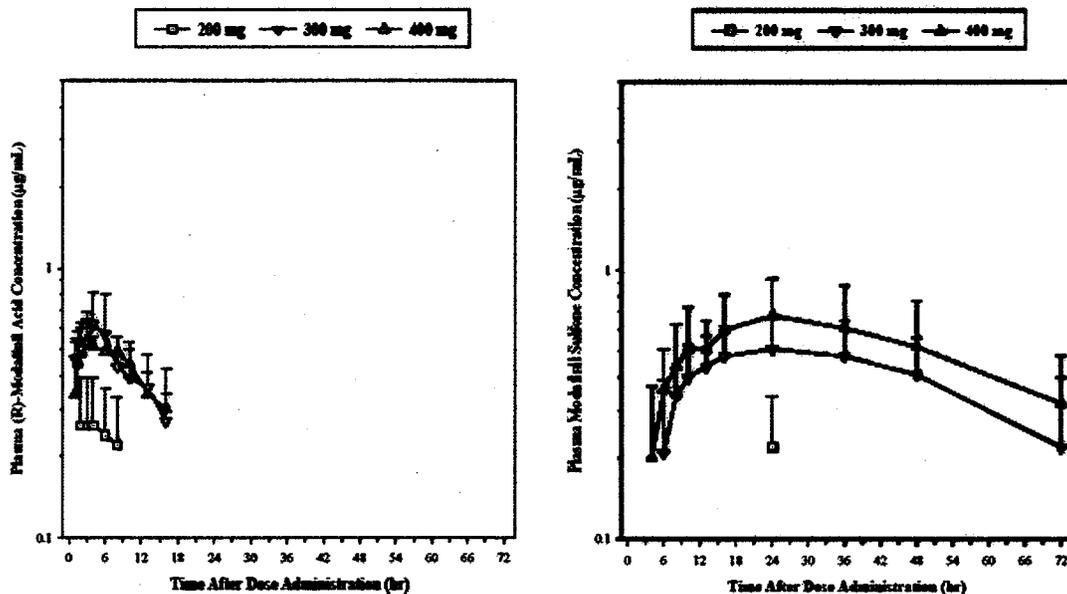
Note: The mean plasma concentrations of (R)-modafinil acid and modafinil sulfone were BLQ (<0.20 µg/mL) at all of the sampling times following administration of the 50- and 100-mg doses of (R)-modafinil.

**Figure 3.** Individual C<sub>max</sub> and AUC<sub>0-∞</sub> values of (R)-modafinil as a function of the dose (N = 4-6 per dose group)



Note: The lines shown represent the best fit of the data and were obtained by unweighted linear regression analysis of the 50-300-mg dose data for C<sub>max</sub> and AUC<sub>0-∞</sub>.

**Figure 4.** Mean (R)-modafinil acid and modafinil sulfone plasma concentration-time profiles following single oral doses of CEP-10953



**Safety Summary:**

No deaths or other serious adverse events, or withdrawals due to adverse events were reported during the study. Most of the adverse events were mild in severity. With active treatment, 2 subjects (33%) each receiving 50 mg, 100 mg (1 fasted [17%] and 1 nonfasted [17%]), and 200 mg, 3 subjects (50%) receiving 300 mg, and 4 subjects (67%) receiving 400 mg of CEP-10953 reported adverse events. No placebo-treated subjects had adverse events. Most of the adverse events were mild in severity. Headache was the most common adverse event and appeared to be dose-related. No clinically meaningful abnormal laboratory values, vital signs, physical examination findings, or ECG findings were reported. Overall, single doses of CEP-10953 were well tolerated.

**CONCLUSION:**

1. Pharmacokinetics of single doses of CEP-10953 under fasting condition was linear and dose-proportional in the range of 50~300 mg. Similar exposure was observed between 300 and 400 mg doses, suggesting saturable absorption. The terminal  $t_{1/2}$  ranged from 11.5 to 14.7 hours, similar to that seen following modafinil dosing.
2. The  $T_{max}$  was increased from 2.3 hours to 6 hours with high-fat meal, suggesting the decreased rate of absorption. However,  $C_{max}$  and  $AUC_{0-\infty}$  were only slightly decreased by ~10% and increased by ~8%, respectively, suggesting minimal food effects on extent of absorption.

**Reviewer's comments:**

- Per FDA's Guidance for Industry for conducting food effect bioavailability study, the highest strength, instead of a lowest strength, of a drug product intended to be marketed should be tested.

- Even though a pilot food effect study can be conducted with minimal number of subjects, a sufficient number of subjects (e.g.,  $\geq N=12$ ) should be included in a properly designed crossover study to achieve adequate power for a formal statistical assessment for food effects.
- This food effect study was conducted on the prototype capsule formulations, instead of either clinical formulations or the TBM formulations. The capsules are qualitatively similar in composition to the clinical formulations which are of identical composition to the TBM formulations. In view of the similarity in formulation composition and in in-vitro dissolution profiles between the prototype and clinical formulations, plus the BE results with TBM formulations, the similar food effect could be anticipated on the armodafinil absorption from NUVIGIL tablets. Even though no major food effect was noted on  $C_{max}$  and AUC, the effect on  $T_{max}$  (delay) could be a concern with a potential for delayed onset of action and higher armodafinil levels later in the day (with a concern for insomnia) when given with food

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